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Combined lung and liver procurement in controlled donation after circulatory death using normothermic abdominal perfusion. Initial experience in two Spanish centers

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Abstract

Combining simultaneously lung and liver procurement in controlled donation after circulatory death (cDCD) using normothermic abdominal perfusion (NRP) for abdominal grafts and cooling and rapid recovery technique (RR) for the lungs increases the complexity of the procurement procedure and might injure the grafts. A total of 19 cDCDs from two centers using this combined procedure were evaluated, and 16 liver and 21 lung transplantations were performed. As controls, 34 donors after brain death (DBDs) were included (29 liver and 41 lung transplantations were performed). Two cDCD liver recipients developed primary nonfunction (12.5%). No cases of ischemic cholangiopathy were observed among cDCD recipients. The 1-year and 2-year liver recipients survival was 87.5% and 87.5% for the cDCD group, and 96% and 84.5% for the DBD group, respectively (P = .496). The 1-year and 2-year lung recipients survival was 84% and 84% for the cDCD group and 90% and 90% for the DBD group, respectively (P = .577). This is the largest experience ever reported in cDCD with the use of NRP combined with RR of the lungs. This combined method offers an outstanding recovery rate and liver and lung recipients survival comparable with those transplanted with DBDs. Further studies are needed to confirm our findings.

KEYWORDS

clinical research/practice, donors and donation: donation after circulatory death (DCD), extracorporeal membrane oxygenation (ECMO), liver transplantation/hepatology, lung transplantation/pulmonology, organ perfusion and preservation, organ procurement and allocation

1 | INTRODUCTION

The imbalance between supply and demand in organ transplantation is a global problem affecting all organs. Controlled donation after circulatory death (cDCD) represents an important source of grafts in countries with an appropriate legal framework, accounting for 30%-40% of organ procurement activity.[1]

In cDCD, the effects of warm ischemia during the hypotensive phase following the withdrawal of life-sustaining therapy (WLST) and after circulatory arrest are further exacerbated during the later period

Abbreviations: cDCD, controlled donation after circulatory death; CIT, cold ischemic time; DBD, donation after brain death; DCD, donation after circulatory death; ECMO, extracorporeal membranous oxygenation; FWIT, functional warm ischemic time; ICU, intensive care unit; ITBL, ischemic-type biliary lesions; NRP, normothermic regional perfusion; RR, rapid recovery; WLST, withdrawal of life-sustaining therapy.

of cold ischemia. These phenomena increase the incidence of ischemic-type biliary lesions (ITBL) and graft loss in liver transplantation recipients, compared to livers obtained from donors after brain death (DBDs).[2] As a result, according to the donor risk index, cDCD status is considered an independent factor strongly associated with liver graft loss and, therefore, with the need for retransplantation or death.[3,4]

In most transplant centers, the recovery of abdominal organs in cDCD is performed using a rapid recovery (RR) technique.[5] Nevertheless, recent years have seen a growing interest in using abdominal normothermic regional perfusion (NRP) with extracorporeal membrane oxygenation (ECMO) devices to restore blood flow after death has been determined and prior to organ recovery in cDCD.[6-11] This in situ preservation strategy could restore cellular energy substrates and improve the quality of ischemically damaged organs. Furthermore, the ability to assess organ function prior to transplantation, allowing better graft selection, might lead to superior outcomes compared to classic cDCD transplantation results.[8-12] NRP also turns an urgent into an elective organ recovery procedure, which could potentially reduce organ damage and losses due to surgical events.[13] Recent studies have demonstrated that NRP improves the number and quality of livers in cDCD.[14,15]

In contrast, lung transplantation using cDCD grafts has been adopted widely worldwide, with outcomes equivalent to those transplanted through DBD. Indeed, most single- and multi-institutional experiences have been described as similarly favorable.[16-18] However, the utilization of cDCD lungs remains poor for several reasons, including less experience with cDCD procurement and inadequate lung management in the intensive care unit (ICU).[19,20]

The lungs are recovered in cDCD donors using the RR technique, decreasing the lung temperature with topical cooling as quickly as possible, whereas NRP seems to be the ideal method for liver grafts. This combined method was first described as a single case report by two United Kingdom (UK) groups.[21,22] A variant of the technique, using premortem interventions, where the risk of potential transdiaphragmatic cooling of the liver is minimized, has been proposed by our group.[10] Nevertheless, there is still some reluctance among professionals in combining the cooling and RR techniques in the lungs with NRP for abdominal grafts. This method increases the complexity of the procurement procedure and might injure the grafts because of the dual temperature (affecting the low temperature to the liver and normothermia to the lungs) or due to inadequate perfusion pressure in the pump as a result of the bleeding into the chest after the heart-lung block is removed or after clamping the vena cava. The aim of this study was to report the initial experience of the use of NRP in liver cDCD donation combined with concomitant lung recovery in two Spanish centers based on a common protocol, focusing on the complications of simultaneous recovery and its impact on liver and lung recipient outcomes.

2 | METHODS

This is a retrospective review of all actual cDCDs performed in two centers using identical procedures in which lungs and liver were simultaneously evaluated, using NRP for abdominal preservation and the RR technique for lung recovery from the start of the two programs (September 2014 and March 2015) to December 2018. As controls, we evaluated all DBD donors in which lungs and liver were simultaneously recovered.

2.1 | Donors

cDCD was considered in patients in whom the treating team had made the decision to WLST. Neurocritical patients were considered as potential cDCD donors only if the Glasgow Coma Scale score was below 5 points. No upper age limit was considered.

Functional warm ischemic time (FWIT) for abdominal grafts was defined as the time from systolic blood pressure <60 mm Hg to when NRP was started (5-minute no-touch period is included). FWIT for lungs was defined as the time from systolic blood pressure <60 mm Hg to the administration of Perfadex solution through the pulmonary artery (5-minute no-touch period is included). For FWIT, an upper time limit of 30 minutes for liver and 60 minutes for lungs was considered.[23]

The ECMO device used was a Maquet Rotaflow (Maquet, Rastatt, Germany).

In accordance with the Spanish regulatory framework, specific informed consent was obtained from the legal representatives of the potential donor for premortem interventions. These consisted of the administration of heparin (500-600 units/kg) and cannulation of the femoral vessels prior to the WLST. Cannulation of the femoral artery (FA) and femoral vein was performed open or percutaneously. An aortic occlusion balloon was placed at the contralateral groin to prevent brain and coronary perfusion during NRP.

To ensure that the thoracic aorta was blocked with the aortic occlusion balloon after determination of death, two arterial lines (one from the femoral arterial cannula and the second one from the left radial artery) were monitored in the potential cDCD donor, as published previously.[10,24]

2.2 | Lung recovery

Once death had been determined and NRP initiated, the thoracic surgeon performed a quick sternotomy. At the same time, the donor is reintubated and ventilated 5 minutes after NRP with 100% oxygen and positive end-expiratory pressure of 5 cmH_2O. The pulmonary artery is cannulated for cold flush perfusion with Perfadex (50 mL/kg). Only one liter of 4°C saline is delivered in both hemithoraxes for topical cooling. Finally, the superior vena cava is ligated to separate the thoracic and abdominal compartments. Once the lungs have been preserved with Perfadex solution, pulmonary extraction is initiated with the same technique as in the DBD donors. Thus the heart-lung block was removed, and cautious hemostasis was ensured. The azygos vein was ligated, and the thoracic cavity was checked to detect any other bleeding point to perform an adequate hemostasis. To avoid a low blood flow in the pump because of the absence of venous return from the thorax and head, 1-1.5 liters of

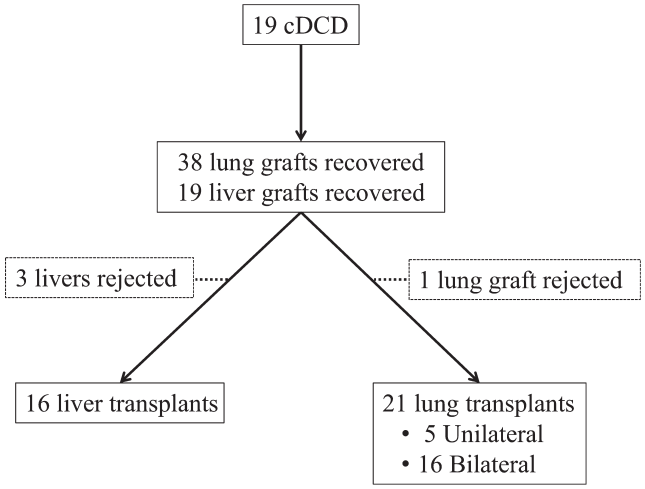


FIGURE 1 Study profile. Two liver grafts were rejected for an increasing of liver enzymes during NRP. One case was rejected for macroscopic evaluation during recovery. One left lung graft was rejected because no unilateral recipient was available

serum saline was administered to the cDCD donor just before the vena cava ligation.

2.3 | Liver recovery

Once death was declared, the thoracic aortic balloon was filled and NRP was started. The aim with abdominal NRP was to maintain a pump flow of 2-2.4 L/min.

After the thoracic surgeon had perfused the pulmonary artery with preservation solution, a laparotomy was performed to assess the quality of the abdominal grafts and a cannula was placed in the inferior mesenteric vein (IMV). After 2 hours of NRP, the ECMO device was then stopped and a rapid dual (FA and IMV) cold organ perfusion was performed.

A continuous pressure of 60-65 mm Hg in the FA cannula, temperature of 37°C, pH of 7.35-7.45, and a hematocrit >25% were targeted.

Blood samples from the ECMO device were obtained just after starting NRP and at least every 30 minutes. Biochemistry analysis, serum lactate levels, and hematocrit were analyzed. If alanine transaminase (ALT) or aspartate transaminase (AST) were more than four times the upper normal limit during NRP, the liver was discarded, even with a normal macroscopic appearance. Lactate levels were also monitored during NRP.

2.4 | Outcome data

Information was collected on organs recovered and transplanted from cDCD donors during the study period. Reasons for organ discard were also analyzed. Recipient outcome data for patients and grafts from cDCD donors were obtained from the donor center database or from those centers in which some grafts were eventually transplanted.

Primary nonfunction (PNF) for the liver was defined as immediate graft failure resulting in either emergent retransplantation or death. Early allograft dysfunction (EAD) was assessed according to both Olthoff's definition[25] and the Model for Early Allograft Function (MEAF) score.[26] The diagnosis of ITBL was made in the posttransplant period based on the presence of nonanastomotic biliary strictures, with or without prestenotic dilatations, in the presence of a patent hepatic artery.[27] Liver allocation was based on the laboratory Model for End-Stage Liver Disease (MELD) system without additional MELD exception points.

Primary graft dysfunction for the lungs was defined according to the International Society for Heart and Lung Transplantation definition.[28]

TABLE 1 Donor characteristics and technical data

	DBD (n = 34)	cDCD (n = 19)	*P*
Gender (male)	13 (38.2%)	10 (52.6%)	.311
Age (years)	62 (IQR 52-67)	54 (IQR 47-59)	.007
Cause of death			
Brain hemorrhage	18 (52.9%)	5 (26.3%)	.009
Ischemic stroke	5 (14.7%)	3 (15.8%)	
Anoxic brain injury	3 (8.8%)	7 (36.8%)	
Traumatic brain injury	4 (11.8%)	0	
ALS	0	3 (15.8%)	
Others	4 (11.8%)	1 (5.3%)	
ICU stay (days)	2 (IQR 1-4)	7 (IQR 4-9)	.0001
Withdrawal to asystole (minutes)		11 (IQR 7-14)	
WIT for liver grafts (minutes)		16 (IQR 12-19)	
FWIT for liver grafts (minutes)		12 (IQR 10-13)	
WIT for lung grafts (minutes)		38 (IQR 26-43)	
FWIT for lung grafts (minutes)		34 (IQR 24-36)	
NRP duration (minutes)		114 (IQR 58-121)	
Blood units transfused		3 (IQR 1-7)	
Liver grafts transplanted	29 (85.3%)	16 (84.2%)	.605
Lung grafts transplanted	60 (88.2%)	37 (97.4%)	.101

DBD, donation after brain death; cDCD, controlled donation after circulatory death; ALS, amyotrophic lateral sclerosis; ICU, intensive care unit; WIT, warm ischemic time; FWIT, functional warm ischemic time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Min, minute; NRP, Normothermic Regional Perfusion.

Cold ischemia time (CIT) for recipients was defined as the time from the end of abdominal NRP to liver reperfusion in the recipient. For lung recipients, CIT was defined as the time from Perfadex® administration to organ perfusion in recipients.

All transplant recipients had a minimum 1-month follow-up. The outcome for the recipients was recorded at 3 months, 1 year, and 2 years after the transplant procedures. A magnetic resonance cholangiopancreatography was performed when biliary complications were suspected based on symptoms, clinical signs, or laboratory studies. In liver recipients with a T-tube, a per-protocol cholangiogram was performed on day 7 and month 3.

2.5 | Statistical analysis

A descriptive analysis of the sample was performed. Results are presented here as absolute numbers and percentages for categorical variables, and as measures of central tendency and dispersion for continuous variables. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality of distribution of the data. Comparisons between cDCD and DBD donors and recipients were performed with the Student's *t* test or the Mann–Whitney *U* test for continuous variables according to the sample distribution. To compare categorical variables, the χ^2 test was performed. Repeated measures analysis of quantitative variables was carried out using the Friedman test.

Patient and graft survival data were studied according to the Kaplan-Meier method.

3 | RESULTS

A total of 19 cDCDs were performed (Figure 1) and 34 DBDs were included as controls. Demographic characteristics and technical features are shown in Table 1.

3.1 | Liver transplantation

A total of 19 liver grafts were assessed from the cDCD group. The median NRP time was 114 minutes (interquartile range [IQR]: 57-120 minutes). The liver enzymes remained stable during NRP, while the median lactate value decreased significantly (see Figure 2). Sixteen livers (84.2%) were finally transplanted and three (15.8%) were eventually rejected, in two cases due to rising ALT/AST levels during NRP and in one case due to suboptimal macroscopic aspect, also during NRP. In the DBD group, a total of 29 livers were finally transplanted (85.3%); 5 were rejected after macroscopic evaluation. Liver recipient demographics are presented in Table 2.

Median follow-up was 6 months (IQR: 3-18 months) for the cDCD group and 16 months (IQR: 12-20 months) for the DBD group. In the cDCD group, there were two cases of PNF (12.5%), resulting in the recipients' death, and no cases in the DBD group (*P* = .121). One patient in each group was retransplanted within the first month due to hepatic artery thrombosis (*P* = .590). The other 13 liver recipients had neither clinical nor radiological evidence of ITBL. Five cDCD recipients developed EAD (according to Olthoff's criteria), with a median MEAF score of 3.7 (IQR 3.2-4.5), suggesting a very low severity of EAD. No differences were observed in the peak of transaminases, rate of EAD, ICU, or hospital stay between groups (see Table 2).

The two cases of PNF were relatively young (36 and 57 years) with short FWIT (14 and 13 minutes) and CIT (285 and 365 minutes), comparable to the rest of the cohort. Recipients were in their 60s with a MELD score of 22 and 14.

Both cases had a shorter period of NRP for technical reasons (40 and 65 minutes, respectively) and higher profile of transaminases and lactate than the other recipients (Figure 2). Nevertheless, other grafts from the same donors were successfully transplanted: pancreas, kidneys, and lungs in the first case and lungs and kidneys in the second one.

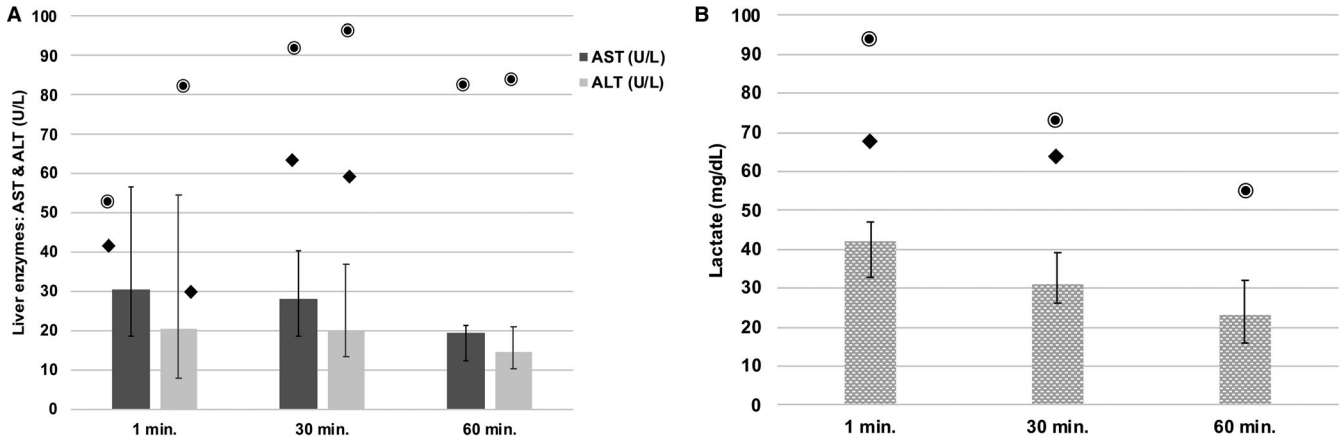


FIGURE 2 Time course of the transaminases (AST and ALT) (A) AND serum lactate (B) during NRP period. Sampled data are given as median and interquartile range. min., minute; AST, aspartate transaminase; ALT, alanine transaminase. The ◉ symbol and the ♦ symbol represent the two liver recipients who developed primary nonfunction. For AST the *P*-value was .368. For ALT the *P*-value was .567. The lactate level along the time was statistically significant (*P* < .001)

The 3-month, 1-year, and 2-year patient survival was 87.5%, 87.5%, and 87.5% for the cDCD group, and 96%, 96%, and 84.5% for the DBD group, respectively (P = .496; see Figure 3A).

We also analyzed all cDCD donors (n = 24) obtained in the same period in which only the liver was recovered; no differences were observed in PNF (P = .157) or recipient survival (P = .313). Nevertheless, the duration of NRP was longer than in liver-lungs DCD donors (120 [IQR: 117-123] vs 114 [57-120]; P = .021).

3.2 | Lung transplantation

From these 19 cDCDs a total of 21 lung recipients were transplanted (16 bilateral lung transplants [BLTs] and five unilateral lung transplants [ULTs]). One left graft was rejected because no compatible recipient was available.

A total of 41 lung transplantations were performed with DBD donors: 19 BLT and 22 ULT. A total of six lung grafts were rejected during recovery, both grafts in one DBD donor and four single grafts. The main characteristics of lung recipients are presented in Table 3. No differences were observed in the partial pressure of oxygen in arterial blood/fraction of inspired oxygen (PaO_2/FiO_2) at ICU admission, primary graft dysfunction, bronchiolitis obliterans syndrome, mechanical ventilation, or ICU stay between groups. Hospital stay was lower in cDCD recipients compared to DBDs (see Table 3).

Mean follow-up was 6 months (IQR: 4-19 months) for the cDCD group and 16 months (IQR: 11-24 months) for the DBD group.

The 3-month, 1-year, and 2-year patient survival was 90%, 84%, and 84% for the cDCD group and 90%, 90%, and 90% for the DBD group, respectively (P = .577; see Figure 3B).

4 | DISCUSSION

This is the largest experience published to date describing the simultaneous recovery of liver (using NRP) and lungs (with the RR technique) in cDCD donors. The two cDCD programs were implemented in September 2014 and March 2015, and NRP was the only procurement method in all cases. Initially, only kidneys were recovered, later livers and pancreata, and finally, in March 2015 and January 2017, lungs were also recovered. Indeed, 3 cDCD donors were obtained in 2016, 6 in 2017, and 10 in 2018. Today, both programs are fully developed, recovering kidneys, livers, pancreata, and lungs.

Although donor age is by far one of the most important factors related to the recipient's outcome in cDCD,[29] we did not make any particular selection. Indeed, our median donor age was 54, older than most published experiences in liver transplantation with cDCD[8,14,30-34] and lung transplantation.[16,18,35] Nevertheless, it is remarkable that the high recovery rates observed in our cDCD donors (97.4% lungs and 84.2% livers) with comparable outcomes to DBD recipients. No case of ITBL was observed in the cDCD liver transplant group, in accordance with recently reported studies.[11,14,15] The published ITBL incidence has been around 16% in cDCD using RR technique.[30]

TABLE 2 Liver recipients' characteristics and outcomes

	DBD (n = 29)	cDCD (n = 16)	P
Gender (male)	20 (69%)	10 (71.4%)	.472
Age (years)	60 (IQR 53-64)	60 (IQR 52-64)	.849
Indication			
Alcohol-related liver disease	13 (44.8%)	9 (56.3%)	.142
Hepatitis C cirrhosis	7 (24.1%)	5 (31.3%)	
Budd Chiari	0	1 (6.2%)	
Primary sclerosing cholangitis	1 (3.5%)	1 (6.2%)	
Others	8 (27.6%)	0(0%)	
MELD	15 (IQR: 13-18)	12 (IQR: 8-21)	.207
Cold ischemic time (minutes)	324 (113)	311 (88)	.690
Surgery time (minutes)	275 (240-325)	270 (197-312)	.277
Units of blood during surgery	2 (IQR: 1-7)	2 (IQR: 0-7)	.866
Maximum ALT (U/L)	813 (IQR 525-1511)	1287 (IQR 642-1436)	.480
Maximum AST (U/L)	706 (IQR 445-1201)	999 (IQR 481-1588)	.495
INR (at 7th day)	1.1 (IQR 1-1.3)	1.2 (IQR 1.2-1.4)	.056
Bilirubin at 7th day (mg/dL)	1.5 (IQR 1-2.1)	2.4 (IQR 1.7-4)	.049
Early allograft dysfunction	5 (17.2%)	3 (18.8%)	.600
PNF	0 (0%)	2 (12.5%)	.121
Hepatic artery thrombosis in first month	1(3.4%)	1 (6.3%)	.590
ICU stay (days)	5 (IQR 3-65)	5 (IQR 3-7)	.682
Hospital (stay)	21 (IQR 14-30	14 (IQR 13-26	.294
Early retransplant	1 (3.4%)	1 (6.3%)	.590

Abbreviations: MELD, Model for End-stage Liver Disease; PNF, Primary nonfunction; ICU, intensive care unit; ALT, alanine aminotransferase; ALT, aspartate aminotransferase; IQR, interquartile range; INR, International Normalized Ratio; Min, minute.

We were unable to find a clear reason for the PNF in both cases. Both cases occurred during our very early learning curve (third and eighth cases), and duration of NRP was lower than usual (40 and 65 minutes, respectively) because it was stopped for decreasing blood flow in the pump. We can hypothesize that the pump problems that led us to stop NRP could have caused significant ischemic damage to the liver, leading to an increase in transaminases and lactate that, although not significant, were clearly higher than that observed in the rest of the donors, as shown in Figure 2. We believe that the reduction in the NRP to below an hour seems to be the main reason for these two unfortunate cases, as a longer NRP could have allowed us to recognize more significant changes in the liver function

tests or macroscopic aspect that might have allowed us to predict graft dysfunction.

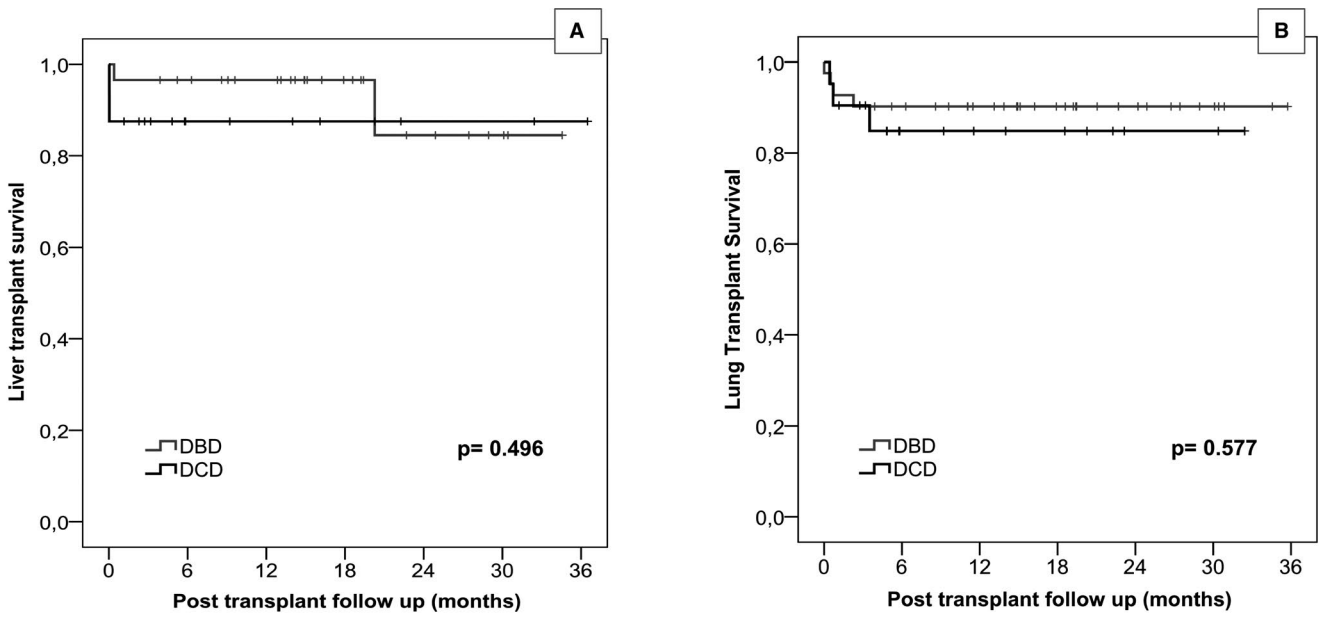
Other causes such as slight increases in biomarkers, less-than-ideal recipients with higher MELD values, or a second transplant might have increased the risk of PNF. However, this should be confirmed in larger series.

The outcomes in lung recipients were identical in the cDCD and DBD groups, and no differences were observed in primary graft dysfunction, mechanical ventilation, or ICU stay. It is highly remarkable that even with a much longer ICU stay for cDCD donors (compared to DBDs), which increases the possibility of lung damage or lung infection, a higher PaO_2/FiO_2 at ICU admission was observed in cDCD recipients. We did not make any special selection for lung recipients in the cDCD group, who were older (median 58 years) than in most of the published series, and recipient outcomes were excellent and identical to those observed in DBDs. In no case were lungs transplanted using ex vivo lung perfusion (EVLP). Our approach to EVLP is to use it always in uncontrolled DCD donors,[36] but in cDCD and DBD donors, it is used only in cases of unexpected low PaO_2 during evaluation with the presence of lung edema or uncertainty about the lung quality at retrieval.

Knowledge gained over the years has allowed experienced centers to better select grafts for cDCD liver transplantation, to the point that outcomes may be comparable to those achieved with livers arising through DBD.[37-39] However, these good results were obtained using very young cDCD donors,[30,32,37,40] with a high liver discard rate.[41]

The use of NRP to restore blood flow to the liver prior to cold storage and its benefits has been well characterized in experimental studies[42] and in several clinical experiences in Spain, the UK, and the United States US.[8-11] Two recent studies comparing liver transplantation obtained with NRP vs the RR technique demonstrated that NRP improved early allograft function, decreased ITBL and graft loss, and improved graft survival. Indeed, the multivariate analysis emphasized the potential of NRP as an independent factor for preventing ITBL.[14,15]

Unlike liver transplantation, lung transplantation using cDCD has been adopted widely worldwide, with outcomes equivalent to those transplanted through DBD. However, lungs are recovered from only 10%-20% of organ donors,[43] although several strategies such as increasing the availability of lungs from DCD,[16,17,36] better donor management,[44,45] and normothermic ex vivo lung strategies[46] have been proposed to expand the lung donor pool. Unfortunately, the utilization of cDCD lungs still remains low in most countries.[19,47] The use of NRP to preserve abdominal grafts could increase the complexity of donor management and represent a potential conflict with the current approach to cDCD lung procurement. Spain had 12.3 DCD donors per million population in 2017, with cDCD lung transplantations accounting for less than 9% of the total lung transplantations carried out.[48] Although NRP is used increasingly for cDCD donation in the US, France, the UK, and Spain, potential reasons for the low recovery of lungs include the fear of liver teams regarding the low flow in the pump during NRP after vena cava clamping, as



Number at risk	Time (months) 0	6	12	18	24	30
DBD	29	26	22	11	6	3
DCD	16	7	6	4	2	1

Number at risk	Time (months) 0	6	12	18	24	30
DBD	41	35	29	19	12	5
DCD	21	10	7	6	2	0

FIGURE 3 Kaplan-Meier survival curves for cDCD and DBD liver recipients (A). Kaplan-Meier survival curves for cDCD and DBD lung recipients (B). cDCD, controlled donation after circulatory death; DBD, donation after brain death

well as the complexity of the combined procurement procedure, which might injure the grafts because of the dual temperature by affecting the low temperature to the liver and the normothermia to the lungs.

The use of NRP in cDCD donors combined with RR of lungs was first proposed by two UK groups.[21,22] Recently, our group published a variant of this technique, adding premortem interventions to minimize FWIT and complications during recovery.[10] Our results confirm that this combined retrieval method is safe for lung grafts, and that abdominal grafts may benefit from the use of NRP as a preservation procedure. Curiously, despite the ischemia, the transaminases barely increased, and remained stable or even decreased during the NRP. This experience has already been described[11] and is probably explained by the short FWIT due to the use of premortem cannulation.

One of the complications of this combined organ procurement was the volume loss through bleeding into the chest after the heart-lung block was removed. This blood loss could decrease the pump flow in the ECMO circuit, increasing the risk for inadequate perfusion pressure for the abdominal organs. Significant volume loss occurred through the cut azygos vein, and this required careful hemostatic control. Strict monitoring during NRP is mandatory, and blood samples from the ECMO device were obtained just after starting NRP and at least every 30 minutes. Infusion of volume with cross-matched, group-specific blood and volume expanders was required in most cases. Accordingly, 1 L of serum saline was quickly infused in the ECMO circuit just before the vena cava was clamped to prevent a reduction in the pump flow.

The optimal duration of abdominal NRP in cDCD is yet to be determined. In our protocol, abdominal NRP is usually maintained for 90-120 minutes. This allows cellular energy substrates to be restored, and to carefully assess the suitability of the grafts,[12,34] mainly the liver, based on the macroscopic examination and ALT and AST levels 60 minutes after abdominal NRP. NRP permits real-time monitoring of transaminases and lactate levels while maintaining the donor with adequate blood perfusion. In our experience, lactate levels, which increase due to anaerobic metabolism during cardiac arrest,[49] were found to be decreased during NRP, reflecting the adequate organ perfusion and clearance capacity of the functioning liver. In our initial cases, liver validation was based on macroscopic evaluation, FWIT, and evolution of the

TABLE 3 Lung recipients' characteristics and outcomes

	N: 41	cDCD N: 21	*P*
Gender (male)	26 (63.4%)	13 (61.9%)	.907
Age (years)	60 (IQR 55-64)	58 (IQR 42-60)	.024
Indication			
Pulmonary fibrosis	21 (51.2%)	7 (33.3%)	.249
COPD	12 (29.3%)	8 (38.2%)	
Cystic fibrosis	3 (7.3%)	2 (9.5%)	
Pulmonary hypertension	0	2 (9.5%)	
Others	5 (12.2%)	2 (9.5%)	
Bilateral lung transplantation	19 (46.3%)	16 (76.2%)	.025
Cold ischemic time first graft (minutes)	263 (75)	293 (71)	.134
Cold ischemic time second graft (minutes)	365 (88)	283 (67)	.519
Use of ECMO during surgery	7 (17.7%)	4 (19%)	.553
Primary graft dysfunction			.328
0	31 (75.6%)	15 (71.4%)	
1	3 (7.4%)	1 (4.8%)	
2	4 (9.6%)	1 (4.8%)	
3	3 (7.4%)	4 (19%)	
PaO_2/FiO_2 at ICU admission	262 (IQR 165-337)	332 (IQR 287-337)	.032
PaO_2/FiO_2 at 24 h	308 (IQR 274-364)	342 (IQR 295-385)	.316
Mechanical ventilation (days)	1 (IQR 1-3)	2 (IQR 1-13)	.158
ICU stay	6 (IQR 4-11)	6 (IQR 4-21)	.450
Hospital stay (days)	27 (IQR 23-33)	24 (IQR 4-19)	.018
BOS	3 (7.7%)	0 (0%)	.267

Abbreviations: COPD, Chronic obstructive pulmonary disease; min, minute; H, hours; ICU, Intensive Care Unit; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation; BOS, bronchiolitis obliterans *syndrome*; PaO_2/FiO_2, partial pressure of oxygen in arterial blood/fraction of inspired oxygen.

transaminases during NRP. Although initially, lactate values were only monitored, today, we do believe that the lactate level has a role in decision making as an excellent biomarker of inadequate perfusion.

An extended withdrawal period is detrimental to the viability of grafts and prolonged FWIT is a strong indicator of poor graft survival.[2,50,51] In current practice, FWIT >30 minutes is applied as a contraindication for liver and 60 minutes for lungs in most centers,[23] but the strict upper limit of FWIT remains controversial.[52] According to the Spanish regulatory framework, premortem interventions are permitted (specific informed consent from the legal representatives of the potential donor is mandatory). Therefore, the FWIT is reduced by nearly 10-15 minutes compared to those countries where premortem interventions are not allowed. Therefore, in our view, there is no need to use copious volumes of cold saline for topical cooling of the lungs, because the FWIT for lungs is also shortened. The risk of potential trans-diaphragmatic cooling of the liver is thereby minimized, decreasing the concerns among clinicians for differences in temperature between thorax and abdomen during the recovery procedure.

There were ethical concerns about the use of abdominal NRP and premortem interventions in cDCD,[53] such as the possibility of restoring brain circulation after the declaration of death if the aortic occlusion balloon technique fails. A specific methodology to avoid restoring circulation to the brain after the determination of death when using NRP and antemortem cannulation has been described recently[10] and validated in a multicenter study.[24] This proposal avoids the aforementioned ethical concern, guaranteeing the absence of cerebral resuscitation.

This combined procedure increases logistical issues and the complexity of the whole organ procurement process, so the experience of all the individuals involved is critical in this matter. Unfortunately, it remains unclear what professional background is needed for donor management, when there are so many pitfalls and potential for errors.[54] The involvement of an experienced intensivist in the management of potential DBD donors has been shown to increase the number of transplantable organs.[55] This may also be applicable to the cDCD setting, and in particular to this combined organ procurement.

Although our results are encouraging on many accounts, such as organ recovery rate superior to those obtained with DBD donors in Spain[56] and in most of the published series for livers and lungs,[1,8,9,48] there are several limitations in our study. First, the number of cases is small, and these results need to be replicated in larger studies. Second, the rate of PNF was higher than expected, although they occurred during the very early learning curve and were probably related to technical problems with the NRP.

In summary, this is the largest experience ever reported with the use of abdominal NRP combined with RR of the lungs. This combined method offers an outstanding recovery rate, is safe for lung grafts, and liver grafts may benefit from the use of NRP as a preservation procedure. Liver and lung recipients transplanted with this combined technique had outcomes equivalent to those transplanted through DBD, although PNF was higher than desirable in the cDCD group. Further studies are needed to confirm our findings in combined liver and lung procurement procedure in this initial promising experience.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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