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Featured Article

Electrical graft assessment of machine-perfused hearts donated after circulatory death

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Background: Normothermic ex situ heart perfusion (ESHP) has increased the donor pool with hearts donated after circulatory death (DCD), but functional assessment during ESHP using lactate trends is suboptimal. This study presents the clinical use of high-resolution cardiac mapping to assess electrical function of human DCD hearts on ESHP, where low-voltage-areas might be indicative of myocardial injury.

Methods: Hearts were procured following circulatory arrest of the donor and restarted on normothermic ESHP. DCD hearts were transported to the recipient hospital and lactate concentrations were regularly measured in the perfusate. High-resolution epicardial mapping of the left (LV) and right ventricle (RV) was performed with a 192-electrode array during normothermic ESHP prior to transplantation. Unipolar potential voltages and slopes, conduction velocity and the amount of low-voltage potentials and conduction block were calculated from these recordings.

Results: Electrical mapping was performed on ten DCD hearts transported on ESHP with sequential cardiac transplantation, showing safety and feasibility of the technique. Median potential voltage of the LV and RV was 15.7 mV (14.0–17.4 mV) and 11.3 mV (8.3–11.9 mV) respectively, and low-voltage potentials were minimally present. In comparison, the electrical function of one rejected heart with increasing lactate trend did not differ from the transplanted hearts.

Conclusions: High-resolution electrical mapping of DCD hearts on ESHP may serve as novel additional diagnostic tool for assessing graft function, especially in marginal donors.

Keywords: Heart transplantation; machine perfusion; donation after circulatory death; cardiac mapping

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Introduction

The introduction of normothermic ex situ heart perfusion (ESHP) has led to successful enlargement of the cardiac donor pool using marginal and donated after circulatory death (DCD) hearts (1). However, DCD hearts experience significant injury as a result of functional warm ischemic time (FWIT). During normothermic ESHP, donor hearts are transported in a beating state, allowing for viability assessment which is essential to prevent graft failure after transplantation (2). Current assessment strategies rely on visual contractility evaluation of an unloaded heart and

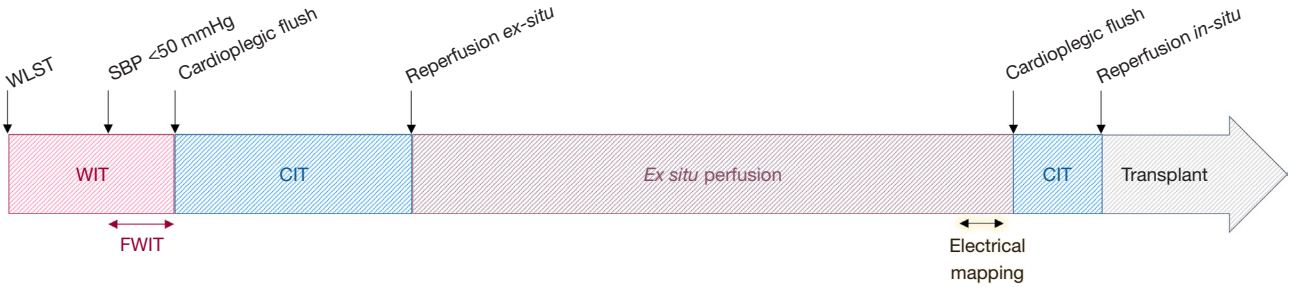

Figure 1 Timeline of events during DCD procedure with *ex situ* perfusion of the donor heart. Electrical mapping was performed just before cardioplegic flush of the heart on the machine. WLST, withdrawal of life-sustaining therapy; WIT, warm ischemic time; SBP, systolic blood pressure; FWIT, functional warm ischemic time; CIT, cold ischemic time; DCD, donated after circulatory death.

lactate trends in the perfusate. However, lactate profiles are not sensitive enough to assess graft functionality (3,4) and visual inspections are inherently subjective.

Furthermore, hemodynamic parameters, such as ejection fraction, cannot be assessed on the only currently available clinical device for ESHP [Transmedics Organ Care System (OCS) Heart] due to perfusion in Langendorff mode (2,5). Therefore, more functional tools with direct feedback have to be developed to assess cardiac performance during ESHP (6).

We previously reported on the use of electrical mapping as novel assessment strategy for hearts on normothermic ESHP in a porcine DCD model (7). In this experimental setup, we showed that electrophysiological parameters, such as potential voltage, could distinguish between hearts with different warm ischemic profiles whereas lactate profiles could not. Therefore, we argued that electrical markers could serve as a novel adjunct strategy to assess cardiac function. In the current study, the use of this electrical mapping approach is described in the clinical setting of cardiac transplantation with human DCD hearts transported on ESHP.

Methods

Patients were allocated as DCD donors for cardiac transplantation and provided consent for research in accordance with the Dutch law on organ donation. Organ recipients provided informed consent for additional measurements on the donor hearts prior to transplantation (MEC 2023-0035) and for anonymous use of their medical details for scientific publication on DCD transplantation (MEC 2020-0106), as approved by the institutional medical ethics committee.

Direct DCD heart procurement and *ex situ* perfusion

Donor hearts were procured in standard manner after declaration of death and a five-minute no-touch period following circulatory arrest. FWIT started when systolic blood pressure dropped below 50 mmHg and ended with cardioplegic flush of the donor heart (*Figure 1*). Hearts were revived on the OCS as previously described (2,5), and transported to the Erasmus Medical Center. Blood gas and lactate levels were measured in the blood-priming perfusate and corrections were made accordingly (5).

Electrical mapping

Upon arrival at our hospital, high-resolution epicardial mapping of the donor heart was performed on the OCS, before cooling of the donor heart and cardioplegia administration (*Figure 1*) (7,8). Sterile drapes were placed on the OCS and a steel wire was carefully wrapped around the aorta as the indifferent electrode. The pacemaker's stimulation function was temporarily turned off to record the heart's intrinsic electrophysiological characteristics. The mapping equipment consisted of a 192-electrode array (electrode diameter 0.45 mm, inter-electrode distance 2 mm) (Delft University of Technology, the Netherlands) connected to a custom-made computerized mapping system (*Figure 2*). The epicardial surface of the heart was systematically mapped by moving the electrode-array over the left (LV) and right ventricle (RV) (*Figure 3*). The electrode was positioned parallel to the posterior interventricular coronary artery, starting at the atrioventricular groove. The electrode was shifted from the posterior to the anterior wall of each ventricle. Five seconds were recorded at every mapping position.

Detailed methods on electrical data analysis are provided

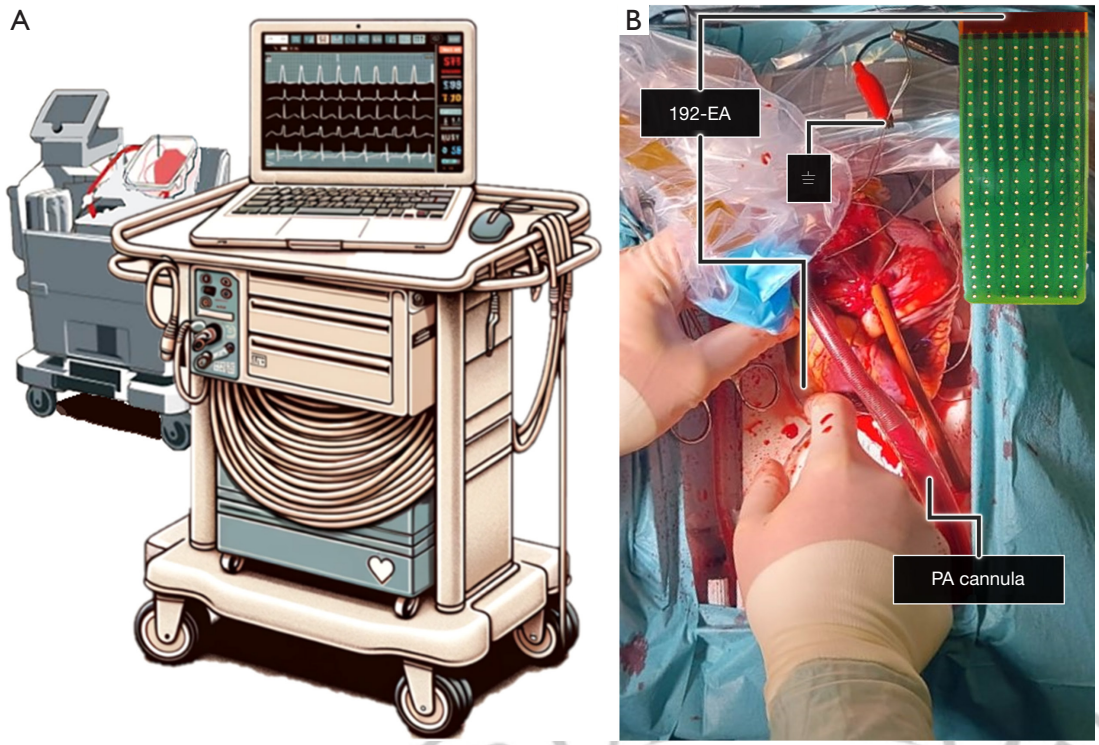

Figure 2 High-resolution electrical mapping of the epicardial surface of a DCD heart transported on *ex situ* perfusion. (A) Mapping during ESHP was performed with an electrophysiological recorder connected to a laptop. (B) A sterile 192-EA was positioned on the epicardium by the surgeon. An indifferent electrode (⏚) was positioned around the aorta as steel wire making contact with the adventitial tissue. EA, electrode array; PA, pulmonary artery; DCD, donated after circulatory death.

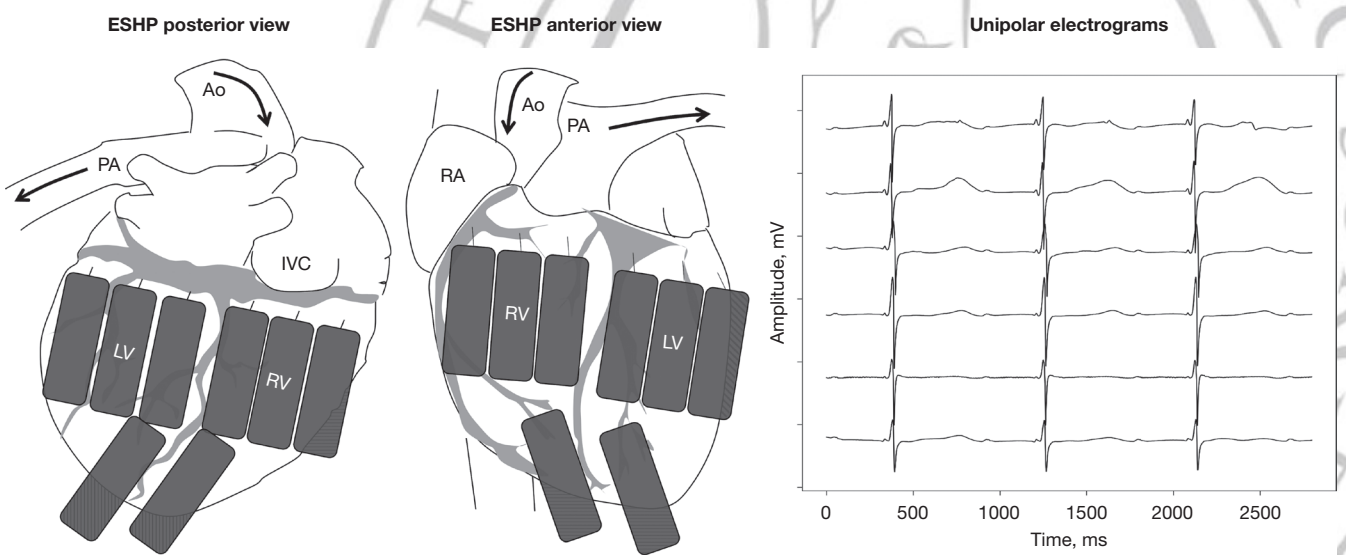

Figure 3 Schematic mapping scheme of the ventricular surface of hearts on *ex situ* perfusion. 192 unique unipolar electrograms were recorded at each mapping site. ESHP, ex situ heart perfusion; Ao, aorta; PA, pulmonary artery; IVC, inferior vena cava; LV, left ventricle; RV, right ventricle; RA, right atrium.

Table 1 Lactate concentrations during *ex situ* perfusion of 10 DCD transplanted hearts

Ex situ perfusion time	Lactate
Reperfusion	6.4±1.6 mmol/L
1 hour	6.4±1.5 mmol/L
2 hours	5.8±1.5 mmol/L
3 hours	5.0±1.4 mmol/L
Gradient	–0.6±0.5 mmol/L/h

Values are presented as average ± standard deviation. DCD, donated after circulatory death.

Table 2 Electrophysiological characteristics of 10 DCD hearts on *ex situ* perfusion that were subsequently transplanted

Characteristics	Transplanted DCD hearts (n=10)
Unipolar potential characteristics	
Voltage (mV)	
LV	15.7 (14.0–17.4)
RV	11.3 (8.3–11.9)
Low-voltage (%)	
LV	0.2 (0.1–0.3)
RV	0.2 (0.1–1.1)
Slope (–V/s)	
LV	1.7 (1.4–2.2)
RV	1.0 (0.7–1.1)
Conduction characteristics	
Conduction velocity (cm/s)	
LV	106 (98–113)
RV	89 (77–92)
Conduction block (%)	
LV	0.5 (0.0–1.5)
RV	2.9 (1.8–5.2)

Values are presented as median (interquartile range). DCD, donated after circulatory death; LV, left ventricle; RV, right ventricle.

in the Supplementary file (Appendix 1). In short, color-coded voltage maps were created by quantifying peak-to-peak amplitudes of unipolar extracellular potentials at each electrode, and local activation time maps were created to study abnormalities in myocardial conduction. Medians and interquartile ranges of potential voltage, slope, and conduction velocity and the amount of low-voltage potentials (voltage: LV <2.0 mV and RV <1.0 mV) and conduction block (inter-electrode time difference ≥12 ms) were calculated for the LV and RV of each donor heart.

Results

Patient and allograft characteristics

Epicardial mapping was performed on ten *ex situ* perfused DCD hearts [median donor age 38 years (31–44 years), 40% male] with a median FWIT of 15 minutes (15–18 minutes) and time on ESHP of 274 minutes (228–334 minutes). All transplanted hearts showed a decreasing lactate trend during ESHP (*Table 1*) and good visual contractile function. One additional DCD heart (donor age: 28 years) that was rejected for transplantation due to an increasing lactate trend (1.2 mmol/L/h starting from 5.6 mmol/L/h) was used to allow for comparison with the transplanted hearts.

Electrical function

Table 2 provides electrophysiological characteristics of ten DCD hearts on ESHP. In total, more than one hundred thousand unipolar potentials were recorded from the ventricular surface. No procedure-related complications occurred during the mapping and sterility was maintained in all cases. Average recording time was 213±41 seconds.

Median voltage was 15.7 mV (14.0–17.4 mV) and 11.3 mV (8.3–11.9 mV) for the LV and RV respectively, and the amount of low-voltage potentials was minimal (*Table 2*). *Figure 4* provides exemplary voltage maps, demonstrating how potential voltages are displayed during ESHP. Dark red colored areas indicate sites from which low-voltage potentials were recorded.

Conduction velocity was higher in the LV [106 cm/s (98–113 cm/s)] compared to the RV [89 cm/s (77–92 cm/s)] and in both ventricles only minimal areas of conduction block were found [LV: 0.5% (0.0–1.5%), RV: 2.9% (1.8–5.2%)] (*Table 2*).

Electrical function of the rejected donor heart

Unipolar potential voltages of the DCD heart that was rejected for transplantation due to increasing lactate levels (LV: 19.4 mV, RV: 10.4 mV) were comparable to the ten transplanted DCD hearts. Moreover, this heart presented

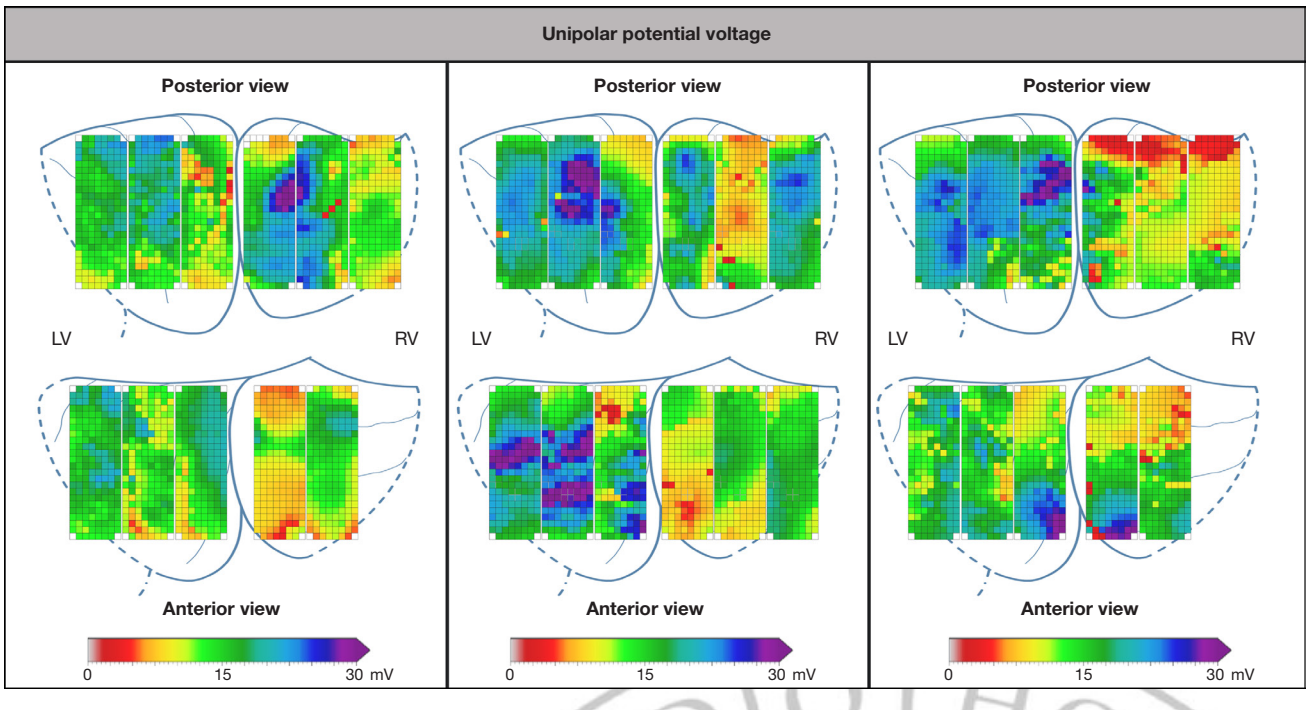

Figure 4 Exemplary voltage maps of three DCD hearts on *ex situ* perfusion. Red colors depict potential voltages ≤5 mV. Potential voltages were measured as peak-to-peak amplitude from the steepest negative deflections of unipolar electrograms and displayed as median per electrode. LV, left ventricle; RV, right ventricle; DCD, donated after circulatory death.

without areas of low-voltage. Also, conduction velocity was similar (LV: 107 cm/s, RV: 99 cm/s) and the amount of conduction block (LV: 0%, RV: 0.4%) was not higher in this heart.

Post-operative outcomes

After ESHP and electrical mapping, donor hearts were cooled on OCS and transplanted, after which patients were transferred to the intensive care unit (ICU). Median recipient age was 26 years (25–51 years), the majority were male (70%), and five (50%) patients had a left ventricular assist device *in situ* prior to transplantation. All patients were alive thirty days after transplantation, with a median ICU stay of 7 days (4–10 days). Two patients required extracorporeal membrane oxygenation (ECMO) support four and five days, respectively, post-transplantation due to acute cardiac stunning and poor biventricular function. One of these hearts showed electrical abnormalities (reduced potential voltages, slopes and conduction velocities, and more conduction block) during electrical mapping on ESHP, which was not seen in the other heart (Table S1).

Discussion

Given the suboptimal graft assessment experience with lactate, there is an urgent need for additional functional parameters for hearts on ESHP (3,4). This is the first clinical report of an electrical mapping procedure of DCD hearts on normothermic ESHP, which has great potential as a novel adjunct for graft quality assessment.

Clinical experience

Epicardial mapping was performed on ten hearts on ESHP without adverse events, demonstrating safety of the technique, and supported by our group's experience in over 1,500 patients undergoing cardiac surgery (8). Mapping can be performed in three to four minutes, providing real-time visualization of electrograms and color-coded potential voltage maps. Differences in potential voltage distribution across the epicardium could reveal localized areas of ischemic damage, whereas lactate levels only indicate global metabolic (dys)function.

The rationale to use electrophysiological determination

of ischemia is based on its use in daily practice in diagnosing myocardial infarction. Nevertheless, such an approach has not yet been used in the setting of organ preservation. In general, a high amount of low-voltage potentials or conduction block is indicative of myocardial ischemic injury (9) which has been corroborated by our previous work on ischemic porcine hearts on ESHP (7). Within the current study, no high amounts of low-voltage potentials or areas of conduction block were observed, as expected in healthy human donor hearts. Of interest, one heart got rejected for transplantation on the basis of an increasing lactate trend, yet, electrical function was comparable to the transplanted hearts. This raises the question of whether this heart could have successfully been transplanted, as others have already showed successful transplantation of hearts with rising lactates (3). In such cases, we believe that functional parameters, like electrophysiological properties, can aid in decision-making regarding the organ's suitability for transplantation. We hypothesize that an elevation in lactate levels concomitant with impaired electrical function, indicated by the prevalent occurrence of low-voltage potentials, should alert the surgical team to consider rejection of the heart. Otherwise, hearts could possibly be accepted for transplantation despite increasing lactate levels. Thus, addition of a real-time mapping technique could aid in graft evaluation, particularly for marginal donors and hearts with increasing lactate trends, and possibly allow more transplantations.

Future research is required to investigate whether electrical markers could predict the need for ECMO support after cardiac transplantation. Yet, this is also contingent on the recipient's condition.

Feasibility

The equipment needed for the presented technique should be available in any center with a clinical electrophysiology lab. Mapping was performed in the recipient hospital as it was difficult to bring the current equipment on organ transplantation transport. In the future, we hope to develop a portable mapping device, where electrodes can be temporarily fixated covering the entire epicardial surface of the donor heart, so electrical assessment is continuously available and hands-free.

The presented electrophysiological characteristics can be interpreted as normal electrical function of DCD hearts on ESHP. However, more experience in a larger series is needed to validate the specificity of our technique, also including transplanted hearts with an increasing lactate trend during ESHP.

Conclusions

Our high-resolution electrical mapping approach of DCD hearts on ESHP is safe and feasible, and may serve as novel additional diagnostic tool for assessing graft function of marginal donor hearts.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Appendix 1 Methods

Electrical recordings were analogue-to-digital converted (16 bits), sampled with a rate of 1 kHz, amplified (gain 1,000) and filtered (bandwidth 0.5–400 Hz). Mapping data were analyzed using custom-made software (1) by annotating the steepest negative slope (LV ≤–0.2 mV/ms and RV ≤–0.1 mV/ms) of unipolar potential deflections (amplitude ≥0.5 mV). All annotations were visually verified by two authors (J.A. and N.d.G.) and ectopic beats were excluded from analysis. Color-coded maps were created visualizing quantified features of unipolar extracellular potentials including unipolar extracellular potential voltages (peak-to-peak amplitudes) and slopes at each electrode. Low-voltage was defined as the proportion of unipolar potentials with an amplitude <2.0 or <1.0 mV for the LV or RV, respectively, in accordance with previous studies (2). Local activation time (LAT) maps were created to study abnormalities in myocardial conduction. Conduction block (CB) was determined as a difference in LAT of ≥12 ms between two adjacent electrodes and the prevalence of CB was calculated as percentage of all conduction times. Local effective conduction velocity (CV) was computed from LATs of neighboring electrodes (longitudinal, transversal, and diagonal) using discrete velocity vectors (3). Areas of simultaneous activation were excluded from analysis to avoid inclusion of far-field potentials. Median unipolar potential voltage, potential slope, and CV and the amount of low-voltage potentials and CB were calculated for the LV and RV of each donor heart.

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Table S1 Potential characteristics and conduction characteristics of two donor hearts during *ex situ* heart perfusion (A and B) that required extracorporeal membrane oxygenation support post-transplantation

ECMO	Unipolar potential characteristics			Conduction characteristics	
	Voltage (mV)	Low-voltage (%)	Slope (-V/s)	Conduction velocity (cm/s)	Conduction block (%)
A					
LV	16.6 (10.0–22.2)	0.10	0.9 (0.5–1.5)	87 (63–112)	8.5
RV	7.9 (5.4–9.9)	1.56	0.6 (0.4–0.9)	75 (47–103)	6.2
B					
LV	16.4 (12.4–23.8)	0.22	3.0 (1.3–6.0)	112 (79–141)	0
RV	12.0 (8.0–15.2)	0.36	1.2 (0.8–2.0)	88 (59–122)	1.5

Heart A showed electrical abnormalities (lower RV voltage with more low-voltage potentials; reduced potential slopes; and reduced conduction velocities with more conduction block) compared to the hearts that did not require ECMO support. Heart B did not show these electrical abnormalities.

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