Universidad de Alcalá

Programa de Doctorado en Ciencias de la Salud

Donación tras muerte circulatoria no controlada y Reanimación con circulación extracorpórea en paradas cardíacas extrahospitalarias

Una estrategia integradora como solución a los conflictos existentes

Tesis Doctoral presentada por

IVAN ORTEGA DEBALLON

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Director:
DR. ANTONIO MARTIN DUCE

Alcalá de Henares, Julio 2016

CASE WESTERN RESERVE UNIVERSITY
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May 13, 2016

Dear Thesis Committee Members:

It is my honor to offer my support of the designation of "international doctorate" for the outstanding thesis material submitted by Professor Ivan Ortega-Deballon. It is my firm opinion that Professor Ortega-Deballon's doctoral work represents a research program that not only has great potential for future work, but also constitutes a significant and substantial contribution as it stands today. As well, Professor Ortega-Deballon's research has the all too rare quality of relevance for multiple domains, including the domains of clinical care, ethics, law, and health policy.

In my estimation, Professor Ortega-Deballon's thesis work as it stands makes several valuable original contributions to the international literature concerning uDCD, ECPR and OHCA. The primary contribution is that there are OHCA patients currently treated as "dead" under many standard uDCD protocols who may actually survive with an acceptable quality of life (good neurological recovery) if treated under emerging ECPR protocols (perhaps 13% or more). This primary contribution, when supplemented by additional research, yields a number of secondary contributions. These include the need for (1) standardization of uDCD protocols and outcomes, (2) large prospective ECPR studies to identify appropriate standards of care for subsets of OHCA patients, and (3) the need to reconcile uDCD and ECPR so that both survival with good neurological recovery *and* procurement of organs for transplant can be maximized. Though these contributions stem from Ortega-Deballon's work as it stands, the three secondary contributions clearly lay the groundwork for future research. It seems clear that Ortega-Deballon is well positioned to lead the way in helping to identify the subset of OHCA patients for whom ECPR is appropriate (thereby maximizing survival with quality of life) and, in light of this, helping to modify existing uDCD policies and practices so that organ procurement can be maximized without compromising patient rights or interests.

As mentioned above, Professor Orega-Deballon's research as it stands, as well as the potential it holds, has the rare quality of being highly relevant for multiple domains. In the clinical domain, patients who are not currently benefiting from ECPR, a subset of OHCA patients in refractory cardiac arrest, might do so. If Ortega-Deballon is correct, uDCD practices should be altered to account for this but without compromising the ability to procure organs should such patients die. In the domains of ethics and law, the success of ECPR raises questions about whether some patients who are now treated under uDCD protocols are really dead when they are deemed to be. Furthermore, Ortega-Deballon's research raises questions about the rights and interests of such patients and the truthfulness of some current practices in discussions with their families under uDCD as it is currently done. In the domain of health policy, a proper, data informed and conceptually clear approach to both uDCD and ECPR promises to support two important health policy

goals: (1) improvement of OHCA survival with good neurologic recovery rates and (2) maximal procurement of organs from those who do not survive OHCA through uDCD.

I want to conclude by reiterating that it is my honor to support of the designation of "international doctorate" for the Professor Ivan Ortega-Deballon's outstanding thesis work. It is my opinion that Professor Ortega-Deballon's work clearly merits this designation both as it stands and in its potential for future research. Do not hesitate to contact me should you think I can be of any further assistance on this matter.

Sincerely,

Mark P. Aulisio, PhD
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May 17,2016

IVAN ORTEGA DEBALLON
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Dear Academic Commission:

I am writing to comment on the significance of the dissertation presented by Ivan Ortega Deballon, entitled "Uncontrolled Donation after Circulatory Death and Extracorporeal Resuscitation in Out-of-Hospital Cardiac Arrest." This dissertation represents an original and important contribution to the scientific literature related to uncontrolled donation after circulatory death (UDCD).

The issues surrounding organ donation are very complex and vary from culture to culture. The priorities for optimizing success for organ recipients with the need to maximize potential life-saving resuscitation of the potential donors occasionally come into conflict In particular, Spain's approach to donation by Maastricht Type 2b donors (failing CPR) is considered the most advanced program in the world. I have participated in or commented on attempts to replicate similar program in the United States, none of which have been sustainable so far. However, more countries in Europe and North America are now developing extracorporeal life support (ECLS) programs, in imitation of successful programs in Asia, that provide advanced resuscitation to the same potential UDCD donor pool (failing CPR).

Ortega-Deballon addresses directly the conflict in priorities between uncontrolled donation in Maastricht Type 2B donors and the implementation of ECLS. Further, he proposes solutions and paths that will optimally respect the rights and welfare of both patients who may become donors and potential organ recipients. He does this in five papers, which I reviewed. These included a commentary on the clinical, ethical, legal and policy implications of ECLS and UDC; a systematic review of the effectiveness of UDCD programs; a systematic review of the conflicts and comparison between UDCD and ECLS; a discussion of ethics related to these competing programs; and a systematic review of effectiveness of ECLS.

Ortega-Deballon's analysis is thoughtful and informed by his direct experience with resuscitation and UDCD. His methodology for review of the literature is of the highest quality and has provided important additions to the scientific literature. The writing and assembly of this dissertation represents the quality and quantity of work I would expect in a doctoral thesis.

Finally, the conclusions of this dissertation have immediate implications. The available data imply that a small proportion (~13%) of potential organ donors under current UDCD programs might be resuscitated with ECLS programs. Because the logistical barriers to implement ECLS and UDCD are identical (specialized teams, cardiopulmonary bypass machines, specific protocols), society must decide how to optimally invest its resources. The existence of a potentially salvageable group of patients within the potential UDCD donor pool was one reason that some institutions in the United States have elected to invest in ECLS programs instead. Further, the potential choice of programs needs to be discussed publically and transparently in order to maximally respect the autonomy of patients.

Based on my review, I would consider this dissertation an excellent and impactful contribution to the literature. How Spain navigates the practical and immediate question of whether a patient undergoing resuscitation is eligible for ECLS or UDCD will inform all of Europe and North America.

Sincerely,

Clifton W. Callaway, MD, PhD
Professor and Vice-Chair of Emergency Medicine
Ronald D. Stewart Endowed Chair of Emergency Medicine Research

TESIS DOCTORAL

POR COMPENDIO DE PUBLICACIONES

Título: Donación tras muerte circulatoria no controlada y Reanimación con circulación extracorpórea en paradas cardíacas extrahospitalarias

Subtítulo: Una estrategia integradora como solución a los conflictos existentes

INDICE

AGRADECIMIENTOS

A mis padres, porque siempre han creído en mis proyectos, incluso los que se truncaron.

A mis niños, María y Miguel, sin duda mi mejor proyecto, Sin ellos nada de esto hubiese sido ni existido, simplemente. Por ellos lo haría una y mil veces más…

A Edurne, por darles la vida y hacer que, sobre todo ahora, ellos sean mi único proyecto; por haberme dado la oportunidad de empezar de nuevo de una forma más inteligente y con nuevas oportunidades, tras lo que otros llamarían *fracaso.*

A David Rodríguez-Arias, amigo, consejero, profesor y mi *"Pepito Grillo".* Te admiro en el fondo y en la forma. Gracias por sacarme de quicio, a veces.

A Alfredo Serrano, apasionado conmigo por un cuidado de calidad y de calidez a los pacientes. Por ellos y para ellos, y sus familias, lo intentamos todo durante años, volando juntos de aquí para allá. Gracias por enseñarme, soportarme y acompañarme durante mi prurito investigador.

A la *Fundación "La Caixa"* por apostar por mi proyecto y concederme una Beca de investigación predoctoral en Canadá, con la que estaba cayendo en España, asegurándome un éxito en mi labor que ni yo podía sospechar. Vosotros lo hicísteis posible; yo lo di todo.

A mis colegas del *Montreal Children's Hospital* y del *Research Institute* del *McGill University Health Center*. Especialmente a mi mentor y supervisor en Canadá, Sam D. Shemie y a mi colega de investigación, Laura Hornby. A él, por darme la oportunidad y creer en mí cuando, por fin, comprendió el proyecto. A ella, por haber sido mi apoyo siempre pero sobre todo cuando más lo necesitaba; y lo necesité mucho…

A Anne-Marie Lagacé, del *Centre de Prélèvement d'Organes* (CPO) del *Hôpital du Sacré-Cœur de Montréal*. Ella, con su familia, supo estar siempre disponible, escucharme y levantarme cuando me caía. Al resto del equipo del CPO, Marie-Claude, Veronique, Virginie y todos los demás, por acogerme. A Pierre-Marsolais, que aparecía y desparecía como el Guadiana: *"siempre con el mismo son, pero con distinta agua"*. ¡Sigue en tu lucha!

A Ingrid Soto por sus ánimos, su compañía y su ayuda experta con las traducciones.

A mi Director, Antonio Martín-Duce, por estar disponible cada vez que me hizo falta. Por dejarme volar libre y por creer en mi tesón. Por la minuciosidad de tus revisiones, tan necesarias cuando me sentía ya exhausto. Lo hiciste todo más fácil…

A María Cristina Pérez, porque en la recta final, seguro sin saberlo, pintabas de azul el cielo de mis cuadros. Ojalá algún día pudiera hacer yo lo mismo; *quid pro quo.* Gracias… de corazón.

A Rosi, Mabel y Juan Carlos, por los desayunos. Cada mañana habéis sido la espita de escape en mis quehaceres, llegando a meta.

A mis compañeros del Departamento de Enfermería en la Universidad de Alcalá de Henares, por aguantar mi música, mis andanzas, mis carreras y mis sudores, dedicándome siempre palabras de ánimo en la recta final: a Jorge, Paco, Purificación, Juan Ángel y Ana, Juan Manuel, Mar y Luis, Cristina, Pacucha, Ángel y todos los demás. Cada uno me ayudó, como mejor sabía, con sus mejores armas.

A Canadá, por la experiencia vivida. No siempre grata, nunca fácil. Pero definitivamente provechosa. Como con el *Viaje a Ítaca* de Kavafis, *"sin ella nunca habría partido"*. Ahora, terminado el viaje, he entendido mucho mejor *mi travesía*… ¡Ya lo creo!

A mis pacientes y sus familias, por permitirme cuidarles hasta el extremo; nunca mejor dicho…

Y por todos aquellos por los que nada más pude hacer, al no existir aún la logística para ello y sí los conocimientos...

Esta investigación y mi tesis es por y para vosotros.
Espero no tener nunca más el conflicto de desahuciar a un paciente para el que exista la opción de salvar su vida. ¡Nunca más!

A los que quisieron regalar sus órganos, cuando os dimos la opción de hacerlo, a pesar de vuestra muerte inesperada y en pleno duelo. Gracias.

A la vida, que me ha dado tanto…

Vale

LIST OF ABBREVIATIONS – LISTADO DE ABREVIATURAS

WIT: *Warm ischemic time.* Tiempo de isquemia caliente.

DBD: *Donation after brain death.* Donación tras determinación de la muerte por criterio cerebral o neurológico.

ONT: Organización Nacional de Trasplantes.

DCD: *Donation after circulatory death.* Donación tras determinación de la muerte por criterio circulatorio o (paro) cardíaco.

EMS: *Emergency medical services.* Servicios de emergencia médicos.

RCP: *Cardiopulmonary resuscitation.* Reanimación cardiopulmonar.

uDCD: *uncontrolled Donation after circulatory death*. Donación tras muerte circulatoria no controlada.

ECMO: *Extracorporeal membrane oxygenation.* Oxigenación por membrana extracorpórea.

ECPR: *Extracorporeal resuscitation.* Reanimación mediante oxigenación por membrana extracorpórea.

OHCA: *Out-of-hospital cardiac arrest*. Parada cardíaca extrahospitalaria.

1. STATE OF THE ART: ORGAN DONATION AND OUT-OF-HOSPITAL CARDIAC ARREST.

1.1. Uncontrolled donation after circulatory death in a context of a global trend of organ shortage for transplantation

The practice of organ donation and transplantation began over half a century ago [1] using organs and tissues from cadavers determined dead by circulatory criteria [2], following an unexpected cardiac arrest [3]. The technical difficulties in preserving these organs and tissues, a process referred to as warm ischemic time (WIT) [4], were not appreciated for years, and efforts were focused on donors after brain death (DBD). Subsequently, in 1968, the Committee of the Harvard Medical School [5] defined this criterion of death in an ad hoc report in which it explicitly recognized the need to increase the organ donation rate. The criterion of brain death was thus established and, in 1981, a report from the Medical Consultants of the President's Commission [6] established the diagnostic requirements that declare a patient dead based on the irreversible cessation of brain function, which is equivalent to death as a universal concept.

The growing demand for organ transplantation is in line with the increasing life expectancy in developed societies [7]. At the same time, there has been an improvement in road safety and a subsequent decrease in morbidity and mortality from road traffic accidents, especially among motorcyclists due to the compulsory use of a helmet. In addition to this, the effective and multidisciplinary management of patients in specific units, suffering traumatic brain injuries or acute cerebrovascular diseases, has resulted in the gradual decrease of brain deaths in the intensive care units of hospitals in Spain [8].

Faced with this situation and the correlative decrease of the donation rate because of the lack of donors (see Figure 1), the Spanish National Transplant Organization (ONT) implemented transversal organ donation programmes following a determination of death by circulatory criteria (Donation after Circulatory Death, DCD).

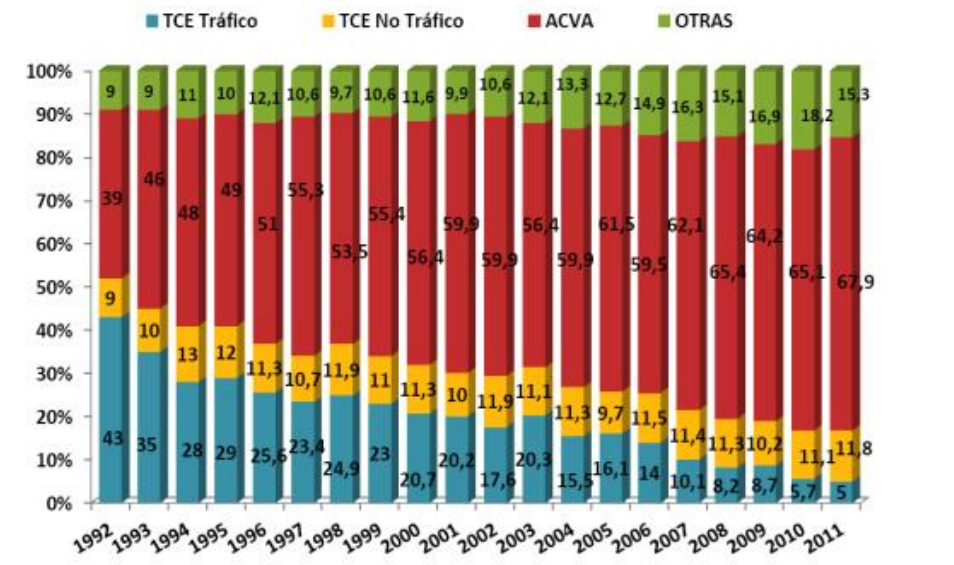

Figure 1. Causes of hospital death in Spain in % (1992-2011). TCE: Traumatic Brain Injury. Tráfico: Road accident. ACVA: Stroke. Source: www.ont.es

These programmes regard the Emergency Medical Services (EMS), hospital services (e.g., emergency departments, intensive care units, transplant coordination services, surgical departments, laboratories, pathology departments and administrative services), the ONT and society as a whole as potential organ donors and potential organ recipients and their families.

All of these fundamental links are coordinated by various programmes [4,9-15], which are currently obtaining similar [14], or even better results [15] than DBD programmes, regarding the number of transplant recipients and the quality of life of them after transplantation. However, until now, there has not been any systematic review of the so-called programs for uncontrolled donation after circulatory death (uDCD).

First, it is necessary to identify the types of donors internationally classified by the 1995 Maastricht Conference [16,17] before specially focusing on donor type 2 category (uDCD).

Maastricht Classification of 1995 [17]

According to the Maastricht Consensus Conference held in 1995, there are four types of cardio-circulatory death donors:

Type 1: Dead on arrival at the hospital. These are patients taken to the hospital without receiving any medical assistance or any cardiopulmonary resuscitation efforts. In Spain, this type of potential donors is uncommon because of the quality and effectiveness of the EMS.

Type 2: Unsuccessful CPR. This involves most of the DCD cases and it can happen either in-hospital (subtype 2a) or out-of-hospital (subtype 2b). This refers to, patients who are either admitted to the intensive care units or resuscitation units, or out-of-hospital patients treated by the EMS after suffering an unexpected cardiac arrest, which is the so-called sudden death syndrome. This subtype (2b) includes almost 95% of cases of DCD in Spain. In my PhD research, I focused on programmes for uDCD (subtype 2b), brought to hospitals by EMS. Spain is currently the international leader and pioneer of these programmes. My research questions arise from my professional experience as a nurse practitioner with the EMS, where I provided care to patients suffering unexpected or sudden cardiac arrest; therefore, I was also involved in recruiting potential donors for the uDCD program. After resuscitation was considered unsuccessful, we selected and managed the deceased patient as a potential organ donor.

Type 3: Controlled cardiac arrest. This category refers to patients with an irreversible loss of brain function (e.g., due to a trauma brain injury, brain tumour, massive brain haemorrhage) who do not meet the brain death criteria. They are taken to the operating theatre where life support measures are interrupted and cardiac arrest is expected. This is also known as controlled donors after circulatory death according to the Maastricht Conference classification. After declaring death, organs are rapidly

retrieved. This procedure is followed after consent has been given by the patient who had agreed to this ending if such a situation were ever to occur, or the patient's relatives may have authorized donation after discussion with health care professionals.

Type 4: Organ procurement from brain death donors who suffer a cardiac arrest during the procedure of neurologic determination of death or while waiting for the transplant team's diagnosis.

1.2. Processing the DCD Programme with potential out-of-hospital donors (uDCD)

The out-of-hospital DCD (uDCD) programmes involve patients who have had an unexpected out-of-hospital cardiac arrest and who, following a specific period of attempting cardiopulmonary resuscitation (CPR) are transported to the hospital as potential donors. After the standard CPR attempt, nothing is done to save their lives but shift to preserving the organs. These donors correspond to the 2b subtype of the Maastricht Conference known as uncontrolled donation, since the warm ischemic time (WIT) cannot be known with precision. The EMS unit team treating the patient is responsible for initiating the protocol [4]. (See **Table 1.** Timeline and development of the uDCD programme).

uDCD TIMELINE AND ACTIONS
0-90 min. Alert of uDCD after unsuccessful CPR. Alert the medical care team. Transfer to hospital. Proceed to catheterization with the purpose of organ preservation.
90-120 min. Connecting the body to extracorporeal circulation (See **Figure 2**).
120-240 min. Informing and requesting authorization from the family. Legal request for organ retrieval.

Table 1. Timeline and development of the uDCD program.

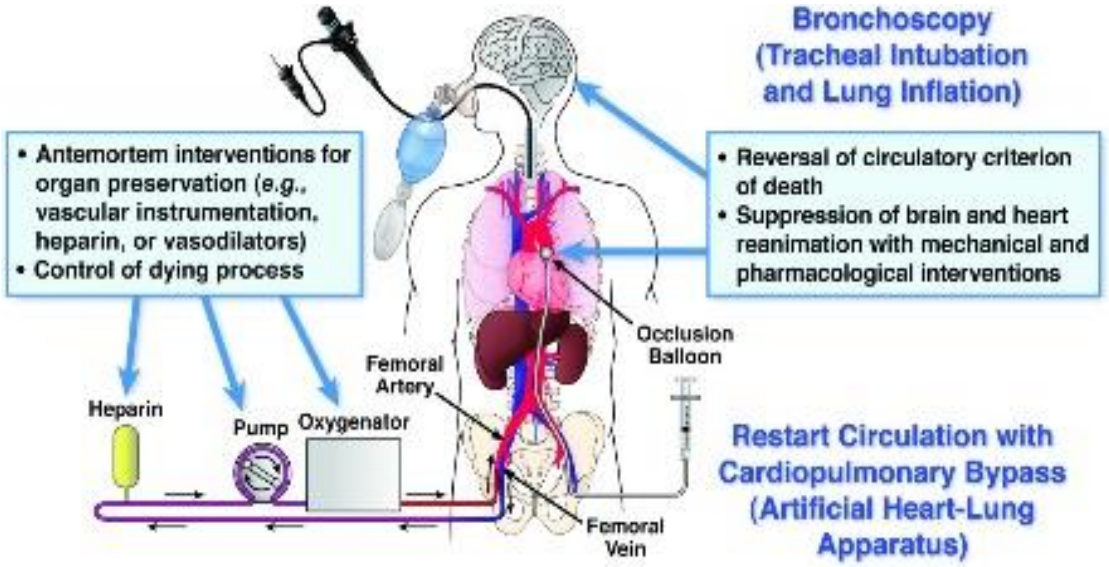

Figura 2. Circulación extracorpórea con membrana de oxígeno (ECMO) para preservación de órganos.

Fuente: http://peh-med.biomedcentral.com/articles/10.1186/1747-5341-4-15

1.3. The out-of-hospital cardiac arrest: incidence and actual results after cardiopulmonary resuscitation

Out-of-hospital cardiac arrest (OHCA) is currently one of the biggest challenges in Western medicine because of its high incidence and mortality. Globally, sudden cardiac arrest is the leading cause of death in previously healthy people. The overall incidence, in adults, is 62 cases per 100,000 people per year [18,19]. In the United States (US) alone, 325,000 people die each year from sudden death or OHCA while the incidence reported in Europe is 350,000 people per year [18,19]. These statistics are equivalent to the number of people who die each year in all the US from four types of cancer, car accidents, suicide, house fires, firearms injuries, AIDS and Alzheimer's disease combined (see **Figure 3**)

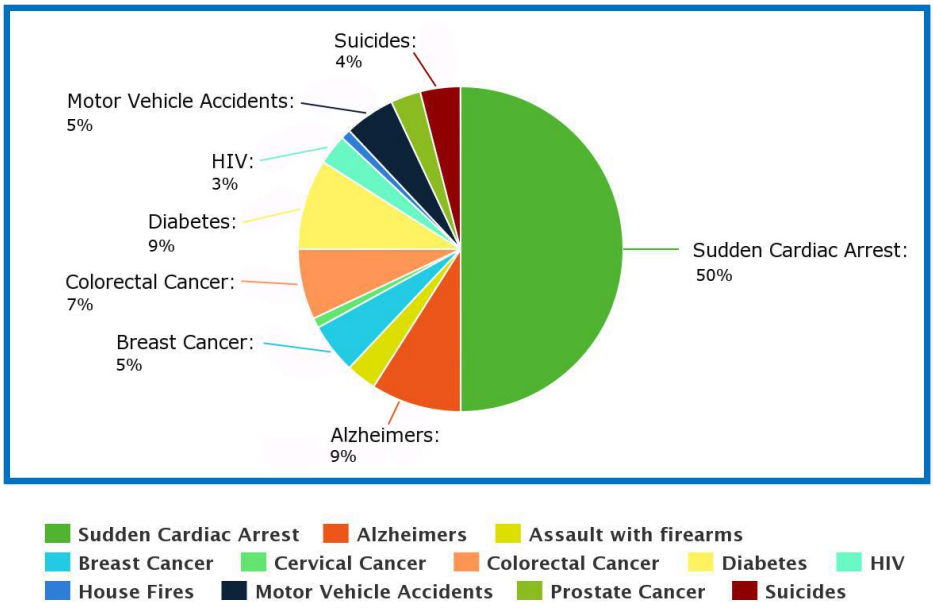

Figura 3. Causas de muerte en Estados Unidos 2015.

Fuente: www.aedtotalsolution.com/statistics

Despite advances in resuscitation and the progressive improvement in the clinical response provided by EMS, survival rates have barely improved in recent decades, with a survival rate at the time of hospital admission ranging from 5% to 20%, depending on the type of assistance, the country and the quality of care delivered- [20].

Therefore, OHCA not only causes an extremely high number of deaths, resulting from particular epidemiology, but also causes serious neurologic sequelae in a large proportion of the survivors (see **Figure 4**).

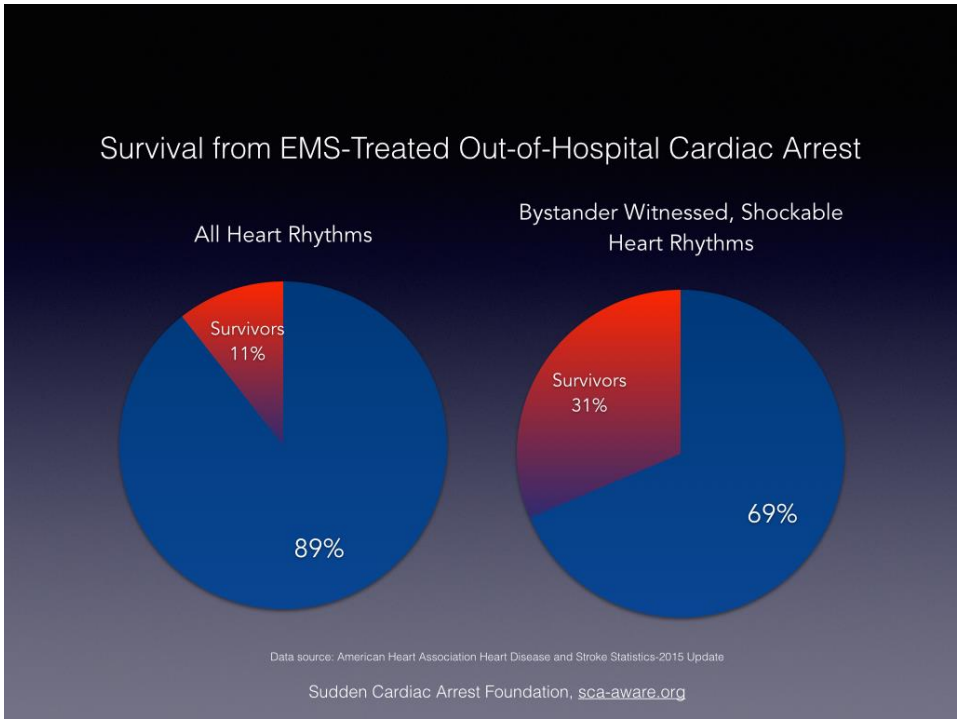

Figura 4. Supervivencia global tras muertes súbitas tratadas por EMS. Diferencia entre paradas cardíacas no presenciadas *versus* presenciadas y con reanimación por testigos.

Thus, the reported overall survival in modern societies is especially alarming: 6% for North America, 9% for Europe, 11% for Australia and 2% for Japan [18,19].

2. LAS PRIORIDADES EN LAS POLÍTICAS DE SALUD ANTE ESTAS 2 SITUACIONES: VISIÓN INTERNACIONAL.

En los últimos años, ha crecido el número de programas de donación tras una parada cardíaca no esperada (uDCD). Sólo en España, existían 7 programas activos en 6 comunidades autónomas [21] distintas en 2012, y al menos otros tantos están actualmente en proyecto avanzado de implementación [22].

Al mismo tiempo, son crecientes en el extranjero los programas de reanimación cardiopulmonar no convencional que, conforme a la mejor evidencia científica actual, seleccionan a víctimas de paradas cardíacas no esperadas. Sin embargo, ninguno de ellos existe actualmente en España [23]. Estos programas de reanimación mantenida, brindan un puente de cuidados ininterrumpidos y de alta calidad que se complementan con técnicas y tratamientos dirigidos a identificar y tratar la causa primaria que provocó el colapso cardiorespiratorio. La circulación extracorpórea por membrana oxigenada (*extracorporeal membrane oxygenation*, ECMO) es el centro de estas estrategias salvadoras y, cuando se aplica durante la reanimación de emergencia, se denomina más específicamente reanimación extracorpórea (*extracorporeal resuscitation*, ECPR). (Ver **Figura 5**).

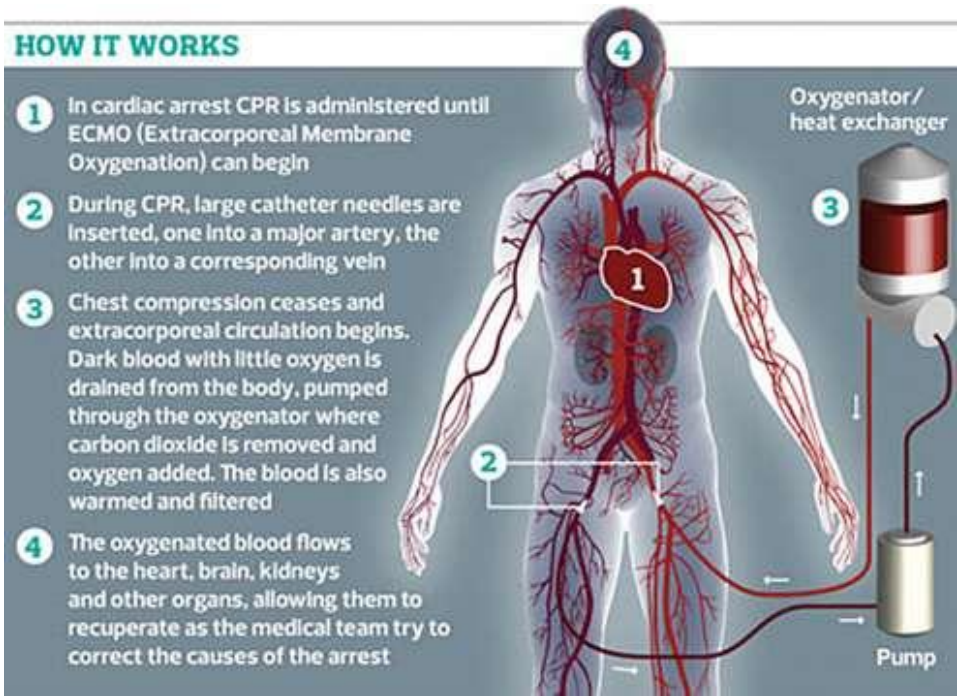

Figura 5. Circulación extracorpórea (ECMO) durante la reanimación (ECPR)

Diferentes países de Europa -actualmente, Francia, Italia, Checoslovaquia, Alemania, Suiza, Austria, Bélgica y Países Escandinavos, entre otros- y del resto del mundo -Australia, Japón, China, Estados Unidos- están obteniendo resultados prometedores, en términos de supervivencia con calidad de vida [24,25].

Es preciso insistir: en España todavía no existen programas de este tipo sino tan sólo un proyecto -en fase de estudio de viabilidad- en Madrid [26].

3. JUSTIFICACIÓN DE LA TESIS DOCTORAL: PREGUNTAS DE INVESTIGACIÓN Y OBJETIVOS.

Mientras España ha sido pionera en los programas de donación tras muerte circulatoria no controlada (uDCD) [27], no ocurre lo mismo con los programas de reanimación cardiopulmonar mediante circulación extracorpórea (ECPR) para intentar mejorar la supervivencia de pacientes que sufren una parada cardíaca inesperada en el ámbito extrahospitalario [23]. En otros países, ha ocurrido exactamente lo contrario; mientras los programas de uDCD no se han implementado, los programas de ECPR son una prioridad asistencial para intentar mejorar la supervivencia tras parada cardiorespiratoria extrahospitalaria, o muerte súbita [28].

Desde mi labor asistencial en el ámbito de la emergencia médica, pude constatar que el perfil de pacientes que se beneficiaría de un programa de reanimación cardiopulmonar por circulación extracorpórea (ECPR) era coincidente con el de los potenciales donantes que trasladábamos en España (uDCD) [29-32]. En estos donantes, procedemos a preservar sus órganos pero sin luchar ya por recuperarles como pacientes, al considerarles médicamente desahuciados desde un punto de vista clínico [33]. Este fue el origen de las cuestiones de investigación que dieron lugar a esta tesis doctoral, y que, como mostraré, tienen implicaciones clínicas, éticas, legales y gestoras [23,34].

En resumen, actualmente en España no existen programas implementados de reanimación cardiopulmonar que empleen la circulación extracorpórea (ECPR) como medio para aumentar la supervivencia de esos pacientes jóvenes y previamente sanos. Y, a la vez, la misma técnica de la circulación extracorpórea (ECMO) está siendo ofrecida para preservar los órganos de esos mismos individuos jóvenes y previamente sanos -a quienes se está considerando irrecuperables- con el fin de obtener sus órganos para un trasplante posterior. Y en esto último, somos país pionero y referente internacional.

En este estado de cosas, las **preguntas de investigación** que se coligen y **que justifican los objetivos de esta tesis doctoral** son:

Desde un punto de vista clínico y asistencial:

a. ¿Podemos mejorar la supervivencia con calidad de vida de los pacientes en parada cardíaca extrahospitalaria refractaria a medidas de reanimación cardiopulmonar convencional?

b. ¿Cuál es el perfil de pacientes que -conforme a la mejor evidencia clínica actual- podría beneficiarse de la técnica de circulación extracorpórea durante la reanimación (ECPR)?

Desde un punto de vista ético y legal:

a. Los potenciales donantes de órganos incluidos en los programas de muerte circulatoria no controlada (uDCD) tras sufrir un paro cardíaco extrahospitalario, ¿se encuentran realmente en situación irreversible y, por tanto, pueden declararse fallecidos?

b. La información dada por los profesionales sanitarios a los familiares de los potenciales donantes -y a la sociedad en su conjunto-, ¿es veraz, transparente y acorde con la legislación y deontología vigentes -derecho a la información al paciente o usuario del sistema de salud-?

Desde un punto de vista de políticas gestoras y asistenciales de salud:

Teniendo en cuenta:

Primero. Que la parada cardíaca extrahospitalaria es -desde una visión epidemiológica globalizada- un problema de salud pública de primera magnitud por su alta incidencia y por su elevada mortalidad global y morbilidad neurológica;

Segundo. Que la carestía de órganos disponibles para trasplante es una realidad mundial y también lo es el incremento progresivo del número de personas que fallecen en las listas de espera porque el órgano que podría salvar su vida -o mejorar su calidad de vida- no está disponible para trasplante,

a. ¿Es posible una estrategia integradora que haga compatibles estos objetivos: (1) prioritariamente, mejorar las tasas de supervivencia con calidad de vida de pacientes en parada cardíaca extrahospitalaria y (2), subsidiariamente, -caso de no ser posible salvar al paciente- preservar sus órganos tras su muerte, aumentando la tasa de donación y trasplantes?

b. Esa estrategia integradora de reanimación cardiopulmonar y/o preservación de órganos mediante circulación extracorpórea: ¿ayudaría a resolver los conflictos asistenciales, éticos, legales y gestores existentes actualmente?

En definitiva, la presente investigación predoctoral tiene por objetivos (1) facilitar el proceso deliberativo en cuestiones como la determinación de la muerte por criterio circulatorio, la transparencia en la información a familiares de pacientes y/o donantes y la veracidad del sistema de donación de órganos cadavérica ante la sociedad.

Además, pretende (2) incrementar el nivel de evidencia científica en el uso clínico de la circulación extracorpórea, para salvar a ciertos pacientes en parada cardíaca refractaria -aún hoy considerados prematuramente como insalvables y manejados ya como donantes cadáver-

Si estas aportaciones no fuesen implementadas, y los protocolos de donación tras muerte circulatoria no controlada (uDCD) siguiesen creciendo, en el futuro se prevé un incremento del número de casos de donantes cadáver que -como ya ha ocurrido- [23,35-37] recuperarán las funciones circulatoria y/o neurológica *(sic)*. Esto pondría en serio riesgo la confianza en el sistema español de donación de órganos y trasplantes por parte de los profesionales sanitarios y de la sociedad en su conjunto [38-47].

Sin embargo, una clarificación de las políticas de salud, priorizando la estrategia salvadora (ECPR) para individuos seleccionados en parada cardíaca refractaria -pero sin abandonar la opción de la donación (uDCD) entre los no supervivientes- supondría una mejora tanto de las tasas de supervivencia a la muerte súbita extrahospitalaria (1) como de las tasas de órganos disponibles para trasplante (2), mediante un empleo más eficiente (3) de los mismos recursos humanos y materiales ya implementados actualmente solo para la estrategia de la donación [23,27,28,31,34].

Knowing is not enough; we must apply.
Willing is not enough; we must do. **Goethe**

La presente tesis doctoral es el resultado de una trayectoria investigadora que comienza cuando, desde el ámbito asistencial en la emergencia extrahospitalaria, me planteo cuestiones que hacen preciso revisar los dos criterios de determinación de la muerte: el criterio cerebral y el criterio circulatorio [40-43,46,48-53]. La existencia del programa de uDCD en la cartera de servicios de las instituciones en las que, aún hoy, presto mi labor asistencial -y la compatibilización de esta con mi labor docente e investigadora en el ámbito universitario- fueron las causas que propiciaron esta inquietud por profundizar en el objeto de la presente tesis doctoral. Mi perfil mixto de jurista, profesional sanitario y docente interesado por las cuestiones de la ética al final de la vida y la información a pacientes y familiares hizo que se delimitasen más las preguntas de investigación [29, 54,55].

Como profesional sanitario de la emergencia médica –tras ahondar en el estudio de la ECPR y de sus posibilidades- apostaba por una mayor eficacia en la reanimación cardiopulmonar de los pacientes que sufren una muerte súbita. Como instructor en reanimación cardiopulmonar, transmitía en el proceso docente estas posibilidades a los alumnos de grado y posgrado de la Facultad de Medicina y Ciencias de la Salud.

Tuve la oportunidad de participar a nivel internacional tanto en comités de expertos como en los congresos monográficos sobre donación cadavérica y reanimación, así como codirigir diferentes *workshop* que abordaban -mediante el proceso deliberativo multidisciplinar- estos aspectos. (Ver **Anexo VI**. Actividades del periodo de investigación predoctoral).

4. METODOLOGÍA

Para poder responder -mediante la aplicación del método científico- a las cuestiones de investigación descritas, y con el objetivo de encontrar soluciones a los conflictos identificados en la práctica clínica, realizamos sendas revisiones sistemáticas internacionales de los programas de uDCD (Ver **Anexo III**) y de la estrategia de ECPR (Ver **Anexo V**) para pacientes adultos en parada cardíaca refractaria.

Esta metodología se ve reflejada en las **5 publicaciones que conforman el núcleo de la presente tesis doctoral** -cuya líneas argumental, metodológica y cronológica son correlativas- convirtiéndose en una trayectoria única que busca responder a los dilemas identificados, a las preguntas de investigación y persigue alcanzar los objetivos definidos en cada publicación. Así, y de forma consecuente con las conclusiones obtenidas en la publicación precedente, la publicación siguiente se deriva de la anterior.

Conforme a esta metodología, se han obtenido unos resultados, basados en la mejor evidencia disponible. Los compartiré como **conclusiones finales** (Ver **apartado 10, Conclusions from this dissertation**). El impacto de esta investigación es el objeto del **Anexo VII** (Implicaciones de la tesis doctoral)

Por lo tanto, las 5 publicaciones presentadas como núcleo de la presente tesis doctoral siguen la siguiente trayectoria investigadora:

1. Un artículo que el comité editorial de *The Lancet* nos solicita (*Comment*) [56] con el fin de que identifiquemos y describamos los conflictos existentes entre las estrategias de uDCD y ECPR, así como las consecuencias asistenciales, éticas, legales y en políticas de salud derivadas de los mismos (Ver **resumen en apartado 5**. PRIMER ARTICULO y publicación completa en **Anexo I**).

Se consideró que el estado de la cuestión presentaba problemas de tal interés y potencial repercusión, que la revista optó por este formato, tras recibir nuestro manuscrito. Por su elevado factor de impacto y su visibilidad internacional en las comunidades científicas e investigadoras, no sólo biomédicas sino también de las ciencias humanas y sociales,

numerosas y muy variadas reacciones se produjeron tras esta publicación [57-62]. De ella se derivó, de forma directa aunque no única, la siguiente.

2. Un artículo que el comité editorial de *Emergencias* considera oportuno (*Punto de Vista*) [63], tras el impacto suscitado por el primer artículo. En efecto, las comunidades científica y clínica del ámbito de la reanimación y de los cuidados críticos -y más específicamente los servicios de emergencia médica (EMS) del medio extrahospitalario en España- eran artífices diarios de los programas de uDCD, en continuo crecimiento y expansión. Mientras tanto, ningún programa de ECPR existe en todo el país.

Se proponen -por vez primera- soluciones basadas en una estrategia integradora, derivada del análisis de los conflictos identificados y expuestos en *The Lancet*, señalando áreas de mejora necesarias. (Ver **resumen en apartado 6**. SEGUNDO ARTICULO y publicación completa en **Anexo II**). Un análisis comparativo cuantitativo -y una metodología que evaluara el nivel de evidencia de las recomendaciones y la efectividad y resultados de los programas de uDCD a nivel mundial- exigía una revisión sistemática, cuyo protocolo se registró y publicó en PROSPERO (International Prospective Registry of Systematic Reviews, de la

Universidad de York). Ver **Anexo VII.13** (Implicaciones futuras e impacto de la tesis doctoral).

3. Una primera **revisión sistemática** en *Critical Care* [64], cuyo objetivo principal es que las comunidades científicas y clínicas de cuidados críticos, reanimación y donación y trasplantes conozcan el estado de la cuestión internacional de los programas de uDCD: protocolos y recomendaciones existentes, procedimientos empleados, resultados y calidad de los mismos (Ver **resumen en apartado 7**. TERCER ARTICULO y publicación completa en **Anexo III**).

Nuestro objetivo principal fue que las conclusiones de esta revisión facilitaran la toma de decisiones futuras de los responsables de establecer prioridades asistenciales en políticas de salud, ante la carestía global de órganos para trasplante.

Esta revisión sistemática identifica muy concretos y relevantes conflictos éticos, legales y gestores entre la técnica preservadora de órganos (ECMO) -para intentar obtener más y mejores órganos para el trasplante tras certificar con premura la muerte del individuo- y los plausibles intentos de reanimación -procedimientos para salvar la vida del

aún paciente- tras una parada cardíaca extrahospitalaria en pacientes potencialmente recuperables (ECPR).

4. Como consecuencia de los artículos precedentes, creíamos necesario un debate más extenso de los dilemas éticos, legales, gestores y asistenciales derivados de la coexistencia de estrategias -a menudo excluyentes- como son la preservación de órganos para trasplante (ECMO preservadora) en donantes considerados fallecidos y la reanimación extracorpórea (ECPR) de pacientes tras muerte súbita.

La revista *Éthique et Santé*, centrada en estos conflictos -con un formato que acoge manuscritos más extensos sobre ética y final de la vida- nos permitía abordar estas cuestiones y sus implicaciones [65]. (Ver **resumen en apartado 8**. CUARTO ARTICULO y publicación completa en **Anexo IV**).

Pudimos aportar -de este modo- recomendaciones que respondían a las incertidumbres sobre la definición, criterios y diagnóstico de la muerte por criterio circulatorio en el contexto de la donación de órganos. Los dilemas y sus consecuencias éticas, legales y clínicas se suceden de forma lógica, incorporando ya los datos cuantitativos derivados de las dos

revisiones sistemáticas previas. Pero también otros cualitativos que son fruto del esfuerzo deliberativo y multidisciplinar propiciado por los encuentros de expertos a nivel nacional e internacional (Ver **Anexo VI**. Actividades del período de investigación predoctoral)

5. Finalmente, una revisión sistemática publicada en *Resuscitation* [66] de los programas de reanimación cardiopulmonar mediante la técnica de circulación extracorpórea (ECPR) resultaba una necesidad metodológica derivada de lo avanzado en las publicaciones precedentes (Ver **resumen en apartado 9**. QUINTO ARTICULO y publicación completa en **Anexo V**).

El protocolo de esta revisión sistemática, se registró y publicó en PROSPERO (International Prospective Registry of Systematic Reviews, de la Universidad de York). Ver **Anexo VII** (Implicaciones de la tesis doctoral).

Así, para incrementar el nivel de evidencia científica respecto a las indicaciones y al perfil de pacientes beneficiarios de esta técnica, un análisis internacional de los programas y recomendaciones, de su nivel de evidencia y calidad, así como de los resultados obtenidos en términos de supervivencia con calidad de vida neurológica de los pacientes, viene a responder a las preguntas de investigación de esta tesis: (1) un subgrupo de

pacientes en parada cardiorespiratoria extrahospitalaria -hasta ahora considerados irrecuperables- no solo son recuperables (22%), sino que sobreviven con buena recuperación neurológica (13%) si se aplica la ECPR de forma selectiva y eficaz. (2) La implementación de los programas de ECPR permite -de forma añadida- identificar potenciales donantes entre los no supervivientes a la parada cardiorespiratoria. (3) Ambas estrategias son complementarias y no excluyentes, resolviendo así algunos de los conflictos clínicos, éticos, legales y gestores identificados.

5. **PRIMER ARTICULO: Protocols for uncontrolled donation after circulatory death.** (Ver en **Anexo I** publicación completa)

Resumen: ciertos países apuestan por estos protocolos como modo de hacer frente a la falta de órganos para trasplante. España es pionero en este tipo de donantes, que son trasladados desde el ámbito extrahospitalario por los servicios de emergencia médica tras sufrir una parada cardíaca inesperada. Son individuos que no han sido recuperados, tras considerarse infructuosas las maniobras de reanimación.

Estos protocolos, si bien obtienen órganos válidos para trasplante, plantean cuestiones éticas como son: iniciar maniobras de preservación de

los órganos antes de consultar su parecer a los familiares o explorar cuál era la voluntad del paciente; dudas respecto a la irreversibilidad del proceso, lo que cuestiona la validez de los criterios de determinación de la muerte del paciente -tanto circulatorio como neurológico-. Este segundo aspecto, presenta implicaciones no solo éticas y legales sino también clínicas puesto que en otros países -donde no se han implementado los programas de uDCD- la continuación de maniobras de reanimación en pacientes seleccionados con el objetivo de salvar su vida ha conllevado una incremento de la tasa de supervivencia -evidenciando que un subgrupo de ellos pueden ser salvados y recuperarse sin secuelas neurológicas-.

En definitiva, mientras España defiende y lidera los programas de donación no controlada como estrategia para incrementar el número de órganos disponibles para trasplante, otros países no aceptan ni el procedimiento ni las técnicas empleadas durante el proceso de determinación de la muerte del paciente y la posterior preservación de sus órganos -al considerar que son dudosos desde un punto de vista médico y ético-.

Nuestra propuesta consiste en asegurar que el paciente idóneo se beneficie de las técnicas de reanimación que pueden salvar su vida conforme a la mejor y más actual evidencia. Si -pese a ello- no se consigue

recuperar al paciente, entonces debería ofrecerse la opción de la donación de órganos a los familiares, tras certificar la muerte del paciente y primando la veracidad y transparencia de la información en cada etapa del proceso. Los objetivos han de ser claros y la prioridad absoluta el beneficio del paciente para -solo después de agotarse tal posibilidad- pensar en el beneficio del potencial receptor de órganos. Consideramos, en consecuencia, que los protocolos de donación tras muerte circulatoria no controlada (uDCD) existentes en España necesitan ser revisados, pues comprometen los intereses de los donantes y ponen en peligro la confianza de la sociedad en el proceso de donación y trasplantes.

6. **SEGUNDO ARTICULO: Donación en asistolia en emergencias *versus* reanimación cardiopulmonar no convencional: ¿obtenemos órganos o intentamos salvar vidas?** (Ver en **Anexo II** publicación completa)

Resumen: Mientras en España se expanden los programas de uDCD, en otros países de Europa -y resto del mundo- se están implementando programas de reanimación cardiopulmonar que intentan salvar la vida de ciertos pacientes en parada cardíaca -en España serían candidatos para la donación cadavérica al no existir alternativa de estrategia terapéutica para ellos, una vez considerada infructuosa su reanimación-.

Proponemos un protocolo (Ver **Figura 6**) que lleve a cabo una sinergia de esfuerzos pero jerarquizando las prioridades asistenciales del siguiente modo: (1) seleccionar qué pacientes en parada cardíaca refractaria a reanimación deben ser candidatos a una reanimación no convencional con circulación extracorpórea y -caso de no recuperar al paciente con calidad de vida y/o sin daños neurológicos importantes- (2) ofrecer la opción de la donación de órganos una vez extinguida toda opción salvadora. De este modo, respondemos a cada paciente en parada cardíaca súbita atendiendo a la causa primaria que provocó su colapso cardiocirculatorio. Lo hacemos conforme a la mejor evidencia médica actual, conforme a la ética y deontología profesionales y haciendo, además, un uso racional de los recursos humanos, técnicos y materiales -tras establecer prioridades asistenciales y gestoras en beneficio de mejores resultados-.

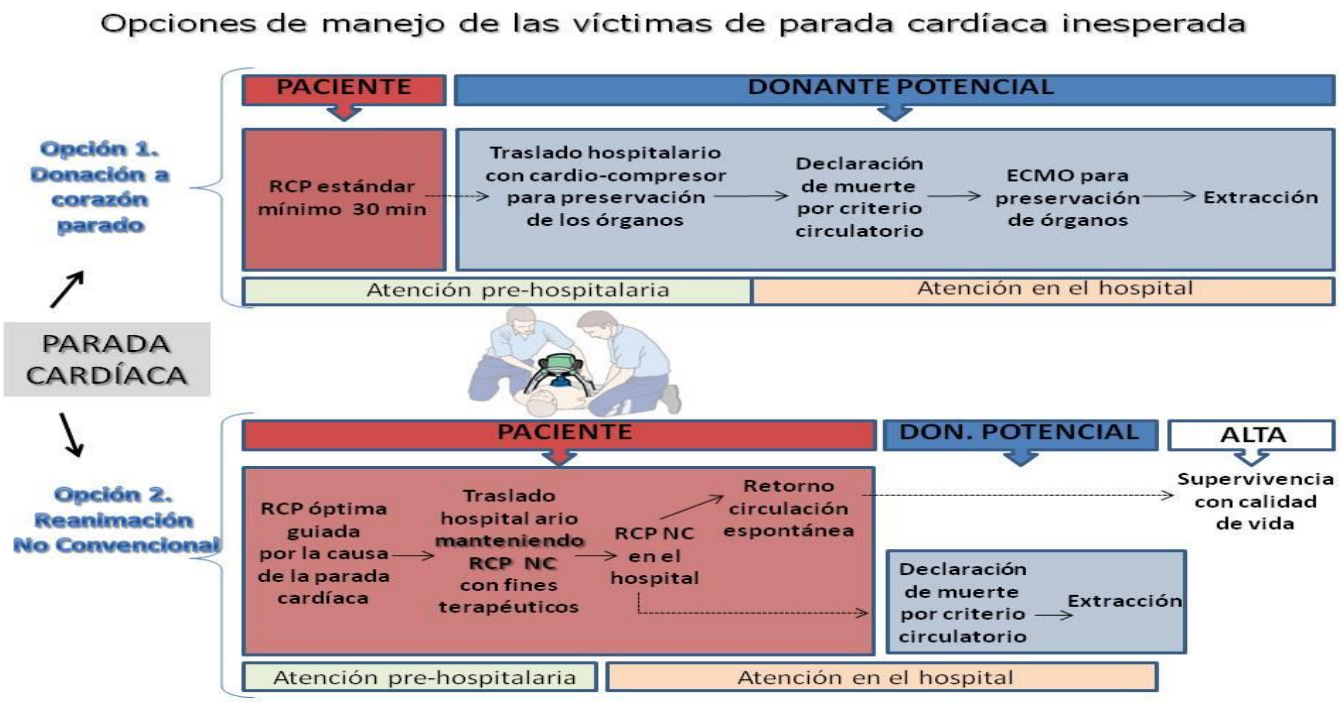

Figura 6. Opción 1 (existente actualmente) *versus* opción 2 (propuesta por nosotros).

7. **TERCER ARTICULO: Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes.** (Ver en **Anexo III** publicación completa)

Resumen: El mayor factor limitante para el trasplante de órganos es la falta de órganos disponibles para la cirugía. Aunque algunos países han explorado la opción de los programas de uDCD, poco es sabido sobre estas prácticas y sus resultados. Esta es la primera revisión sistemática internacional que pretende informar a gestores y políticos de la salud -además de las comunidades científica, clínica e investigadora- sobre estos protocolos, sus características y su eficacia y eficiencia en términos de resultados. De igual modo, se evalúa por primera vez el nivel de evidencia de las recomendaciones para la implementación de nuevos protocolos.

Tras esta revisión sistemática -en la que 18 protocolos y 6 recomendaciones fueron objeto de análisis comparativo- pudimos concluir que el nivel de evidencia de las recomendaciones es bajo.

Además, los resultados obtenidos en cantidad y calidad de órganos resultaron buenos respecto a riñones, prometedores para pulmones y muy

limitados para hígados -con una tasa de descarte muy alta por los daños isquémicos sufridos durante el proceso-.

Conclusiones: aunque se identificaron múltiples barreras procedimentales, médicas, económicas y ético-legales, la estrategia de la donación tras parada cardíaca no controlada (uDCD) es posible y viable para incrementar el número de órganos disponibles para trasplante. Es precisa una mayor homogeneidad de los protocolos y del modo de presentar los resultados de los mismos. Además, detectamos la necesidad de una investigación focalizada en las posibilidades salvadoras de la circulación extracorpórea durante la reanimación (ECPR) -asociada a otras terapias- para el tratamiento de ciertos pacientes en parada cardíaca refractaria a medidas convencionales de reanimación. Todo ello, favorecería mantener la confianza en los programas de uDCD, no solo por los profesionales sanitarios sino también por la sociedad en su conjunto.

8. **CUARTO ARTICULO: Le débat bioéthique sur le don d'organes: est-ce que tout s'arrête lorsque le cœur cesse de battre?** (Ver en **Anexo IV** publicación completa)

Resumen: Determinar exactamente en qué momento se produce la muerte del individuo ha sido un desafío a lo largo de la Historia. Lo que hoy sabemos es que la muerte no es un evento único, sino un proceso de degradación de las diferentes partes que conforman el cuerpo humano. Pero las consecuencias de determinar en un momento u otro la muerte son múltiples a nivel médico, legal, social y filosófico.

En lo que respecta a la donación de órganos y trasplantes, por un lado no es posible extraer órganos vitales de personas que no hayan sido aún declaradas fallecidas. Pero, por otro lado, esperar demasiado tiempo puede comprometer la calidad de los órganos y su posterior trasplante. Los problemas teóricos y prácticos que emanan de la declaración de la muerte en el contexto de la donación de órganos tienen su origen en el desafío de obtener órganos en condiciones óptimas sin afectar el cuidado al final de la vida de los potenciales donantes -y que son todavía pacientes-.

En este artículo, se debaten diferentes cuestiones, a saber: el momento en que un individuo pasa de ser considerado paciente a ser considerado potencial donante de órganos ya fallecido; las implicaciones de ser considerado simultáneamente paciente y donante potencial; la constatación de que ciertos individuos manejados ya como donantes potenciales han sobrevivido como pacientes, y sus consecuencias; el concepto de *irreversibilidad* de la parada cardiocirculatoria y sus incongruencias; el estado neurológico de los pacientes declarados muertos por criterio circulatorio y el uso del balón intra-aórtico durante el proceso de preservación; las posibilidades de la circulación extracorpórea como técnica de reanimación de pacientes y/o de preservación de órganos de donantes y los conflictos de intereses derivados de ambas opciones.

Por último, se ofrecen alternativas a los debates identificados mediante una estrategia integradora y un protocolo que pretende optimizar los recursos existentes: mejorando los resultados -tanto en términos de supervivencia de ciertos pacientes en parada cardíaca refractaria como el incremento del número de órganos en donantes fallecidos, tras ofrecerles la mejor opción ante su proceso individual de salud/enfermedad-.

9. **QUINTO ARTICULO: Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes.** (Ver en **Anexo V** publicación completa)

Resumen: El empleo de la técnica de circulación extracorpórea durante la reanimación (ECPR) facilita la perfusión a los órganos y sustituye la función circulatoria hasta el retorno espontáneo de ésta. La presente revisión sistemática evalúa los elementos definitorios de los protocolos existentes a nivel internacional y expone loa resultados conseguidos en términos de (1) supervivencia de los pacientes salvados y de (2) calidad de los órganos obtenidos entre los no supervivientes, tras ser manejados como donantes.

El objetivo principal de la revisión es mejorar el conocimiento de las prácticas asistenciales y delimitar las indicaciones y mejores prácticas de la reanimación extracorpórea. Así, incrementaríamos el nivel de evidencia para facilitar la toma de decisiones en políticas sanitarias y clarificaríamos la intersección de la estrategia salvadora

durante la reanimación con la de la preservación de órganos en la estrategia de donación cadavérica.

Aunque no existen aún estudios randomizados controlados concluidos -el mayor nivel de evidencia clínica que se podría conseguir- que comparen la eficacia de la reanimación convencional con la reanimación extracorpórea (ECPR) -por las dificultades éticas que este diseño metodológico en el ámbito de la reanimación conlleva- los estudios evaluados en nuestra revisión obtuvieron un nivel de evidencia entre *suficiente* y *bueno*. Pudimos delimitar el perfil de pacientes que más se beneficiaría de esta estrategia: adultos víctimas de una parada cardíaca presenciada por testigos, refractaria a reanimación convencional y cuyo ritmo inicial es desfibrilable -se beneficia de un choque eléctrico- cuando, además, la causa subyacente del colapso es potencialmente reversible. La revascularización coronaria asociada a soporte hemodinámico y/o hipotermia terapéutica neuroprotectora se ofrecen de forma variable, como tampoco son homogéneos en las diferentes experiencias internacionales el tiempo total de reanimación y el tiempo hasta la canulación del paciente e inicio de la circulación extracorpórea.

A pesar de la heterogeneidad objetivada -lo que impidió la realización de un meta-análisis- los resultados obtenidos son: 22% de supervivencia global, que incluye 13% de supervivencia con buena recuperación neurológica. De forma adicional, 88 potenciales donantes de órganos fueron identificados, entre las poblaciones de tan solo algunos estudios, y 17 fueron donantes reales -existiendo aún un margen muy superior de potenciales donantes en las poblaciones de no supervivientes-.

En conclusión, la reanimación mediante circulación extracorpórea (ECPR) en paradas cardíacas refractarias extrahospitalarias de adultos seleccionados permite mejorar la supervivencia con calidad de vida neurológica en un 13%. Estos pacientes, no tenían prácticamente ninguna opción clínica hasta ahora. Pero además, entre aquellos que no sobreviven a la ECPR -o lo hacen con daño neurológico grave- hay un importante porcentaje de potenciales donantes de órganos que son válidos para el trasplante.

10. CONCLUSIONS FROM THIS DISSERTATION.

From a clinical point of view:

1. According to the best and most current evidence, at least 13% of adult patients in refractory cardiac arrest whose underlying primary cause is reversible could be resuscitated without neurologic sequelae through extracorporeal resuscitation (ECPR).

2. The ECPR approach is not currently available in Spain, although human and technical means do exist for its feasibility. Such strategy requires ensuring the quality of resuscitation from collapse to start of ECPR.

3. In countries (e.g. Spain) where programmes for uDCD are currently active, a subgroup of individuals already considered as deceased donors are actually still patients.

From an ethical and legal perspective:

1. Not all organ donors currently included in programmes for uDCD are irreversibly dead and therefore should not be considered hopeless patients, as is happening.

2. Accordingly, the information given by health professionals to families of potential donors is not always truthful, transparent and consistent with existing laws and ethics regarding their interests and rights. This fact jeopardizes trust in the system of organ donation and transplantation in countries like Spain.

From a standpoint of health management policies:

1. There is a synergic strategy that makes compatible the objectives of (1) improving survival rates of patients suffering for an OHCA. But when is not possible to save their life, (2) it may be feasible to preserve their organs after declaring death and to increase the pool of organs available for later transplantation.

2. This comprehensive approach –i.e: CPR and / or organ preservation supported by extracorporeal resuscitation- is my proposal to mitigate the clinical, ethical, legal and health policy conflicts that have been currently identified. By doing so, we could **save more lives, in one way or another, using the same resources which today (in Spain) are only available for organ preservation purposes**.

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ANEXOS

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ANEXO I

Primer artículo

D-11-08181
S0140-6736(11)61784-4

Protocols for uncontrolled donation after circulatory death

Organ shortages have led some countries, including Spain, France, and the USA, to start programmes of uncontrolled donation after circulatory death.[1] In these protocols, donors are people who have had unexpected out-of-hospital cardiac arrest. After ordinary life support attempts (30 min of advanced cardiopulmonary resuscitation [CPR]) by an emergency medical service are judged futile, patients are transported to the hospital with continuing mechanical chest compression and other interventions to preserve the organs, and declared dead at the hospital after a no-touch period of asystole (usually 5 min). Then, normothermic extracorporeal membrane oxygenation (ECMO) or in-situ cooling is started to preserve the organs until authorisation for donation is given by the family.[1]

Although uncontrolled donation after circulatory death protocols have good results in terms of graft survival, they also raise several ethical concerns.[1] Criticism has mainly focused on whether use of invasive measures to preserve organs is acceptable before the patient's wishes have been established or the family has given authorisation.[2] However, a more important concern is that some donors might not have irreversibly lost either circulatory function or all brain function at the time of organ retrieval.[1] This concern is reinforced by findings on the effect that non-conventional resuscitation procedures and organ preservation techniques can have on donors' vital functions.[3–7]

Increasing evidence suggests that some people with cardiac arrest, for whom ordinary out-of-hospital resuscitation efforts have failed, can benefit from continuing CPR combined with other non-conventional resuscitation procedures (figure). These procedures are intended to treat the cause of cardiac arrest as soon as possible while preserving neurological function. Non-conventional resuscitation involves several techniques, including thrombolysis treatment during CPR,[3,8] transfer to the intensive care unit with induced mild hypothermia,[5,6] ECMO as a bridge to extracorporeal life support devices in the intensive care unit,[4] percutaneous coronary intervention in a catheterisation laboratory,[9] and, if needed, insertion of an intra-aortic balloon pump.[6] Emergency and intensive care services in many countries, including Austria, Sweden, Japan, France, and the USA, have reported that various combinations of these techniques are associated with promising survival rates with good neurological outcomes (cerebral performance categories scale 1–2) after discharge from hospital.[3,5,9,10]

As a result of increasing evidence to support the effectiveness of such interventions in selected patients, international resuscitation guidelines have been modified and now recommend treatment of the known or suspected causes of refractory cardiac arrest before CPR is discontinued.[11,12] Uncontrolled donation

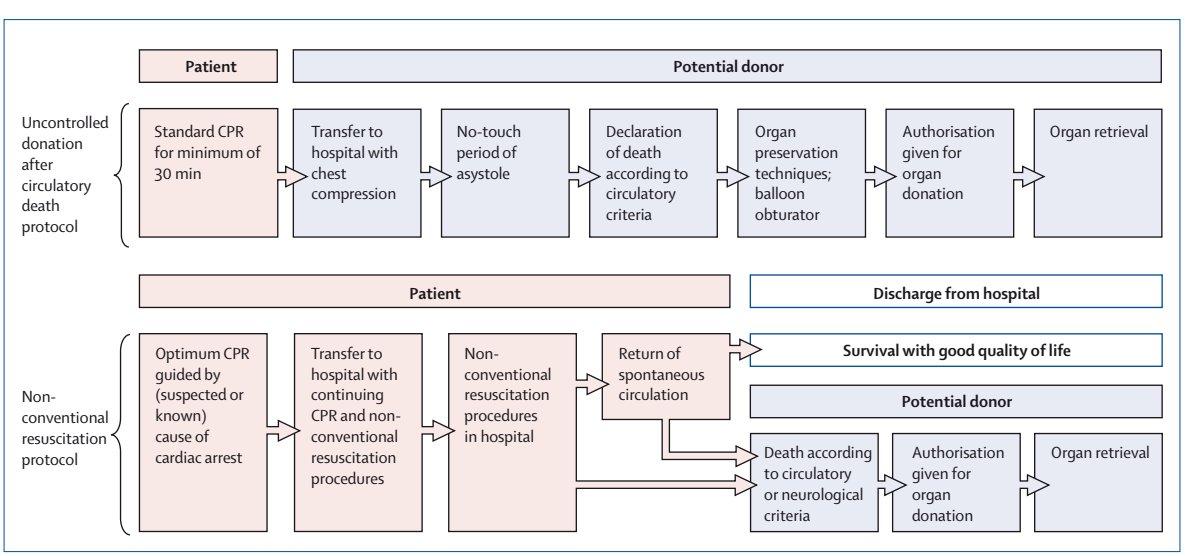

Figure: **Management options for patients with out-of-hospital cardiac arrest**
CPR=cardiopulmonary resuscitation.

programmes that overlook this recommendation might be failing to offer the updated standard of treatment to certain patients with out-of-hospital cardiac arrest. Moreover, some interventions that are strictly intended to preserve the organs—eg, vasodilators, anticoagulants, and preservation fluids—can actually compromise the patient's chances of survival.[13] However, not all patients with out-of-hospital cardiac arrest are likely to benefit from non-conventional resuscitation procedures.[10] Criteria should be developed to classify patients as either entitled to these innovative therapies or suitable for organ donation.

Another concern is that ECMO, while intended to preserve the organs, can restore the donor's brain function by reinstituting brain blood flow and, according to a panel of experts from the Health Resources and Services Administration, can "retroactively negate the cause of death" of patients already declared dead.[14] To avoid this situation and ensure that the patient's condition is irreversible, Wall and co-workers[1] and Bernat and his colleagues[14] recommend blocking the aorta with a balloon obturator to separate the brain from the organs being perfused.[1,14] Although this procedure might prevent patients from regaining consciousness,[14] it can also be seen as contributing to death.[1]

If uncontrolled donation after circulatory death programmes are to achieve their full potential for increasing organ supply, these ethical challenges need to be satisfactorily and transparently addressed. We suggest three options for management of patients with out-of-hospital cardiac arrest. First, uncontrolled donation after circulatory death should be considered only when available therapeutic options are unsuccessful or not clinically indicated, to avoid precluding some potentially recoverable patients from receiving optimum treatment. Second, only individuals with an irreversible loss of consciousness should be candidates for organ donation. Finally, families of patients who are potentially suitable for uncontrolled donation after circulatory death should be told that the patient has been transferred to the hospital with continuing chest compressions solely to maintain the viability of organs for transplantation.

Existing uncontrolled donation after circulatory death protocols might compromise donors' interests and potentially threaten the favourable public perception of organ donation. Strategies to increase the organ supply that come at the price of a substantial violation of ethical standards will not solve the problem of organ shortage.

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We thank Carissa Véliz, William Harvey, Walter Glannon, Stuart Youngner, Maxwell Smith, Neil Lazar, and Scott A Singer for their suggestions. This work was financially supported by the Kontuz! project (FFI2011-24414). DRA received the Phyllis and Albert Sussman Accommodation Subsidy for a stay at The Hastings Center while he participated in the writing of this Comment.

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ANEXO II

Segundo artículo

PUNTO DE VISTA

Donación en asistolia en emergencias *versus* reanimación cardiopulmonar no convencional: ¿obtenemos órganos o intentamos salvar vidas?

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Introducción

En los últimos años, ha crecido el número de programas de donación tras una parada cardiaca no esperada (*uncontrolled donation after circulatory determination of death,* uDCDD). Sólo en España, existen 7 programas activos, en 6 Comunidades Autónomas distintas, y al menos otros tantos en proyecto avanzado.

Igualmente, son crecientes los programas de reanimación cardiopulmonar no convencional (RCP NC) que, conforme a la mejor evidencia científica actual, seleccionan a víctimas de paradas cardiorrespiratorias (PCR) inesperadas, y les ofrecen una reanimación cardiopulmonar mantenida y de alta calidad, como puente a determinadas técnicas y tratamientos que tratan la causa, conocida o sospechada, origen del colapso cardiocirculatorio. Diferentes países de Europa y del resto del mundo están obteniendo resultados prometedores, en lo que a supervivencia con calidad de vida se refiere. En España, todavía no existen programas de este tipo activos, lo que hace que se planteen cuestiones eticolegales que afectan a las prioridades asistenciales y gestoras de los servicios de emergencias. En resumen, los programas de RCP NC no están implantados en ninguna de las regiones donde sí lo están los de uDCDD. Así, ciertos pacientes víctimas de PCR que podrían haberse beneficiado de programas de RCP NC han sido incluidos como candidatos de los programas de uDCDD, al no existir alternativa logística ni asistencialmente protocolizada. Proponemos un protocolo que incluye la opción de una RCP NC que mejore las posibilidades de supervivencia en pacientes seleccionados víctimas de una PCR inesperada, sin restar con ello potenciales candidatos para la donación a corazón parado, excepto, evidente y afortunadamente, aquéllos que a partir de ahora recuperaríamos y que hasta ahora se convertían en donantes. Este protocolo propuesto es conforme con los conocimientos y mejores evidencias actuales y medios técnicos y humanos ya disponibles, y establece las prioridades gestoras y asistenciales que han de regir a todo servicio de emergencias médicas: salvar la vida de pacientes críticos, y la recuperación de éstos sin secuelas. Dar vida con calidad de vida y, sólo cuando esto no es posible, dar vida más allá de la muerte incoercible del paciente, si es su deseo o lo autoriza su familia, mediante la donación de sus órganos.

¿Qué es lo que ha cambiado?

Varios fenómenos recientes justifican una reflexión sobre los programas activos de uDCDD. El primero es la proliferación de estos programas en toda España[1], en otros países de Europa y en Estados Unidos[2]. Los protocolos de uDCDD aumentan el número de órganos para trasplante en un momento en el que las listas de espera crecen mientras el número de donantes en muerte encefálica disminuye, gracias a los logros alcanzados por las políticas sanitarias preventivas y asistenciales. El segundo hecho lo constituyen las evidencias que alientan a profesionales de la medicina de emergencias en general, y prehospitalaria en particular, a tratar de forma no convencional las PCR inesperadas[3]. En este sentido, las

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Fecha de recepción: 11-1-2012. **Fecha de aceptación:** 5-2-2012.
Conflicto de intereses: Ninguno.

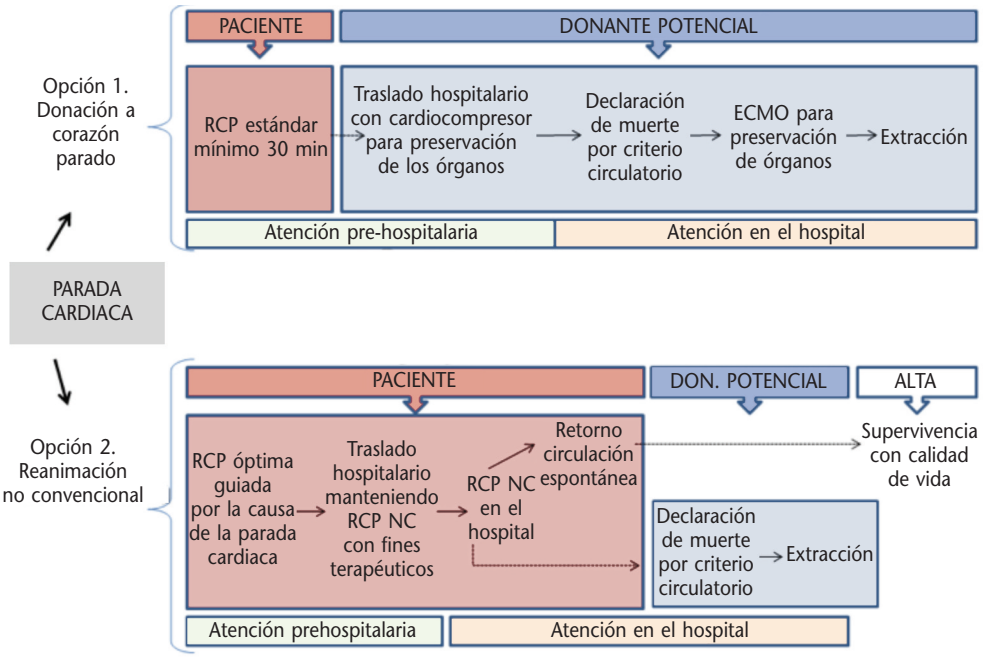

Figura 1. Opciones de manejo de las víctimas de parada cardiaca inesperada. Tomado de ref. 1. DON: donante.

últimas recomendaciones internacionales de resucitación (ILCOR, AHA, ERC 2010)[4] abogan porque ésta sea mínimamente interrumpida, de alta calidad, guiada por la causa de la PCR y mantenida hasta facilitar al paciente cuidados específicos que puedan revertir su proceso. Existen resultados prometedores, en términos de supervivencia con calidad de vida neurológica (*Cerebral Performance Category scale,* CPC 1-2) tras una PCR inesperada, obtenidos por diversos grupos en esos países[5-9] tras la implementación de programas de RCP NC.

Diferentes tipos de reanimación cardiopulmonar no convencional actualmente utilizados

Las víctimas de una PCR inesperada, seleccionadas previamente conforme a un modelo predictivo, reciben una reanimación de calidad y mínimamente interrumpida *in itinere* que incide en la causa originaria de la PCR refractaria. Los porcentajes de supervivencia sin secuelas son un acicate para instaurar programas que incluyen como opciones asistenciales: a) cateterismo cardiaco (ACTP) durante la RCP, en PCR de origen coronario; b) soporte vital con circulación extracorpórea (ECLS-ECMO) en PCR por *shock* cardiogénico refractario; c) trombolisis durante la resucitación, cuando el origen de la PCR es tromboembolismo y cardiopulmonar; y d) simultáneamente a lo anterior, hipotermia moderada inducida terapéuticamente durante la RCP.

Conflictos éticos derivados de la situación actual

El tercer hecho, consecuencia de los dos anteriores, es la coexistencia en tiempo y lugar de protocolos de uDCD con programas de RCP NC, o bien la existencia del primero, pero no del segundo, a pesar que los recursos humanos, asistenciales y técnicos necesarios para ambos resultan casi idénticos. Ambas situaciones dan lugar a varios dilemas éticos y de gestión de los recursos sanitarios.

Los criterios científico-técnicos y éticos para discriminar, de entre las víctimas de una PCR, a pacientes de potenciales donantes, deben ser claros y transparentes tanto asistencialmente y como para el gestor. Donde hoy no existen ambas opciones, se origina un conflicto para los profesionales sanitarios: ¿por qué no implementamos programas de RCP NC para incrementar la superviviencia de los pacientes y no sólo somos excelentes preservando órganos de potenciales donantes? Evitaremos que exista una percepción social de sospecha y desconfianza ante la posibilidad que la donación pudiera comprometer una atención sanitaria de óptima calidad[10].

Conclusiones y reflexión final

Si es cierto que los protocolos de uDCD y los programas de RCP NC pueden y deben coexistir, no lo es menos que aquéllos deben supeditarse al fracaso de éstos. Sólo una vez que se haya intentado, sin éxito, todo esfuerzo disponible, científicamente indicado y éticamente justificable, debería plantearse trasladar a una víctima de parada cardiaca extrahospitalaria como potencial donante de órganos, con el objetivo socialmente loable de dar vida más allá de una muerte ya presente, pero en todo caso incoercible (Figura 1).

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FE DE ERRORES

En el artículo "Marcadores de gravedad en el herpes zóster y la varicela del adulto" publicado en Emergencias 2012;24:277-282, hay que añadir en la Adenda al Hospital Universitario Gregorio Marañón de Madrid.

Universidad de Alcalá

ANEXO III

Tercer artículo

Ortega-Deballon et al. Critical Care (2015) 19:268
DOI 10.1186/s13054-015-0985-7

CRITICAL CARE

RESEARCH Open Access

Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes

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Abstract

Introduction: A chronic shortage of organs remains the main factor limiting organ transplantation. Many countries have explored the option of uncontrolled donation after circulatory death (uDCD) in order to expand the donor pool. Little is known regarding the variability of practices and outcomes between existing protocols. This systematic review addresses this knowledge gap informing policy makers, researchers, and clinicians for future protocol implementation.

Methods: We searched MEDLINE, EMBASE, and Google Scholar electronic databases from 2005 to March 2015 as well as the reference lists of selected studies, abstracts, unpublished reports, personal libraries, professional organization reports, and government agency statements on uDCD. We contacted leading authors and organizations to request their protocols and guidelines. Two reviewers extracted main variables. In studies reporting transplant outcomes, we added type, quantity, quality of organs procured, and complications reported. Internal validity and the quality of the studies reporting outcomes were assessed, as were the methodological rigour and transparency in which a guideline was developed. The review was included in the international prospective register of systematic reviews (Prospero, CRD42014015258).

Results: Six guidelines and 18 outcome studies were analysed. The six guidelines are based on limited evidence and major differences exist between them at each step of the uDCD process. The outcome studies report good results for kidney, liver, and lung transplantation with high discard rates for livers.

Conclusions: Despite procedural, medical, economic, legal, and ethical challenges, the uDCD strategy is a viable option for increasing the organ donation pool. Variations in practice and heterogeneity of outcomes preclude a meta-analysis and prevented the linking of outcomes to specific uDCD protocols. Further standardization of protocols and outcomes is required, as is further research into the role of extracorporeal resuscitation and other novel therapies for treatment of some refractory cardiac arrest. It is essential to ensure the maintenance of trust in uDCD programs by health professionals and the public.

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Introduction

A chronic shortage of organs remains the main factor limiting organ transplantation for patients with end-stage organ failure. Although organ transplants save thousands of lives and transform the quality of life of thousands more, many people will die or remain on renal replacement therapy because the organ supply falls drastically short of demand. In Europe, nearly 99,000 patients were waiting for an organ in 2013 whilst the number of deceased donors has remained stable at approximately 9900 [1]. This is also the case in the US, where 30,000 patients were on waiting lists and the number of deceased donors was 8268 [1]. In Canada, the situation is equally concerning. At the end of 2013, 4433 patients were on the waiting lists and only 553 actual deceased donors were obtained that year [2]. The mismatch between supply and demand for organs has led policy makers and health institutions to develop new strategies aimed at expanding the organ donor pool. As a result, many countries worldwide have explored the option of donation after circulatory death (DCD).

The DCD procedure seeks to obtain solid organs from patients previously declared dead following the cessation of their circulatory and respiratory functions. There are two distinct methods: controlled DCD (cDCD) and uncontrolled DCD (uDCD). The cDCD occurs after an anticipated in-hospital cardiac arrest, generally but not exclusively in intensive care unit patients who have suffered a catastrophic brain injury and for whom a decision has been made to withdraw life-sustaining therapies (WLST). In this scenario, consent for cDCD is obtained, WLST occurs and a variable amount of time later, death is declared, and organs are procured. The uDCD is initiated following an unexpected, and usually out-of-hospital, refractory cardiac arrest. After resuscitation attempts are judged futile, interventions—ongoing cardiac compressions and mechanical ventilation—are initiated to preserve organs for donation. The diagnosis of death may occur after resuscitation is terminated on scene or after arrival to the hospital. There is a "no touch" period after which death is determined and organ preservation may be restarted. After hospital arrival, cannulation and organ preservation with extracorporeal perfusion or *in situ* cooling begin. Consent requirements for donation and organ preservation vary by region and may occur before or after cannulation.

Protocols for uDCD have already been implemented in Spain, France, Italy, the UK, and The Netherlands [3]. Protocols have also been developed in other countries, such as Belgium, Switzerland, and Austria, and in Saint Petersburg (Russia) and in New York City [4]. These international experiences have demonstrated that uDCD is an effective way to increase the availability of solid organs for transplantation [5]. Although uDCD appears to have promising results in terms of graft survival, it raises several medical, ethical, legal, economic, and logistic challenges at the intersection of cardiac arrest, resuscitation, organ donation, and organ preservation after declaring death [6, 7]. Little is known regarding the variability of practices between existing protocols [8] and less still regarding the comparative effectiveness of implementing a particular protocol [9].

The purpose of this systematic review is to address this knowledge gap by compiling and analyzing the defining elements and reported transplant outcomes of the currently active protocols and guidelines for uDCD. To the best of our knowledge, no systematic review has been conducted to specifically evaluate and compare the practices and outcomes of uDCD protocols, nor has any evaluation of the quality of guidelines for implementing such protocols been performed. This review will inform uDCD protocol and practice development, which has applicability to policy makers, researchers, and clinicians to assist in future protocol implementation.

Methods

Design of the study and search strategy

We conducted a systematic review of the literature in accordance with reviews in health care from the Center for Reviews and Dissemination, from the University of York [10]. We used a modified PICOTS format: Population: potential uDCD candidates; Intervention: active protocols for uDCD; Control: not applicable; Outcomes: in terms of (a) define elements of international practices on protocols for uDCD and, when reported (b) grafts obtained or transplanted (or both), as well as graft or patient survival and complications (or both); Time: 2005 to March 2015; and Setting: any organization that has produced a recommendation or protocol for uDCD.

We developed a comprehensive search strategy with the help of a qualified librarian. We searched MEDLINE, EMBASE, and Google Scholar electronic databases from 2005 to March 2015. The search included English, French, Italian, and Spanish and was limited to human studies. We manually searched the reference lists of selected studies and the grey literature for unpublished reports, personal libraries, professional organization, and government agency statements on uDCD. We also contacted leading authors and organizations in the field of uDCD to request their protocols and guidelines.

Eligibility criteria

Our inclusion criteria for review were any kind of report proposing a clinical procedure for uDCD endorsed by a government agency, professional organization, professional society, or regional health-care organization. We excluded any editorials, letters, abstracts, or personal

opinion articles that were not supported by the aforementioned organizations.

Study selection

Two trained reviewers (IO-D and LH) screened all citations. We retrieved the full texts of selected citations and independently reviewed them to assess study eligibility. Disagreements were resolved by consensus or with the intervention of a third expert reviewer (SDS). We used EndNote manager software (EndNote X7.1 version by Thomson Reuters) to manage the collection of publications. Figure 1 describes the study selection process.

Data extraction and quality assessment

Two reviewers (IO-D and LH) extracted data. We created an Excel (Excel version 2013 by Microsoft Office, Microsoft Corporation, Redmond, WA, USA) data collection tool that was piloted in a sample from the list of included studies. The final version of the spreadsheet included the following variables: name of the authors, country, language, setting, year, type of study and method, eligibility criteria for population, intervention and timelines during process, organ preservation details, death determination characteristics, type and time of consent, and any ethical, legal, and logistic issues described. For the studies reporting transplant outcomes, we added type, quantity, quality of organs procured, and complications reported. Internal validity of the studies was assessed independently by two reviewers (IO-D and LH). The quality of the studies reporting outcomes was assessed by using the Downs and Black scale [11]. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument version II [12] was used to assess the methodological rigour and transparency of guidelines. Up to three reviewers assessed each guideline.

Data synthesis

We anticipated heterogeneity in selected studies and guidelines. Variability was apparent in eligibility criteria, organs obtained, timelines along the ischaemia process, determination of circulatory death practices, ischaemia definition, and techniques for organ preservation. Therefore, pooling of study data was not feasible and a meta-analysis was not possible. Rather, data analysis consisted of a tabulation of characteristics from studies and guidelines.

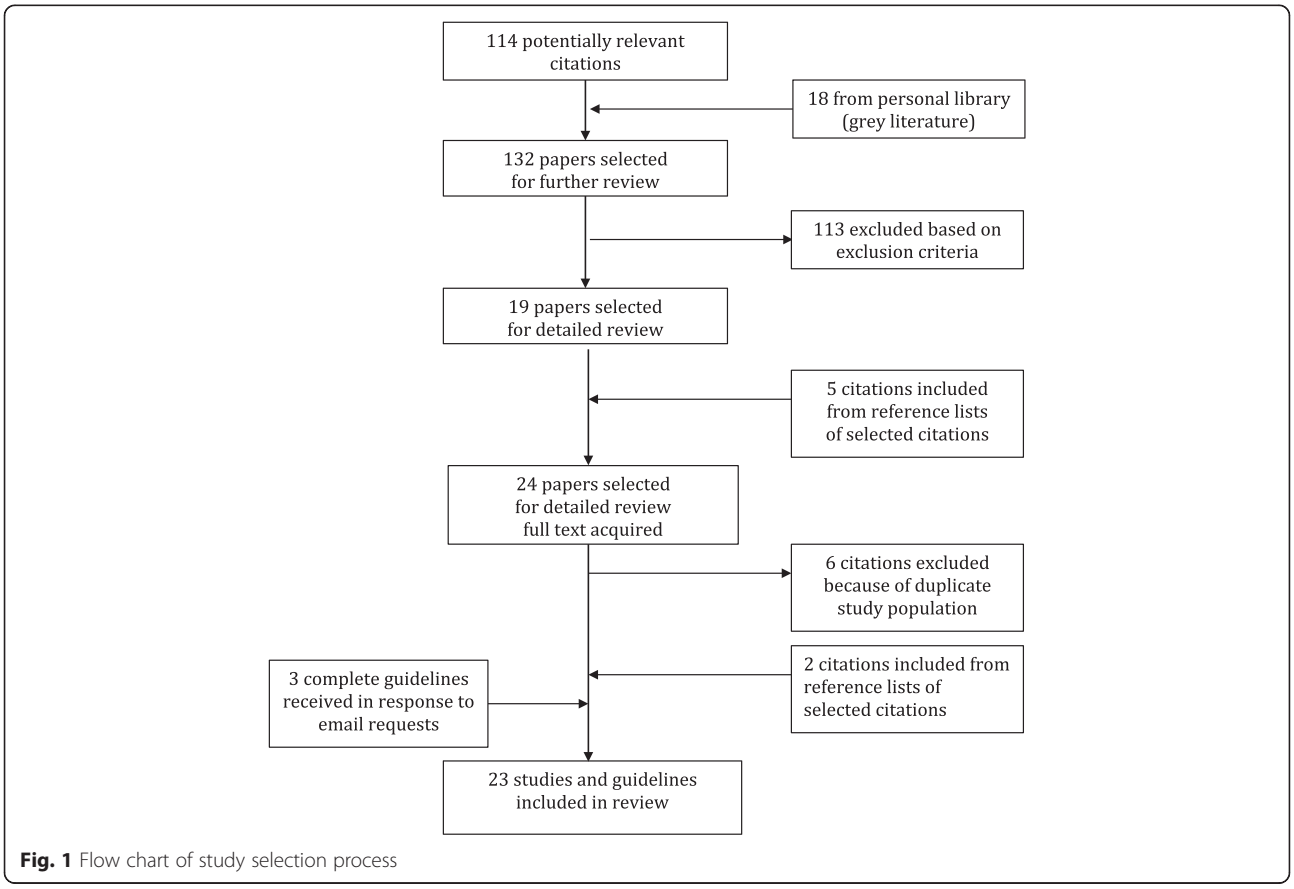

Fig. 1 Flow chart of study selection process

Review end points

This systematic review aimed to address the following question: What are the defining elements and reported outcomes of currently active protocols and recommendations for uDCD?

Results

After launching the search strategy (Fig. 1), we obtained 114 potentially relevant citations, in addition to 18 from grey literature, resulting in a total of 132 references for further review. Of these, 113 were excluded after a first screening for the following reasons: not relevant ($n = 42$); editorials, surveys, or opinions ($n = 32$); referring to results from cDCD ($n = 19$); duplicated data ($n = 16$); and case reports or abstracts ($n = 4$). The resulting 19 references were selected for further review, and five new citations were included from their reference lists. Therefore, a total of 24 references were screened after acquiring the full-text version. Following the full-text review, six citations were excluded because the study population was duplicated while two other citations from reference lists were included. During the second screening, we contacted agencies of different countries involved in implementation of protocols for uDCD and received three more guidelines in response to our request. Thus, a final total of 23 references—17 studies [13–29], five guidelines [4, 30–33], and one article [34] that included both a full guideline description and transplant outcomes—was included. Thus, for the purpose of this review, six guidelines and 18 outcome studies were analysed.

Main characteristics of guidelines

Figure 2 is an illustrative example of the uDCD procedure timelines and clinical pathway described within the guidelines. Timelines begin with a cardiac arrest, followed by initiation of cardiopulmonary resuscitation (CPR), termination of CPR, continuation of organ-preserving interventions, diagnosis of death, and cannulation for organ preservation. As will be further described below, there are variable periods of no-flow and low-flow states that may impact on pre- and post-mortem ischemic organ injury and there is variability in the timing of, and requirement for consent for, donation or organ preservation or both.

In our review, we included six guidelines from as many countries. The main characteristics are described in Table 1 ("Guidelines" section) and summarized here.

Cardiac arrest location and uncontrolled donation after circulatory death donor definition

All of the guidelines describe potential uDCD donors as those patients suffering an out-of hospital refractory cardiac arrest after failed resuscitation in the field. The guidelines from France, Italy, and Switzerland also consider in-hospital patients as potential donors. Age limits for donors most commonly included adults and older teenagers, but children were also eligible in some regions of Spain (Table 1).

Geographic implementation and organs procured

In the case of France and Spain, national recommendations do exist for uDCD. The uDCD strategy has been implemented in Spain since 1995 with the pioneering

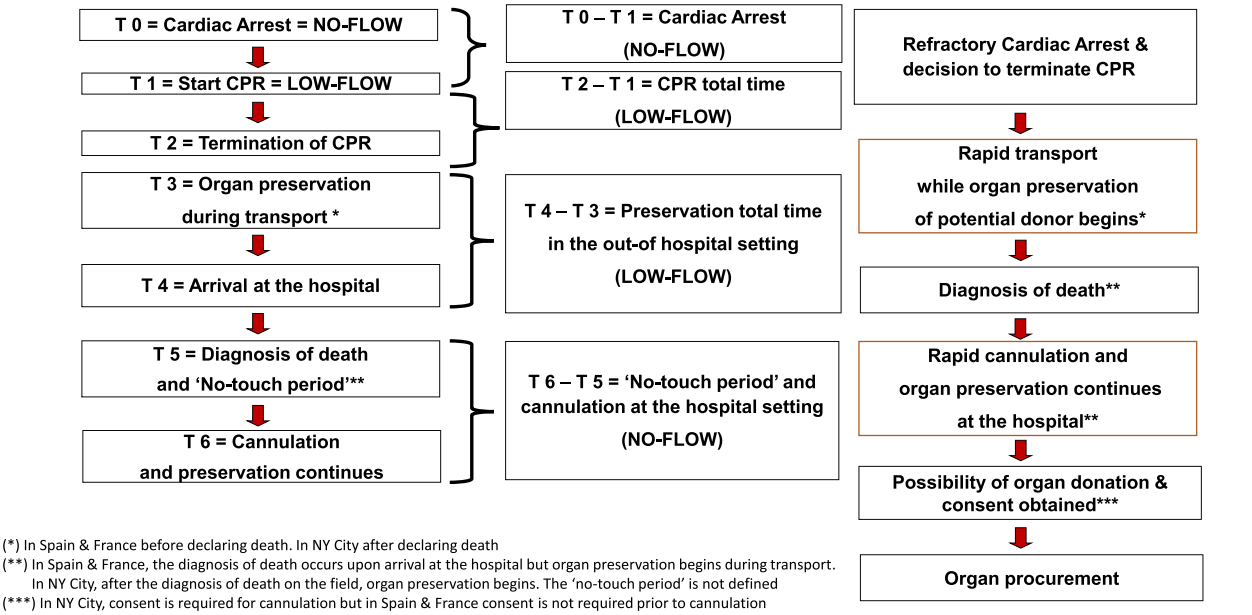

Fig. 2 Timelines and clinical pathway in the process of uncontrolled donation after circulatory death (DCD). *CPR* cardiopulmonary resuscitation

Table 1 Characteristics of included guidelines and eligible outcome studies

Guidelines ($n = 6$)				
National/Regional Guideline Country; region (year)	Language	Population targeted	Location of cardiac arrest	Organ(s)
FRANCE (2007) [30]	French	Adult	Out of hospital and in hospital	Kidney and liver
ITALY; Pavia (2011) [34]	English	Adult and children (≥15 years)	Out of hospital and in hospital	Kidney
SWITZERLAND (2011) [32]	French	Adult and children (≥16 years)	Out of hospital and in hospital	Kidney
US; New York City (2011) [4]	English	Adult and children	Out of hospital	Kidney and liver (phased in)
SPAIN [31];				
Alicante (2012)	Spanish	Adult and children (≥14 years)	Out of hospital	Kidney, liver, and lung
Barcelona (2012)		Adult and children (≥14 years)		Kidney and liver
Castilla La Mancha (2012)		Adult and children (≥7 years)		Kidney, liver, and lung
Granada (2012)		Adult and children (≥7 years)		Kidney, liver, and lung
Galicia (2012)		Adult and children (≥14 years)		Kidney and liver
Madrid City and Region (2012)		Adult and children		Kidney, liver, and lung
UK; Scotland (2013) [33]	English	Adult and children (≥16 years)	Out of hospital	Kidney, Liver and lungs
Eligible outcome studies ($n = 18$)				
Study/Country, Region	Study design	Population studied	Location of cardiac arrest	Organ(s)
Gámez 2005 [13]/Spain, Madrid	Case series	Adult	Out of hospital	Lung
Gagandeep 2006 [14]/USA, Nationwide	Database review comparison to DBD and cDCD	Adult and children	in hospital	Kidney
Sánchez-Fructuoso 2006 [15]/Spain, Madrid	Retrospective cohort	Adult	Out of hospital and in hospital	Kidney
Fondevila 2007 [16]/Spain, Barcelona	Retrospective cohort with Matched DBD controls	Age not specified	Out of hospital	Liver
Suárez 2008 [17]/Spain, La Coruna	Retrospective cohort compared to HBD	Adult	Out of hospital and in hospital	Liver
Fieux 2009 [18]/France, Paris	Prospective cohort	Adult	Out of hospital	Kidney
Gómez Gutiérrez 2009 [19]/Spain, La Coruña and Madrid	Case series	Adult	Out of hospital	Liver
Jiménez-Galanes 2009 [20]/Spain, Madrid	Prospective case Control matched to DBD	Adult	Out of hospital	Liver
Ribalta 2009 [29]/Spain, Cataluña	Retrospective cohort	Adult and children	Out of hospital	Kidney and liver
Mateos-Rodríguez 2010 [21]/Spain, Madrid	Retrospective cohort	Adult and children	Out of hospital	Kidney, liver, and lungs
Mateos-Rodríguez 2010 [22]/Spain, Madrid	Retrospective cohort	Adult	Out of hospital	Kidney
Geraci and Sepe 2011 [34]/Italy, Pavia	Retrospective Cohort	Adult	In hospital	Kidney

Table 1 Characteristics of included guidelines and eligible outcome studies *(Continued)*

Hoogland 2011 [23]/The Netherlands, Maastricht	Retrospective cohort compared with cDCD	Adult	Out of hospital	Kidney
Rodríguez 2011 [24]/Spain, Madrid and Santander	Retrospective cohort	Adult and children	Out of hospital	Lungs
Fondevila 2012 [25]/Spain, Barcelona	Retrospective cohort	Adult	Out of Hospital	Liver
Gómez-de-Antonio 2012 [26]/Spain, Madrid	Prospective cohort	Adult	Out of hospital	Lung
Hanf 2012 [27]/France, Lyon	Prospective cohort compared with ECD and SPK	Adult	Out of hospital	Kidney
Reznick 2013 [28]/Russia, St Petersburg	Retrospective cohort	Adult	In hospital	Kidney

Extended criteria donors (ECDs) were all donors at least 60 years old and those 50–59 years old with at least two of the other three conditions (cerebrovascular cause of death, renal insufficiency with serum creatinine less than or equal to 1.5 mg/dl, and hypertension)

DBD donation after brain death, *cDCD* controlled donation after circulatory death, *HBD* heart beating donors, *SPK* simultaneous non-sensitized kidney pancreas transplanted patients that received kidneys from optimal donors

Please note that the article by Geraci and Sepe (2011) was included in both the "Guidelines" and "Eligible outcome studies" sections of this table because it included both a guideline for a protocol and its preliminary results

Madrid program, yet national recommendations were not published until 2012. In France, guidelines were published in 2007 and only after this were several uDCD programs implemented. In the case of Italy, the protocol has also achieved results but is operating only in the region of Pavia. The protocol of New York City, though running, has not reported any transplant outcomes. In Scotland, a standard operating procedure is being piloted at Edinburgh. Spanish recommendations include seven uDCD protocols operating in six different regions, including Madrid which has two programs. At present, the guidelines from both Spain and the UK include procedures for recovering kidneys, livers, and lungs. France is recovering kidneys and livers. In Italy, kidneys are being procured. Switzerland, New York City, and Scotland consider only kidney procurement. A summary of the specific details of the uDCD process contained within the guidelines is included in Table 2 ("Guidelines" section) and this process is further described here.

Death declaration and time restrictions

For the studies that provided a definition of refractory cardiac arrest, it is defined as 30 minutes of failed resuscitation. Death determination in France and Switzerland obliges the absence of circulation, spontaneous ventilation, and the performance of a rapid neurologic assessment to confirm the absence of consciousness, spontaneous motor activity, and brainstem reflexes. A rapid neurological testing is also performed in the New York City protocol in the prehospital setting. Scotland determines death in the emergency department after 5 minutes of absent cardiopulmonary activity defined by the absence of respiratory effort and no electrical activity on the electrocardiogram, no cardiac movement on focused echocardiography, or no pressure wave visible on the arterial line tracing. A "no-touch period", defined as a hands-off interval, during which no interventions to the body are allowed, is required for declaring death. This period follows the decision to stop resuscitation or organ preservation attempts and varies widely between protocols, ranging from 5 to 20 minutes. There is also wide variation with respect to the maximum allowable times for each of the following periods: cardiac arrest prior to CPR (range of 15 to 30 minutes), CPR to cannulation (range of 90 to 120 minutes), and cannulation to organ procurement (range of 120 to 360 minutes).

Organ preservation

All six guidelines recommend femoral arterial and venous cannulation and extracorporeal membrane oxygenation (ECMO) (re-initiation of circulation with an oxygenated solution). Spain recommends both normothermic and hypothermic conditions, whereas France recommends hypothermic ECMO. Scotland, Italy, and New York City use normothermic ECMO. In Spain and France, depending on center experience, the organ preservation techniques may also include *in situ* cooling with flushing of cold preservation fluids into the abdominal cavity and/or pleural spaces. Switzerland considers *in situ* cooling preservation and normothermic ECMO. The *ex vivo* renal perfusion machine is being used in Spain, France, and Italy and was proposed in Scotland and New York City. Spain has recently expanded the use of *ex vivo* organ perfusion for lung preservation in some centers.

Ethical, legal, and logistic issues

To a variable extent, all of the included guidelines address a number of ethical, legal, and logistic issues associated with uDCD. Table 2 describes various issues in guidelines, including information provided to next of kin in the field (4/6), organ preservation initiated in the ambulance during transport (4/6), consent for cannulation and procurement (5/6), objective of inserting an intra-aortic balloon (3/6), health providers' attitudes and beliefs (4/6), role of ECMO organ-preserving versus lifesaving technique (1/6), and cost-effectiveness considerations (4/6).

Guideline appraisal

To assess the rigour of clinical practice guideline development, the six documents from countries with national or regional guidelines were evaluated. Additional file 1 contains an appraisal of each of the guidelines. In accordance with the AGREE II appraisal process, scaled scores for each of six different domains are presented. After a global interpretation of the quality scores, we observed that lower scores for all the guidelines assessed were in the domains of "Rigour of development", "Applicability", and "Editorial independence". The higher-quality scores were obtained in the domains of "Scope and purpose" and "Clarity of presentation". In regard to the domain of "Stakeholder involvement", the quality scores were low or fair for all assessed guidelines, with the exception of the New York City protocol, which obtained the highest score.

Main characteristics and protocol details of studies reporting transplant outcomes

Our review included 18 studies that reported outcomes for recipients of organs recovered by uDCD protocols. The main characteristics of the studies are described in Table 1 ("Eligible outcome studies" section) and are summarized here.

Types of studies and organs procured

The included studies were carried out at centres in Spain, France, the US, The Netherlands, and Russia. There were no randomized controlled trials; all studies were observational in nature. Three studies were prospective cohorts [18, 26, 27], one study was a prospective case control [20], one was a retrospective cohort with matched controls [16],

Table 2 Summary of specific details of included guidelines and eligible outcome studies

	Death declaration		Time restrictions			
	Definition of refractory cardiac arrest (time of CPR in min)	"No touch" time (min)	Max arrest time with no CPR (min)	Max time - CPR to cannulation (min)	Max time - cardiac arrest to cannulation (min)	Max time – cannulation to procurement (min)
Guidelines ($n = 6$)						
France (2007) [30]	30 ACLS	5	30	90 mCPR 120 aCPR	120 mCPR 150 aCPR	180 ISC 240 ECMO
Italy; Pavia (2011) [34]	NS	20	15	110	125	360
Switzerland (2011) [32]	20	10	30	120	150	180
US; New York City (2011) [4]	30	NS	NS	120	NS	240
Spain; Alicante, Barcelona, Castilla La Mancha, Granada, Galicia, Madrid City and Region (2012) [31]	Failed CPR	5	15 A, C, Gr, M 20 Ga 30 B	120	150	120 ISC 240–360 ECMO
UK; Scotland (2013) [33]	Failed CPR	5	15	105	120	NS
Eligible outcome studies ($n = 18$)						
Gámez 2005 [13]/Spain, Madrid	30	5	15	105	120	240
Gagandeep 2006 [14]/USA, Nationwide	NS	NS	NS	NS	NS	NS
Sánchez-Fructuoso 2006 [15]/Spain, Madrid	30	5	15	105	120	240
Fondevila 2007 [16]/Spain, Barcelona	NS	5	15	135	150	240
Suárez 2008 [17]/Spain, La Coruna	NS	5	15	105	120	240
Fieux 2009 [18]/France, Paris	30 ACLS	5	30	90 mCPR 120 aCPR	120 mCPR 150 aCPR	180 ISC 240 ECMO
Gómez Gutierrez 2009 [19]/Spain, La Coruña and Madrid	Failed CPR	5	NS	NS	120	130
Jiménez-Galanes 2009 [20]/Spain, Madrid	Failed CPR	5	15	135	150	240-270
Ribalta 2009 [29]/Spain, Cataluña	Failed CPR	5	30	120	150	NS
Mateos-Rodríguez 2010 [21]/Spain, Madrid	Failed CPR	5	15	105	120	NS
Mateos-Rodríguez 2010 [22]/Spain, Madrid	30	5	15	105	120	240
Geraci and Sepe 2011 [34]/Italy, Pavia	NS	20	15	110	125	360
Hoogland 2011 [23]/The Netherlands, Maastricht	NS	5	NS	90	NS	NS
Rodríguez 2011 [24]/Spain, Madrid and Santander	NS	5	10	110	120	240
Fondevila 2012 [25]/Spain, Barcelona	20	5	15	150	165	240
Gomez-de-Antonio 2012 [26]/Spain, Madrid	NS	5	15	105	120	240
Hanf 2012 [27]/France, Lyon	30	5	30	90 mCPR 120 aCPR	120 mCPR 150 aCPR	180
Reznick 2013 [28]/Russia, Saint Petersburg	Failed CPR	NS	60[a]	NS	NS	NS

Table 2 Summary of specific details of included guidelines and eligible outcome studies

Organ preservation					Ethical and legal issues addressed						Logistic issues	
Cannulation permitted prior to consent	n-ECMO used	h-ECMO used	*In situ* cooling	Pulsatile perfusion	Information given to next of kin on the field	Organ preservation initiated in ambulance during transport	Consent for cannulation of the cadaver for organ preservation	Objective of intra-aortic balloon	Health providers' attitudes and beliefs	ECMO: organ preservation versus lifesaving technique	Cost-effectiveness evaluation	Coordination efforts needed
N	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y
N	Y	N	N	Y	N	Y	Y	N	N	N	Y	Y
Y	Y	N	Y	N	N	N	N	N	N	N	N	N
N	Y	N	N	Y	Y	Y OPV	Y	Y	Y	Y	Y	Y
Y	Y A B C Gr M	Y M	Y A Ga Gr	Y B M	Y	Y	Y	Y	Y	N	Y	y
Y	Y	N	N	Y	N	N	Y	Y	Y	N	Y	Y
Y	N	Y	Y	N	N	N	N	N	N	N	N	Y
NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	Y	Y
Y	N	Y	Y	Y	N	N	N	N	N	N	N	N
Y	Y	N	N	Y	N	N	Y	N	N	N	N	N
Y	Y	Y	N	N	N	N	N	N	N	N	N	N
N	N	Y	Y	Y	Y	Y	Y	N	Y	N	N	Y
Y	Y	N	Y	N	N	N	N	N	Y	N	N	Y
Y	Y	N	N	NS	N	N	Y	N	N	N	N	Y
Y	NS	NS	NS	Y	N	N	N	N	N	N	N	Y
Y	Y	NS	N	NS	N	N	N	N	N	Y	N	Y
Y	Y	N	NS	NS	N	N	N	N	N	Y	N	Y
N	Y	N	N	Y	N	Y	Y	N	N	N	Y	Y
Y	N	N	Y	Y	N	N	Y	N	N	Y	N	Y
Y	N	N	Y	Y	N	N	N	N	N	N	N	N
Y	Y	N	N	N	N	N	Y	N	N	N	Y	N
Y	N	N	Y	Y after2009	N	N	N	N	N	N	N	N
NS	Y	N	Y	Y	N	N	N	N	N	N	N	N
Y	Y	N	N	NS	N	N	Y	N	N	Y	N	Y

CPR cardiopulmonary resuscitation, *n-ECMO* normothermic extracorporeal membrane oxygenation, *h-ECMO* hypothermic extracorporeal membrane oxygenation, *ECMO* extracorporeal membrane oxygenation, *ACLS* advanced cardiac life support, *mCPR* manual cardiopulmonary resuscitation, *aCPR* automated cardiopulmonary resuscitation, *ISC in situ* cooling, *OPV* organ preservation vehicle, *N* the procedure is not used or the issue is not discussed, *Y* the procedure is used or issue is discussed, *NS* not specified (no information specified in guideline or study), *A* Alicante, *C* Castilla La Mancha, *Gr* Granada, *M* Madrid City and Region, *Ga* Galicia, *B* Barcelona

[a]time is after failed CPR until Organ Procurement Organization arrival

three were retrospective cohorts with comparisons to cDCD or donation after brain death [14, 17, 23], eight were retrospective cohorts [15, 21, 22, 24, 25, 28, 29, 34], and two were case series [13, 19]. The organs procured were kidneys (10 studies), livers (seven studies), and lungs (four studies). Although one study reported results for all three organs [21] and another for two organs [29], most studies were focused on single-organ procurement.

Age of donors and location of cardiac arrest

Potential donors were mostly young adults (between 18 and 65 years), and only a few studies included pediatric populations [14, 21, 24, 29]. Trends to limit the upper age when liver or lungs are procured do exist [13, 16, 17, 19, 20, 24–26]. The potential donors were recruited mainly outside the hospital (OHCA) in Europe, although some studies from Spain [15, 17] and one from Italy [34] also enrolled potential donors after presenting in-hospital cardiac arrest (IHCA). Outcome studies from the US [14] and Russia [28] restricted uDCD donors to IHCA. A summary of the specific details of the uDCD process for the studies reporting outcomes is included in Table 2 ("Eligible Outcome Studies" section) and this process is further described here.

Refractory cardiac arrest to death declaration

Based on the illustrative uDCD clinical pathway timelines in Fig. 2, permissible timelines are reviewed in Table 2. Maximum times limits were reported for each of the following intervals: cardiac arrest prior to CPR (no-flow, range of 10 to 30 minutes), CPR to cannulation (low flow, range of 90 to 150 minutes for OHCA), and cannulation to organ procurement (range of 130 to 270 minutes). There is wide variability among studies with respect to the criteria for determining when a sudden cardiac arrest is considered to be refractory to resuscitation. Most reports refer to failed CPR without defining CPR duration. In the studies in which it was specified, death determination was based only on circulatory criteria, with the exception of the two French studies [18, 27] in which an additional neurologic screening was performed according to legal requirements. In the Russian single-center experience [28], always after an IHCA, resuscitation attempts were stopped after being judged futile and then a "no-touch period", of up to 60 minutes, occurred while waiting for the organ procurement team to arrive. Based on these findings, the so-called warm ischemic time (WIT), resulting from the addition of "no-flow" and "low-flow" periods until the beginning of in-hospital preservation techniques that were instituted, ranged from 120 to 150 minutes.

Organ preservation

Three different organ-preserving options were described: *in situ* cooling preservation of abdominal organs or lungs and hypothermic (h-ECMO) and normothermic (n-ECMO) extracorporeal membrane oxygenation. Both h-ECMO and n-ECMO recirculate a preservation liquid and oxygenated blood through the body of the donor. The insertion of an inflated intra-aortic balloon was widely used when the ECMO technique was deployed to isolate the perfusion of abdominal organs and to avoid the reperfusion of the heart and brain [16, 17, 21, 22, 25]. A trend in the use of the *ex vivo* perfusion machine was observed [15, 16, 18, 23, 24, 29]. The time of organ preservation using the above-described techniques (so-called "cold ischemic time") varied from 180 to 270 minutes.

Ethical, legal, and logistic issues

Heterogeneity in practice was evidenced in terms of the requirement and timing of consent for both beginning preservation and the procurement of organs as well as for who the consent is obtained from (donor next of kin or recipient of an organ procured from uDCD donor or both). In addition, a number of ethical, legal, and logistic issues derived from daily practice were discussed by the authors. These included the type of information provided to next of kin in the field, consent requirements (if any), stated goals of intervention for pre-hospital and in-hospital organ preservation, and the potential conflict of interest between lifesaving and organ-preserving ECMO.

Appraisal of outcome study quality

Additional file 2 contains the quality assessment of the outcome studies. All studies were observational in nature and therefore by design were generally of low quality. Most presented high risk of confounding, risk of bias, and threats to external validity.

Transplant outcomes

We reviewed the outcomes from 10 studies procuring kidneys, seven procuring livers and four where lungs were obtained (Table 3). Larger sample sizes were derived from the Spanish experience [15, 17, 19–22, 24–26] and the two reported multicenter retrospective cohort reviews [14, 23]. Kidneys transplanted from uDCD donors demonstrated fair [14, 15, 23, 28] or poor [18, 27] early results in terms of delayed graft function, although all studies reported good results for graft and patient survival in the short and medium terms. Liver transplants from uDCD donors reported a low percentage of primary non-function and acceptable graft and patient survivals, but in all cases this was at the expense of discarding a high proportion of potential livers [16, 17, 19–21, 25, 29]. Although the experience with transplanted lungs is still limited, there are significant rates of acute rejection and primary non-function of the graft as well as medical complications

Table 3 Outcomes of included studies ($n = 18$)

Outcome studies by organ type	Time period	Total donors n	Total recipients n	Outcomes
Lung – 3 studies				
• 1 case series [13]	2002 to 2009	66	67	Time to extubation: 21 hours–144 days
• 1 retrospective cohort [24]				Hospital stay: 20–59 days
• 1 prospective cohort [26]				Primary graft dysfunction: 17–46.9 %
				1-year patient survival: 68 %
				3-year patient survival 57 %
				5-year patient survival 51 %
No comparisons were made to outcomes using cDCD or DBD donors.				
Kidney – 8 studies				
• 1 database review [14]	1981 to 2011	750	629[a]	Primary graft non-function: 0–22 %
• 5 retrospective cohort [15, 22, 23, 28, 34]				Delayed graft function: 51–92 %
• 2 prospective cohort [18, 27]				1-year graft survival: 87.4–100 %
				3-year graft survival: 100 %
				5-year graft survival: 63–82.1 %
				10-year graft survival: 50 %
				1-year patient survival: 95–100 %
				3-year patient survival: 100 %
				5-year patient survival: 78–90 %
				10-year patient survival: 61 %
Three studies compared outcomes with DBD donors; two studies reported no significant differences in primary graft non-function, graft survival, and patient survival, but delayed graft function was significantly higher for recipients of uDCD kidneys.				
One study compared outcomes with cDCD donors and reported no difference in any of the outcomes.				
Liver – 5 studies				
• 1 case series [19]	1994 to 2010	122	122	Primary graft non-function: 10–18 %
• 3 retrospective cohort [16, 17, 25]				1-year graft survival: 50–80 %
• 1 prospective case–control [20]				5-year graft survival: 49 %
				1-year patient survival: 70–85.5 %
				5-year patient survival: 62 %
Four studies compared outcomes with DBD donors and reported no significant differences in 1-year graft and patient survival and 5-year patient survival, but primary graft non-function was significantly higher and 5-year graft survival was significantly lower for recipients of uDCD livers				
Kidney and liver – 1 study				
• 1 retrospective cohort [29]	2008	34 K 4 L	NR	No outcomes reported
Kidney, liver, and lung – 1 study				
• 1 retrospective cohort [21]	2005 to 2008	82	158 K 16 L 13 LG	Primary graft non-function of kidneys: 9 %
				Rejection rate of kidneys: 9 %
				Acute rejection rate of liver: 25 %
				No outcomes reported for lungs

cDCD controlled donation after circulatory of death, *DBD* donation after brain death, *uDCD* uncontrolled donation after circulatory death, *K* kidney, *L* liver, *NR* not reported, *LG* lung

[a]Gangandeep did not report number of recipients and Fieux 2009 reported outcomes for 24/31 recipients. (Complete outcome data can be found in Additional file 3)

[13, 24, 26]. However, short- and medium-term graft and patient survival are improving considerably based on the results of the most recent study [26]. (Complete outcome data can be found in Additional file 3).

Discussion

uDCD is a complex and labour-intensive process. Although there has been an extended experience with uDCD in Spain, pioneering the strategy with seven programs, the

international experience remains at an early stage of development and thus critical analysis and summative evaluation are difficult. The purpose of this review was to assemble and evaluate the uDCD guidelines and outcomes in order to inform the medical, ethical, legal, and logistic issues to be addressed in the ongoing development of future protocols and health policy. We summarize two sources to inform practice: international guidelines and transplant outcome reports. We have created an illustration of the clinical pathway and timelines that describe the process (Fig. 2).

Several countries in Europe (France, Italy, Scotland, Spain, and Switzerland) have guidelines for uDCD. In North America, after several failed attempts to implement this strategy [35], New York City is the only area to have developed uDCD guidelines. Assessment of uDCD guidelines by using the AGREE II appraisal process revealed that although most of the guidelines scored well in relation to the domains of "Scope and purpose", "Stakeholder involvement", and "Clarity of presentation", improvements were necessary in the domains of "Rigour of development" and "Editorial independence".

We evidenced wide variability of recommendations regarding the definitions of and time limits associated with death declaration as well as "no flow" and "low flow" periods. The practices associated with ante-mortem or post-mortem intervention, the logistic pathway, and the organ-preserving techniques used throughout process were also inconsistent.

The heterogeneity of the outcome studies prevents any meaningful comparison between programs. With these limitations in mind, it appears that uDCD can provide viable, good-quality organs. There will need to be better consistency and clarity in the reporting of outcomes, standardized definitions of each step of the ischaemia process and higher homogeneity of follow-up times for both graft and patient survival.

All of the reviewed guidelines included specific concerns with ethical, legal, and logistic implications. Many authors [5–7, 9, 22, 23, 31, 35–53] have pointed out that protocols for uDCD entail specific challenges. These issues, if unresolved, may hinder further worldwide development of uDCD strategy [9]. Specifically, authors have expressed concerns with respect to irreversibility of cardiac arrest, cannulation of the potential donor for the purpose of organ preservation without prior consent, possible re-establishment of oxygenated reperfusion of the brain after declaring death, and potential conflict of interests between resuscitation attempts and organ-preserving measures. Some authors have recommended a clarification of the abovementioned concerns before the further implementation of protocols for uDCD [6, 37, 41, 42, 44], whereas others have called for a moratoria in currently active protocols [43]. A bundle of novel therapies are in evolution for treating selected patients suffering from a refractory cardiac arrest (e.g., extracorporeal resuscitation and support, percutaneous coronary intervention, intra-aortic balloon pump, thrombolysis, and mild hypothermia, all deployed during or early after resuscitation attempts). Results, where this approach has been already implemented, are encouraging in terms of long-term survival with good neurologic recovery in some of these patients [54–63]. The availability of these interventions poses potential conflicts of interest between life-saving and organ-preserving strategies [41, 42, 46]. Some of us [7, 51, 64, 65], and many other authors [38–42, 46, 48, 49, 53, 66], have suggested different approaches, seeking to save lives, when still feasible, but providing also the option of organ donation when all lifesaving clinical efforts have been exhausted. Thus, a joint venture between clinical and research communities in transplantation and resuscitation should combine both strategies in order to improve resuscitation outcomes while expanding uDCD.

This systematic review has several limitations. Although organisations provided us with draft protocols or guidelines for uDCD, only fully developed guidelines were included in the review, reducing the overall scope of guidelines to assess. The AGREE II appraisal process was used to assess the quality of guideline development. Though well supported, this tool is not the only accepted method for this purpose. The lack of homogenous data from the studies reporting transplant outcomes also precluded a meta-analysis and prevented the linking of outcomes to specific protocols used for the uDCD process.

Conclusions

To the best of our knowledge, this is the first systematic review to compare the worldwide variability in practices, protocols, and transplant outcomes for uDCD in order to inform future protocol development and health policy. We conclude that uDCD is a viable option for increasing the organ donation pool. Despite variations in practice and heterogeneity of outcomes, uDCD yields success in kidney, liver, and lung transplantation. The implementation of uDCD has significant medical and logistic complexities, and international leaders should be recognized for their efforts. Depending on regional perspectives, there are a number of procedural, medical, legal, and ethical challenges that include definitions of refractory cardiac arrest, time limits for organ ischaemia, timing and type of consent required, determination of death, and organ-preserving interventions. Given the limited levels of evidence on which the current guidelines are based as well as the lack of both standardized definitions and processes between guidelines, it is not possible to recommend one protocol over another. Further standardization of guidelines and outcomes is

required. Further research is required into the role of extracorporeal resuscitation and other novel therapies for treatment of refractory cardiac arrest of cardiac origin. The maintenance of trust by health professionals and by the public is recognized as a key point for the long-term success and widespread implementation of the valuable and promising uDCD strategy.

Key messages

- The uDCD is a viable option for increasing the organ donation pool, yielding success in kidney, liver, and lung transplantation.
- Depending on regional perspectives, there are a number of procedural, medical, legal, and ethical challenges such as definitions of refractory cardiac arrest, time limits for organ ischaemia, timing and type of consent required, determination of death, and organ-preserving interventions.
- Current guidelines for uDCD are based on limited levels of evidence
- Standardization of definitions and processes would avoid the current existing variability in practices and heterogeneity of outcomes
- The maintenance of trust by health professionals and by the public is a key point for the long-term success and widespread implementation of the uDCD strategy.

Additional files

Additional file 1: Guideline assessment with AGREE II (Appraisal of Guidelines for Research and Evaluation II) tool.

Additional file 2: Quality assessment with Downs and Black scale.

Additional file 3: Outcomes of included studies.

Abbreviations

AGREE: Appraisal of Guidelines for Research and Evaluation; cDCD: Controlled donation after circulatory death; CPR: Cardiopulmonary resuscitation; DCD: Donation after circulatory death; ECMO: Extracorporeal membrane oxygenation; h-ECMO: Hypothermic extracorporeal membrane oxygenation; IHCA: In-hospital cardiac arrest; n-ECMO: Normothermic extracorporeal membrane oxygenation; OHCA: Out-of hospital cardiac arrest; uDCD: Uncontrolled donation after circulatory death; WLST: Withdrawal of life-sustaining therapies.

Competing interests

LH is a paid research consultant for Canadian Blood Services. The authors declare that they have no competing interests.

Authors' contributions

IO-D and LH carried out the systematic review, conceived of the protocol, and drafted the manuscript. SDS participated in its design and supervised and reviewed the whole process. All authors critically reviewed and approved the final manuscript.

Acknowledgements

We thank Patricia Fontela, Alex Amar, Ingrid Soto, David Rodriguez-Arias, Anne-Marie Lagacé, and the team from the Centre de Prèlévement d'Organes at the Hôpital du Sacré-Coeur de Montréal, Canada, for their suggestions, comments, and support during the conception and revision of this manuscript. This manuscript would not have been possible without the continued support of the staff at Canadian Blood Services, including Sylvia Torrance and Kimberly Young. IO-D was financially supported by a predoctoral research grant from Fundación "La Caixa", Barcelona, Spain. This systematic review is part of his PhD project. He also received the Phyllis and Albert Sussman Accommodation Subsidy for a stay at The Hastings Center (Garrison, NY, USA) while he participated in the writing of this systematic review.

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Received: 27 March 2015 Accepted: 12 June 2015
Published online: 24 June 2015

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ANEXO IV

Cuarto artículo

Éthique et santé (2015) 12, 156—165

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ARTICLE ORIGINAL

Le débat bioéthique sur le don d'organes : est-ce que tout s'arrête lorsque le cœur cesse de battre ?

The bioethical debate on organ donation: Does it end when the heart stops beating?

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Disponible sur Internet le 31 août 2015

MOTS CLÉS
Don d'organes ;
Don non contrôlé ;
Détermination de la mort ;
Mort circulatoire ;
Mort neurologique ;
Réanimation ;
Arrêt cardiaque ;
Bioéthique ;
Urgences préhospitalières

Résumé Déterminer le moment exact où se produit la mort humaine a été un défi constant tout au long de l'Histoire. Hélas, généralement la mort ne survient pas de manière abrupte, à un moment précis ni à toutes les parties de l'organisme de façon simultanée. La résistance des cellules humaines à la dégradation due à une privation d'oxygène varie en fonction du type de cellule. Il est possible, par exemple, de greffer avec succès les cornées d'un défunt jusqu'à sept jours après qu'il soit déclaré mort. En fait, l'absence absolue de toute activité résiduelle dans l'organisme ne pourrait se confirmer que beaucoup plus de temps après la perte du pouls, une fois que le processus de putréfaction est généralisé. Naturellement, il est peu souhaitable d'attendre jusqu'à ce moment-là pour pouvoir enfin déclarer la mort d'un individu. Nous, les personnes, avons des raisons pour déclarer la mort beaucoup plus tôt. Par exemple, nous avons besoin de faire le deuil et de ne pas repousser les rites funéraires en excès. Traditionnellement, pour s'assurer que la mort des malades était bien réelle, on attendait plusieurs jours avant

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http://dx.doi.org/10.1016/j.etiqe.2015.06.001

de procéder à l'inhumation. De telles mesures de précaution s'avéraient un peu risquées en périodes d'épidémie, parce que les cadavres sont un vecteur dans la transmission de maladies. D'après Winslow, la peur d'être enterré vivant augmentait pendant ces périodes. De nos jours, il y a d'autres raisons qui nous poussent à déclarer la mort plus tôt. Par exemple, l'accès à des lits de soins de santé pour des patients avec pronostic de récupération qui attendent la ressource rare et la possibilité de sauver des vies grâce au don d'organes. D'un côté, il n'est pas permis d'extraire des organes vitaux à des personnes en vie, mais, de l'autre, attendre trop longtemps pourrait compromettre la qualité des organes à extraire et les probabilités de succès du greffon. Les problèmes théoriques et pratiques issus de la déclaration de la mort dans le contexte du don d'organes ont leur origine dans le défi d'obtenir des organes en conditions optimales sans que cela n'affecte la fin de vie des donneurs potentiels.

KEYWORDS
Organ donation;
Uncontrolled donation after circulatory determination of death;
Determination of death;
Circulatory death;
Brain death;
Resuscitation;
Cardiac arrest;
Bioethics;
Prehospital emergency care

Summary To determine when exactly human death occurs has been a constant challenge throughout history. Usually the death does not occur abruptly, at a specific time or to all parts of the body simultaneously. The resilience of human cells to degradation because of oxygen deprivation varies depending on the cell type. It is possible, for example, to successfully graft the corneas of a deceased up to seven days after death. In fact, the absolute absence of any residual activity in the body could not be confirmed before a long period after absence of pulse, once the putrefaction process is widespread. Naturally, it is undesirable to wait until that time to finally declare death of an individual. The whole society and human beings have many reasons to declare the death much earlier. For example, we need to begin the mourning process and not to delay the funeral rites in excess. Traditionally, to ensure that death actually happened, people waited several days prior to burial. Such precautions proved a health public issue in times of epidemics, because the corpses are a vector in the transmission of diseases. According to Winslow, fear of being buried alive increased during these periods. Nowadays, there are other reasons that lead us to declare death earlier. For example, access to health care resources for patients with a better prognosis, facing scarce means and considering the possibility of saving lives through organ donation. On the one hand, it is not possible to extract vital organs to living people, but on the other, waiting too long could compromise the quality of organs to be extracted and the probability of success of the transplant. The theoretical and practical problems arising from the declaration of death in the context of organ donation have their origin in the challenge of obtaining organs in optimal conditions without affecting the end of life care of potential donors.

D'après la Commission européenne, plus de 60 000 personnes en Europe sont dans l'attente d'une greffe et chaque jour 12 de ces patients en listes d'attente décèdent. Le besoin de répondre à l'urgence croissante — souvent vitale — de ceux qui sont dans l'attente d'un organe explique le recours à des solutions créatives pour l'obtention d'organes, ainsi qu'une partie des enjeux éthiques que soulève le don d'organes actuellement. Ces enjeux se caractérisent par la difficulté d'arriver à des compromis acceptables entre la maximisation du bénéfice pour les récepteurs et le respect de certaines valeurs amplement partagées, telles que la sécurité et l'intégrité des donneurs, ou encore le respect des décisions individuelles [1—3]. Chaque pays a mis en place des stratégies spécifiques pour faire face au problème global du manque d'organes. Parmi eux, l'Espagne est très réputée internationalement par sa capacité prouvée à obtenir et greffer des organes avec succès [4,5]. Une des stratégies adoptées par l'Espagne, qui la rend pays pionnier en la matière et sur laquelle elle base son succès, est le don en asystolie (DA) ; plus concrètement, les « *protocoles de don après déclaration du décès suite à un arrêt circulatoire non contrôlé* » (aussi appelés « *Maastricht II* »). Ces protocoles se différencient de ceux qui ont lieu après décès cardiocirculatoire contrôlé [6] (Maastricht III) dans le fait que les patients sont victimes d'un arrêt circulatoire inattendu, généralement hors de l'hôpital.

Protocoles don d'organes existants dans le monde de décès cardiocirculatoire

Les États-Unis, le Canada, le Royaume-Uni et les Pays-Bas, entre autres, ont plus d'expérience dans les protocoles Maastricht III (mis on œuvre dans le milieu hospitalier et caractérisés par une décision de retrait des traitements

de maintien des fonctions vitales [TMFV], qui mène à un arrêt circulatoire attendu). Ces protocoles ont commencé à s'implanter aussi en Espagne [5]. Ces deux types de protocoles posent de problèmes éthiques spécifiques [7—9] sur lesquels nous ne pourrons pas nous attarder ici. Depuis les années 1990, il existe une grande quantité de publications étrangères autour des aspects bioéthiques du don en asystolie (DA) après déclaration du décès suite à un arrêt circulatoire contrôlé [10].

Absence de débat bioéthique sur les programmes de don d'organes après décès cardiocirculatoire non contrôlé

En revanche, on peut encore dire qu'il n'existe pas de débat éthique équivalent autour du don d'organes après décès cardiocirculatoire non contrôlé et, pourtant, quelques-uns de ces patients auraient pu bénéficier de certaines mesures non conventionnelles de réanimation cardio-respiratoire (RCR-NC) avant d'abandonner définitivement la RCR et commencer à les traiter comme donneurs potentiels. Nous ne voulons pas insinuer que le processus du don en lui-même enlève des opportunités de survie à ces patients, mais qu'il existe certainement quelques opportunités et elles ne sont pas proposées.

D'un autre côté, nous y affirmons que les mesures actuellement en place pour la préservation des organes de ce type de donneur pourraient avoir la fonction, inattendue et non intentionnelle, de préserver — voire rétablir — les fonctions cardiaque et neurologique chez ces individus, comme il est en effet déjà arrivé par le passé [11,12].

La conclusion qui se dégage logiquement de ces deux affirmations est que quelques-uns de ces donneurs pourraient ne pas satisfaire aux critères établis par la loi pour le diagnostic de la mort (ni le critère neurologique ni le critère cardiocirculatoire). Nous y en concluons également — en accord avec d'autres auteurs sur ce point là — que, dans des cas très concrets et en fonction de l'étendue des dommages neurologiques du donneur, il ne peut pas être exclu que l'individu préserve une certaine capacité d'éprouver une forme de souffrance pendant ce processus là [13—15]. Cette possibilité serait exclue — ou au moins réduite au maximum — avec l'insertion d'un ballon obturant l'aorte au niveau surrénal qui empêcherait le sang oxygéné de circuler jusqu'au cerveau. Cette pratique — qui, en elle-même, ne nous semble pas injustifiable — pourrait cependant être considérée comme une cause proche de la mort du donneur [9,14—16]. Ce point de vue a suscité des opinions très intéressantes à propos du thème, ce qui nous invite à réfléchir en profondeur sur le débat scientifique et bioéthique.

Quelques auteurs argumentent que les protocoles standard de réanimation cardio-respiratoire (30 minutes de RCR avancée, avant d'activer le protocole de don en asystolie préhospitalière) permettent d'établir avec une certitude acceptable l'irréversibilité de l'arrêt cardiaque. D'autre part, ils nient qu'il existe la possibilité que le donneur garde un niveau de conscience ou qu'il éprouve de la souffrance, une affirmation qui, à leur avis, manque de rigueur et contredit toutes les données empiriques et physiologiques dont nous disposons [17]. Enfin, ils affirment qu'insuffler un ballon intravasculaire dans le donneur n'a pas pour objectif d'éviter la reperfusion cérébrale ni de nier rétroactivement la mort, ni n'altère le diagnostic ni le pronostic du donneur [17].

D'autre part, d'autres auteurs mettent en doute que la mise en place systématique de mesures de réanimation non conventionnelles soit appropriée, en particulier dans l'actuel contexte de crise, dû à la contestable relation coût-bénéfice. Ils signalent, plus concrètement, que notre proposition d'étendre la RCR à des mesures non conventionnelles de réanimation pourrait entraîner l'apparition de cas de patients avec des dommages neurologiques graves [4].

Nous considérons que l'existence d'opinions divergentes autour d'un sujet aussi controversé que le don en asystolie est quelque chose d'extrêmement positif. Nous voudrions continuer à enrichir le débat en abordant ainsi quelques questions essentielles sur ce thème.

À quel moment faut-il ne plus considérer l'individu comme un patient et commencer à le considérer comme un donneur potentiel ?

Les services préhospitaliers médicalisés, dont l'Espagne dispose, sont parmi les mieux équipés du monde [18]. C'est justement grâce aux ressources humaines et matérielles dont on dispose au sein des urgences médicales préhospitalières qu'on a pu instaurer en Espagne — contrairement à ce qui se passe dans d'autres pays — avec succès les «*protocoles de don après décès cardiocirculatoire non contrôlé*» (aussi appelés «*Maastricht II*») [5,18]. Quand on clôt les efforts habituels de réanimation (généralement 30 minutes de RCR avancée), si l'individu a été considéré donneur potentiel d'organes, les membres de l'équipe médicale préhospitalière continuent à réaliser des manœuvres sur la victime de l'arrêt cardiaque réfractaire, non pas pour la réanimer, mais pour préserver ses organes (dont la qualité des organes est menacée de façon imminente par le manque de flux sanguin ou ischémie). Mais étonnamment, il y a eu des cas où, contre tout pronostic, ces mesures employées uniquement pour la préservation des organes ont provoqué un rétablissement partiel ou complet des fonctions vitales de certains donneurs [11,12]. Nous ne connaissons pas l'incidence totale de ces cas. Nous rentrerons dans le détail de la portée et les conséquences de ces cas plus tard. La question qui se pose ici est jusqu'à quel point aurait-t-on dû continuer cet effort de réanimation des patients plutôt que de l'interrompre une fois les 30 minutes génériques écoulées.

Les mesures de préservation (massage thoracique et assistance ventilatoire dans un premier temps, et circulation extracorporelle à l'hôpital) pourraient ressembler — sans pour autant être identiques — à celles qui auraient été mises en place dans le but de sauver des vies. Ceci, et le fait que les mesures sont appliquées par les mêmes professionnels des services des urgences médicales, explique que la famille — quand elle n'est pas informée du but de telles interventions — présume que leur être cher continue à recevoir une assistance de type thérapeutique après ces 30 minutes et pendant son transfert en unité mobile hospitalière — ambulance ou hélicoptère — à l'hôpital. Le fait que le constat de décès des donneurs n'est signé, ni en France ni

en Espagne, qu'après l'arrivée à l'hôpital (même s'il pouvait être signé dans la rue, comme c'est le cas pour les individus qui ne deviennent pas donneurs dans les deux pays) pourrait expliquer l'ambiguïté du statut de ces individus entre le moment où les efforts de réanimation sont clos, dans la rue, et le moment où le constat de décès est signé, à l'hôpital.

Quelles sont les conséquences dérivées d'être considérées, simultanément, patient et donneur potentiel ?

Avant l'implantation des « *protocoles de don après décès cardiocirculatoire non contrôlé* » (en 1986 et, plus systématiquement, pendant les années 1990 [5]), tout individu en état d'arrêt cardio-respiratoire était déclaré mort sur place par le médecin du service des urgences si au bout d'un minimum de 30 minutes de RCR avancée on n'arrivait pas à inverser cet état. Cette pratique est toujours habituelle, sauf pour les individus qui répondent à des critères de don en asystolie extrahospitalière [5]. Dans les régions espagnoles avec des hôpitaux ayant mis en place ces protocoles (Madrid, Catalogne, Galice, Andalousie, Castille-La Manche, Cantabrie et Communauté valenciennes), ces possibles donneurs ne sont pas déclarés légalement morts sur place ; on attend leur arrivé à l'hôpital pour le faire. Pendant leur transfert et jusqu'à ce qu'ils sont déclarés morts, ces individus sont dans une sorte de flou juridique. On ne peut pas dire qu'ils soient des patients, puisque les mesures de préservation (compressions thoraciques et ventilation assistée) ont pour seul but celui de préserver leurs organes [5]. Mais il ne s'agit pas non plus de cadavres, puisque leur décès n'a pas été légalement certifié. Ils sont dans une unité mobile hospitalière — ambulance ou hélicoptère — mais on a déjà contacté l'équipe de prélèvement d'organes de l'hôpital pour les prévenir de l'existence d'un candidat au don avant de commencer leur transfert. En fait, à partir du moment où un individu est considéré donneur potentiel, il n'est plus transféré à l'hôpital qui lui correspondrait en fonction de son domicile ou de sa pathologie, mais bien celui avec un programme de don après décès cardiocirculatoire en place [19].

Puisque au bout des 30 minutes de RCR avancée on ne cherche plus à sauver la vie de ces individus, mais uniquement à préserver leurs organes dans les meilleures conditions possibles pour un possible receveur, l'expression la plus adéquate pour parler de ces manœuvres n'est plus « *réanimation cardio-respiratoire basique* », mais « *préservation des organes* » [5]. Si, en effet, le but était (encore) de sauver la vie du patient, ça n'aurait pas de sens de ne plus chercher les possibles causes réversibles de l'arrêt circulatoire [20,21], ni de cesser d'administrer des médicaments vasoactifs (adrénaline) — indiquée dans les manœuvres de réanimation avancée tous les 3—5 minutes — et d'autres fluides [5]. Il est difficile de comprendre également pourquoi ce serait uniquement les individus qui remplissent des critères d'inclusion dans les protocoles de don après décès cardiocirculatoire qui pourraient bénéficier de cette « *RCR basique* ». Le choix de la terminologie n'est absolument pas banal, puisqu'il permet de dissoudre l'ambiguïté du statut vital (vivant/mort) de ces individus (patients ou donneurs) entre le moment où l'on cesse la RCR avancée dans la rue (ou le domicile) jusqu'à ce que le constat de décès soit établi à l'hôpital. Pourquoi les donneurs potentiels ne sont-ils pas déclarés morts — ce qu'on pourrait faire — alors qu'on a déjà décidé que les efforts de réanimation sont futiles ?

Si on n'établit pas plus tôt le constat de décès des donneurs potentiels, ce n'est pas pour des raisons logistiques (manque de personnel qualifié pour le faire) ou techniques (manque d'éléments pour le diagnostic), mais pour des raisons stratégiques. D'un côté, il a été argué que déclarer le décès avant le transfert à l'hôpital obligerait à aborder avec la famille, dans des circonstances peu appropriées, une conversation hâtive sur le don, ce qui pourrait générer un plus grand nombre de refus des familles [5,22,23]. D'un autre côté, transférer en ambulance un cadavre pourrait constituer une infraction à la législation en vigueur de la police funéraire (articles 29 et 41 du décret espagnol 2263/1974, du 20 juillet, approuvant le règlement de la police sanitaire funéraire). Puisque la fonction des véhicules des urgences — ambulance ou hélicoptère — est le transfert de patients — et non pas de cadavres — dans les meilleures conditions à un centre hospitalier, l'utilisation de ces moyens publics avec un but autre que celui pour lequel ils ont été conçus pourrait constituer une cause suffisante et objectivable de responsabilité due à une mauvaise utilisation des ressources publiques (article 106.2 Constitution espagnole et article 139.1 LRJ—PAC, loi sur le régime juridique et la procédure administrative commune en Espagne).

Pour certains auteurs, transférer un donneur à l'hôpital sans fournir des informations véridiques [19] et sans le consentement préalable des proches [16] pourrait poser des problèmes, car cette façon de procéder pourrait entraver le deuil de la famille [24]. Un dernier aspect de cette pratique qui pourrait être objet de débat est qu'elle précise l'emploie de moyens onéreux et rares et elle implique également un possible coût d'opportunité (puisque ces moyens, pendant ce temps-là, ne peuvent pas être employés pour des fins thérapeutiques des urgences préhospitalières) [25].

Certains donneurs potentiels survivent, mais pas la plupart : futilité de la RCR et risque d'acharnement thérapeutique

Malgré le fait qu'il est évident que les mesures pour la préservation des organes ne sont pas les mêmes — ni en termes d'objectifs ni en termes de procédures — à celles employées pour inverser un arrêt circulatoire, il y a eu des cas où le donneur potentiel est arrivé en vie à l'hôpital ; il est même déjà arrivé qu'il ait quitté l'hôpital sans séquelles neurologiques quelques jours plus tard. Malheureusement, on ne dispose que de très peu d'information sur l'incidence de ces cas. Mateos-Rodriguez et al. affirment que des 31 individus transférés en 2009 par leur service des urgences préhospitalières avec des compressions thoraciques — faisant partie du protocole du don —, trois d'entre eux ont retrouvé une circulation spontanée avant leur arrivée à l'hôpital et un d'entre eux a eu un « *bon rétablissement avec fonction neurologique* » [12]. La raison pour laquelle ces cas sont arrivés est peut-être due au fait que les mesures de

préservation (compresseur thoracique mécanique et ventilation) simulent une RCP de très haute qualité [19]. Mateos-Rodriguez et al. concluent que « *si ces individus n'avaient pas été inclus dans le protocole de don en asystolie, la réanimation aurait été interrompue au bout de 30 minutes et les patients n'auraient pas survécu* » [12]. Cette conclusion raisonnable soulève, en même temps, les doutes suivants : ces patients auraient-ils eu un meilleur rétablissement si la réanimation ne s'était arrêtée en aucun moment (en réajustant les objectifs et en mettant la logistique à disposition d'essayer d'inverser l'arrêt cardiaque du patient) pendant leur transfert à l'hôpital, c'est-à-dire si l'on avait continué à tout moment de tout mettre en œuvre pour préserver leurs fonctions vitales, et pas seulement leurs organes ? Comment peut-on concevoir que d'autres patients qui sont devenus donneurs auraient pu bénéficier de telles mesures ?

Les progrès dans le domaine de la médecine offrent des nouvelles possibilités pour inverser des circonstances qui étaient, encore récemment, irréversibles. L'escalade procédurale et thérapeutique est potentiellement illimitée, ce qui rend nécessaire la mise en place d'une limite. Quelques réussites ne justifient pas une politique de santé qui exige des efforts maximalistes, systématiques et déraisonnables pour réanimer toutes les victimes d'un arrêt cardiaque [4]. C'est quelque chose de fondamental. Ainsi, comme les professionnels des soins intensifs ont réussi à contrer petit à petit le mythe selon lequel sauver des vies à tout prix est le seul objectif de leur profession [26], les professionnels des urgences préhospitalières savent aussi que la mort de quelques-uns de leurs patients n'est pas nécessairement synonyme d'échec professionnel [19]. Il y a des patients à qui on ne peut pas et on ne doit pas offrir (par exemple, dans le cas du triage dans les situations de nombreuses victimes ou des catastrophes) d'alternative thérapeutique [19]. La qualité de vie et la justice distributive, malgré la difficulté de définir de tels concepts, sont des critères dont il faut tenir compte et qui pourraient justifier une limitation de l'effort thérapeutique [4].

Quand un individu est victime d'un arrêt cardiorespiratoire, il risque d'être soumis à des dommages neurologiques d'importance variable, qui pourraient être totaux (décès neurologique). L'étendue de ce dommage et la rapidité à laquelle il survient dépendent de facteurs aussi hétérogènes que la cause et le type d'arrêt, le préalable état de santé de l'individu, le temps de réponse du service préhospitalier d'urgence, la qualité de la réanimation fournie, l'âge du patient ou même la température ambiante ou corporelle. Il est difficile de deviner au préalable les patients qui vont se rétablir et ceux qui ne le feront pas. À notre avis, quand on sait qu'il n'y a pas de possibilité de retrouver la conscience (ou cette possibilité est tellement lointaine qu'elle est négligeable), continuer la réanimation pourrait être éthiquement moins justifiable que de laisser mourir ce patient [19,26]. Mais il y a de plus en plus de preuves indiquant que certains patients pourraient en effet bénéficier de ces procédures [27—33]. Afin de discerner quels patients devraient être candidats à une RCR-NC et quels patients devraient être considérés candidats au don, nous avons suggéré le besoin de compter sur un modèle prédictif qui établirait le profil des patients qui pourraient bénéficier de ces techniques [34].

La signification d'« *irréversible* »

La mort circulatoire est définie par la législation espagnole comme « *l'arrêt sans équivoque et irréversible de la fonction circulatoire* ».

Un phénomène irréversible est celui qui ne peut pas revenir à un état ou à une condition antérieurs. Ce concept contraste avec l'adjectif — plus faible — « *permanent* ». La perte permanente de la fonction cardiaque n'est pas celle qui ne peut pas être inversée, mais celle qui ne va pas l'être. Par exemple, parce que l'on a pris la décision consensuelle de ne pas inverser cet état. Si une personne tombe à l'eau depuis un bateau en pleine tempête et aucun membre de l'équipage ne sait nager, il serait probablement peu judicieux de se jeter à l'eau pour lui sauver la vie. Mais dire que la personne est déjà morte parce qu'on ne fera rien pour la sauver est de toute évidence intenable. Si une condition de fait n'est pas inversée, elle est permanente ; mais si cette condition n'aurait jamais pu être inversée, on dit à ce moment-là qu'elle est irréversible. Le fait qu'inverser un arrêt cardiaque soit peu approprié ou même éthiquement injustifiable n'implique pas que cet arrêt soit irréversible ni, par conséquent, si l'on suit la définition légale de la mort, que la personne soit morte [35].

Pour rendre plus facile l'implantation des protocoles de don après décès cardiocirculatoire (DDC) contrôlé (Maastricht III), plusieurs auteurs ont proposé de changer le concept de « *perte irréversible* » par celui de « *perte permanente* » de la fonction circulatoire. James Bernat — neurologue et défenseur du DDC contrôlé — pense que la notion d'arrêt irréversible peut être valablement remplacée par celle d'arrêt permanent [36]. D'après lui, l'exigence d'irréversibilité n'est pas que la fonction circulatoire ne peut pas être rétablie par personne dans aucune circonstance et à aucun moment, ni même une interprétation plus légère — que la fonction circulatoire ne peut pas être rétablie par les professionnels présents sur le moment et avec les moyens disponibles à cet endroit précis —, mais l'interprétation la plus légère possible de permanence : la fonction circulatoire ne se rétablira pas parce que l'on a pris la décision moralement justifiable de ne pas inverser un état potentiellement réversible. Cette interprétation plus légère d'irréversibilité est-elle scientifiquement et éthiquement acceptable pour déterminer la mort d'un individu ?

Quand quelqu'un souffre d'un arrêt cardiaque en raison d'une limitation de l'effort thérapeutique, cette décision de limitation peut être absolument justifiable, mais cela ne veut pas dire que l'arrêt soit irréversible ni, par conséquent, que le patient soit déjà mort. Le patient va bientôt mourir, mais il ne l'est pas encore, puisque son arrêt est permanent mais pas irréversible [14,35—39]. Un patient ne peut être considéré décédé quand le temps écoulé depuis l'arrêt circulatoire n'est pas suffisant pour garantir que cet arrêt est, en effet, irréversible. D'un point de vue pragmatique, on pourrait dire que ces digressions sont tout à fait hors de propos pour le DDC non contrôlé, plus fréquent en Espagne (Maastricht II), puisque dans ces cas (différents des protocoles Maastricht III), il n'y a pas de limitation de l'effort thérapeutique. L'absence de cette limitation nous semble très douteuse dans les cas où l'on ne propose pas des mesures à disposition pour la

réanimation cardio-respiratoire, mesures qui pourraient ne pas être conventionnelles, mais elles sont thérapeutiques.

Les personnes victimes d'un arrêt circulatoire qui ne reçoivent pas de RCR finissent par évoluer, en un délai bref mais indéterminé de temps, vers un décès neurologique qui empêche la restitution de toute fonction organique significative [40]. Cependant, c'est justement ceci qui n'est pas le cas dans le contexte du DDC non contrôlé, puisque la RCR, dans un premier temps, et les mesures pour la préservation des organes après font obstacle à la progression naturelle de l'arrêt circulatoire vers un arrêt circulatoire irréversible [41] et un décès neurologique [14].

C'est un fait connu que la probabilité de recirculation spontanée après un arrêt circulatoire dépend de la qualité de la réanimation cardio-respiratoire pratiquée au patient, et de si celle-ci est en effet pratiquée.

Ceci est pertinent dans l'évaluation spécifique de la possible inversion de la fonction circulatoire dans les deux types de don en asystolie. Dans l'analyse de la documentation publiée à ce sujet, Hornby et al. concluent que « *nous n'avons pas trouvé d'étude informant de l'apparition de l'autoréanimation en l'absence de RCR* », mais elle a été signalée « *entre quelques secondes et jusqu'à 33 minutes après avoir interrompu une RCR infructueuse* » [41]. Selon eux, la probabilité d'un rétablissement spontané du pouls est plus grande et on a besoin de plus de temps pour pouvoir l'exclure dans les protocoles de don en asystolie non contrôlée que dans l'asystolie contrôlée [41]. Le concept commun d'irréversibilité suggère que, si un organisme cesse de fonctionner mais sa fonction peut être restituée à l'aide d'un dispositif que l'on détient mais qu'on décide de ne pas utiliser, on ne peut pas parler d'irréversibilité, ni, par conséquent, de mort [42]. L'emploi de la notion de permanence pour remplacer celle d'irréversibilité a un autre inconvénient théorique et pratique. Généralement, on assume que la mort est un état de fait, et non pas une évaluation soumise à la façon de traiter l'individu que l'on estime adéquate. Or, si l'on accepte — comme vraisemblablement le font les législations de la plupart des pays du monde, y compris l'Espagne — que la mort est un fait objectif déterminable par des experts (des médecins) et non pas une construction sociale soumise à des décisions morales, le fait qu'une intervention potentiellement salvatrice soit moralement inacceptable ne peut pas être une justification adéquate pour déterminer la mort de quelqu'un. Marquis a argumenté de manière convaincante que l'emploi de « *permanence* » à la place de « *irréversibilité* » — comme Bernat et al. proposent — conduit à des perplexités insurmontables dans la pratique. Tandis que « *irréversible* » est appliqué à des phénomènes absolument inaltérables (par exemple, la mort), « *permanent* » est une propriété contingente qui dépend de facteurs contextuels tels que la disponibilité de ressources humaines, la volonté d'inverser une situation ou, comme c'est le cas dans le DDC contrôlé, la morale existante conformément à laquelle on ne doit pas essayer de réanimer ces patients [35]. Une des conséquences de permettre que les arguments moraux déterminent le diagnostic clinique de la mort est que deux personnes qui partagent une même condition médicale pourraient se trouver dans des états vitaux différents en fonction des volontés de leurs médecins ou de la contingence d'un consensus moral dominant. Un autre point étonnant qui résulte du fait d'avoir accepté que la perte permanente de la fonction circulatoire remplace la notion de perte irréversible, c'est que les patients déclarés morts selon des critères de mort cardiaque après 75 secondes d'arrêt cardiocirculatoire ont pu devenir des donneurs de cœur (*sic*) [43]. Robert Veatch a ironiquement qualifié ces cas avec l'expression « *inverser l'irréversible* » [39]. Au-delà de ces débats, qui malgré le fait d'être conceptuels ont bien des implications pratiques, si pendant un protocole de DDC le patient retrouve son pouls, ce fait prouve par lui-même que l'arrêt n'aurait jamais dû être qualifié d'irréversible (ni le patient, donc, décédé selon le critère circulatoire).

Nous tenons à souligner que ce ne serait pas justifiable, ni même pas possible, de réanimer de manière maximaliste tous les patients « *aux dépens de ce qui pourrait arriver* ». Nous rejetons catégoriquement et ouvertement la possibilité d'agir d'une telle façon. Cependant, il n'est pas souhaitable non plus que certains patients soient en train de ne pas bénéficier des possibilités réelles de survie avec une bonne qualité de vie si les moyens humains et techniques, ainsi que les connaissances médicales pour y parvenir existent. Or, la nécessité de développer un modèle prédictif s'impose pour pouvoir sélectionner, parmi les différents patients en arrêt cardiaque, seulement ceux qui seraient plus susceptibles de bénéficier individuellement d'une RCR non conventionnelle [34].

Vers une utilisation adéquate et soutenable des mesures non conventionnelles de réanimation cardio-respiratoire

Plusieurs études récentes montrent des pourcentages non négligeables (et, en tout cas, très au-dessus des pourcentages traditionnels) de survie avec une bonne qualité de vie de patients sélectionnés dont le profil et l'étiologie entraient dans le cadre d'une réanimation cardio-respiratoire non conventionnelle (RCR-NC) [27—33]. On sait, par exemple, qu'autour de 70 % des arrêts cardiaques préhospitaliers pourraient bénéficier d'un cathétérisme cardiaque d'urgence puisqu'ils seraient causés par une même maladie coronarienne. Également, il a été prouvé que 54 % des arrêts non causés par une maladie coronarienne pourraient aussi bénéficier de cette technique si une telle intervention était proposée aux patients à leur arrivée à l'hôpital [44]. Même si Dumas et al. ont inclus dans leur longue série uniquement des patients qui ont retrouvé leur pouls après la RCR, Bonnemeier et al., eux, ont trouvé des pourcentages de survie proches à 50 % avec CPC1—2 (sans séquelle neurologique majeure) sur des patients sélectionnés avec des critères d'âge très amples, allant jusqu'à 81 ans [32].

Les décisions sur la réanimation d'urgence en dehors de l'hôpital — ou dans n'importe quel autre service — doivent tenir compte les meilleures évidences disponibles. Actuellement, plusieurs pays emploient déjà des techniques de RCR-NC, telles que la thrombolyse pendant la RCR, la coronarographie d'urgence pendant la RCR, la circulation extracorporelle avec oxygénateur à membranes (ECMO) pendant la RCR, l'hypothermie thérapeutique ou la combinaison de plusieurs de ces techniques [27—33]. En Espagne, jusqu'à présent, les protocoles ne prévoient pas qu'un donneur

potentiel d'organes bénéficie de telles interventions, malgré le fait que certains d'entre eux pourraient en bénéficier.

Les causes potentiellement réversibles des arrêts cardio-respiratoires sont également identifiées, ainsi que le profil des patients qui pourraient bénéficier — de par leur pathologie ou le type d'événement qui leur est arrivé — de ce type de RCR-NC.

Un bilan coût-bénéfice positif pourrait être atteint si les professionnels des urgences et soins critiques sélectionnaient parmi tous ces individus (en fonction de l'étiologie de l'arrêt cardiaque, la situation clinique et les antécédents) ceux qui doivent être traités comme patients et ceux qui devraient devenir candidats au don [34,45—49]. Nous partageons l'avis de Corsiglia selon lequel les programmes de réanimation cardio-respiratoire non conventionnelle et les protocoles de DDC peuvent et doivent coexister, n'étant absolument pas exclusifs, mais complémentaires [34,50,51]. Le don doit être subordonné à l'échec de la meilleure réanimation disponible pour chaque patient. C'est uniquement après avoir réalisé, sans succès, tous les efforts disponibles — non seulement scientifiquement indiqués mais aussi éthiquement justifiables — qu'il faudrait considérer une victime d'un arrêt cardiaque comme donneur potentiel d'organes, avec l'objectif socialement souhaitable de donner la vie au-delà d'une mort inévitable. Si l'on suit, donc, la branche du protocole de DDC que nous proposons, la préservation de ces organes se ferait aussi avec d'excellents critères de qualité, puisque les moyens techniques mis en place et la logistique du programme marcheraient dans une course contre le temps, tout en réduisant au maximum le temps d'ischémie chaude des organes, dont les effets ont été prouvés délétères pour la qualité et l'efficacité de la greffe sur le receveur final de l'organe. Si, en plus, on informe la famille de façon honnête et en toute transparence de la raison du transfert de la victime, conformément à la déontologie et à la réglementation en vigueur, une bonne partie des questions éthiques, légales et de gestion ici identifiées seraient, à notre avis, résolues.

Les critères pour différencier, parmi les victimes d'un arrêt cardio-respiratoire, les patients et les potentiels donneurs doivent être clairs et transparents, faire l'objet d'un consensus éthique, et être basés sur de l'évidence actualisée. Ainsi, nous proposons, sur la Fig. 1, un protocole qui inclut l'option d'une RCR-NC qui améliore les possibilités de survie de patients sélectionnés victimes d'un arrêt cardiaque inattendu, sans pour autant enlever des candidats potentiels au DDC, sauf pour ceux désormais rétablis. Le protocole proposé est en accord avec les connaissances et évidences les plus actuelles et il ne nécessite que des moyens techniques et humains déjà disponibles. Il essaie d'établir les priorités de gestion et assistance qui devront régir tout service d'urgences médicales : premièrement, sauver la vie des patients en état critique, en cherchant leur rétablissement sans séquelles ; deuxièmement, et uniquement quand ce qui précède n'est pas possible, donner la vie, avec une bonne qualité de vie, aux receveurs d'organes [34].

Ne pas subordonner le don à l'échec du meilleur standard de réanimation disponible génère le risque de considérer comme des donneurs certains patients qui non seulement ne sont pas morts (puisqu'ils ne présentent pas une condition irréversible), mais aussi qui pourraient avoir des opportunités de rétablissement avec une bonne qualité de vie si on leur propose des moyens techniques et d'assistance qui ne sont loin de ceux qui sont utilisés pour le processus de préservation et de don [34,50—53]. Faire appel au don quand il y a encore une indication pour réaliser une RCR non conventionnelle pose le problème légal de traiter comme des donneurs d'organes des personnes que l'on ne peut pas considérer décédés [52]. L'état actuel des choses a donné lieu à des cas où des patients, prématurément traités comme donneurs, ont récupéré totalement ou partiellement leurs fonctions vitales. On peut raisonnablement prévoir que ces cas continueront à se produire si des changements ne sont pas introduits dans le sens de notre proposition. Par ailleurs, on pourra toujours raisonnablement soupçonner que d'autres patients et donneurs auraient pu retrouver une vie avec une bonne qualité de vie si l'on en avait fait plus pour traiter les causes de leur arrêt et pour préserver leurs fonctions neurologiques, et pas seulement leurs organes [50—53].

Nous trouvons extrêmement préoccupant le risque que certains patients, résultant de l'application de mesures non conventionnelles de RCP, finissent par trouver leurs fonctions circulatoires mais avec des graves séquelles neurologiques.

Nous trouvons que celle-ci est la plus importante objection à notre proposition, et nous ne voulons pas lui enlever son importance. Nonobstant, il faut rappeler, d'un côté, que ce risque n'est pas spécifique à notre proposition, puisque toute RCR y fait face, sans pour autant ne plus prendre en compte leur potentiel pour sauver des vies en la réalisant sur des patients à qui, selon des critères scientifiques et éthiques, doivent la recevoir. Les services préhospitaliers d'urgences et des soins critiques qui reçoivent ces patients disposent déjà de protocoles qui ont fait l'objet d'un consensus autour de l'abstention ou la limitation de l'effort thérapeutique en cas de futilité [20,21] basés sur des standards scientifiques, éthiques (par exemple, le besoin d'avoir une prise collégiale de décisions, prendre en compte les instructions préalables, s'il y en a, ainsi que les décisions de la famille) et respectueux des lois [54—56].

Quel est l'état neurologique des donneurs après décès cardiocirculatoire non contrôlé ?

On affirme que certains donneurs en asystolie pourraient conserver une possibilité d'éprouver de la douleur suite à l'emploi de la recirculation normo-thermique dans le but de la préservation des organes. Ce risque, reconnu par le groupe d'experts désignés par la Health Resources and Services Administration des États-Unis, y compris Bernat lui-même [14], résulte du fait que la mort cérébrale et la mort circulatoire ne sont pas nécessairement impliquées l'une dans l'autre ; la première ne nous mène pas nécessairement à la deuxième et vice-versa [8,40]. Ceci donne lieu à la possibilité que les cerveaux des donneurs qui remplissent les critères légaux de mort circulatoire ne sont pas totalement et irréversiblement détruits pendant le processus de don en asystolie. Le manque d'unité entre les notions de décès neurologique et de mort cardiocirculatoire est à la base de ce problème qui a d'importantes implications pratiques. Pour commencer, il n'y a même pas d'unité dans le diagnostic

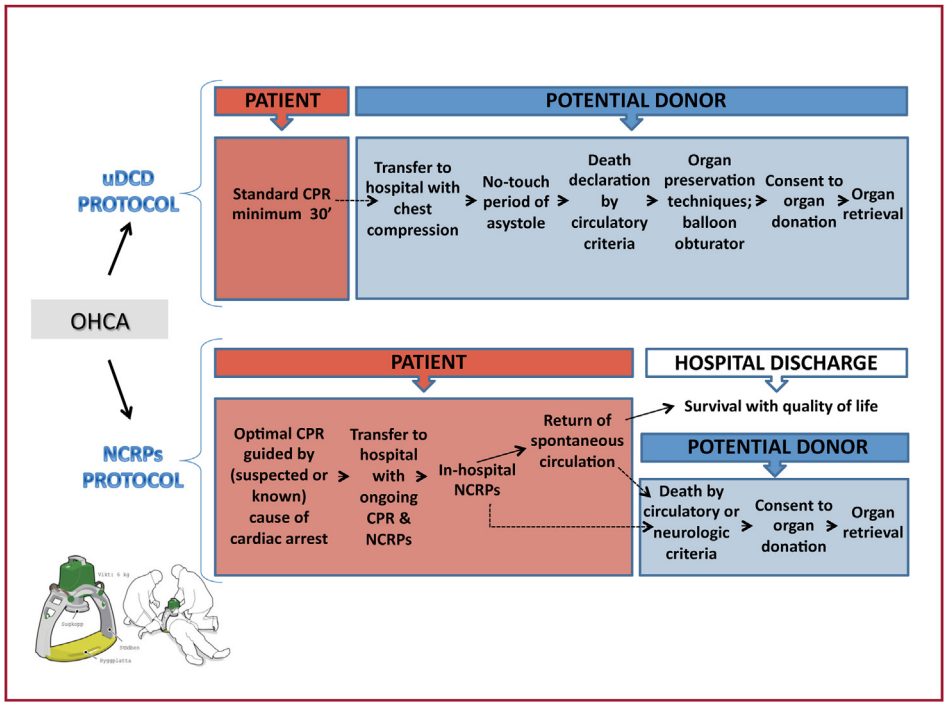

Figure 1. Prise en charge des victimes d'arrêt cardiaque inattendu. uDCD : don d'organes non-contrôlée (Maastricht II) ou don d'organes après un arrêt cardiaque ; NCRPs : réanimation non conventionnelle.

des deux conditions : les tests instrumentaux nécessaires pour déterminer la mort cérébrale ne sont pas exigés par la loi, ni pratiqués, pour le DDC, puisque la perte irréversible des fonctions circulatoires est légalement considérée comme un critère suffisant pour déterminer la mort. Dans le DDC, on procède à une exploration clinique de l'état neurologique des donneurs, qui est elle-même moins exhaustive que l'exploration en cas de décès neurologique, qui requière des tests instrumentaux confirmatoires (décret royal espagnol 2070/1999).

Des doutes existent pour savoir si les périodes d'attente des protocoles de DDC actuels suffisent pour garantir la perte totale des fonctions cérébrales — c'est-à-dire, si la perte desdites fonctions est vraiment irréversible — surtout parce qu'on peut diagnostiquer la mort en l'absence d'une lésion cérébrale préalable [57]. Dans les deux protocoles de DDC, on suppose que pendant la période entre l'arrêt de la fonction circulatoire et la détermination de la mort a lieu la perte également irréversible de toutes les fonctions cérébrales [58]. Ces protocoles ne violeraient pas la règle du donneur mort (*dead donor rule*) si la perte de circulation équivalait à la perte irréversible de la fonction cérébrale. En fait, c'est bien le cas (même si ce n'est pas immédiat) quand on n'essaie pas de rétablir l'activité cardiaque ou la circulation [36]. Or, l'activité cérébrale peut être restaurée si on commence à mettre en œuvre les moyens adéquats. Cela est d'autant plus important qu'on ne sait pas la durée maximale qui peut s'écouler entre le moment où le cerveau ne reçoit plus de sang oxygéné et le rétablissement du flux sanguin avant la perte des fonctions neurologiques responsables de la conscience et de la cognition ? Malheureusement, cette question cruciale n'a pas encore de réponse [40]. La seule preuve empirique que l'on possède à ce sujet est issue des modèles animaux. Ces études indiquent la possibilité de succès dans la restauration de la fonction cérébrale normale jusqu'à 11 minutes après l'arrêt circulatoire [59]. L'utilisation de l'ECMO dans ces protocoles peut avoir la fonction, non intentionnelle, de restaurer une certaine fonction cérébrale sur le donneur en rétablissant le flux sanguin au cerveau après avoir déclaré l'individu mort selon le critère circulatoire. Bernat et al. ont reconnu ce problème ; l'emploi de l'ECMO sur le donneur (DCD) crée un problème pour la détermination de la mort à caractère rétroactif, puisqu'il annule la justification physiologique pour déclarer le décès (DCD) du donneur cadavérique. L'ECMO, en permettant la reperfusion du cerveau et, ainsi, en prévenant sa destruction, interrompt la progression autrement inévitable de la perte permanente de la circulation et de la respiration de manière irréversible. La restauration de la circulation cérébrale suggère en plus la possibilité d'une sorte de capacité de conscience maintenue chez les donneurs et, donc, leur potentiel d'éprouver de la douleur [14].

Si la mort circulatoire et la mort cérébrale ne sont pas nécessairement — mais uniquement contingentement — associées (le cerveau peut continuer à fonctionner malgré le fait que le cœur ait arrêté irréversiblement de battre spontanément), la perte de la circulation n'est pas toujours un bon indicateur du décès neurologique.

Le fait que l'arrêt circulatoire mène nécessairement, et dans un bref délai de temps, à la destruction cérébrale est seulement vrai quand les individus victimes d'un arrêt cardiaque ne sont pas réanimés. Une fois que l'on abandonne la RCR et que l'on arrête d'intervenir sur cet individu, en principe rien n'empêche que l'arrêt du flux sanguin au cerveau finisse par produire une anoxie massive, causant le décès neurologique. C'est pour cela que le critère circulatoire est

toujours valide dans la plupart des morts. Mais pas pour les donneurs potentiels d'organes, qui continuent à recevoir des interventions qui, tout en étant conçues pour préserver leurs organes, sont susceptibles de conserver le flux de sang oxygénée au cerveau. Les protocoles de DDC ont mis en cause la présomption traditionnelle que la mort est un concept unifié et que les deux critères pour le diagnostic de la mort sont interchangeables [15].

Pour éviter la possibilité de restituer les fonctions cérébrales à quelqu'un déjà déclaré mort, il est courant de prendre de mesures afin de bloquer l'aorte, en restreignant la perfusion aux organes et en l'excluant ainsi au cerveau [5,14,16].

Dans le document de consensus sur le DDC publié par la Organización Nacional de Transplantes en 2012 [5], il est dit : « *Il convient également d'insérer un cathéter à ballonnet au niveau de l'aorte thoracique descendante pour éviter la perfusion coronaire et cérébrale, puis une hypothétique récupération de l'activité cardiaque et cérébrale.* » Cette déclaration coïncide avec l'opinion d'experts étrangers qui conseillent l'insertion du cathéter pour éviter le flux cérébral [14,60].

Reconnaître que le blocage de l'aorte remplit cette fonction amène à reconnaître que l'effet possible d'une telle intervention est la causalité du décès neurologique. À notre avis, admettre ceci n'implique pas de juger cette mesure comme éthiquement injustifiable car, en fait, cela peut protéger le donneur de dommages. Par contre, ceci implique certainement le fait de reconnaître que le patient — gravement malade et probablement inconscient — n'est pas encore mort, du moins selon les critères neurologiques.

Déclaration d'intérêts

Les auteurs déclarent ne pas avoir de conflits d'intérêts en relation avec cet article.

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Universidad de Alcalá

ANEXO V

Quinto artículo

Resuscitation 101 (2016) 12–20

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review article

Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: A systematic review of international practices and outcomes☆

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ARTICLE INFO

Article history:
Received 4 August 2015
Received in revised form 5 November 2015
Accepted 21 January 2016

Keywords:
Extracorporeal resuscitation
Out-of-hospital cardiac arrest
Refractory cardiac arrest
Cardiopulmonary resuscitation
Deceased organ donation
Anoxic brain injury

ABSTRACT

Aim: Extracorporeal resuscitation during cardiopulmonary resuscitation (ECPR) deploys rapid cardiopulmonary bypass to sustain oxygenated circulation until the return of spontaneous circulation (ROSC). The purpose of this systematic review is to address the defining elements and outcomes (quality survival and organ donation) of currently active protocols for ECPR in refractory out-of-hospital cardiac arrest (OHCA) of cardiac origin in adult patients. The results may inform policy and practices for ECPR and help clarify the corrresponding intersection with deceased organ donation.
Methods: We searched Medline, Embase, Cochrane and seven other electronic databases from 2005 to 2015, with no language restrictions. Internal validity and the quality of the studies reporting outcomes and guidelines were assessed. The review was included in the international prospective register of systematic reviews (Prospero, CRD42014015259).
Results: One guideline and 20 outcome studies were analyzed. Half of the studies were prospective observational studies assessed to be of *fair* to *good* methodological quality. The remainder were retrospective cohorts, case series, and case studies. Ages ranged from 16 to 75 years and initial *shockable* cardiac rhythms, witnessed events, and a reversible primary cause of cardiac arrest were considered favorable prognostic factors. CPR duration and time to hospital cannulation varied considerably. Coronary revascularization, hemodynamic interventions and targeted temperature management neuroprotection were variable. A total of 833 patients receiving this ECPR approach had an overall reported survival rate of

Abbreviations: ECPR, extracorporeal resuscitation; ROSC, return of spontaneous circulation; OHCA, out-of-hospital cardiac arrest; CPC, cerebral performance category; GOS, Glasgow Outcome Scale; LOE, level of evidence; ILCOR, International Liaison Committee on Resuscitation; RCTs, randomized controlled trials; TTM, targeted temperature management; IABP, intra-aortic balloon pump; DBD, donation after brain death; cDCD, controlled donation after circulatory determination of death; ELSO, extracorporeal life support organization.

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2016.01.018.

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http://dx.doi.org/10.1016/j.resuscitation.2016.01.018

22%, including 13% with good neurological recovery. Additionally, 88 potential and 17 actual deceased organ donors were identified among the non-survivor population in 8 out of 20 included studies. Study heterogeneity precluded a meta-analysis preventing any meaningful comparison between protocols, interventions and outcomes.

Conclusions: ECPR is feasible for refractory OHCA of cardiac origin in adult patients. It may enable neurologically good survival in selected patients, who practically have no other alternative in order to save their lives with quality of life, and contribute to organ donation in those who die. Large, prospective studies are required to clarify patient selection, modifiable outcome variables, risk-benefit and cost-effectiveness.

Introduction

Sudden cardiac arrest is the main cause of death worldwide in previously healthy people. The global incidence of OHCA in adults is 62 cases per 100,000 persons per year, from which 75 to 85% have a cardiac origin.[1] Despite recent improvements in enhancing successful resuscitation in the prehospital setting, overall outcomes remain poor in most venues.[1] The overall reported survival to hospital discharge is 6% in North America,[1] 9% in Europe, 11% in Australia and 2% in Japan.[2]

Extracorporeal resuscitation deploys a modified form of cardiopulmonary bypass, maintaining circulation until an effective cardiac output can be restored. This technique enhances coronary blood flow and preserves the heart's viability, increasing the chance of ROSC. The supply of oxygenated blood flow to the the body and brain prevents organ dysfunction and increases the likelihood of survival with a good neurological recovery.[3] It is referred to as ECPR for patients in cardiac arrest when conventional resuscitation attempts fail, and it provides oxygenated circulation to extend the time window to diagnose and treat the underlying primary cause of the arrest. In recent years, ECPR has been proposed as an effective therapy not only for in-hospital cardiac arrest, but also for OHCA.[4,5] However, the results have been mixed due to heterogeneity in study populations, interventions and patient follow-up. In OHCA events, adult patients are known to be younger, previously healthy and the cause of cardiac arrest is more likely of cardiac origin. Therefore, these sudden death episodes are potentially more reversible than in patients who suffer an in-hospital cardiac arrest associated with many comorbidities. Given ROSC is not achieved in the majority of refractory OHCAs[1,2] the ECPR strategy may be a final option for these selected patients "*too healthy to die*".[6]

The purpose of this systematic review is to address the defining elements and outcomes (quality survival and organ donation) of currently active protocols for ECPR in refractory OHCA of cardiac origin in adult patients. Further understanding of survival outcomes versus risks of anoxic brain injury and death may inform policy and practices for ECPR and the corrresponding intersection with deceased organ donation and transplantation.

Methods

Design of the study and search strategy

A systematic review of the literature was conducted according to health care reviews from the University of York's Center for Reviews and Dissemination.[7]

Medline (OvidSP), Embase (OvidSP), Cochrane (Wiley) and seven other electronic databases were searched by an expert librarian (EG) from January 1st, 2005 to May 25, 2015 with no language restrictions. Articles identified included variations of the terms ECPR or extracorporeal circulation, found as textwords in the Title/Abstract or MeSH. These were combined with variations of resuscitation, out of hospital, in hospital, cardiac and organ donation terms found in the Title/Abstract or MeSH. We also searched Google Scholar, clinicaltrial.gov, as well as reference lists of included studies, abstracts, unpublished reports, personal libraries (IO-D), professional organization reports and government agency statements on ECPR. Two reviewers (IO-D & LH) extracted main variables. Internal validity and the quality of the studies reporting outcomes and guidelines were assessed. The review was included in the international prospective register of systematic reviews (Prospero, CRD42014015259) (see Additional file 1 for search strategy details).

We used a modified PICOTS format. **P**opulation: adults with refractory OHCA of cardiac origin, who were considered candidates for ECPR; **I**ntervention: ongoing resuscitation during transport, followed by ECPR and other adjuncitve therapies until and/or early after ROSC; **C**ontrol: although most of the selected studies are single-arm studies, conventional resuscitation was compared to the ECPR strategy in applicable studies; **O**utcomes: description of practices based on ECPR protocols applied to the population, survival with quality of life according to a cerebral performance category (CPC) score 1–2 or Glasgow Outcome Scale (GOS) score 4–5 at discharge, and potential organ donation; **T**ime: from January 2005 to May 2015; **S**etting: organizations that produced recommendations or conducted studies consistent with our eligibility criteria.

Eligibility criteria

Studies reporting results from ECPR in adult patients with refractory OHCA of cardiac origin and recommendations for ECPR endorsed by any professional society or health care authority were included. We excluded editorials, reviews, abstracts, letters or personal opinions. Human studies that included patients with cardiac arrest of non-cardiac origin (e.g. trauma, massive bleeding, hypothermia, poisoning, near drowning, etc.) and animal studies were also excluded. Two trained reviewers (IO-D & LH) selected the studies and screened citations, retrieved the full texts and independently reviewed them to assess study eligibility. Disagreements were resolved by consensus or after input of two other expert reviewers (SDS & FB). We used EndNote manager software (EndNote X7.1 version, by Thomson Reuters) to manage the collection of publications. Fig. 1 presents the flow chart study selection process (PRISMA).

Data extraction and quality assessment

Two reviewers (IO-D and LH) extracted data after creating an Excel (Excel version 2013, by Microsoft Office) data collection tool that was piloted in a sample from included studies. The spreadsheet tabulated the following variables: authors, country, setting, year of protocol, methodology, eligibility criteria, number of cases, interventions, timelines, results (survival with quality of life and potential/actual deceased donors) and conclusions.

The internal validity of the studies was assessed (See Table 1) independently by four reviewers (IO-D, LH, SDS & FB) and guideline

Table 1
Characteristics and outcomes of included studies.

Study country, region	Study design	Time period	LOE (quality)	Sample size	Age[a] (years) male %	Cardiac rhythm no. (%)	No flow[b] period (min)	Low flow[b] period (min)	Survival at discharge (or as indicated) no. (%)	Neurological outcome at discharge (or as indicated) no. (%)	Organ donor no. (potential/actual)
Shin et al.[17] Korea, Seoul	Case report	2006	4 (fair)	1	37 (100)	1 (100) VF	0	approx 120	1 (100)	1 (100) CPC-1	NA
Nagao et al.[15,c] Japan, Tokyo	Prospective observational	November 2000 December 2007	4 (good)	171	MR	143 (84) VF/VT 18 (10) PEA 10 (6) AS	MR	MR	33(19)	21 (12) CPC-1,2	NR
Lebreton et al.[21] France, Paris	Case report	2010	4 (fair)	1	48 (100)	1 (100) AS	<1	<59	0 (0)	NA	NR
Le Guen et al.[20,c] France, Paris	Prospective observational	January 2008 August 2010	4 (good)	51	42 (90)	32 (63) VF 15 (29) AS 4 (8) PEA	3	NR	2 (4) **at 28 d**	2 (4) GOS 4,5 **at 6 months**	NR
Megarbane et al.[22] France, Paris	Prospective observational	2005–2008	4 (good)	47	MR	MR	MR	MR	1 (2)	1 (2) CPC-1	NR
Avalli et al.[26,c] Italy, Monza	Retrospective database review	January 2006 February 2011	4 (good)	18	46 (94)	16 (89) VF/VT 2 (11) AS/PEA	1	77	1 (5) **at 28 d**	1 (5) GOS ≥4 **at 6 months**	10 DBD/NR
Haneya et al.[24,c] Germany, Resenburg	Retrospective database review	January 2007 January 2012	4 (good)	26	48 (65)	12 (46) VF/VT 2 (8) PEA 12 (46) AS	NR	70 (55–110)	4 (15)	NR for OHCA alone	NR
Shinar et al.[30] US/San Diego	Case report	2011	4 (fair)	1	59 (100)	1 (100) VF	0	61	1 (100)	1 (100) CPC-1	NA
Fagnoul et al.[28,g] Belgium, Brussels	Prospective observational	January 2012 December 2012	4 (good)	7	MR	MR	MR	MR	2 (29)	2 (29) CPC-1	3 DBD, 1 DCD/1 DBD, 1DCD
Lamhaut et al.[19] France, Paris	Pilot prospective observational	January 2011 January 2012	4 (fair)	7	42 (86)	5 (71) VF/VT	4 (mean)	72 (mean)	2 (28) **at 7 d**	1 (14%) CPC 1 **at 90 d**	3 DBD/2 DBD
Leick et al.[25] Germany, Bad Nauheim	Retrospective chart review	January 2010 December 2011	4 (good)	28	MR	MR	MR	MR	11 (39)	8 (29) CPC-1	NR
Maekawa et al.[13] Japan, Sapporo	Post hoc analysis of prospective observational	January 2000 September 2004	3 (good)	53	54 (83)	31(60) VF/VT	2	49	17 (32)	8 (15) CPC-1,2 **at 90 d**	44/0[d]
Mojoli et al.[27] Italy, Pavia	Prospective observational	January 2008 June 2011	4 (fair)	7	55	NR	7	93 (no flow included)	0 (0)	NA	3 DBD, 1 DCD/2 DBD, 1 DCD
Tazarourte et al.[23,f] France, Ile de France region	Retrospective observational	2008–2010	4 (good)	27	39 (56)	VF 7 (26) PEA 6 (22) AS 14 (52)	2	140 (no flow included)	1 (4)	1 (4) CPC-1	10 DBD/10 DBD
Kim et al.[12,c] Korea, Seoul	Post hoc analysis of prospective observational	May 2006 December 2013	3 (good)	55	53 (75)	31 (56) VF/VT 14 (26) AS 10 (18) PEA	7	62	9 (16)	8 (15) CPC-1,2 1 (2) CPC-4	NR

Table 1 (*Continued*)

Study country, region	Study design	Time period	LOE (quality)	Sample size	Age[a] (years) male %	Cardiac rhythm no. (%)	No flow[b] period (min)	Low flow[b] period (min)	Survival at discharge (or as indicated) no. (%)	Neurological outcome at discharge (or as indicated) no. (%)	Organ donor no. (potential/actual)
Mochizuki et al.[14] Japan, Matsumoto	Retrospective database review	April 2004 March 2013	4 (good)	32	51 (78)	MR	MR	MR	8 (25) **at 30 d**	5 (16) CPC-1,2 **at 30 d**	5 DBD, 5DCD/0
Putzer et al.[29] Austria, Innsbruck	Case study	NR	4 (fair)	1	43 (100)	1 (100) VF	<5	107	1 (100)	1 CPC-1	NA
Sakamoto et al.[16] Japan, Yokohama City	Prospective observational	September 2008 September 2011	2 (good)	260	56.3 (90)	NR	NR	NR	69 (27) **at 30 d**	32 (12) CPC-1,2 37 (14) CPC-3,4 **at 30 d**	NR
Stub et al.[31] Australia, Melbourne	Prospective observational	"32 month period"	4 (fair)	9	MR	MR	MR	MR	5 (56)	3 (33)CPC-1	3/0 (type not specified)
Wang et al.[18] Taiwan,Taipei	Prospective observational	January 2007 September 2012	4 (good)	31	50.7 (75)	15 (48) VF/VT 16 (52) AS/PEA	NR	67.5 (no flow included)	12 (39)	8 (26) CPC-1,2	NR
Totals				833					**180 (22)**	**104 (13)[e] good neurologic recovery**	**34 DBD, 7 DCD and 47 not specified/15 DBD, 2 DCD**

LOE, Level of Evidence and study quality were assessed according ILCOR guidelines[8]; *No-flow* period defined as time from collapse to bystander or EMS CPR; *Low-flow* period defined as time from bystander or EMS CPR to ECPR; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; AS, asystole; DBD, organ donation after brain death; DCD, organ donation after circulatory death; MR, results were mixed with those of other study populations in publication so we are unable to present results for out of hospital cardiac arrest patients alone; NA, not applicable; NR, not reported; GOS, Glasgow Outcome Scale score; CPC, Glasgow–Pittsburgh Cerebral Performance Categories.

[a] Unless otherwise indicated, values presented are means for cohort studies and individual values for case studies.

[b] Unless otherwise indicated, values presented are medians for cohort studies and individual values for case studies.

[c] Study populations included a small percentage of patients whose cardiac arrest was from non-cardiac causes. The percentage of patients with non-cardiac causes were: 14% for Le Guen et al. (2011)[20]; 17% for Avalli et al. (2012)[26]; 39% for Haneya et al. (2012),[24] NB: in this study pulmonary embolism was considered a non-cardiac cause; and 11% for Kim et al. (2014).[12]

[d] This percentage (13%, 104/807) does not include study by Haneya et al. (2012)[24] as it did not report CPC score in OHCA alone.

[e] 44 subjects were poor function status patients. There were no organ donors since cDCD is not permitted and DBD cannot be certified under ECMO by law in Japan.

[f] This study has a total sample size is 27 but only 14 underwent ECPR; the rest were immediately considered as potential donors.

[g] Additional data not presented in publication was provided by author in the form of a personal communication.

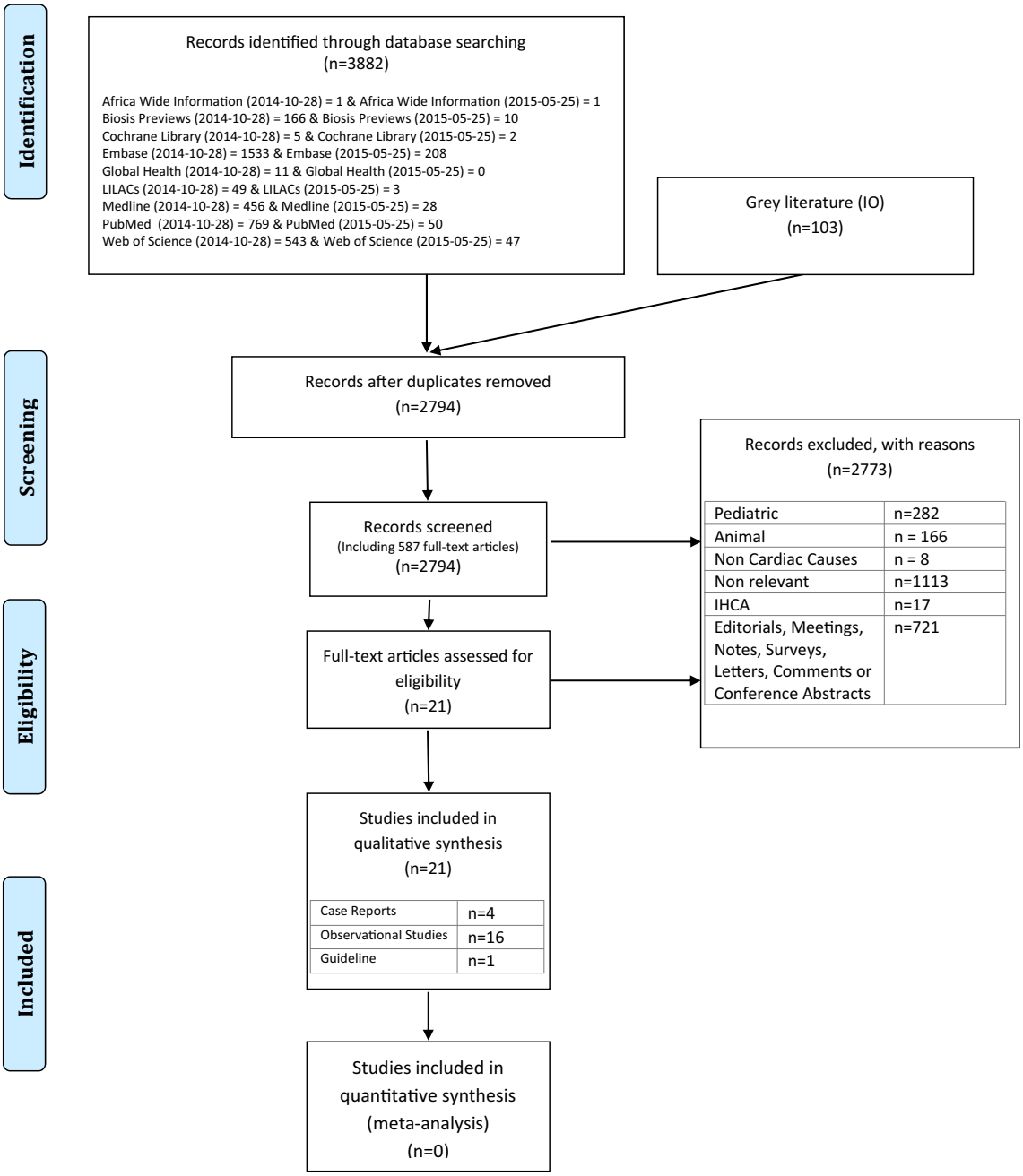

Fig. 1. PRISMA flow chart study selection.

quality (see Additional file 2) by three reviewers (IO-D, LH, FB). For the assessment of studies reporting outcomes we used the level of evidence (LOE) scale tool previously used by the International Liaison Committee on Resuscitation (ILCOR).[8] The guideline assessment was performed with the Appraisal of Guidelines for Research & Evaluation (AGREE) instrument, version II.[9]

Data synthesis

We anticipated clinical heterogeneity in selected studies due to the variability in eligibility criteria of study populations and ECPR procedures. Statistical heterogeneity was identified in relation to disparities in sample size, interventions and timelines along the OHCA process and in post-resuscitation care, as well as in the benefit/harm risk analysis. This heterogeneity also existed in the criteria for defining a good neurological recovery in survivors and for defining potential deceased donors among non-survivors. Therefore, comparison of data was not feasible, precluding any meta-analysis. Rather, we did a tabulation of characteristics of studies (See Table 1). To reduce the heterogeneity we focused our analysis on a subgroup of patients suffering OHCA of cardiac origin. We contacted the authors of all the included studies for further details from their databases.

Results

A cumulative of 3882 potentially relevant citations were obtained, in addition to 103 from gray literature and 466 from citation tracking, resulting in a total of 2794 references for further review after duplicates were removed. Of these, 2773 were excluded in a first screening for the reasons specified (Fig. 1). Therefore, a final total of 21 references, 20 studies and 1 guideline, were

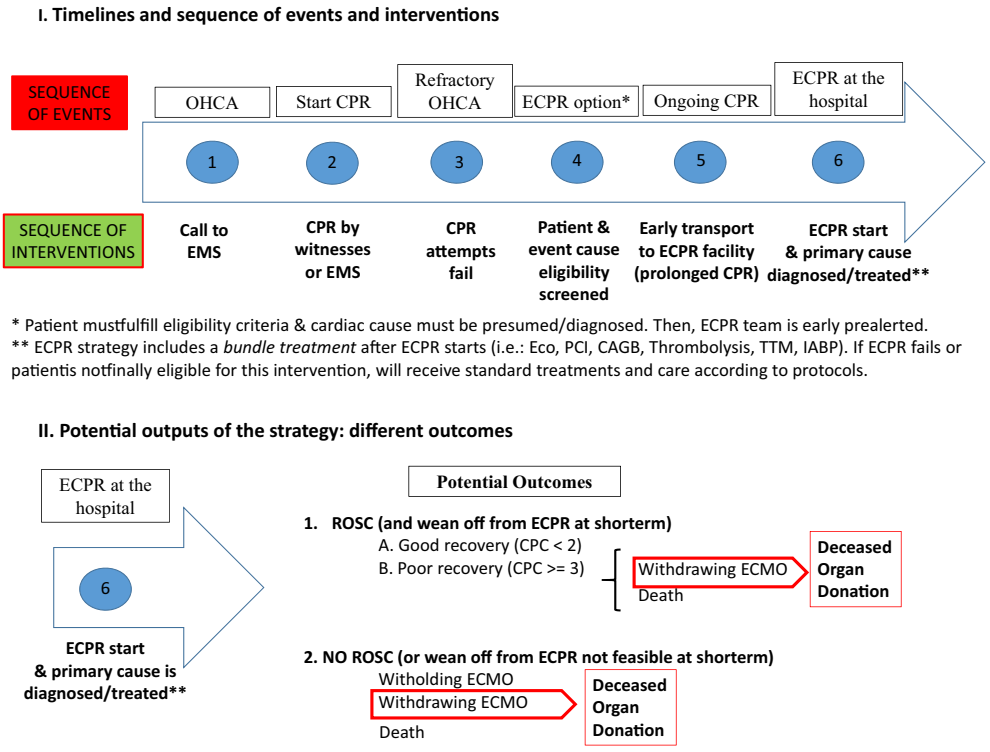

Fig. 2. ECPR strategy – timelines, int and outcomes.

included in our analysis. Fig. 2 depicts timelines, events, interventions and potential outcomes during the ECPR process. Various clinical endpoints may include: ROSC with good neurological recovery (CPC 1–2); ROSC with poor neurological outcome (CPC ≥ 3) leading to poor quality survival or death and/or organ donation; no ROSC and withdrawal of ECMO leading to death and/or organ donation.

ECPR studies

Twenty studies reporting outcomes were reviewed and are summarized in Table 1. There were no published randomized controlled trials (RCTs) although two (NCT01511666 and NCT01605409) are currently enrolling patients in Prague and Vienna.[10,11] Four of the selected studies were conducted in Japan, 2 in Korea and 1 in Taiwan,[12–18] 5 in France,[19–23] 2 in Germany[24,25] and 2 in Italy.[26,27] The remaining case series and reports were from Belgium,[28] Austria,[29] USA[30] and Australia.[31]

The large majority of included studies were case reports, case series, and retrospective cohort studies, all of them LOE of 4. Maekawa et al.[13] and Kim et al.[12] performed a post hoc analysis of a prospective observational study, LOE 3. Sakamoto et al.[16] completed a large prospective observational study (LOE 2) which is the strongest level of evidence identified. Most of the included studies presented high risk of confounding bias and threats to external validity because of their observational design. However, the methodological quality assessment of the 20 included studies resulted in a rating of *good* for 14 studies[12–16,18,20,22–28] and *fair* for the other 6[17,19,21,29–31] (see Table 1).

Guideline appraisal

This review identified only one guideline on the specific management of refractory cardiac arrest with ECPR. It was developed by a group of experts and endorsed by different professional societies and resuscitation boards from France. Considerations include a potentially reversible cardiac arrest cause (e.g. hypothermia or intoxication), limitations to the duration of *no-flow* and *low-flow* periods, the presence of signs of life during resuscitation as well as the level of end tidal carbon dioxide detected during the resuscitation attempts. In order to assess the rigor of clinical practice guideline development, we used the AGREE II tool. In the Additional file 2 we include the scores for each of 6 different domains. The objectives and targeted users were well described and identified. Although recommendations were presented with clarity, the domains related to the "*Stakeholder Involvement*", the "*Rigor of Development*" and "*Editorial Independence*" obtained low scores. The authors acknowledged the low LOE 5 for their recommendations. Despite methodological limitations, the strength of the guideline is clarity of eligibility criteria and it provides a useful and simple decision tool for physicians and nurses in the field.

Patient characteristics

In most studies, age of patients ranged from 16 to 75 years. The *no-flow* time periods were generally less than 5 min (range from 0 to 7) and the *low-flow* time periods were variable (range from 49 to 140, with *no-flow* period included in some studies). Factors identified as favorable prognosis included witnessed events, initial *shockable* cardiac rhythms and the identification of a potentially reversible cause of cardiac arrest. The duration of time defining failed conventional resuscitation and refractory cardiac arrest varied between studies, ranging from 10 to 30 min prior to initiating the ECPR process. The main exclusion criteria were the pre-existence of severe comorbidities, neurological disabilities, a valid *do not attempt resuscitation* order and the identification of a primary non-cardiac etiology (Table 2).

Table 2
Commonly cited ECPR inclusion and exclusion criteria and bundle treatments performed.

Inclusion criteria
- Age cutoffs, usually <75 years (low end: 10 years; high end: no upper age)
- Rhythm at the time of CPR (when included, specified as favorable to ventricular arrhythmias or "shockable" rhythms)
- Time interval from collapse to initiation of resuscitation (no flow), generally ≤5 mins (up to <15 mins)
- Witnessed cardiac arrest
- Etiology of arrest, to be of "presumed", "assumed", or "suspected" cardiac etiology
- No ROSC despite optimal CPR, usually by 30 mins (as low as 10 mins) – refractory cardiac arrest definition

Exclusion criteria
- Do not resuscitate order
- Severe activities-of-daily-living disability
- Non-cardiac causes of arrest such as severe trauma, uncontrollable bleeding, irreversible brain damage, drug overdose, poisoning, submersion, etc.
- Severe comorbidities (e.g. Often specify as those that would preclude admission to ICU, i.e. terminal illnesses, malignancies, etc.)
- Hypothermia

Bundle treatment options used during ECPR
- Catheter Lab (e.g. PCI, CABG, etc.) ONLY: 2 studies[23,30]
- Catheter Lab + TTM: 8 studies[12,21,22,24,25,28,29,31]
- Catheter Lab + IABP: 1 study[17]
- Catheter Lab + IABP + TTM: 9 studies[13–16,18–20,26,27]

CPR, cardiopulmonary resuscitation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; TTM, targeted temperature management, also known as therapeutic mild hypothermia; IABP, intra-aortic balloon pump.

ECPR process

In all studies ECPR was deployed upon arrival to the hospital with a pre-alerted ECPR team on standby, except in Paris where ECPR is usually performed in the field.[19,21] Followed by a variable *door-to-cannulation* period of time, the *bundle treatment* approach included coronary revascularization in the catheterization lab, and in some studies adjunctive therapies were also deployed (Table 2). These co-interventions were targeted temperature management (TTM) for neurological protection and/or the use of an intra-aortic balloon pump (IABP).

Outcomes

This systematic review identified a cumulative total of 833 patients in 20 studies. While there was some variability in time points of reported outcomes, the overall reported survival rate was 22%, including 13% having a good neurological recovery (CPC 1–2 or GOS 4–5, see Table 1). In addition to these short-term results, three studies[12,13,19] reported patient outcomes at 3 months with an overall survival rate of 21% (24/115), including 15% (17/115) having good neurological function and five studies[16,20,22,26,30] reported patient outcomes at 6 months with an overall survival rate of 16% (61/377), including 9% (34/377) having good neurological function.

Three studies[19,23,26] reported on potential organ donors from the group of non-survivors with anoxic brain injury, including donation after brain death (DBD) and controlled donation after circulatory determination of death (cDCD). After contacting all authors, data on organ donation outcomes were provided from 5 additional studies[13,14,27,28,31] (Table 1). A total of 88 potential deceased donors among non-survivors from 8 out of the 20 included studies were identified. Of these potential donors, 17 (19%) became actual donors: 15 DBD and 2 cDCD. Most donors were identified after inability of ECPR to achieve neurological recovery. However one study managed 13/27 patients as potential donors in the prehospital phase of care based on the duration of *no-flow* period of the cardiac arrest event.[23]

Discussion

To our knowledge, this is the first systematic review that summarizes the defining elements and outcomes of ECPR studies in refractory OHCA of cardiac origin in adult patients. Potential outcomes of this strategy include survival with good neurological recovery, survival with poor neurological recovery, or anoxic brain injury resulting in death with or without organ donation. In order to inform practice, we have created an illustrated timeline of the ECPR process and depicted the potential scenarios and outcomes (Fig. 2).

Cumulatively, we report 833 OHCA patients in 20 studies, with an overall survival rate of 22%, including 13% with good neurological recovery. For those studies reporting longer-term outcomes, overall survival rates were 21%, including 15% good neurological function at 3 months and 16% including 9% good neurological function at 6 months. Eight of twenty studies outlined 88 potential organ donors, 19% of which became actual organ donors. The vast majority of previously reported outcomes are related to in-hospital cardiac arrest and do not report neurological or organ donation outcomes. Although this review focuses on refractory OHCA of cardiac origin, the results are comparable to previous adult ECPR reports that include various mixes of in/out of hospital cardiac arrest and cardiogenic shock.[32] Previously reported survival rates to hospital discharge range from 29 to 47%, including the large Extracorporeal Life Support Organization (ELSO) registry report of 4200 ECPR patients.[6,33,34]

Given that this review is based largely on existing case reports, case series or small observational studies, heterogeneity was evidenced in both populations and interventions. There is variability in patient selection, age limits, duration of *no-flow*, the moment when the OHCA is considered refractory to conventional resuscitation, logistics and clinical pathways, time from cardiac arrest to cannulation, interventions deployed, and levels of care provided before and after ROSC. The decision to offer ECPR was often made on a case-by-case basis at the discretion of the resuscitation team leader,[12,14,18,35] which may lead to reporting bias.[36] Randomized controlled trials in OHCA are registered (NCT01511666 and NCT01605409), and currently enrolling patients.[10,11]

What remains unresolved are the optimal patient characteristics, variables associated with good neurological outcomes and the cost-benefit analysis of this complex and resource intensive intervention,[3,37] The main variables determining neurological outcome[38,39] presumably are: the duration without cardiac output until resuscitation begins (*no-flow* period), quality of CPR, and the duration with low cardiac output during resuscitation attempts (*low-flow* period). ILCOR reviews[40,41] suggest that the presence of witnesses, shorter duration of resuscitation prior to ECPR, a *shockable* initial rhythm, and the early identification/treatment of the reversible cause of arrest were factors positively associated with survival to discharge. Although the ILCOR does not recommend the ECPR strategy routinely, it states that in settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support (Class IIb, LOE C-LD).[42]

Innovative strategies seeking to minimize the *no-to-low flow* period include cannulation in the field followed by rapid deployment of mobile ECPR.[19,21] The effectiveness should be compared to early transport under high-quality ongoing resuscitation and ECPR institution after arrival to the hospital. Novel therapies are in evolution[43,44] to enhance cardiac and neurological recovery (Table 2), including percutaneous coronary intervention, intra-aortic balloon pump, thrombolysis and targeted temperature management. When offered during or early after resuscitation attempts, results were encouraging.[13,16,31,45–47]

In addition to survival outcomes, this review suggests that organ donation after death, while poorly reported, should be included as a relevant outcome in ECPR studies. It is likely that the number of potential donors with irreversible anoxic brain injury may be underestimated as some jurisdictions do not offer donation option under these circumstances. For example, through personal correspondence, Maekawa[13] reported 44 patients with a poor neurological outcome following ECPR, but explained that at the time of the study, controlled DCD was not performed in Japan, and DBD could only be certified in hemodynamically stable patients which exclude ECPR.

Any innovative resuscitation intervention that improves patient outcome has direct benefits to the patient, and may have an indirect societal benefit arising from patients who will inevitably die but can become organ donors. However, these positive consequences must also be balanced by the potential for undesirable outcomes. Some authors have reported higher survival with good neurological recovery compared to conventional resuscitation, but also higher rates of coma and permanent vegetative state.[12,16] Thus, it has been stated that the ECPR strategy can lead to the so-called *bridge to nowhere* in which a patient, not likely to recover, not going to die, is dependent on ongoing life support,[36] posing burdens to patient, family and the health care system. However, this review demonstrates that survival with poor neurological outcome overall was 9% and for those studies reporting outcomes at 3 and 6 months it was 6% and 7%, respectively.

This systematic review has several limitations. Study heterogeneity precluded a meta-analysis preventing any meaningful comparison between protocols, interventions and outcomes. The lack of standardization of definitions at each step of the process and the lack of homogeneity of good outcomes and follow-up times for survivors hindered a more consistent and clear presentation of results. Finally, we were unable to perform any guideline comparisons; only one guideline was identified. Despite these limitations, ECPR is feasible for refractory OHCA of cardiac origin in adult patients. ECPR may increase the neurologically good survival in selected patients. Prospective studies are required to clarify patient selection and modifiable outcome variables. Further investigation is needed to determine whether ECPR cannulation is more effective when performed in pre-hospital or in-hospital settings. A cost-effectiveness analysis of the ECPR strategy is required to inform policy. The deceased organ donation option may be considered a secondary outcome when patient survival with quality of life is not achieved.

Conclusions

This systematic review describes and compares the international variability in practices, protocols and outcomes for the ECPR strategy in adult patients who suffered a refractory OHCA, informing future protocol development and health policy. The review highlights the need for standardization of definitions and of study outcomes to improve study homogeneity and clarity of findings. We advocate, aligned with ILCOR recommendations,[48] that future studies report the following outcomes: survival and neurological status (CPC score) at 24 h, 1 month, 3 months, 6 months and 1 year as well as outcomes pertaining to organ donation potential in non-survivors such as the mechanism (neurologic versus circulatory) of death and the number of actual donors.

The ECPR strategy is a viable last option for increasing the probability of survival in a potentially hopeless scenario. A bundle of novel therapies are feasible to treat preselected adult patients suffering from a refractory OHCA of cardiac origin. The process includes ECPR and other co-interventions such as percutaneous coronary intervention, intra-aortic balloon pump, thrombolysis and targeted temperature management. When deployed during and/or soon after resuscitation attempts, despite variations in practice and heterogeneity of outcomes, these interventions yield a good neurological survival in 12% of adults suffering a refractory OHCA. Importantly, prior to ECPR strategy implementation, these patients would not have had practically any chance for survival. Moreover, this strategy has the potential to increase the pool of solid organs available for transplant from non-survivors. This secondary outcome should not be disregarded, from a cost-effectiveness point of view, in a global context of organ shortage; it may be a more comprehensive approach to the end-of-life scenario drawn by sudden cardiac arrest events, a major public health burden worldwide.

Author's contributions

IO-D and LH carried out the systematic review, conceived of the protocol and drafted the manuscript. SDS and FB supervised and participated in the review of study selection and in the quality assessment process. EG carried out the search strategy and led the management of references, designing the figures related to this part. All authors critically reviewed and approved the final manuscript.

Conflict of interest statement

LH is a paid research consultant for Canadian Blood Services. The other authors declare that they have no competing interests.

Acknowledgements

We thank Ingrid Soto, Jan Belohlavek, David Rodrúguez-Arias and Alfredo Serrano for their support, suggestions and comments during the conception and revision of this manuscript.

IO-D was financially supported by a PhD research grant from Fundación 'La Caixa', Barcelona, Spain. This Systematic Review is part of his PhD project. He also received the Phyllis and Albert Sussman Accommodation Subsidy for a stay at The Hastings Center, Garrison, New York, USA, while he participated in the writing of this systematic review. IO-D declares that this systematic review would have never been possible without the personal support of Maria and Miguel Ortega.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.resuscitation.2016.01.018.

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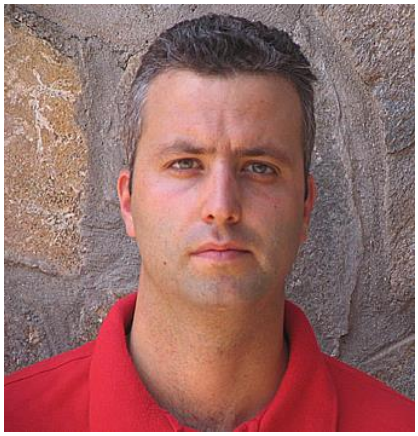
Universidad de Alcalá

ANEXO VI

Actividad durante la investigación predoctoral

Ivan Ortega Deballon
Research Associate from Spain. PhDc.



Ivan will be working within the Deceased Organ Donation initiatives, sharing his background of 15 years in uncontrolled Donation after Circulatory Death strategy from the Emergency Medicine field when sudden cardiac arrest happens and after resuscitation attempts has been performed.

He is interested in working on the complex intersection of pre-mortem life-saving versus post-mortem organ-preserving interventions such as CPR and ECMO-ECLS. His PhD project core focus on performing SRs for answering these research questions:

In cases of REFRACTORY CARDIAC ARREST:

1. What are the patients that may benefit from HIGH QUALITY ONGOING CPR & ECLS/PCI intra-arrest/Hypothermia, seeking for the underlying cause of cardiac arrest (reversible causes)
2. What are the conditions that signal futility for life support and, thereafter, eligibility for organ donation
3. What are the medically, legally and ethically acceptable interventions for uncontrolled DCD
4. Could we do both strategies (HQ CPR & uDCD) compatible by a comprehensive approach, resulting in a positive both cost-effectiveness result, clinically evidence based and ethically sound?

Ivan is a specialist in law (LL.B.) and in medical ethics. He is also an Emergency Flight Nurse Practitioner (NP) and has been working in emergency nursing care in the Helicopter Emergency Medical Service in Madrid, Spain where he is responsible for the care of potential organ donors during transport.

He teaches at several universities in Madrid and he is associate professor at the Faculty of Medicine and Health Sciences of the University of Alcala de Henares, where he has done a Masters in University Teaching. He belongs to the Teaching Innovation Group of this University, recently honored after his works in High Fidelity clinical simulation in the learning process (Advanced Life Support training and Resuscitation) where improves not only technical skills on resuscitation but also communication abilities (breaking bad news).

His doctoral thesis project has been accepted (PhD candidate) on the topic of the relationship between current practices of programs for uncontrolled donation after circulatory death (DCD) and international high-quality resuscitation research projects.

He is involved in several projects that seek for the public access to Automated External Defibrillation (AED) looking for increasing the survival outcomes rates of out-of-hospital cardiac arrest. He has been participating in uncontrolled DCD since 2000, involved in the care of more than 60 potential donors as part of his work in the HEMS of Madrid which is currently the most active uDCD program worldwide.

Obra Social "la Caixa"

TO WHOM IT MAY CONCERN

Caja de Ahorros y Pensiones de Barcelona, "la Caixa", is the Spain's leading savings bank. Its main business is to provide retail banking services throughout Spain.

As a savings bank, "la Caixa" devotes a significant part of its net profit to social and cultural ends, which are channeled through "la Caixa" Foundation. The Foundation's primary aim is to meet those social needs not yet covered by public administrations or other institutions. It carries out works on many fields, such as plastic arts, science, music, social works, libraries, education or the environment.

Among these activities, noteworthy is the fellowship program for further study abroad. This program is intended to provide to our best graduate students the opportunity to extend their graduate studies in Canada, the United Sates, Great Britain, Germany, France, Spain, China or India for one or two years and then bring them back to Spain so that they can contribute to improve the scientific and technological level of our country. This program began in 1982 and has awarded over 3.000 fellowships to date.

This year in particular, the competition has been very keen and the Selection Committee has received many applications from very well qualified students applying for one of the 5 fellowships to extend studies in Canada.

This fellowship is granted for one year, though it can be extended to a maximum of 24 months in total, provided the fellow remains in good academic standing. This fellowship includes:

- Return air ticket from their home town to the receiving university
- Tuition fees of the university where the fellow has been admitted
- A monthly stipend of CA$ 2.150 to cover room and board
- One payment of CA$ 2.150 to cover books and miscellaneous expenses
- Health/accident insurance policy
- Visa expenses

Therefore, it is a pleasure to CERTIFY that **Mr Iván Ortega Deballón** has been awarded one of the above stated fellowships to extend studies in Canada.

And to be kept on record for all suitable purposes, I issue this certificate in Barcelona on 3rd August, 2012.

Obra Social "la Caixa"
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RAPPORT ANNUEL

2013-2014-2015

Activité de recherche annuelle réalisée par Ivan Ortega Deballon grâce à la bourse d'études supérieures Fundacion La Caixa

TABLE DES MATIERES

Iván Ortega-Deballon se incorporó el 11 de Septiembre de 2013 al Research Institute, McGill University Health Centre, adscrito como **Research Assistant** a los siguientes departamentos, institutos y servicios :

McGill University Health Centre, Research Institute

Critical Care Division, Montreal Children's Hospital (Pediatric Intensive Care Unit & ECMO team)

En Octubre de 2013, se icoroporó como **Research Assistant y Deceased Organ Donation Consultant** al Laboratorio de Siumulación Clinica del Centre de Prelevement d' Organes del H pital du Sacr -Cœur de Montréal, adscrito a la Intensive Care Unit – Soins Intensifs

Ha realizado y superado el curso ***de Pediatric Health Research Epidemiology Statistics Curricula (PHERSCA)*** de la McGill University así como el ***Canadian Child Health Scientist Program*** (CCHSP) del Pediatric Chairs of Canada.

Iván Ortega-Deballon **ha concluido 2 revisiones sistemáticas de la literatura, que conforman el núcleo central de su tesis doctoral**. Durante su período de investigación doctoral internacional, Iván Ortega-Deballon ha dirigido como **PRIMER AUTOR** las revisiones sistemáticas tituladas :

Protocols for uncontrolled donation after circulatory death: a systematic review of international recommendations, practices and outcomes

IVAN ORTEGA-DEBALLON, LAURA HORNBY, SAM D. SHEMIE

Que ha sido publicada como Open Access en ***Critical Care*** (Impact Factor 5.08) y cuyo protocolo fue hecho público y registrado previamente en el Prospective International Register for Systematic reviews de la Universidad de York, UK. El link disponible es: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015258

Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes

IVAN ORTEGA-DEBALLON, LAURA HORNBY, SAM D. SHEMIE, FARHAN BHANJI, ELENA GUADAGNO

TABLE DES MATIERES

Que ha sido finalizada y esta en fase de sumisión para publicacion en la revista ***Resuscitation*** (Impact Factor 3.96) y cuyo protocolo fue hecho público y registrado previamente en el Prospective International Register for Systematic reviews de la Universidad de York, UK. El link http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015259

Por otro lado, Iván Ortega-Deballon ha publicado como **PRIMER AUTOR** dos (2) capítulos diferentes sobre Uncontrolled Donation after Circulatory Determination of Death durante su estancia en Canada; uno publicado por la plataforma *Ethical, Legal & Psychosocial Aspects on Organ donation & Transplantation (ELPAT),* de la European Society of Transplantation (ESOT) y otro por *Springer*, dirigido y editado por la Universidad Ludwig Maximiliam de Munich, Germany. Del mismo modo, *Oxford University Press* ha editado un tercer (3) capítulo en el que Iván Ortega-Deballon es segundo autor junto a su supervisor Dr. Sam D. Shemie. El capítulo versa sobre Ethical and Legal Aspects. Deceased Donation in Pediatric patients.
Ivan Ortega-Deballon ha publicado tambien como **PRIMER AUTOR** **2 artículos** sobre ***Extracorporeal Resuscitation for Refractory Cardiac Arrest y Uncontrolled Donation After Circulatory Death.*** El primero, en la revista *Academic Emergency Medicine*, de la Society of Critical Care Medicine (Impact Factor 2.2) y otro en *Heart Lung & Vessels* como Invited Editorial

Iván Ortega-Deballon ha demostrado una excelente capacidad de trabajo, se ha integrado en el equipo de investigación dirgiendo proyectos de envergadura e impacto internacionales y su producción cientifica es digna de mención en cantidad y calidad. Su capacidad de trabajo en equipo y su análisis riguroso de la literatura, su comprensión y rigurosidad metodológica y su potente e innovador proyecto integrador de los cuidados críticos, de la emergencia extrahospitalaria y de la donación de organos son dignos de mención y están teniendo una visibilidad importante, fomentando un cambio de paradigma en la respuesta a la parada cardíaca extrahospitalaria de forma integral y el modo de realizar docencia en simulación clínica en este ámbito.

Podemos afirmar que en el ambito de la ***Extracorporeal Resuscitation y de la Deceased Donation after Criculatory Determination of Death***, Iván Ortega-Deballon se ha convertido en un investigador reconocido internacionalmente como experto.

En el ambito de la **Simulación Clinica**, ha desarrollado Casos Clinicos y ECOES para evaluar el aprendizaje tanto en *Soporte Vital* como en *técnicas de comunicación de malas noticias, entrevista familiar y estrategia de donación de órganos*. Ha sido pionero en la introducción de esta **Innovación Docente.** Del mismo modo ha participado como docente en Soporte Vital como Instructor de la AHA en e McGill University Sim Centre, impartiendo como instructor 2 cursos de PALS (AHA). Con Trauma Secours Inc. ha participado como instructor de reanimación por la Foundation des Maladies du Cœur dependiente de la AHA, impartiendo cursos de RCR (BLS + DEA + First Aid & Anaphylaxia). Iván Ortega-Deballon, superó el curso de la CSST (Ministerio de Trabajo), siendo nombrado *Instructeur des Secouristes au Milieu du Travail* por el Gobierno de Quebec, Canada.

TABLE DES MATIERES

Finalmente, ha participado clínicamente en el ámbito de los **cuidados críticos adultos y pediátricos y ha realizado estancias en el servicio de emergencias extrahospitalarias de Urgence Santé, Montréal.Québec,Canada.** Ha participado con el Equipo de Cuidados Avanzados del Servicio de PARAMEDICS-911, respondiendo a paradas cardíacas refractarias extrahospitalarias, realizando un transporte precoz de las víctimas bajo cuidados de reanimación de alta calidad continuados durante el transporte y hacia centros de referencia útil para patologia cardiovascular.
A continuación se detalla la **ACTIVIDAD DOCENTE UNIVERSITARIA y las PRESENTACIONES A CONGRESOS Y JORNADAS** realizadas por Iván Ortega-Deballon hasta el dia 17 de Junio de 2015, cuando finalizó su periodo de investigación predoctoral internacional.

Deseamos a Iván Ortega-Deballon un éxito que auguramos por su valía personal y profesional y su gran preparación científica, ética, legal y humana.

Estamos seguros de que la defensa de su proyecto de tesis doctoral en la Universidad de Alcalá de Henares en Madrid, Spain será exitosa y de gran impacto en la actividad clínica asistencial y en el ámbito docente, como ya ha sucedido

Ha sido una satisfacción poder contar con la presencia de Iván Ortega-Deballon, con el cual seguiremos realizando proyectos conjuntos en el futuro

Lo que firmo en Montréal, Québec (Canada) el 17 de Junio de 2015.

Dr Sam D. Shemie

Sam D. Shemie
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Professor of Pediatrics, McGill University

Medical Advisor, Deceased Donation
Canadian Blood Services

TABLE DES MATIERES

PRESENTATIONS

TITRE DE TABLEAU

DESCRIPTION	LIEU	DATE
Insights on the so-called Spanish Model of Organ Donation	Pediatric Intensive Care Unit – Weekly Rounds Critical Care Division Montreal Children's Hospital	6/11/2013
Strategies to face with a worldwide organ shortage: the Spanish Model of Organ Donation	Unite des Soins Intensifs Hôpital du Sacre-Coeur de Montreal ICU Rounds	5/12/2013
Refractory cardiac arrest: do we go beyond, do we increase the organ donation pool or both?	Unite des Soins Intensifs Hôpital du Sacre-Coeur de Montreal ICU Rounds	9/1/2014
Criteria for Determination of Death and Implications for Organ Donation	Institut de Recherches Cliniques de Montreal Montreal Neuroethics Network	16/1/2014
Death, dying process and Organ Donation	Neuroethics. Biomedical Ethics Unit. McGill University. Social Studies of Medicine Department	30/1/2014
Organ Donation after death: ethical considerations	Institute of Health & Social Policy - McGill	26/2/2014
Pre-hospital Emergency Medical Services in Europe: When time is Essential	Trauma Rounds – McGill University Health Centre Montreal Children's Hospital (MCH)	10/3/2014

PRESENTATIONS

Presentation du projet au Centre de Prelevement d'Organes (CPO)	Unite de Soins Intensifs de l'Hôpital du sacre-Cœur de Montreal (HSCM)	25/03/2014
Deceased Donation Initiatives	Canadian Blood Services – Ottawa	10/04/2014
Resuscitation in Motion 2014 : Refractory cardiac arrest, do we go beyond, do we preserve organs for donation or both?	Toronto. St Michael's Hospital & Li Shin King Institute	28/04/2014
A comprehensive approach to refractory out-of-hospital cardiac arrest	Foundation Francois de Champlain - Montreal	1/05/2014
Canadian Child Clinician Health Study Program-Annual Meeting (Van, BC)	Invited and sponsored as Rising Researcher	5-8/06/2014
Canadian National Transplant Research Program	Invited as trainee to the Annual Meeting (Hal, NS)	10-12/06/2014
Spanish Model on Organ Donation and strategies implemented: *benchmarking*	Lecture for Fellwoships in the ICU of Hôpital du Sacre-Coeur de Montreal Centre de Prelevement d'Organes (CPO)	26/06/2014
What we can do as health providers in the prehospital setting when a refractory OHCA occurs	Foundation François de Champlain	09/09/2014
A project for implementing a	Departement de Medecine	20/08/2014

PRESENTATIONS

comprehensive approach to refractory cardiac arrest	Prehospitaliere de l' Hôpital du Sacre-Coeur de Montreal		
Protocols for uncontrolled donation after ciruclatory death: the potential	Canadian Transplant Forum: 15th Annual Meeting – Toronto		21&22/11/2014
Réflexions sur le modèle espagnol du don d'organes et une proposition globale des soins à la fin de la vie après la mort circulatoire non contrôlée	Transplant Quebec, Montreal	5/12/2014	
Protocols for uncontrolled donation after ciruclatory death: the potential in Quebec of a new approach with ECPR strategy for refractory Cardiac Arrest	Comité d'Ethique de Transplant Quebec		21/3/2015
HEMS Model in Madrid, Spain and Disaster experiences at Madrid Terrorism Attack (11M2004) and Tsunami of Indonesia (2004-12)	Case Western Reserve University – Cleveland, Ohio.		5/5/2015
2nd Annual Meeting Montebello-Quebec	Canadian National Transplant Research Program (CNTRP)	Pecha-Kucha	8-10/6/2015

L'Hôpital de Montréal pour enfants
The Montreal Children's Hospital

Centre universitaire de santé McGill
McGill University Health Centre

Thursday, October 10, 2013

Mailing Address
Adresse de retour

Room/Bureau C-808
2300 Tupper
Montreal, Quebec
Canada H3H 1P3
Tel:(514) 412-4400, ext: 22696
Fax:(514) 412-4205

Ivan Ortega
102-75 Glengarry Avenue
Town of Mount Royal, QC
H3R 1A2

Dear Ivan,

I am pleased to offer you a contract in the role as research associate in organ and tissue donation with our interdisciplinary organ donation research program in the Division of Critical Care at the Montreal Children's hospital McGill University Health Centre, and with the Loeb Chair and Research Consortium at the University of Ottawa. You will be working on research and health policy related to organ donation and death determination.

This contract is for a one year duration at two days per week, from the period September 1, 2013 to August 31, 2014 to be renewed upon mutual agreement for an additional year. The salary support will be $882.62 per month [plus the standard MUHC rate of 5.3% fringe benefits (statutory holidays) and 8% vacation pay]. Since this is not a full time position, these percentages are paid to you directly rather than taken as actual holidays.

Total will be $1000.00 per month. We will pay you on a monthly basis.

This contract is dependent on mutual agreement and satisfaction after a 3-month trial period. In this role, you will work from home and provide your own access to McGill libraries. In addition, the expectation is that we will meet in person on a weekly basis.

I very much look forward to working together.

Best regards,

Sam Shemie, MD
Division of Critical Care,
Montreal Children's Hospital,
McGill University Health Centre

Medical Director,
Extracorporeal Life Support Program

Professor of Pediatrics,
McGill University

Loeb Chair and Research Consortium in Organ and Tissue Donation,
Faculty of Arts, University of Ottawa

Medical Director, Donation, Canadian Blood Services

Ivan Ortega _____ Date _____

SS/kp

HÔPITAL DU SACRÉ-COEUR
DE MONTRÉAL

HSCM

Por el presente escrito

CERTIFICO y DOY FE

Que Ivan Ortega Deballon, con NIF 51067077 Q es Enfermero e Investigador Asociado y se encuentra trabajando **de forma continuada desde Octubre de 2013 y continua actualmente,** realizando a diario una labor asistencial, docente e investigadora en el Centro de Extraccion de Organos de nuestro Hospital (Centre de Prélèvement d'Organes - Hôpital du Sacré-Coeur de Montréal) adscrito a la Unidad de Cuidados Intensivos del citado centro

Lo que hago constar a efectos de su presentacion en la Universidad de Alcala de Henares, Madrid (Espana) para el proceso de contratacion de Profesor Asociado

Hecho en Montreal, Quebec, Canada a 17 de Enero de 2015

Anne-Marie Lagacé

Anne-Marie Lagacé, M. Sc. Inf.
Conseillère clinique, Centre de Prélèvement d'Organes

Centre affilié
universitaire suprarégional

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5400, boul. Gouin Ouest
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Téléphone: (514) 338-2222
www.hscm.ca

AFFILIÉ À
Université de Montréal

THE HASTINGS CENTER

September 17, 2014

Ivan Ortega Deballon
102-75 Glengarry Avenue
H3R1A2. TMR, QC
CANADA

Dear Ivan,

I am very pleased to inform you that your application to be a Visiting Scholar at The Hastings Center has been accepted. Your visit will run for a period of two weeks beginning January 30, 2015 and ending on February 16, 2015. If you need to change or discuss these dates please immediately contact my administrative assistant Vicki Peyton at peytonv@thehastingscenter.org.

Please read the attached document "Notes for Visiting Scholars." It provides important information about our location, business hours, your lunchtime presentations, the Center's apartment, and your workspace. Please note that while visiting scholars can use a common computer in the library for internet access, you are encouraged to bring your own laptop computer.

As you requested, we have reserved a bedroom for you in the Center's onsite three bedroom co-ed apartment. The weekly cost is $200.00 per week to be paid to the Center and covers use of one of the apartment's three bedrooms, private or shared bath, shared living room, and shared kitchen and laundry ***(Please note: that we are waiving the $200.00 per week rental fee, but you are required to pay a $200.00 deposit upon your arrival)***. Up to three visiting scholars may be sharing the apartment at any one time. The deposit will be returned to you at the end of your stay provided the apartment is left in a satisfactory condition.

Please plan to arrive at the Center on a weekday between 9:00am and Noon. If your flight arrives too late for you to travel to the Center before Noon, I would like to suggest that you plan on staying in a hotel at the airport or in New York City, and traveling to the Center the following morning. If you need to look for a hotel in New York City or near the airports, I suggest that you search on www.hotels.com. The most economical means of transportation is to take a cab or bus from the airport to Grand Central Station in New York City. When you arrive at Grand Central Station you would take the Metro-North, Hudson Line, to the Garrison Train Station. These trains run hourly. This station is located only about five minutes from the Center. A staff member will be happy to pick you up at the Garrison Train Station since there are no cabs or public transportation. Your second option for ground transportation is a private car, but this can be quite expensive. This could cost anywhere from $166 to $200 one way. If you Vicki Peyton will be in touch with you before your arrival date to touch base with you about your arrival plans and to setup your lunch presentation.

I suggest that you visit our website at www.thehastingscenter.org, where you will be able to acquaint yourself with our facilities and staff before your visit. If you have any questions about the Center or your upcoming visit, please contact Vicki Peyton at peytonv@thehastingscenter.org or by phone on 845-424-4040 x203.

My colleagues and I are delighted that you will be joining us as a visiting scholar, and we look forward to meeting you.

Sincerely,

Michael Gusmano
Research Scholar

21 Malcolm Gordon Road, Garrison, New York 10524
Tel: 845-424-4040—Fax: 845-424-4545—Email: mail@thehastingscenter.org
Web: www.thehastingscenter.org

The Hastings Center

February 13, 2015

Reference: The Hastings Center Visiting Scholar Program – Ivan Ortega-Deballon

To Whom It May Concern:

This letter attests that Ivan Ortega-Deballon was a visiting scholar at The Hastings from January 30, 2014 to February 13, 2015. Ivan presented his research topic on ***Ethics in practice: Extracorporeal Resuscitation and uncontrolled Donation after Circulatory Death: the red thin line between life and death?***

If you need further information or clarification, please do not hesitate to contact me.

Sincerely,

Michael K. Gusmano

Michael Gusmano
Research Scholar

21 MALCOLM GORDON ROAD, GARRISON, NEW YORK 10524 • 845.424.4040 • FAX: 845.424.4545 • WWW.THEHASTINGSCENTER.ORG

GOBIERNO DE ESPAÑA
MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

CSIC
CENTRO DE CIENCIAS HUMANAS Y SOCIALES
Instituto de Filosofía

A/a Fundació Víctor Grifols i Lucas
C/ Jesús i Maria, 6
08022 Barcelona – España
+34 935 710 410

A quien corresponda:

En calidad de Directora del Instituto de Filosofía del Consejo Superior de Investigaciones Científicas, les comunico que nuestra institución autoriza la iniciativa de Don Iván Ortega Deballón y Don David Rodríguez-Arias Vailhen de adscribir a nuestro Instituto de Filosofía –sito en el Centro de Ciencias Humanas y Sociales del CSIC- el proyecto de investigación **'ODISEAS' (Organ Donation in Spanish Emergency Ambulance Services) y** se adhiere a ella con todo entusiasmo. Consideramos que los objetivos de este proyecto plantean dilemas éticos, legales y psicosociales de envergadura y con importantes consecuencias en los individuos, las instituciones sociosanitarias y la sociedad en su conjunto, por lo que resulta de gran relevancia e interés para las investigaciones que aquí realizamos, especialmente en la línea "Conceptos y valores" del Instituto de Filosofía, cuyos integrantes poseen a su vez amplia experiencia en el abordaje de estas cuestiones.

Por todo ello, auguramos una repercusión interesante para la comunidad científica e investigadora, en concreto en lo que respecta a los debates éticos en el ámbito de la donación de órganos, y el Instituto de Filosofía sólo puede expresar su deseo de prestar la mayor colaboración institucional que sea posible para el buen desarrollo de tal iniciativa, y para los efectos que sean oportunos firmo la presente en Madrid a 28 de mayo de 2012,

INSTITUTO DE FILOSOFIA
Albasanz, 26-28
C.S.I.C.

Fdo: Concha Roldán

Directora

C/ ALBASANZ 26-28
28037 MADRID. ESPAÑA
TEL.: 916 022 300
FAX: 916 022 971
http://www.cchs.csic.es

Canadian National TRANSPLANT Research Program | Programme national de recherche en TRANSPLANTATION du Canada

February 12, 2014

Dear Ivan,

On behalf of the 116 investigators from across the Canadian National Transplant Research Program, it is our pleasure to accept your application into the CNTRP Academic Training Program. We received excellent applications from throughout the country *and our selection committee scored your application one of the highest*. We are thrilled to have you as part of the CNTRP's first round of trainees and we look forward to working with you to create a robust and comprehensive national training program.

Since this training program is national in scope, most of our learning will take place online using web-linked videoconferences and online learning modules, in addition to *in person* training meetings. We are currently developing our inventory of modules, as well as the schedule for our bi-monthly training seminars, which we will share once available. *Since you are one of our top rated trainees, we would like to encourage you to work with us to develop your own training module based on your area of expertise.* The Training Program is intended to give you the necessary training to succeed in the field of donation and transplantation. We will develop content covering scientific, clinical, legal and ethical topics, however we are keen to focus on topics that are important to your career development. Please send us a list of the research topics you are the most interested in learning to help us further refine our curriculum for this year.

We will have a virtual **Orientation Training Session in March** to meet the new trainees, meet the Training Leads, and learn more about the program [details to follow]. In order for the trainees to learn about each other, we would like you to use parts of your application to create a *one-paragraph description* of yourself that we can share with the other trainees and post on our internal-website. Please send this summary and a picture of yourself to us when you confirm your participation for the Orientation Training Session.

Upcoming Dates:

- The CNTRP will present an update during the Canadian Society of Transplantation meeting in Montreal on Thursday February 27 at 2pm in the Centre Sheraton. We encourage you to attend this presentation and connect with us during the CST.

- The first Annual CNTRP meeting is taking place on June 10-12 in Halifax, Nova Scotia, which we expect you to attend. Please save this date in your calendars and we will provide additional information shortly.

We thank you for your interest in the CNTRP Academic Training Program and we look forward to your dedication, enthusiasm and involvement in building this new program. Do not hesitate to contact us if you have any questions about your application or this program.

Sincerely,

Dr. Lee Anne Tibbles
Lead, CNTRP Training Program

Dr. Lori West
Director, CNTRP

Dr. Silvy Lachance
Co-Lead, CNTRP Training Program

Dr. Sonny Dhanani
Co-Lead, CNTRP Training Program

15th annual Canadian Transplant Forum

Challenges in Living and Deceased Kidney Donation

May 12, 2014

Mr. Ivan Ortega-Deballon
Montreal Children's Hospital
2300 Rue Tupper
Montreal, QC H3H 1P3
Canada

Re: Invitation to speak at the 15th annual Canadian Transplant Forum

Dear Mr. Ortega-Deballon,

It is my pleasure to invite you to participate as a speaker at the *15th annual Canadian Transplant Forum*, which will take place November 21-22, 2014 in Toronto, Ontario. The program has been developed with the guidance of a scientific steering committee and is solely sponsored through an educational grant from Astellas Pharma Canada, Inc.

It is our intent to apply for Section 1 credits under the Maintenance of Certification program of the Royal College of Physicians and Surgeons of Canada.

The Forum steering Committee – comprised of Drs. Michel Lallier, David Rush, R. Jean Shapiro and Jeffrey Zaltzman – has developed an exciting, topical agenda, and would be pleased to have your expertise as part of the program. The theme for this years Forum is "Challenges in Living and Deceased Kidney Donation", a copy of the preliminary agenda is attached for your reference.

You are invited to participate as follows:

Topic: Uncontrolled DCD - The Potential
Date: Friday, November 21, 2014
Time: 3:50 - 4:30 p.m. (30-min. lecture; 10-min. questions)

Should you agree to participate, a detailed briefing as drafted by the steering committee, will be provided to help you in developing your presentation.

In recognition of the work required to prepare for, and participate in the Forum, you would receive an honorarium of $1,500 Cdn. Additionally, the cost of 1 night at the InterContinental Toronto Centre Hotel in Toronto, and one Flex Class-class return airfare will be covered. STA Communications will be pleased to assist you with all hotel and travel reservations.

Certificate of Participation

Ivan Ortega

Has fulfilled the Core Curriculum requirements of the
Pediatric Health Research Epidemiology Statistics CurriculA (PHRESCA)

May 13, 2015
Date

E. Constantin, MD CM, MSc(Epi), FRCPC
Course Director

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

Centre universitaire de santé McGill
Institut de recherche

McGill University Health Centre
Research Institute

20 March 2014

Ivan Ortega
102-75 Glengarry Ave
Montreal, QC
HR3 1A2

Dear Ivan,

Thank you for registering for RiM2014 and submitting an abstract for presentation. We are pleased to confirm that the RiM2014 organizing committee has chosen your submission “Refractory cardiac arrest: do we go beyond, do we increase the organ donation pool, or both?” for presentation during the Scientific Sessions.

All presentations at RiM2014 follow the Pecha Kucha style (6 minutes, 20 slides) and we ask you to familiarize yourself with the format by visiting http://www.emergencymedicine.utoronto.ca/Resuscitation/PechaKucha2014.htm

All presentations will be pre-loaded to avoid confusion during the conference. Please submit your presentation via email (cprsinfo@smh.ca) on or before Friday April 25 2014. Your presentation timeslot will be confirmed at a later date.

We look forward to your participation at RiM2014!

Andrea Meeson
for the RiM2014 Organizing Committee

CURRENT DEBATES ON DONATION AFTER CIRCULATORY DEATH

Project Overview

The tragic shortage of organs for transplantation has inevitably led to the introduction of new techniques and protocols (roughly termed "donation after circulatory death" or DCD) for increasing the number of procured organs. These innovations, in turn, have challenged some traditional practices and beliefs and have raised important ethical questions. This project aims to identify and discuss these ethical questions. We are requesting support for a three day workshop involving international, multidisciplinary scholars with recognized expertise in the topic. This workshop will be a key step in realizing the project's ultimate goal—producing a unique and well-integrated edited volume that takes a candid look at the ethical and conceptual problems of DCD while at the same time suggesting best practices that balance concern for these problems with the continued maximization of organ retrieval for transplantation

Justification

The ever-increasing demand for organs has led a number of countries to initiate protocols of organ donation after circulatory death (DCD). Donation after circulatory death is a form of deceased donation that takes place after the cessation of circulatory function –but without determination of the cessation of (all) brain function (Institute of Medicine, 1999). There are two categories of DCD: uncontrolled DCD (uDCD) and controlled DCD (cDCD). So called *controlled* DCD occurs in a hospital when life support is removed and organs are retrieved shortly thereafter. *Uncontrolled* DCD can be distinguished from controlled DCD in that the organ donation process begins as a result of an unexpected cardiac arrest –usually outside the hospital. After resuscitation attempts are judged futile and the patient is declared dead, interventions –including extra-corporeal membrane oxygenation (ECMO)- are restarted to preserve organs. In the US, Canada, the Netherlands and the United Kingdom most DCD protocols are cDCD, while in Spain and France cDCD has been excluded from policy for a long time because of ethical and pragmatic reasons (Cabrol 2007; Matesanz 1996; Rodriguez-Arias et al. 2010). However, pressure to increase organ donation (OD) rates has very recently led Spain to initiate cDCD (Saralegui, 2011). On the other hand, a uDCD program has been recently started in New York City (Wall, 2008). Although DCD protocols have good results in terms of graft survival, they raise several ethical concerns. These concerns are specific for each type of protocol.

Controlled DCD has raised the concerns that:

1. Circulatory function might not have irreversibly stopped at the time of organ procurement. (Youngner 1999; Veatch 2008; Bernat et al 2010) This circumstance has been particularly troublesome in recent cases of successful heart transplant from babies who had been considered dead according to circulatory criteria, only 75 seconds after their hearts stopped beating. (Boucek 2008) Robert Veatch has called this "reversing the irreversible" (Veatch 2008, 672). In order to justify such protocols, Bernat and a HRSA panel of experts have suggested changing the legal criterion that required "irreversible cessation of the heart function" to "permanent cessation of circulatory function". This proposal has created further conceptual debate (Marquis 2010; Miller, Truog et al. 2010; Rodríguez-Arias, Smith et al. 2011a).

2. There is a risk that the very possibility of retrieving organs from them may compromise the end-of-life care of potential cDCD donors (Huddle, Schwartz et al. 2008). To avoid this risk, the decision to stop life sustaining treatment must be taken before and separately from any consideration of organ donation. (President's Council 2008) Despite these precautions, a significant minority of health professionals manifest more ethical concern with cDCD than with both donation after brain death and uDCD. (Rodríguez-Arias, Tortosa

et al. 2012) The fact that some countries, such as Spain, incentivize donor identification by transplant coordinators who are at the same time intensivists may erase the "firewall" between patient-centered care and organ procurement thereby compromising the former.

3. Finally, the practice of organ retrieval after voluntary euthanasia in Belgium has raised a new set of ethical concerns. (Ysebaert, Van Beeumen et al. 2009; Wilkinson and Savulescu 2010)

Uncontrolled DCD has raised different issues:

1. Whether the use of invasive interventions to preserve organs is acceptable before the patient's wishes have been established or the family has given authorization (Childress 2008).

2. Some uDCD donors might not have irreversibly lost either circulatory function or all brain function at the time of organ retrieval. (Rodríguez-Arias & Ortega, 2012) This concern is reinforced by findings that some patients with cardiac arrest for whom ordinary out-of hospital resuscitation efforts have been abandoned, could have benefited from continued CPR combined with other nonconventional resuscitation procedures (Massetti, Tasle et al. 2005; Thiagarajan, Brogan et al. 2009; Nagao, Kikushima et al. 2010). These procedures are intended to treat the cause of cardiac arrest as soon as possible while preserving neurological functions. A decision not to use these new techniques could be seen as putting organ recipients' interests before those of potential donors.

3. Another issue that has been raised in both DCD protocols, is that brain death is not rigorously demonstrated and can only be assumed. This raises the fundamental question of the relationship between brain death and circulatory death. In other words, do the two legally accepted criteria to determine death (neurological and circulatory) describe the same phenomenon (death)? (Rodríguez-Arias, Tortosa et al. 2012). In controlled DCD, questions have been raised about whether the waiting periods in existing protocols are enough to ensure total brain failure—that the functions of the entire brain are irreversibly lost. This concern is especially poignant since DCD may occur in the absence of a prior brain injury (Menikoff 1998; Youngner, Arnold et al. 1999). In uncontrolled DCD, the warning has been raised that ECMO, while intended to preserve the organs, can restore the donor's brain function by reinstituting brain blood flow (Shemie; Bernat et al). Proponents of DCD protocols have traditionally assumed that, in the period between cessation of circulatory function and the determination of death, loss of all brain function has also become irreversible (Capron 1999). Advocates of DCD thus claim that those protocols do not violate the "dead donor rule" —which establishes *that individuals must be dead before retrieval takes place*— because loss of circulation quickly results in irreversible loss of brain function if no attempt to restore cardiac activity is undertaken (Bernat 2010). In fact, brain activity can actually be restored if the appropriate means (e.g. ECMO) are initiated (Shemie 2007). Bernat and colleagues (Bernat et al. 2010) have acknowledged this possibility, by saying:

> "[T]he use of ECMO in the [DCD] donor creates a problem with death determination because it retroactively negates the physiologic justification for declaring the [DCD] donor dead. By allowing reperfusion of the brain and thereby preventing brain destruction, it interrupts the otherwise inevitable progression from permanent loss of circulation and respiration to irreversible loss. Restoring brain circulation also raises the possibility of retaining donor consciousness and the consequent potential for suffering". (p. 967)

To avoid that possibility, HRSA (Bernat, Capron et al. 2010) and proponents of the New York City uncontrolled DCD protocol (Wall, Kaufman et al. 2011) have recommended that an intra-aortic balloon be inserted to block all blood flow to the brain. However, some have questioned whether such intervention could be seen as the proximate cause of these individuals' death (Joffe, Carcillo et al. 2011).

Donation after circulatory death is currently getting the attention of many medical and bioethics journals. Sessions in this workshop will attempt to include interventions covering all the topics that are at stake in current debates, including: end-of-life decision making; conflicts of interest; DCD organ donation after voluntary euthanasia; irreversibility, permanence and the circulatory determination of death; cardiopulmonary vs neurological determinations of death; uncontrolled DCD and non-conventional resuscitation procedures; transparency in DCD programs; and DCD and informed consent.

Specific Goals

The overall goal of this project is to enhance the international discussion of these issues and to seek optimal solutions for them. To accomplish this goal we will bring together a group of the leading scholars who have raised questions about DCD with a smaller group of senior scholars who have written over the years about the ethics and policy implications of transplantation but have not "taken sides" in the debates about DCD. The workshop (and the ensuing publications and presentations) will be based on the critiques of DCD followed by the thoughtful responses and suggestions by the senior "neutral" bioethicists.

More *specific goals* to be achieved by this meeting:

- The creation of an integrated edited book (Rodríguez-Arias and Youngner eds.) that examines the problems and potential solutions;
- The presentation of the book findings at main bioethics and organ tansplantation international meetings: ASBH (American Society of Bioethics and Humanities); ESOT (European Society of Organ Transplantation) and its division ELPAT (Ethical, Legal and Psychosocial Aspects of Transplantation); AST (American Transplantation Society)
- The publication of a shorter summary of the book findings in a major medical journal.

Detailed List of Participants

- A. Charo, JD, University Of Wisconsin School of Law
- A.R. Joffe: MD, Stollery Children's Hospital, Edmonton, Alberta, Canada
- A.M. Capron: Professor, School of Law, U of Southern California, Pacific Center for Health Policy and Ethics
- A. Caplan: Ph.D, New York University
- D. Rodríguez-Arias: Ph.D Institute of Philosophy, Spanish National Research Council
- D. Brock, PhD, Harvard University
- I. Ortega: Nurs D., Associate Professor UAH University, Madrid; EMS Helicopter
- S. Shemie: M.D., Montreal Children's Hospital, McGill University Health Centre
- S. Wall: M.D, Jacobi Medical Center, Bronx, NY
- S. Youngner: M.D. Director of the Department of Bioethics, Case Western Reserve University, Cleveland
- W. Glannon: Professor of Philosophy, University of Calgary
- James Bernat: M.D. Neurology and Medicine Dartmouth Medical School Hanover, NH

Other potential participants: A.R. Manara (MD, NHS, UK), Alan Shewmon (MD, UCLA), Bruno Riou (MD, AP-HP, Paris), James Doig (M.D., Associate Professor, University of Calgary) , David Bracco (MD, McGill University), David. J. Isch (Office of Ethics, Methodist Fort Worth University, TX), David A. Zygun (M.D. Assistant Professor, University of Calgary), Dominic Bell (Critical Care & Anaesthesia, The General Infirmary at Leeds), Dominic Wilkinson (M.D. Associate Professor, Adelaide University), Don Marquis (Professor Ph.D., Indiana), Francis Delmonico (MD, New England Organ Bank, Harvard Medical School), Jerry Menikoff: M.D. (J.D, Director of the Office for Human Research Protections, Dep. of Health & Human Services), Joan L. McGregor (Ph.D, Dept of Philosophy, Arizona State University), Janet Radcliffe-Richards (Professor, Oxford University), James F. Childress (Professor, University of Virginia), Joseph L. Verheijde (Professor, University of Arizona), Kristin Zeiler (Department of

Medical and Health Science, Linkoping University), Lewis. R. Goldfrank (M.D. NYU, Emerg Med Serv.), Linda Wright (MSc, U of Toronto Joint Center for Bioethics), Lorenzo Peña (PhD, IFS, CCHS-CSIC), Margaret Lock (Professor, McGuill, MT), Maxwell Smith (MSc, Joint Center for Bioethics, University of Toronto), Michael DeVita (MD, Pittsburgh), Michael Potts (Ph.D Methodist University Fayetteville, NC), Michael Bos (Professor, Health Council of the Netherlands), Mildred Z. Solomon (Ed.D., Hastings Center), Mohamed Y. Rady (M.D., Department of Critical Care Medicine, Mayo Clinic, Phoenix, AZ), Nereo Zamperetti (M.D. Verona University), Nancy Dubler (Professor of Bioethics, Columbia University, NY), S. Welin (Professor, Philosophy Department, Linkoping University), Robert Truog (Professor, Harvard University), Robert Veatch (Professor, Georgetown Univ, Kenn Inst of Ethics), Txetxu Ausín (PhD, IFS, CCHS-CSIC).

Target Audience

Organ Procurement Organizations, Members of the World Health Organization, health professionals related to organ transplantation (intensivists, anesthesiologists, surgeons, neurologists, emergency medical services), transplantation policy makers, patients associations.

Objectives and Expected Outcome

Several short-term *objectives* will achieve the above goals:

- Maximum opportunity for interchange between scholars throughout the project.
  This objective will be achieved by:
  - Structuring the workshop to emphasize discussion over formal presentation;
  - Assigning specific and unique topics to each of the critics;
  - Sharing of rough drafts of manuscripts before the workshop;
  - Revision of manuscripts after the workshop to take advantage of discussion during the workshop;
  - Careful editorial review of "final" manuscripts, including, at the editors' discretion, possible questions and suggestions from other participating scholars;
  - Cross referencing of manuscripts within the book.
- Securing the services of a seasoned editor to assist with readying the manuscript for publication. Financing for this aspect of the project will be covered by funds available to one of the editors (SJY) for such purposes;
- Submission of workshops and panels at various national and international bioethics and transplant meetings.

Timeline

Year		2012								2013											
Month		M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N	D
Call for applicants																					
TASKS	Contact participants																				
	Structure the workshop																				
	Request for draft manuscr																				
	1st drafts manuscripts																				
	Workshop																				
	Fin. and scientific reports																				
	Reception manuscripts																				
	Reception commentaries																				
	Revision manuscripts																				
	Revision commentaries																				
	Book proposal to editor																				
Conferences, Workshops: 2014																					
Dissemination of results: 2014																					

Hôpital de Montréal pour enfants
Centre universitaire de santé McGill

Montreal Children's Hospital
McGill University Health Centre

Traumatologie
Trauma

- Programme de traumatologie
  Trauma Program
- Programme de neurotraumatologie
  Neurotrauma Program
- Programme des grands brûlés
  Burn Program
- Programme de prévention des blessures
  Injury Prevention Program
- Programme de TCCL / Clinique de commotions cérébrales
  MTBI Program / Concussion Clinic
- Programme de recherche en traumatologie
  Trauma Research Program

SCHIRPT/CHIRPP
Système canadien hospitalier d'information et de recherche en prévention des traumatismes
Canadian Hospitals Injury Reporting and Prevention Program

2300 Tupper, C-831
Montréal (Québec)
H3H 1P3
Tel: 514-412-4400 ext. 23310
Fax: 514-412-4254
www.hopitalpourenfants.com/trauma
www.thechildren.com/trauma

March 19, 2014

To whom this may concern,

This is to certify that Ivan Ortega-Deballon has participated as an invited speaker at the Montreal Children's Hospital Trauma Rounds Series.
Mr. Ortega presented "Pre-hospital Emergency Medical Services in Europe: When time is Essential" on March 10, 2014.

Trauma Rounds are approved for credits by the Office for Continuing Health Professional Education (CHPE). The Office for CHPE, Faculty of Medicine, McGill University is fully accredited by the Committee on Accreditation of Canadian Medical Education (CACME).

Sincerely,

Debbie Friedman BSc. pht. M. Mgmt.
Trauma Director / Directrice de la traumatologie
Director Canadian Hospitals Injury Reporting and Prevention Program (CHIRPP)
Directrice Système canadien hospitalier d'information et de recherche en prévention des traumatismes (SCHIRPT)
Assistant Professor, Department of Pediatrics, Faculty of Medicine, McGill University
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Amanda Fitzgerald
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Centre universitaire de santé McGill
Trauma Rounds
Administrative Procedures Specialist - Trauma
The Montreal Children's Hospital
McGill University Health Centre
amanda.fitzgerald@muhc.mcgill.ca

Centre de santé et de services sociaux de Laval

Le 22 avril, 2015

A l'attention de :

Directeur de thèse de D. Ivan Ortega Deballon
Facultad de Medicina y Ciencias de la Salud, Departamento de Enfermeria.
Universidad de Alcala de Henares de Madrid, Spain

Objet : Participation à la Semaine Nationale du Don d'Organes et de Tissus 2015
CSSS Laval

Directeur de thèse,

Je tiens à remercier Mr. Ortega pour sa participation à la Semaine Nationale du Don d'Organes et de Tissus à l'hôpital Cité de la Santé. Le mardi 21 avril, 2015 M. Ortega a donné deux conférences stimulantes (1 heure chacun) au sujet de : MODÈLE ESPAGNOL DE DON D'ORGANES ET NOUVEAU PROTOCOL POTENTIEL AU CANADA (ECPR and uDCD).

Plusieurs membres de l'équipe multidisciplinaire étaient présents et ont trouvé le sujet très intéressant.

Je tiens à le remercier encore pour son implication.

Merci et bonne journée.

Mme. Shelley Cogland- au nom du comité de don d'organes et de tissus
Infirmière de liaison en don d'organes
CSSS Laval
450-668-1010 poste : 23279
shelley.cogland@transplantquebec.ca

RESUMEN COMUNICACIÓN

TÍTULO

GESTIÓN CONFORME A LA ÉTICA Y A LA NORMA, LOS PROGRAMAS DE DONACIÓN DE ÓRGANOS A CORAZÓN PARADO EXTRAHOSPITALARIOS (DCPE) Y LA REANIMACIÓN DE LA PARADA CARDIORRESPIRATORIA (PCR)

INTRODUCCIÓN

Los límites que separan la Vida y la Muerte son,
en el mejor de los casos, sombríos y vagos.
¿Quién dirá dónde acaba uno
y dónde empieza el otro?
Edgar Allan Poe, 1844

Hace ya más de medio siglo [1] que se inició la donación y trasplante de órganos y tejidos provenientes de cadáveres cuya muerte es determinada por criterios circulatorios [2], tras paro cardíaco inesperado [3]. Las dificultades técnicas en la preservación de estos órganos y tejidos, durante lo que se convino en denominar tiempo de isquemia caliente (warm ischemic time, WIT [4]) hizo que se desestimasen estos durante años, centrando los esfuerzos en el grupo de donantes determinados fallecidos por criterios de muerte encefálica (donors after brain death, DBD).
La creciente demanda de órganos para trasplante convive con el aumento de la esperanza de vida en las sociedades desarrolladas [6]. Por otro lado, se ha producido una mejora en la seguridad vial y una consiguiente reducción de morbimortalidad por accidentes de tráfico, especialmente entre los motoristas por el uso obligatorio del casco. A esto se añade el manejo más eficaz y multidisciplinar, en unidades específicas, de pacientes con lesiones traumáticas craneoencefálicas o enfermedades cerebrovasculares agudas. Todo ello conlleva un paulatino descenso de los diagnósticos de muerte encefálica en las unidades de cuidados intensivos hospitalarios en nuestro país. [7]
Ante esta realidad, y dado el correlativo descenso de las tasas de donación de órganos al existir menos candidatos, tras un proceso reflexivo previo sobre la situación, se implementan desde la Organización Nacional de Trasplantes (ONT) programas transversales de donación de órganos tras determinación de la muerte por criterios circulatorios (Donor after Circulatory Determination of Death, DCDD). Estos, involucran a servicios prehospitalarios de emergencia médica (SEM), servicios hospitalarios (urgencias, unidades de cuidados intensivos, coordinación de trasplantes, unidades quirúrgicas, servicios de laboratorio, anatomía patología y servicios administrativos, entre otros), pero también a la propia ONT y a la sociedad (potenciales donantes y potenciales receptores, así como sus familias). Todos estos eslabones, absolutamente esenciales, se coordinan para conformar unos programas [4,8-15] que, actualmente, obtienen similares resultados [14], en ciertos casos superiores, [15] en lo que a supervivencia con calidad de vida a largo plazo de los receptores trasplantados se refiere.

OBJETIVOS

* Analizar desde un enfoque gestor-ético-legal-enfermero los porgramas de DCPE
* Proponer un manejo integral de la PCR que optimice los recusos asistenciales sin olvidar la normativa vigente, la ética profesional y tendiendo a la excelencia en los cuidados

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MATERIAL Y MÉTODO

* Se analiza el protocolo existente de DCPE en la Comunidad de Madrid (que se ha adoptado en otras 6 Comunidades Autónomas de España y en ciertos departamentos de Francia)
* Se detectan mediante análisis matricial DAFO las debilidades, amenazas, fortalezas y oportunidades
* Se proponen mejoras en la gestión de los RR.MM y RR.HH en los programas de DCPE (Ver protocolo propuesto de manejo integral de la PCR)

RESULTADOS

Procedimiento del programa de DCDD con potenciales donantes traídos desde el ámbito extrahospitalario (uncontrolled Donation after Circulatory Determination of Death, uDCDD)

Los DCDD extrahospitalarios (programas de uDCDD) incluyen a aquellos pacientes que, habiendo sufrido una parada cardíaca extrahospitalaria (PCE), tras un tiempo de reanimación (RCP) determinado, son trasladados ya como potenciales donantes. Por lo tanto, nada se hace desde ese momento por salvar su vida, sino por preservar sus órganos. Es decir, corresponden al tipo II de Maastricht, llamados donantes incontrolados porque no podemos conocer con exactitud el tiempo de isquemia caliente (WIT) y porque el suceso desencadenante de la PCE ha sido súbito e inesperado.
Para que se inicie el protocolo, el equipo de la unidad del SEM que está atendiendo al paciente debe activarlo. [4]

Gestión de los recursos en un SEM con programa de uDCDD.

En todos los programas de uDCDD actualmente activos en España, el SEM pone sus recursos a disposición del potencial donante. Hablamos de los vectores de transporte (UVIs móviles terrestres o incluso aéreas, si la distancia al hospital hace que el cumplimiento del WIT se haga difícil) [5]
Otros programas internacionales de uDCDD, como el existente en New York City [15] han resuelto de forma pionera un aspecto operativo de interés. Cuando se detecta un potencial donante de órganos, un vehículo denominado de preservación de órganos (organ preservation vehicle, OPV) con personal y material específico para este tipo de procedimientos, se desplaza hasta el punto donde se encuentra la unidad del SEM local atendiendo la PCE. El estatus ya no es de víctima, sino de fallecido, ya que se certifica la misma in situ previamente por el equipo médico del OPV. Se inicia, sólo entonces, el traslado, que es realizado en el OPV, recurso que no pertenece al operativo asistencial del SEM, sino que existe ad hoc para responder a las necesidades logísticas planteadas por el programa de uDCDD. Por lo tanto, ni el vehículo en que se hace, ni el personal que lo tripula es restado al operativo que atiende las situaciones de emergencia de los ciudadanos.
Sin embargo, en España [8,14] y Francia, [10,13,16] los medios humanos (médicos, enfermeras y técnicos de emergencias), los recursos (unidades de Soporte Vital Avanzado tipo UVI móvil, bien terrestres, bien aéreas) y los medios materiales (compresores torácicos automáticos, CTA) pertenecen al SEM. [4] Esto nos lleva a analizar el programa de uDCDD desde un criterio gestor. En concreto, debemos referirnos al concepto economicista de coste de oportunidad, definido [17] como el valor de la mejor de aquellas alternativas no elegidas al decidir dedicar recursos escasos a un propósito y no al otro.

RESUMEN COMUNICACIÓN

En los actuales programas de uDCDD de España y Francia, se traslada en una UVI móvil, bien por vía terrestre o, incluso, en un helicóptero sanitario en caso de hacerse el traslado desde zonas alejadas del hospital, a un potencial donante. Ya no es ni tratado ni considerado como paciente, puesto que todo intento de reanimación ha sido considerado fútil tras intentarse esta durante un tiempo que, en principio, nunca debiera ser inferior a los 30 minutos según los estándares cláiscos. El traslado de ese potencial donante es realizado por un equipo de profesionales completo (1 Médico de Emergencias, 1 Enfermera de Emergencias y 2 Técnicos de Emergencias). Dejamos de tener ese recurso tan especializado a disposición de la población ante cualquier urgencia médica durante un tiempo nunca inferior a los 90 minutos que dura el proceso. [4]
¿Estamos asumiendo y aceptando este elevadísimo coste de oportunidad?
Un análisis entre el coste y el beneficio al asumir este tipo de gestión y de las repercusiones de estos criterios, debe realizarse. No olvidemos que la víctima, potencial donante, trasladada en un medio tan escaso como necesario, puede no ser donante real finalmente por negativa familiar o por múltiples causas de tipo médico o legal. La última revisión del programa de uDCDD en Madrid muestra que, en un 44% de los casos en que se inició el protocolo, este no finalizó en obtención de órganos, por una u otra causa. [18] Obsérvese que en el 100% de los casos, se emplearon los recursos especialísimos antes descritos (sic) y, claro está, en el 100% de las ocasiones dejaron de estar disponibles para cumplir su misión esencial: atender urgencias y emergencias. Entre las causas de no obtención de órganos al final del proceso se incluyen:

1º. Las propias del donante como, por ejemplo, contraindicación médica, patologías conocidas solo en el hospital, edad excluida del protocolo, o la recuperación de pulso o signos de circulación (sic).
2º. Otras externas como la negativa del hospital receptor, de la familia tras pedir la autorización para la extracción de los órganos del cadáver ya canulado en quirófano previamente, la negativa judicial al procedimiento o fallos logísticos (el donante no puede ser canulado para iniciarse la preservación, o tras canularse y conectarse a circuito extracorpóreo, esta técnica no es eficaz y se suspende) y excesos de tiempo en el proceso hospitalario (superando el WIT límite). [2,4]

Todo esto ha generado cierto malestar en profesionales de los SEM de España y Francia. Ellos, buscando una actuación coherente con la profesionalidad, la humanidad, la ética y la legislación, han solicitado una modificación del protocolo conforme a la lex artis tanto a nivel médico y asistencial como desde la gestión eficaz, eficiente y equitativa de los recursos del SEM. [19,20,21]
El coste de oportunidad cuando los recursos son tan limitados y especializados y, sobre todo, dedicados a la asistencia a emergencias médicas, es elevadísimo cuando las decisiones de cómo gestionarlos puede llegar a postergar el principio universal de persecución de la excelencia profesional denominado patients first ethic; los pacientes, por encima de todo. [22-25]

CONCLUSIONES

Conclusiones y propuesta de solución

Los profesionales de enfermería, como artistas del cuidado y depositarios de la confianza de los pacientes y sus familias, no sólo en su dimensión asistencial sino también como gestores de recursos materiales y de procesos, proponemos un criterio en la gestión de los recursos de emergencias que sea acorde con la excelencia profesional. (Figura 1, que no me permite el sistema incluir)

En concreto, establecemos las siguientes prioridades gestoras:

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1.- Todos los recursos móviles de emergencia de Soporte Vital Avanzado deben disponer de compresores torácicos automáticos (CTA) para poder asegurar los siguientes cuidados
a.- RCP de alta calidad e ininterrumpida durante el traslado (Ongoing CPR) en pacientes seleccionados por un modelo predictivo, para revertir las causas que provocan la PCE en el hospital (mediante cateterismo de emergencia en patología coronaria, mediante circulación extracorpórea o ECMO en shock cardiogénico refractario, mediante trombólisis si el origen es embolismo cardiopulmonar, o mediante hipotermia moderada inducida terapéuticamente, etc)
b.- Sólo cuando la Ongoing CPR sea considerada fútil ab initio o cuando las técnicas hospitalarias fracasen o no se instauren por criterios de futilidad, ese paciente podrá ser considerado potencial donante.
2.- Un recurso tan escaso y especializado como un Helicóptero Sanitario o una UVI móvil terrestre no es el recurso más idóneo, desde el principio de la justicia distributiva de los recursos, para realizar un protocolo de uDCDD. Sobre todo en aquellas regiones donde el Helicóptero y/o la UVI móvil son únicos, emplearlos en este tipo de misiones supone asumir un coste de oportunidad que deriva en conflictos éticos y asistenciales con posibles repercusiones legales por responsabilidad patrimonial (por mal funcionamiento de los servicios públicos).
3.- La prioridad absoluta de un SEM debe ser salvar vidas e intentar evitar secuelas. Sólo subsidiariamente, y tras estar inmersos en programas de excelencia de Ongoing CPR, cabe plantearse estarlo en los de uDCDD. En ninguna región de España se realizan hoy, todavía, los primeros. En 6 regiones de España, sin embargo, se realizan los segundos. ¿Optamos por salvar vidas de pacientes o por preservar órganos de potenciales donantes?. Como Enfermeros de Urgencias y Emergencias y como gestores de los recursos nos preguntamos: ¿Podemos, debemos y queremos hacer las cosas mejor?. Si tenemos los medios, los conocimientos y la voluntad, entonces la respuesta es SÍ. Los medios existen, la evidencia creciente también. ¿Cómo nos podrá fallar la voluntad cuando tendemos a aunar excelencia asistencial y gestora?. El reto está en nuestras manos.

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IHSP WORKSHOP

Organ Donation After Death: Ethical Considerations

Valerie Gateau, CERSES, Université Paris Descartes
"The Ethics of Organ Salvaging on Deceased Persons"

Jurgen De Wispelaere, Institute for Health and Social Policy, McGill University
"Family Ties? Why Family Involvement in Posthumous Organ Donation Matters"

Ivan Ortega-Deballon, Division of Critical Care Medicine, Montreal Children's Hospital
"Death Determination, Dying Process and Organ Donation Options"

Wednesday, February 26, 2014
9:30 AM-1:00 PM

Institute for Health and Social Policy
Charles Meredith House
1130 Pine Avenue West

All are welcome – but space is limited
Venue is wheelchair accessible

IHSP

McGill

Institute for Health and Social Policy
L'Institut des politiques sociales et de la santé

26/2/2014

To whom it may concern

This is to certify that IVAN ORTEGA -DEBALLON, Research Associate at the Deceased Organ Donation Research Program, Critical Care Division - Montreal Children's Hospital, has participated as an invited speaker to the "Organ Donation After Death: Ethical Considerations" workshop, held on Wednesday, February 26, 2014 at the Institute for Health and Social Policy, McGill University with a paper on "Death determination, dying process and organ donation options".

Sincerely

Jurgen De Wispelaere
MERHC Postdoctoral Fellow
IHSP, McGill University
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Montreal, Quebec
CANADA H3A 2A7
Fax: 514-398-8455

July 10, 2014

Thank you to: Iván Ortega-Deballon

Dear Ivan,

I am writing to express my deep appreciation for your presentation titled “Criteria for Determination of Death and Implications for Organ Donation”, which you presented in our graduate seminar *Ethics in Advanced Practice* (NUR2 642), during the winter 2014 session. This course is a required course in our Master’s of Nursing Program.

Your presentation was very engaging and highlighted important controversies and innovations in organ donation. Many students spoke very highly about your presentation.

Thank you for sharing your precious time and extraordinary expertise!

Sincerely,

Franco A. Carnevale, RN, PhD
Professor, Ingram School of Nursing
Associate Member, Department of Pediatrics
Affiliate Member, Biomedical Ethics Unit
Adjunct Professor, Counselling Psychology
McGill University

Email: franco.carnevale@mcgill.ca

“Criteria for determination of death and implications for organ donation”

Ivan Ortega Deballon, LL.B., ACNS, Registered Flight Nurse, PhD Candidate.

Montreal Children's Hospital, McGill University, *Montréal, Canada*

Thursday, January 16th, 12:00pm–1:00pm

110, avenue des Pins Ouest

Room André-Barbeau, Institut de recherches cliniques de Montréal (IRCM)

The Montréal Neuroethics Network

Special Seminar by Ivan Ortega Deballon, Montreal Children’s Hospital, McGill University, Montreal, Canada

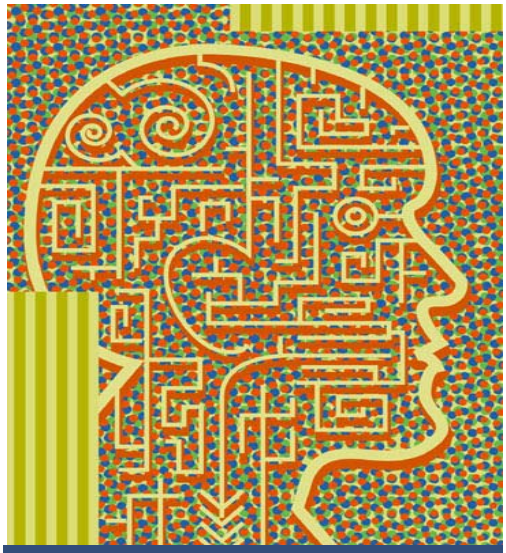
The **Montreal Neuroethics Network** promotes neuroethics training, education and dialogue by exposing various audiences to neuroethics issues; fostering collaboration and mutual learning; and ensure Montreal's leadership in addressing ethical and social issues in neuroscience and healthcare delivery through inter-institutional collaborations.

For additional information, email:
neuroethics@ircm.qc.ca

All are welcome but please note that space is limited for this seminar. Please RSVP by January 15th at veljko.dubljevic@ircm.qc.ca.

Ivan Ortega is a Research Associate at the Division of Critical Care Medicine, Montreal Children’s Hospital (MCH). He is working within the Deceased Organ Donation research program at MCH and the Loeb Chair and Research Consortium at the University of Ottawa. He is interested in working on the complex intersection of pre-mortem life-saving versus post-mortem organ-preserving interventions such as CPR and ECMO. He is also involved with health policy development relevant to deceased donation with Canadian Blood Services.

Ivan is a specialist in law and in medical ethics. He is also an Emergency Nurse Practitioner and has worked in emergency nursing care in the Helicopter Emergency Medical Service in Madrid, Spain where he was responsible for the care of potential organ donors during transport.



“Criteria for determination of death and implications for organ donation”

Ivan Ortega Deballon, LL.B., ACNS, Infirmier, candidat au doctorat.

Université McGill, Montréal, Canada

Jeudi le 16 janvier, 12h00 à 13h00

110, avenue des Pins Ouest

Salle André-Barbeau, Institut de recherches cliniques de Montréal (IRCM)

Le Réseau neuroéthique de Montréal

Séminaire spécial d’Ivan Ortega Deballon, Université McGill, Montréal, Canada

Le **Réseau neuroéthique de Montréal** encourage la formation et le dialogue en neuroéthique en exposant divers publics aux enjeux neuroéthiques, favorise la collaboration et l'apprentissage mutuel et assure le leadership de Montréal dans le traitement des questions éthiques et sociales reliées aux neurosciences et aux soins de santé par le biais de collaborations interinstitutionnelles.

Pour plus d’information, communiquez par courriel: neuroethics@ircm.qc.ca

Tous sont les bienvenus mais SVP réservez d’ici le 15 janvier auprès de veljko.dubljevic@ircm.qc.ca afin de vous inscrire.

Ivan Ortega est un associé de recherche à la Division de la médecine de soins intensifs, Hôpital de Montréal pour enfants (HME). Il travaille au sein du programme de recherche de dons d'organes pour les donneurs décédés au HME et de la Chaire Loeb à l'Université d'Ottawa. Il s’intéresse à l'intersection complexe entre les interventions pour le sauvetage pré-mortem versus les interventions post-mortem visant la préservation des organes tels que la RCR et l'ECMO. Il est également impliqué dans le développement de la politique de santé à l’égard du don d’organes après le décès pour la Société canadienne du sang.

Ivan est un spécialiste en droit et en éthique médicale. Il est également un infirmier praticien d'urgence et a travaillé en soins infirmiers d'urgence au service médical d'urgence par hélicoptère à Madrid, en Espagne, où il était responsable de la prise en charge des donneurs d'organes potentiels pendant le transport.

Semaine nationale du don d'organes et de tissus 2015

❖Vendredi, 17 avril 2015 - » 10h00 à 14h00
Transplant & Héma- Québec Kiosques
Entrée de la cafétéria

❖Mardi, le 21 avril 2015 - » 11h30 à 12h15
- » 12h30 à 13h15
Dîner-Causerie
MODÈLE ESPAGNOL DE DON D'ORGANES ET NOUVEAU PROTOCOL POTENTIEL AU CANADA
Ivan Ortega Deballon, ll. B., ACNS, infirmier, candidat au doctorat, Université McGill
Auditorium du bloc D, DS-020
***Le dîner sera offert mais en quantités limitées. S'il vous plaît appelez 23279 pour s'inscrire avant le 17 avril 2015

PASSE LE RELAIS- CONSENTI AU DON D'ORGANES ET DE TISSUS

Centre de santé et de services sociaux de Laval

HÉMA-QUÉBEC

TRANSPLANT QUÉBEC

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Head: Prof. Aleš Linhart, MD, DrSc.

Subject: Confirmation for Ivan Ortega-Deballon

To whom it may concern:

I confirm, that Ass. Prof. Ivan Orteg-Deballon presented at our department the lecture entitled **Protocols for uncontrolled donation after circulatory death: a systematic review of international guidelines, practices and transplant outcomes.**

Sincerely,

VŠEOBECNÁ FAKULTNÍ NEMOCNICE V PRAZE 02004 II INTERNÍ KLINIKA U NEMOCNICE 2 128 08 PRAHA 2

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ANEXO VII

Implicaciones de la Tesis Doctoral

PUBLICACIONES

ARTICULOS Y CAPITULOS DE LIBROS DERIVADOS DE LA TESIS DOCTORAL

"Donación tras muerte circulatoria no controlada y
Reanimación con circulación extracorpórea en paradas cardíacas extrahospitalarias"

Iván Ortega Deballon

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Part 1: Executive Summary

2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

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Introduction

Publication of the *2015 American Heart Association* (AHA) *Guidelines Update for Cardiopulmonary Resuscitation* (CPR) *and Emergency Cardiovascular Care* (ECC) marks 49 years since the first CPR guidelines were published in 1966 by an Ad Hoc Committee on Cardiopulmonary Resuscitation established by the National Academy of Sciences of the National Research Council.[1] Since that time, periodic revisions to the Guidelines have been published by the AHA in 1974,[2] 1980,[3] 1986,[4] 1992,[5] 2000,[6] 2005,[7] 2010,[8] and now 2015. The *2010 AHA Guidelines for CPR and ECC* provided a comprehensive review of evidence-based recommendations for resuscitation, ECC, and first aid. The *2015 AHA Guidelines Update for CPR and ECC* focuses on topics with significant new science or ongoing controversy, and so serves as an update to the *2010 AHA Guidelines for CPR and ECC* rather than a complete revision of the Guidelines.

The purpose of this Executive Summary is to provide an overview of the new or revised recommendations contained in the 2015 Guidelines Update. This document does not contain extensive reference citations; the reader is referred to Parts 3 through 9 for more detailed review of the scientific evidence and the recommendations on which they are based.

There have been several changes to the organization of the 2015 Guidelines Update compared with 2010. "Part 4: Systems of Care and Continuous Quality Improvement" is an important new Part that focuses on the integrated structures and processes that are necessary to create systems of care for both in-hospital and out-of-hospital resuscitation capable of measuring and improving quality and patient outcomes. This Part replaces the "CPR Overview" Part of the 2010 Guidelines.

Another new Part of the 2015 Guidelines Update is "Part 14: Education," which focuses on evidence-based recommendations to facilitate widespread, consistent, efficient and effective implementation of the AHA Guidelines for CPR and ECC into practice. These recommendations will target resuscitation education of both lay rescuers and healthcare providers. This Part replaces the 2010 Part titled "Education, Implementation, and Teams." The 2015 Guidelines Update does not include a separate Part on adult stroke because the content would replicate that already offered in the most recent AHA/American Stroke Association guidelines for the management of acute stroke.[9,10]

Finally, the 2015 Guidelines Update marks the beginning of a new era for the AHA Guidelines for CPR and ECC, because the Guidelines will transition from a 5-year cycle of periodic revisions and updates to a Web-based format that is continuously updated. The first release of the Web-based integrated Guidelines, now available online at ECCguidelines.heart.org is based on the comprehensive 2010 Guidelines plus the 2015 Guidelines Update. Moving forward, these Guidelines will be updated by using a continuous evidence evaluation process to facilitate more rapid translation of new scientific discoveries into daily patient care.

Creation of practice guidelines is only 1 link in the chain of knowledge translation that starts with laboratory and clinical science and culminates in improved patient outcomes. The AHA ECC Committee has set an impact goal of doubling bystander CPR rates and doubling cardiac arrest survival by 2020. Much work will be needed across the entire spectrum of knowledge translation to reach this important goal.

Evidence Review and Guidelines Development Process

The process used to generate the *2015 AHA Guidelines Update for CPR and ECC* was significantly different from the process used in prior releases of the Guidelines, and marks the planned transition from a 5-year cycle of evidence review to a continuous evidence evaluation process. The AHA continues to partner with the International Liaison Committee on Resuscitation (ILCOR) in the evidence review process. However, for 2015, ILCOR prioritized topics for systematic review based on clinical significance and availability of new

The American Heart Association requests that this document be cited as follows: Neumar RW, Shuster M, Callaway CW, Gent LM, Atkins DL, Bhanji F, Brooks SC, de Caen AR, Donnino MW, Ferrer JME, Kleinman ME, Kronick SL, Lavonas EJ, Link MS, Mancini ME, Morrison LJ, O'Connor RE, Sampson RA, Schexnayder SM, Singletary EM, Sinz EH, Travers AH, Wyckoff MH, Hazinski MF. Part 1: executive summary: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2015;132(suppl 2):S315–S367.

(*Circulation.* 2015;132[suppl 2]:S315–S367. DOI: 10.1161/CIR.0000000000000252.)

***Circulation* is available at http://circ.ahajournals.org** **DOI: 10.1161/CIR.0000000000000252**

evidence. Each priority topic was defined as a question in PICO (population, intervention, comparator, outcome) format. Many of the topics reviewed in 2010 did not have new published evidence or controversial aspects, so they were not reviewed in 2015. In 2015, 165 PICO questions were addressed by systematic reviews, whereas in 2010, 274 PICO questions were addressed by evidence evaluation. In addition, ILCOR adopted the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process for evidence evaluation and expanded the opportunity for public comment. The output of the GRADE process was used to generate the *2015 International Consensus on CPR and ECC Science With Treatment Recommendations* (CoSTR).[11,12]

The recommendations of the ILCOR 2015 CoSTR were used to inform the recommendations in the *2015 AHA Guidelines Update for CPR and ECC*. The wording of these recommendations is based on the AHA classification system for evidentiary review (see "Part 2: Evidence Evaluation and Management of Conflicts of Interest").

The *2015 AHA Guidelines Update for CPR and ECC* contains 315 classified recommendations. There are 78 Class I recommendations (25%), 217 Class II recommendations (68%), and 20 Class III recommendations (7%). Overall, 3 (1%) are based on Level of Evidence (LOE) A, 50 (15%) are based on LOE B-R (randomized studies), 46 (15%) are based on LOE B-NR (nonrandomized studies), 145 (46%) are based on LOE C-LD (limited data), and 73 (23%) are based on LOE C-EO (consensus of expert opinion). These results highlight the persistent knowledge gap in resuscitation science that needs to be addressed through expanded research initiatives and funding opportunities.

As noted above, the transition from a 5-year cycle to a continuous evidence evaluation and Guidelines update process will be initiated by the 2015 online publication of the AHA Integrated Guidelines for CPR and ECC at ECCguidelines.heart.org. The initial content will be a compilation of the 2010 Guidelines and the 2015 Guidelines Update. In the future, the Scientific Evidence Evaluation and Review System (SEERS) Web-based resource will also be periodically updated with results of the ILCOR continuous evidence evaluation process at www.ilcor.org/seers.

Part 3: Ethical Issues

As resuscitation practice evolves, ethical considerations must also evolve. Managing the multiple decisions associated with resuscitation is challenging from many perspectives, especially when healthcare providers are dealing with the ethics surrounding decisions to provide or withhold emergency cardiovascular interventions.

Ethical issues surrounding resuscitation are complex and vary across settings (in or out of hospital), providers (basic or advanced), patient population (neonatal, pediatric, or adult), and whether to start or when to terminate CPR. Although the ethical principles involved have not changed dramatically since the 2010 Guidelines were published, the data that inform many ethical discussions have been updated through the evidence review process. The 2015 ILCOR evidence review process and resultant 2015 Guidelines Update include several recommendations that have implications for ethical decision making in these challenging areas.

Significant New and Updated Recommendations That May Inform Ethical Decisions

- The use of extracorporeal CPR (ECPR) for cardiac arrest
- Intra-arrest prognostic factors for infants, children, and adults
- Prognostication for newborns, infants, children, and adults after cardiac arrest
- Function of transplanted organs recovered after cardiac arrest

New resuscitation strategies, such as ECPR, have made the decision to discontinue cardiac arrest measures more complicated (see "Part 6: Alternative Techniques and Ancillary Devices for Cardiopulmonary Resuscitation" and "Part 7: Adult Advanced Cardiovascular Life Support"). Understanding the appropriate use, implications, and likely benefits related to such new treatments will have an impact on decision making. There is new information regarding prognostication for newborns, infants, children, and adults with cardiac arrest and/or after cardiac arrest (see "Part 13: Neonatal Resuscitation," "Part 12: Pediatric Advanced Life Support," and "Part 8: Post–Cardiac Arrest Care"). The increased use of targeted temperature management has led to new challenges for predicting neurologic outcomes in comatose post–cardiac arrest patients, and the latest data about the accuracy of particular tests and studies should be used to guide decisions about goals of care and limiting interventions.

With new information about the success rate for transplanted organs obtained from victims of cardiac arrest, there is ongoing discussion about the ethical implications around organ donation in an emergency setting. Some of the different viewpoints on important ethical concerns are summarized in "Part 3: Ethical Issues." There is also an enhanced awareness that although children and adolescents cannot make legally binding decisions, information should be shared with them to the extent possible, using appropriate language and information for their level of development. Finally, the phrase "limitations of care" has been changed to "limitations of interventions," and there is increasing availability of the Physician Orders for Life-Sustaining Treatment (POLST) form, a new method of legally identifying people who wish to have specific limits on interventions at the end of life, both in and out of healthcare facilities.

Part 4: Systems of Care and Continuous Quality Improvement

Almost all aspects of resuscitation, from recognition of cardiopulmonary compromise, through cardiac arrest and resuscitation and post–cardiac arrest care, to the return to productive life, can be discussed in terms of a system or systems of care. Systems of care consist of multiple working parts that are interdependent, each having an effect on every other aspect of the care within that system. To bring about any improvement, providers must recognize the interdependency of the various parts of the system. There is also increasing recognition that out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA) systems of care must function differently. "Part 4: Systems of Care and Continuous Quality Improvement" in this 2015 Guidelines Update makes a clear distinction between the two systems, noting that OHCA frequently is the result of an unexpected event with a reactive element, whereas

and adjuncts to conventional CPR have been developed with the aim of enhancing coronary and cerebral perfusion during resuscitation from cardiac arrest. Since the 2010 Guidelines were published, a number of clinical trials have provided new data regarding the effectiveness of these alternatives. Compared with conventional CPR, many of these techniques and devices require specialized equipment and training. Some have been tested in only highly selected subgroups of cardiac arrest patients; this selection must be noted when rescuers or healthcare systems consider implementation of the devices.

Significant New and Updated Recommendations

- The Resuscitation Outcomes Consortium (ROC) Prehospital Resuscitation Impedance Valve and Early Versus Delayed Analysis (PRIMED) study (n=8718)[14] failed to demonstrate improved outcomes with the use of an impedance threshold device (ITD) as an adjunct to conventional CPR when compared with use of a sham device. This negative high-quality study prompted a Class III: No Benefit recommendation regarding routine use of the ITD.
- One large randomized controlled trial evaluated the use of active compression-decompression CPR plus an ITD.[15] The writing group found interpretation of the true clinical effect of active compression-decompression CPR plus an ITD challenging because of wide confidence intervals around the effect estimate and also because of methodological concerns. The finding of improved neurologically intact survival in the study, however, supported a recommendation that this combination may be a reasonable alternative with available equipment and properly trained providers.
- Three randomized clinical trials comparing the use of mechanical chest compression devices with conventional CPR have been published since the 2010 Guidelines. None of these studies demonstrated superiority of mechanical chest compressions over conventional CPR. Manual chest compressions remain the standard of care for the treatment of cardiac arrest, but mechanical chest compression devices may be a reasonable alternative for use by properly trained personnel. The use of the mechanical chest compression devices may be considered in specific settings where the delivery of high-quality manual compressions may be challenging or dangerous for the provider (eg, prolonged CPR during hypothermic cardiac arrest, CPR in a moving ambulance, CPR in the angiography suite, CPR during preparation for ECPR), provided that rescuers strictly limit interruptions in CPR during deployment and removal of the device (Class IIb, LOE C-EO).
- Although several observational studies have been published documenting the use of ECPR, no randomized controlled trials have evaluated the effect of this therapy on survival.

Knowledge Gaps

- Are mechanical chest compression devices superior to manual chest compressions in special situations such as a moving ambulance, prolonged CPR, or procedures such as coronary angiography?
- What is the impact of implementing ECPR as part of the system of care for OHCA?

Part 7: Adult Advanced Cardiovascular Life Support

The major changes in the 2015 advanced cardiovascular life support (ACLS) guidelines include recommendations regarding prognostication during CPR based on end-tidal carbon dioxide measurements, use of vasopressin during resuscitation, timing of epinephrine administration stratified by shockable or nonshockable rhythms, and the possibility of bundling steroids, vasopressin, and epinephrine administration for treatment of IHCA. In addition, vasopressin has been removed from the pulseless arrest algorithm. Recommendations regarding physiologic monitoring of CPR were reviewed, although there is little new evidence.

Significant New and Updated Recommendations

- Based on new data, the recommendation for use of the maximal feasible inspired oxygen during CPR was strengthened. This recommendation applies only while CPR is ongoing and does not apply to care after ROSC.
- The new 2015 Guidelines Update continues to state that physiologic monitoring during CPR may be useful, but there has yet to be a clinical trial demonstrating that goal-directed CPR based on physiologic parameters improves outcomes.
- Recommendations for ultrasound use during cardiac arrest are largely unchanged, except for the explicit proviso that the use of ultrasound should not interfere with provision of high-quality CPR and conventional ACLS therapy.
- Continuous waveform capnography remained a Class I recommendation for confirming placement of an endotracheal tube. Ultrasound was added as an additional method for confirmation of endotracheal tube placement.
- The defibrillation strategies addressed by the 2015 ILCOR review resulted in minimal changes in defibrillation recommendations.
- The Class of Recommendation for use of standard dose epinephrine (1 mg every 3 to 5 minutes) was unchanged but reinforced by a single new prospective randomized clinical trial demonstrating improved ROSC and survival to hospital admission that was inadequately powered to measure impact on long-term outcomes.
- Vasopressin was removed from the ACLS Cardiac Arrest Algorithm as a vasopressor therapy in recognition of equivalence of effect with other available interventions (eg, epinephrine). This modification valued the simplicity of approach toward cardiac arrest when 2 therapies were found to be equivalent.
- The recommendations for timing of epinephrine administration were updated and stratified based on the initial presenting rhythm, recognizing the potential difference in pathophysiologic disease. For those with a nonshockable rhythm, it may be reasonable to administer epinephrine as soon as feasible. For those with a shockable rhythm, there is insufficient evidence to make a recommendation

about the optimal timing of epinephrine administration, because defibrillation is a major focus of resuscitation.

- The use of steroids in cardiac arrest is controversial. In OHCA, administration of steroids did not improve survival to hospital discharge in 2 studies, and routine use is of uncertain benefit. The data regarding the use of steroids for IHCA were more vexing. In 2 randomized controlled trials led by the same investigators, a pharmacologic bundle that included methylprednisolone, vasopressin, and epinephrine administered during cardiac arrest followed by hydrocortisone given after ROSC improved survival. Whether the improved survival was a result of the bundle or of the steroid therapy alone could not be assessed. As a result of this study, in IHCA, the combination of intra-arrest vasopressin, epinephrine, and methylprednisolone and postarrest hydrocortisone as described by Mentzelopoulos et al[16] may be considered; however, further studies are needed before the routine use of this therapeutic strategy can be recommended (Class IIb, LOE C-LD).
- Prognostication during CPR was also a very active topic. There were reasonably good data indicating that low partial pressure of end-tidal carbon dioxide (P_{ETCO_2}) in intubated patients after 20 minutes of CPR is strongly associated with failure of resuscitation. Importantly, this parameter should not be used in isolation and should not be used in nonintubated patients.
- ECPR, also known as venoarterial extracorporeal membrane oxygenation, may be considered as an alternative to conventional CPR for select patients with refractory cardiac arrest when the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support.

Knowledge Gaps

- More knowledge is needed about the impact on survival and neurologic outcome when physiologic targets and ultrasound are used to guide resuscitation during cardiac arrest.
- The dose-response curve for defibrillation of shockable rhythms is unknown, and the initial shock energy, subsequent shock energies, and maximum shock energies for each waveform are unknown.
- More information is needed to identify the ideal current delivery to the myocardium that will result in defibrillation, and the optimal way to deliver it. The selected energy is a poor comparator for assessing different waveforms, because impedance compensation and subtleties in waveform shape result in a different transmyocardial current among devices at any given selected energy.
- Is a hands-on defibrillation strategy with ongoing chest compressions superior to current hands-off strategies with pauses for defibrillation?
- What is the dose-response effect of epinephrine during cardiac arrest?
- The efficacy of bundled treatments, such as epinephrine, vasopressin, and steroids, should be evaluated, and further studies are warranted as to whether the bundle with synergistic effects or a single agent is related to any observed treatment effect.
- There are no randomized trials for any antiarrhythmic drug as a second-line agent for refractory ventricular fibrillation/pulseless ventricular tachycardia, and there are no trials evaluating the initiation or continuation of antiarrhythmics in the post–cardiac arrest period.
- Controlled clinical trials are needed to assess the clinical benefits of ECPR versus traditional CPR for patients with refractory cardiac arrest and to determine which populations would most benefit.

When ROSC is not rapidly achieved after cardiac arrest, several options exist to provide prolonged circulatory support. These options include mechanical CPR devices, and use of endovascular ventricular assist devices, intra-aortic balloon counterpulsation, and ECPR have all been described. The role of these modalities, alone or in combination, is not well understood. (For additional information, see "Part 6: Alternative Techniques and Ancillary Devices for Cardiopulmonary Resuscitation.")

Part 8: Post–Cardiac Arrest Care

Post–cardiac arrest care research has advanced significantly over the past decade. Multiple studies and trials detail the heterogeneity of patients and the spectrum of pathophysiology after cardiac arrest. Post–cardiac arrest care should be titrated based on arrest etiology, comorbid disease, and illness severity. Thus, the 2015 Guidelines Update integrates available data to help experienced clinicians make the complex set of therapeutic decisions required for these patients. The central principles of postarrest care are (1) to identify and treat the underlying etiology of the cardiac arrest, (2) to mitigate ischemia-reperfusion injury and prevent secondary organ injury, and (3) to make accurate estimates of prognosis to guide the clinical team and to inform the family when selecting goals of continued care.

New Developments

Early coronary angiography and coronary intervention are recommended for patients with ST elevation as well as for patients without ST elevation, when an acute coronary event is suspected. The decision to perform coronary angiography should not include consideration of neurologic status, because of the unreliability of early prognostic signs. Targeted temperature management is still recommended for at least 24 hours in comatose patients after cardiac arrest, but clinicians may choose a target temperature from the wider range of 32°C to 36°C. Estimating the prognosis of patients after cardiac arrest is best accomplished by using multiple modalities of testing: clinical examination, neurophysiological testing, and imaging.

Significant New and Updated Recommendations

One of the most common causes of cardiac arrest outside of the hospital is acute coronary occlusion. Quickly identifying and treating this cause is associated with better survival and better functional recovery. Therefore, coronary angiography should be performed emergently (rather than later in the hospital stay or not at all) for OHCA patients with suspected cardiac etiology of arrest and ST elevation on ECG. Emergency coronary angiography is reasonable for select (eg, electrically or hemodynamically unstable) adults who are without ST

Part 1: Executive Summary: 2015 Guidelines Update Writing Group Disclosures, *Continued*

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Elizabeth H. Sinz	Pennsylvania State University College of Medicine	None	None	None	None	None	American Heart Association†	None
Andrew H. Travers	Emergency Health Services, Nova Scotia	None	None	None	None	None	American Heart Association†	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Appendix

2015 Guidelines Update: Master List of Recommendations

Year Last Reviewed	Topic	Recommendation	Comments
Part 3: Ethical Issues			
2015	The Use of Extracorporeal CPR in OHCA	There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support (Class IIb, LOE C-LD).	new for 2015
2015	Intra-arrest Prognostic Factors for Cardiac Arrest in Infants and Children	Multiple variables should be used when attempting to prognosticate outcomes during cardiac arrest (Class I, LOE C-LD).	new for 2015
2015	The Use of a Prognostic Score in the Delivery Room for Preterm Infants	However, in individual cases, when counseling a family and constructing a prognosis for survival at gestations below 25 weeks, it is reasonable to consider variables such as perceived accuracy of gestational age assignment, the presence or absence of chorioamnionitis, and the level of care available for location of delivery. It is also recognized that decisions about appropriateness of resuscitation below 25 weeks of gestation will be influenced by region-specific guidelines. In making this statement, a higher value was placed on the lack of evidence for a generalized prospective approach to changing important outcomes over improved retrospective accuracy and locally validated counseling policies. The most useful data for antenatal counseling provides outcome figures for infants alive at the onset of labor, not only for those born alive or admitted to a neonatal intensive care unit (Class IIb, LOE C-LD)	new for 2015
2015	Terminating Resuscitative Efforts in Term Infants	We suggest that, in infants with an Apgar score of 0 after 10 minutes of resuscitation, if the heart rate remains undetectable, it may be reasonable to stop assisted ventilations; however, the decision to continue or discontinue resuscitative efforts must be individualized. Variables to be considered may include whether the resuscitation was considered optimal; availability of advanced neonatal care, such as therapeutic hypothermia; specific circumstances before delivery (eg, known timing of the insult); and wishes expressed by the family (Class IIb, LOE C-LD)	updated for 2015
2015	The Use of ECPR in IHCA	There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support. (Class IIb, LOE C-LD).	new for 2015
2015	The Use of ECPR in IHCA	ECPR may be considered for pediatric patients with cardiac diagnoses who have IHCA in settings with existing ECMO protocols, expertise, and equipment (Class IIb, LOE C-LD).	new for 2015
2015	Terminating Cardiac Arrest Resuscitative Efforts in Pediatric IHCA	Multiple variables should be used when attempting to prognosticate outcomes during cardiac arrest (Class I, LOE C-LD).	new for 2015
2015	Prognostication During CPR	In intubated patients, failure to achieve an $ETCO_2$ of greater than 10 mm Hg by waveform capnography after 20 minutes of CPR may be considered as one component of a multimodal approach to decide when to end resuscitative efforts but should not be used in isolation (Class IIb, LOE C-LD).	new for 2015

(*Continued*)

2015 Guidelines Update: Master List of Recommendations, *Continued*

Year Last Reviewed	Topic	Recommendation	Comments
2015	Prognostic Testing in Adult Patients After Cardiac Arrest: Blood Markers	When performed with other prognostic tests at 72 hours or more after cardiac arrest, it may be reasonable to consider high serum values of NSE at 48 to 72 hours after cardiac arrest to support the prognosis of a poor neurologic outcome (Class IIb, LOE B-NR), especially if repeated sampling reveals persistently high values (Class IIb, LOE C-LD).	updated for 2015
2015	Ethics of Organ and Tissue Donation	We recommend that all patients who are resuscitated from cardiac arrest but who subsequently progress to death or brain death be evaluated for organ donation (Class I, LOE B-NR).	updated for 2015
2015	Ethics of Organ and Tissue Donation	Patients who do not have ROSC after resuscitation efforts and who would otherwise have termination of efforts may be considered candidates for kidney or liver donation in settings where programs exist (Class IIb, LOE B-NR).	new for 2015
The following recommendations were not reviewed in 2015. For more information, see the *2010 AHA Guidelines for CPR and ECC*, "Part 3: Ethics."			
2010	Principle of Futility	Conditions such as irreversible brain damage or brain death cannot be reliably assessed or predicted at the time of cardiac arrest. Withholding resuscitation and the discontinuation of life-sustaining treatment during or after resuscitation are ethically equivalent. In situations where the prognosis is uncertain, a trial of treatment may be initiated while further information is gathered to help determine the likelihood of survival, the patient's preferences, and the expected clinical course (Class IIb, LOE C).	not reviewed in 2015
2010	Terminating Resuscitative Efforts in a BLS Out-of-Hospital System	It is recommended that regional or local EMS authorities use the BLS termination rule to develop protocols for the termination of resuscitative efforts by BLS providers for adult victims of cardiac arrest in areas where advanced life support is not available or may be significantly delayed (Class I, LOE A).	not reviewed in 2015
2010	Terminating Resuscitative Efforts in a BLS Out-of-Hospital System	The reliability and validity of this rule is uncertain if modified (Class IIb, LOE A).	not reviewed in 2015
2010	Terminating Resuscitative Efforts in an ALS Out-of-Hospital System	An ALS termination of resuscitation rule was derived from a diverse population of rural and urban EMS settings. This rule recommends considering terminating resuscitation when ALL of the following criteria apply before moving to the ambulance for transport: (1) arrest was not witnessed; (2) no bystander CPR was provided; (3) no ROSC after full ALS care in the field; and (4) no AED shocks were delivered. This rule has been retrospectively externally validated for adult patients in several regions in the US, Canada, and Europe, and it is reasonable to employ this rule in all ALS services (Class IIa, LOE B).	not reviewed in 2015
2010	Terminating Resuscitative Efforts in a Combined BLS and ALS Out-of-Hospital System	In a tiered ALS- and BLS-provider system, the use of a universal rule can avoid confusion at the scene of a cardiac arrest without compromising diagnostic accuracy. The BLS rule is reasonable to use in these services (Class IIa, LOE B).	not reviewed in 2015
2010	Providing Emotional Support to the Family During Resuscitative Efforts in Cardiac Arrest	In the absence of data documenting harm and in light of data suggesting that it may be helpful, offering select family members the opportunity to be present during a resuscitation is reasonable and desirable (assuming that the patient, if an adult, has not raised a prior objection) (Class IIa, LOE C for adults and Class I, LOE B for pediatric patients).	not reviewed in 2015
2010	Providing Emotional Support to the Family During Resuscitative Efforts in Cardiac Arrest	In the absence of data documenting harm and in light of data suggesting that it may be helpful, offering select family members the opportunity to be present during a resuscitation is reasonable and desirable (assuming that the patient, if an adult, has not raised a prior objection) (Class IIa, LOE C for adults and Class I, LOE B for pediatric patients).	not reviewed in 2015
2010	Ethics of Organ and Tissue Donation	It is reasonable to suggest that all communities should optimize retrieval of tissue and organ donations in brain dead post–cardiac arrest patients (in-hospital) and those pronounced dead in the out-of-hospital setting (Class IIa, LOE B).	not reviewed in 2015
2010	Ethics of Organ and Tissue Donation	Medical directors of EMS agencies, emergency departments (EDs), and critical care units (CCUs) should develop protocols and implementation plans with the regional organ and tissue donation program to optimize donation following a cardiac arrest death (Class I, LOE C)	not reviewed in 2015
2010	Criteria for Not Starting CPR in Newly Born Infant IHCA	There are prescribed recommendations to guide the initiation of resuscitative efforts in newly born infants. When gestational age, birth weight, or congenital anomalies are associated with almost certain early death and when unacceptably high morbidity is likely among the rare survivors, resuscitation is not indicated. Examples may include extreme prematurity (gestational age <23 weeks or birth weight <400 g, anencephaly, and some major chromosomal abnormalities such as trisomy 13 (Class IIb, LOE C).	not reviewed in 2015
2010	Criteria for Not Starting CPR in Newly Born Infant IHCA	In conditions associated with uncertain prognosis where survival is borderline, the morbidity rate is relatively high, and the anticipated burden to the child is high, parental desires concerning initiation of resuscitation should be supported (Class IIb, LOE C).	not reviewed in 2015

(*Continued*)

2015 Guidelines Update: Master List of Recommendations, *Continued*

Year Last Reviewed	Topic	Recommendation	Comments
2015	Devices to Support Circulation: Mechanical Chest Compression Devices: Piston Device	The evidence does not demonstrate a benefit with the use of mechanical piston devices for chest compressions versus manual chest compressions in patients with cardiac arrest. Manual chest compressions remain the standard of care for the treatment of cardiac arrest, but mechanical chest compressions using a piston device may be a reasonable alternative for use by properly trained personnel (Class IIb, LOE B-R).	new for 2015
2015	Devices to Support Circulation: Mechanical Chest Compression Devices: Piston Device	The use of piston devices for CPR may be considered in specific settings where the delivery of high-quality manual compressions may be challenging or dangerous for the provider (eg, prolonged CPR during hypothermic cardiac arrest, CPR in a moving ambulance, CPR in the angiography suite, CPR during preparation for extracorporeal CPR [ECPR]), provided that rescuers strictly limit interruptions in CPR during deployment and removal of the device (Class IIb, LOE C-EO).	new for 2015
2015	Devices to Support Circulation: Load-Distributing Band Devices	The evidence does not demonstrate a benefit with the use of LDB-CPR for chest compressions versus manual chest compressions in patients with cardiac arrest. Manual chest compressions remain the standard of care for the treatment of cardiac arrest, but LDB-CPR may be a reasonable alternative for use by properly trained personnel (Class IIb, LOE B-R).	new for 2015
2015	Devices to Support Circulation: Load-Distributing Band Devices	The use of LDB-CPR may be considered in specific settings where the delivery of high-quality manual compressions may be challenging or dangerous for the provider (eg, prolonged CPR during hypothermic cardiac arrest, CPR in a moving ambulance, CPR in the angiography suite, CPR during preparation for ECPR), provided that rescuers strictly limit interruptions in CPR during deployment and removal of the devices (Class IIb, LOE E).	new for 2015
2015	Extracorporeal Techniques and Invasive Perfusion Devices: Extracorporeal CPR	There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. It may be considered for select patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support (Class IIb, LOE C-LD).	new for 2015
The following recommendations were not reviewed in 2015. For more information, see the *2010 AHA Guidelines for CPR and ECC*, "Part 7: CPR Techniques and Devices."			
2010	Open-Chest CPR	Open-chest CPR can be useful if cardiac arrest develops during surgery when the chest or abdomen is already open, or in the early postoperative period after cardiothoracic surgery (Class IIa, LOE C).	not reviewed in 2015
2010	Open-Chest CPR	A resuscitative thoracotomy to facilitate open-chest CPR may be considered in very select circumstances of adults and children with out-of-hospital cardiac arrest from penetrating trauma with short transport times to a trauma facility (Class IIb, LOE C).	not reviewed in 2015
2010	Interposed Abdominal Compression CPR	IAC-CPR may be considered during in-hospital resuscitation when sufficient personnel trained in its use are available (Class IIb, LOE B).	not reviewed in 2015
2010	"Cough" CPR	"Cough" CPR may be considered in settings such as the cardiac catheterization laboratory for conscious, supine, and monitored patients if the patient can be instructed and coached to cough forcefully every 1 to 3 seconds during the initial seconds of an arrhythmic cardiac arrest. It should not delay definitive treatment (Class IIb, LOE C).	not reviewed in 2015
2010	Prone CPR	When the patient cannot be placed in the supine position, it may be reasonable for rescuers to provide CPR with the patient in the prone position, particularly in hospitalized patients with an advanced airway in place (Class IIb, LOE C).	not reviewed in 2015
2010	Precordial Thump	The precordial thump should not be used for unwitnessed out-of-hospital cardiac arrest (Class III, LOE C).	not reviewed in 2015
2010	Precordial Thump	The precordial thump may be considered for patients with witnessed, monitored, unstable ventricular tachycardia including pulseless VT if a defibrillator is not immediately ready for use (Class IIb, LOE C), but it should not delay CPR and shock delivery.	not reviewed in 2015
2010	Automatic Transport Ventilators	During prolonged resuscitation efforts, the use of an ATV (pneumatically powered and time- or pressure-cycled) may provide ventilation and oxygenation similar to that possible with the use of a manual resuscitation bag, while allowing the Emergency Medical Services (EMS) team to perform other tasks (Class IIb, LOE C).	not reviewed in 2015
2010	Manually Triggered, Oxygen-Powered, Flow-Limited Resuscitators	Manually triggered, oxygen-powered, flow-limited resuscitators may be considered for the management of patients who do not have an advanced airway in place and for whom a mask is being used for ventilation during CPR (Class IIb, LOE C).	not reviewed in 2015
2010	Manually Triggered, Oxygen-Powered, Flow-Limited Resuscitators	Rescuers should avoid using the automatic mode of the oxygen-powered, flow-limited resuscitator during CPR because it may generate high positive end-expiratory pressure (PEEP) that may impede venous return during chest compressions and compromise forward blood flow (Class III, LOE C).	not reviewed in 2015
2010	Active Compression-Decompression CPR	There is insufficient evidence to recommend for or against the routine use of ACD-CPR. ACD-CPR may be considered for use when providers are adequately trained and monitored (Class IIb, LOE B).	not reviewed in 2015
Part 8: Adult Advanced Cardiovascular Life Support			
2015	Adjuncts to CPR	When supplementary oxygen is available, it may be reasonable to use the maximal feasible inspired oxygen concentration during CPR (Class IIb, LOE C-EO).	updated for 2015

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2015 Guidelines Update: Master List of Recommendations, *Continued*

Year Last Reviewed	Topic	Recommendation	Comments
2015	Management of Cardiac Arrest	Vasopressin in combination with epinephrine offers no advantage as a substitute for standard-dose epinephrine in cardiac arrest (Class IIb, LOE B-R).	new for 2015
2015	Management of Cardiac Arrest	It may be reasonable to administer epinephrine as soon as feasible after the onset of cardiac arrest due to an initial nonshockable rhythm (Class IIb, LOE C-LD).	updated for 2015
2015	Management of Cardiac Arrest	In IHCA, the combination of intra-arrest vasopressin, epinephrine, and methylprednisolone and post-arrest hydrocortisone as described by Mentzelopoulos et al may be considered; however, further studies are needed before recommending the routine use of this therapeutic strategy (Class IIb, LOE C-LD).	new for 2015
2015	Management of Cardiac Arrest	For patients with OHCA, use of steroids during CPR is of uncertain benefit (Class IIb, LOE C-LD).	new for 2015
2015	Management of Cardiac Arrest	In intubated patients, failure to achieve an $ETCO_2$ of greater than 10 mm Hg by waveform capnography after 20 minutes of CPR may be considered as one component of a multimodal approach to decide when to end resuscitative efforts but should not be used in isolation (Class IIb, LOE C-LD).	new for 2015
2015	Management of Cardiac Arrest	In nonintubated patients, a specific $ETCO_2$ cutoff value at any time during CPR should not be used as an indication to end resuscitative efforts (Class III: Harm, LOE C-EO).	new for 2015
2015	Management of Cardiac Arrest	There is insufficient evidence to recommend the routine use of ECPR for patients with cardiac arrest. In settings where it can be rapidly implemented, ECPR may be considered for select cardiac arrest patients for whom the suspected etiology of the cardiac arrest is potentially reversible during a limited period of mechanical cardiorespiratory support. (Class IIb, LOE C-LD).	new for 2015
The following recommendations were not reviewed in 2015. For more information, see the *2010 AHA Guidelines for CPR and ECC*, "Part 8: Adult Advanced Cardiovascular Life Support" and "Part 6: Electrical Therapies: Automated External Defibrillators, Defibrillation, Cardioversion, and Pacing."			
2010	Cricoid Pressure	The routine use of cricoid pressure in cardiac arrest is not recommended (Class III, LOE C).	not reviewed in 2015
2010	Oropharyngeal Airways	To facilitate delivery of ventilations with a bag-mask device, oropharyngeal airways can be used in unconscious (unresponsive) patients with no cough or gag reflex and should be inserted only by persons trained in their use (Class IIa, LOE C).	not reviewed in 2015
2010	Nasopharyngeal Airways	In the presence of known or suspected basal skull fracture or severe coagulopathy, an oral airway is preferred (Class IIa, LOE C).	not reviewed in 2015
2010	Postintubation Airway Management	The endotracheal tube should be secured with tape or a commercial device (Class I, LOE C).	not reviewed in 2015
2010	Postintubation Airway Management	One out-of-hospital study and 2 studies in an intensive care setting indicate that backboards, commercial devices for securing the endotracheal tube, and other strategies provide equivalent methods for preventing inadvertent tube displacement when compared with traditional methods of securing the tube (tape). These devices may be considered during patient transport (Class IIb, LOE C).	not reviewed in 2015
2010	Automatic Transport Ventilators	In both out-of-hospital and in-hospital settings, automatic transport ventilators (ATVs) can be useful for ventilation of adult patients in noncardiac arrest who have an advanced airway in place (Class IIb, LOE C).	not reviewed in 2015
2010	Automatic Transport Ventilators	During prolonged resuscitative efforts the use of an ATV (pneumatically powered and time- or pressure-cycled) may allow the EMS team to perform other tasks while providing adequate ventilation and oxygenation (Class IIb, LOE C).	not reviewed in 2015
2010	Automatic Versus Manual Modes for Multimodal Defibrillators	Current evidence indicates that the benefit of using a multimodal defibrillator in manual instead of automatic mode during cardiac arrest is uncertain (Class IIb, LOE C).	not reviewed in 2015
2010	CPR Before Defibrillation	Performing CPR while a defibrillator is readied for use is strongly recommended for all patients in cardiac arrest (Class I, LOE B)	not reviewed in 2015
2010	CPR Before Defibrillation	At this time the benefit of delaying defibrillation to perform CPR before defibrillation is unclear (Class IIb, LOE B).	not reviewed in 2015
2010	Drug Therapy for PEA/ Asystole	Available evidence suggests that the routine use of atropine during PEA or asystole is unlikely to have a therapeutic benefit (Class IIb, LOE B).	not reviewed in 2015
2010	Coronary Perfusion Pressure and Arterial Relaxation Pressure	It is reasonable to consider using arterial relaxation "diastolic" pressure to monitor CPR quality, optimize chest compressions, and guide vasopressor therapy. (Class IIb, LOE C).	not reviewed in 2015
2010	Coronary Perfusion Pressure and Arterial Relaxation Pressure	If the arterial relaxation "diastolic" pressure is <20 mm Hg, it is reasonable to consider trying to improve quality of CPR by optimizing chest compression parameters or giving a vasopressor or both (Class IIb, LOE C).	not reviewed in 2015

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2015 Guidelines Update: Master List of Recommendations, *Continued*

Year Last Reviewed	Topic	Recommendation	Comments
2015	Other Critical Care Interventions	In comatose post–cardiac arrest patients who are not treated with TTM, it may be reasonable to consider the presence of burst suppression on EEG at 72 hours or more after cardiac arrest, in combination with other predictors, to predict a poor neurologic outcome (FPR, 1%; 95% CI, 0%–11%; Class IIb, LOE B-NR).	updated for 2015
2015	Other Critical Care Interventions	In patients who are comatose after resuscitation from cardiac arrest regardless of treatment with TTM, it is reasonable to consider bilateral absence of the N20 SSEP wave 24 to 72 hours after cardiac arrest or after rewarming a predictor of poor outcome (FPR, 1%; 95% CI, 0%–3%; Class IIa, LOE B-NR).	updated for 2015
2015	Other Critical Care Interventions	In patients who are comatose after resuscitation from cardiac arrest and not treated with TTM, it may be reasonable to use the presence of a marked reduction of the GWR on brain CT obtained within 2 hours after cardiac arrest to predict poor outcome (Class IIb, LOE B-NR).	new for 2015
2015	Other Critical Care Interventions	It may be reasonable to consider extensive restriction of diffusion on brain MRI at 2 to 6 days after cardiac arrest in combination with other established predictors to predict a poor neurologic outcome (Class IIb, LOE B-NR).	new for 2015
2015	Other Critical Care Interventions	Given the possibility of high FPRs, blood levels of NSE and S-100B should not be used alone to predict a poor neurologic outcome (Class III: Harm, LOE C-LD).	updated for 2015
2015	Other Critical Care Interventions	When performed with other prognostic tests at 72 hours or more after cardiac arrest, it may be reasonable to consider high serum values of NSE at 48 to 72 hours after cardiac arrest to support the prognosis of a poor neurologic outcome (Class IIb, LOE B-NR), especially if repeated sampling reveals persistently high values (Class IIb, LOE C-LD).	updated for 2015
2015	Other Critical Care Interventions	We recommend that all patients who are resuscitated from cardiac arrest but who subsequently progress to death or brain death be evaluated for organ donation (Class I, LOE B-NR).	updated for 2015
2015	Other Critical Care Interventions	Patients who do not have ROSC after resuscitation efforts and who would otherwise have termination of efforts may be considered candidates for kidney or liver donation in settings where programs exist (Class IIb, LOE B-NR).	new for 2015
The following recommendations were not reviewed in 2015. For more information, see the *2010 AHA Guidelines for CPR and ECC*, "Part 9: Post–Cardiac Arrest Care"			
2010	Systems of Care for Improving Post–Cardiac Arrest Outcomes	A comprehensive, structured, multidisciplinary system of care should be implemented in a consistent manner for the treatment of post–cardiac arrest patients (Class I, LOE B).	not reviewed in 2015
2010	Treatment of Pulmonary Embolism After CPR	In post–cardiac arrest patients with arrest due to presumed or known pulmonary embolism, fibrinolytics may be considered (Class IIb, LOE C).	not reviewed in 2015
2010	Sedation After Cardiac Arrest	It is reasonable to consider the titrated use of sedation and analgesia in critically ill patients who require mechanical ventilation or shivering suppression during induced hypothermia after cardiac arrest (Class IIb, LOE C).	not reviewed in 2015
2010	Cardiovascular System	A 12-lead ECG should be obtained as soon as possible after ROSC to determine whether acute ST elevation is present (Class I, LOE B).	not reviewed in 2015
2010	Neuroprotective Drugs	The routine use of coenzyme Q10 in patients treated with hypothermia is uncertain (Class IIb, LOE B).	not reviewed in 2015
2010	Evoked Potentials	Bilateral absence of the N20 cortical response to median nerve stimulation after 24 hours predicts poor outcome in comatose cardiac arrest survivors not treated with therapeutic hypothermia (Class IIa, LOE A).	not reviewed in 2015
Part 9: Acute Coronary Syndromes			
2015	Diagnostic Interventions in ACS	Prehospital 12-lead ECG should be acquired early for patients with possible ACS (Class I, LOE B-NR).	new for 2015
2015	Diagnostic Interventions in ACS	Prehospital notification of the receiving hospital (if fibrinolysis is the likely reperfusion strategy) and/or prehospital activation of the catheterization laboratory should occur for all patients with a recognized STEMI on prehospital ECG (Class I, LOE B-NR).	updated for 2015
2015	Diagnostic Interventions in ACS	Because of high false-negative rates, we recommend that computer-assisted ECG interpretation not be used as a sole means to diagnose STEMI (Class III: Harm, LOE B-NR).	new for 2015
2015	Diagnostic Interventions in ACS	We recommend that computer-assisted ECG interpretation may be used in conjunction with physician or trained provider interpretation to recognize STEMI (Class IIb, LOE C-LD).	updated for 2015
2015	Diagnostic Interventions in ACS	While transmission of the prehospital ECG to the ED physician may improve PPV and therapeutic decision-making regarding adult patients with suspected STEMI, if transmission is not performed, it may be reasonable for trained non-physician ECG interpretation to be used as the basis for decision-making, including activation of the catheterization laboratory, administration of fibrinolysis, and selection of destination hospital. (Class IIa, LOE B-NR).	new for 2015
2015	Diagnostic Interventions in ACS	We recommend against using hs-cTnT and cTnI alone measured at 0 and 2 hours (without performing clinical risk stratification) to exclude the diagnosis of ACS (Class III: Harm, LOE B-NR).	new for 2015

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2015 Guidelines Update: Master List of Recommendations, *Continued*

Year Last Reviewed	Topic	Recommendation	Comments
2015	Role of Intravenous Lipid Emulsion Therapy in Management of Cardiac Arrest Due to Poisoning	It may be reasonable to administer ILE, concomitant with standard resuscitative care, to patients with local anesthetic systemic toxicity and particularly to patients who have premonitory neurotoxicity or cardiac arrest due to bupivacaine toxicity (Class IIb, LOE C-EO).	new for 2015
2015	Role of Intravenous Lipid Emulsion Therapy in Management of Cardiac Arrest Due to Poisoning	It may be reasonable to administer ILE to patients with other forms of drug toxicity who are failing standard resuscitative measures (Class IIb, LOE C-EO).	updated for 2015
2015	Cardiac Arrest During Percutaneous Coronary Intervention	It may be reasonable to use mechanical CPR devices to provide chest compressions to patients in cardiac arrest during PCI (Class IIb, LOE C-EO).	updated for 2015
2015	Cardiac Arrest During Percutaneous Coronary Intervention	It may be reasonable to use ECPR as a rescue treatment when initial therapy is failing for cardiac arrest that occurs during PCI (Class IIb, LOE C-LD).	new for 2015
2015	Cardiac Arrest During Percutaneous Coronary Intervention	Institutional guidelines should include the selection of appropriate candidates for use of mechanical support devices to ensure that these devices are used as a bridge to recovery, surgery or transplant, or other device (Class I, LOE C-EO).	new for 2015
The following recommendations were not reviewed in 2015. For more information, see the *2010 AHA Guidelines for CPR and ECC*, "Part 12: Cardiac Arrest in Special Situations."			
2010	Cardiac Arrest Associated With Asthma	Therefore, since the effects of auto-PEEP in an asthmatic patient with cardiac arrest are likely quite severe, a ventilation strategy of low respiratory rate and tidal volume is reasonable (Class IIa, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Asthma	During arrest a brief disconnection from the bag mask or ventilator may be considered, and compression of the chest wall to relieve air-trapping can be effective (Class IIa, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Asthma	For all asthmatic patients with cardiac arrest, and especially for patients in whom ventilation is difficult, the possible diagnosis of a tension pneumothorax should be considered and treated (Class I, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Given the potential for the rapid development of oropharyngeal or laryngeal edema, immediate referral to a health professional with expertise in advanced airway placement is recommended (Class I, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Epinephrine should be administered early by IM injection to all patients with signs of a systemic allergic reaction, especially hypotension, airway swelling, or difficulty breathing (Class I, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	The recommended dose is 0.2 to 0.5 mg (1:1000) IM to be repeated every 5 to 15 minutes in the absence of clinical improvement (Class I, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	In both anaphylaxis and cardiac arrest the immediate use of an epinephrine autoinjector is recommended if available (Class I, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Planning for advanced airway management, including a surgical airway, is recommended (Class I, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Vasogenic shock from anaphylaxis may require aggressive fluid resuscitation (Class IIa, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	When an IV line is in place, it is reasonable to consider the IV route as an alternative to IM administration of epinephrine in anaphylactic shock (Class IIa, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Because fatal overdose of epinephrine has been reported, close hemodynamic monitoring is recommended (Class I, LOE B).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	IV infusion of epinephrine is a reasonable alternative to IV boluses for treatment of anaphylaxis in patients not in cardiac arrest (Class IIa, LOE C) and may be considered in postarrest management (Class IIb, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Alternative vasoactive drugs (vasopressin, norepinephrine, methoxamine, and metaraminol) may be considered in cardiac arrest secondary to anaphylaxis that does not respond to epinephrine (Class IIb, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Adjuvant use of antihistamines (H1 and H2 antagonist), inhaled β-adrenergic agents, and IV corticosteroids has been successful in management of the patient with anaphylaxis and may be considered in cardiac arrest due to anaphylaxis (Class IIb, LOE C).	not reviewed in 2015
2010	Cardiac Arrest Associated With Anaphylaxis	Cardiopulmonary bypass has been successful in isolated case reports of anaphylaxis followed by cardiac arrest. Use of these advanced techniques may be considered in clinical situations where the required professional skills and equipment are immediately available (Class IIb, LOE C).	not reviewed in 2015

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Intensive Care Med
DOI 10.1007/s00134-015-4051-3

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European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care

Received: 22 August 2015
Accepted: 1 September 2015

This article is being simultaneously published in *Intensive Care Medicine* and *Resuscitation* [ISSN: 0300-9572 (print version) ISSN: 1873-1570 (electronic version)].

Electronic supplementary material The references for this article are contained in the supplementary material (doi: 10.1007/s00134-015-4051-3; available to authorized users).

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Abstract The European Resuscitation Council and the European Society of Intensive Care Medicine have collaborated to produce these post-resuscitation care guidelines, which are based on the 2015 International Consensus on Cardiopulmonary Resuscitation Science with Treatment Recommendations. Recent changes in post-resuscitation care include: (a) greater emphasis on the need for urgent coronary catheterisation and percutaneous coronary intervention following out-of-hospital cardiac arrest of likely cardiac cause; (b) targeted temperature management remains important but there is now an option to target a temperature of 36 °C instead of the previously recommended 32–34 °C; (c) prognostication is now undertaken using a multimodal strategy and there is emphasis on allowing sufficient time for neurological recovery and to enable sedatives to be cleared; (d) increased emphasis on rehabilitation after survival from a cardiac arrest.

Published online: 13 October 2015

Summary of changes since 2010 guidelines

In 2010, post-resuscitation care was incorporated into the Advanced Life Support section of the European Resuscitation Council (ERC) Guidelines [1]. The ERC and the European Society of Intensive Care Medicine (ESICM) have collaborated to produce these post-resuscitation care guidelines, which recognise the importance of high-quality post-resuscitation care as a vital link in the Chain of Survival [2]. These post-resuscitation care guidelines are being co-published in *Resuscitation* and *Intensive Care Medicine*.

The most important changes in post-resuscitation care since 2010 include:

- There is a greater emphasis on the need for urgent coronary catheterisation and percutaneous coronary intervention (PCI) following out-of-hospital cardiac arrest of likely cardiac cause.
- Targeted temperature management remains important but there is now an option to target a temperature of 36 °C instead of the previously recommended 32–34 °C.
- Prognostication is now undertaken using a multimodal strategy and there is emphasis on allowing sufficient time for neurological recovery and to enable sedatives to be cleared.
- A novel section has been added which addresses rehabilitation after survival from a cardiac arrest. Recommendations include the systematic organisation of follow-up care, which should include screening for potential cognitive and emotional impairments and provision of information.

The international consensus on cardiopulmonary resuscitation science and the guidelines process

The International Liaison Committee on Resuscitation (ILCOR, www.ilcor.org) includes representatives from the American Heart Association (AHA), the European Resuscitation Council (ERC), the Heart and Stroke Foundation of Canada (HSFC), the Australian and New Zealand Committee on Resuscitation (ANZCOR), the Resuscitation Council of Southern Africa (RCSA), the Inter-American Heart Foundation (IAHF), and the Resuscitation Council of Asia (RCA). Since 2000, researchers from the ILCOR member councils have evaluated resuscitation science in 5-yearly cycles. The most recent International Consensus Conference was held in Dallas in February 2015 and the published conclusions and recommendations from this process form the basis of the ERC Guidelines 2015 and for these ERC–ESICM post-resuscitation care guidelines. During the 3 years leading up to this conference, 250 evidence reviewers from 39 countries reviewed thousands of relevant, peer-reviewed publications to address 169 specific resuscitation questions, each in the standard population, intervention, comparison, outcome (PICO) format. To assess the quality of the evidence and the strength of the recommendations, ILCOR adopted the grading of recommendations assessment, development and evaluation (GRADE) methodology. Each PICO question was reviewed by at least two evidence reviewers who drafted a science statement based on their interpretation of all relevant data on the specific topic and the relevant ILCOR task force added consensus draft treatment recommendations. Final wording of science statements and treatment recommendations was completed after further review by ILCOR member organisations and by the editorial board, and published in *Resuscitation* and *Circulation* as the 2015 Consensus on Science and Treatment Recommendations (CoSTR). These ERC–ESICM guidelines on post-resuscitation care are based on the 2015 CoSTR document and represent consensus among the writing group, which included representatives of the ERC and the ESICM.

Introduction

Successful return of spontaneous circulation (ROSC) is the first step toward the goal of complete recovery from cardiac arrest. The complex pathophysiological processes that occur following whole body ischaemia during cardiac arrest and the subsequent reperfusion response during CPR and following successful resuscitation have been termed the post-cardiac arrest syndrome [3]. Depending on the cause of the arrest, and the severity of the post-cardiac arrest syndrome, many patients will require multiple organ support and the treatment they receive during this post-resuscitation period influences significantly the overall outcome and particularly the quality of neurological recovery [4–11]. The post-resuscitation phase starts at the location where ROSC is achieved but, once stabilised, the patient is transferred to the most appropriate high-care area [e.g., emergency room, cardiac catheterisation laboratory or intensive care unit (ICU)] for continued diagnosis, monitoring and treatment. The post-resuscitation care algorithm (Fig. 1) outlines some of the key interventions required to optimise outcome for these patients.

Some patients do awake rapidly following cardiac arrest—in some reports it is as high as 15–46 % of the out-of hospital cardiac arrest patients admitted to hospital [12–14]. Response times, rates of bystander CPR, times to defibrillation and the duration of CPR impact on these numbers [14]. Although we have no data, it is reasonable

available in many languages at http://www.mocatest.org). In cases where there are signs of cognitive impairments, refer to a neuropsychologist for neuropsychological assessment or to a specialist in rehabilitation medicine for a rehabilitation programme [377].

- Screening for emotional problems. Ask whether the patient experiences any emotional problems, such as symptoms of depression, anxiety or posttraumatic stress. General measures that can be used include the Hospital Anxiety and Depression Scale (HADS) and the Impact of Event Scale [378, 379]. In case of emotional problems refer to a psychologist or psychiatrist for further examination and treatment [355].
- Provision of information. Give active information on the potential non-cardiac consequences of a cardiac arrest including cognitive impairment, emotional problems and fatigue. Other topics that can be addressed include heart disease, ICDs, regaining daily activities, partner relationships and sexuality, dealing with health care providers and caregiver strain [365]. It is best to combine written information with the possibility for personal consultation. An example of an information booklet is available (in Dutch and English) [373, 374].

Organ donation

Organ donation should be considered in those who have achieved ROSC and who fulfil criteria for death using neurological criteria [380]. In those comatose patients in whom a decision is made to withdraw life-sustaining therapy, organ donation should be considered after circulatory death occurs. Organ donation can also be considered in individuals where CPR is not successful in achieving ROSC. All decisions concerning organ donation must follow local legal and ethical requirements, as these vary in different settings.

Non-randomised studies have shown that graft survival at 1 year is similar from donors who have had CPR compared with donors who have not had CPR: adult hearts (3230 organs [381–387]), adult lungs (1031 organs [383, 385, 388]), adult kidneys (5000 organs [381, 383]), adult livers (2911 organs [381, 383]), and adult intestines (25 organs [383]).

Non-randomised studies have also shown that graft survival at 1 year was similar when organs recovered from donors with ongoing CPR were compared to other types of donors for adult kidneys (199 organs [389–391]) or adult livers (60 organs [390, 392, 393]).

Solid organs have been successfully transplanted after circulatory death. This group of patients offers an opportunity to increase the organ donor pool. Organ retrieval from donation after circulatory death (DCD) donors is classified as controlled or uncontrolled [394, 395]. Controlled donation occurs after planned withdrawal of treatment following non-survivable injuries and illnesses. Uncontrolled donation describes donation from patients with unsuccessful CPR in whom a decision has been made that CPR should be stopped. Once death has been diagnosed, the assessment of which includes a predefined period of observation to ensure a spontaneous circulation does not return [396], organ preservation and retrieval takes place. Aspects or uncontrolled organ donation are complex and controversial as some of the same techniques used during CPR to attempt to achieve ROSC are also used for organ preservation after death has been confirmed, e.g. mechanical chest compression and extracorporeal circulation. Locally agreed protocols must therefore be followed.

Screening for inherited disorders

Many sudden death victims have silent structural heart disease, most often coronary artery disease, but also primary arrhythmia syndromes, cardiomyopathies, familial hypercholesterolaemia and premature ischaemic heart disease. Screening for inherited disorders is crucial for primary prevention in relatives as it may enable preventive antiarrhythmic treatment and medical follow-up [397–399]. This screening should be performed using clinical examination, electrophysiology and cardiac imaging. In selected cases, genetic mutations associated with inherited cardiac diseases should also be searched [400].

Cardiac arrest centres

There is wide variability in survival among hospitals caring for patients after resuscitation from cardiac arrest [9, 13, 16, 17, 401–403]. Many studies have reported an association between survival to hospital discharge and transport to a cardiac arrest centre but there is inconsistency in the hospital factors that are most related to patient outcome [4, 5, 9, 17, 401, 404–416]. There is also inconsistency in the services that together define a cardiac arrest centre. Most experts agree that such a centre must have a cardiac catheterisation laboratory that is immediately accessible 24/7 and the facility to provide targeted temperature management. The availability of a neurology service that can provide neuroelectrophysiological monitoring [electroencephalography (EEG)] and investigations [e.g. EEG and somatosensory evoked potentials (SSEPs)] is also essential.

There is some low-level evidence that ICUs admitting more than 50 post-cardiac arrest patients per year produce

better survival rates than those admitting less than 20 cases per year [17]; however, differences in case mix could account for these differences. An observational study showed that unadjusted survival to discharge was greater in hospitals that received ≥40 cardiac arrest patients/year compared with those that received <40 per year, but this difference disappeared after adjustment for patient factors [404].

Several studies with historic control groups have shown improved survival after implementation of a comprehensive package of post-resuscitation care that includes mild induced hypothermia and percutaneous coronary intervention [7, 10, 11, 417]. There is also evidence of improved survival after out-of-hospital cardiac arrest in large hospitals with cardiac catheter facilities compared with smaller hospitals with no cardiac catheter facilities [9]. In a study of 3981 patients arriving with a sustained pulse at one of 151 hospitals, the Resuscitation Outcome Consortium (ROC) investigators have shown that early coronary intervention and mild induced hypothermia were associated with a favourable outcome [84]. These interventions were more frequent in hospitals that treated higher number of OHCA patients per year.

Several studies of OHCA arrest failed to demonstrate any effect of transport interval from the scene to the receiving hospital on survival to hospital discharge if ROSC was achieved at the scene and transport intervals were short (3 to 11 min) [406, 412, 413]. This implies that it may be safe to bypass local hospitals and transport the post-cardiac arrest patient to a regional cardiac arrest centre. There is indirect evidence that regional cardiac resuscitation systems of care improve outcome after ST elevation myocardial infarction (STEMI) [407, 418–441].

The implication from all these data is that specialist cardiac arrest centres and systems of care may be effective [442–445]. Despite the lack of high quality data to support implementation of cardiac arrest centres, it seems likely that regionalisation of post-cardiac arrest care will be adopted in most countries.

Compliance with ethical standards

Conflicts of interest

Jerry P. Nolan, Editor-in-Chief *Resuscitation*.
Jasmeet Soar, Editor *Resuscitation*.
Alain Cariou, speakers honorarium BARD-France.
Tobias Cronberg, no conflict of interest reported.
Veronique R.M. Moulaert, no conflict of interest reported.
Charles D. Deakin, Director Prometheus Medical Ltd.
Bernd W. Böttiger, no conflict of interest reported.
Hans Friberg, speakers honorarium Bard Medical-Natus Inc.
Kjetil Sunde, no conflict of interest reported.
Claudio Sandroni, no conflict of interest reported.

The non beating heart donation In trauma an cardiac arrest patient

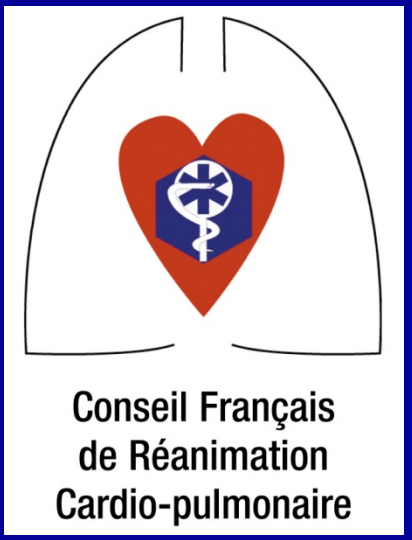
With a focus on French practice

Pr. Pierre CARLI , MD

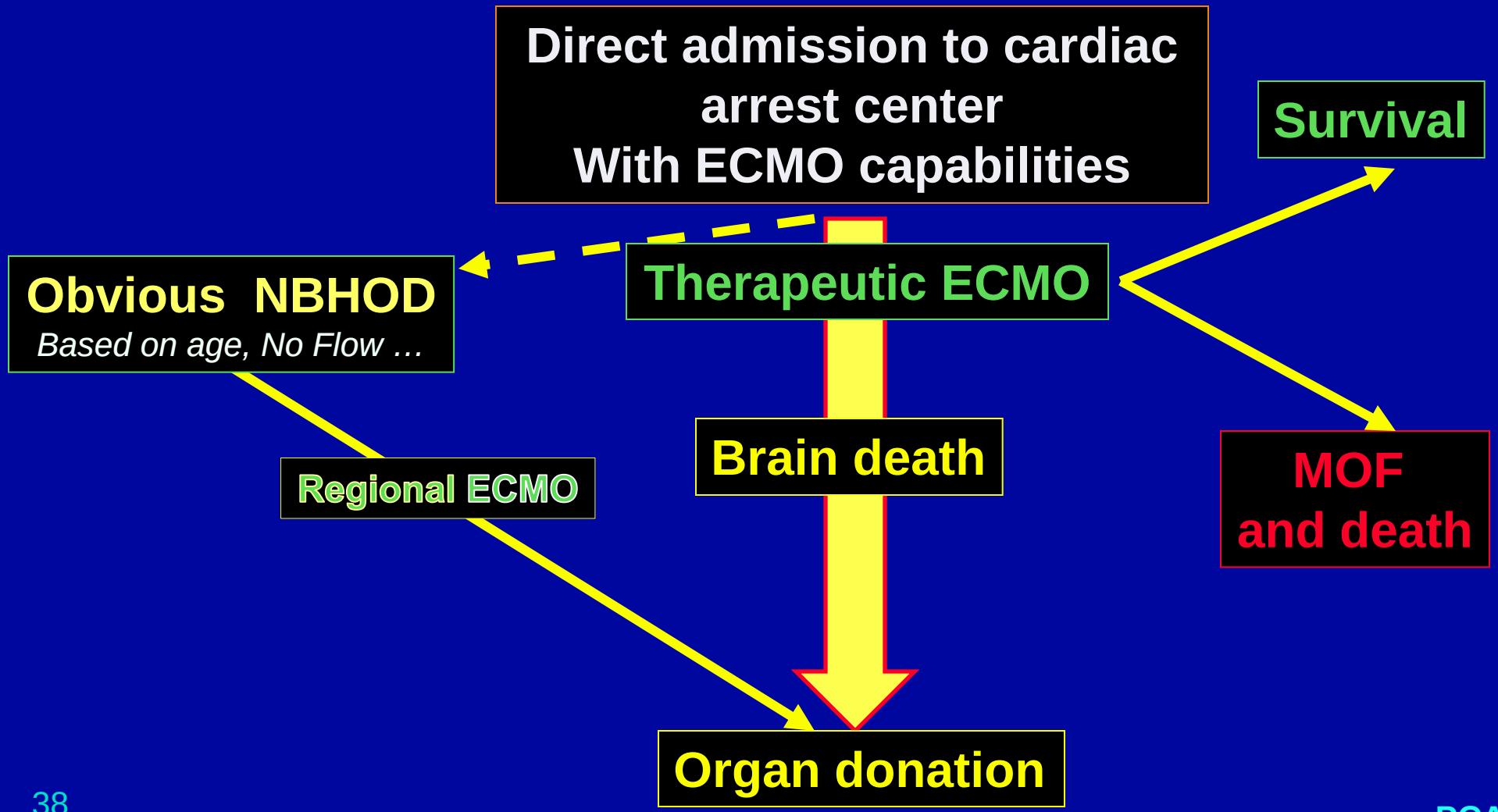
SAMU de Paris

Hôpital Necker

Paris, France



A new management for refractory OHCA not declared dead on scene



Organ donation : A positive side effect of (prehospital) early ECLS CPR

- Non beating heart donor (uncontrolled donation)
  - No ROSC during ECLS
  - Enough time to check impossibility of survival
- Brain death after ROSC during ECLS
  - General criteria of brain death
  - No Mastricht 3 procedure in France

Organ donation : A positive side effect of (prehospital) early ECLS CPR

- **No more ethical issue :**
  - **Possibility of therapeutic for all the patients**
- **Improvement of quality of the harvested organs :**
  - **Reduction of low flow and of prolonged mechanical CPR**
- **Funding of ECLS - CPR :**
  - **Increase of transplantation funded by national program**

Conclusion

- NBHOD is an important potential source of organ donation
- NBHOD has obvious indications : Prolonged no flow or special circumstances (fatal TBI ?)
- The development of ECLS for OHCA raises ethical concern
- However ECLS provides “per se” NBHOD and after late ROSC brain death patients

Prague EMS all resuscitated cardiac arrests
Mar 2013-Sep 2015
N =1554

All CPRs for possible cardiac cause
N = 1398

Excluded N = 156 **(CPC 1/2 = 12; 7,7 %)**
- traumatic N = 64
- drowning N = 14
- respiratory N = 55
- intoxications N = 23

Excluded N = 1341
- age > 65 years N=753 **(CPC 1/2 = 81; 10,8 %)**
- age < 18 years N = 16 (CPC 1/2 = 2; 12,5 %)
- not wittnessed N =132 **(CPC 1/2 = 9; 6,8%)**
- wittnessed N = 440

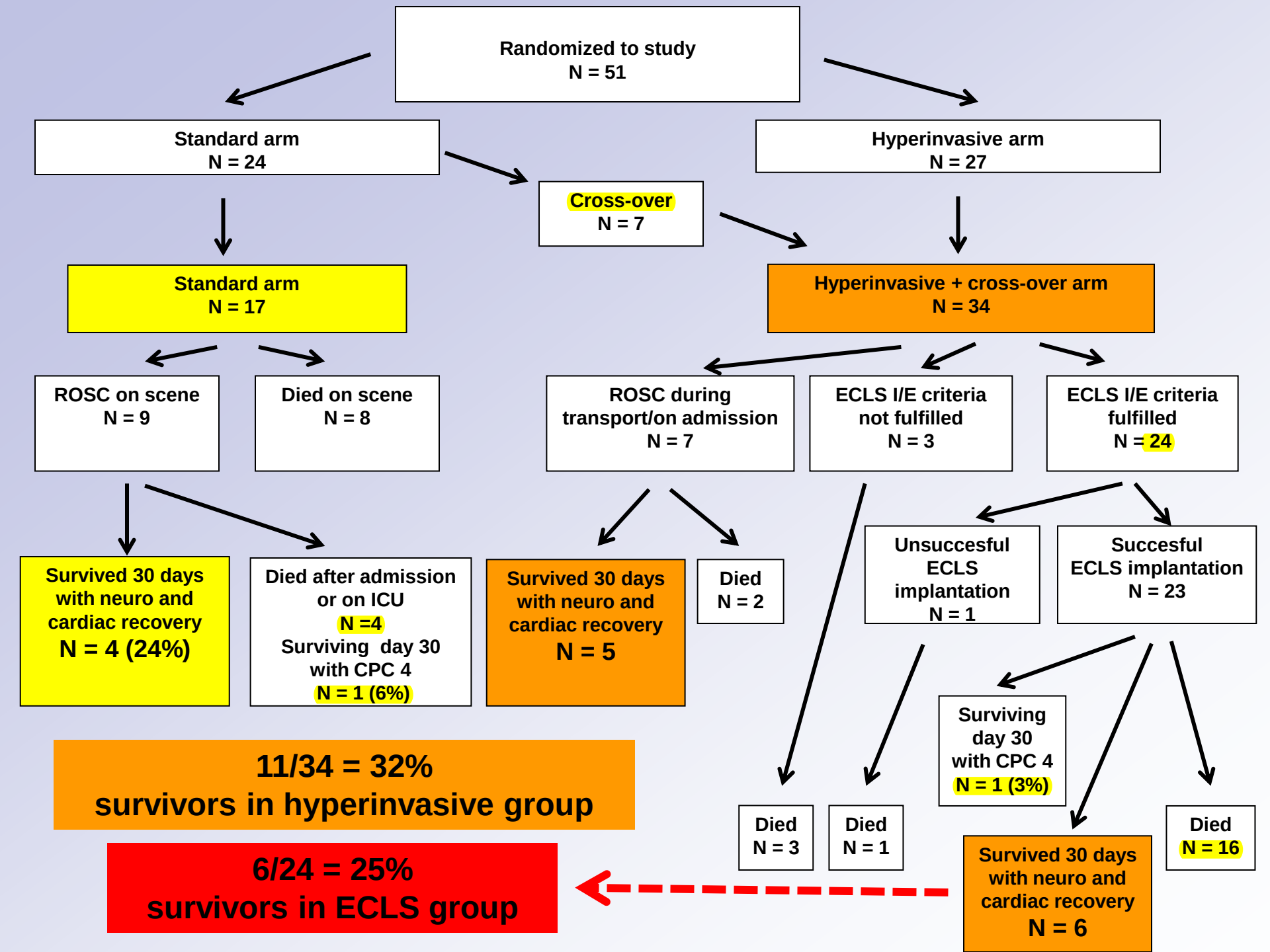
•ROSC on scene, not considered for study N =282 (CPC 1/2 = 126; 44,68%)

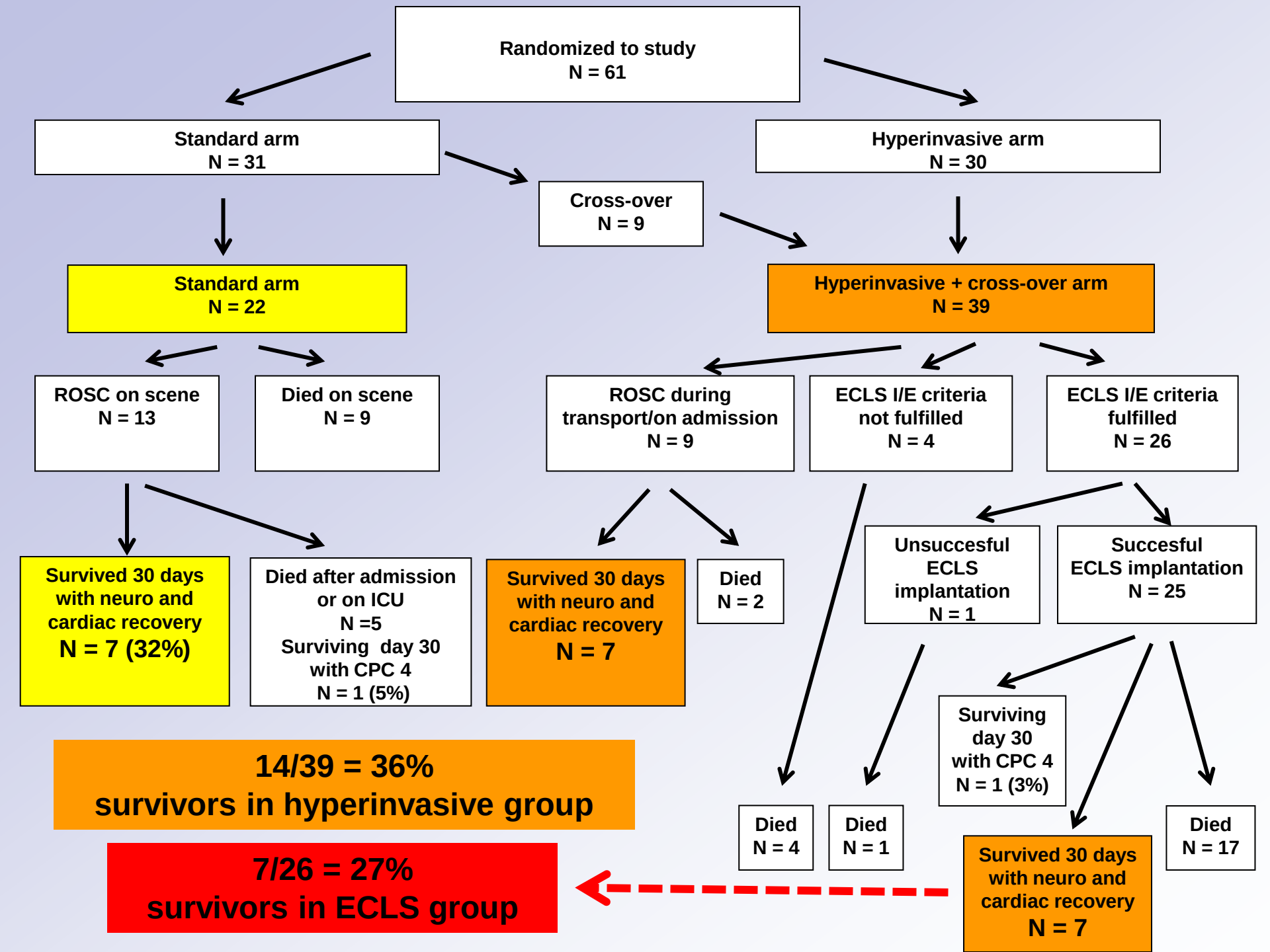
•died on scene, not considered for study N= 158

Considered for study inclusion
Transported under CPR to hospital
N = 57

Excluded N = 6 **(CPC 1/2 = 0; 0,0 %)**
- capacity not available or emergency physician´s decision not to enroll

Randomized to study
N = 51

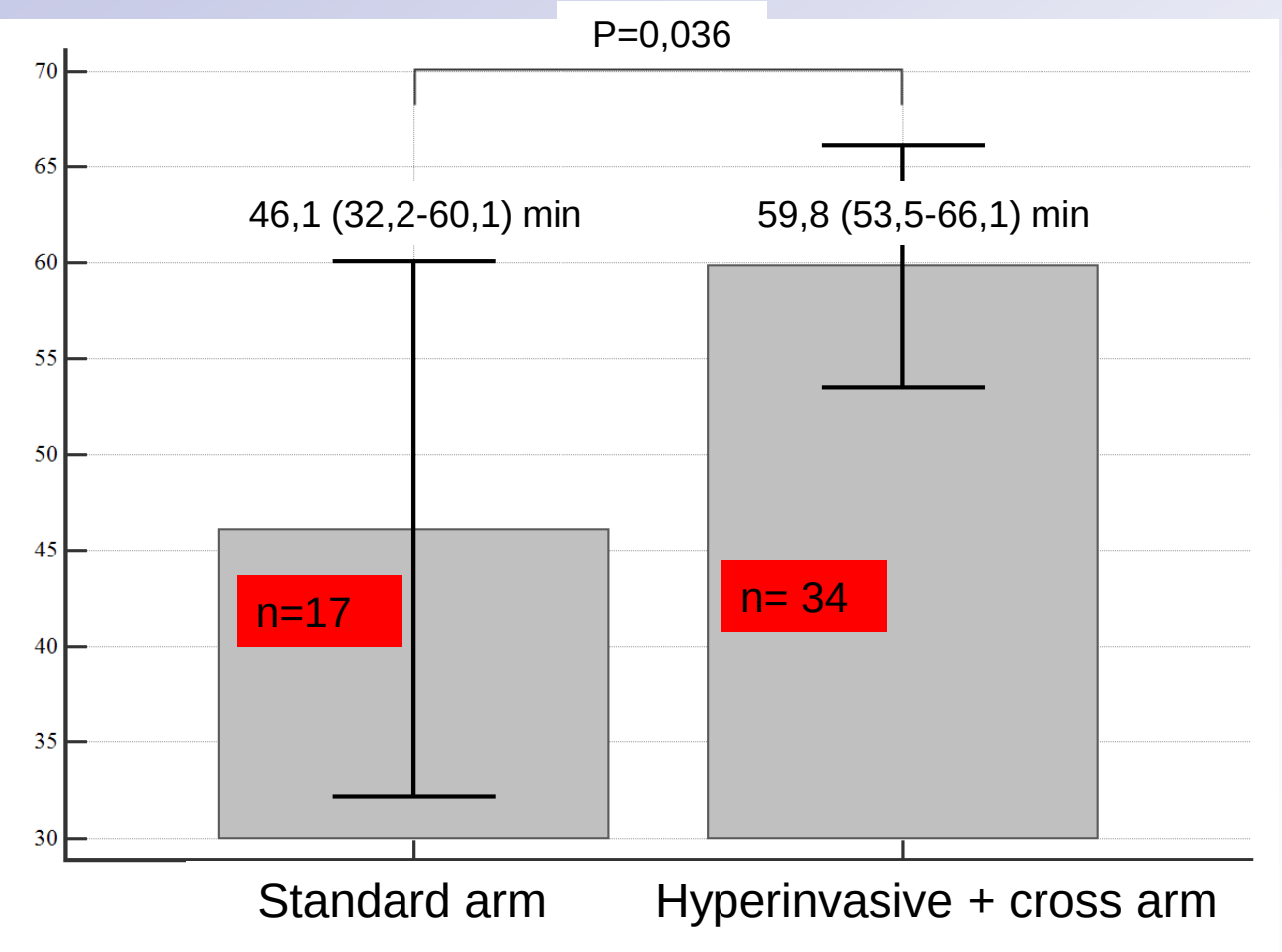

Randomized to study
N = 51
Standard arm
N = 24
Hyperinvasive arm
N = 27
Cross-over
N = 7
Standard arm
N = 17
Hyperinvasive + cross-over arm
N = 34
ROSC on scene
N = 9
Died on scene
N = 8
ROSC during transport/on admission
N = 7
ECLS I/E criteria not fulfilled
N = 3
ECLS I/E criteria fulfilled
N = 24
Survived 30 days with neuro and cardiac recovery
N = 4 (24%)
Died after admission or on ICU
N =4
Surviving day 30 with CPC 4
N = 1 (6%)
Survived 30 days with neuro and cardiac recovery
N = 5
Died
N = 2
Unsuccesful ECLS implantation
N = 1
Succesful ECLS implantation
N = 23
Surviving day 30 with CPC 4
N = 1 (3%)
Died
N = 3
Died
N = 1
Died
N = 16
Survived 30 days with neuro and cardiac recovery
N = 6
11/34 = 32%
survivors in hyperinvasive group
6/24 = 25%
survivors in ECLS group


Randomized to study
N = 61
Standard arm
N = 31
Hyperinvasive arm
N = 30
Cross-over
N = 9
Standard arm
N = 22
Hyperinvasive + cross-over arm
N = 39
ROSC on scene
N = 13
Died on scene
N = 9
ROSC during transport/on admission
N = 9
ECLS I/E criteria not fulfilled
N = 4
ECLS I/E criteria fulfilled
N = 26
Survived 30 days with neuro and cardiac recovery
N = 7 (32%)
Died after admission or on ICU
N =5
Surviving day 30 with CPC 4
N = 1 (5%)
Survived 30 days with neuro and cardiac recovery
N = 7
Died
N = 2
Unsuccesful ECLS implantation
N = 1
Succesful ECLS implantation
N = 25
Surviving day 30 with CPC 4
N = 1 (3%)
Died
N = 4
Died
N = 1
Died
N = 17
Survived 30 days with neuro and cardiac recovery
N = 7
14/39 = 36%
survivors in hyperinvasive group
7/26 = 27%
survivors in ECLS group

Cardiac arrest time

= time to death/ROSC/ECLS

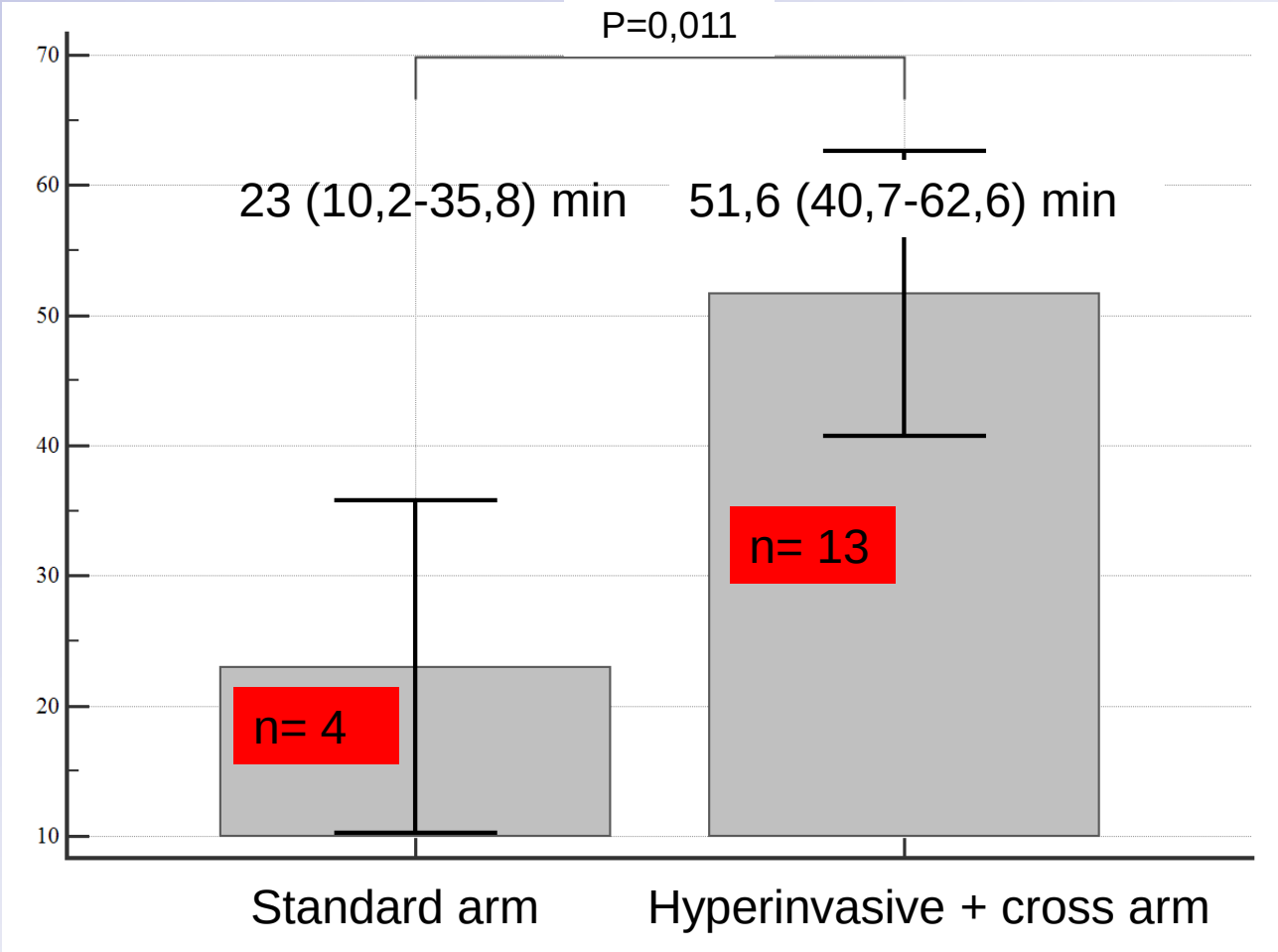
(overall)



Cardiac arrest time

= time to death/ROSC/ECLS

30 day survival

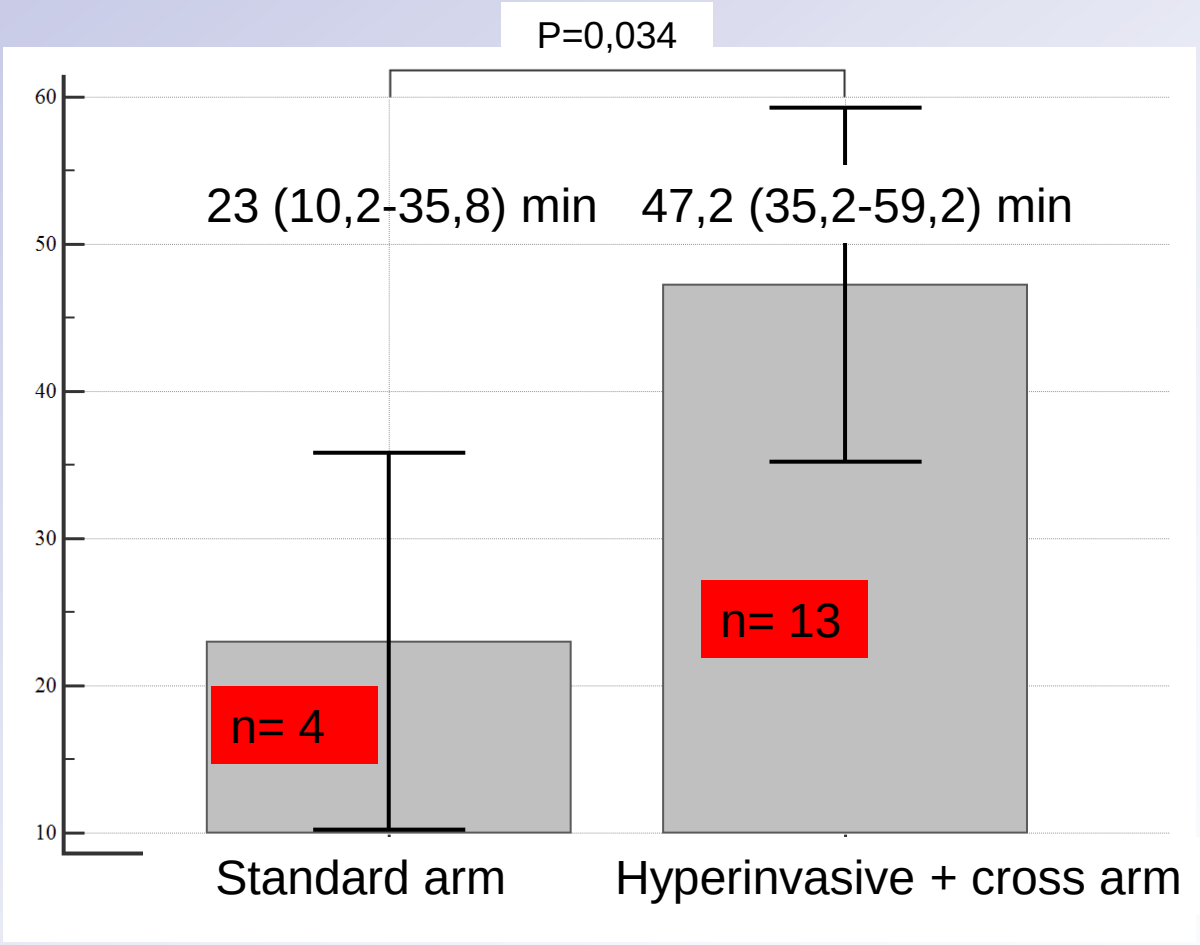


Cardiac arrest time

= time to death/ROSC/ECLS

„cardiac recovery“

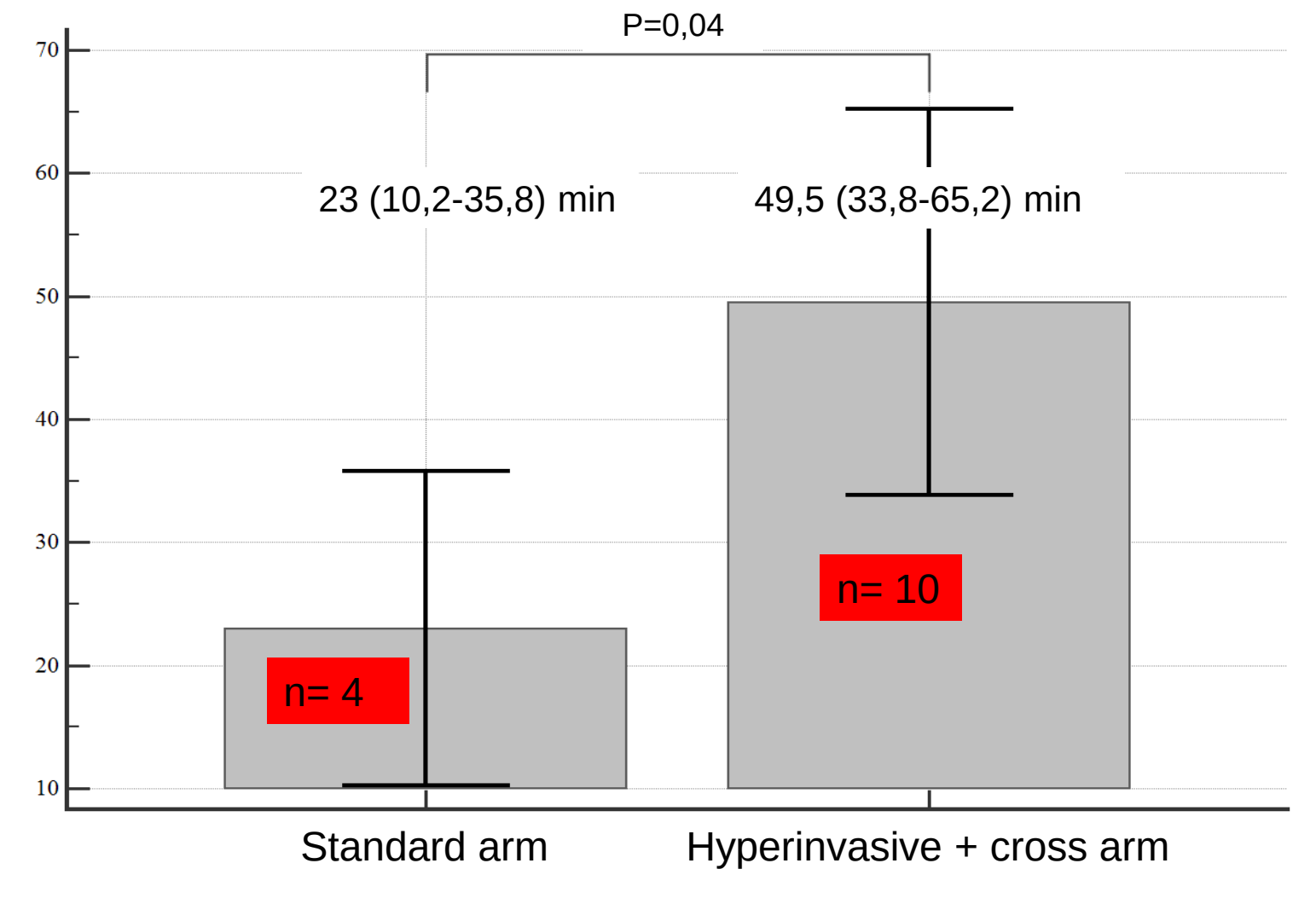
defined as no need for ECLS or pharmacological support for 24 hours



Cardiac arrest time

= time to death/ROSC/ECLS

„neuro recovery“



Generalitat de Catalunya
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emergències mèdiques

Sobrevivir a la Muerte Súbita.

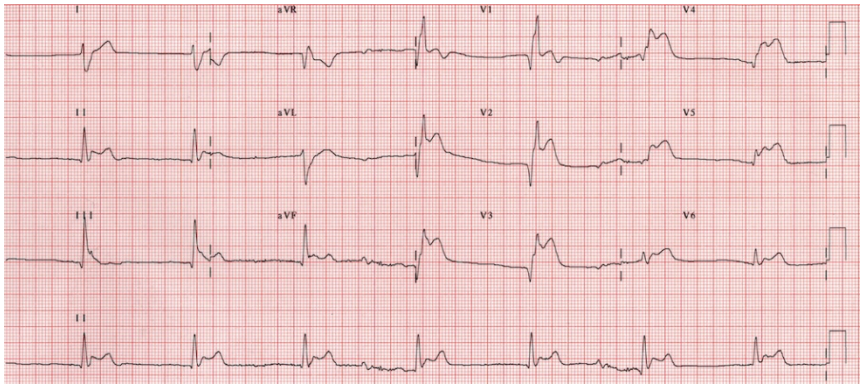
Estudio de supervivencia en la muerte súbita refractaria con revascularización coronaria durante la reanimación en la provincia de Tarragona.

Guillermo Cañardo Cervera
Médico SEM Tarragona i Terres de l'Ebre.

Muerte súbita

Se puede definir como muerte inesperada, sin síntomas precedentes la mayoría de las veces o que, en casos de existir éstos, ocurren pocos segundos antes de que la muerte sobrevenga, y sin causa traumática que la explique.

En la mayoría de los casos la MS sobreviene como consecuencia de un evento cardiovascular (60- 70 % de los casos) , siendo la cardiopatía coronaria , con o sin antecedentes conocidos, responsable del 70 a 80 % de ellos.



Muerte súbita

La parada cardiaca (PC) en el medio extrahospitalario constituye uno de los mayores retos en el mundo occidental, estimando entre 400.000 y 700.000 las muertes súbitas (MS) anuales en la Unión Europea y por encima de 350-450.000 en EE. UU.

El 80% tienen lugar en domicilio, con una mortalidad próxima al 90% y grados variables de disfunción cerebral grave en más de la mitad de los supervivientes.

Para una incidencia de MS sobre 53/100.000 habitantes, unos 40-50.000 pacientes sufren una PC extrahospitalaria en España.

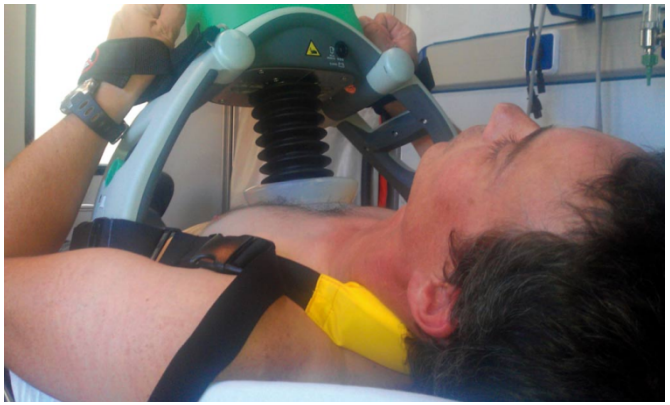
Servei Català de la Salut

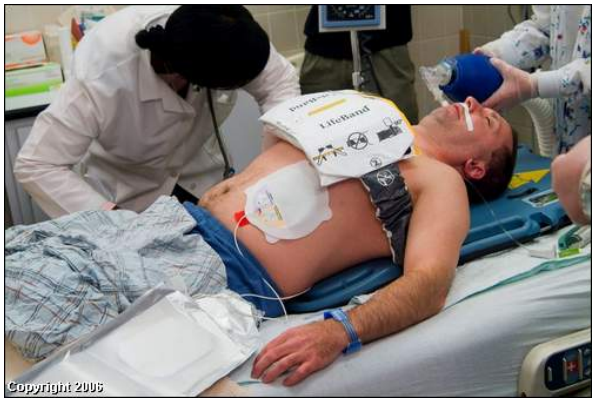
Objetivo del estudio

Aumentar la supervivencia en la MS extrahospitalaria mediante la utilización de compresor torácico externo y revascularización coronaria durante la reanimación.

Cadena de la vida

- **Mecanismos de compresión torácica mecánica**: tanto *Autopulse*® (*Load-distributing LifeBand*® -Zoll, Chelsmford, MA-) como *Lucas*™ *1* (*Lund University Cardiac Arrest System*) y *Lucas*™ *2* generan compresiones torácicas de forma continua y sin interrupciones, manteniendo tanto la presión de perfusión cerebral (fase de compresión) como, especialmente, la presión de perfusión coronaria (PPC) (fase de descompresión), principal factor determinante de la Recuperación de la Circulación Espontánea (RCE)





Cardiac arrest

Recommendations	Class	Level
All medical and paramedical personnel caring for a patient with suspected myocardial infarction must have access to defibrillation equipment and be trained in cardiac life support.	I	C
It is recommended to initiate ECG monitoring at the point of FMC in all patients with suspected myocardial infarction.	I	C
Therapeutic hypothermia is indicated early after resuscitation of cardiac arrest patients who are comatose or in deep sedation.	I	B
Immediate angiography with a view to primary PCI is recommended in patients with resuscitated cardiac arrest whose ECG shows STEMI.	I	B
Immediate angiography with a view to primary PCI should be considered in survivors of cardiac arrest without diagnostic ECG ST-segment elevation but with a high suspicion of ongoing infarction.	IIa	B

ECG = electrocardiogram; FMC = first medical contacts; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

www.escardio.org/guidelines

European Heart Journal 2012 - doi:10.1093/eurheartj/ehs215

EUROPEAN SOCIETY OF CARDIOLOGY®

Revascularización durante la reanimación.

- **Código IAM con parada refractaria:** Identificado el paciente en RCP refractaria de probable causa coronaria, los CTM hacen posible mantener las PPC y cerebral durante el traslado del paciente a la sala de hemodinámica. De esta forma la RCP mecánica sirve a modo de puente para que el paciente pueda recibir su tratamiento etiológico específico: **«Código IAM de Parada Refractaria»**

Servei Català de la Salut

Código IAM con parada refractaria.

La atención del paciente en RCP refractaria se basa en:

1) una adecuada selección de los pacientes en PCR de causa coronaria;
2) una evacuación precoz del paciente utilizando alguno de los actuales compresores torácicos mecánicos;
3) la revascularización coronaria urgente del paciente durante la RCP
4) la aplicación de cuidados intensivos post-resucitación, hipotermia incluida.

El intervalo máximo disponible colapso-balón no debe superar los 90 minutos.

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REVISIÓN

Revascularización coronaria durante la resucitación cardiopulmonar. Código puente

A. Serrano Moraza[a,b,1], F. del Nogal Sáez[c] y F. Alfonso Manterola[d]

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Recibido el 6 de septiembre de 2011; aceptado el 7 de enero de 2012

Experimental and clinical use of ongoing mechanical cardiopulmonary resuscitation during angiography and percutaneous coronary intervention

Kjetil Sunde, MD, PhD

Background: Coronary heart disease is the most frequent cause of cardiac arrest. Return of spontaneous circulation is often not achieved during resuscitation due to the inability to restore coronary blood flow.

Objective: To review the literature with the aim of documenting if coronary angiography and subsequent percutaneous coronary intervention is feasible during continuous mechanical chest compressions.

Results: One experimental pig study, some case reports (of different size), and one recent abstract have documented the use of continuous mechanical chest compressions with the Lund University Cardiac Arrest System during angiographic procedures and subsequent percutaneous coronary intervention during cardiac arrest. If the arrest occurs in-hospital, especially during the angiographic procedure, the potential for successful outcome seems to be better.

Conclusions: Coronary angiography and percutaneous coronary intervention is feasible during continuous mechanical chest compressions. This could be an alternative approach in cardiac arrest patients with suspected myocardial infarction who do not achieve return of spontaneous circulation with traditional resuscitation techniques. (Crit Care Med 2008; 36:[Suppl.]:S405–S408)

KEY WORDS: heart arrest; mechanical CPR; angioplasty

Resuscitation (2007) **73**, 29—39

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CLINICAL PAPER

Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest☆

Kjetil Sunde[a,b,*], Morten Pytte[a,b], Dag Jacobsen[c], Arild Mangschau[d], Lars Petter Jensen[a], Christian Smedsrud[a], Tomas Draegni[a], Petter Andreas Steen[a]

[a] *Department of Anaesthesiology, Ulleval University Hospital, Oslo, Norway*
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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

Should We Emergently Revascularize Occluded Coronaries for Cardiac Arrest?: Rapid-Response Extracorporeal Membrane Oxygenation and Intra-Arrest Percutaneous Coronary Intervention

Eisuke Kagawa, Keigo Dote, Masaya Kato, Shota Sasaki, Yoshinori Nakano, Masato Kajikawa, Akifumi Higashi, Kiho Itakura, Akihiko Sera, Ichiro Inoue, Takuji Kawagoe, Masaharu Ishihara, Yuji Shimatani and Satoshi Kurisu

Circulation. 2012;126:1605-1613; originally published online August 16, 2012;

Código IAM con parada refractaria.

- INDICACIONES

- PCR presenciada con RCP del testigo<10min. o por unidad SVB<15min .
- Acceso a RCP avanzada con aplicación eficaz de compresor torácico mecánico .
- RCP avanzada refractaria, definida como ausencia de pulso tras 10min. de su inicio.
- Sospecha razonada de PCR de etiología coronaria de acuerdo con patrón y criterios clínicos de presentación.
- Rango de edad comprendido, inicialmente, entre 18 y 70 años .
- RCP no contraindicada [enfermedad degenerativa y/o terminal, órdenes de no RCP, instrucciones anticipadas, voluntades previas, testamento vital, etc.]

Tabla 3 Factores predictivos de enfermedad coronaria como causa de la PCR

Patrón epidemiológico

- Paciente en grupo de elevada prevalencia para enfermedad coronaria (edad, sexo, etc.)
- Existencia previa de enfermedad coronaria documentada (IAM, angina previos, angioplastia, bypass coronario previo, etc.)
- Presencia de uno o más factores de alto riesgo para enfermedad coronaria: diabetes mellitus, hipertensión arterial, obesidad, consumo excesivo de tabaco

Diagnóstico previo de SCA previo a la PCR [de minutos a horas]

Con los siguientes patrones:

- Patrón clínico + ECG compatible:
  - Elevación específica del segmento ST en dos o más derivaciones contiguas:
  VPP 96%, VPN 42%, S 42%, E 95%30
  - Pero también: depresión ST, trastornos de conducción, etc.
  VPP 56%30
- Marcadores enzimáticos/químicos de SCA:
  - Troponina T S 96%, E 80% para IAM30
  - CK MB S 96% E 73% para IAM30
  - Otros

Forma de presentación. Historia clínica inmediata previa a la PC

- Contexto clínico del paciente
  Ej1: paciente que cae desplomado con la mano en el pecho o dolor torácico de segundos de duración
  Ej2: paciente con dolor epigástrico de 24 h de evolución que ahora está inconsciente
- Forma de presentación y asociación demostrada o sospechada entre SCA y PC

a Todos estos factores deben valorarse solos o en asociación, a fin de realizar una estimación del riesgo coronario del paciente
b A partir de su valoración se realizará una estratificación de riesgo
Ej: factores de alto riesgo para SCACEST37,38.

- Troponina cardiaca positiva
- Diabetes mellitus
- Inestabilidad hemodinámica o rítmica
- Desviación del segmento ST en el electrocardiograma
  Ej: factores de alto riesgo para SCASEST:
- Disfunción sistólica del ventrículo izquierdo

Código IAM con Parada Refractaria.

- CONTRAINDICACIONES

• Ausencia de alguno de los requisitos señalados en la tabla de indicaciones

• No es posible activar el procedimiento o, por diferentes motivos, el Centro Coordinador no puede conseguirlo

• No es posible mantener la calidad de las compresiones torácicas durante el traslado [ej: evacuación por escaleras, piso a diferente nivel, difícil acceso, rescate complejo, etc.]

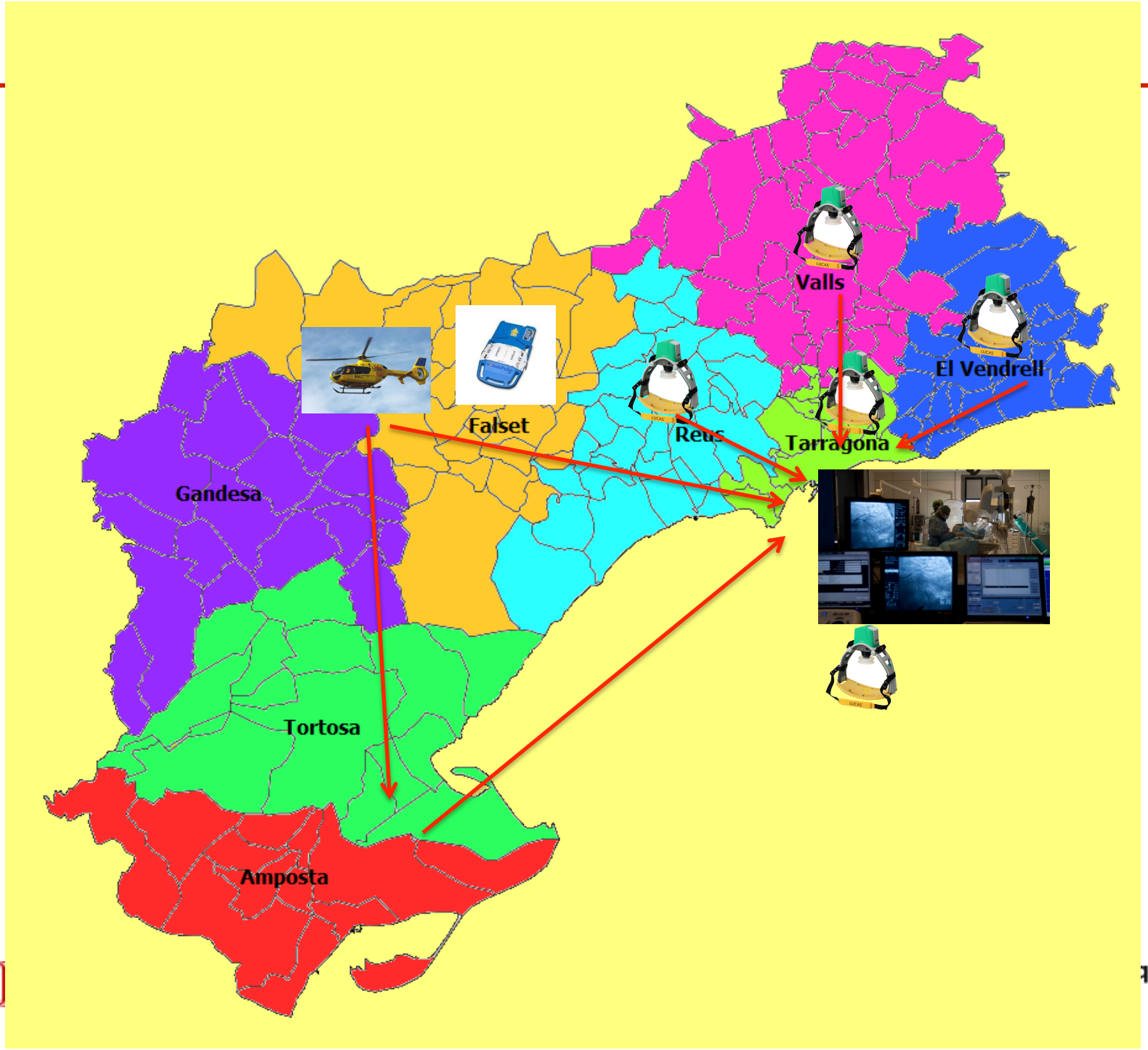
• Fallo del sistema mecánico de compresión

• Otras situaciones que, a juicio del equipo de emergencia, puedan comprometer la eficacia de las compresiones torácicas y/o la viabilidad de la perfusión cerebral del paciente

Nota técnica: *Lucas*™ posible desde 16 años y/o tamaño compatible. *Autopulse*® posible desde los 18 años. Permite 15 grados de inclinación horizontal.

Generalitat de Catalunya
Departament de Salut

CatSalut
Servei Català de la Salut


Valls
El Vendrell
Falset
Reus
Tarragona
Gandesa
Tortosa
Amposta

Prehospital nonconventional CPR: for whom and when?

Lionel Lamhaut

D.A.R. - SAMU de Paris – France

Sudden death expertise center

Necker University Hospital

Refractory Cardiac arrest

- No return of spontaneous cardiac activity > 20-30 min
- No hope of recovering cardiac activity
- No hope of getting a satisfactory brain activity

Refractory OHCA :
No ROSC after 30 min of ACLS

Cardiac arrest parameters

No Flow ?

Low Flow ?

Circumstances ?

Declared Dead on scene

Continuous circulatory and respiratory support

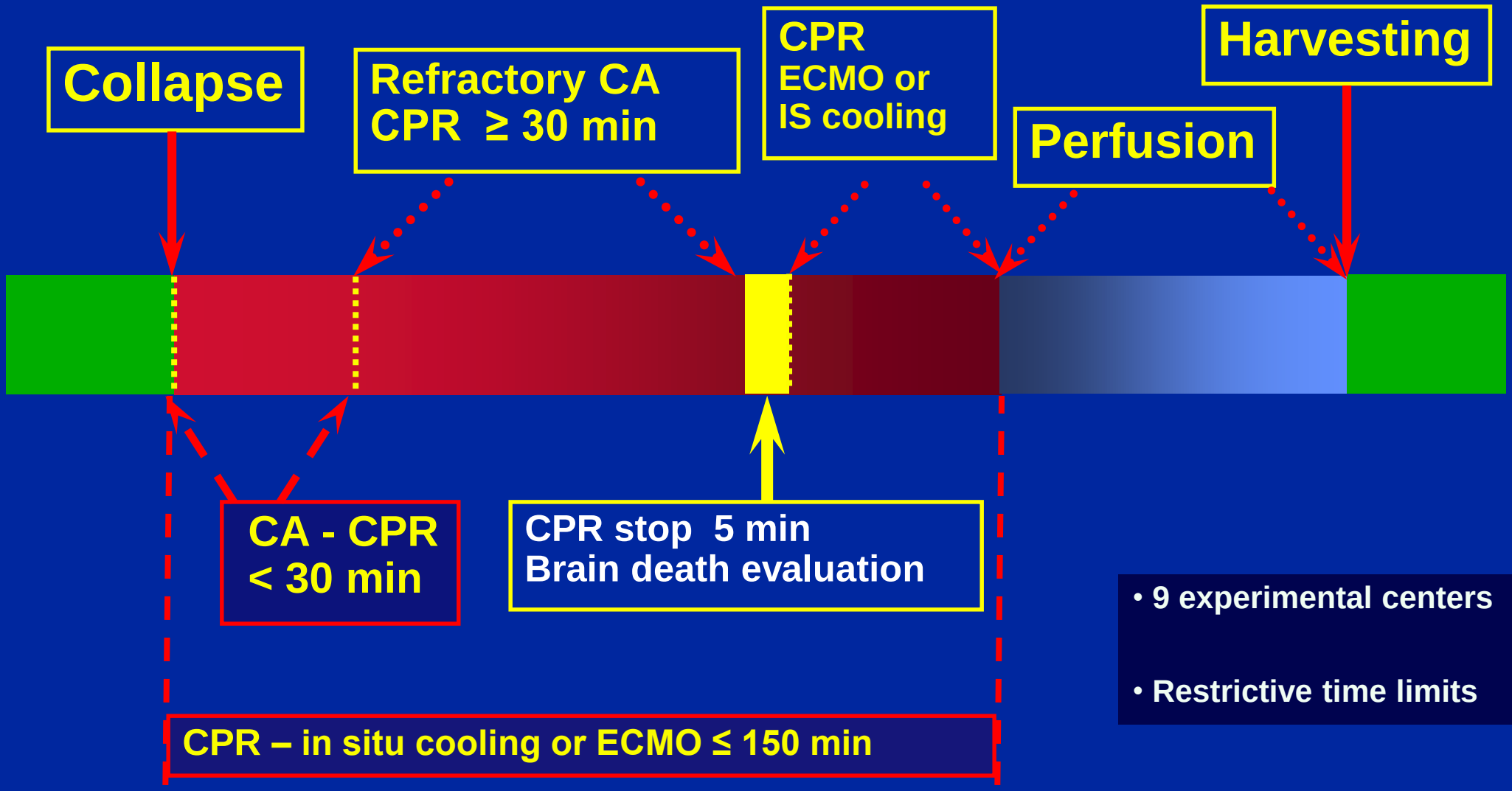
Mechanical Cardiac massage

Non Heart beating Donation

Therapeutic ECLS

Revascularization

NHBD
The 2006 French National Protocol



- 9 experimental centers
- Restrictive time limits

Refractory OHCA : Possible Orientation

Cardiac arrest parameters

No flow < 5 min
ou
signs of life
ou
neuroprotection

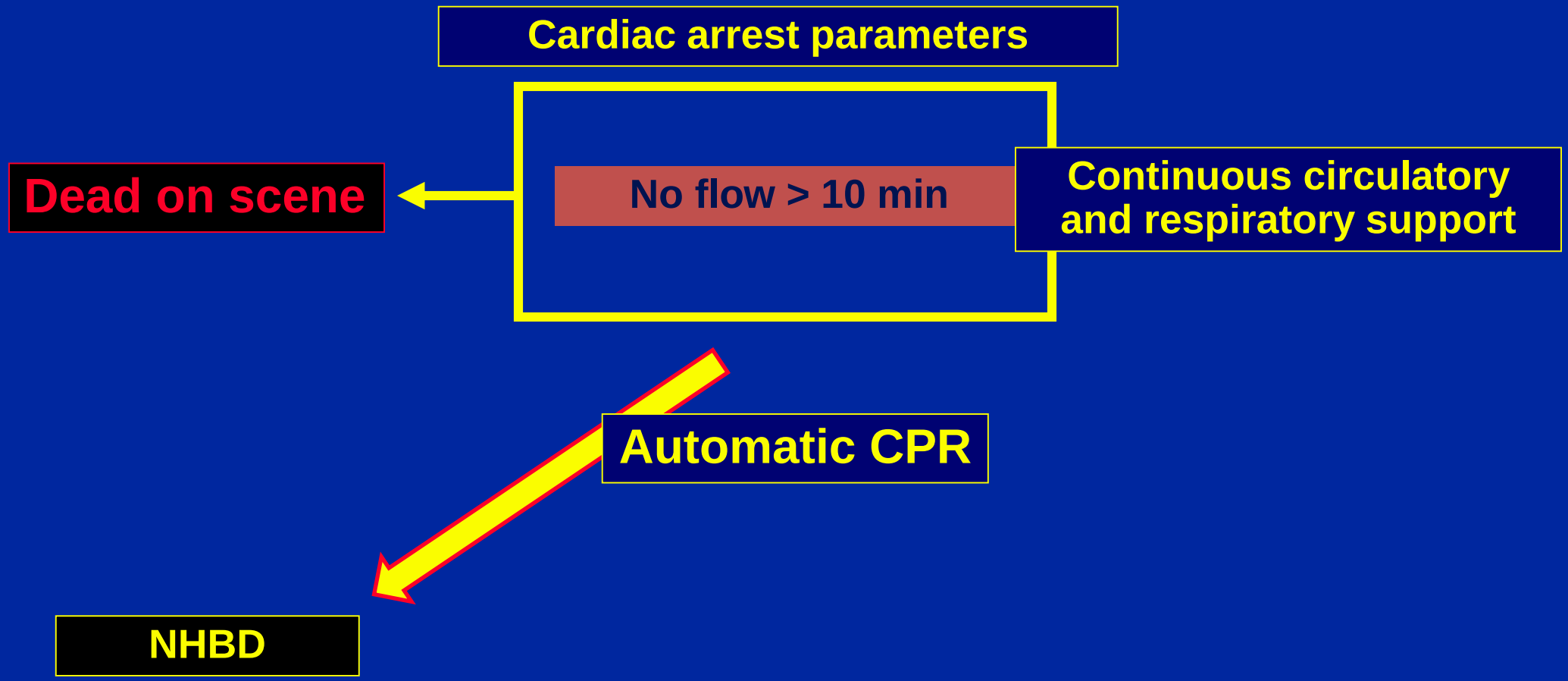
Continuous circulatory and respiratory support

Automatic CPR

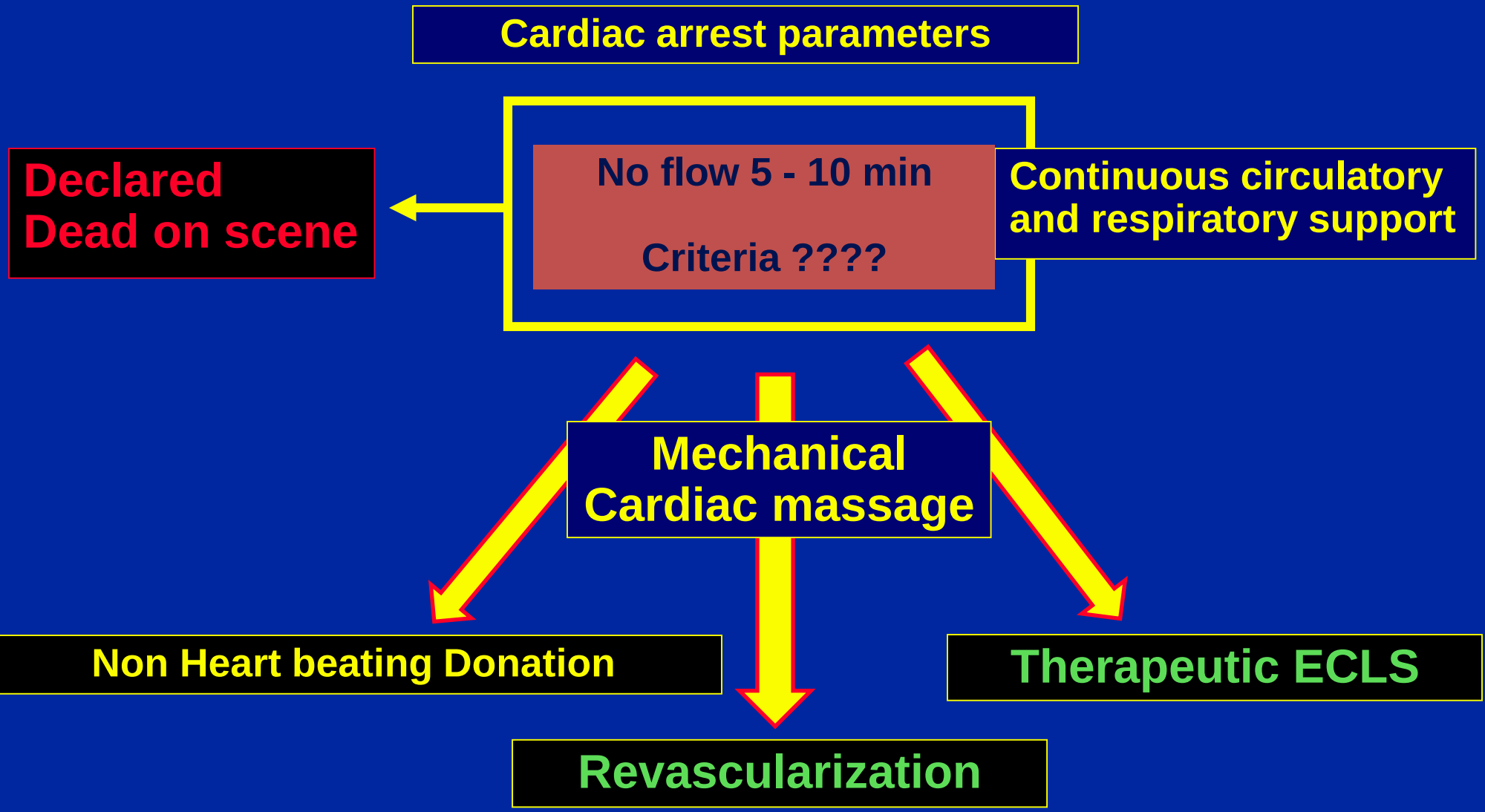
Therapeutic ECLS

Revascularization: PCI under CPR

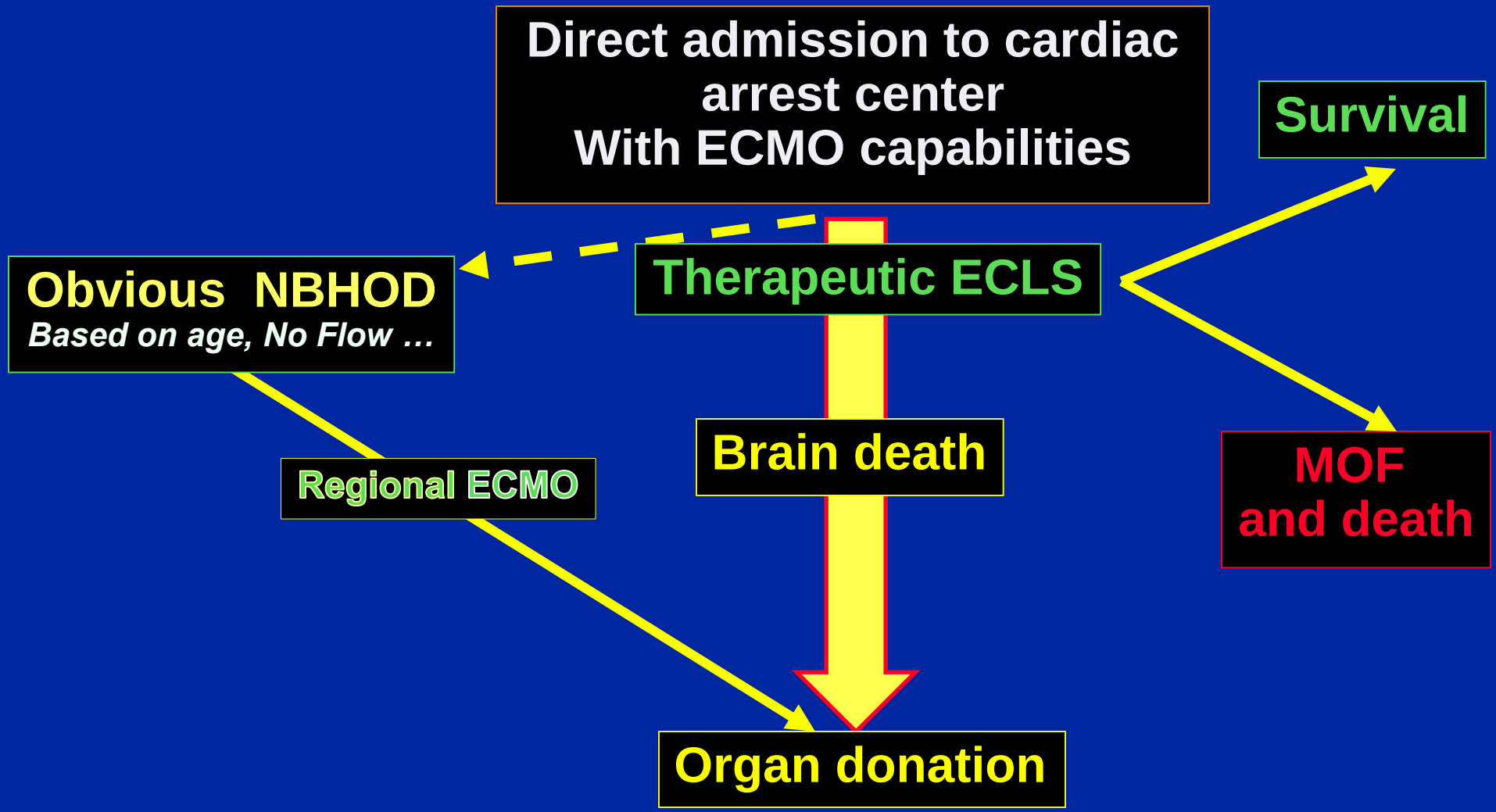
Refractory OHCA : Possible Orientation



Refractory OHCA : Possible Orientation



A new management for refractory OHCA not declared dead on scene



Résumé

Le CEDIT a été saisi par l'AGEPS pour évaluer l'intérêt de l'oxygénation extracorporelle par membrane (ECMO), pour la prise en charge **pré-hospitalière** des arrêts cardiaques. Cette saisine fait suite à une demande de l'hôpital Necker pour utiliser le dispositif Cardiohelp® (entreprise Maquet), notamment par les unités SAMU 75.

Aspects techniques : la mise en place extrahospitalière d'un système d'ECMO veino-artériel soulève des questions quant au matériel, aux conditions et à l'environnement dans lesquels elle se pratique. La description technique des appareils d'ECMO a déjà été réalisée dans des avis précédents. Aujourd'hui, de par sa forme compacte et son poids réduit, l'appareil le plus adapté à une utilisation extrahospitalière est Cardiohelp®. La mise en place des canules expose le patient à des risques infectieux, hémorragiques et ischémiques si le personnel arrivant sur les lieux de l'intervention n'est pas suffisamment formé et habitué à cette pratique de terrain.

Aspects médicaux : chez les patients en arrêt cardiaque réfractaire, la mise en place précoce à l'hôpital d'un 'ECMO (délais inférieurs à 1h, voire à 30 min.) accroît la survie avec état neurologique favorable. La faisabilité de la mise en place d'une ECMO en milieu extrahospitalier a fait l'objet d'une étude sur 7 patients par une équipe du SAMU de Paris et reste donc à confirmer ; il n'y a pas d'autres données disponibles actuellement. L'étude prospective comparative envisagée par l'équipe de Necker a comme objectif de montrer l'intérêt clinique de la mise en place d'une ECMO en milieu extrahospitalier et devrait fournir des arguments médicaux manquants en termes de preuve médicale.

Aspects médico-économiques : aucune étude médico-économique n'est disponible à ce jour sur l'utilisation de l'ECMO pré-hospitalier. Dans le cadre de l'étude envisagée par l'équipe de Necker, le recueil de données économiques pourrait être réalisé afin de déterminer en même temps l'impact médical et médico-économique de cette nouvelle modalité de prise en charge, par rapport à l'alternative existante.

Il est à noter que dans le cadre de l'alternative qui est la prise en charge hospitalière, des appareils ECMO classiques moins coûteux que Cardiohelp® pourraient être utilisés.

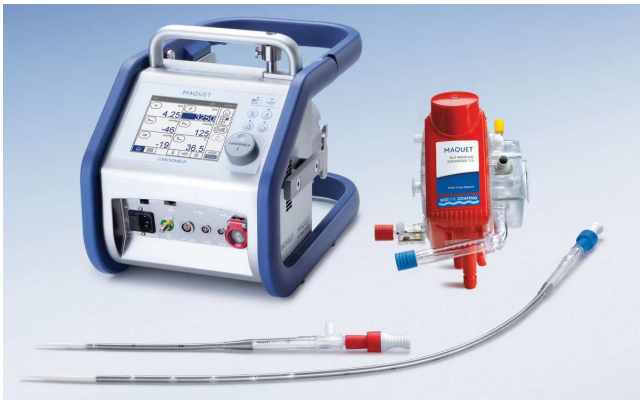
Aspects organisationnels et éthiques : la mise en place précoce d'une ECMO pour les patients en arrêt cardiaque réfractaire nécessite une politique d'organisation et d'intégration des équipes d'interventions mobiles et hospitalières, combinant à la fois la sécurité (ex : maîtrise du risque septique) et rapidité pour la mise en place de l'ECMO.

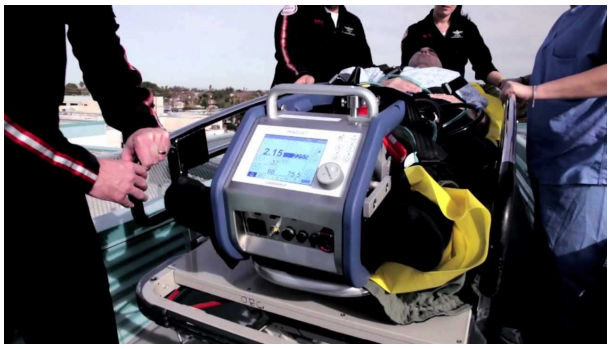
Selon le principe de déconnexion entre la décision d'arrêt des thérapeutiques et celle de prélèvement Maastricht III, une ECMO n'est posée que pour le bénéfice du patient en arrêt cardiaque. En cas d'échec, la décision d'arrêt des thérapeutiques est prise. C'est à partir de ce

moment-là qu'il est possible d'envisager un prélèvement d'organe. A la lumière de cette réflexion, il pourrait être pertinent de s'interroger sur les difficultés de garantir le principe de déconnexion dans des conditions d'exercice en pratique réelle en extrahospitalier.

Recommandations du CEDIT :

- Les quelques cas publiés plaident pour la faisabilité de l'ECMO veino-artérielle réalisée en pré-hospitalier, mais le niveau de preuve est faible et cette faisabilité reste à confirmer. Il n'y a pas actuellement d'élément probant d'efficacité et de sécurité cliniques.
- Les quelques éléments de présomption pourraient justifier une étude clinique comparant la prise en charge hospitalière et pré-hospitalière. L'étude doit montrer l'intérêt clinique de l'ECMO extrahospitalier et fournir des arguments médicaux manquants en termes de preuve médicale (ex : appréhender le risque septique et les conséquences ischémiques sur le membre canulé).
- Compte tenu des incertitudes médicales, médico-économiques et organisationnelles, le CEDIT recommande que toute utilisation de l'ECMO veino-artérielle pré-hospitalière à l'AP-HP soit faite uniquement dans le cadre d'une étude clinique faisant appel à une coopération inter-équipes.
- Le CEDIT souhaite réévaluer l'utilisation pré-hospitalière de l'ECMO à la lumière des résultats de cette étude.
- L'importance du sujet pourrait justifier une évaluation nationale.





Appareil Cardiohelp®

L'utilisation de l'ECMO pré-hospitalière soulève 2 difficultés techniques :

- la mise en place des canules par voie périphérique dans un environnement extrahospitalier
- la faisabilité de cet abord par un urgentiste non chirurgien

La faisabilité de cet abord par un urgentiste non chirurgien a été étudiée par une équipe utilisant l'ECMO à l'AP-HP. Cependant, même dans un cadre hospitalier, la note du Directeur de la Politique Médicale de novembre 2012 en limite l'utilisation : « chez l'adulte, les collégiales concernées s'accordent à estimer que l'activité d'ECMO devrait être réalisée par un nombre limité de services de réanimation adossés à des unités de chirurgie cardiaque ou thoracique ».

Aspects médicotechniques de la mise en place des canules d'ECMO par voie périphérique

L'ECMO veino-artérielle envisagée en pré-hospitalier nécessite la mise en place d'un système de canules dans la veine et l'artère fémorale. Trois approches existent pour cette mise en place (*peripheral cannulation*) : percutanée, semi-ouverte, ouverte.

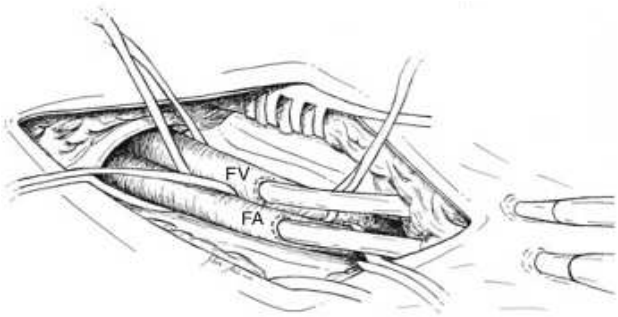


Figure 1 Cathétérisme fémoral semi-ouvert

L'approche percutanée utilise généralement la technique de Seldinger. Le vaisseau (artère ou veine fémorale) est ponctionné à l'aide d'un trocart creux. Le trocart est ensuite inséré à l'endroit voulu, un guidage par échographie permettant d'assister cette ponction. Un guide métallique est inséré à l'intérieur de la lumière du trocart. Puis le trocart est retiré en coulissant le long du guide. Finalement, le cathéter est hissé le long du guide métallique qui est alors retiré. Cette technique de mise en place de canules fémorales percutanée avec écho-guidage est décrite par Benassi [2].

L'approche semi-ouverte, dite technique « semi-Seldinger », repose sur les mêmes principes que la technique de Seldinger, à ceci près qu'une incision est faite au-dessus de la veine fémorale afin d'insérer les cathéters en supervision directe.

Enfin, l'approche ouverte consiste à réaliser une dissection complète et à insérer directement les cathéters dans les vaisseaux. Cette technique est habituellement réalisée par des chirurgiens [3].

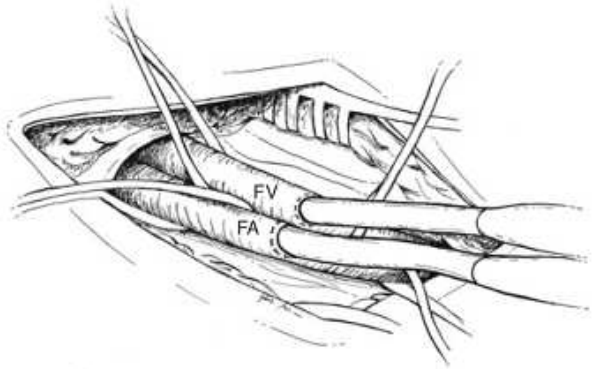


Figure 2 Cathétérisme fémoral ouvert

En résumé, la mise en place extrahospitalière d'un système d'ECMO veino-artériel soulève des questions difficiles quant au matériel, aux conditions et à l'environnement dans lesquels elle se pratique. La mise en place des canules expose le patient à des risques infectieux, hémorragiques et ischémiques si le personnel arrivant sur les lieux de l'intervention n'est pas suffisamment formé et habitué à cette pratique de terrain. Le Dr Lionel Lamhaut (SAMU Necker) privilégie l'approche semi-ouverte qui lui semble plus rapide et plus sure que l'approche percutanée [4]. La faisabilité de cet abord par un urgentiste non chirurgien a été étudiée par une équipe utilisant l'ECMO à l'AP-HP.

3. Aspects médicaux

La mise en place d'une ECMO sur les lieux de prise en charge initiale relève de la stratégie de déplacement des moyens médicaux près du patient (stratégie désignée par certains sous le nom de « *stay and play* »). Cette stratégie s'oppose à la stratégie de transport précoce du patient vers son lieu de prise en charge permanente (« *scoop and run* »).

3.1. L'arrêt cardiaque extrahospitalier

En France, environ 50 000 décès seraient imputables chaque année à un arrêt cardiaque. En dehors de l'hôpital, le taux de survie sans séquelles neurologiques se situe entre 3 et 5% [5]. La coronaropathie associée à un trouble de rythme serait la cause principale, faisant des hommes de plus de 50 ans la principale population touchée. Chez les patients plus jeunes, les cardiopathies congénitales sont la cause principale des arrêts cardiaques.

La prise en charge est actuellement codifiée par les recommandations de 2010 du *European Resuscitation Council* [6] et fait appel au massage cardiaque externe, à l'utilisation des défibrillateurs et, dans un contexte plus spécifique, à l'hypothermie thérapeutique. Une « chaine de survie » en 4 étapes y est décrite : alerte donnée par le premier témoin, réalisation des gestes élémentaires de survie (massage cardiaque et suppléance respiratoire), défibrillation et enfin réanimation médicalisée.

Le pronostic des patients peut se mesurer en termes de survie et de complications neurologiques. Selon les recommandations de 2010, le pronostic s'alourdit avec l'augmentation du délai entre la survenue de l'arrêt cardiaque et sa prise en charge, mais aussi avec la durée de la réanimation cardio-pulmonaire. Au-delà de 15 à 20 minutes de réanimation cardio-pulmonaire spécialisée sans activité électrique, même transitoire, le taux de survie chute de façon significative et s'approche de zéro après 30 minutes, dans des conditions normothermiques [7]

L'arrêt cardio-respiratoire réfractaire est défini par l'absence de Reprise d'Activité Circulatoire Spontanée (RACS) après 30 minutes de réanimation [8] chez un patient normotherme et non intoxiqué. Certaines situations incitent à prolonger les manœuvres pendant plus longtemps. Les dispositifs de massage cardiaque automatiques facilitent la réalisation du massage cardiaque pendant le transport mais n'ont pas permis d'améliorer le pronostic des patients en arrêt cardiaque [9]

Plus récemment, des améliorations des appareils ECMO et la publication d'études ont permis d'envisager l'intérêt de cette technique, réalisée à l'hôpital pour les arrêts cardiaques intra-hospitaliers, voire extrahospitaliers (cf. ci-après). L'utilisation de l'ECMO pré-hospitalière est désormais envisagée pour tenter d'améliorer la survie et le pronostic neurologique des patients en arrêt cardiaque extrahospitalier.

Avant d'aborder la section suivante, il est utile de rappeler que toute réanimation cardio-pulmonaire peut avoir des répercussions, tant du point de vue individuel (bénéfices en termes de survie du patient et d'amélioration du pronostic neurologique) que du point de vue sociétal (don d'organe, acceptabilité sociale).

3.2. Analyse des données disponibles

Actuellement, la littérature n'offre pas de réponse à la question des bénéfices individuels de l'ECMO pré-hospitalière. En revanche, elle permet de mettre en évidence des éléments de présomption :

- l'introduction de l'ECMO a permis d'améliorer le pronostic des patients avec arrêt cardiaque extrahospitalier, pris en charge à l'hôpital.
- la précocité de la prise en charge améliore le pronostic des patients [10]
- l'ECMO pré-hospitalière permettrait de réduire le délai de *low flow* mais pas celui de *no flow*.

Les principales caractéristiques retrouvées dans la littérature sont :

- le taux de survie
- l'évaluation neurologique : le score le plus utilisé est le *Cerebral Performance Categories (CPC)* constitué de 5 niveaux : patient conscient avec fonctions supérieures normales ou faiblement altérées (niveau 1), patient conscient avec fonctions supérieures

moyennement altérées (niveau 2), patient conscient avec fonctions supérieures très altérées (niveau 3), patient dans le coma ou dans un état végétatif (niveau 4), patient en mort encéphalique ou décédé (niveau 5)

- le temps avant la mise en place de l'ECMO

3.2.1. ECMO réalisée à l'hôpital

Une étude de Le Guen [11] a examiné la faisabilité et l'efficacité de l'ECMO à l'hôpital (étude réalisée à l'AP-HP) sur 51 patients ayant eu un arrêt cardiaque extrahospitalier. Le délai médian entre l'arrêt cardiaque et les mesures de réanimation usuelles était de 120 minutes et aucun patient n'a pu bénéficier d'une ECMO avant 75 min. Deux patients seulement (4%) étaient vivants un mois plus tard et avaient un état neurologique satisfaisant. Ces résultats sont comparables à ceux trouvés dans la littérature sur la prise en charge des patients en arrêt cardiaque mais sans l'utilisation d'une ECMO. Cette série montre que l'ECMO ne pourra pas améliorer la survie des patients si une diminution du délai de prise en charge n'a pas lieu. Il semble que le facteur limitant soit le temps de transport (voir tableau 1).

Tableau 1 Délais de prise en charge selon Le Guen

Temps en minutes jusqu'à…	Médiane*	Min-Max
l'initiation des mesures de réanimation de base	3 [1-6]	0-22
l'initiation des mesures de réanimation avancées	12 [5-23]	0-40
la mise en place d'un dispositif automatique de massage cardiaque	41 [30-55]	15-110
l'arrivée en soins intensifs	90 [65-115]	48-175
la mise en place d'une ECMO	120 [102-149]	75-195

** Résultat présentés sous la forme Médiane [1re quartile – 3e quartile]*

L'étude publiée par Fagnoul en 2013 [12], réalisée dans une unité de soins intensifs à Bruxelles, a montré que lors de la prise en charge de 24 patients ayant un arrêt cardiaque (10 intra-hospitalier et 14 extrahospitalier) 6/24 ont survécu. Les survivants bénéficiaient tous d'une ECMO mise en place dans l'heure suivant l'arrêt. Parmi les 18 patients qui n'ont pas survécu, le don d'organes a été possible dans 4 cas, dont 2 finalement acceptés. Cette étude souligne l'importance du délai entre l'arrêt cardiaque et la mise en place d'une ECMO. Pour les auteurs, l'ECMO doit être posée dans les 60 minutes suivant l'arrêt.

Tableau 2 Prise en charge des patients en arrêt cardiaque selon Fagnoul

	Patients vivants (N=6)	Patients décédés (N=18)
Arrêt cardiaque intrahospitalier	3	7
Arrêt cardiaque extrahospitalier	3	11
Temps (en minutes) avant mise en place d'une ECMO*	41 [39–58]	60 [55–77]

** Résultat présentés sous la forme Médiane [1re quartile – 3e quartile]*

Dans un article de 2014 [13], Fagnoul estimait que la pratique de l'ECMO à l'hôpital était faisable pour les arrêts cardiaques extrahospitaliers, bien que ces derniers posaient des défis plus importants que les arrêts intrahospitaliers. Pour les 15-20% des patients qui survivaient le délai entre l'arrêt cardiaque et l'ECMO était inférieur à 60 minutes.

Sakamoto a réalisé en 2014 [14] une étude observationnelle prospective multicentrique ayant comparé l'ECMO (n=260) réalisée à l'hôpital à une prise en charge conventionnelle (n=194), chez des adultes ayant un arrêt cardiaque extrahospitalier avec une tachycardie ou une fibrillation ventriculaire. Le critère principal de jugement était le *Cerebral Performance Categories* (CPC), mesuré à 1 et 6 mois. En analyse en intention de traiter, une différence significative a été mise en évidence. La survie avec CPC favorable (1 ou 2) était de 12,3% (32/260) dans le groupe ECMO contre 1,5% (3/194) dans le groupe conventionnel à 1 mois, et de 11,2% (29/260) contre 2,6% (5/194) à 6 mois. Les résultats sont comparables en analyse per protocole (voir tableau 3)

Tableau 3 Résultats de l'étude de Sakamoto (per protocole)

Etude de Sakamoto (analyse per protocole)	Groupe E-CPR (N=256)	Groupe non E-CPR (N=190)
Temps entre l'appel téléphonique et l'arrivée à l'hôpital	29,8 min	30,5 min
Score CPC à 6 mois (per protocole): 1 2 3 4 5	 25 4 8 18 177	 4 1 1 0 152
CPC 1 ou 2 (per protocole)	29 (12,4%)	5 (3,1%)

Les auteurs concluent que l'utilisation de l'ECMO était associée à une amélioration neurologique des patients. La particularité de cette étude est la rapidité de la prise en charge hospitalière. En effet, le temps moyen entre l'appel téléphonique du centre d'urgence et l'arrivée à l'hôpital était de l'ordre d'une demi-heure. Ainsi, l'organisation japonaise permet de combiner la rapidité de la mise en place d'une ECMO et la sécurité de l'environnement où l'ECMO est posée. Sans ECMO, le taux de survie avec un pronostic neurologique favorable est comparable à ce qu'on trouve dans la littérature internationale. Avec l'ECMO, le taux de survie est multiplié par 4. Cette étude permet d'envisager les bénéfices qu'apporterait une mise en place précoce de l'ECMO en France.

Maekawa a réalisé en 2013 une étude [15] reposant sur le suivi prospectif de 162 patients ayant eu un arrêt cardiaque et chez qui une réanimation cardio-pulmonaire a été pratiquée sans succès pendant plus de 20 min (53 patient dans le groupe E-CPR et 109 dans le groupe réanimation cardio-pulmonaire classique). L'analyse a porté sur 2 groupes (E-CPR et réanimation conventionnelle) constitués de 24 patients appariés selon le score de propension (voir tableau 4). Le score de propension était construit à partir des variables âge, sexe et autonomie de la personne. Le critère de jugement principal était la survie avec un état neurologique normal à 3 mois. Cette survie était plus importante dans le groupe E-CPR que dans le groupe réanimation conventionnelle (29,2% [7/24] vs. 8,3% [2/24], log-rank p = 0,018).

Tableau 4 Résultats de l'étude de Maekawa, groupe appariés selon un score de propension

Etude de Maekawa (groupes appariés)	Groupe E-CPR (N=24)	Groupe non E-CPR (N=24)
Temps entre l'arrêt cardiaque et les soins de réanimation avancés (en min)	23 [14-27]	20 [16-27]
Survie à 3 mois	9 (37,5%)	2 (8,3%)
CPC favorable (1 ou 2) à 3 mois	7 (29,2%)	2 (8,3%)

Cette étude observationnelle, tout en confirmant l'efficience du système de prise en charge japonais, montre l'intérêt potentiel de l'ECMO précoce dans la prise en charge des arrêts cardiaque, avec un taux de patients CPC de 1 ou 2 multiplié par 3,5 entre la prise en charge classique et la prise en charge par ECMO.

Wang a publié en 2014 [16] une étude rétrospective sur 230 patients avec arrêt cardiaque ayant bénéficié d'une E-CPR, dont 199 événements intra-hospitaliers (IHCA) et 31 événements extrahospitaliers (OHCA). Le critère de jugement principal était la survie à la sortie de l'hôpital. Le critère de jugement secondaire était une issue neurologique favorable définie comme un CPC de 1 ou 2. Le taux de survie à la sortie de l'hôpital était de 38,7% dans le groupe OHCA et

de 31,2% dans le groupe IHCA sans différence significative observée (p=0,26). Le taux de patients présentant un état neurologique favorable était de 25,5% dans le groupe OHCA et de 25,1% dans le groupe IHCA, sans différence significative observée (p=0,55). Mais les différences entre les deux populations n'ont pas permis de comparer les résultats, ni de tirer des conclusions fortes sur cette comparabilité. En effet, le temps entre l'arrêt cardiaque et la mise en place de l'ECMO était plus court dans le groupe IHCA (44,4±24,7 min vs. 67,5±30,6 min, p<0,05), et l'ECMO était maintenue moins longtemps dans le groupe OHCA patients (61±48h vs. 94±122h, p<0,05). Cette étude met en évidence une relation entre le temps d'ischémie, la survie et le CPC (voir tableau 5). On remarque que les individus ayant survécu avec ou sans CPC favorable ont la plupart eu des temps d'ischémie inférieurs à 60 min.

Tableau 5 Relation entre temps d'ischémie, survie et CPC selon Wang

Wang	Survie		CPC 1 ou 2	
Temps d'ischémie	Extrahospitalier (N=31)	Hospitalier (N=199)	Extrahospitalier (N=31)	Hospitalier (N=199)
< 30min	0	26	0	24
< 45 min	5	46	4	41
< 60 min	8	56	7	47
< 75 min	12	58	8	48
< 90 min	12	60	8	49
Total	12	62	8	50

Avalli a publié en 2012 [17], une étude rétrospective incluant 42 patients ayant un arrêt cardiaque réfractaire (circulation spontanée non-retrouvée après 30 minutes de réanimation cardio-pulmonaire). Le critère de jugement principal était la survie à 28 jours avec atteinte neurologique légère. L'atteinte neurologique était mesuré par le *Glasgow Outcome Scale* (GCO, 1 = mort; 2 = état végétatif persistant; 3 = déficit neurologique sévère comprenant un faible état de conscience, déficit moteur important, aphasie et besoin d'aide permanent; 4 = déficit neurologique léger et 5 = bon état neurologique). La survie des patients avec arrêt intra-hospitalier était meilleure que celle des patients avec arrêt extrahospitalier (résultat neurologique favorable de 38% versus 5%, p<0,05). Ceci peut s'expliquer par le fait qu'un délai minimum de 25 min était nécessaire pour qu'une ECMO soit mise en place à l'hôpital, et que pour les patients ayant eu un arrêt cardiaque extrahospitalier, ce délai n'était pas inférieur à 60 min. Le délai médian pour la mise en place d'une ECMO dans le groupe OHCA était de 77 min (Q1-Q3= [69–101]).

Leick a publié en 2013 [18] une étude rétrospective réalisée en Allemagne dont l'objectif était d'identifier les facteurs prédictifs de mortalité chez 28 patients en arrêt cardiaque extrahospitalier ayant bénéficié d'une ECMO mise en place à l'hôpital. Pour les 11 patients ayant survécu, le temps médian avant la mise en place d'une ECMO était de 25,0 min [21,0–30,0], contre 42,5 min [28,0–56,5] pour les patients décédés. Les auteurs recommandent un délai de moins de 30 min pour la mise en place d'une ECMO afin d'améliorer la survie à 30 jours.

Stub a publié en 2015 [19] une étude observationnelle prospective monocentrique réalisée en Australie chez 26 patients en arrêt cardiaque réfractaire (11 en extrahospitalier et 15 en intrahospitalier). Dans cette étude le facteur temps apparait déterminant pour le succès de l'ECMO (voir tableau 6). Les patients ayant survécu avaient, pour la plupart, bénéficié d'une ECMO dans l'heure.

Tableau 6 Résultats de l'étude de Stub

Etude de Stub	Patients vivants (N=14)	Patients décédés (N=12)
Arrêt cardiaque intrahospitalier	9 (64%)	6 (50%)
Arrêt cardiaque extrahospitalier	5 (36%)	6 (50%)
Patients ayant bénéficié d'une ECMO	12 (86%)	12 (100%)
Temps médian entre l'arrêt et la mise en place de l'ECMO	40 [27–57]	78 [48–101]
CPC (1 ou 2)	14 (100%)	-

Les causes de décès des 12 patients étaient : état de mort encéphalique (4 patients), défaillance multiviscérale (3 patients), hémorragie intracrânienne (2 patients), hémorragie (2 patients) (1 saignement intraabdominale dû à une lésion hépatique et 1 saignement intrathoracique dû à une fracture de cote).

3.2.2. ECMO pré-hospitalière

En 2010, dans un article relatif aux indications cardiologiques de l'ECMO, une équipe de la Pitié-Salpêtrière autour du Pr. Leprince [20] estimait que ce type de prise en charge réalisée à l'hôpital a des limites pour l'arrêt extrahospitalier, notamment à cause des délais entre l'arrêt et la mise en place de l'ECMO. Les auteurs estimaient qu'il faudrait peut-être envisager de déplacer l'ECMO jusqu'au patient plutôt que de transférer le patient à l'hôpital sous massage cardiaque.

Dans le cadre d'une mise au point publiée en 2010 [21], le Pr. Pierre Carli estimait que la simplification et la diminution de la taille du matériel d'ECMO a rendu celui-ci utilisable dans les unités mobiles hospitalières des SAMU. Des premiers résultats positifs obtenus pour les arrêts cardiaques réversibles suite à des intoxications par médicaments cardiotropes, ont motivé de nombreuses équipes à adopter cette technique.

En fait, la seule étude disponible avec l'ECMO pré-hospitalier est une étude pilote réalisée à Necker incluant sept patients [22] ayant comme objectif d''analyser la faisabilité et la sécurité de l'utilisation de l'ECMO (appareil Cardiohelp®). Le délai moyen entre la survenue de l'arrêt et la mise en place de l'ECMO était de 79 minutes. La durée moyenne pour mettre en place l'ECMO, une fois l'équipe en place, était de 22 min. Parmi les sept patients, six sont décédés (deux patients en état de mort cérébrale des organes ont pu être prélevés) et un patient a survécu sans séquelles. Les auteurs suggéraient que la pratique de l'ECMO par des non-chirurgiens, avant l'admission à l'hôpital des patients, serait faisable et sure.

Une étude est envisagée à l'hôpital Necker. Le protocole (version 7 du 15 mars 2015, en annexe) nous a été communiqué par l'investigateur principal, le Dr. Lamhaut. Une version antérieure du protocole a obtenu l'avis favorable du CPP IDF II le 5 janvier 2015. Fin avril 2015, l'étude n'est pas enregistrée dans clinicaltrials.gov. Le promoteur est l'entreprise Maquet, fabricant du Cardiohelp®. L'objectif attendu est une augmentation de la survie des arrêts cardiaques extrahospitaliers réfractaires de bon pronostic neurologique de 5% à 20 %. Il s'agit d'une étude randomisée comparant la stratégie d'utilisation pré-hospitalière (n=105) à la stratégie d'utilisation intra-hospitalière de l'ECMO (n=105), en cas d'arrêt cardiaque extrahospitalier réfractaire. La durée prévue de cette étude est de 3 ans. Le critère principal de jugement est la survie à la sortie de réanimation ou à 6 mois. Parmi les critères secondaires on peut citer le statut neurologique des survivants (évaluée par le *Cerebral Performance Category*) et le nombre de prélèvements d'organes réalisés. Les critères d'inclusion sont : patients entre 18 et 65 ans ayant un arrêt cardiaque réfractaire de cause médicale, en absence d'une comorbidité majeure, avec un massage cardiaque externe commencé dans les 5 premières minutes suivant l'arrêt cardiaque. Le déroulement de l'étude serait le suivant : lors de la prise en charge d'un arrêt cardiaque extrahospitalier avec un *no flow* inférieur à 5 minutes, une équipe mobile d'ECMO est prévue d'être envoyée sur place à la 10ème minute. Le patient est inclus et randomisé entre 20 et 30 minutes après la survenue de l'arrêt cardiaque. Il s'agit donc de comparer une stratégie de type « *stay and play* » à 2 équipes (1 équipe pour le diagnostic, 1 équipe pour la mise en place de l'ECMO) à une stratégie de type « *scoop and run* »

3.2.3. En résumé

Les études disponibles montrent qu'il serait possible d'accroître la survie avec état neurologique favorable chez les patients présentant un arrêt cardiaque réfractaire, si le temps de mise en

place d'une ECMO était inférieur à 1h. Certaines études vont jusqu'à évoquer un délai inférieur à 30 min. Les études japonaises montrent que le taux de survie avec bon état neurologique pourrait être multiplié par 3. La faisabilité de la mise en place d'une ECMO en milieu extrahospitalier a été étudiée par une équipe du SAMU de Paris. Une étude envisagée par le Dr. Lamhaut a comme objectif de démontrer l'intérêt clinique de la mise en place d'une ECMO en milieu extrahospitalier à Paris. Les données de la littérature internationale concordent avec l'objectif attendu de cette étude, à savoir une augmentation de la survie des arrêts cardiaques extrahospitaliers réfractaires de bon pronostic neurologique de 5% à 20 %.

4. Aspects médico-économiques

Le coût d'une console Cardiohelp® serait d'environ 75°000 € (source AGEPS). Ces coûts sont nettement supérieurs aux coûts d'une ECMO classique (console ECMO entre 25°000 et 50°000€). De même, le kit consommable HLS set advanced 7.0 se situe entre 3°694 et 4°200€, tandis que le coût de consommable d'une ECMO standard est d'environ 3°000€.

Dans son étude de coûts [23], l'UMAC de Martinique a rapporté un coût moyen de prise en charge sous assistance circulatoire de 4°816 € pour les patients en Martinique, 17°936 € en provenance de Guadeloupe et 37°786 € pour les malades venant de Guyane, pour un coût de matériel ECMO compris entre 3°000 et 6°000€.

Aucune étude médico-économique n'est disponible à ce jour sur l'utilisation de l'ECMO pré-hospitalier. Dans le cadre de l'étude envisagée par l'équipe de Necker, le recueil de données économiques pourrait être réalisé afin de déterminer en même temps l'impact médical et médico-économique de cette nouvelle modalité de prise en charge, par rapport à l'alternative existante.

Il est à noter que dans le cadre de l'alternative hospitalière de type *scoop and run*, des appareils ECMO classiques moins coûteux que Cardiohelp® pourraient être utilisés.

5. Acceptabilité sociale

Dans le cadre de ce dossier, les aspects éthiques et organisationnels ont une importance majeure. Toute réanimation cardio-pulmonaire peut avoir des bénéfices pour le patient (amélioration de la survie et du pronostic neurologique) et une répercussion en termes de santé publique (permettre le prélèvement des organes en vue de transplantations).

5.1. Aspects éthiques

Cette pratique soulève d'importantes questions éthiques car la décision de poser une ECMO en cas d'arrêt cardiaque réfractaire nécessite de prendre en considération l'intention aussi bien

que les conséquences de l'acte. Il soulève la question difficile de la poursuite de la réanimation pour le bénéfice du patient ou, en cas d'échec, pour le prélèvement de ses organes.

La décision d'arrêter une réanimation inefficace ne peut être prise que par un médecin. Elle doit tenir compte du délai écoulé entre l'arrêt cardiaque et les premiers gestes de réanimation par les témoins, la durée de la réanimation spécialisée, et vérifier que tous les moyens disponibles ont été utilisés. Il est accepté qu'une asystolie persistante depuis plus de 20 minutes, réfractaire à une réanimation bien conduite et en l'absence de cause curable, justifie l'arrêt de la réanimation.

En lien avec ce point, la législation française (décret n° 2007-705 du 4 mai 2007) autorise désormais toute personne, même non médecin, à utiliser un défibrillateur automatisé externe (DAE) pour une victime d'un arrêt cardiaque.

Concernant le prélèvement d'organes, la classification de Maastricht établit quatre types de donneurs potentiels à cœur non battant :

- Type 1 : personne en arrêt cardiaque sans possibilité de premiers secours
- Type 2 : personne en arrêt cardiaque avec premier recours inefficace
- Type 3 : personne en arrêt cardiaque après décision d'arrêt des traitements
- Type 4 : personne en mort encéphalique faisant un arrêt cardiaque

L'agence de biomédecine considère également deux situations distinctes :

- Donneurs décédés en mort encéphalique (DDME)
- Donneurs décédés après arrêt cardiaque (DDAC).

En France, 90% des prélèvements d'organes sont réalisés sur des DDME. En 2005, les prélèvements sur DDAC Maastricht I et II ont été autorisés. La loi du 22 avril 2005 relative aux droits des malades et à la fin de vie [24] rend également possible le prélèvement d'organe dans le cadre de la catégorie III de Maastricht. Cependant, l'extension du programme de don d'organes après arrêt circulatoire aux donneurs de la catégorie III de Maastricht n'a été rendu effective qu'à la suite d'une réflexion éthique ayant mené à la rédaction de recommandations, en octobre 2014, mentionnant les conditions précises dans lesquelles ce don doit être effectué [25].

Le rapport du philosophe Éric Fourneret pour l'agence de biomédecine a servi de support à cette réflexion [26]. Plusieurs éléments sont rappelés, comme le principe de la déconnexion de la décision d'arrêt des thérapeutiques, de celle du prélèvement MIII. Selon ce principe de déconnexion, une ECMO n'est posée que pour le bénéfice du patient en arrêt cardiaque. En cas d'échec, la décision d'arrêt des thérapeutiques est prise. C'est à partir de ce moment-là qu'il est possible d'envisager un prélèvement d'organe. A la lumière de cette réflexion, il pourrait être pertinent de s'interroger sur les difficultés de garantir le principe de déconnexion dans des conditions d'exercice en pratique réelle.

La place de l'évaluation neurologique est importante dans la décision d'arrêt des thérapeutiques. L'ECMO peut être poursuivie jusqu'à évaluation neurologique (*Bridge to Neurologic Assessment*).

A ce stade de la réflexion, poser une ECMO en pré-hospitalier ne peut être réalisé que dans le but de soigner l'individu en arrêt cardiaque et non dans un but de prélèvement d'organes. Dans le cas contraire, cette décision, en plus de poser des questions éthiques, pourrait être mal comprise par la population et condamner cette innovation pouvant par ailleurs être utile en dehors de tout contexte de don d'organe.

5.2. Aspects organisationnels

Le point de vue organisationnel est essentiel car il s'agit d'une nouveauté dont il faut déceler les conséquences médicales. La question est de savoir où faudrait-il implanter les ECMO à ce type de patients : en pré-hospitalier, c'est-à-dire sur place par les équipes des SAMU (voir figure 3), ou à l'hôpital, une fois le patient ramené le plus rapidement possible par les différents moyens existants.

Dans chacune de ces situations, des avantages et des inconvénients existent ce qui rend nécessaire une réflexion organisationnelle autant que médicale. Aucune donnée ne permet actuellement de mettre en avant une stratégie. Par ailleurs, il faut distinguer la mise en place d'une ECMO en pré-hospitalier comme décrite ici, de la situation d'un transport inter-hospitalier après la mise en place à l'hôpital, telle que pratiquée par les UMAC (par exemple celle de la Pitié Salpêtrière) ou en Suisse [27].

Le recours à l'ECMO en pré-hospitalier, permet là encore d'envisager 2 stratégies. Une première stratégie est celle où l'équipe du SAMU prenant en charge le patient met en place elle-même l'ECMO (stratégie à 1 équipe). La seconde stratégie est celle où l'équipe du SAMU prenant en charge le patient fait appel à une 2ème équipe afin de mettre en place l'ECMO (stratégie à 2 équipes). La première stratégie a l'avantage d'être précoce et de permettre d'espérer un meilleur pronostic (pour la survie et l'état neurologique). Elle a pour principaux inconvénients de nécessiter une ECMO pour toutes les équipes SAMU intervenant en première intention, et une personne compétente et aguerrie à la pose d'ECMO lors de chaque intervention. La deuxième stratégie permet d'éviter cette difficulté de formation spécialisée des équipes, mais allonge le temps de prise en charge. Si ce temps est trop important, une stratégie de type *scoop and run* pourrait être supérieure afin que la 1re équipe amène directement le patient à l'hôpital. Actuellement, aucune étude ne nous permet de comparer toutes ces stratégies.

Figure 3 ECMO extrahospitalier, expérience du SAMU de Paris (Photographies du Dr Lionel Lamhaut)

5.3. Formation des urgentistes

La formation des équipes est essentielle. Actuellement l'ECMO en milieu hospitalier est posée et réalisée le plus souvent par des chirurgiens ou des anesthésistes - réanimateurs, alors que les équipes des SAMU incluent majoritairement des urgentistes, dont l'essentiel provient de la médecine générale non spécifiquement formés à cette pratique. Une formation approfondie à l'implantation de l'ECMO veino-artérielle est d'autant plus nécessaire que les conditions dans lesquelles cela se fera sont très éloignées du cadre plus favorable et sécurisé de l'hôpital. Une formation insuffisante à l'utilisation de l'ECMO risquerait de condamner cette innovation organisationnelle et ses bénéfices potentiels pour les patients.

5.4. En résumé

La mise en place précoce d'une ECMO pour les patients en arrêt cardiaque réfractaire nécessite une politique d'organisation et d'intégration des équipes d'interventions mobiles et

hospitalières. La meilleure stratégie doit combiner à la fois la sécurité pour la mise en place de l'ECMO chez le patient et la rapidité de cette mise en place. Selon le principe de déconnexion entre la décision d'arrêt des thérapeutiques et celle de prélèvement MIII, une ECMO n'est posée que pour le bénéfice du patient en arrêt cardiaque. En cas d'échec, la décision d'arrêt des thérapeutiques est prise. C'est à partir de ce moment-là qu'il est possible d'envisager un prélèvement d'organe. A la lumière de cette réflexion, il pourrait être pertinent de s'interroger sur les difficultés de garantir le principe de déconnexion dans des conditions d'exercice en pratique réelle.

6. Discussion

Du point de vue technique, une telle activité nécessiterait l'utilisation d'un appareil d'ECMO portable, de moyens de transport rapides, la formation des équipes du SAMU à ce nouveau geste et surtout la disponibilité permanente d'un médecin formé à la technique. Aujourd'hui, de par sa forme compacte et son poids réduit, l'appareil le plus adapté à ce type d'utilisation est Cardiohelp® de l'entreprise Maquet. La faisabilité de cet abord par un urgentiste non chirurgien a été étudiée par une équipe utilisant l'ECMO à l'AP-HP.

Du point de vue médical, l'utilisation de l'ECMO pré-hospitalière pour l'arrêt cardiaque offre des pistes d'évolution pour augmenter la survie avec un bon état neurologique, bien qu'aucune étude comparative randomisée n'ait examiné l'efficacité de la prise en charge de type « *stay and play* » par rapport à la stratégie de type « *scoop and run* ». L'étude prospective comparative envisagée par l'équipe de Necker pourrait fournir des arguments médicaux manquants en termes de preuve médicale et favoriser ainsi la diffusion de la pratique de l'ECMO pré-hospitalier. Il convient que cette étude explique également comment la perfusion du membre canulé sera assuré afin d'éviter les conséquences ischémiques, parfois dramatiques pour les survivants. De même, il convient que l'étude appréhende le risque septique qui semble plus important lors d'une réalisation à « ciel ouvert », que dans un environnement hospitalier.

Du point de vue médico-économique, aucune étude n'a été réalisée jusqu'à présent, ce qui est normal compte tenu du caractère novateur de cette méthode. Il serait utile que des données économiques soient recueillies à l'occasion de l'étude réalisée par l'équipe de Necker. Ces données économiques pourraient apporter des éléments utiles aux décisions ultérieures qui pourront être prises tant du point de vue de l'AP-HP que du point de vue national.

Cette approche, plus encore que la réanimation cardio-pulmonaire classique, soulève d'importantes questions éthiques. Faut-il ou pas mettre en place une ECMO ? Quand et pour quel type de patient ? Quel bénéfice escompter ? Quel impact une telle activité pourrait-t-elle avoir sur la législation en vigueur ? Certains aspects organisationnels et éthiques dépassent les compétences juridiques de l'AP-HP et nécessitent probablement un recours à des organismes nationaux.

Du point de vue organisationnel, la difficulté d'utilisation de l'ECMO en pré-hospitalier provient de la nature même de l'environnement que les personnels médicaux du SAMU rencontrent (environnement non assuré en termes d'hygiène ou des conditions pour la pose de l'ECMO, délais de prise en charge, nécessité d'une formation spécifique pour l'utilisation de l'ECMO). Ces éléments vont conditionner l'efficacité en pratique réelle de cette technique, le niveau de la preuve médicale est donc intimement lié au contexte d'intervention et du champ d'action du SAMU.

Cette technique soulève de très importantes questions pour le fonctionnement du système de soins français dans son ensemble et devrait faire l'objet d'une réflexion globale, au niveau national.

7. Recommandations du CEDIT

- Les quelques cas publiés plaident pour la faisabilité de l'ECMO veino-artérielle réalisée en pré-hospitalier, mais le niveau de preuve est faible et cette faisabilité reste à confirmer. Il n'y a pas actuellement d'élément probant d'efficacité et de sécurité cliniques.
- Les quelques éléments de présomption pourraient justifier une étude clinique comparant la prise en charge hospitalière et pré-hospitalière. L'étude doit montrer l'intérêt clinique de l'ECMO extrahospitalier et fournir des arguments médicaux manquants en termes de preuve médicale (ex : appréhender le risque septique et les conséquences ischémiques sur le membre canulé).
- Compte tenu des incertitudes médicales, médico-économiques et organisationnelles, le CEDIT recommande que toute utilisation de l'ECMO veino-artérielle pré-hospitalière à l'AP-HP soit faite uniquement dans le cadre d'une étude clinique faisant appel à une coopération inter-équipes.
- Le CEDIT souhaite réévaluer l'utilisation pré-hospitalière de l'ECMO à la lumière des résultats de cette étude.
- L'importance du sujet pourrait justifier une évaluation nationale.

1 PROTOCOL SUMMARY

Title: A comparative study between a pre-hospital and an in-hospital circulatory support strategy (ECMO) in refractory cardiac arrest.

Introduction and hypothesis:

Cardiac arrest (CA) or sudden death affects approximately 40,000 people in France. It is still a major cause of death in a young population. Management of CA is defined by international recommendations, detailed by learned societies in each country. It includes several links that are interconnected for its optimisation. This "survival chain" associates: early alert, early external cardiac massage, early defibrillation, early specialised intensive care and specific hospital management. Despite all these improvements, no progress, or little has been made in the survival of CA victims over the past few years in industrialised countries, and the survival rate in France is 3% to 5%.

Refractory cardiac arrest is defined as failure, after 30 minutes of specialised resuscitation. It used to be the standard to admit that there was no hope of spontaneous cardiac activity and satisfactory neurological recovery after this period, except in cases of CA with neuroprotection (intoxication, hypothermia).

External circulatory support such as "extracorporeal membrane oxygenation" (ECMO) makes it possible to replace the circulatory activity of the myocardium and the respiratory activity of the lungs. The indications that are currently recognized in adults are:

- haemodynamic failure due to medical causes or after heart surgery
- respiratory failure (Acute Respiratory Distress Syndrome - ARDS) due to medical causes (infection, etc...) or post-surgery.

This technology was developed over the past 10 years, possibly as a result of several factors. The first is technological with miniaturisation and simplification of ECMOs. This simplification is associated with an increase in the safety of use resulting from multi-setting monitoring built into ECMOs.

The second factor is the extension of indications beyond cardiac surgery. In fact, medical intensive care teams are now accustomed to ECMO management without the intervention of cardiovascular surgeons. Specific training enables non-surgeon physicians to use this technique either in a hospital setting with a cardiac surgery centre, or a network between a hospital without cardiac surgery and a tertiary care centre.

In in-hospital cardiac arrest (CA) some teams use ECMO with an improvement in the survival rate of 20% in comparison to standard resuscitation. This use demonstrates the possibility of neurological recovery independent of the recovery of spontaneous cardiac activity which can be differed.

These results encouraged the use of ECMOs in cases of out-of-hospital refractory cardiac arrests. Patients who are victims of CA are resuscitated for 30 minutes on the spot where the CA occurs. They are then transferred to a specialised centre. The significant improvement in survival noted in in-hospital CAs was not observed in the French series of studies concerning out-of-hospital CAs. This survival is currently estimated at 4%. This difference can be partly

explained by the difference in time between the beginning of cardiac massage and the implementation of circulatory support by ECMO ("low flow" period). This time period is directly correlated to survival. The French studies find an average period of approximately 120 minutes of low flow which corresponds to approximately 5% survival. This time period can be explained by the time required for the following:

- 30 minutes of specialised resuscitation
- placement on a stretcher
- transport to hospital
- ECMO implementation.

Since 2011 a strategy has been developed to shorten these time periods with the installation of the circulatory support system at the place where the cardiac arrest occurs. This strategy has proven its feasibility.

To demonstrate the superiority of this strategy in terms of survival, we would like to conduct a randomised comparative study of two strategies: 1) installation of an ECMO between the 20th minute to the 30 minute of CA, directly at the site of the CA, by emergency physicians and/or specifically trained resuscitators 2) On-site resuscitation optimised with secondary transfer to the hospital for the implementation of support. The purpose is to increase by 5% to 20% the survival of victims of out-of-hospital refractory cardiac arrests with a good neurological prognosis.

Main objective:

The hypothesis is that pre-hospital ECMO will result in survival for 20% of the patients, considering that the percentage of survival with in-hospital ECMO is less than 5%.

Main judgement criterion:

Survival with good neurological outcome (CPC 1 or 2) on discharge from intensive care or at 6 months

Secondary judgement criteria:

Success rate of the implementation of ECMO

ECMO implementation time

Immediate complications: haemorrhage, infection

Number of organ harvesting

The quality of survivors' neurological status according to the CPC neurological classification at D 28, 2 months and 1 year

Predictive indicators of the prognosis during cardiac arrest via cerebral and biological monitoring

Inclusion criteria:

Eligible patients have the following combination of criteria:

- Adults over 18 years of age and under 65 years of age
- **And** Refractory cardiac arrest (defined by the failure of professionals to resuscitate at the 20th minute of cardiac arrest with a minimum of 3 AED or equivalent analyse)

- **And** Beginning of external cardiac massage within the first 5 minutes after cardiac arrest (no flow < 5 min.) **with** shockable rhythm ***or*** the presence of signs of life during resuscitation (any rhythm): spontaneous movement, absence of mydriasis and/or pupillary response, respiration
- **And** Medical cause of the cardiac arrest
- **And** ETCO2 above 10 mm Hg at the time of inclusion
- **And** Absence of major co-morbidity.
- **And** ECMO team available

Non-inclusion criteria:

– Children under 18 years of age

– Adults over 65 years of age

– Period of more than 5 minutes without cardiac massage after collapsing

– Known co-morbidity that compromises the prognosis for short or medium-term survival

– Cardiac arrest during transportation times

Methodology, type of study: This is a prospective randomised study of current care

Sample size (SS, power, risk): A total number of 105 patients in each group will make it possible to demonstrate at the alpha risk of 5% and a power of 1-β=90%, a significant difference in favour of early pre-hospital ECMO compared to the current practice with in-hospital ECMO.

Study procedure:

Baseline visit: patient inclusion

When a victim of cardiac arrest with strict "no flow" for less than 5 minutes is taken under care in an out-of hospital setting, a mobile ECMO team is rushed to the spot at the 10th minute of cardiac arrest. The 2 physicians in this team verify the inclusion criteria. The patient is included when all the eligibility criteria are between the 20^{h} minute and the 30 minutes of cardiac arrest. Treatment starts immediately after randomisation. The success rate and ECMO implementation time are noted and compared. The family is informed.

3rd visit: End of study visit on discharge from intensive care or at 6 months: This visit should evaluate the patient outcome. The CPC score and the number of transfusions and infections during hospitalisation are evaluated.

Duration of the study: 3 years

Participation period for one patient: 1 Year

Number of investigator sites: ?

Expected results: An increase by 5% to 20% survival of victims of out-of-hospital refractory cardiac arrest, with a good neurological prognosis.

favourable and prolonged resuscitation efficiently provides spontaneous circulation (signs of the patient awaking during CPR). Under these circumstances, in France and several other European countries, the decision can be made to continue ECM and transport the refractory CA victim. It was made possible by the development of mechanical external cardiac massage devices such as Autopulse ®(12) and Lucas® (13)(14) which enable prolonged ECM during transport by the emergency service. However, this continuation of resuscitation can only be considered if it enables another subsequent treatment for the patient. Two options are possible. The patient can be declared dead and become a potential organ donor in the framework of an organ harvesting procedure in a patient after "cardiac death". This harvesting, which is highly organised according to regulations, can only be done in certain hospitals authorised by the French Biomedicine Agency.

Or, resuscitation can be prolonged by the use of extracorporeal circulatory support.

2.1.2. The progress of extracorporeal circulatory support and cardiac arrest

Circulatory support is a technique that has been in common use for many years now perioperatively in cardiac surgery. One of its simplest forms, ECMO (extracorporeal membrane oxygenation) is being used more and more often outside of this field, notably in paediatrics and in the care of ARDS or refractory shock in adults. This technique has notably been widely introduced in general intensive care in the treatment of H1N1 malignant influenzas that affect young subjects (15). In parallel with this extension of the indications for ECMO, the technical development of equipment was a major factor. ECMO devices, which are particularly easy to use, miniaturised and energy autonomous, are available. They make it possible to use ECMO during inter-hospital transport by ambulance or helicopter. In France, several teaching hospitals have therefore developed mobile teams called UMAC (mobile circulatory support unit) that enable the implementation of ECMO in intensive care units where there was none, and the transport of patients on circulatory and respiratory support to a reference centre. (16)

2.1.3. The implementation of ECMO in CA

It quickly became evident that the possibility of having artificial circulatory activity that enables efficient perfusion by oxygenated blood was important for CA victims whose heart had stopped beating. The first research, conducted primarily during refractory CAs that occurred in

the hospital setting, demonstrated the unexpected possibility for survival in patients who, without this option would be dead, and for whom resuscitation would have been stopped. In 2003 in Taiwan, Chen et al. noted a survival rate of almost 30% in a series of CAs that occurred in the hospital setting (17) (18). In Caen, France, the same phenomenon was noted: the survival of 8 out of 40 patients who benefited from ECMO following refractory CA (19). This technique proved to be highly adapted when the cause of the CA was potentially reversible. Mégarbane et al. noted the survival of 3 out of 12 victims of CA following acute intoxication with cardiotoxic drugs (20).

In international recommendations, circulatory support is still only recommended in paediatrics. However, these indisputable successes in adults led to an attempt to rationalise the use of therapeutic ECMO in France (21). The indications considered as possible include the existence of hypothermia, intoxication, signs of life during CPR, and CPR (low-flow) of less than 100 minutes.

The development of ECMO programmes for the treatment of refractory CA demonstrated a difference in prognosis between in-hospital and out-of-hospital CAs. In-hospital CAs quickly benefit from the implementation of ECMO. Out-of-hospital CA victims have late access to this possibility of resuscitation. In fact they require resuscitation of at least 30 minutes in the field to be considered as refractory, followed by transport under mechanical ECM until arrival at a centre with ECMO. Le Guen et al. noted that in a series of patients who were victims of sudden death in Paris in out-of-hospital settings, only 2 out of 51 patients survived in good neurological condition (22). Most of these patients had extended low-flow periods before the implementation of ECMO. A negative correlation between the duration of resuscitation before ECMO and survival explains this poor prognostic result. In addition, resuscitation prolonged by mechanical ECM is burdened by its own morbidity as Agostinucci et al. emphasized (23). This negative influence before access to ECMO is also noted by Chen et al. (24) in the hospital setting. The prognosis rapidly decreases when resuscitation is prolonged: more than 40% survival if resuscitation lasts less than 30 minutes; 17% when it surpasses 60 minutes. This difference in survival between in-hospital and out-of-hospital CA is also noted in another series of French studies (Gay, AFAR abstract). The prognosis for out-of-hospital CA is even worse when it is accompanied by prolonged CPR. Morbidity is also higher among these patients. Cadarelli et al. included all the research and case histories published up until 2008 in a meta-analysis and demonstrated the harmful effect of prolonged CPR (25). In this analysis, the speed at which ECMO is implemented appears to be a prognostic factor similar to patients' age and the total duration of circulatory support. Therefore, ECMO that is started after more than 30

minutes of CPR results in a decrease in survival. Kilbaught et al. (26) emphasize that it is actually the time factor that makes the difference between in-hospital and out-of-hospital CAs. In their pre-hospital emergency system, very rapid transport of patients during CPR to start ECMO upon arrival in the emergency service is possible. With this strategy, they demonstrate that the difference in prognosis between in-hospital and out-of-hospital CAs is eliminated when the time for implementation of ECMO is comparable. As a result, ECMO is used earlier and earlier in hospitals in Japan with results currently being published that appear to be very positive for survival.

2.1.4 The concepts of pre-hospital ECMO

The analysis of the international literature shows that ECMO might be a management method that improves the survival of CA victims.

However, in the context of out-of-hospital sudden death in a medicalised emergency system and in the framework of French regulations, there are two limiting factors:

- the obligation for resuscitation for 30 minutes before categorically announcing that the CA is refractory and whether or not to choose another treatment option.
- the possibility to have access to ECMO within the closest time period to the 30 minutes of CPR, which appears to be an important threshold in determining the prognosis.

Pre-hospital ECMO, which is the basis of the research concept being proposed, includes arteriovenous cannulation and the implementation of the extracorporeal system (pump, oxygenator) in a non-healthcare setting. It is therefore different from the in-hospital transport of patients on ECMO since the preceding steps take place in a hospital. The implementation of ECMO in hospital studies can be rapid, approximately 20 minutes in the Japanese study series and according to our experience (27). ECMO for out-of-hospital refractory CAs was the subject of a few clinical cases, in children (28) and in sports events (29) . Its feasibility by the ambulance service pre-hospital teams was confirmed in our last studies(30)(27).

The improvement in survival with early ECMO, close to a 30-minute period of CPR should also be demonstrated. It is only based on the extrapolation of the results of very fast transport and almost without specialised resuscitation of victims of sudden death close to a hospital with ECMO.

Confirmation of this concept is therefore of particular importance and in fact:

- it would provide the prospect of a new treatment possibility for patients whose chances for survival are extremely slim, because prolonged CPR is required to have access to a hospital ECMO. It is an essential step before conducting a multi-centre randomised study to demonstrate the beneficial effect on survival.

- it would make it possible to stress the pertinence of the French teams' approach in this field, notably in comparison to European countries (Germany, Spain, etc...) that already have a medicalised pre-hospital emergency system, or that are currently developing it, like Japan.

- finally, it might also result in a better determination of the place of therapeutic ECMO and as a result, clarify the indications for organ harvesting after "cardiac death" in victims of pre-hospital sudden death.

In brief, the objective of this project is to evaluate the advantage of pre-hospital ECMO in improving patient survival.

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RESEARCH PROTOCOL

Uncontrolled Donation after Death by Cardiocirculatory Criteria: A Potential Solution to the Shortage of Organs in Quebec?

Version 1

Principal Investigator:
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Based on PhD project from
Ivan Ortega

January 23, 2015

1. RATIONALE

1.1 Organs Available for Transplantation Insufficient to Meet Population Needs

While transplantation has become the definitive treatment for many people suffering end-stage organ failure, demand exceeds supply. For many years, donation after neurological death represented the principal source of organs for transplantation. In the last decade, prevention measures, improvements in neurocritical care, and decompressive craniectomy have led to a significant decrease in the number of non-directed donors (NDDs).[1] Moreover, the leading cause of death is shifting from traumatic brain injury to cerebrovascular injury.[2, 3] This characteristic is associated with a decreased quality of organs recovered.[2] In such situations, alternative sources for organ donation must be identified. Cardiac-arrest patients could provide a solution to this organ shortage. There is a growing body of evidence suggesting that graft function from cardiac-arrest donors may be comparable to that of donors not experiencing cardiac arrest.[4, 5]

1.2 Quebec's Waiting List: Two-Thirds of Patients Waiting for Kidney Grafts

Across Quebec in 2013, 154 deceased donors and 55 living donors provided organs for transplantation. In fact, while Quebec is home to one-fourth of Canada's population, it accounts for one-third of the nation's organ donors. [3] Demand for organs within Quebec, however, far outstrips the supply. Moreover, this situation holds true across Canada and around the developed world. For instance, data from the Canadian Institute for Health Information show that, at the end of 2013, 1047 people in Quebec were registered on a transplant waiting list, while only 546 (52%) received transplants and 38 (4%) died before a suitable organ was available. [6]

As of December 31, 2014, 993 people in Quebec need organ transplants, specifically kidney (712), liver (108), lung (84), heart (57), kidney–pancreas (13), pancreas (14), and other combinations (5). [3]

1.3 Uncontrolled Donation after Cardiac Death (uDCD) as a Potential Life-Saving Approach for Quebeckers

In response to the persisting organ shortage, the organ-donation scientific community must explore other strategies. As such, Quebec implemented a program of controlled DCD, created a standardized procedure, bought a new ex vivo machine to increase the number of organs recovered, and recently authorized one center to have an ICU physician exclusively dedicated to organ donation. These solutions will not in and of themselves resolve the gap between the number of organs available and transplantation needs.

Spain—the world's leader for organ donations—created its first uDCD program in 1989.[7] They represent more than 11,5% of deceased donors. At that time, only kidneys were recovered. In 2014, 116 kidneys and 8 livers were recovered from uncontrolled DCD donors.[(8)

2. BACKGROUND

2.1 Overview of the Province of Quebec, Canada

Quebec is Canada's second largest province with a population of 8,116,133 distributed over an area of 1,542,056 km^2 (in comparison, Spain has an area of 504,645 km^2). The median age is 41.9 years old and more than 35.2% of the province's population is 65 or older. [9]The annual rate of death is 7.7/1000 (n = 63,000). [9]

2.2 Cardiovascular Disease: A Leading Cause of Death

Cardiovascular diseases (CVDs) are the top cause of death globally (WHO http://www.who.int/mediacentre/factsheets/fs317/en/). More people die annually of CVDs than from any other cause. In 2011, 31% (n = 14,700 people) of all causes of death in Quebec were of cardiovascular origin. [9]

2.3 Emergency Medical Services in Quebec

When an individual experiences a cardiac arrest outside of a hospital, emergency medical services (EMS) are activated. Depending on the individual's location (rural or urban), firefighters acting as first responders may arrive first at the scene. In many areas, however, a team of two paramedics arrive first and will proceed with resuscitation measures according to the basic life-support standards of the American Heart Association. Some such responders, but not all, have been trained in advanced cardiovascular life support (ACLS) and can treat their patients accordingly. In very rare circumstances, a physician will assist the EMS team. Few data are available on the performance of our EMS in Quebec. In one study, however, the median response time between dispatch receiving the call and the initiation of resuscitative measures by EMS personnel was 7.6 minutes. [10]

Once resuscitative measures have been initiated, the patient is taken to the nearest hospital for further stabilization. Under some specific conditions, a patient may be transferred directly to a tertiary-care center. One common example is cardiac arrest likely due to myocardial infarction. These tertiary-care centers are able to perform emergency cardiac catheterization with revascularization and have intensive-care units with all the equipment needed for postresuscitation care. The province has 13 centers with this expertise.[11] Seven of them are also organ-procurement centers (OPCs).

2.4 Organizations Involved in the Management of Each Organ Donor

Community and tertiary-care hospitals have the role of **recognizing** potential organ donors and **referring** them to the provincial organ-procurement organization, Transplant Quebec (TQ). Transplant Quebec oversees all organ-donation activities in the province. Quebec's Critical Care Transport Service (many different companies) **transfers** potential organ donors to one of the province's seven OPCs. In collaboration with a physician at the sending or receiving hospital, a TQ registered nurse (hereinafter the Organ Donation and Transplantation Coordinator or ODTC) informs families about organ donation and solicits **consent**. These health-care professionals offer advice about the medical **management** of these potential donors and about the **declaration of death** made by an ICU physician. The **allocation** of organs to recipients and all aspects of organ **recovery** are coordinated centrally

at TQ in collaboration with the ODTC, the ICU physician, and the recovery and transplantation teams.

2.5 In Spain: Eligibility for Uncontrolled Donation in 3 Situations

(i) People who have experienced an unexpected out-of-hospital cardiopulmonary arrest and who are potential organ donors (Modified Mastricht type IIa). This is the largest group.

(ii) People who have experienced an unexpected in-hospital cardiopulmonary arrest and who are potential organ donors (Modified Mastricht type IIb).

(iii) People who are hospitalized donors presumed to meet the neurological criteria of death or who previously consented to cDCD and who have experienced an unexpected cardiopulmonary arrest (Mastricht type IV). This group is small and elicits little controversy.

2.6 A Process Involving Emergency Medical Services

Cardiac arrest occurs most often outside the hospital. Advanced cardiopulmonary resuscitation is initiated by paramedics with the support of an emergency physician and continued while the patient is being transferred to a designated hospital. In the absence of spontaneous circulation after ≈30 minutes, the CPR is considered unsuccessful. The patient is **declared dead** after the absence of spontaneous breathing and electrocardiographic activity for 5 minutes as notified by one physician. Once the declaration of death has been made, the transplant coordinator initiates a series of steps necessary for **organ preservation**. These steps include, but are not limited to, mechanical ventilation, cardiopulmonary chest compression, heparin administration, and cannulation of femoral vessels for extracorporeal circulation. **Donor and organ assessment** begins after initiation of extracorporeal circulation. Blood tests are systematically ordered and diagnostic imaging exams are prescribed under specific circumstances. The assessment phase continues until and up to full exposition of the abdominal organs in the operating room. Throughout this process, donors or specific organs can be discarded based on abnormal laboratory or diagnostic imaging results, premortem biopsy, and macroscopic assessment by surgeons at the time of organ recovery. Organ donation following uncontrolled cardiocirculatory death can save up to four lives.

These results must be interpreted with caution because (1) there is substantial variability in results between centers likely caused by differences in preservation techniques, experience, and expertise in each hospital and (2) variations in warm ischemic time and the definition of graft outcomes between studies.

2.7 Influence of Specific Donor Variables and Warm Ischemic Time on Graft Outcomes

Specific criteria should be met to consider a patient in cardiocirculatory arrest as a potential uncontrolled donor after cardiac death. These criteria are, in fact, donor characteristics influencing graft outcomes from an uncontrolled DCD. The issues central to the outcome of kidney or liver transplantation are donor age, CPR duration, warm ischemic time, and access to preservation interventions.

2.7.1 Donor Age

Most uDCD protocols use an age cutoff of 65 years.[12] The evidence supporting this criteria is relatively weak. Cohort studies of kidneys recipient from donors ≥65 years old have shown a decrease in glomerular filtration rate (GFR). However incidence of delayed graft function or graft survival were comparable.[13, 14]

2.7.2 Time to CPR Initiation[FD1]

Multiple aspects of cardiopulmonary resuscitation are important considerations in the context of organ donation: (1) time to CPR initiation, (2) availability of advanced cardiac life-support measures, (3) method used for external chest compression, and (4) CPR duration (which implies the proximity of a center with extracorporeal-membrane-oxygenation [ECMO] expertise). Most protocols recommend initiation of CPR within 15 to 30 minutes after cardiac arrest. [15] Time to initiation of CPR as an independent variable was studied by Maessen in 1987.[16] (CPR initiated after 30 minutes was associated with poor graft outcomes. Mechanical chest compression compared to manual chest compression yielded similar results in terms of the number of kidneys transplanted and the incidence of primary graft failure.[17] No studies specifically compared basic cardiac life support to advanced cardiac life support and time from cardiac arrest to initiation of organ preservation techniques in the context of organ donation. In a landmark paper, Ortega et al. reported a variation from 90 to 150 minutes from the time of CPR initiation to cannulation of the vessels for the purpose of organ preservation.

2.7.3 Warm Ischemic Time

The duration of warm ischemia represents the clinically important difference between controlled and uncontrolled donation after cardiocirculatory death.[18] Warm ischemic time is defined as the time elapsed between the cardiocirculatory arrest (witnessed or not) and reperfusion of the organs or initiation of cold perfusion .[19]

Clinical evidence suggests an association between the duration of warm ischemia and graft outcome. Compared to NDD liver transplantation, the transplantation of uDCD livers is associated with a 10% to 25% increase in primary graft function a XXX increase in biliary complications, a one-year graft survival rate of 50% to 80%, and a patient survival rate of 70% to 85.5%. (20)Neither hepatic artery thrombosis nor stenosis appears significantly higher than after NDD liver transplantation.

Compared to liver transplantation, kidneys recovered from uncontrolled DCD donors have overall better results. Delayed graft function, acute rejection, graft survival, and two-year patient survival are similar to cDCD kidney transplantation. ([21]

3. RESEARCH QUESTION

What proportion of patients who had a cardiac arrest at the CHUS in 2014 were eligible for organ donation after cardiocirculatory death?

4. OBJECTIVES

4.1 Principal Objective
To assess the effect of the implementation of a uDCD program on the number of additional donors.

4.2 Secondary Objectives
1. To assess the effect of the implementation of a uDCD program on the number of additional organs suitable for transplantation.
2. To measure the number of DCD donors from cardiac-arrest patients.
3. To measure the number of NDD donors from cardiac-arrest patients.
4. To describe potential obstacles and solutions related to the implementation of a uDCD program in Canada.
5. To identify areas of future research.

5. METHODS

5.1 Study Design
This one-year retrospective cohort study will assess the potential contribution of a uDCD program in one health-care center.

5.2 Study Setting
This study will be conducted in one organ-donation center in Quebec that is a teaching hospital and referral center for interventional cardiology. It serves a mixed urban and rural population of 350,000.

5.3 Eligibility Criteria
The study population will include all patients treated for cardiocirculatory arrest at the CHUS in 2014. Patients with (1) a status of no resuscitation, (2) a clear cause of death, and (3) infants less than 1 year old will be excluded.

5.4 Chart Identification[FD2]

5.5 Data Sources
The data sources for this study will be patient hospital charts, which will include a copy of the ambulance report.

5.6 Data Collection[FD3]

5.6.1 Baseline Characteristics
Age, sex, organ-donor registration, and premorbid data (infectious disease, drug abuse, chronic comorbidities) will be recorded for each patient.

5.6.2 Cardiopulmonary Resuscitation
For each episode of cardiopulmonary resuscitation, we will collect the etiology of the arrest, time and date of collapse, time of CPR initiation and its duration, initial rhythm, method of

chest compression, airway protection, drugs administered, use of monitoring, location, and the presence of witnesses.
Additional data will be included if the cardiac arrest occurred outside the hospital (paramedic time of notification, time to hospital).

5.6.3 Data related to Death
Data related to the patient's death such as the cause of death, circumstances relevant to organ donation (violent death, trauma, withdraw of life support therapy), death declaration (date, time, location,) and approach for tissue donation will be recorded. If withdrawal of life support occurred, data relevant to the organ-donation process (OPO notification, approach for organ donation) will be obtained.

5.6.4 Outcome Data
The type (DCD, NDD) and organs recovered will be recorded for each donor patient. For patients who did not become organ donors, organs yield (if not donors but eligible to organ donation) and disposition will be reported.

5.7 Development of Case Report Forms (CRFs) and a Data Manual
Before launching the study, we will design and test the CRFs and a corresponding instruction manual. The principal investigator and one coinvestigator will collect all data. The first five charts will be collected in parallel to assess the interrater reliability. We will launch the study after a kappa of at least 0.70 for the items most important to our primary outcome has been reached.

5.8 Outcomes

5.8.1 Primary Outcome
Number of potential patients suitable for organ donation:
Defined as (must meet all criteria):
- Age ≤70 years old
- Absence of obvious cause of death (rigor mortis, decapitation, overwhelming traumatic injury)
- Absence of surgical cause of cardiac arrest
- No sign of IV drug abuse
- Less than 30 minutes without CPR

5.8.2 Secondary Outcomes
Number of potential organs recovered, defined as 1 kidney or 1 liver = 1 organ
Number of organ donors, defined as NDD or cDCD from which at least one organ was recovered.
Number of potential eye donors
Number of potential tissue donors
Number of eye donors
Number of tissue donors
[FD4]

5.9 Sample Size[FD5]

This is a retrospective cohort study and therefore does not lend itself to sample-size determination for hypothesis testing. Our goals in determining the sample size for this study are (1) to include as many patients in cardiocirculatory arrest as possible (for precision) and (2) to collect representative annual data (for maximal relevance).

5.10 Statistical Analysis

The primary and secondary outcomes are descriptive statistics. Accordingly, we will report continuous data with means (standard deviation) or medians (first quartile, third quartile) and dichotomic data with proportions, as appropriate. We will address missing data using the method described by Kenward.[4] All tests will be two-sided with a nominal p value of 0.05. Reporting of this study will follow the STROBE Statement (www.strobe-statement.org).

5.11 Effort to Limit Bias

This study includes features to minimize the biases that are inherent in retrospective studies. To minimize selection bias and ensure a representative sample, we will enroll all patients with a history of cardiac arrest. To minimize biased data abstraction, we will provide a data instruction manual. To ensure data accuracy, we will test the CRF with the first five patients and compare data collection between reviewers. We will proceed with descriptive analyses exclusively. No measure of associations between interventions (or specific characteristics) and outcomes will be conducted.

5.12 Ethics

Data will be collected after the patient's discharge from the hospital or the patient's death. Data will be codified and secured in a computer. The encoding key will be stored on another computer in a locked office at the "Centre de Recherche du CHUS."

For this study, consent from patients (or their relatives) is not required. Research Ethics Board (REB) approval and authorization from the *Directeur des Services Professionnels* will be obtained prior to the beginning of this study.

5.13 Expected Outcomes and Future Directions

Organ donation is the most efficient life-saving intervention. Conducting this retrospective study will allow us to quantitatively measure the value of creating an uncontrolled-donation-after-cardiocirculatory-death program. It will also identify areas of improvement for donor identification at our center. Finally, it will generate areas for future research.

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Relationship between Time-to-ROSC and Survival in Out-of-hospital Cardiac Arrest ECPR Candidates: When is the Best Time to Consider Transport to Hospital?

Brian Grunau, Joshua Reynolds, Frank Scheuermeyer, Robert Stenstom, Dion Stub, Sarah Pennington, Sheldon Cheskes, Krishnan Ramanathan, Jim Christenson

Abstract

Objective: Extracorporeal cardiopulmonary resuscitation (ECPR) may improve outcomes for refractory out-of-hospital cardiac arrest (OHCA). Transport of intra-arrest patients to hospital however, may decrease CPR quality, potentially reducing survival for those who would have achieved return-of-spontaneous-circulation (ROSC) with further on-scene resuscitation. We examined time-to-ROSC and patient outcomes for the optimal time to consider transport. **Methods**: From a prospective registry of consecutive adult non-traumatic OHCA's, we identified a hypothetical ECPR-eligible cohort of EMS-treated patients with age ≤ 65, witnessed arrest, and bystander CPR or EMS arrival < 10 minutes. We assessed the relationship between time-to-ROSC and survival, and constructed a ROC curve to illustrate the ability of a pulseless state to predict non-survival with conventional resuscitation. **Results**: Of 6,571 EMS-treated cases, 1,206 were included with 27% surviving. Increasing time–to–ROSC (per minute) was negatively associated with survival (adjusted OR 0.91; 95%CI 0.89–0.93%). The yield of survivors per minute of resuscitation increased from commencement and started to decline in the 8th minute. Fifty percent and 90% of survivors had achieved ROSC by 8.0 and 24 min, respectively, at which times the probability of survival for those with initial shockable rhythms was 31% and 10%, and for non-shockable rhythms was 5.2% and 1.6%. The ROC curve illustrated that the 16th minute of resuscitation maximized sensitivity and specificity (AUC = 0.87, 95% CI 0.85–0.89). **Conclusion:** Transport for ECPR should be considered between 8 to 24 minutes of professional on-scene resuscitation, with 16 minutes balancing the risks and benefits of early and later transport. Earlier transport within this window may be preferred if high quality CPR can be maintained during transport and for those with initial non-shockable rhythms. **Key words:** cardiac arrest; cardiopulmonary resuscitation; extracorporeal membrane oxygenation; emergency medical services

PREHOSPITAL EMERGENCY CARE 2016;Early Online:1–8

Introduction

Emergency Medical Services (EMS) in North America attend 134 cases of out-of-hospital cardiac arrest (OHCA) per 100,000 adult citizens annually, with survival rates ranging from 3%–16%.[1,2] Since most conventional resuscitative therapies are available in the prehospital environment, transporting patients with OHCA refractory to standard resuscitation to hospital, without implementing additional treatment strategies, is of questionable benefit and potentially endangers paramedic safety.[3,4]

Circulatory support with extracorporeal cardiopulmonary resuscitation (ECPR) may improve the chances of survival of select patients with cardiac arrest refractory to conventional resuscitation. ECPR is the incorporation of veno-arterial extracorporeal membranous oxygenation (ECMO) into cardiac arrest resuscitation, and has been used since 1966.[5] Mounting observational data suggest that ECPR is a beneficial therapy for select patients with OHCA, with most protocols focusing on younger patients with rapid arrest recognition and CPR initiation.[6–9]

An emergency medical system considering utilization of ECPR for refractory OHCA must balance two potentially competing factors: CPR quality and early access to ECPR. First, extrication and transport of patients with refractory arrest are associated with pauses in chest compressions,[10] which has been associated with decreased survival.[11] Thus, earlier transport for those who would have achieved return of spontaneous circulation (ROSC) with continued on-scene conventional resuscitation may worsen outcomes. EMS systems that employ longer durations of attempted prehospital resuscitation, with low rates of transport to hospital for refractory cardiac arrest, have demonstrated superior outcomes than comparators.[1,4,12] On

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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doi: 10.3109/10903127.2016.1149652

the other hand, lower arrest-to-ECPR intervals are associated with improved neurological outcomes and the majority of neurologically intact survivors have ECPR established within 60–75 min.[7,8,13–18] Acknowledging that a minimum of 15–30 min is typically required to cannulate and commence ECPR,[8,9] patients would likely have to arrive at hospital no more than 45 min after cardiac arrest to achieve this time goal. Thus, earlier transport for those who will not achieve ROSC with continued on-scene conventional resuscitation, for the purpose of hospital-based ECPR therapy, would likely result in improved outcomes.

Unfortunately, at the beginning of resuscitation one does not know who will achieve ROSC with conventional resuscitation. For this reason, we sought to demonstrate the survival curves for ECPR-eligible patients to determine if there was a natural inflection point during conventional resuscitation when further prehospital efforts yielded little additional benefit, but still fell within the time frame of transport to an ECPR-capable center. We reviewed a cohort of OHCA patients in a provincial EMS system fulfilling a set of hypothetical ECPR criteria to describe the relationship of time-to-ROSC and outcomes, in order to inform decision-making when considering transport to hospital for ECPR.

METHODS

Study Setting

This study took place in the four major metropolitan regions in the province of British Columbia: Victoria, Vancouver, the Fraser Valley, and Kelowna. These communities contain a collective population of approximately 3.3 million (72% of the total provincial population)[19] and each contain at least one hospital with ECMO capacity. There were no ECPR programs or use of mechanical CPR devices during the study period.

The provincial British Columbia Emergency Health Services (BCEHS) and individual municipal fire department first responders provide coordinated prehospital emergency medical care through a 9-1-1 emergency service. All fire department personnel are trained in basic cardiopulmonary life-support[20] including the use of automated external defibrillators (AED). BCEHS is organized in teams of two paramedics per vehicle, with either basic (BLS) or advanced (ALS) life-support certification. BCAS policy dictates which patients must be provided resuscitative treatments (see Appendix 1).[21] There was no termination of resuscitation guideline used by the BCEHS during the study period.

The institutional ethics review boards of Providence Health Care and the University of British Columbia approved this study.

Study Design and Selection of Participants

All consecutive non-traumatic OHCA occurring in the study regions were prospectively identified and data collected as part of the Resuscitation Outcomes Consortium[22] cardiac arrest registry between 2007 and 2011 inclusive. Based on previous ECPR protocols[9,23,24] and other data,[25,26] we constructed a hypothetical post-hoc ECPR-eligible cohort, including patients if the following set of criteria were met: (1) age 18–65 years (inclusive); (2) witnessed arrest; and (3) bystander CPR (performed by laypersons or EMS if the arrest was EMS-witnessed) or EMS arrival in less than 10 min. Patients were excluded from analysis if there was no attempt at resuscitation.

Data Collection

All prehospital data, including time-stamped diagnostics, treatments administered, patient characteristics, and prehospital outcomes, were prospectively collected from standardized EMS template charting and survival at hospital discharge was recorded.[22]

Outcome Measures and Variable Definitions

The primary endpoint was survival to hospital discharge.[27] The primary independent variable of interest was time-to-ROSC, defined as the interval between the initiation of chest compressions by a professional rescuer and first ROSC. ROSC was defined as a palpable pulse in any vessel for any length of time. Patients were categorized by initial rhythm: (1) "shockable," including ventricular fibrillation, pulseless ventricular tachycardia, and unknown rhythms that were shocked with the AED; and, (2) "non-shockable" including pulseless electrical activity, asystole, and unknown rhythms that were not shocked by the AED.

Data Analysis

We used Microsoft Excel 2008 (Microsoft Corp, Redmond, WA, USA) and Statistica™ (Dell Corp, Round Rock, Texas, USA) for analysis. Categorical variables are reported as percentages and 95% confidence intervals. Continuous variables are presented as means with standard deviations (if normally distributed) or medians with interquartile ranges (IQR). We used unmatched logistic regression to evaluate the association between survival and time-to-ROSC. Unadjusted odds ratios and 95% confidence intervals are based on univariable models. We then adjusted for covariates known to be associated with outcomes in OHCA: age, gender, arrest in a public location, bystander CPR, initial rhythm, time to EMS arrival, and EMS-witnessed arrest.[28,29]

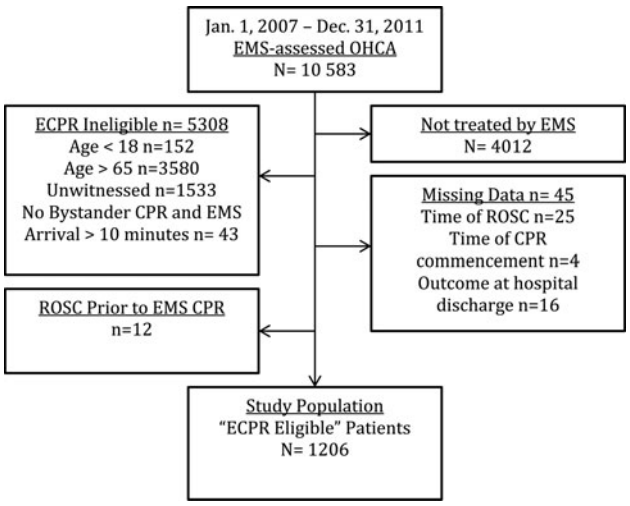

FIGURE 1. Study flow.

To visualize and describe our dataset, we constructed several curves. First, among survivors we demonstrated the proportion of patients with ROSC prior to successive one-minute increments of professional resuscitation. Based on previous work,[28] we highlighted the durations of professional resuscitation at which time 50%, 75%, 90%, and 99% of survivors had achieved ROSC. Second, among those who remained pulseless at increasing time junctures from the commencement of resuscitation, we illustrated the proportion who survived to hospital discharge.

We constructed a receiver operating characteristic (ROC) curve to illustrate the ability of a pulseless state (a "positive test") to predict non-survival with conventional resuscitation, at incremental time junctures of resuscitation. The true positive rate was the proportion of those in a pulseless state who did not survive to hospital discharge. The false positive rate was the proportion of those in a pulseless state who survived to hospital discharge. We determined the time juncture in the resuscitation that yielded the best test performance.

RESULTS

Characteristics of Study Subjects

Of 10,583 consecutive EMS-assessed cases of OHCA in the study period, 6,571 were treated by EMS (overall 12% of EMS-treated cases survived to hospital discharge). A total of 1206 patients met our set of hypothetical ECPR criteria and were included in this study (Figure 1).

Main Results

Patient characteristics of the full ECPR-eligible cohort and subgroups characterized by initial rhythm are shown in Table 1. The median age was 55 years (IQR 47–60), and 75% were male. Of 753 (62%) patients with ROSC, 750 (99.6%) achieved ROSC in the prehospital setting. A total of 195 patients (16%) had transport to hospital initiated prior to achieving ROSC. The median duration of resuscitation prior to termination in those who did not achieve ROSC was 37 min (IQR 30–47 min). The median time-to-ROSC among survivors and non-survivors at hospital discharge was 8.1 min (IQR 4.7–14.0) and 17.1 min (IQR 11.0–24.0), respectively. Overall, 328 (27%) survived to hospital discharge (Table 2).

In adjusted models, increasing time-to-ROSC (per minute) was negatively associated with survival to hospital discharge (adjusted OR = 0.91; 95% CI = 0.89–0.93; Table 3). Figure 2A demonstrates the proportion of survivors who achieved ROSC prior to incremental time junctures. The yield of survivors per minute of resuscitation increased from

TABLE 1. Characteristics of study population

	Full Cohort		Initial Shockable Rhythms		Initial Non-Shockable Rhythms	
	n or median (% or IQR)	Missing	*n* or median (% or IQR)	Missing	*n* or median (% or IQR)	Missing
Number	1206		569*		616*	
Age (years)	55 (47–60)	0	55 (49–60)	0	54 (45–60)	0
Male sex	908 (75)	0	473 (83)	0	417 (68)	0
Public Location	395 (33)	1	568 (44)	1	140 (23)	0
Bystander Witnessed	960 (80)	0	497 (87)	0	444 (72)	0
Bystander CPR	622 (65†)	0	337 (68†)	0	268 (60†)	0
Witnessed by EMS	246 (20)	0	72 (13)	0	172 (28)	0
9-1-1 Call to EMS arrival, min	6.7 (5.3–8.6)	0	6.3 (5.2–8.2)	0	7.2 (5.4–8.8)	0
ALS Involvement	1098 (90)	0	519 (91)	0	551 (89)	0
Advanced Airway	1200 (81)	6	567 (81)	2	612 (80)	4
Initial Shockable Rhythm	569 (48)	21	569 (100)	0	0 (0)	0
Epinephrine Administered	858 (72)	17	368 (66)	10	471 (77)	7
Epinephrine Dose, mg	5 (2–7)		4 (2–7)		5 (3–7)	
Transported to Hospital	891 (74)	0	474 (83)	0	401 (65)	0

*Patients with missing data on initial rhythm were excluded from the subgroups based on initial rhythm.
†EMS-witnessed arrests excluded from the denominator of this proportion.
IQR = interquartile range; CPR = cardiopulmonary resuscitation; EMS = emergency medical services; min = minutes; ALS = advanced life support paramedic.

TABLE 2. Patient outcomes

	Full Cohort *n* or median (% or IQR)	Initial Shockable Rhythms* *n* or median (% or IQR)	Initial Non-Shockable Rhythms* *n* or median (% or IQR)
ROSC	753(62)	428(75)	310(50)
Time To ROSC (minutes)	13.0(7.2–20.8)	12.0(6.8–19.2)	15.3(7.8–23.0)
Survival to Hospital Discharge	328(27)	255(45)	67(11)

*Patients with missing data on initial rhythm were excluded from the subgroups based on initial rhythm.
ROSC = return of spontaneous circulation.

commencement, peaked in the seventh minute, and started declining in the eighth minute. Figure 3 demonstrates the probability of survival to hospital discharge among patients in a persistent pulseless state, at increasing junctures since the commencement of resuscitation (both for the full cohort and stratified by initial rhythm). The time junctures at which 50%, 75%, 90%, and 99% of survivors had achieved ROSC were 8.0, 14.0, 23.7, and 38.8 min, at which point the probability of survival among pulseless patients was 17% (95% CI 15–19%), 10% (95% CI 8.2–12%), 5.4% (95% CI 3.6,7.2%), and 0.84% (95% CI 0.02–1.7%), respectively.

The ROC curve, describing the ability of the pulseless state to predict non-survival, illustrates that the 16th minute of resuscitation maximizes sensitivity and specificity (area under the curve = 0.87, 95% CI 0.85–0.89; Figure 4). At this juncture 9.0% (95% CI 6.9–11%) of those who remained pulseless survived to hospital discharge.

Of the 569 patients with initial shockable rhythms, 75% achieved ROSC and 45% survived to hospital discharge (Table 2). The time junctures at which 50%, 75%, 90%, and 99% of survivors had achieved ROSC were 8.5, 14.7, 23.0, and 39.0 min, respectively. Of the 616 patients with initial non-shockable rhythms, 50% achieved ROSC and 11% survived to hospital discharge. The time junctures at which 50%, 75%, 90%, and 99% of survivors had achieved ROSC were 6.1, 12.8, 23.9, and 36.0 min, respectively.

DISCUSSION

ECPR is a complex therapy requiring time-sensitive initiation; however, it holds promise for a subset of patients with rapid high quality CPR (to maintain cerebral perfusion), for whom ROSC is not achievable with conventional resuscitation. The challenge is to determine how and when to identify patients who will prove refractory to conventional resuscitation, and who may have an increased chance of survival if transported to hospital for ECPR.

We explored the relationship between time-to-ROSC and survival among potential ECPR candidates—younger patients with early CPR initiation after OHCA—and estimated the incremental benefits of increasing durations of conventional resuscitation. Our data indicate that there is no clear juncture in the resuscitation at which the likelihood of survival drops precipitously, but rather starting in the 8th min there is a slow transition to progressively lower yield of further conventional efforts. Although no single time juncture was identified, the timeframe of 8–24 min after commencement of professional resuscitation appears to be a reasonable window to consider transport to hospital for ECPR for several reasons. In the 8th min of resuscitation, the incremental benefit of conventional therapies had started to decline, and at the end of this minute 50% of survivors had already achieved ROSC. By 24 min, 90% of survivors had already achieved ROSC and further on-scene efforts approach the logistical limits that would still allow a patient to be transported to hospital within a collapse-to-ECPR interval compatible with survival.[7]

Our ROC curve indicates that a lack of a pulse at 16 min (which falls in the middle of the 8–24 min window) has the best performance for predicting non-survival, which balances the risk of earlier transport to

TABLE 3. Logistic regression models for survival to hospital discharge

Variable (referent)	Crude OR (95% CI)	Adjusted OR (95% CI)
Gender (female)	1.6(1.14 – 2.26)	1.43(0.95 – 2.17)
Age in years (per year increase)	1.00(0.98 – 1.02)	0.99(0.97 – 1.01)
Public location	1.88(1.39 – 2.55)	1.08(0.75 – 1.57)
Bystander CPR*	1.42(1.02 – 1.98)	1.25(0.83 – 1.89)
Witnessed by EMS	1.29(0.89 – 1.85)	1.52(0.91 – 2.51)
Time from 9-1-1 call to EMS arrival (per minute increase)	0.94(0.89 – 0.99)	0.94(0.88 – 0.99)
Initial Shockable rhythm	5.35(3.83 – 7.46)	5.75(3.89 – 8.49)
Time to ROSC (per minute increase)	0.91(0.89 – 0.93)	0.91(0.89 – 0.93)

*By Layperson or EMS if EMS-witnessed.
CPR = cardiopulmonary resuscitation; EMS = emergency medical services; ROSC = return of spontaneous circulation.

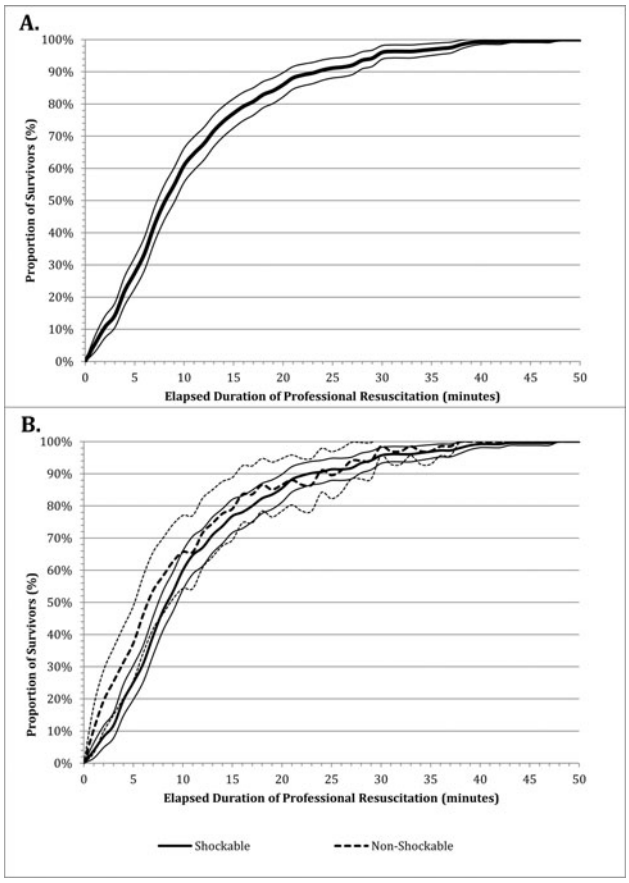

FIGURE 2. Proportion of survivors achieving ROSC prior to incremental durations of resuscitation (with 95% CI), among (A) the full cohort and (B) dichotomized by initial cardiac rhythm.

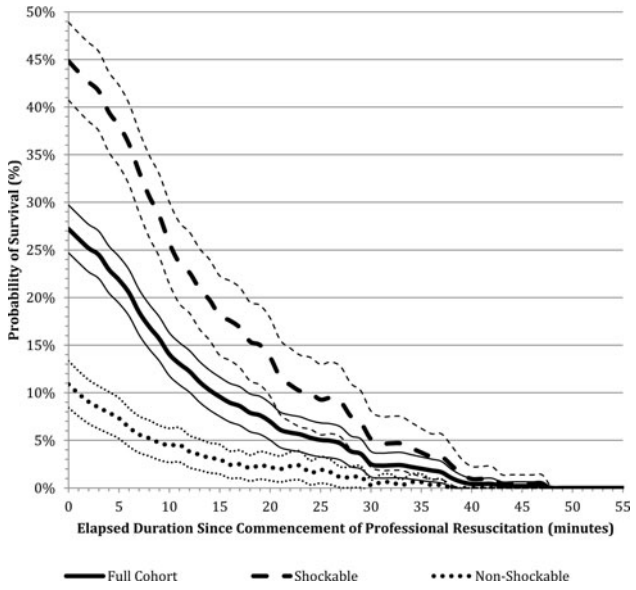

FIGURE 3. Probability of survival among pulseless patients, at increasing durations of time since commencement of resuscitation (with 95% CI).

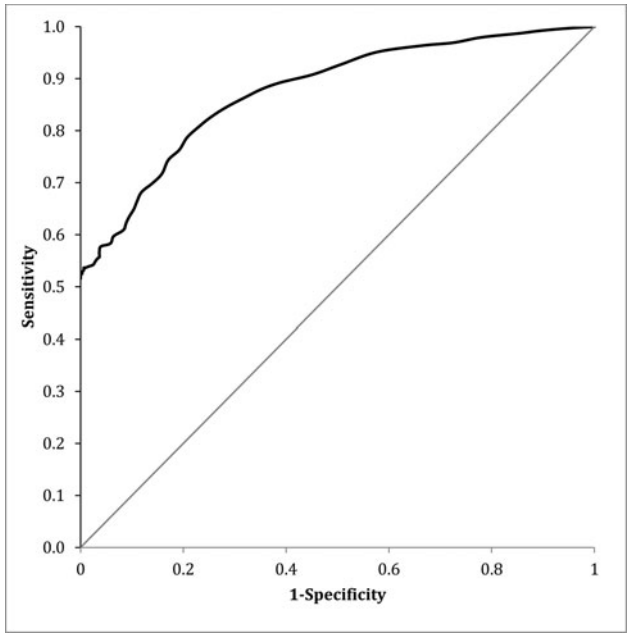

FIGURE 4. ROC curve for *No Pulse* as a positive test to predict non-survival at increasing time junctures from commencement of resuscitation.

a patient who would have achieved ROSC with further on-scene conventional therapies, and the risk of later transport to an ECPR-eligible patient who will never achieve ROSC. However, this assumes that the risks of earlier and later transport are equally important, which may not be the case for most patients. When considering when to transport within the 8–24 min time window two critical patient level factors deserve consideration: (1) the quality of CPR that can be performed during extrication and transport and (2) the initial cardiac rhythm. CPR quality is a crucial variable in resuscitation and can vary substantially, especially during extrication and transport.[11,30,31] If one can be confident in consistent high-quality transport CPR, then transport of an ECPR candidate to hospital should take place after 8 min of failed high-quality conventional efforts. If high-quality CPR during transport cannot be assured, depending on the quality impact, consideration should be made for later transport within the 8–24 min window, or continued on-scene resuscitation until termination. Mechanical chest compression devices may play a key role in maintaining CPR quality for ECPR-eligible patients that are transported to hospital.[32] However, as studies comparing the outcomes of patients treated with these high-cost devices to manual CPR have demonstrated worse[33,34] or neutral results,[35–37] EMS systems may lack enthusiasm to incorporate mechanical compression systems into routine management.

One novel aspect of our study is the stratification of survival curves by shockable and non-shockable initial cardiac rhythms. Although the proportion of survivors achieving ROSC prior to increasing durations of

resuscitation was similar (Figure 2B), there were large differences in the probability of survival of those who remained pulseless (Figure 3). After 8 min of resuscitation, the probability of survival among those with initial shockable rhythms dropped only to 31%; however, among those with non-shockable rhythms fell to 5.2%. As the probability of survival for shockable patients at 8 min remains relatively high, longer on-scene conventional resuscitation may be preferable unless transport CPR quality can be ensured. Conversely, the probability of survival for patients with non-shockable rhythms fell to 5.2%, demonstrating the small benefit of additional on-scene efforts. Importantly, survival of non-shockable patients treated with ECPR have been reported as high as 29%–35%,[8,9,13] and thus prioritizing early transport of patients with non-shockable rhythms may be appropriate.

In addition, two system related factors may warrant consideration: (1) the outcomes of conventional resuscitation within the EMS system; and (2) the outcomes of the local ECPR system; both of which have been shown to vary considerably in different regions.[1,9,15] If the EMS baseline outcomes with conventional resuscitation are poor and the local ECPR system has high rates of positive outcomes, this would favor earlier transport for ECPR therapies. However, if this were the case, system quality improvement in fundamental conventional resuscitation may yield a greater benefit than a resource-intensive ECPR program. Conversely, if a local ECPR program yields few survivors, then one should prioritize conventional resuscitation and ensure continual high-quality CPR, with possible later transport to an ECPR site if persistent refractory arrest.

When considering the possible benefits of incorporating ECPR into a local algorithm for refractory OHCA, the analysis must take place at the overall EMS system level. Whereas previous studies have reported the outcomes of patients who were transported to hospital and treated with ECPR, this negates the impact on the rest of the system including the possible detrimental effect of intra-arrest transport on CPR quality. Furthermore, there are additional resource-intensive logistical factors that require planning, albeit for a relatively small number of patients who would be eligible. Experience gleaned from the development STEMI protocols in the recent years may have high yield for ECPR protocols, including the prehospital identification of eligible patients, prehospital ECPR team activation, and bypass of other hospitals to designated ECPR centers[38–40] In-hospital ECPR teams that could be rapidly mobilized would be required. These protocols would need to prioritize rapid arrest-to-ECMO times, however with the recognition that there would be a proportion of false positive prehospital activations for those who would achieve ROSC in the intervening time prior to actual cannulation.

Previous studies have estimated the time juncture in resuscitation at which one might consider ECPR, however no studies have specifically examined the patient subset that would be considered eligible for this therapy. Potential ECPR candidates may be systematically different from the general population of OHCA patients in regard to time-to-ROSC and outcomes. Reynolds et al. analyzed data from 1,042 OHCA patients, of whom 11% survived to hospital discharge. They reported that within 16.1 min of CPR, 90% of patients with a favorable functional outcome had achieved ROSC; the probability of a good functional outcome among those still receiving chest compressions at this juncture was 1%.[28] Arima et al. examined a cohort of 172 patients with initial shockable rhythms and demonstrated decreasing rates of survival with increasing durations to ROSC. Of those with resuscitation for > 30 minutes, only 1.4% had favorable outcomes.[34] From a cohort of patients who were transported to hospital, of whom 10% were chosen for ECPR, Kim et al. constructed a ROC curve from those not treated with ECPR and concluded the ideal time to consider ECPR was 21 min.[18]

No published prospective randomized trials have compared ECPR to conventional care. Outcomes of highly selected patients treated with ECPR—whom clinicians deemed unlikely to survive with conventional therapies—have been published, but the lack of comparator groups makes the true benefit of ECPR difficult to ascertain. The best outcomes are seen with early ECPR initiation;[13] however, a proportion of these could have achieved ROSC with conventional means. It is also unclear whether achieving earlier perfusion through ECPR, in patients who would achieve later ROSC with conventional resuscitation, confers benefit. Our data demonstrate the outcomes of potentially ECPR-eligible patients treated with conventional methods, and could be used as an estimate of the probability of survival with conventional resuscitation, to compare to patients treated with ECPR in other studies. In our study, although a single survivor regained ROSC at 47 min, the vast majority of survivors achieved ROSC much earlier. As previous data indicate that ECPR performed on patients with OHCA tend to be initiated at or after the 45-min juncture,[7,9] it appears likely that ECPR does confer benefit over conventional resuscitation when initiated at this time.

The aim of this study was not to determine the effectiveness of ECPR therapy or on-scene conventional resuscitation, but rather sought to guide management decisions in EMS systems considering the possible risks of early transport to hospital, in view of the potential benefits of transport to hospital for ECPR. For this reason we considered survival to be a more appropriate and conservative primary outcome than neurological outcomes— whereas non-surviving study subjects favored earlier transport in our analysis as they had "nothing to lose" (and had potential gain from ECPR), this is not true for those who survived with unfavorable neurological outcomes for whom

management decisions have the potential to further worsen the outcomes.

Limitations

This study was performed in the metropolitan regions within one province in Canada which demonstrate a high rate of survival from OHCA[1]; population characteristics, medical management, and outcomes of OHCA may vary in different settings. Namely, a standardized protocol for early termination of resuscitation was not utilized[35] and the majority of patients in whom ROSC was not achieved were treated exclusively the prehospital setting without transport to hospital. Whereas prehospital resuscitation and protocolized hospital care followed AHA guidelines, we cannot account for individual patient treatment. Unstructured withdrawal of care (in the prehospital and hospital setting including those pre-ROSC and post-arrest) is a limitation, as providers' perception of poor predicted outcome leading to cessation of efforts thereby confers a poor outcome. Our survival curve illustrating the proportion of survivors among those who remained pulseless at increasing time junctures included patients who were no longer receiving resuscitation; although it is likely that these patients would not have survived with longer attempts this may have resulted in an underestimation of survival. Our ECPR criteria, although based on existing data, may not be the optimal criteria to identify patients who would most likely benefit with ECPR. In particular, it is likely appropriate to expand the eligibility of those who have OHCA secondary to hypothermia.[41] Furthermore, there may have been patients included in our cohort with certain characteristics that made them inappropriate for ECPR therapies. We used the start of professional CPR as the time at which to compare the time of ROSC; while duration from the arrest to ROSC may be of interest, reliable data on actual arrest times are unavailable. When developing a prehospital protocol, however, the duration of on-scene resuscitative efforts is likely the most pragmatic time period to use, rather than requiring personnel to estimate and calculate the duration of arrest. Finally, there were 21 (1.7%) patients within our ECPR group for whom data on the initial rhythm were unavailable, precluding inclusion in the rhythm subgroup analysis.

CONCLUSION

Our data suggest that transport to hospital for ECPR should be considered between 8 to 24 min of elapsed conventional on-scene resuscitation, with 16 min balancing the risks and benefits of early and later transport equally. Earlier transport in this window may be preferred if high quality CPR can be maintained during transport and for those with initial non-shockable rhythms.

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APPENDIX 1

BCAS policy indicates that all patients must be provided resuscitative treatments for cardiac arrest except in the following circumstances:

"(1)"Obvious Death" defined as rigor mortis, decapitation, post-mortem levity, tissue decomposition, thoracic or abdominal transection, incineration of the torso or head, or complete destruction or removal of vital organ;
(2)The patient has been unresponsive and without respirations and no CPR performed for > 15 minutes (excluding those with hypothermia);
(3)There is a "No CPR" order in effect; or,
(4)Underwater submersion for > 60 minutes."[1]

DOI: 10.13184/eidon.39.2013.44-48

Entrevista a Rafael Matesanz

Diego Gracia

Presidente de la Fundación de Ciencias de la Salud

RAFAEL MATESANZ

Se atribuye a Thomas Alba Edison, el padre de más de mil inventos, entre otros la bombilla, una frase que dice: *Genius is one percent inspiration and ninety-nine percent perspiration.*No sé si Rafael Matesanz es un genio. Todo depende de cómo se defina ese sinuoso y ambiguo término. Sí sé, sin embargo, que ha conseguido poner a punto y liderar durante veinticinco años uno de los sectores más desarrollados y mejor cualificados, tanto nacional como internacionalmente, de la medicina española, la Organización Nacional de Trasplantes. Y que eso lo ha conseguido a base de inspiración, pero sobre todo mediante el tesón y la persistencia en el trabajo cotidiano. No sé si Rafal Matesanz cree mucho en eso de la inspiración, pero es casi seguro que concuerda con Picasso, cuando tras poner en duda que tal cosa existiese, añadía que, por si acaso, prefería que, de llegar, le encontrara trabajando. Recuerdo ahora las palabras de Eugenio d'Ors en una conferencia pronunciada en la Residencia de Estudiantes en 1915 y que lleva por título *Aprendizaje y heroísmo.* Para evitar que caigan en el olvido, los autores del monumento que el filósofo tiene frente al museo del Prado y de espaldas al Ministerio de Sanidad, Servicios Sociales e Igualdad, quisieron grabarlas en piedra. Cada vez que me acerco al Ministerio de Sanidad no puedo menos de recordarlas. Dicen así: "Todo pasa, una sola cosa te será contada y es tu obra bien hecha. Noble es el que se exige y hombre, tan solo, quien cada día renueva su entusiasmo..."Y las recuerdo ahora porque Rafael Matesanz es uno de esos

españoles, quisiera creer que uno entre muchos, que han convertido ese epitafio en santo y seña de su vida, la obra bien hecha.

En 1989 puso en marcha la Organización Nacional de Trasplantes y desde entonces ha sido su alma. Durante estos veinticinco años ha puesto a punto el llamado “modelo español”, así conocido en el mundo entero. Si algo le caracteriza es su capacidad organizativa. Él ha sabido ver que la donación de órganos no es tanto cosa de altruismo ciudadano cuanto de organización y gestión. Hoy esta es una premisa básica en el mundo de los trasplantes, que desde España se ha extendido a Europa y a la mayor parte del mundo. Él ideó la figura del “coordinador de trasplantes”, la pieza fundamental en todo el complejo proceso que va del fallecimiento de un potencial donante a la colocación del órgano en el cuerpo del receptor, pasando por el acompañamiento en su duelo a los familiares del fallecido y la búsqueda de la anuencia de éstos a la donación. Son muchos elementos, cada uno de los cuales ha de funcionar a la perfección, porque el fallo en uno cualquiera da al traste con el objetivo final, que consiste nada más y nada menos que en salvar una vida. El resultado de todo esto es que desde 1992, España está a la cabeza en la tasa de trasplantes.

Transcribo algunas de las cifras que ofrecen Matesanz y sus colaboradores en el artículo publicado en la revista *Transplant International* del año 2011 y que lleva este significativo título: *Spanish experience as a leading country: what kind of measures were taken?* En él se dice que España ocupa una posición privilegiada en el mundo de la donación y trasplante de órganos, con 33-35 donaciones por millón y 85 trasplantes, también por millón de habitantes. Conviene recordar que a la altura de 1989 el porcentaje de donaciones por millón era de 15 y el de trasplantes de 34, y que el número total de trasplantes era inferior a 1500, frente a los 4000 actuales.

DG. Estas cifras son hoy bien conocidas por todos los profesionales sanitarios, en España y fuera de ella. Por eso resulta redundante insistir sobre ellas. Pero sí interesa abordar otras cuestiones que han ido apareciendo en los últimos años y que resultan algo inquietantes. La primera de ellas son los efectos de la actual crisis económica en el sistema de trasplantes. ¿Cómo ha afectado o está afectando la crisis a la organización que usted dirige?

RM. *Influye de muchas maneras y ninguna buena. De entrada, un sistema que se basa en que los profesionales sanitarios, gracias a un trabajo duro y sin horarios, obtengan lo mejor de la generosidad de la población, se encuentra con que estos profesionales han perdido entre el 20 y el 30% de su poder adquisitivo, trabajan con menos camas, menos presupuesto y todo tipo de dificultades. Además, esa población a la que se le pide su solidaridad, se da de bruces con una realidad en la que la crisis social y de valores y el descrédito de casi todo es casi más grave que la económica. Y sin embargo ahí seguimos, a la cabeza del mundo tras 5 años de crisis. Decididamente tenemos una sociedad mejor de lo que creemos o estamos dispuestos a admitir.*

DG. Hay otra cuestión que reaparece insistentemente en la literatura de los últimos años. Las mayores y mejores medidas de seguridad en el tráfico rodado, tanto de coches como de motos, ha hecho que los donantes óptimos de hace algunas décadas, chicos jóvenes que tras sufrir un accidente de motocicleta se encontraban en muerte encefálica, hayan disminuido drásticamente. Un ejemplo muy característico de lo que está sucediendo acabamos de verlo tras las vacaciones de Semana Santa de 2013. Las personas fallecidas por accidentes de tráfico en las carreteras españolas han sido 26, la cifra más baja desde el año 1959, y 19 menos que el año anterior. Una consecuencia de esto es que cada vez se trasplantan órganos de personas de más edad, fallecidas muchas de ellas de accidentes cerebrovasculares. ¿Cómo está afectando esto al sistema de trasplantes? ¿Ha habido que extremar los controles para evitar la posible transmisión al receptor de enfermedades en los donantes?

RM. *La donación y el trasplante son un fiel reflejo de lo que ocurre en la sociedad. En un país desarrollado, y España lo es, las muertes evitables, y las que se producen en accidentes de tráfico o laborales lo son, simplemente se evitan. Algo que le gente no sabe es que de acuerdo con los datos de EUROSTAT, España está entre los cinco países de Europa con menor mortalidad tanto por accidentes de tráfico como por accidentes cerebrovasculares: las dos situaciones responsables del 90% de las muertes encefálicas y por tanto de la donación de órganos. Y sin embargo somos los que más donantes reales tenemos: es como el milagro de los panes y los peces gracias al sistema organizativo y al soporte de la población. Naturalmente, ello significa una edad elevadísima de nuestros donantes, pero también de los receptores: somos una sociedad muy envejecida, y a la vez implica unos mayores controles de los órganos que se trasplantan y también de los enfermos que los reciben. Afortunadamente ha sido un proceso progresivo del que hemos ido aprendiendo y hoy está perfectamente asumido.*

DG. Además del aprovechamiento de órganos de personas de más edad, que hace no muchos años se rechazaban como donantes o se consideraban donantes subóptimos, está el tema de la donación de vivo. Recuerdo que el año 1985 publicó Thomas Starzel en el *Hastings Center Report,* una de las revistas líderes en el mundo de la bioética, un artículo titulado *Will Live Organ Donations No Longer Be Justified?,* en el que el gran cirujano de trasplantes afirmaba, con todo el peso de su autoridad, que a la vista del mejor control del rechazo inmunológico como consecuencia de la introducción de las nuevas drogas inmunosupresoras, en especial la ciclosporina, consideraba que ya no había razones para justificar la donación de vivo, habida cuenta de los problemas que podía plantear al donante. Hoy las cosas se ven de modo muy distinto. ¿Cómo ve usted la donación de vivo?

RM. *Es un complemento necesario de la donación de personas fallecidas, porque en los trasplantes la demanda va siempre por delante de la oferta y de ninguna manera hay colisión entre ambas sino, insisto, complementariedad. En España las cifras enormes de donación de cadáver nos hicieron dejar a un lado la de vivo durante los noventa porque pensábamos (médicos y pacientes) que no merecía la pena someter a un riesgo a una persona sana cuando las posibilidades de trasplante eran tan altas. Hoy en cambio hemos apostado claramente por la donación de vivo renal, sobre todo por dos razones: los resultados son mejores que en los de cadáver (riñones más jóvenes y con menor deterioro por la muerte encefálica y el tiempo de isquemia) y además, gracias a los países que llevan muchos años trasplantando de vivo en gran cantidad (USA y los escandinavos sobre todo), sabemos que si se descartan como donantes aquellas personas con factores de riesgo (diabetes, hipertensión, obesidad, litiasis, etc.), donar un riñón es seguro incluso a muy largo plazo, con un riesgo asumible, que nunca es igual a cero porque en medicina eso no existe. Aparte de ello, las técnicas quirúrgicas han mejorado muchísimo. En poco más de 10 años hemos pasado de un 1-2% de trasplantes de vivo a un 15%, que ya está más o menos en la media europea.*

Por lo que se refiere al hígado cabe decir lo mismo, sobre todo por lo que se refiere a los receptores infantiles a los que sus padres donan el lóbulo izquierdo con un riesgo para el donante superior al renal, pero asumible. En el caso de la donación adulto–adulto, los riesgos son mayores y son técnicas que se hacen en bastante menor número.

DG. Además de la mejor utilización de órganos hace años considerados subóptimos y del nuevo auge de la donación de vivo, está la nueva vía abierta por la llamada donación en asistolia. Es, quizá, el punto hoy más debatido en las revistas que yo sigo, las de bioética. Concretamente, la revista antes citada, el *Hastings Center Report,* **ha dedicado su primer número del año 2013 a este tema. En él se da cuenta de las experiencias española y francesa con las donaciones a partir de paradas cardiacas ocurridas fuera del hospital. Un informe del Consejo de Europa afirma que en 2010, en España se trasplantaron 158 riñones y en Francia 79 de donantes en asistolia.**

RM.*En realidad no es nada nuevo ya que esto se inició en los años ochenta en los Hospitales Clínicos de Barcelona y Madrid, se estandarizó por parte de la comunidad internacional en Maastricht en 1994 y en España gracias al documento de consenso promovido por la ONT en 1995. Permaneció restringido a pocos hospitales y una actividad total bastante baja hasta que, a mediados de la pasada década, se erigió como una de las escasas vías de crecimiento que quedaban en la donación de órganos, con lo que desde la ONT y toda la red de coordinación se decidió darle un impulso en toda España. Ello se vió favorecido por el enorme desarrollo de los servicios de emergencia en todo el país durante la época de bonanza económica y, todo hay que decirlo, por el entusiasmo con que los médicos de urgencias y emergencias han recibido el mensaje de colaboración en el proceso de donación. Durante el año 2012, la donación en asistolia (muy mayoritariamente de este tipo) ha representado nada menos que el 10% del total de donantes y en la Comunidad de Madrid, el 40%. Es una realidad afortunadamente creciente y en la que vamos a seguir insistiendo*

DG. Usted conoce bien la polémica que ha surgido a propósito de la utilización de órganos de fallecidos por parada cardiorrespiratoria fuera del hospital (los llamados en la literatura anglosajona uDCDD, *Uncontrolled Donation after Circulatory Determination of Death* **y en la literatura española Donación en asistolia no controlada) y las paradas ocurridas en el hospital (cDCDD,** *Controlled Donation after Circulatory Determination of Death***, o en español, Donación en asistolia controlada). España ha aceptado el primero de esos criterios y ha establecido una moratoria para el segundo. ¿Puede explicarnos esto?**

RM. *Del documento de 1995 se derivó el decreto de 1999 en el que se abría la posibilidad a ambos tipos, lo que ha sido corroborado y mejorado en el nuevo decreto del año 2012. Lo que pasa es que en los noventa todos estuvimos de acuerdo en que la sociedad española no estaba aún preparada para los DCD controlados o DCD III. Este tipo de donación es característica de los países protestantes en los que hace muchos años que se viene practicando ampliamente la limitación del esfuerzo terapéutico en pacientes terminales, que es la base de este tipo de donantes (Holanda, Reino Unido, USA, Australia, Canadá). Esta es una de las razones por las que en estos países hay menos muertes encefálicas que en los países católicos del sur de Europa (los latinos, sobre todo). La gente se muere igual, como es obvio, pero de forma distinta: más muertes encefálicas en los países católicos del sur de Europa, porque las medidas terapéuticas se extreman al máximo en pacientes ancianos, con accidentes cerebro-vasculares sobre todo.*

En España estas prácticas en el final de la vida son más recientes, aunque se han generalizado a gran velocidad en los últimos años, hasta situarse en niveles parecidos a los de estos países (hay datos de la SEMICYUC que así lo demuestran), igual que otros muchos aspectos de nuestra vida diaria. Por ello, en el 2010 comenzamos con un programa piloto de DCD III en el País Vasco, con muy buenos resultados, que en este momento se ha extendido ya a otros 11 hospitales. Hoy tenemos ya 21 programas de asistolia entre los II y III en 9

CCAA y somos el único país que ha abordado seriamente las dos modalidades, con pleno apoyo de los profesionales sanitarios y plena aceptación de la población, lo cual habla muy bien de la madurez de nuestro país en estos temas.

DG. En la literatura de los últimos años han surgido voces críticas que dicen que el masaje cardiaco y la ventilación mecánica de estas personas que se llevan a cabo tras el diagnóstico de muerte en asistolia a fin de preservar la calidad biológica de sus órganos, puede invalidar el diagnóstico de muerte realizado con antelación, o al menos permite la oxigenación encefálica, con lo que podría darse el caso de que una persona muerta cardiopulmonarmente no lo estuviera encefálicamente. Por supuesto, a la llegada al hospital se interrumpen esas maniobras durante al menos cinco minutos, tras los cuales se vuelve a diagnosticar la muerte y acto seguido se bloquea la aorta con un balón obturador. Las dudas surgen respecto a la actuación durante el traslado, habida cuenta de que, además, se interviene antes de pedir el permiso a los familiares. Entre las voces españolas, las más persistentes han sido las de David Rodríguez Arias e Iván Ortega Deballon, insistiendo en que algunos de estos pacientes podrían beneficiarse de las llamadas medidas no convencionales de reanimación cardiopulmonar, y que las medidas de preservación de los órganos pueden en ciertos casos restablecer las funciones cardiacas y neurológicas. La ONT ha elaborado un documento de consenso sobre el tema de la donación en asistolia en 2012. Me gustaría que nos explicara su posición a este respecto.

RM. *En estos temas en que jugamos con la vida y la muerte hay que tener las ideas muy claras y mucho me temo que no es el caso de las dos personas que ha citado, de las que curiosamente ninguna es médico (un filósofo y un enfermero). Todas las técnicas de RCP tienen un único objetivo: reanimar al enfermo y que ese corazón vuelva a latir si ello es medicamente posible. Probablemente no hay ninguna otra actividad clínica que esté tan protocolizada en todo el mundo en cuanto a tiempos, maniobras etc. Nadie del mundo de la donación o el trasplante puede ni debe entrar a discutir estos protocolos y esto tiene que quedar muy claro porque es la piedra angular del asunto.*

Solo cuando los profesionales de la reanimación agotan esas medidas, es cuando comienza el proceso de la donación, perfectamente protocolizado, en el que es necesario seguir manteniendo el flujo de sangre en los órganos que se van a trasplantar. Hay que recordar que siempre se pide el consentimiento familiar y judicial al llegar al hospital y que la ley de consentimiento presunto permite y da soporte a la realización de todas las maniobras previas a la donación que en caso de no prosperar simplemente se suspenden.

Pero es fundamental entender que ya se han abandonado las maniobras de reanimación, y lo que no puede ser es que se dé por sentado que esa persona ha fallecido salvo en el caso de que pueda donar órganos, en cuyo caso, según estos señores, vuelve a estar potencialmente vivo. Si en el futuro el protocolo de reanimación se modificara por parte de la comunidad científica internacional introduciendo otra tecnología, el proceso de donación se adaptaría a esta

situación, insisto, sin interferir en la discusión de estos protocolos.

En el fondo, lo que subyace en este tipo de publicaciones y la razón de que "se compren" sin pestañear en la literatura anglosajona, es que ninguno de estos países ha conseguido desarrollar uno de estos programas, pese a que lo han intentado, mientras que países europeos y con consentimiento presunto, como España y Francia, sí lo han hecho. Si además las críticas vienen de aquí (algo muy nuestro, por cierto), pues mejor que mejor. Sin embargo, la realidad es que este problema no existe ni para la comunidad científica ni para la sociedad española, que lo tiene perfectamente asumido.

DG. La última de las vías que creo que se han puesto en práctica para incrementar los órganos para trasplante es la llamada "donación cruzada", en el que los familiares de un enfermo están dispuestos a donar un órgano a un desconocido que lo necesita, habida cuenta que ese órgano no es compatible ni por tanto trasplantable al familiar enfermo que tienen, a condición de que otra familia en que sucede algo similar haga lo mismo. ¿Cuál es la experiencia con este nuevo tipo de donación?

RM.*La donación cruzada es en realidad una donación renal de vivo en la que donante y receptor se intercambian entre dos parejas con el fin de conseguir la compatibilidad de grupo sanguíneo o inmunológica que no tiene con su familiar. En el caso de poder combinar varias de estas parejas se forma una cadena, que puede llegar a ser de muchos eslabones. En España se han hecho ya 32 de estas donaciones cruzadas, con un ritmo claramente creciente, y en realidad su mayor valor ha sido potenciar la donación de vivo en general, al tiempo que conseguir un trasplante a pacientes que de otra forma lo habrían tenido bastante más difícil. Creo que ha sido una muy buena iniciativa este programa.*

DG. Un tema preocupante es el de la comercialización de órganos, de la que periódicamente aparecen noticias en los medios de comunicación. Desde sus comienzos las organizaciones de donación y trasplante de órganos han venido defendiendo el principio de "no comercialización del cuerpo humano", ya presente en el Derecho romano. Por esa razón no se permite la donación de vivo más que entre parientes o allegados. Pero con cierta frecuencia llegan noticias, sobre todo de países en vías de desarrollo, sobre mercado de órganos, unas veces procedentes de personas a las que se ha ejecutado, y otras de sujetos vivos que ponen a la venta parte de su cuerpo. ¿Cómo ve el futuro de este tema? ¿Acabará habiendo comercio de órganos?

RM. *El llamado turismo de trasplantes es una triste realidad que según la OMS puede llegar a suponer entre un 5-10% de los trasplantes que se hacen en el mundo, sobre todo renales. La dinámica es siempre la misma: ciudadanos de países ricos o ricos de países pobres, compran riñones de personas pobres en países sin un Estado fuerte que controle esta práctica. La comunidad internacional se ha manifestado mayoritariamente en contra de estas prácticas, pero lamentablemente hay algunos ideólogos, sobre todo norteamericanos, que tienden a filosofar dando cobertura ideológica a un "mercado regulado". Es una*

forma más de explotación.

DG. Una última pregunta. Los avances en reprogramación celular y en fabricación de tejidos y hasta de órganos a partir de células troncales de los propios receptores han sido tan espectaculares en estos últimos años, que parece abrirse una vía nueva de enorme potencial en el futuro. Parece que la "medicina regenerativa" se convertirá en una de las ramas fundamentales de la medicina en las próximas décadas. ¿Cómo contempla esa posibilidad?

RM.*La medicina regenerativa es la gran esperanza del siglo XXI en este campo. Sin embargo, hay que tener paciencia, porque lo cierto es que hasta ahora han sido muchos los avances en el animal de experimentación pero pocos consolidados en la clínica. Hay que dar tiempo al tiempo y sobre todo no crear falsas esperanzas en muchas enfermedades hoy por hoy incurables. La utilización política, religiosa o partidista de este tema me parece de una desfachatez inadmisible, y por desgracia en España sabemos mucho de ello.*

Gracias, Dr. Matesanz, no sólo por la entrevista y por sus clarificadoras respuestas, sino también por todo su trabajo al frente de la Organización Nacional de Trasplantes. Y felicidades por su reciente nombramiento como Académico Correspondiente Honorario de la Real Academia Nacional de Medicina. Decían los viejos libros de ascética que ciertas hazañas hechas por grandes personajes eran dignas de admirar pero no de imitar. En su caso creo que no es así, y que lo conseguido por la ONT es un buen ejemplo para todos

PUNTO DE VISTA

Bioética de la información familiar en la donación en asistolia extrahospitalaria

Ethics in approaching families about organ donation from patients in out-of-hospital asystole

José Miguel Pérez Villares[1], Ramón Lara Rosales[2], Eladio Gil Piñero[3], Enrique Bravo Escudero[4], Francisco Alarcos Martínez[5], Beatriz Domínguez-Gil[6]

Introducción

La tasa de donación en España continúa siendo la más elevada del mundo[1] con 36 donantes por millón de población (pmp) en el año 2014. A distancia nos siguen: EEUU con 25,8 donantes pmp, y otros países de la Unión Europea como Bélgica con 30 y Francia con 25,9[2]. A pesar de todos los esfuerzos realizados, se evidencia en los últimos años una tendencia hacia la estabilización de la actividad trasplantadora[3]. El número de donantes obtenidos es insuficiente para satisfacer la demanda de trasplante de nuestra población, lo que ocasiona que entre el 7 y el 9% de los pacientes en lista de espera fallezca antes de ser trasplantados y que un porcentaje similar sea excluido de la lista de espera, frecuentemente por un agravamiento de su situación clínica.

Para adaptarse a esta situación, la Organización Nacional de Trasplantes desarrolla un Plan Estratégico Nacional para la Mejora de la Donación y el Trasplante de órganos en España: el Plan Donación 404. Con el objetivo general de aumentar la disponibilidad de órganos para trasplante, el plan se concreta en cinco áreas, siendo una de ellas el fomento de la donación en asistolia (DA). Respecto a este tipo de donación, conviene señalar dos hechos fundamentales: la redacción del Documento de Consenso Nacional sobre Donación en Asistolia del año 2012[5], donde se proporciona una serie de recomendaciones para el desarrollo de nuevos programas de estas características y/o para la mejora de la efectividad de los programas ya existentes, y la publicación del Real Decreto 1723/2012, de 28 de diciembre, por el que se Regulan las Actividades de Obtención, Utilización Clínica y Coordinación Territorial de los Órganos Humanos Destinados al Trasplante y se Establecen Requisitos de Calidad y Seguridad, que sienta las bases regulatorias para la realización de procesos de DA[6].

Mientras que en el año 1995 tan solo el 3,3% del total de donantes en España procedían de la DA, en el año 2014 este porcentaje alcanzó el 11%, con un total de 193 donantes (4,2 DA pmp), si bien lejos todavía de la actividad alcanzada en algunos países de nuestro entorno, como Holanda y Reino Unido[7].

En España predomina la DA no controlada (DANC), tras una resucitación cardiopulmonar (RCP) infructuosa, mientras que en los países mencionados lo es la donación en asistolia controlada tras limitación de tratamientos de soporte vital. La DANC ha sido desarrollada de manera pionera en España (siendo la mayoría donantes fallecidos tras una parada cardiorrespiratoria –PCR– extrahospitalaria), con escasa reproducibilidad del programa en otros países, exceptuando Francia. Las dificultades se deben en gran medida a problemas organizativos, dado que un programa de DANC no puede desarrollarse sin un sistema de emergencias extendido, consolidado y de calidad y sin una adecuada coordinación intrahospitalaria[8]. También hay discrepancias ético-legales en cuanto al inicio de maniobras de preservación en base a consentimiento presunto a la donación, así como sobre el proceso de comunicación con los familiares de los pacientes[9]. Finalmente, un tema importante de discusión es el relativo a la determinación del fallecimiento por criterios cardiocirculatorios[10-13].

Uno de los aspectos más complejos del proceso de DANC extrahospitalaria es el de la entrevista familiar, que sigue siendo motivo de preocupación fuera y dentro de España. La información a las familias previamente a su traslado al centro hospitalario es un tema sobre el que se dispone de poca información, y sobre el que no se ha aplicado una metodología deliberativa. Frecuentemente se ha enfocado el tema tomando en consideración los valores de las familias en contraposición a los valores de los pacientes en lista de espera. No se ha considerado suficientemente la autonomía del posible donante, ni la de los familiares, ni tampoco las condiciones necesarias para un consentimiento informado correcto. Tampoco se ha considerado la información como un proceso bidireccional, en el que el profesional debe buscar el momento y el espacio más adecuados para suministrar una información adaptada a la solicitud de la familia, de modo que la información se convierta en herramienta terapéutica, iniciándose por el médico de emergencias y finalizándose por el coordinador de trasplantes. Los objetivos de este punto de vista son:

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Información del artículo: Recibido: 6-3-2015. Aceptado: 6-5-2015. *Online:* 13-1-2016.

1. Analizar los valores en juego en el proceso de información a los familiares en el proceso de DANC extrahospitalaria.

2. Proponer un protocolo de información a los familiares, que respete todos los valores implicados.

Se ha analizado la información disponible en la literatura utilizando la base de datos Medline, así como la experiencia clínica de los equipos españoles que disponen de este tipo de programas. Se ha aplicado la metodología de análisis ético de casos clínicos para llegar a una decisión prudente que se refleje en el diseño de un procedimiento de información a familiares.

Análisis de los valores en juego en el proceso de información a los familiares

Atención a las familias: protección

La Ley 30/1979, de 27 de octubre, sobre extracción y trasplante de órganos, en su Artículo 5.2. especifica: *"La extracción de órganos u otras piezas anatómicas de fallecidos podrá realizarse con fines terapéuticos o científicos, en el caso de que estos no hubieran dejado constancia expresa de su oposición"*[14]. La ley española es por tanto una ley de consentimiento presunto (*opting-out consent policy* en terminología anglosajona).

Toda persona que fallezca en territorio nacional es potencialmente un donante de órganos, salvo que en vida hubiera expresado de forma clara su oposición a la donación. No obstante, uno de los pilares del éxito del modelo español radica en el hecho de que nunca se aplica esa norma de forma impositiva. Siempre es la familia del donante la que accede a la donación si así lo considera. La familia firma un consentimiento mediante el cual ratifica que el potencial donante nunca había hecho mención expresa de su oposición a donar una vez fallecido. Por tanto, es necesario preguntar a las familias sobre si conocían si el potencial donante se oponía a la donación de órganos, pero lógicamente, como condición previa, hay que comunicarles el fallecimiento de su familiar. Esto conduce a los profesionales a una situación extremadamente compleja, especialmente en el contexto de la DANC extrahospitalaria, que hay que manejar con prudencia.

La familia puede necesitar ayuda para decidir en condiciones de incertidumbre. La información se debe adaptar en la cantidad, el ritmo, los límites y las formas a las necesidades de los familiares. La información debe entenderse como un proceso, y no como una actuación clínica aislada. El familiar tiene que integrar la información en una situación caótica, que expone su fragilidad. Por este motivo el profesional debe ser respetuoso y prudente. El manejo de la información puede ser beneficioso, pero también puede hacer daño. El respeto, por tanto, debe empapar la gestión de la información, individualizando las necesidades concretas de cada familia, sin generalizaciones ni juicios *a priori.* Este respeto obliga a permitir que la familia escoja los ritmos y los límites de su descubrimiento. Además, se necesita un espacio físico digno y un espacio de tiempo suficiente.

La comunicación de malas noticias en situaciones de emergencia debe reunir unos requisitos mínimos. Si el paciente acaba de fallecer, se comenzará con una descripción detallada de cómo ocurrieron los hechos, el tratamiento aplicado y la respuesta a este, para acabar informando del fallecimiento. Para tener una buena comunicación con la familia, es indispensable proceder con calma. No hay un tiempo estipulado para dar una mala noticia. El tiempo necesario para informar de un fallecimiento debe ser aquel que permita notificarlo de una forma cuidadosa y respetuosa. Es recomendable que el espacio físico reúna condiciones adecuadas de comodidad, apacibilidad y, sobre todo, privacidad. Es difícil, por no decir imposible, aplicar estas recomendaciones en un procedimiento de DANC extrahospitalario, en el que el tiempo es el gran enemigo. Debe tenerse en cuenta que, después de todas las actuaciones anteriores, debería dejarse transcurrir un tiempo antes de solicitar la donación de órganos, lo que consume todavía más tiempo, haciendo imposible el procedimiento[15].

Hacerlo en menos tiempo supondría que la intervención, lejos de ser positiva para la familia, resultaría perjudicial. Dentro de las intervenciones psicológicas en emergencias, un aspecto que se debe tener en cuenta a la hora de comunicar el fallecimiento y solicitar la donación de órgano, se refiere al hecho de colaborar sumando, y no restando, a la resolución del conflicto. El objetivo es que después de la intervención, se haya avanzado en disminuir el sufrimiento, y no en aumentarlo, sin generar un problema más, o aumentar la tensión y la presión sobre la familia, al tener que tomar una decisión tan importante, con tan poco tiempo. Están definidas como segunda agresión, según Arana: *"Aquellas intervenciones que teniendo como objetivo el colaborar o ser parte de un procedimiento de recuperación o intervención, atentan involuntaria y directamente contra la indemnidad psicológica del involucrado"*.

Es evidente, además, que por ejemplo la cocina de una casa, mientras que el resto del equipo continúa dando masaje cardiaco en la sala de estar adyacente, no constituye un espacio físico adecuado para informar a una familia del fallecimiento de su ser querido, asistir al duelo y posteriormente solicitar la donación de órganos. El traslado del potencial donante al hospital permite atender a las familias en unas condiciones dignas, tanto en cuanto al espacio físico y al tiempo que se les puede dedicar, como en cuanto a la cualificación y experiencia de los profesionales que van a comunicar las malas noticias y presentar la opción de la donación. Es muy importante que las personas que participen en la entrevista tengan formación específica para los roles que asumen. Estos entrañan una elevada dificultad y requieren formación y entrenamiento específico.

Atención a las familias: ayuda

La solicitud de donación se ve condicionada por la decisión que tome la familia en un momento de intenso *shock* emocional. Los profesionales sanitarios tienen la obligación de ayudar a estos familiares a aceptar la

muerte como un hecho irreversible. Se debe proponer a la familia que acepte la donación como el único resultado positivo de esta situación dramática, siempre que se tenga la seguridad de que han aceptado la muerte. No se debe hablar de donación sin que los familiares comprendan y asuman el fallecimiento de su ser querido.

La familia se encuentra en situación de crisis, se enfrenta a una situación en la que un suceso incontrolable, imprevisible, inesperado y masivo le ha provocado un impacto que puede llegar a ser incapacitante a nivel cognitivo, afectivo y motor, acompañado de la pérdida de control de la situación y de la capacidad de adoptar respuestas eficaces. De modo transitorio, la familia puede encontrarse imposibilitada para resolver adecuadamente los problemas presentes, y más aún, para abordar situaciones novedosas o procesar información compleja. Puede llegar a padecer un estado de confusión y desorientación que requiera de un tutelaje y apoyo para poder afrontar, integrar y superar la situación[17,18].

Ante esta situación, la evidencia práctica y los estudios realizados sobre la entrevista de donación de órganos ponen de manifiesto que parece necesario establecer una separación entre el momento en que se comunica a la familia la muerte de su ser querido y el momento en que se solicita la donación de los órganos. La separación de estos dos contenidos de la entrevista de donación no implica que se deje a los familiares solos hasta el planteamiento de la solicitud, antes al contrario. La comunicación de la muerte del paciente produce en sus allegados un cúmulo de emociones, reacciones y expresión de necesidades de todo tipo, que se ha de atender y cumplimentar. Precisamente es en ese momento en el que los familiares empiezan a sufrir los efectos de la situación de crisis, cuando el apoyo psicológico y el alivio de las emociones han de realizarse, cercanos a la presentación del suceso que provoca la crisis misma. Esta primera ayuda psicológica debe ser rápida, de corta duración. El objetivo no es responsabilizarse del estado emocional de los familiares y ocuparse de su evolución, sino aliviar los primeros signos de sufrimiento debido a la muerte de un ser querido y facilitar la toma de decisiones. Esta forma de estructurar la entrevista familiar también se conoce como Modelo Alicante de entrevista de donación[19,20]. Este modelo, que es el aplicado en el Hospital Virgen de las Nieves de Granada, consta de tres fases:

1) Comunicación de la muerte: de una forma gradual, de lo conocido a lo nuevo y realizado por las personas que posteriormente harán el acompañamiento y la solicitud de donación.

2) Prestación de alivio emocional, valorando las necesidades, sobre todo las emocionales, que tiene en ese momento la familia, adecuando el apoyo a sus respuestas, mediante la escucha y la valoración positiva de sus manifestaciones verbales y no verbales.

3) Planteamiento de la opción de la donación sin divagaciones, como algo positivo para la familia y para el recuerdo y evitando la confrontación (Figura 1).

Este proceso puede hacerse más complejo, según Buckman *et al.,* en función de las circunstancias, pero siempre se seguirá una metodología basada en un conjunto de etapas que serán recorridas de manera ordenada, consecutiva y con el ritmo que la familia indique[21].

La primera fase es la de preparación. Ha de decidirse dónde dar la noticia. Siempre se debe buscar intimidad, eliminar barreras, disponer de material que pueda ser necesario durante la entrevista y evitar interrupciones. Decidir a quién se va a dar la noticia, sólo a la familia íntima, siempre considerando aquello que favorezca al receptor de la mala noticia. Escoger el mejor momento significa que ha de estarse lo suficientemente informado y disponer de una estrategia a seguir. No necesariamente significa que se disponga de toda la información del proceso.

La siguiente fase es la de percepción. Se trata de descubrir qué es lo que los familiares saben hasta el momento con preguntas abiertas: "antes de hablar, pregunta". Los familiares pueden manifestar no estar informados. Puede que sea así, puede que se trate de una actitud de negación, o puede también que traten de tener una segunda versión ante un nuevo facultativo. No se debe entrar en cuál de ellas es cierta, ya que la única opción en este momento es aceptar que demandan más información y ese es el punto de partida.

Se debe, a continuación, descubrir qué es lo que los familiares quieren saber. La información es un derecho y no una obligación. Según el Artículo 5 de la Ley 41/2002, de 14 de noviembre, Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica, el titular del derecho a la información es el paciente. El profesional debe estar dispuesto a adecuarse a ese nivel de exigencia, pero también intentando dar el máximo de información. Cuanta mayor colaboración se necesite de la persona posteriormente, mayor será el grado de información necesaria para que la fase de planificación fluya correctamente.

Recorridas estas fases, se entra en la comunicación de la noticia. Es importante empezar anunciando de forma indirecta que se va a dar una mala noticia, con

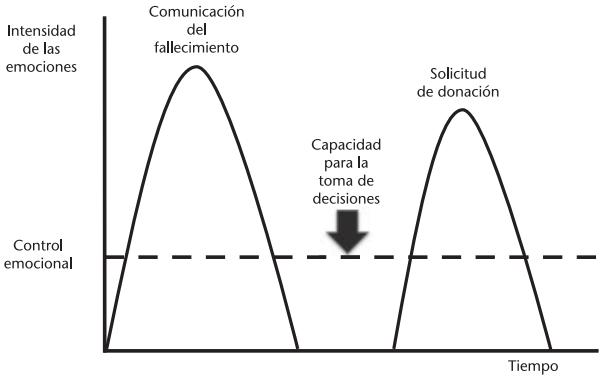

Figura 1. Evolución en el tiempo de la intensidad de las emociones.

frases como "siento tener que comunicarles", o "lamento no tener buenas noticias", lo que en la literatura anglosajona denominan *"warning shots"*.

La transmisión de una mala noticia debe ser sensible, honesta, cálida y respetuosa. El profesional debe ser claro y conciso, utilizar lenguaje sencillo y metáforas para mejorar la comprensión y hacer resúmenes de la información dada. Es muy importante seguir el ritmo del receptor de la noticia. Inmediatamente después de haber recibido una mala noticia, el receptor no presta más atención a lo que se le dice, por lo que será muy importante respetar los silencios y hacer resúmenes en mensajes cortos y sencillos de la información dada.

Debe comprobarse que la familia está comprendiendo lo que se le dice. La negación y el bloqueo dificultan que la familia integre mucha de la información que se le da y hacen que distorsione su interpretación.

Quizás a partir de este momento empieza la fase más compleja. Es probable que los familiares, habiendo entendido ya la magnitud de la mala noticia, estén poco receptivos a recibir más información y que por el contrario emerjan reacciones emocionales que pueden ser muy diversas y frente a las que se debe estar preparado para reaccionar adecuadamente. Se trata de responder a las emociones de los familiares de manera que se puedan reconducir reacciones no aceptables como la violencia, o no adaptativas como la acusación, y establecer una relación que persiga conseguir una verdadera ayuda en ese momento y que debe ser por encima de todo, asertiva.

La etapa de planificación. Cuando las personas tienen un plan claro de futuro, disminuye su ansiedad. La incertidumbre es una fuente de ansiedad muy importante. Puede incluso llegar al extremo de que, al confirmársele lo temido, disminuya la angustia sufrida hasta ese momento, porque la familia ya sabe a qué atenerse y empieza a desarrollar sus propios mecanismos de adaptación.

Parece claro que, con independencia del modelo que se utilice para informar a las familias, este requiere tiempo y formación previa, así como una práctica habitual, que garantice un nivel de conocimiento y habilidades suficiente como para que la comunicación del fallecimiento y la solicitud de donación se convierta en una ayuda para la familia. En España, este perfil lo cumple el coordinador de trasplantes, con excelentes resultados[22].

La familia se encuentra en situación de crisis vital debida a la pérdida de un ser querido y evolucionará inevitablemente hacia el inicio del duelo. El profesional debe ser respetuoso con el tiempo que necesite para asumir la pérdida. La entrevista de donación debe facilitar la transición de la situación de crisis al inicio del duelo. La mayoría de las familias que han pasado por la experiencia de la donación, agradecen a esta el poder recordar la pérdida con menos sufrimiento. De modo que parece razonable que la comunicación del fallecimiento y la solicitud de la donación de órganos se haga en el medio hospitalario, y sea realizada por el coordinador de trasplantes.

Atención al paciente en lista de espera para trasplante: responsabilidad

El resultado final de la escasez relativa de órganos para trasplante es un mayor tiempo en lista de espera de los pacientes, que se deterioran y/o mueren en espera por recibir un órgano. Se ha calculado que 10 pacientes europeos fallecen diariamente en lista de espera para trasplante[4].

Por este motivo, el objetivo primordial del coordinador de trasplantes es la obtención de órganos de calidad para el trasplante, pero esta responsabilidad no solo le corresponde a él, sino que es compartida por todos los agentes sanitarios, incluidos los profesionales de los servicios de emergencias. La participación de los profesionales de emergencias extrahospitalarias en la detección de posibles donantes entre los pacientes que no responden a las maniobras de RCA es fundamental. Es necesario implicar a los profesionales de emergencias en la cultura de la donación y el trasplante, y mejorar su formación en este campo. De esta manera, se puede contribuir a la disminución de la mortalidad en lista de espera para trasplante, al extender los programas de DANC.

Atención al potencial donante de órganos: respeto

Siguiendo a Pablo Simon *et al.*[23], las situaciones en que clásicamente se ha considerado que no obtener el consentimiento informado es una excepción moralmente legítima serían:

1. Urgencia vital que requiere actuación profesional inmediata, sin que exista tiempo o posibilidad de comunicarse con el paciente.
2. Incapacidad del paciente, lo que obliga a que el proceso de consentimiento informado se realice con sus representantes.
3. Grave riesgo para la salud pública, lo que puede incluso legitimar actuaciones sanitarias coactivas, aunque no corresponde al médico adoptarlas por su cuenta.
4. Imperativo legal o judicial.

En el proceso de DANC extrahospitalaria, la situación es de extrema emergencia. Un retraso innecesario puede hacer que, en caso de que la donación siga adelante, se pierda un tiempo precioso para asegurar la perfusión de los órganos, y por tanto su funcionamiento en el paciente que los recibe. No se trata de no consultar la voluntad del potencial donante a sus familias, sino de realizar esa consulta en el medio hospitalario, donde mientras se hace la consulta, se puede asegurar la perfusión de los órganos hasta que la familia tome su decisión.

Además, dada la situación clínica del potencial donante, este no puede decidir, por tanto el profesional se encuentra ante un escenario de toma de decisiones por representación. La información deber ser suficiente y transparente. Dado que el potencial donante a corazón parado se encuentra incapacitado, la decisión sobre la donación de órganos la debe tomar su familia, una vez

consultado el Registro de Voluntades Vitales Anticipadas. La consulta al Registro de Voluntades Vitales Anticipadas se podrá iniciar, conforme al procedimiento establecido en la Agencia Pública, con las garantías adecuadas, y sin que la consulta, en sí misma, suspenda la actuación de los equipos de emergencias. La familia tomará su decisión según el criterio subjetivo, según el criterio del juicio sustitutivo, o según el criterio del mayor beneficio. En cualquier caso, sería el coordinador de trasplantes, en el medio hospitalario, la persona y el lugar adecuados para asegurar que la decisión respete los valores del potencial donante de órganos.

Desde el punto de vista ético, la información que se debe dar es aquella que la familia subjetivamente necesite para poder tomar una decisión. En este mismo sentido, se entiende la información "completa y continuada" de la que habla la Ley General de Sanidad[24]. También la información "adecuada" a que hace referencia el Convenio de Oviedo sobre derechos humanos y biomedicina en su Artículo 9, que recomienda que, con respecto a una intervención médica, sean tomados en consideración los deseos expresados anteriormente, por un paciente que, en el momento de la intervención, no se encuentra en situación de expresar su voluntad[25]. También son coherentes con estos principios, los del Código de Deontología Médica del Consejo General de Colegios Oficiales de Médicos, en cuyo Capítulo III, el cual trata sobre las "Relaciones del médico con sus pacientes", indica en su artículo 15: *"El medico informara de forma comprensible, con veracidad, ponderacion y prudencia. Cuando la informacion incluya datos de gravedad o mal pronostico, se esforzara en transmitirla con delicadeza de manera que no perjudique"*[26].

La información debe ser comprensible. Ya se ha comentado anteriormente cómo se puede asegurar esta comprensión, en el estado emocional en que se encuentran las familias. Finalmente, tras recibir la información suficiente y comprensible, la familia, tras el proceso de deliberación, debe tomar una decisión, que es de aceptación o rechazo de la solicitud de donación propuesta. Este proceso de deliberación es fundamental; la familia puede pedir un periodo de reflexión, puede plantear dudas, preocupaciones, que hay que responder. Para ello es fundamental disponer de un tiempo mínimo, que en el escenario extrahospitalario no se tiene, siendo una razón más para plantear la donación en el medio hospitalario.

La Ley 2/2010 sobre la Dignidad de la Persona en el Proceso de la Muerte de la Junta de Andalucía[27], en su fundamentación bioética, manifiesta: *"Todos los seres humanos aspiran a vivir dignamente, el ordenamiento jurídico trata de concretar y simultáneamente proteger esta aspiración. Morir constituye el acto final de la biografía personal de cada ser humano y no puede ser separada de aquella como algo distinto. Por tanto, el imperativo de la vida digna alcanza también a la muerte. Una vida digna requiere una muerte digna"*.

Por tanto, respetar la dignidad de las personas que se encuentran en el proceso de la muerte, supone permitirle elegir la posibilidad de donar sus órganos, como respeto a su autonomía personal y a la libertad de cada cual para gestionar su propia biografía de acuerdo a sus valores. Es en este contexto de respeto a la dignidad de la persona, a su autonomía, en el que se encuentra el proceso de exploración de su voluntad de donar, que inicia el equipo de emergencias extrahospitalarias, y finaliza el equipo de coordinación de trasplantes.

Profesionales de los sistemas de emergencias médicas: procedimiento de información a familiares

La preocupación por parte de los profesionales de los servicios de emergencias extrahospitalarios sobre la información a los familiares de los donantes se centra en si se debe informar a las familias de la condición de potencial donante a corazón parado de su ser querido antes del traslado al hospital. Para que la comunicación no sea maleficente hacia las familias, debe realizarse en unas condiciones de espacio, tiempo, y formación y experiencia de los profesionales, que es difícil encajar en las condiciones en las que trabajan los equipos de emergencias extrahospitalarios. Por otra parte, no se puede dejar de tener en cuenta la mortalidad de los pacientes en lista de espera para trasplante. Dado que el modelo español de donación y trasplante es un referente mundial, y que en este modelo, una de las claves es la figura del coordinador de trasplantes, parece razonable trasladar en el tiempo y en el espacio la comunicación del fallecimiento y la solicitud de la donación hasta el medio hospitalario. En el hospital se dispone de tiempo, condiciones ambientales, y profesionales preparados para ello.

Esto no excluye a los profesionales de emergencias del proceso de información y consentimiento de los familiares y allegados, antes al contrario debe entenderse como un proceso que comienza con la intervención de los equipos de emergencias, y finaliza con la actuación de los coordinadores de trasplantes. Este proceso de información debe ser gradual, iniciado por los profesionales de emergencias, pero proporcionando, en cada momento, la información que la familia puede asimilar y comprender, conforme a las circunstancias y evitando el encarnizamiento informativo.

Los dos escenarios describen un cuaderno de ruta, progresivo, que conforme a las circunstancias, señala la información que en cada caso, y dentro de un proceso único, se facilita a la familia. Esta adecuación de la información a las circunstancias se encuentra amparada por la *lex artis* y por la propia normativa, la Ley de Autonomía del Paciente de 2002, que en su Artículo 4.2. expone que la información clínica se comunicará al paciente de forma comprensible y adecuada a sus necesidades y le ayudará a tomar decisiones de acuerdo con su propia y libre voluntad[28].

Es recomendable que los profesionales anoten en la historia clínica del paciente las condiciones de información a los familiares y, en su caso, el escenario informativo en el que se ha desarrollado la actuación.

En opinión de los autores, con este procedimiento de información a familiares, se puede respetar la mayoría de los valores en juego: autonomía del potencial donante de órganos y de su familia, no maleficencia de la información hacia la familia, beneficencia de la información a la familia y beneficencia y justicia para los pacientes en lista de espera para trasplante.

Se proporciona a continuación una propuesta de actuación informativa de acuerdo a dos escenarios diferenciados. En cualquier caso, este procedimiento solo se desarrolla en el momento en el que el médico del equipo de emergencias está completamente seguro de que ya no existe indicación de seguir reanimando al paciente. A su vez, el procedimiento solo se activa cuando la intención del traslado es la consideración del paciente como donante potencial en asistolia. Si la intención del traslado es aplicar técnicas especiales de reanimación o continuar la reanimación, el procedimiento no se aplica, pues no se habría activado el protocolo de DA.

Escenario 1: no hay familiares presentes

En base al consentimiento tácito para ser donante, se procede al traslado al centro hospitalario útil para la preservación y extracción de los órganos.

Escenario 2: familiares presentes

Fase 1ª (se comunican los tres ítems): Se informa por iniciativa del equipo, aunque no haya solicitud de información por parte de los familiares.

1. Su familiar se encuentra en situación de parada cardiorrespiratoria y no responde a tratamiento.
2. La situación es extremadamente grave, prepárense para lo peor.
3. Lo trasladamos urgentemente al hospital (especificar nombre del centro hospitalario).

Si la familia no solicita más información, se traslada al centro hospitalario. Si la familia expresa su desacuerdo con el traslado, se suspenden inmediatamente las maniobras de soporte vital avanzado.

Fase 2ª (se comunican los tres ítems): si los familiares solicitan más información.

1. Se traslada al centro hospitalario señalado porque en este centro se le puede mantener hasta confirmar o no el fallecimiento de su familiar.
2. Si no ha fallecido, se seguirá luchando por su vida.
3. Si ha fallecido, el equipo de coordinación de trasplantes le planteará la posibilidad de donar sus órganos.

Si la familia no solicita más información, se traslada al centro hospitalario. Si la familia expresa su desacuerdo con el traslado, se suspenden inmediatamente las maniobras de soporte vital avanzado.

Fase 3ª (se comunican los tres ítems): si los familiares solicitan más información todavía.

1. Es muy importante trasladarlo cuanto antes al hospital.
2. En el hospital hay un equipo de profesionales preparados para atenderles y responder a todas sus preguntas.

Si la familia expresa su desacuerdo al traslado, se suspenden inmediatamente las maniobras de soporte vital avanzado.

Este protocolo se viene aplicando desde 2010 en el programa de DANC de Granada[29], y ha sido aprobado por el Comité de Ética Asistencial de la Empresa Pública de Emergencias Sanitarias 061. Es lógica también la preocupación por la posible existencia de un conflicto de fines en los equipos de emergencias, entre sus funciones asistenciales tradicionales y las nuevas oportunidades de la DA. Debe señalarse que el "balance asistencial", esto es, los beneficios obtenidos por los pacientes en lista de espera de trasplantes, justifica sin duda el nuevo rol que se les asigna. En todo caso, los procedimientos deben garantizar una transferencia hospitalaria rápida del donante, para garantizar la disponibilidad de los equipos.

Consideraciones finales

En la información a los familiares hay que respetar la autonomía, no hacer maleficencia y velar por la justicia. Por tanto, en el derecho a la información hay que equilibrar tres conceptos: el derecho a no saber, el encarnizamiento informativo y la verdad tolerable (es decir, informar con delicadeza, diplomacia y afecto). Debe evitarse que el encarnizamiento informativo se convierta en una nueva medicina defensiva; a la familia hay que darle la información que quiere y con arreglo a lo que tolere. Se trata del "tiempo de la familia" y no de "nuestro tiempo".

Aunque entre los servicios de emergencias extrahospitalarias, las consideraciones éticas de la información a los familiares de potenciales donantes en asistolia es una preocupación legítima y honrosa, deben respetarse los "tiempos de la familia", considerando la información como un proceso continuo que se adapta en cada momento a la situación de la familia, iniciándose por el médico de emergencias en el medio extrahospitalario, continúandolo y finalizándolo los coordinadores de trasplante en el medio hospitalario, donde se confirma y se comunica el fallecimiento del paciente.

La solicitud de información por parte de la familia debe ser respondida de modo veraz y transparente, explicando el motivo de su traslado al hospital. De este modo, la información será el principio de una relación de ayuda a la familia y, a la vez, se preservará el derecho de los pacientes, que están en lista de espera de trasplantes, a la vida.

Conflicto de intereses

Los autores declaran no tener conflicto de interés en relación al presente artículo.

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11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

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12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Fundacion 'La Caixa'. Predoctoral Research Fellowship for Ivan Ortega

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
What are the defining elements of currently active protocols and recommendations for uncontrolled Donation after Circulatory Death (uDCD) strategy? We used a modified PICOTS format: Population: potential uDCD candidates; Intervention: protocols for uDCD currently active and recommendations for implementing such a protocols; Control: not applicable; Outcomes: In terms of (a) Defining elements of worldwide practices on protocols for uDCD and, when reported, in terms of (b) grafts actually obtained and/or transplanted, as well as graft and/or patient survival and complications; Time: 2005 to present; and Setting: any organization that produced a recommendation or protocol for uDCD The end goal of this systematic review is to apply the knowledge gained to the implementation of new protocols and leading practices in areas working to develop or initiate the uDCD strategy. Therefore, we believe this review will be useful for policy makers, researchers and clinicians. Following the strategy of benchmarking, we intend to better define the most effective practices in uDCD to inform future protocol implementation.

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Search Strategy: To identify all eligible publications, we developed a comprehensive search strategy with the help of a qualified librarian. We searched MEDLINE database, EMBASE database and Google Scholar electronic databases from 2005 to September 2014. We opened study language to English, French, Italian and Spanish and limited to human studies. We manually searched the reference lists of selected studies as well as the so-called grey literature for abstracts, unpublished reports, personal libraries, professional organization reports/position statements and government agency statements on uDCD. We also contacted leading authors and organizations in the field of uDCD to request their protocols and guidelines. Eligibility Criteria: Our inclusion criteria for review were any kind of report proposing a clinical procedure for uDCD endorsed by a government agency, professional organization, professional society or regional health care organization. We excluded any editorials, letters, abstracts or personal opinion articles that were not endorsed by a recognized organization.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

http://www.crd.york.ac.uk/PROSPEROFILES/15258_STRATEGY_20141029.pdf

I give permission for this file to be made publicly available

Yes

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

A chronic shortage of organs remains the main factor limiting organ transplantation for patients with end stage organ diseases. Although organ transplants save thousands of lives and transform the quality of life of thousands more, many people will die or remain on renal replacement therapy because the organ supply falls drastically short of demand. In Western Europe, nearly 40,000 patients are waiting for a kidney each year whilst the number of cadaveric donors remains stable at around 5,000. This is also the case in the USA where 30,000 patients are on the waiting list and the number of cadaveric donors is also around 5,000 per year. Canada data are also troubling. In 2013, 4,686 patients were in the waiting lists while 540 actual deceased donors were obtained. The mismatch between supply and demand for organs has led policy makers and health institutions to develop new strategies aimed at expanding the organ donor pool. As a result, many countries worldwide are exploring the option of Donation after Circulatory Death (DCD). The DCD procedure seeks to obtain solid organs from patients previously declared dead following the cessation of their circulatory and respiratory functions. There are two distinct methods for obtaining organs this way: controlled DCD (cDCD) and uncontrolled DCD (uDCD). The former occurs in-hospital, generally in patients who have suffered a catastrophic brain injury and for whom a decision has been made to withdraw life sustaining therapies (WLST) because of a bad prognosis for survival. In this scenario, consent for cDCD is obtained, WLST occurs, death is declared and organs are procured. The latter is initiated following an unexpected, and not reversed, cardiac arrest. After resuscitation attempts are judged futile and, though usually but not always, after the patient has been declared dead, interventions start to preserve organs. This systematic review will focus on these so-called protocols for uncontrolled DCD. Protocols for uDCD are already implemented in some regions of Spain, France, Italy, UK and Netherlands. Currently, other regions of these countries and other different countries such as Belgium, Switzerland, Austria and Russia, in addition to some Latin American countries as well as the city of New York, are developing similar protocols. It is widely accepted that implementing a program for uDCD is an effective way to increase the availability of solid organs for transplantation. However, little is known regarding the variability of practices between existing protocols and less still regarding the potential and effectiveness of implementing a specific protocol. Although protocols for uDCD have promising results in terms of graft survival, they also raise several ethical, legal, and logistic concerns in caring at the end-of-life stage. To date, no systematic review has been conducted to evaluate specifically the practices and outcomes of uDCD protocols, nor has an evaluation of the quality of recommendations for implementing such protocols been performed. The purpose of this systematic review is to address this knowledge gap through the defining elements and outcomes reported of the currently active protocols and recommendations for uDCD. By comparing and analyzing all these information across organizations and settings worldwide, and by an appraisal of the variability in recommendation quality, we aim to provide essential data regarding uDCD protocols and outcomes.

19 Participants/population

Give summary criteria for the participants or populations being studied by the review. The preferred format includes

details of both inclusion and exclusion criteria.
We used a modified PICOTS format: Population: potential uDCD candidates;

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Intervention: protocols for uDCD currently active and recommendations for implementing such a protocols

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Control: not applicable;

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Eligibility Criteria: Our inclusion criteria for review were any kind of report proposing a clinical procedure for uDCD endorsed by a government agency, professional organization, professional society or regional health care organization. We excluded any editorials, letters, abstracts or personal opinion articles that were not endorsed by a recognized organization.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Time: 2005 to present; and Setting: any organization that produced a recommendation or protocol for uDCD

24 Primary outcome(s)
Give the most important outcomes.
Outcomes: In terms of (a) Defining elements of worldwide practices on protocols for uDCD and, when reported, in terms of (b) grafts actually obtained and/or transplanted, as well as graft and/or patient survival and complications.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
The purpose of this systematic review is to address this knowledge gap through the defining elements and outcomes reported of the currently active protocols and recommendations for uDCD. By comparing and analyzing all these information across organizations and settings worldwide, and by an appraisal of the variability in recommendation quality, we aim to provide essential data regarding uDCD protocols and outcomes. The end goal of this systematic review is to apply the knowledge gained to the implementation of new protocols and leading practices in areas working to develop or initiate the uDCD strategy. Therefore, we believe this review will be useful for policy makers, researchers and clinicians. Following the strategy of benchmarking (10), we intend to better define the most effective practices in uDCD to inform future protocol implementation.

Give information on timing and effect measures, as appropriate.

26 Data extraction, (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Study selection: Two trained reviewers (IO-D & LH) will screen all citations based on titles and abstracts. We will retrieve the full texts of selected citations and independently review them to assess study eligibility. Disagreements will be resolved by consensus and/or with the intervention of a third expert reviewer (SDS). We are going to use EndNote manager software (EndNote X7.1 version, by Thomson Reuters) to manage the collection of publications. Data Extraction Two reviewers (IO-D and LH) will extract data. We are creating with Excel (Excel version 2013, by Microsoft Office) a data collection tool that will be piloted in a sample from the final list of included studies and protocols. The final version of the spreadsheet will include the following variables: name of the author/s, country, language of publication, setting, year, type of study and method, eligibility criteria for population, intervention and timelines during process, organ preservation details, death determination characteristics, type and time of consent and any ethical, legal and logistic issues described. For the studies reporting transplant outcomes, we will add type, quantity, quality of organs procured and complications reported. Internal validity of the studies will be assessed independently by two reviewers (IO-D and LH).

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
The quality of the studies reporting outcomes will be assessed using the Downs and Black scale and the protocols and recommendations will be assessed by up to three reviewers with the Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument, version II

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
We anticipate heterogeneity in both the studies reporting outcomes and the recommendations for implementing protocols for uDCD, based on the different eligibility criteria, organs obtained, timelines on cardiac arrest, determination of circulatory death, ischemia times and techniques for organ preservation. Therefore, pooling of study and recommendation results would not be feasible and a meta-analysis would not be performed. Rather, our data analysis will consist of a tabulation of characteristics from both the included studies and recommendations, enabling a description of the variability in practice in the former and of the level of evidence supporting the latter.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned

Review general information

30 Type of review
Select the type of review from the drop down list.
Intervention, Other

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Canada

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=15258&UserID=9286

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.
http://www.crd.york.ac.uk/PROSPERO/register_new_review.asp?RecordID=15258&UserID=9286

I give permission for this file to be made publicly available
Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
We will produce a synthesis of the characteristics of all included studies, reports and recommendations (e.g. date of publication, country of origin, supporting organization(s), etc). We will assess for each report the main domains covered by the uDCD recommendations and protocols and the specific elements covered for each domain. The methodological quality of each recommendation or protocol will be assessed using the AGREE II instrument. This systematic review will be conducted with full methodological rigor to ensure publication in a high-impact peer-reviewed journal.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
DECEASED DONATION

UNCONTROLLED DONATION

DONATION AFTER CIRCULATORY DEATH

RECOMMENDATIONS

GUIDELINES

OUTCOMES

SYSTEMATIC REVIEW

NON HEART BEATING DONATION

ORGAN PRESERVATION

EXTRACORPOREAL MEMBRANE OXIGENATION

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Completed and published

01/07/2015

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.
Open access paper published in Critical Care

40 Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
http://ccforum.com/content/19/1/268

Give the URL where available.
http://ccforum.com/content/19/1/268

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Extracorporeal resuscitation for refractory out-of-hospital cardiac arrest in adults: a systematic review of international practices and outcomes

2 Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
31/05/2014

4 Anticipated completion date
Give the date by which the review is expected to be completed.
31/07/2015

5 Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.
We are continuously updating this protocol

Review team details

6 Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Professor Ortega-Deballon

7 Named contact email
Enter the electronic mail address of the named contact.
iviortega@gmail.com

8 Named contact address
Enter the full postal address for the named contact.
102-75 GLENGARRY AVENUE TMR. H3R 1A2, Quebec, Canada

9 Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
+15146926173

10 Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
'None'

Website address:

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Professor	IVAN	ORTEGA-DEBALLON	Servicio de Urgencias Medicas de Madrid - SUMMA 112 Madrid, Spain. Faculty of Medicine and Health Sciences - Universidad de Alcala de Henares, Madrid. Spain. Canadian National Transplant Research Program. Centre de Prélèvement d'Organes - Hôpital du Sacré-Coeur de Montréal. Deceased Organ Donation Program at Critical Care Division - Montreal Children's Hospital. Research Institute McGill University Health Centre. The Loeb Chair and Research Consortium for Ethics in Organ & Tissues Donation. University of Ottawa.
Mrs	LAURA	HORNBY	
Dr	SAM D.	SHEMIE	
Dr	FARHAN	BHANJI	
Miss	ELENA	GUADAGNO	

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Fundacion 'La Caixa' (Spain) awarded Ivan Ortega with a predoctoral fellowship for supporting him while conducting this Systematic Review in Montreal, Quebec (Canada)

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
Question 1: What are the defining elements (eligibility criteria, interventions used and timelines) of the currently active protocols for Extracorporeal Resuscitation (E-CPR) in refractory out-of-hospital cardiac arrest (OHCA) in adult patients?

Question 2: Which are the results of the ECPR strategy to adults patients suffering for refractory OHCA of cardiac origin compared to conventional CPR in terms of:a. Survival with good quality of life (Cerebral Performance Category 1-2) at discharge. Increase of organ donation pool for transplantation purposes between non-survivors or between patients with bad neurologic prognosis after ECPR-ECMO

16 Searches

Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

Search Strategy: Comprehensive search strategy without language restrictions will be performed using MEDLINE database, EMBASE database, Google Scholar from 2005 and updated until authors are ready for final abstraction. Clinicaltrial.gov will be consulted for unpublished protocols or studies. All studies and protocols including ECPR strategy in refractory OHCA adult patients will be included. Reference lists of all eligible documents will be searched for additional references. Authors of included studies will be contacted for more detailed data Inclusion criteria for review: 1. Any kind of study reporting results after offering ECPR approach as main strategy to adult patients suffering refractory OHCA. 2. Any kind of report proposing a clinical procedure (protocol) for ECPR endorsed by a professional society or health care organization. Exclusion criteria: Editorials, letters, abstracts or personal opinions that were not endorsed by one of the groups or referred to studies reporting results. Studies using animal models will also be excluded.

17 URL to search strategy

If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

http://www.crd.york.ac.uk/PROSPEROFILES/15259_STRATEGY_20141029.pdf

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No

18 Condition or domain being studied

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Sudden cardiac arrest is currently the main cause of death worldwide in previously healthy people. In fact, the global incidence of out of hospital cardiac arrest (OHCA) in adults is 62 cases per 100,000 habitants person years, from which 75-85% have a cardiac origin cause. Despite recent improvements in enhancing succesful resuscitation in the prehospital setting, overall outcomes remain poor in most venues. In North America, the survival to hospital discharge is 6% , 9% in Europe, 11% in Australia and 2% in Japan. The extracorporeal resuscitation (ECPR) consists of a system that incorporates a rapid cardiopulmonary bypass through main arteries and vessels, allowing the maintenance of circulation until an effective cardiac output has been achieved. ECPR enhances coronary blood flow and preserves the heart viability, reducing the time to return of spontaneous circulation (ROSC). Supplying oxygenated blood flow to all the organs of the body, brain included, prevents organ dysfunction and increases the likelihood of survival with a full neurologic recovery. Moreover, during ECPR, the underlying primary cause of cardiac arrest can be definitively diagnosed and treated. In recent years, ECPR has been proposed as an effective therapy not only for in-hospital cardiac arrest but also for OHCA . However, outcomes with this novel therapy have been mixed due to heterogeneity in populations, interventions and outcomes in terms of long-term full recovery of patients discharged. Today, the question whether resuscitation attempts in some refractory OHCA must be disrupted or not still remains. Historically, 30 minutes of downtime was proposed as the threshold for the cessation of resuscitation, which left little hope for patients who may have achieved ROSC at the minute 31st. Data presented on more than 30,000 patients suffering OHCA suggested a resuscitative effort of 38 minutes was needed for 99% sensitivity for 30 day favorable neurologic outcome, independent of whether bystander resuscitation was performed. An unexplored secondary benefit of this novel approach would be that in patients who would have achieved ROSC but with severe neurologic damage, ECPR would have served to increase the organ donation pool. This could be a worthy way for saving other lives in the current worldwide organ shortage trend. Therefore, is it time for modern resuscitation to evolve beyond arbitrary ceilings on duration of efforts and deem futility in the context of available therapeutic options (ECPR)? When should the emergency medical services declare death on the field and when should they play the role of a bridge between the prehospital setting and ECPR for treating the underlying primary cause of the cardiac arrest? And last, but not least, should we add the deceased organ donation option as a secondary end goal to this comprehensive approach to refractory cardiac arrest? Importantly, the last updated guidelines on resuscitation answer positively to all of the aforementioned questions. While the utility of ECPR in refractory OHCA is one of the more exciting developments of both these mechanical circulatory support and gas exchange, there is no still systematic review of the growing literature underpinning its use. Giving the option of organ donation to patients who achieve ROSC after ECPR, but with a bad neurologic prognosis, is an approach that still does not exist. Implementing ECPR in the setting of undifferentiated cardiac arrest is daunting. But it is also true that taking in total the body of recent outcomes, stopping resuscitation attempts when ECPR facilities are available and a reversible and treatable cause of cardiac arrest does exist, would not be aligned with guidelines on resuscitation. Thus, examining downtime on resuscitation attempts suggests that delineation of futility is less a line and more of a moving target in these

selected patients.

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Adults suffering for refractory OHCA of cardiac origin, who were considered candidates for ECPR strategy

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Intervention: ongoing resuscitation during transport, followed by ECPR approach* (*) ECPR approach will include necessarily extracorporeal reusictiation (according to ELSO definition) but may include also other bunch of strategies (e.g. induced therapeutic hypothermia, percutaneous coronary intervention, intra-aortic balloon pump, thrombolysis, LVAD...), but only following an ECPR already instituted ASAP

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Control: Conventional CPR* (*) Conventional CPR, or resusictation, is defined as advanced cardiac life support (ACLS) algorithms according to ILCOR updated guidelines

22 Types of study to be included initially
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Inclusion criteria for review: 1. Any kind of study reporting results after offering ECPR approach as main strategy to adult patients suffering refractory OHCA of cardiac origin. 2. Any kind of report proposing a clinical procedure (protocol) for ECPR endorsed by a professional society or health care organization. Exclusion criteria: Editorials, letters, abstracts or personal opinions that were not endorsed by one of the groups or referred to studies reporting results. Studies using animal models will also be excluded. Cases of refractory cardiac arrest with underlying primary cause different than cardiac cause, excluded. Pediatric patients, excluded Study selection: Three reviewers (IO-D & LH) will determine the final inclusion/exclusion of studies. Disagreement will be resolved by consensus and/or with the intervention of a third reviewer (SDS). EndNote manager software will be used to manage the collection of references.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Setting: any organization that produced a recommendation or conducted a study or trial for ECPR in adult patients suffering from refractory OHCA of cardiac origin

24 Primary outcome(s)
Give the most important outcomes.
1. Description of practices based on protocols for ECPR to the studied population: how many protocols do exist, what countries do they come from, what are the eligibility criteria for selecting patients, the main domains covered by protocols and level of evidence of its recommendations or outcomes 2. Survival with quality of life (CPC 1-2) after discharge

Give information on timing and effect measures, as appropriate.
Time: 2005 to present (2005 is the starting point because the ECPR strategy was considered on International Resuscitation Guidelines from this moment, ILCOR-ERC-AHA)

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
Additional results derived from ECPR approach, when reported (i.e: potential donors for transplantation purposes)

Give information on timing and effect measures, as appropriate.
Time: 2005 to present (2005 is the starting point because the ECPR strategy was considered on International Resuscitation Guidelines from this moment, ILCOR)

26 Data extraction, (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

Data extraction: Different reviewers should extract data independently from the final list of studies. Disagreement must be resolved by consensus and/or with the intervention of a third reviewer. Missing data will be requested from study authors. A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: - Question 1: name of the author/s, country, setting, year of protocol, the name of the study conducted, methodology, population, eligibility criteria, intervention, timelines, logistics, medical complications and issues - Question 2: name of the author/s, country, setting, year of study, methodology, population, eligibility criteria, intervention/s, results (ROSC, survival with quality of life and potential/actual deceased donors between non-survivors or survivors with a bad neurologic prognosis)

27 Risk of bias (quality) assessment

State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Internal validity of the studies will be assessed by two reviewers independently (IO-D & LH): 1. All studies reporting results will be assessed through the level of evidence scale tool used by the International Liaison Committee on Resuscitation (ILCOR). 2. All protocols and recommendations will be assessed using the Appraisal of Guidelines, Research and Evaluation, version 2, tool (AGREE II).

28 Strategy for data synthesis

Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

Statistical analysis of studies: descriptive statistics and a qualitative synthesis of studies characteristics and quality will be conducted. Tabulation of protocols: mean characteristics of each protocol and level of evidence of recommendations will be performed. Heterogeneity is anticipated because of different eligibility criteria of population and different interventions are commonly used besides ECPR strategy. Not only population but also statistical heterogeneity is anticipated, precluding to perform a MA. Therefore, there will be limited scope for meta-analysis also due to the small number of existing trials. Accordingly, the results will be discussed addressing strengths and limitations of the primary studies and level of evidence of the protocols. An evaluation of implication of the results in practice for implementing future protocols will be also conducted for informing policy makers and scientific community.

29 Analysis of subgroups or subsets

Give any planned exploration of subgroups or subsets within the review. ‘None planned’ is a valid response if no subgroup analyses are planned.

None planned (appart from the fact that we have focused on out-of hospital cardiac arrest in adult patients who suffered from a cardiac cause as underlying primary cause triggering the cardiac arrest (other extracardiac causes has been excluded)

Review general information

30 Type of review

Select the type of review from the drop down list.

Diagnostic, Epidemiologic, Intervention, Prognostic, Other

31 Language

Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.

English

Will a summary/abstract be made available in English?

Yes

32 Country

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.

Canada, Spain

33 Other registration details

Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol

Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
We will produce a synthesis of the characteristics of all included studies reporting results and protocols or recommendations. We will assess results for each study reporting the main characteristics covered by the ECPR approach and the specific elements covered for each domain. The methodological quality of studies reporting results will be assessed with the tool used by ILCOR and each recommendation or protocol will be assessed using the AGREE II instrument. This systematic review will be conducted with full methodological rigor to ensure publication in a high-impact peer-reviewed journal.

Do you intend to publish the review on completion?
Yes

36 Keywords

Give words or phrases that best describe the review. (One word per box, create a new box for each term)
RESUSCITATION

EXTRACORPOREAL RESUSCITATION

EXTRACORPOREAL LIFE SUPPORT

REFRACTORY CARDIAC ARREST

OUT OF HOSPITAL CARDIAC ARREST

DECEASED ORGAN DONATION

DONATION AFTER CIRCULATORY DEATH

UNCONTROLLED DONATION AFTER CIRCULATORY DEATH

NON HEART BEATING DONATION

CARDIAC ARREST

CARDIAC CAUSE

37 Details of any existing review of the same topic by the same authors

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status

Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information

Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.