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## **Ex vivo perfusion of the donor heart: Preliminary experience in high-risk transplantations**

**Abbreviated title:** Ex vivo perfusion of donor heart in high-risk transplantations

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## **Summary**

*Background.* – The number of heart transplantations (HTs) has decreased in France since 2017 (–5%/year) despite a stable rate of patients referred on the waiting list. Ex vivo heart perfusion (EVHP) is an innovative approach for organ preservation, reducing graft ischaemic time and facilitating continuous organ monitoring before transplantation.

*Aim.* – To report our preliminary experience of seven donor hearts preserved with EVHP, including the first heart resuscitated after circulatory-determined death in France.

*Methods.* – Seven hearts were procured from donation after brain death (DBD) for HT or donation after circulatory-determined death (DCD) for research purposes (Protocol PFS20-004, Agence de la Biomédecine, La Plaine Saint-Denis, France). All grafts were preserved using the Organ Care System® (TransMedics Inc., Andover, MA, USA) for normothermic EVHP. Perfusion parameters were adjusted to achieve stable or decreasing arterial lactate trend consistent with suitability for organ transplantation.

*Results.* – Indications for EVHP were assessment of a marginal graft in four cases, prolonged preservation in two cases (anticipated duration for retrieval of recipient's heart > 3 hours) and resuscitation after circulatory-determined death in one case. Median duration of EVHP was 270 (interquartile range 216–343) minutes. five were transplanted, with a median ex situ preservation time (ischaemic time + EVHP time) of 334 (interquartile range 326–444) minutes. The two other grafts were discarded for HT. Three recipients had extracorporeal life support after HT, and presented complete cardiac recovery within a week after HT. One patient died at day 11 because of septic shock. The 3-month survival rate was 75% among recipients. Three months after HT, the left ejection fraction was > 60% in all cases.

*Conclusions.* – EVHP enabled safe prolonged preservation and assessment of marginal grafts. This approach provides an opportunity to expand the donor pool by resuscitating grafts from donors with extended criteria, including controlled DCD.

## **Résumé**

*Contexte.* – Le nombre de transplantations cardiaques (TC) décroît en France depuis 2017 (–5 % par an), malgré un nombre stable de patients inscrits sur liste d'attente. La perfusion cardiaque ex-vivo (PCEV) est

une approche innovante permettant de réduire la durée d'ischémie tout en assurant un monitoring continu du greffon.

*Objectif.* – Nous rapportons notre expérience préliminaire de greffons cardiaques préservés par PCEV, dont le premier greffon ressuscité après décès par arrêt circulatoire contrôlé (DACC) en France.

*Méthodes.* – Sept greffons ont été prélevés sur donneurs en état de mort encéphalique (EME), ou donneur DACC (Protocole PFS20-004, Agence de la Biomédecine, La Plaine Saint-Denis, France). Tous les greffons ont été préservés par l'Organ Care System® (Transmedics Inc., Andover, MA, USA), seule machine transportable pour PCEV en normothermie. L'évolution du lactate artériel était le reflet de la viabilité du greffon en vue d'une HT.

*Résultats.* – La PCEV a été réalisée pour 4 cas de greffons marginaux, 2 cas de préservation prolongée d'organe, et 1 cas de ressuscitation après DACC. La durée médiane de PCEV était de 270 (interquartile : 216–343) minutes. Cinq greffons furent transplantés, avec une durée médiane de préservation (ischémie + PCEV) de 334 (interquartile : 326–444) minutes. Deux greffons ne furent pas transplantés : 1 greffon EME ayant une évolution métabolique défavorable durant la PCEV ; et 1 greffon dont la transplantation n'était pas autorisée (DACC) mais dont l'évolution métabolique était favorable. Trois patients ont eu une assistance circulatoire post-transplantation, avec une récupération de la fonction myocardique complète après 24 heures. Un patient est décédé au 11<sup>e</sup> jour de choc hémorragique réfractaire après la TC. La survie à 3 mois était de 75 % chez les receveurs. Aucun rejet aigu n'est survenu dans les 90 jours après TC et la fonction ventriculaire gauche était > 60 % chez tous les patients.

*Conclusions.* – La PCEV permet une préservation d'organe prolongée et un accès aux greffons marginaux, dont ceux issus de donneurs DACC.

## **KEYWORDS**

Heart transplantation;

Ex vivo heart perfusion;

Controlled donation after circulatory-determined death

## **MOTS CLÉS**

Transplantation cardiaque ;

Perfusion myocardique ex-vivo ;

Donneur décédé d'arrêt circulatoire contrôlé

*Abbreviations:* DBD, donation after brain death; DCD, donation after circulatory-determined death; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; EVHP, ex vivo heart perfusion; HT, heart transplantation; MCS, mechanical circulatory support; OCS, Organ Care System®.

## **Background**

Heart transplantation (HT) is the treatment of choice for patients with advanced heart failure, despite improvements in long-term mechanical circulatory support (MCS). However the disparity between organ supply and the demand for HT has resulted in the growing acceptance of donor hearts with expanded criteria [1]. Indeed the average donor age is now > 50 years in France [2]. Moreover, an increasing percentage of patients with previous cardiac surgeries are being referred for HT, including those with a history of congenital heart disease or with durable MCS. As a consequence, the rate of primary graft failure after HT is high – up to 40% in France [2].

Among the solutions to improve outcomes after HT, ex vivo heart perfusion (EVHP) was initially applied to extend the duration of organ preservation beyond the critical 4-hour period usually allowed with static cold storage [3]. This technology also provides real-time monitoring of organ viability along with continuous metabolic profiling to consider suitability for transplantation. EVHP is particularly valuable in situations where there is a high risk of primary graft failure, such as when the donor heart has extended criteria (cardiovascular co-morbidities, advanced age, left ventricular dysfunction or hypertrophy) or when the HT candidate has undergone several previous open-heart surgeries.

Donation after circulatory-determined death (DCD) represents a promising approach to increase the chance of HT, as shown by favourable early outcomes in the UK and Australia, considering more than 100 HTs since 2015 [4, 5]. DCD hearts may be exposed to myocardial damage secondary to prolonged warm ischaemia after withdrawal of life-sustaining therapies. EVHP is therefore applied for resuscitation and assessment of DCD cardiac allografts before transplantation.

DCD HT is currently not allowed in France. We therefore initiated a clinical programme of EVHP in our institution, along with a research protocol approved by the national transplant regulatory agency (Agence de la Biomédecine, La Plaine Saint-Denis, France) for the scientific assessment of five DCD cardiac allografts (Protocol PFS20-004). Here we report our preliminary clinical experience of six EVHP procedures, including the first donor heart resuscitated after circulatory-determined death.

## **Methods**

The present case series is descriptive. Quantitative variables are reported as median (interquartile range) in the text, and continuous variables for each EVHP run are reported as mean  $\pm$  standard deviation in [Table 1](#). Donor hearts were retrieved from donation after brain death (DBD) in six cases, and from DCD in one case. Donor characteristics are detailed in [Table 1](#) and [Table A.1](#). DCD heart procurement was approved for scientific purpose by the national regulatory agency for organ transplantation (Agence de la Biomédecine, La Plaine Saint-Denis, France, Protocol PFS20-004). Inclusion and exclusion criteria are listed in [Table 2](#).

## **DBD**

Assessment of biventricular function was performed by echocardiography before procurement. Evidence of any valvular disease was investigated, especially the presence of aortic regurgitation  $\geq$  grade 2. A coronary angiogram was recommended in case of donor age  $> 55$  years (or  $> 45$  years with cardiovascular co-morbidities). After median sternotomy, visual examination of the heart was performed. After injection of heparin (3 mg/kg), blood collection (1200–1500 mL) was obtained after cannulation of the right atrium to prime the circuit of the ex vivo perfusion machine. Diastolic cardiac arrest was achieved using an ice-cold hyperkalaemic crystalloid cardioplegia solution (1000 mL; Plegisol®; Pfizer, Paris, France). The heart was explanted conventionally, and a patent foramen ovale was closed systematically when present. The aorta and pulmonary artery were instrumented using dedicated cannulas for EVHP (Organ Care System® [OCS]; TransMedics Inc., Andover, MA, USA). The collected blood was added in the ex vivo perfusion module after leucocyte filtering, and was mixed with a priming solution containing electrolytes, dextro-insulin, mannitol, vitamins and steroids ([Appendix A](#)).

## **DCD**

The family agreed on end-of-life care and consented to organ donation. Packed red blood cells were procured from the Etablissement Français du Sang (research protocol 20/EFS/027) for priming of the OCS circuit ([Appendix B](#)). The heart was retrieved in accordance with the research protocol approved by the Agence de la Biomédecine (PFS20-004). Two 6-French sheaths were introduced in the right femoral vessels under echocardiographic guidance. Withdrawal of life-sustaining therapy occurred in the operating

room. Consistent with the French DCD protocol, heparin ( $3 \text{ mg.kg}^{-1}$ ) was administered when systolic blood pressure was  $< 60 \text{ mmHg}$  [6]. Functional warm ischaemia of the heart was considered when mean blood pressure was  $< 45 \text{ mmHg}$ . Five minutes after mechanical asystole, death was confirmed, and a sternotomy was performed. In the meantime, normothermic regional perfusion of the abdominal organs was initiated after percutaneous cannulation of the femoral vessels. An intra-aortic balloon was inflated in the descending thoracic aorta under fluoroscopic guidance, to avoid brain perfusion. The superior and inferior vena cava were controlled, and an aortic cross clamp was applied to isolate the heart. Ice-cold crystalloid cardioplegia was then delivered, and the donor heart was retrieved and instrumented for EVHP.

## **EVHP**

We used the OCS transportable ex vivo perfusion machine. Every EVHP run involved two cardiac surgeons and one intensivist. The OCS technology provided warm ( $34 \text{ }^{\circ}\text{C}$ ), oxygenated and nutrient-enriched ex vivo perfusion for the isolated heart. The EVHP protocol has been reported previously and is summarized in [Appendix A](#) [3]. Metabolic monitoring was performed during EVHP by regular measurement of arterial and venous lactate concentrations using an automated i-STAT® analyser (Abbott, Princeton, NJ, USA). A favourable EVHP was achieved when stable or decreasing trend for arterial lactate was observed, along with venous lactate concentration lower than arterial lactate concentration, consistent with myocardial lactate extraction.

## **Ex situ coronary angiography**

The C-arm had to be accommodated to turn around the OCS, which was elevated on a box to ensure an adequate stand ([Fig. 1](#)). A 5-French sheath was inserted on the arterial line of the OCS for introduction of diagnostic catheters into the aortic root, using a 0.035-inch guide wire. A high osmolality contrast agent was used (Omnipaque™; GE Healthcare AS, Cork, Ireland). The catheterization of the coronary arteries was unusual, especially for the left main coronary artery. The positions of the coronary ostia were inverted on the OCS, with the left ventricle facing the operator. A 5-French left Amplatz catheter was used to intubate the coronary ostia. Coronary angiogram images were obtained by rotating the C-arm by  $90^{\circ}$  to a horizontal beam orientation.



## Recipients

All the recipients included in the transplantation programme of Marie Lannelongue Hospital (University of Paris Saclay, Le Plessis Robinson, France) presented with end-stage cardiomyopathy. The study design was approved by our institutional review board, and informed consent was procured for each patient before HT. Complete diastolic arrest of the donor heart was obtained after cooling and EVHP discontinuation, combined with administration of a cold crystalloid cardioplegia (1000 mL; Plegisol®). The aortic and pulmonary cannulas were removed, and the donor heart was implanted using the bicaval technique [7]. An immunosuppressive strategy was initiated as described previously [7, 8].

## Results

### General EVHP data

Between October 2019 and February 2021, six donor hearts were preserved using the OCS machine. Characteristics of the recipients and donors, along with clinical outcomes, are summarized in [Table 1](#) and [Table A.1](#). Median duration of EVHP was 270 (interquartile range 216–343) minutes. Total ischaemic time included the cardiac ischaemic time from organ retrieval to reperfusion on the OCS, combined with the period between EVHP discontinuation and reperfusion of the donor heart in the recipient. Of note, the first and sixth donor hearts were not transplanted, and were not exposed to the second period of ischaemia. Median total ischaemic time was 116 (interquartile range 30–130) minutes and median overall duration of outside-the-body preservation was 334 (interquartile range 326–444) minutes for the transplanted donor hearts.

### OCS run 1

The donor experienced prolonged hypoxaemia and low flow period. EVHP was performed to assess the viability of the donor heart before transplantation. Over a 296-minute period of EVHP, the arterial lactate concentration continuously increased, despite optimization of the perfusion parameters ([Fig. 2](#)).

Consistent with this impaired metabolic profile, the graft was discarded for transplantation. Pathological

analysis of the donor heart showed no myocardial cell injury. The recipient underwent successful HT three weeks later with a donor heart preserved after static cold storage.

## **OCS run 2**

The donor presented with multiple cardiovascular co-morbidities. Coronary angiography was not performed before organ procurement despite a high risk of coronary artery disease in this patient (58-year-old male, high blood pressure, diabetes mellitus). EVHP was therefore considered for ex situ evaluation, including coronary angiography before HT. The coronary angiogram did not show any significant proximal lesion on the main coronary vessels (Fig. 1). A marked myocardial oedema progressively appeared during EVHP, despite a stable, but not decreasing, trend of arterial lactate (Fig. 2). A primary graft failure complicated the HT, requiring extracorporeal life support (ECLS). Myocardial recovery was effective at day 1 after HT, with a left ventricular ejection fraction of 45–50%. However, the recipient developed acute respiratory distress syndrome secondary to ventilator-associated pneumonia, requiring extracorporeal membrane oxygenation (ECMO) support. Subsequently, the patient presented with massive thrombosis of the oxygenator membrane, leading to urgent exchange of the ECMO circuit at day 6. The patient died from septic shock at day 11.

## **OCS run 3**

The donor heart was placed on the EVHP machine for evaluation and optimal reperfusion because urgent HT in a recipient under ECLS was considered to be at high risk of primary graft failure; indeed, she presented a segmental pulmonary embolism related to heparin-induced thrombocytopenia under ECLS. Pulmonary resistances were assessed under ECLS, and were considered as unreliable, with the risk of minimizing them. The lactate trend was favourable over the EVHP period, enabling transplantation (Fig. 2). ECLS was maintained, despite acceptable initial myocardial function, in case of postoperative refractory cardiogenic shock in this patient with complex vascular accesses (severe obesity), and was removed at day 2 after HT, with normal cardiac allograft function. The recipient presented successive multiple pulmonary and left groin infections, with recurrent mediastinal infections that needed surgical revisions; she was discharged home at day 94 after a rehabilitation programme.

## **OCS run 4**

The donor heart was placed on OCS for prolonged preservation because of an anticipated duration of > 3 hours for surgical approach and excision of the recipient's heart. EVHP was uneventful, with a favourable lactate trend. HT was performed, associated with moderate allograft dysfunction requiring epinephrine infusion (1 mg.h<sup>-1</sup>). The recipient developed early ventilation-related pneumonia complicated with severe general sepsis and mediastinitis requiring surgical revision at postoperative day 12. Tracheotomy was considered after unsuccessful weaning from mechanical ventilation. The patient was discharged from hospital 7 months after HT; he still presented minor respiratory disorders but was able to return home with a homecare programme and respiratory rehabilitation.

## **OCS run 5**

The donor heart was placed on OCS for prolonged preservation because of the complex surgical approach in the recipient's chest, at risk of extended graft ischaemia. Favourable decreasing lactate trend was observed during EVHP (Fig. 2). The course after HT was uneventful, and the patient was discharged at day 23 with normal biventricular function.

## **OCS run 6**

The OCS run was performed in the setting of a preclinical study investigating the metabolomic profiling of DCD hearts (PFS20-004). End-of-life of the donor was decided collegially, and consent for organ donation was obtained in accordance with the national protocol for controlled DCD (Agence de la Biomédecine, La Plaine Saint-Denis, France). Timeline events and metabolic profile of the graft during EVHP are reported in Fig. 3. The total ischaemic time was 61 minutes, including 29 minutes of functional warm ischaemic time during the agonal period (from mean blood pressure < 45 mmHg to cardioplegia infusion) and 32 minutes for donor heart retrieval and instrumentation (from cardioplegia flush to initiation of EVHP). Perfusate and myocardial samples were collected every 30 minutes, and frozen for metabolomic analysis. EVHP was maintained for 250 minutes with favourable lactate trend, consistent with suitability for transplantation (Fig. 3).

## OCS run 7

The donor heart was instrumented on OCS for prolonged preservation (time of transit > 3 hours) and for assessment of viability of this marginal graft (age of the donor, high blood pressure, spontaneous vertebral artery dissection, recent coronavirus disease 2019 [COVID-19]). The EVHP period was uneventful, with a stable lactate trend and effective myocardial consumption of lactate (Fig. 2). The recipient was a 55-year-old male who presented an end-stage dilated cardiomyopathy with normal coronary arteries, requiring 14 days before peripheral ECLS for circulatory arrest related to a refractory rhythmic storm. ECLS was continued after HT to prevent primary graft failure of the marginal graft, which was perfused for more than 530 minutes with the OCS machine. ECLS was retrieved at day 4 after HT. No other postoperative event occurred, and the recipient was discharged from hospital at day 41, with a left ventricular ejection fraction of 60%.

## Discussion

Normothermic ex-vivo heart perfusion with OCS was first described in 2008 [9, 10]. This new method of heart preservation for HT experienced initial difficulty in settling into the current practices of the different HT teams, because of economic aspects and the risk of loss of the cardiac graft related to malfunction of the machine. However, the safety and efficacy of this technique was demonstrated progressively, allowing it to spread to other HT teams, and opened access to the DCD cardiac allograft [11]. Currently, more than 1100 HTs have been performed worldwide using the OCS for brainstem-dead donors with or without extended criteria and DCD donors (Table 3). Here, we report our preliminary experience of six donor hearts preserved using EVHP. Four donor hearts were transplanted and three patients were alive at 3 months after HT. The indications for EVHP were threefold: (1) evaluation of marginal grafts before transplantation acceptance; (2) extended ex situ preservation of the graft in the setting of complex surgical procedure in the recipient; and (3) resuscitation of the heart after controlled circulatory-determined death. All donor hearts shared a suitable metabolic profile during EVHP, except one that was discarded for transplantation. Lactate trend during EVHP was the only biomarker of organ viability, despite the correlation between lactate extraction and early outcomes after transplantation not having been validated

to date. We considered these preliminary results as encouraging, as our donor hearts shared extended criteria for transplantation. Our findings are consistent with the EXPAND trial, reporting 81% of transplantation acceptance for reperfused hearts from donors with extended criteria [12]. The favourable early outcomes of this North American study should, however, be interpreted with caution, as only 13% of donors were aged > 55 years, whereas the median donor age is currently > 50 years in France [2].

The average duration of ex situ preservation of the transplanted hearts was > 5 hours (350 minutes) in our series, much longer than the 4-hour period usually allowed with static cold storage. The OCS technology allows EVHP for up to 10 hours, initially validated for an anticipated transportation time of > 4 hours [13]. We observed that OCS technology was associated with favourable early outcomes, except in one case requiring prolonged ECLS for primary graft failure. Two patients presented with mediastinitis after HT; the relationship with OCS preservation is questionable, although both patients shared independent risk factors for postoperative mediastinitis (obesity, diabetes, prolonged mechanical ventilation, tracheostomy). This concern has not been raised to date by other groups, and our results in high-risk recipients (ECLS, durable MCS, marked deformation of the chest wall combined with previous sternotomy) are in accordance with previous reports, underscoring the benefits of EVHP for complex surgical procedures [14-18]. Nevertheless, the OCS machine could not be considered as an ex vivo myocardial rehabilitation machine, based solely on the evaluation of the plasmatic lactate concentration in the perfusate and its myocardial extraction, with a beating heart in a non-working state, and without haemodynamic performance assessment. In the setting of preoperative ECLS, the OCS machine could be used to assess myocardial viability and to extend the preservation period, in selected patients. This dynamic perfusion approach would decrease the risk of primary graft failure, especially when the expected duration for excision of the recipient's failing heart is > 3 hours. The overall graft ischaemic time, including organ retrieval and transplantation, is usually < 120 minutes with the OCS technology, as previously reported, without evidence of adverse outcomes related to iterative ischaemia/reperfusion sequences [3].

Assessment of coronary artery disease is commonly recommended for high-risk cardiac donors. However coronary angiography is not always available in organ procurement centres. This is a major concern, as potentially eligible donor hearts with cardiovascular co-morbidities are frequently declined [19]. The first ex situ coronary angiogram of a beating heart on OCS was performed in 2014, revealing

significant triple vessel disease [20]. More recently, two cases of successful ex situ coronary angiography on DCD hearts during EVHP have been reported [21]. Minor coronary artery disease was remarkable and allowed for organ transplantation. We also report in the present series the feasibility of a coronary angiogram on the OCS, leading to transplantation acceptance of a marginal graft. However, a major myocardial oedema was observed at the end of EVHP, and led to mechanical asystole for 120 minutes after transplant. Although this primary graft failure completely recovered within 24 hours, we were concerned by prolonged exposition to iodinated contrast medium, which may result in deleterious myocardial oedema and impaired allograft function; this is why we used a high osmolality contrast agent to reduce the risk of myocardial oedema. However, the distribution of the contrast medium on the OCS circuit and its clearance are unknown. Finally, the biological effects of ionizing radiation on an isolated organ have been poorly investigated, and may induce early endothelial cell dysfunction, apoptosis and microthrombus formation [22, 23]. Further studies are needed to investigate whether a dose-dependent effect, along with the patient's age and co-morbidities, may influence cardiac radiosensitivity during EVHP.

Recent attention has been drawn to the favourable outcomes of 102 HTs from DCD hearts in Australia and the UK [4, 5]. One-year survival rates were similar for DBD transplantations in these series (95% in Australia and 91% in UK). Messer et al. even reported their 5-year experience using the OCS comparing two different protocols for DCD heart procurement: either direct procurement with rapid sternotomy and in situ cardioplegic flush before retrieval and EVHP; or in situ resuscitation using thoracoabdominal normothermic regional perfusion, allowing for haemodynamic and echocardiographic assessment before organ retrieval [5]. In accordance with the national protocol for DCD organ procurement, only a direct procurement approach for DCD heart retrieval could be considered in France [6]. Ex situ resuscitation of the donor heart combined with continuous monitoring during EVHP is therefore mandatory, to ensure that warm ischaemia following withdrawal of life-sustaining therapy does not impair myocardial viability. The EVHP programme at Marie Lannelongue Hospital began in 2019, and we progressively improved the management of the isolated beating heart during EVHP, first in a piglet model (protocol APAFiS#23716-2020012112432923v1) and then with DBD donor hearts [24]. Our first successful DCD heart resuscitation with favourable metabolic profile during EVHP is a significant step forward the initiation of a DCD HT programme in France. This preliminary experience with the OCS

machine should be carefully considered, and requires more patients to be transplanted with cardiac grafts preserved on OCS and compared with those who have received grafts preserved with static cold storage, to better assess the real effectiveness of this device in our centre. A concern remains considering the overall cost of the OCS, which is currently not reimbursed in France (€45,000 per transplantation). Moreover, two cardiac surgeons and one intensivist are usually required for EVHP. These human resources are more important compared with conventional organ procurement with static cold storage. Charity funding allowed us to start this costly programme, which could not be assumed by our institution. This life-saving therapy is promising to safely expand the donor pool, and to include DCD donor hearts, a major hope for patients waiting for HT in France.

## **Conclusions**

Our preliminary experience of EVHP using the OCS platform from TransMedics for donor hearts allowed for prolonged allograft preservation along with continuous ex vivo monitoring. The first successful resuscitation of a DCD donor heart provides new hope for patients awaiting HT in France.

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## **Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this manuscript.



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## Figure legends

**Figure 1.** Coronary angiogram performed on the Organ Care System® machine. A. Ex vivo perfusion machine setup in the catheterization room. B. The perfusion machine was placed on a support to obtain a coronary angiogram of the three main vessels. C. Coronary angiogram of the left anterior descending artery (LAD) and the circumflex artery (Cx). D. Coronary angiogram of the right coronary artery (RCA).

**Figure 2.** Lactate trend during EVHP with Organ Care System® (OCS). The heart graft from the first run with OCS showed an unfavourable trend of lactate during EVHP, and was therefore discarded for transplantation. The others lactate trends were favourable, with a decreasing or stable lactate trend and myocardial consumption of lactate (venous lactate < arterial lactate).

**Figure 3.** Timeline events and lactate trend related to heart donation and resuscitation after circulatory-determined death. BP: blood pressure; EVHP: ex vivo heart perfusion; NRP: normothermic regional perfusion; OCS: Organ Care System®.

**Figure A.1.** Surgical instrumentation of the cardiac allograft for ex vivo heart perfusion.

**Table 1** Donor, recipient and ex vivo heart perfusion characteristics, organ transportation and outcomes.

	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7
Donor characteristics							
Sex	Female	Male	Female	Male	Male	Female	Male
Age (years)	16	58	57	38	56	37	62
Weight (kg)	60	106	60	85	98	69	78.2
Height (cm)	167	174	165	185	180	163	168
BMI (kg/m <sup>2</sup> )	21.5	35.0	22.0	24.8	30.2	25.9	27.7
Cause of death	Cerebral anoxia	Haemorrhagic stroke	Cerebral anoxia	Haemorrhagic stroke	Ischaemic stroke	Haemorrhagic stroke	Ischaemic stroke
No flow/low flow (minutes)	0/35	0/0	60/20	0/0	0/0	0/0	0/5
LVEF (%)	50	60	55	69	65	60	65
LV hypokinesia	Global	None	None	None	None	None	None
Available coronary angiogram	No	No	No	No	Yes	No	No
Recipient characteristics							
Sex	Male	Male	Female	Male	Male	-	Male
Age (years)	16	57	43	51	60	-	55
Weight (kg)	55	115	93	72	77	-	82
Height (cm)	157	183	155	169	174	-	175
BMI (kg/m <sup>2</sup> )	22.3	34.3	38.7	25.2	25.3	-	26.7
Cause of end-stage cardiac disease	Dilated	Dilated	Anterolateral	End-stage	MI	-	Dilated

	cardiomyopathy	cardiomyopathy	MI	valvular HF (Marfan)			cardiomyopathy
Time on waiting list (days)	18	286	2	126	59	-	4
Previous cardiac surgery ( <i>n</i> )	No	No	No	Yes (3)	Yes (1)	-	No
LVAD before transplantation	No	No	No	No	Yes	-	No
ECLS before transplantation	No	No	Yes	No	No	-	Yes
Systolic PAP (mmHg)	-	46	27 <sup>a</sup>	51	30 <sup>b</sup>	-	-
Diastolic PAP (mmHg)	-	24	15 <sup>a</sup>	16	13 <sup>b</sup>	-	-
Mean PAP (mmHg)	44	30	20 <sup>a</sup>	29	19 <sup>b</sup>	-	-
Cardiac output (L/min)	3.0	4.9	3.4 <sup>a</sup>	3.5	5.1 <sup>b</sup>	-	-
Cardiac index (L/min/m <sup>2</sup> )	1.9	1.9	1.6 <sup>a</sup>	1.88	2.6 <sup>b</sup>	-	-
PVR (Wood units)	2.8	2.0	3.4 <sup>a</sup>	3.1	1.4 <sup>b</sup>	-	-
Organ transportation							
Mode	Car	Car	Car	Aeroplane	Car	Car	Aeroplane
Duration (minutes)	208	41	175	221	189	150	273
Ex-vivo perfusion characteristics							
Indication for EVHP	Marginal	Marginal	Marginal	Prolonged	Prolonged	DCD	Marginal
	allograft	allograft	allograft	preservation	preservation		allograft
Instrumentation of heart on OCS (minutes)	30	32	28	27	29	27	27
Mean aortic pressure (mmHg)	80.0 ± 5.7	80.6 ± 7.9	75.3 ± 3.9	81.4 ± 7.5	85.3 ± 4.7	82.9 ± 5.7	91.8 ± 6.2
Mean coronary blood flow (mL/min)	0.78 ± 0.05	0.84 ± 0.08	0.74 ± 0.04	0.74 ± 0.05	0.79 ± 0.06	0.69 ± 0.09	0.79 ± 0.05

Mean lactate concentration (mg/L)	3.54 ± 1.41	4.85 ± 0.16	3.42 ± 0.75	3.57 ± 0.78	2.69 ± 0.55	3.75 ± 0.51	3.40 ± 0.62
Total cold ischaemic time (minutes)	30	130	133	113	118	27	116
Duration of EVHP (minutes)	296	314	198	254	216	270	343
Total out-of-body preservation time (minutes)	326	444	331	367	334	297	459
Transplantation of the cardiac graft	No <sup>c</sup>	Yes <sup>d</sup>	Yes	Yes	Yes	No <sup>e</sup>	Yes
<b>Outcomes</b>							
ICU length of stay (days)	-	11	50	95	4	-	51
Postoperative ECLS (days)	-	Yes (11)	Yes (2)	No	No	-	Yes (1)
30-day mortality	-	Yes	No	No	No	-	No
LVEF at 1 week (%)	-	-	65	65	65	-	60
AKI requiring RRT (days)	-	Yes (11)	No	No	No	-	No
Death during follow-up	-	-	No	No	No	-	No
ACR during follow-up	-	-	No	No	No	-	No
Time of follow-up (days)	-	-	220	98	61	-	41

Continuous variables are expressed as mean ± standard deviation. ACR: acute cellular rejection; AKI: acute kidney injury; BMI: body mass index; DCD: donation after circulatory-determined death; ECLS: extracorporeal life support; EVHP: ex vivo heart perfusion; HF: heart failure; ICU: intensive care unit; LV: left ventricular; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MI: myocardial infarction; OCS: Organ Care System®; PAP: pulmonary artery pressure; PVR : pulmonary vascular resistance; RRT: renal replacement therapy.

<sup>a</sup> Haemodynamic investigations were performed under ECLS with a Swan-Ganz catheter in the ICU.

<sup>b</sup> Haemodynamic investigations were performed after LVAD implantation.

<sup>c</sup> The first cardiac allograft transported with the OCS was not transplanted because of unfavourable trend of lactate concentration in the perfusate during EVHP.

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<sup>d</sup>The second recipient died at day 11 after heart transplantation, as a result of refractory septic shock and haemorrhagic shock, under extracorporeal membrane oxygenation.

<sup>e</sup>This cardiac allograft was retrieved from a DCD donor involved in a research protocol (PFS20-004, Agence de la Biomédecine, La Plaine Saint-Denis, France); the heart graft was not transplanted, according to the research protocol.



**Table 2** Criteria for heart procurement for donation after circulatory-determined death.

Inclusion criteria	Exclusion criteria
No prospect of recovery despite optimal medical treatment	Medical history of coronary artery disease, congenital heart disease or open heart surgery
Family and intensivists agreement on end of life	Aortic valve regurgitation $\geq$ grade 2 <sup>a</sup>
Family consent to organ donation after circulatory-determined death	Recent cardiopulmonary resuscitation with low flow > 40 minutes
Eligibility for lung donation after circulatory-determined death	Cardiogenic shock requiring continuous inotropic support, including either epinephrine, dobutamine, IABP or ECLS
Donor age ranging from 18 to 55 years	Norepinephrine > 2 mg/h
LVEF > 50% and interventricular septum $\leq$ 15 mm	

ECLS: extracorporeal life support; IABP: intra-aortic balloon pump; LVEF: left ventricular ejection fraction.

<sup>a</sup>Mild-to-severe aortic regurgitation is a contraindication for ex vivo heart perfusion because impaired myocardial preservation is expected as a result of coronary malperfusion.

**Table 3** Worldwide experience of normothermic ex vivo heart perfusion with the Organ Care System®.

	DBD	DCD	Total
Worldwide	821	333	1154
Europe	626	199	825
France <sup>a,b</sup>	25	-	25

DBD: donation after brain death; DCD: donation after circulatory-determined death.

<sup>a</sup> In France, heart transplantation from DCD donors is not allowed.

<sup>b</sup> In France, four heart transplantations using the Organ Care System machine were performed in Pitié Salpêtrière University Hospital, five in Marie Lannelongue Hospital, three in the University Hospital of Rennes and 13 in the University Hospital of Lille (data from TransMedics, Andover, MA, USA).

## Appendix A

### Ex vivo heart perfusion

Briefly, donor hearts were connected to the perfusion machine via selective canulations of the ascending aorta and pulmonary artery. A left ventricular vent was inserted in the left ventricle for deairing. Blood flow was delivered into the aorta in a retrograde manner to achieve myocardial perfusion (Langendorff perfusion mode). Details of cardiac graft instrumentation are shown in [Fig. A.1](#). Once a sinus rhythm was obtained, usually after a 30-Joule cardioversion, the superior and inferior vena cava were closed with running sutures. The pulmonary canula was then connected to the circuit, allowing for assessment of the coronary blood flow. Epicardial electrodes were inserted on the inferior wall of the right ventricle to generate a continuous paced rhythm at 80 beats/min. Pump flow was set to keep a coronary flow within a range of 650–850 mL/min. Infusion of low doses of adenosine provided adequate coronary vascular resistance to achieve a mean aortic pressure of 75–90 mmHg. The perfusate included 1200–1500 mL of donor's blood procured just before aortic cross clamping, through a venous cannula inserted in the right atrium. The OCS machine was primed with the donor's blood filtered with a leukocyte filter and with a mixed solution, including electrolytes, mannitol, insulin and steroids. Blood perfusate provides better myocardial perfusion, improves oxygen delivery and oncotic pressure and contains endogenous free radical scavengers that can regulate the pH of the perfusate [25]. A leukocyte filter was used to reduce the immunological haemolysis induced by leukocyte activation during ex vivo perfusion. In addition, activated leukocytes induced by the contact of the blood and the synthetic circuit of the device during ex vivo perfusion might be a factor of heart oedema. Last, leukocyte filtering also produces less ischaemia-reperfusion damage to the allograft [26]. The priming solution was mixed with the collected blood after leukocyte filtering to ensure sufficient metabolic substrate during the time of ex vivo perfusion, and to regulate the potassium concentration in the perfusate to avoid dyskalaemia with the insulin. The addition of mannitol and steroids to the priming solution limits growth of the amount of proinflammatory cytokines and reduces the myocardial oedema induced by the ischaemia-reperfusion process and the circulation of the perfusate in a synthetic extracorporeal circuit [27].

## Appendix B

### Use of packed red blood cells for OCS priming in case of DCD

According to the protocol characteristics described in the research protocol PFS20-004 and accepted by the French regulation agency (Agence de Biomédecine, La Plaine Saint-Denis, France), the heart retrieval protocol must not interfere with the current Maastricht 3 organ retrieval protocol validated in France. No haemodynamic variation can occur before organ procurement, especially during the period of regional normothermic perfusion of the abdominal organs. Blood collection to prime the OCS circuit could significantly impair the pump flow during normothermic regional perfusion of the abdominal organs. Dhital et al. reported two cases of use of packed red blood cells to complete the priming of the OCS machine, because of an insufficient initial volume of collected blood [28]. In these two cases, adding packed red blood cells resulted in a significant increase in plasmatic potassium (> 6.5 mmol/L) and a decrease in plasmatic calcium and perfusate acidosis. In these two cases, hearts were not transplanted because transfusion significantly impaired myocardial viability. In the first case, no heart activity was obtained after resuscitation. In the second case, blood transfusion resulted in a coronary blood flow drop, whereas mean aortic pressure increased, associated with an acute rise in potassium. These adverse events were the consequence of the preservation of the blood in the blood bank. In the present study, packed red blood cells were treated in a red blood cell recycler device, resulting in a high concentrated volume of red blood cells (haematocrit > 50%) with a low level of potassium and a normal pH. The use of packed red blood cells also decreases the concentration of proinflammatory cytokines in the perfusate, and may limit myocardial oedema, compared with donor's blood.





