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Review Article

Liver Transplant With Donated Graft After Controlled Cardiac Death. Current situation[☆]

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An increasing pressure on the liver transplant waiting list forces us to explore new sources, in order to expand the donor pool. One of the most interesting benevolences and with a promising potential is donation after cardiac death (DCD). Initially, this activity was developed in Spain by means of the Maastricht type II donation in the uncontrolled setting. For different reasons, donation after controlled cardiac death has been reconsidered in our country. The most outstanding circumstance involved in DCD donation is a potential ischaemic stress that could cause severe liver graft cell damage, resulting in an adverse effect on liver transplant results, in terms of complications and outcomes. The complex and particular issues related to DCD donation will be discussed in this review.

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Trasplante hepático con injerto procedente de donación después de muerte cardiocirculatoria controlada. Situación actual

R E S U M E N

La presión en lista de espera de trasplante hepático obliga a la exploración de nuevas fuentes de donación, siendo la utilización de injertos procedentes de donantes después de muerte cardiocirculatoria una de las que reúnen un potencial más prometedor e interesante. Inicialmente, este recurso ha sido utilizado en España a través de la llamada categoría II de Maastricht, previamente denominada asistolia no controlada tipo II. Diferentes motivos han conducido a reconsiderar la donación después de la llamada muerte cardiocirculatoria controlada en el territorio nacional. El fenómeno distintivo en este tipo de donación es el estrés isquémico al que se exponen los órganos del donante con sus importantes implicaciones sobre los resultados. Los aspectos particulares de esta modalidad de trasplante hepático son el objeto de este trabajo.

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Introduction

Expanding the organ donor pool is essential for liver transplantation due to the clear disproportion between candidates on the waiting list and the number of donors, which affects the chance of mortality on the waiting list.

Extended criteria grafts or donors¹ are central for the development of liver transplantation; however, there continues to be only a small proportion of donors in the country today.

Spain has the most solid experience in type II uncontrolled liver transplantation and donation after cardio-circulatory death worldwide²⁻⁶ (Table 1). This procedure comprised 0.7% of all transplant activity in 2011.⁷ This statistic contrasts with the much more extensive use of grafts via controlled donations after cardio-circulatory death in countries such as the UK and the US, where the activity of solid organ transplants performed with donors has reached 35% and 10%, respectively.⁸

The major reasons for the initial reluctance to use potential donors who were removed from life support are the ethical obstacles in the Spanish Consensus Document produced by the Spanish Transplant Groups and the National Transplant Organisation (ONT) in 1995.⁹ However, several factors have led to new assessments of this donor pool in Spain.

As discussed above, the pressure on the waiting list has increased gradually; additionally, the experiences observed in other European countries and the US have offered consistent and promising results with regard to the use of liver grafts.

Importantly, the development of Draft Law 121/000132, which regulates the rights of people at the end of their lives,¹⁰ implies a change in the legal framework that might lead to the development of controlled donations after cardio-circulatory death programmes in Spain. Finally, the ONT has actively

promoted the development of a consensus protocol to establish the basis for this type of organ donation.⁶

Thus, experiences concerning controlled donations after cardio-circulatory death have already begun. Hospital Santiago Apostol of Vitoria¹¹ is pioneering this field, and many donations have been made sporadically in different centres throughout Spain. Most of these donations have involved renal grafts for implantation, although it is expected that liver grafts will soon follow in parallel.

The first use of a liver graft obtained from a controlled donation after cardio-circulatory death in Spain occurred at the University Hospital 12 de Octubre in Madrid on May 11, 2011: a candidate on the waiting list received a successful transplant.¹²

These facts encourage us to carefully analyse the complex and interesting details of this type of donation as well as the results achieved from the use of these grafts.

Warm Ischaemia in Donors

Warm ischaemia in donors has important differences with other types of liver donation. Cardiovascular death (in Maastricht II and III categories)⁵ causes potential ischaemic stress damage, which is of paramount importance in the development of complications among liver transplantation recipients. The transition from a predominantly aerobic metabolism to an anaerobic metabolism that does not meet energy demands can cause serious damage and even cell death. Ischaemic injury to hepatocytes and bile ducts differs: Massive hepatocyte damage will cause primary graft failure immediately, thereby forcing liver re-transplantation, whereas milder degrees of damage can lead to a severe graft dysfunction in which the future viability of the organ depends on its regenerative capacity. Ischaemic injury to the bile ducts

Table 1 – Modified Maastricht Classification (ONT, Madrid 2011) for Donation After Cardio-circulatory Death.

<i>Controlled cardio-circulatory death</i>		
I	Patient dies outside of the hospital	Victims of sudden death (traumatic or not) occurring outside the hospital who are not resuscitated
II	Unsuccessful resuscitation	Patients suffering from cardiac arrest and undergoing unsuccessful resuscitation manoeuvres This category includes two subcategories: II.A. Out-of-hospital Cardiac arrest occurring in an out-of-hospital setting and served by out-of-hospital emergency services personnel who transfer the patient to the hospital with cardiac-resuscitation manoeuvres and life support II. B. Intra-hospital Cardiac arrest occurring in the hospital and witnessed by medical personnel using immediate resuscitation manoeuvres
<i>Controlled cardio-circulatory death</i>		
III	Awaiting cardiac arrest	Patients for whom life sustaining treatments are limited after reaching an agreement between the healthcare team and the family or the patient's representatives
IV	Cardiac arrest after brain-stem death	Patients who suffer cardiac arrest during or after the establishment of a brain death diagnosis but before they enter the operating room. It is likely that doctors will attempt to restore cardiac activity; however, when these measures are unsuccessful, the procedure can be modified to donation after cardio-circulatory death

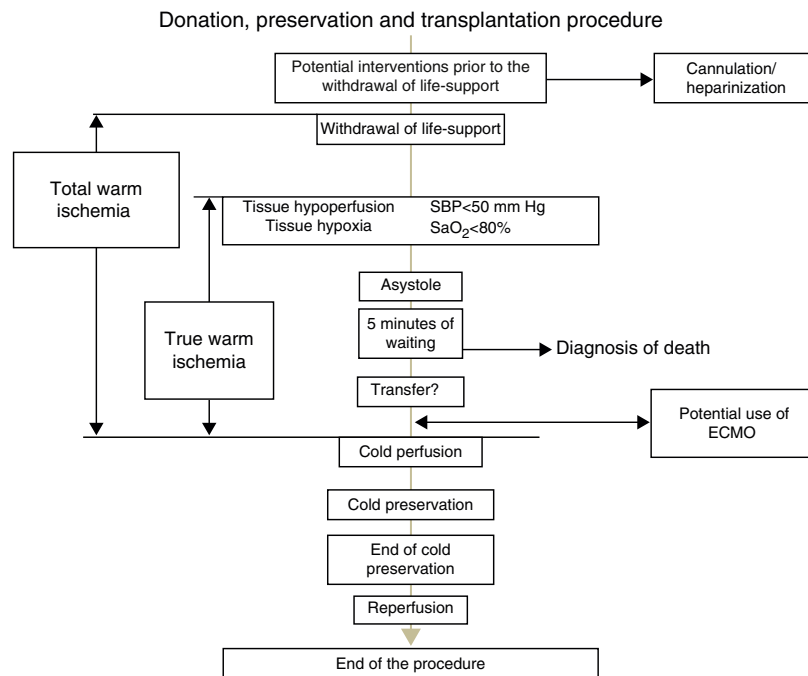


Fig. 1 – Donation, preservation, and transplant protocol for controlled donation after cardio-circulatory death.

will manifest as an inflammatory stenosing disease (also known as ischaemic cholangiopathy), and the transplanted graft viability depends on its intensity. The specific pathophysiological mechanisms involved in the onset of these complications are not well known; nevertheless, the impaired function of the Na/K pump, vascular microthrombosis,¹³ changes in bile salt metabolism,¹⁴ the overproduction of free radicals, or impaired ATP metabolism with hypoxanthine overproduction¹⁵ have all been implicated in the occurrence of these adverse events.

These findings show major differences with donations after brain death in which other systemic inflammatory response events prevail with a marked increase of inflammatory mediators and different consequences for transplant graft viability.¹⁶

The definitions of warm ischaemia times that must be accounted for in liver graft transplants from controlled donation after cardio-circulatory death and that are essential in this type of donation are included in different guides and protocols^{6,17,18} and deserve comment.

Cardio-circulatory death occurs sometime after the withdrawal of life support, and it is recommended that the liver not be used if transplantation does not occur in the first 60 min after life support is withdrawn. Fig. 1 shows the different phases of donation, preservation, and transplant protocol after controlled cardio-circulatory death. Two concepts must be considered: total ischaemia time and functional or real ischaemia time.

First, total warm ischaemia time begins by withdrawing life support measures and concludes with the start of preservation, either by cold perfusion or normothermic recirculation

using an extracorporeal membrane oxygenation (ECMO) device in the donor. However, functional warm ischaemia (also called real warm ischaemia) is more relevant and begins with the first episode of arterial desaturation (Sat PO₂ < 70%–80%), low blood pressure (SBP < 60–50 mmHg), or both observed after the withdrawal of life support. It ends with cold perfusion or ECMO administration, which limits the total warm ischaemia time. The maximum acceptable time for safe liver donation is 30 min of real or functional ischaemia; however, past reports have used slightly prolonged donor warm ischaemia times.¹⁹

In any case, it is remarkable that these warm ischaemia times include 5 min of immediate observation after asystole to certify death, the time needed to transfer the body to the operating room or surgical table (when life support is not withdrawn in the operating room), and the time needed to initiate the necessary preservation manoeuvres via cold perfusion or normothermic recirculation.

Controlled Cardio-circulatory Death and Brain Death

Liver transplant surgeons do not decide when to remove life support. This decision must be made previously and independent of the decision to donate an organ for transplantation. In this sense, certain issues with this type of donation must be taken into account.

Indiscriminate replacement or competition between donation after brain death and controlled donation after cardio-circulatory death are disturbing phenomena (as different

studies^{20,21} have discussed) that should be analysed and prevented. When performed indiscriminately, donation replacement after brain death can negatively affect liver transplantation activity, both qualitatively (i.e., transplant outcomes) and quantitatively (i.e., the number of valid organs).

In its recent document *Donation after Cardio-circulatory Death in Spain: Current Status and Recommendations*,⁶ the ONT referred to the lower overall profitability of this type of donation given the aforementioned quantitative and qualitative aspects. Furthermore, it recommended that the organ donor pool should not be considered as an alternative to donation after brain death. Rather, this approach should be considered primarily in cases in which the progression to donor brain death (patients with severe neurological diseases and catastrophic functional prognosis in most cases) cannot be predicted.

With regard to the negative quantitative aspects of this type of donation, importantly, 3.6 organs were transplanted per donor after brain death on average, and 2.1 organs were transplanted per donor after controlled cardio-circulatory death in the UK.²² However, the use of a graft from a donor after cardio-circulatory death eliminates adverse factors such as steatosis, the need for drugs, cardiac arrest prior to donation, or other events that add to the ischaemic stress of the donation process and exclude a graft that would otherwise be transplanted after brain death. The age of liver donors has increased gradually. Moreover, given that most transplant groups accept a recommended maximum safe age between 60 and 65 years for liver donors after controlled cardio-circulatory death, indiscriminate replacement would also predict a decline in the number of liver donors.

One additional and remarkable problem from controlled donation after cardio-circulatory death is derived from the high proportion of potential donors who, once life support has been withdrawn, only suffer asystole after long warm ischaemia times, which is especially critical in liver donation and which prevents the use of potential grafts. The incidence of donor cancellation for the aforementioned reasons is approximately 40% of the potential donations after cardio-circulatory death in the UK, resulting in the reduction of liver grafts.²²

Technical Aspects

The rapid technique is the most widespread surgical method used to procure these grafts, which was described in Pittsburgh in 1995.²³

This technique is performed after death is declared and is based on immediate access to the infrarenal aorta for the direct administration of a heparinised cold preservation solution. The inferior vena cava is drained, and the supraceliac aorta is clamped at the abdominal or intra-thoracic level afterwards to select the perfusion territory. At the same time, the abdominal organs are cooled externally with cold serum, and portal perfusion is also performed with heparinised solution. The *premortem* percutaneous implantation of a double balloon catheter for selecting the perfusion territory²⁴

streamlines the beginning perfusion process after death; however, it entails requesting the consent of the donor to conduct heparinisation and cannulation, and it increases the cost of the procedure.

New modifications of the procurement technique are currently being investigated.²⁵ One alternative to the rapid cold perfusion technique would be to establish a normothermic recirculation circuit²⁶ similar to those used in the most experienced centres for uncontrolled donation after cardio-circulatory death.^{3,27} The advantages of using this option are based on ischaemic preconditioning and the possibility of determining the markers of graft viability during maintenance. Currently, scientific evidence does not exist for these potential advantages, nor is there an approach to the recommended donor normothermic recirculation maintenance time. These issues are currently under investigation.

Liver Transplantation and Controlled Cardio-circulatory Death Results

This type of donation requires studying the potential complications that occur with greater prevalence in this type of transplantation. The hypoxia and hypotension related to the time elapsed between the withdrawal of life support and early preservation manoeuvres (either by cold perfusion or normothermic recirculation) likely play a decisive role in the development of these phenomena.

As with the analysis of the potential adverse events derived from using such grafts, the economic implications of this type of donation should be known. Specifically, the use of grafts from cardio-circulatory death donors has been estimated to increase the costs of liver transplantation up to 25%, even doubling the costs of retransplantation.²⁸

Complications: Graft Arterial Thrombosis, Primary Graft Failure, Ischaemic Cholangiopathy, and Hepatitis C Virus Reinfection Recurrence Profile

Although arterial thrombosis was a particularly frequent phenomenon among transplants performed with this type of graft in an initial series,²⁹ the most recent studies do not confirm these findings, and this complication appears at a frequency similar to that of conventional grafts.

Primary liver graft failure is the most common manifestation of ischaemic stress; it involves massive hepatocyte death with fulminant hepatic failure immediately after the implantation, and it requires urgent retransplantation to save the recipient's life. This complication has been reported with variable frequency, and has decreased since the initial series. Currently, it constitutes a rare complication, with appearance rates that did not reach 4% in the most recent series.³⁰⁻³³ Multiple factors are involved in the decreased frequency of this phenomenon, which is related to the surgical learning curve as well as improvements in preservation techniques and organ procurement.

Ischaemic cholangiopathy, which is characterised by the presence of hilar, intrahepatic, or both types of biliary

Table 2 – Biliary Complications, Ischaemic Cholangiopathy, and Retransplantation With Ischaemic Cholangiopathy.

Author	Year	# Transplantation after cardio-circulatory death	Biliary complication %	Ischaemic cholangiopathy %
Taner ³⁵	2012	200		12
de Oliveira ²¹	2011	152	19.7	2.5
de Vera ³⁶	2009	141	25	
Foley ³¹	2011	87	47	34
Hong ³⁷	2011	81	29	9.9
Tariciotti ¹⁹	2011	66	12.6	3
Detry ³²	2011	58		
Dubbeld ³³	2011	55		31
Chan ³⁸	2008	52		13.7
Pine ³⁹	2009	39		20.5
Skaro ⁴⁰	2009	32	22	38
Croome ⁴¹	2012	36	25	
Meurisse ⁴²	2012	30	50	33.3

Biliary and ischaemic cholangiopathy complications in a series of liver transplants using grafts from controlled donation after cardio-circulatory death.

strictures in the absence of arterial thrombosis, is another manifestation of tissue hypoperfusion or hypoxia suffered by the donor. This complication is not immediate, and it appears with varying frequency and timing unlike primary graft failure. The fact that 50% of hepatic blood flows through the bile duct system likely explains why an inflammatory response is triggered during intense transient ischaemic injury, ultimately resulting in the appearance of hilar, intrahepatic, or both types of biliary strictures, despite the patent arterial flow at diagnosis.³⁴

The prevalence of this complication was high in the first procedures that used these controlled donors; however, this phenomenon occurred less frequently in the latest series (Table 2). Specifically, the complication rate of biliary ischaemic cholangiopathy was less than 3%,²¹ even with the use of extended criteria grafts from donations after cardio-circulatory death.¹⁷

In either case, ischaemic cholangiopathy appears to be particularly associated with the use of grafts from asystolic donors, and a recent metaanalysis⁴³ confirmed that this complication occurs in 16% of cases. Thus, the risk of using these grafts is more than 10 times higher than when using grafts from brain death donors.

The risk factors associated with the occurrence of this complication have been investigated, and they include older donor age,^{31,36,38,40} high donor weight³⁸ or high donor/recipient weight ratio,⁴⁰ or longer warm³⁵ or cold ischaemia times.^{31,38,42}

Several methods have been used to control the occurrence of this problem, such as arterial pressure perfusion⁴⁴ or tissue plasminogen activation.¹³ The management of this condition also depends on its anatomic characteristics and the consequences of this phenomenon on graft function. In the case of a non-diffuse problem that does not cause significant graft dysfunction, the first approach is based on expansion via the percutaneous method of interventional radiology or endoscopic treatment, which has obtained successful responses in 30% of the cases.³¹

The implications of this complication are extremely far-reaching because it is the most frequent cause of retransplantation when using liver grafts donated after cardio-circulatory death^{28,40,45}; furthermore, most patients who suffer from ischaemic cholangiopathy will require retransplantation.^{31,35,41}

Therefore, retransplantation should be considered early given the numerous procedures that might be needed to manage this complication, its intrinsic risks, the additional costs incurred by endoscopic treatment or interventional radiology, and the low likelihood of resolving the problem.

Recipient Selection

The proper selection of a suitable recipient for a graft with these characteristics remains the subject of study and debate. Theoretically, candidates with more limited functional reserves should have more difficulties with the complications associated with the use of these grafts; therefore, most recent registry studies have shown a significant trend to implant these organs in patients with lower model of end-stage liver disease (MELD) scores or those that are in particularly compromised clinical situations.⁴⁵⁻⁵⁰ Some studies have suggested the presence of a negative effect on candidates with higher MELD scores or worse clinical conditions^{46,47,49,51}; however, this point remains under investigation. In contrast, the appropriate selection of donors and recipients has yielded satisfactory results using these liver grafts, even when transplants are conducted in patients in critical situations.⁵²

With regard to candidate selection, several adverse prognostic factors have been identified, such as the age of recipient,^{46-48,51} donated liver grafts after cardio-circulatory death used for liver retransplantation,^{47,49,51} shared organs⁴⁸ or the presence of hepatocarcinoma^{46,48} or renal failure.^{46,48,51} However, the characteristics of the optimal recipient for this type of transplant are not yet fully defined.

The high prevalence of infection with HCV and its universal recurrence after transplantation in the viremic candidate

Table 3 – Patient and Graft Survival, as Well as Retransplantation Rate, in Series of Liver Transplants Using Grafts From Controlled Donation After Cardio-circulatory Death.

Author	Year	# Transplantation after cardio-circulatory death	Recipient survival			Graft survival			Retransplantation rate %
			%	a1	3 and 5 years	%	a1	3 and 5 years	
Taner ^{35*}	2012	200	92.6	85	80.9	80.9	72.7	68.9	
de Vera ^{36*}	2009	141	79		70	69 ^a		56 ^a	18
Grewal ^{30*}	2009	108	91.5	88.1	88.1	79.3	74.5	71	14.8
Foley ^{31*}	2011	87	84 ^a	68 ^a		69 ^a	56 ^a		19
Hong ³⁷	2011	81				78	62	53	
Tariciotti ¹⁹	2011	63	88–90			82–90			
Detry ³²	2009	58	83.3	66.9		72.4	48.8		
Dubbeld ^{33*}	2011	55	85	50		74	68		18
Hernández ⁵⁵	2011	41	88			78			
Pine ^{39*}	2009	39	82.1 ^a	68.2 ^a		79.5 ^a	63.6 ^a		
Skaro ^{40*}	2009	32	74	74		61 ^a	53 ^a		22
Meurisse ^{42*}	2012	30	93	85	85	90	82	82	3
Fujita ⁵⁶	2007	24	86.8	81.7		69.1	58.6		20.8
Yamamoto ²⁹	2010	24	61.9	42.9	42.9	54.2	37.5	37.5	
Nguyen ^{57*}	2009	19	89.5		89.5	73.7		63.2	15.8
Broomhead ^{58*}	2012	16	94			75 ^a			

Graft and recipient survival in series of liver transplants using grafts from controlled donation after cardio-circulatory death.

*Comparative studies using a control group of donors with beating hearts.

^a Significance denoting less likely survival for a graft or organ recipient after cardio-circulatory death.

force us to define HCV graft reinfection as a major problem in liver transplantation. According to a recent multicentre study,⁴⁷ this phenomenon occurs among candidates undergoing liver transplantation with organs from cardio-circulatory death donors after the withdrawal of life support. Previous studies comparing the evolution of HCV-infected candidates have found worse outcomes associated with these grafts for some patients compared with recurrent HCV when the grafts are transplanted from brain death donors or cardio-circulatory death donors.⁵³ Jay et al. examined 1113 patients⁴⁸ and determined the maximum likelihood of graft loss in a case study of organ transplant from a donor after cardio-circulatory death for a candidate with HCV infection to establish a reference group for transplant patients with an

organ donated after brain death but uninfected with HCV. However, the most recent study based on the United Net of Organ Sharing (UNOS) Registry, United States (which also had a large sample size⁵⁴) concluded that transplants for HCV-positive candidates using these donors must be considered valid because significant negative effects have not been found for this population.

Recipient and Graft Survival

The characteristics of this type of transplant have promoted graft and patient survival; thus, they should be analysed. Most recent transplant studies have generally shown similar survival rates^{19,29,30,32,33,35,37,42,55–58} to those obtained using

Table 4 – Graft and Recipient Survival, as Well as Retransplantation Rate, in Series of Liver Transplants Using Grafts From Controlled Donation After Cardio-circulatory Death.

Author	Year	# Transplantation after cardio-circulatory death	Survival recipient			Graft survival			Retransplantation rate %
			%	a1	3 and 5 years	%	a1	3 and 5 years	
Harring ⁴⁶	2012	2351	84.4	74.8	68.9	75.3	63.9	56.2	
Mathur ⁴⁷	2010	1567					64.9		13.6
Jay ⁴⁸	2011	1113	82	71					14.7
Lee ⁴⁹	2006	874	82.3	75.9	65.3	72.1	61.8	38.8	
Selck ⁴⁵	2008	855				73.8	57.6		21.6 ^a
Merion ⁵⁰	2006	472				70.1	60.5		
Mateo ⁵¹	2006	367				71	60		

Graft and recipient survival in registry studies of liver transplants using grafts from controlled donation after cardio-circulatory death.

^a Included on the retransplantation list.

other organ donor pools (Table 3); however, some have shown significant disadvantages for liver transplantations using organs donated after cardio-circulatory death.^{31,36,39,40,58} Importantly, recent registry studies based on heterogeneous populations (but with consistent sample sizes; Table 4) have shown significantly lower graft survival rates^{45,50,51} and, in certain cases, poorer graft and recipient survival using transplanted organs from cardio-circulatory death donors^{46,48,49} compared with other liver donor pools.

Conclusions

The use of liver grafts from cardio-circulatory death donors provides promising results. This donor pool (which is just beginning in Spain) must be used rationally without competing with the brain death donor pool. Research on preservation techniques will most likely be helpful in the near future to control the specific complications observed in this type of liver transplantation, thereby substantially improving the results.

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Conflict of Interest

The authors declare no conflict of interest.

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