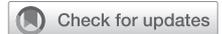# A modified intraventricular balloon method for functional assessment of hearts from donation after circulatory death

Check for updates

Sachiko Kadowaki, MD, PhD,[a,b] Marlee Parker, CPC, CCP,[c] Jian Wang, CPC, CCP,[c] Brigitte Mueller, PhD,[d] Chun-Po Steve Fan, PhD, P.Stat,[d] Jing Li, MD, PhD,[a,b] and Osami Honjo, MD, PhD[a,b]

ABSTRACT

Objective: Functional assessment of hearts during ex-vivo heart perfusion is not well-established. Conventional intraventricular balloon methods for large animals sacrifice the mitral valve. This study assessed the effectiveness of the modified intraventricular balloon method in comparison with other modalities used during working mode in juvenile pigs.

Methods: Following asphyxia circulatory arrest, hearts were ischemic for 15 minutes and then reperfused on an ex-vivo device for 2 hours before switching to working mode. Left ventricular pressure was continuously measured during reperfusion by a saline-filled balloon fixated in the left atrium. Spearman Correlation Coefficients with linear regression lines with confidence intervals were analyzed.

Results: Maximum dp/dt at 90 minutes of reperfusion and minimum dp/dt at 60 minutes of reperfusion showed a moderate positive correlation to that in working mode, respectively (Rs = 0.61, P = .04 and Rs = 0.60, P = .04). At 60 minutes of reperfusion, minimum dp/dt showed moderate positive correlation to tau (Rs = 0.52, P = .08). Myocardial oxygen consumption during reperfusion consistently decreased at least 30% compared to working mode (at 90 minutes as the highest during reperfusion, 3.3 ± 0.8; in working mode, 5.6 ± 1.4, mLO$_2$/min/ 100 g, P < .001).

Conclusions: Functional parameters of contractility and relaxation measured during reperfusion by the modified balloon method showed significant correlations to respective parameters in working mode. This mitral valve sparing technique can be used to predict viability and ventricular function in the early phase of ex-vivo heart perfusion without loading the heart during working mode. (JTCVS Open 2024;18:104-17)
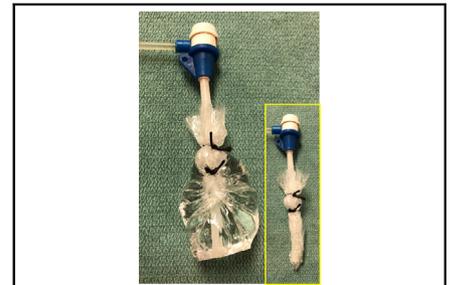
The saline-filled balloon for monitoring cardiac function in the left ventricle.

CENTRAL MESSAGE

The modified intraventricular balloon method provides functional assessment for hearts during ex-vivo heart perfusion and may contribute to better overall assessment of donor hearts prior to transplantation.

PERSPECTIVE

The study revealed significant correlations in ventricular function measured by modified intraventricular balloon (mIVB) at 60-90 minutes after the initiation of ex-vivo heart perfusion (EVHP) to that in working mode. The advantages of mIVB are lower energy demands than working mode and preservation of the mitral valve. Therefore, mIVB could be a reliable assessment of hearts on EVHP in clinical practice.

Accurate assessment of ventricular performance in donor hearts is crucial to heart transplantation, with outcomes being directly associated with donor ventricular performance. In donation after brain death (DBD) donors, ventricular functional assessment by conventional transthoracic echocardiography, clinical markers of cardiac output, and the amount of inotropic support are typically sufficient to assess viability of donor hearts. However, functional assessment

methods for donation after circulatory death (DCD) donor hearts before transplant are lacking. DCD hearts must be carefully considered due to ischemic insult and ischemia–reperfusion injury.[1] Recent clinical series showed reassuring short- and midterm outcomes of DCD heart transplantation in adults comparable with that of heart transplantation using DBD hearts.[2,3]

The commercially available Organ Care System (Trans-Medics, Inc) is an ex-vivo heart perfusion (EVHP) device that enables DCD hearts to be reperfused with normo-thermic blood perfusate in an unloaded condition.[4] However, the assessment of DCD hearts during EVHP consists of visual inspection of ventricular movement and measuring coronary lactate levels.[5] Although lactate trends can indicate the metabolic status of DCD hearts during reperfusion, hemodynamic function is unable to be assessed without loading the ventricles. Adequate functional assessment methods for DCD donor hearts are pivotal in assessing potentially irrecoverable myocardial damage during the DCD process, which may lead to graft failure and suboptimal clinical outcomes if transplanted.

Intraventricular balloons (IVBs) are an effective method for assessing cardiac function in isolated heart perfusion in animals.[6] A pressure transducer is connected to a compliant and thin saline-filled balloon inserted into the left ventricle (LV).[7,8] Historically, existing IVB methods have secured the balloon to the mitral valve (MV) to avoid dislodgement of the balloon from the LV cavity.[9,10] This can severely damage the MV, rendering it nontransplant-able. The IVB method needs to be modified to preserve the MV. This study aims to demonstrate effectiveness of the modified intraventricular balloon (mIVB) method, which preserves the MV, by correlating functional parameters measured by mIVB during the reperfusion phase of EVHP (heart unloaded) to pressure–volume loops and echocardiography in the working mode (WM) phase of EVHP (heart loaded).

METHODS
Study Design
All experiments were performed in accordance with a protocol approved by the Animal Care Committee of the Hospital for Sick Children, in which sample-size and power calculation were reviewed. A graphical abstract of the study is shown in Figure 1. Twelve Yorkshire pigs (10-12 kg, age 4 weeks; Lifetime Solutions Ltd) were used as heart donors. Additional pigs (20 kg, age 8 weeks; Lifetime Solutions Ltd) were used as blood donors. Following DCD heart procurement,[11] the donor hearts were connected to the EVHP circuit; cannulation configuration is shown in Figure E1, A. The donor hearts were reperfused for 2 hours,[11] with functional assessment using the mIVB performed every 30 minutes (Figure 2, A and B). The hearts were then switched to WM to assess cardiac function with a loaded LV. The experimental protocol is shown in Figure E1, B. The DCD heart model, assessment of hemodynamic function of DCD hearts, and measurement of metabolic variables are described in Appendix E1.

mIVB Preparation and Measurement
The balloon was created from commercially available polyethylene plastic wrap (Cling Wrap; Glad) and attached to an 8Fr introducer (AVANTI+) (Figure 2, C). The material of the balloon was chosen based on 3 features required for the intraventricular balloon: flexibility to conform to the contours of the ventricular lumen, compliant to efficiently transmit pressure to the fluid inside the balloon, and thin enough to accurately reflect an isometric increase in wall tension by a comparable increase in the pressure within the balloon.[7] The introducer allows for saline injection into the balloon during placement and insertion of the pressure catheter (VSL; Transonic Inc) when measuring left ventricular pressures (LVPs). Using a 21-G needle, 2 holes were made in the introducer 5 mm proximal to the tip. Figure 2, C(d) highlights 2 ties that are used as markers to straddle the MV annulus for proper positioning of the mIVB in the LV. A purse-string suture in the left atrium around the pulmonary vein orifice was used to secure and insert the mIVB into the LV. Insertion and fixation of the balloon into the LV through the pulmonary vein is best done within 30 minutes of reperfusion before the LV gains strong contractility. Additional stabilization of the transducer was achieved by tying the tourniquet of the purse-string suture through the transducer hub. With the mIVB securely placed in the LV, the pressure catheter was inserted to monitor LVP and to adjust left ventricular end-diastolic pressure (LVEDP). A LVEDP of 3 to 5 mm Hg was determined based on left atrial pressure measured during WM in previous experiments. The mIVB was removed before switching to WM.

Data Analysis
Animal characteristics were summarized using means and standard deviations. To explore the correlation of maximum first derivative of left ventricular pressure (max+dp/dt) measured by mIVB at 90 minutes during reperfusion with that measured by pressure-volume loops and venous lactate in WM, we first demonstrated the relation between the 2 variables using a scatter plot superimposed with a regression line with its corresponding 95% confidence intervals. Next, we calculated the Spearman Correlation between the 2 variables and its 95% confidence intervals. We repeated the same analysis for mIVB minimum first derivative of left ventricular pressure (min–dp/dt) at 60 minutes during reperfusion. Finally, to demonstrate the distributions of max+dp/dt, min-dp/dt, and myocardial oxygen consumption (MVO_2) at 30-minute intervals during 2 hours of reperfusion and in WM, we used separate boxplots and conducted post-hoc comparisons using paired *t*-tests between 2

A Modified Intraventricular Balloon Method for Functional Assessment of Hearts from Donation after Circulatory Death

- 12 pigs (10-12 kg)
- DCD heart model
- EVHP for 2 hours with the mIVB, followed by WM.
- The mitral valve left intact
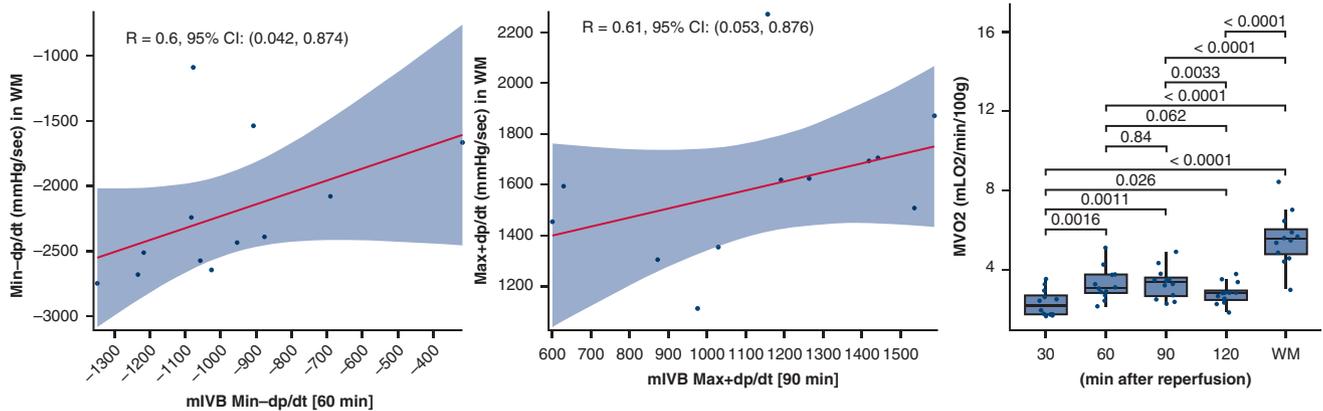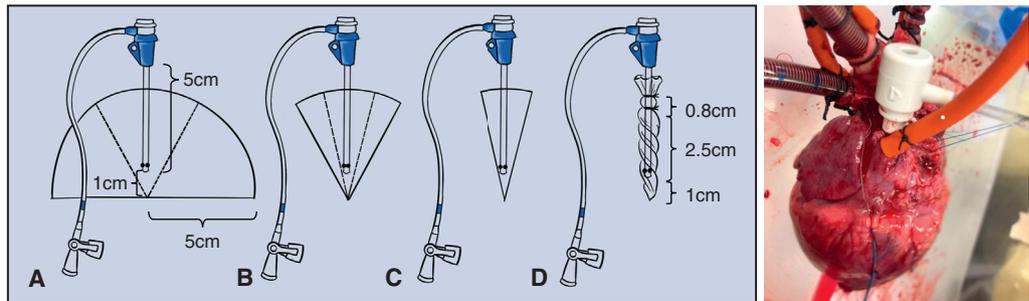
Functional measurements on EVHP in the modified IVB method can be conducted in a cardioprotective manner, while demonstrating correlations with the respective measures of cardiac function under fully pre-loaded conditions.

DCD, donation after circulatory death; EVHP, ex-vivo heart perfusion; mIVB, modified intraventricular balloon; MVO2, myocardial oxygen consumption; WM, working mode.

FIGURE 1. Graphical abstract. Correlation of functional parameters in DCD hearts measured by mIVB to those in working mode. *DCD*, Donations after circulatory death; *EVHP*, ex vivo heart perfusion; *mIVB*, modified intraventricular balloon; *WM*, working mode; *CI*, confidence interval; *MVO₂*, myocardial oxygen consumption.

time points. Statistical analyses assumed a significance level of 5% and were conducted in R, version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

The heart donor pig weights were 9.5 ± 1.4 kg. Warm ischemic time was 24 ± 6 minutes. All hearts regained sinus rhythm spontaneously after reperfusion or after cardioversion. On EVHP, venous lactate levels were monitored and showed 3.5 ± 0.9 mmol/L, 3.7 ± 0.9 mmol/L, 4.0 ± 0.8 mmol/L, 4.2 ± 0.8 mmol/L, and 4.4 ± 0.9 mmol/L at 30 minutes, 60 minutes, 90 minutes, and 120 minutes after reperfusion and in WM, respectively. The mIVB measurement can be performed precisely with reproducibility as long as LVP waveforms are optimized

to LVEDP of 3 to 5 mm Hg by adjusting volume of the balloon. In Figure E2, LVP waveforms exemplifying ones requiring adjustment are shown.

Cardiac Function

The overall difference in max+dp/dt measured using the mIVB during reperfusion and pressure–volume loops in WM was significant ($P < .001$) (Figure 3, *A*). Max+dp/dt was low at 30 minutes after reperfusion (558 ± 301 mm Hg/s), then significantly increased at 60 minutes after reperfusion (1317 ± 299 mm Hg/s). Although it remained stable at 60, 90, and 120 minutes after reperfusion (at 90 minutes; 1141 ± 317, 120 minutes; 1178 ± 420, mm Hg/s), max+dp/dt in WM was significantly greater than those measured during reperfusion, except for the measurement at 60 mi-
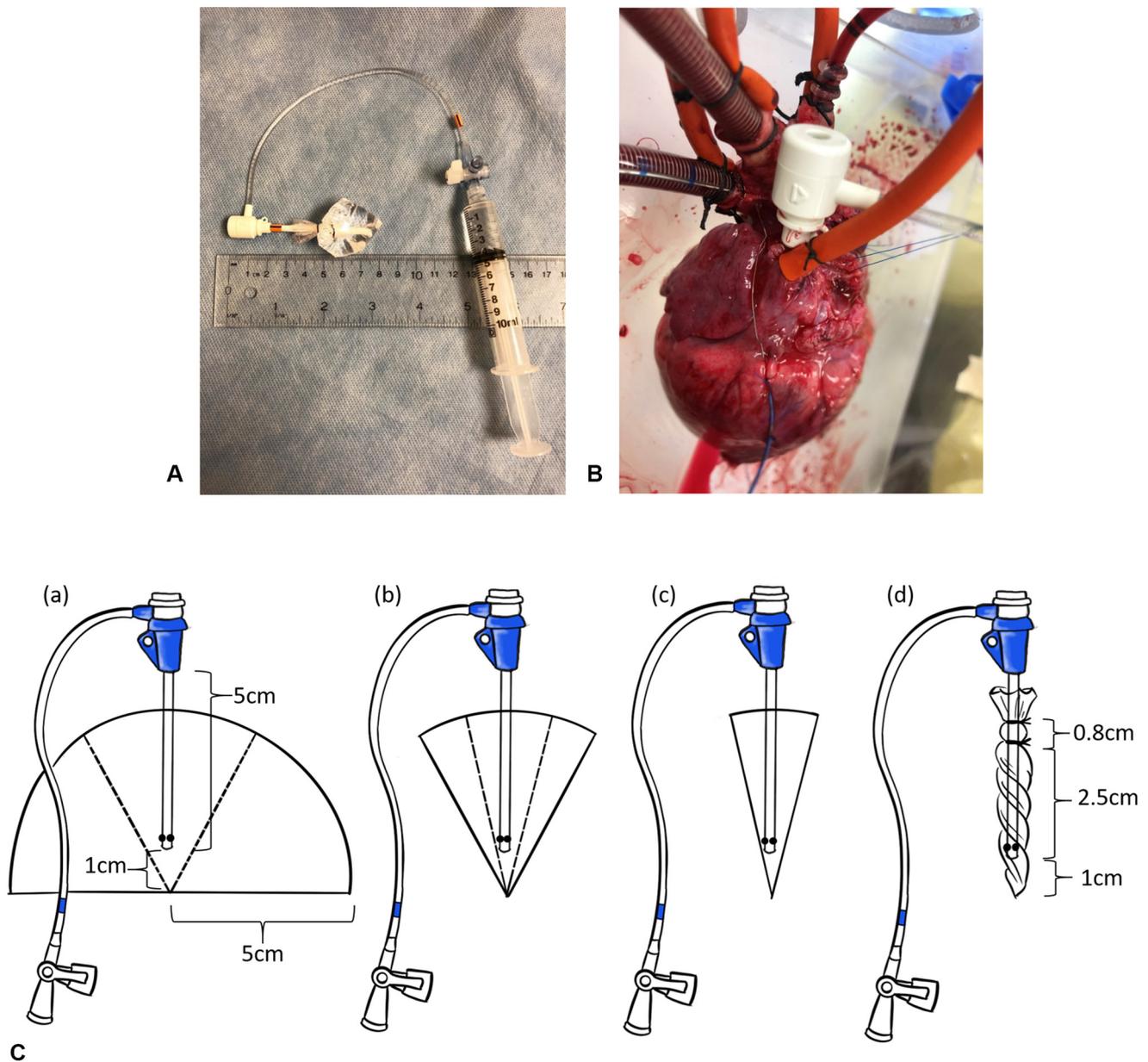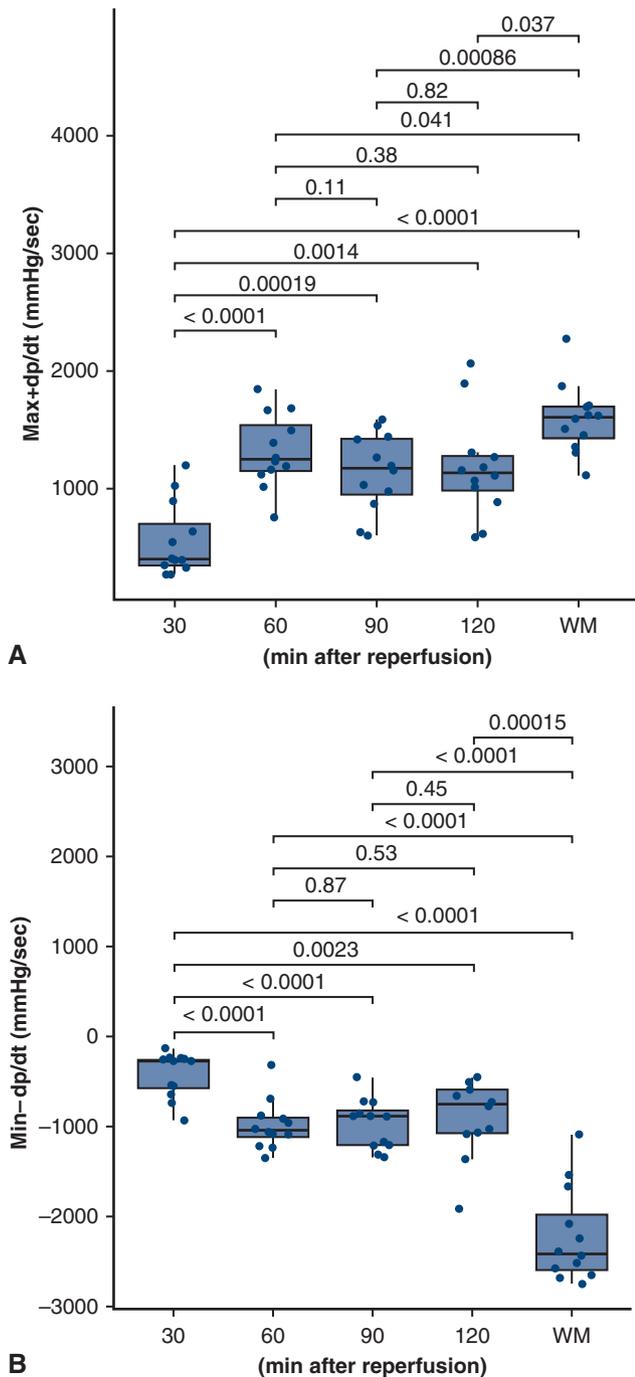
FIGURE 2. Modified intraventricular balloon and its preparation. A, The balloon inflated with saline before use. B, The balloon deployed into the left ventricle. C, (a) The trimmed 8-Fr sheath with holes created by a 21-G needle is inserted into the folded circular-shaped plastic wrap with a 5-cm radius, in which the tip of the sheath is placed at 1 cm away from the center. (b) The wrap is folded alternately from side to side along the *dotted line* in diagram (a) to make a fan-shape. (c) Repeat the process along the *dotted line* shown in diagram (b). (d) The open end of the wrap was tied twice with the sheath at 2.5 cm and 3.3 cm distance from the tip of the sheath with 2-0 silk, respectively. After we confirmed no leaks of saline via inflating the balloon, the entire balloon was deflated and twisted to make it as thin as possible.

nutes after reperfusion. Although min–dp/dt showed a similar trend to max+dp/dt with overall significance ($P < .001$) (Figure 3, B), those being stable across 60 to 120 minutes after reperfusion (at 60 minutes; -982 ± 262, 90 minutes; -970 ± 263, 120 minutes; -895 ± 404, mm Hg/s) demonstrated a significantly lower value than that at 30 minutes after reperfusion

(-420 ± 241 mm Hg/s) and a greater value than that in WM (-2217 ± 503 mm Hg/s).

Correlation of Functional Parameters

Correlation coefficients of max+dp/dt and min-dp/dt measured by the mIVB during reperfusion to hemodynamic, functional, and metabolic parameters in WM are shown in

FIGURE 3. Functional and hemodynamic parameters. Max+dp/dt (A) and min–dp/dt (B) measured by the modified intraventricular balloon method during reperfusion phase and by pressure–volume loops in working mode. *P* values noted in each comparison. *max+dp/dt*, Maximum first derivative of left ventricular pressure; *min–dp/dt*, minimum first derivative of left ventricular pressure; *WM*, working mode.

Table 1. Max+dp/dt measured by the mIVB at 90 minutes of reperfusion showed moderate positive correlation (Rs = 0.61, $P = .04$) to the measurement in WM and moderate negative correlation (Rs = −0.55, $P = .07$) to coronary venous lactate

TABLE 1. Spearman Correlation Coefficients of max+dp/dt and min–dp/dt measured by the mIVB to hemodynamic, functional, and metabolic parameters in working mode

Max+dp/dt (mIVB) at time after reperfusion	60 min	90 min	120 min
Max+dp/dt (cath)	0.21	0.61*	−0.035
EF (echo)	−0.22	0.29	−0.091
EF (cath)	−0.10	0.29	0.13
Cardiac index	−0.15	0.10	0.05
Heart rate	0.20	−0.13	0.26
Coronary vascular resistance	0.43	0.12	0.24
MVO₂	0.41	0.15	0.18
Venous lactate	−0.23	−0.55	−0.50
Min-dp/dt (mIVB) at time after reperfusion			
Min–dp/dt (cath)	0.60*	0.19	−0.14
Deceleration time	−0.10	0.04	0.22
Lateral e′ velocity	−0.43	0.12	−0.01
Septal e′ velocity	−0.55	0.27	0.10
E/A	−0.35	0.13	0.28
Tau	0.52	0.45	0.16
Cardiac index	−0.31	−0.42	−0.24
Heart rate	−0.42	0.15	−0.43
Coronary vascular resistance	0.08	0.39	0.13
MVO₂	−0.17	0.1	0.01
Venous lactate	0.02	0.26	0.42

cath, Measured by pressure–volume catheter; *echo*, measured by echocardiography; *EF*, ejection fraction; *max+dp/dt*, maximum first derivative of left ventricular pressure; *min–dp/dt*, minimum first derivative of left ventricular pressure; *mIVB*, modified intraventricular balloon; *MVO₂*, myocardial oxygen consumption. *$P < .05$.

level in WM (Figure 4). Min–dp/dt measured by the mIVB at 60 minutes of reperfusion showed moderate positive correlation to the measurement in WM (Rs = 0.60, $P = .04$) and to tau (Rs = 0.52, $P = .08$) (Figure 5). Lateral e′ velocity and septal e′ velocity also had mild correlation with min-dp/dt measured by mIVB at 60 minutes after reperfusion (lateral e′ velocity; Rs = −0.43, $P = .17$, septal e′ velocity; Rs = −0.55, $P = .07$) (Figure 5).

Myocardial Oxygen Consumption

MVO₂ measured throughout reperfusion and WM showed significant differences ($P < .001$) (Figure 6). MVO₂ at 30 minutes after reperfusion (2.3 ± 0.6 mLO₂/min/100 g) was significantly lower than those at 60 and 90 minutes after reperfusion and in WM (at 60 minutes after reperfusion; 3.2 ± 0.8, 90 minutes; 3.3 ± 0.8, WM; 5.6 ± 1.3, mLO₂/min/100 g), although there was no significant difference compared with 120 minutes after reperfusion (2.8 ± 0.5 mLO₂/min/100 g). MVO₂ at 60, 90, and 120 minutes after reperfusion did not show statistical
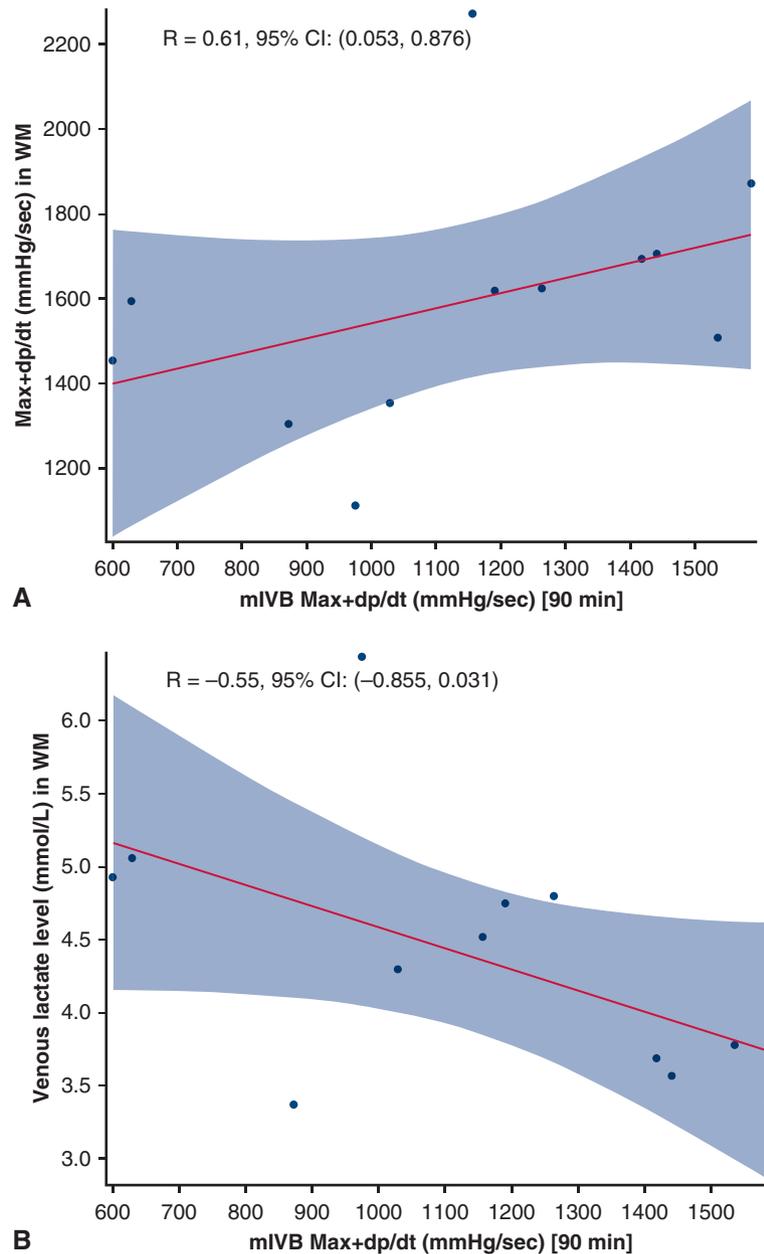
FIGURE 4. Scatter plots and linear regression lines with confidence intervals in max+dp/dt measured by the modified intraventricular balloon at 90 minutes after reperfusion. Correlation coefficients to max+dp/dt measured by pressure–volume loops (A) and to venous lactate level in WM (B). *max+dp/dt*, Maximum first derivative of left ventricular pressure; *WM*, working mode; *CI*, confidence interval; *mIVB*, modified intraventricular balloon.

significance. MVO_2 in WM was significantly greater than those measured during reperfusion.

Features of LVP Waveforms

In all LVP waveforms, LVP peaked in isovolumetric contraction and dropped to minimal LVP during relaxation, then reached isovolumetric contraction in the next cardiac cycle. At 30 minutes after reperfusion, some hearts did not show plateauing of LVP following relaxation and went into the next cardiac cycle immediately after achieving minimal LVP (Figure 7, *A*). However, all LVP

waveforms measured at time points of 60 minutes and longer during reperfusion showed plateauing of LVP prior to isovolumetric contraction in the next cardiac cycle (Figure 7, *B*). The representative LVP waveform in WM is shown in Figure 7, *C*.

DISCUSSION

The mIVB-derived max+dp/dt and min–dp/dt showed significant correlation to the respective pressure–volume loop measurements in WM, specifically at 60 to 90 minutes of reperfusion. The min–dp/dt is more distinctive
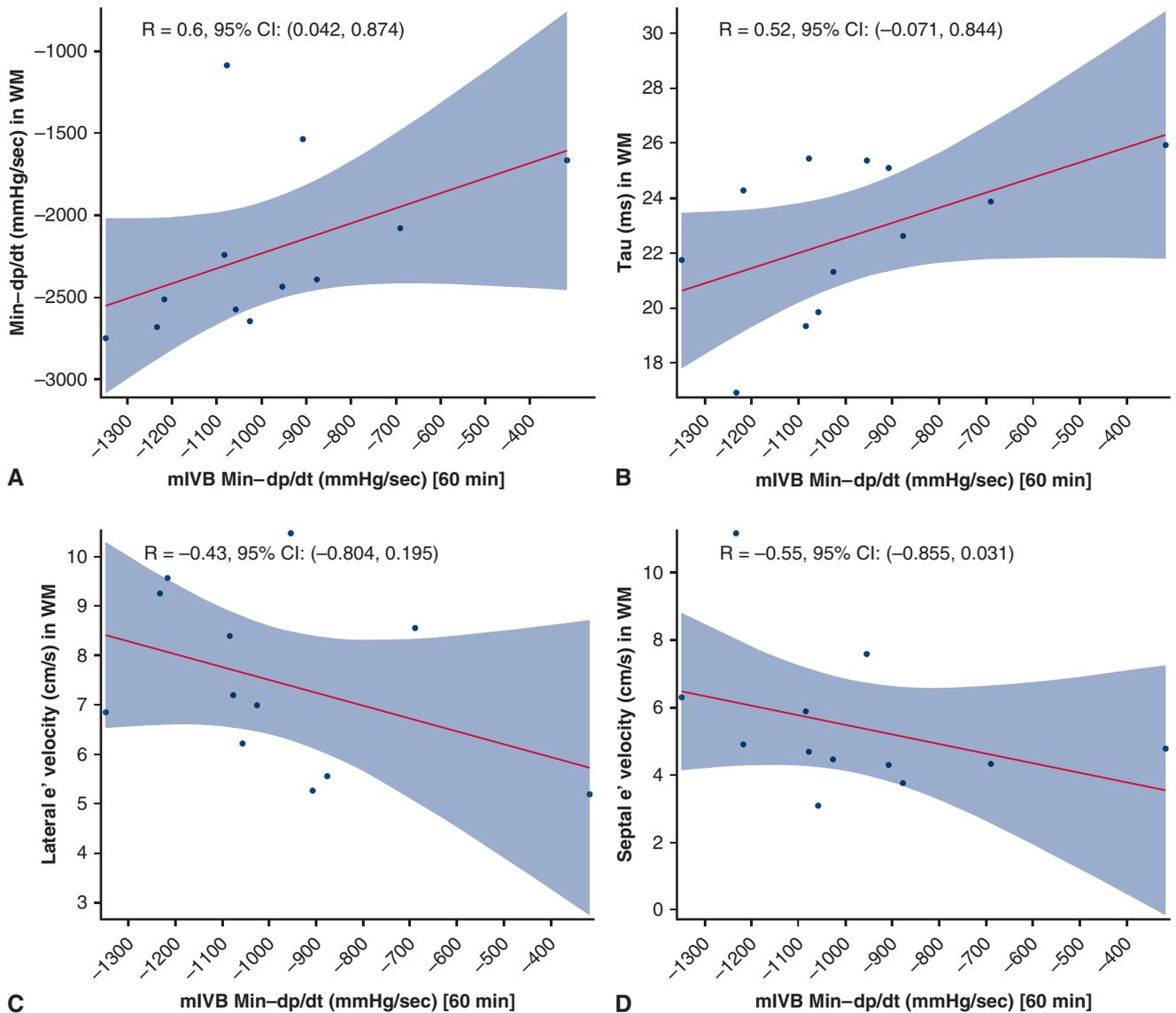
FIGURE 5. Scatter plots and linear regression lines with confidence intervals in min–dp/dt measured by the modified intraventricular balloon at 60 minutes after reperfusion. Correlation coefficients to min–dp/dt (A) and tau (B) measured by pressure–volume loops and lateral e′ velocity (C) and septal e′ velocity (D) measured by echocardiography in WM. *min–dp/dt*, Minimum first derivative of left ventricular pressure; *WM*, working mode; *CI*, confidence interval; *mIVB*, modified intraventricular balloon.

than max+dp/dt and showed mild or moderate correlation with the multiple parameters representing diastolic function. Importantly, DCD hearts used significantly less energy to assess ventricular function with mIVB than with WM. The mIVB method is also advantageous in keeping the MV intact. Therefore, the mIVB method is more protective to DCD hearts than WM and can provide adequate functional assessment of DCD hearts before transplantation.

Correlations of Functional Parameters and Optimal Timing for Cardiac Function Assessment

Max+dp/dt at 90 minutes after reperfusion measured by the mIVB significantly correlated to that in WM, whereas min–dp/dt at 60 and 90 minutes after reperfusion showed significant and mild correlation, respectively, to the corresponding parameters in WM. In general, DCD hearts have some degree of myocardial stunning, represented as mechanical dysfunction that
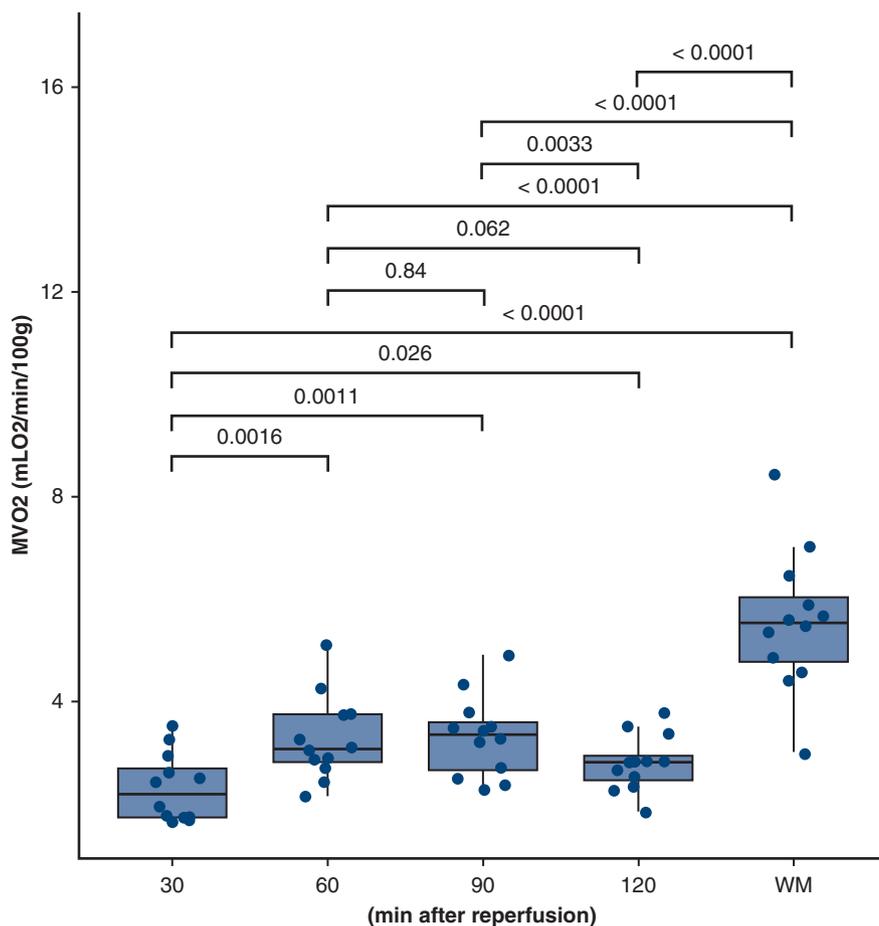
FIGURE 6. Myocardial oxygen consumption during reperfusion phase and in working mode. *P* values noted in each comparison. *MVO$_2$*, Myocardial oxygen consumption; *WM*, working mode.

persists after reperfusion despite the absence of irreversible damage and restoration of normal or near-normal coronary flow.[12] As shown in Figure 3, at 60 minutes after reperfusion max+dp/dt and min–dp/dt peaked, slightly dropped, and then plateaued for the remaining reperfusion period. The functional recovery differs among DCD hearts, but DCD hearts with myocardial stunning may show consistent trends on EVHP. Monitoring these trends with the mIVB method could be beneficial in assessing functional recovery regarding reversible damage after myocardial stunning and, concurrently, provide a better prediction of DCD heart function before transplantation.

Min–dp/dt Measured by the mIVB Correlation With Other Indices of Diastolic Function

Regarding diastolic function in WM, tau demonstrated moderate correlation to Min–dp/dt measured by mIVB, and lateral and septal e′ velocities showed mild correlation to that, although max+dp/dt measured by the mIVB showed correlation only to max+dp/dt in WM. This might suggest that diastolic dysfunction is developed more clearly

than systolic dysfunction in this DCD heart model with marginal ischemic periods.[12] Similarly, our previous study using the same DCD heart model showed significant improvement of diastolic function in the treatment group shown by epicardial echocardiography and pressure–volume loops, which was not distinctively seen in functional parameters related to systolic function.[11] As previously noted, diastolic function is potentially more sensitive to myocardial stunning than systolic function since diastolic abnormalities persisted after coronary recanalization at a time when regional systolic function had fully recovered in a human study.[13] Therefore, min–dp/dt monitored by the mIVB tends to be a reliable indicator to assess diastolic function of DCD hearts.

Energy Efficiency of the mIVB as an Evaluation Method

DCD hearts using the mIVB method during reperfusion required less than 65% of the MVO$_2$ required for WM. The heart is unloaded during reperfusion on EVHP, which reduces the MVO$_2$ requirements to only maintain an ionic environment, protein synthesis, membrane potential, and
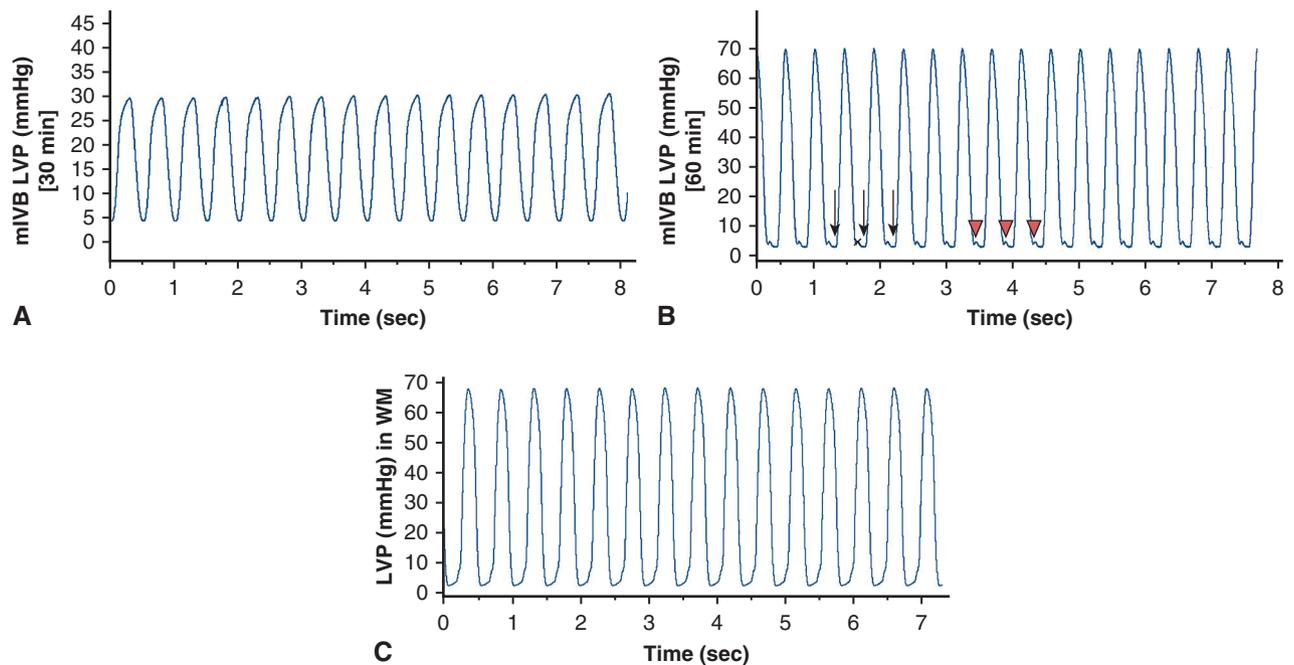
FIGURE 7. Representative left ventricular pressure waveforms. A, At 30 minutes after reperfusion. B, Obtained by the mIVB at 60 minutes of reperfusion, with *arrows* and *arrowheads* showing a plateau corresponding to filling phase and upward notch due to ventricular recoil, respectively. C, Obtained by pressure–volume loops in working mode. *mIVB,* Modified intraventricular balloon; *LVP,* left ventricular pressure; *WM,* working mode.

the release and uptake of calcium by the sarcoplasmic reticulum.[14,15] It is highly advantageous to have the ability to assess an unloaded heart during reperfusion, which is achieved by the mIVB method during EVHP. Comparing DCD hearts during reperfusion with the mIVB method and without the mIVB method (from previous studies), the MVO$_2$ did not increase between the 2 groups during reperfusion or WM (Figure E3), meaning the mIVB method can evaluate hemodynamic function without negatively impacting the hearts. DCD hearts with borderline myocardial function that are loaded during WM potentially fail to counterbalance the increase in energy demand, which can result in deteriorating functional recovery and cause irreversible damage. It is unknown how long a DCD heart can withstand the loading conditions of WM without causing detrimental effects. Therefore, the mIVB method is a noteworthy option to assess cardiac function in an unloaded heart, further preserving myocardial function prior to transplantation.

LVP Waveforms Drawn by the mIVB

LVP waveforms obtained by mIVB are an effective resource to assess functional status of DCD hearts on EVHP. While pressure–volume loops of cardiac cycles consist of 4 phases (isovolumetreic contraction, ejection, isovolumetric relaxation, and filling),[16] mIVB-LVP waveforms consist of isovolumetric contraction and relaxation. If cardiac function is preserved during EVHP, mIVB-LVP waveforms show a plateau between cardiac cycles (Figure 7, *B*). However, during early reperfusion, mIVB-LVP waveforms mostly went into the next cardiac cycle without the plateau phase immediately after reaching the minimum LVP at the end of isovolumetric relaxation (Figure 7, *A*). This might suggest prolonged periods of isovolumetric contraction and relaxation (poor max+dp/dt and min–dp/dt) resulting in the plateau phase being short or diminished during early reperfusion. At 60 minutes of reperfusion, mIVB-LVP waveforms all exhibited a plateau, indicative of improving systolic and diastolic function. Also, a specific feature of mIVB-LVP waveforms is an upward notch following minimum LVP (Figure 7, *B*). The relaxation and filling phases in diastole were represented as active and passive relaxation, respectively.[17] In active relaxation, hearts consume energy to expand the ventricular chamber although passively dilate receiving blood sent from the left atrium during passive relaxation. Based on the dynamics of hearts, the upward notch might represent ventricular recoil reflecting the end of active relaxation. Therefore, anticipated changes of LVP waveforms in the mIVB, characterized by the upward notch and subsequent plateau following minimum LVP,

c-

ould be important indicators to know whether the DCD hearts are progressing toward recovery.

FUTURE DIRECTIONS

Establishing functional measurement in EVHP could potentially revolutionize pediatric heart transplant. Recent reports reveal waiting list mortality in pediatrics ranging from 13% to 25%.[18] The pediatric donor heart refusal rate has been reported between 34% and 50% in the United States and Eurotransplant.[19-22] Schweiger and colleagues[18] highlight the 3 primary reasons for donor heart refusal for children: donor history/characteristics, recipient characteristics, and donor organ quality ("marginal donors"). Conversely, the proportion of DCD donors in adults has increased from 7% to 15% of all donors,[23] whereas DCD heart transplants in children remain notably uncommon. These factors clearly indicate the uncertainty surrounding the functional status of both DBD hearts and DCD hearts. This has caused a significant bottleneck hindering the reduction of waiting list mortality and donor heart refusal rate in children. The mIVB method might contribute to demonstrating the functional recovery of these marginal hearts and potentially increase the donor pool for children.

Study Limitations

First, the optimal timing of functional assessment using the mIVB method might have some variability, given each DCD heart experiences different ischemic periods rather than a definitive timeline. This needs further investigation to estimate the optimal time to evaluate the hearts using the mIVB method. This could be achieved by applying various warm ischemic time ranges. Second, considering that the LVEDP obtained by the pressure-volume catheter was 7 to 8 mm Hg, the 3 to 5 mm Hg of LVEDP provided via the balloon indicates relatively underfilled hearts compared with WM. This might prevent achieving a greater level of correlation in functional parameters measured by the balloon and pressure–volume catheter. However, the loaded status for each heart was eventually determined by the heart's response to an increase in preload via the balloon without triggering ventricular arrhythmia. Therefore, a limitation exists for the applicable LVEDP provided to the hearts via the balloon. There might be inconsistency in making the balloon and a learning curve to properly insert and fixate the balloon into the LV. However, critical assessment of the LVP waveforms and adjustment to get 3 to 5 mm Hg of LVEDP consistently can increase accuracy of functional measurement (shown in Figure E2).

CONCLUSIONS

In a juvenile pig DCD heart model, max+dp/dt and min–dp/dt measured by the mIVB method demonstrated significant correlations to the respective measurements in WM in DCD hearts. Sequential functional monitoring with the mIVB method is also valuable to understand recovery trends of DCD hearts. Therefore, the mIVB method could be applicable to clinical practice safely and give relevant estimations, which have not been obtained without WM, to reveal latent functional capability of DCD hearts before transplantation.

Conflict of Interest Statement

The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

References

1. White CW, Messer SJ, Large SR, et al. Transplantation of hearts donated after circulatory death. *Front Cardiovasc Med*. 2018;5:8.
2. Messer S, Cernic S, Page A, et al. A 5-year single-center early experience of heart transplantation from donation after circulatory-determined death donors. *J Heart Lung Transplant*. 2020;39:1463-1475.
3. Dhital K, Ludhani P, Scheuer S, Connellan M, Macdonald P. DCD donations and outcomes of heart transplantation: the Australian experience. *Indian J Thorac Cardiovasc Surg*. 2020;36:224-232.
4. García Sáez D, Zych B, Sabashnikov A, et al. Evaluation of the organ care system in heart transplantation with an adverse donor/recipient profile. *Ann Thorac Surg*. 2014;98:2099-2105.
5. Wang L, MacGowan GA, Ali S, Dark JH. Ex situ heart perfusion: the past, the present, and the future. *J Heart Lung Transplant*. 2021;40:69-86.
6. Bell RM, Mocanu MM, Yellon DM. Retrograde heart perfusion: the Langendorff technique of isolated heart perfusion. *J Mol Cell Cardiol*. 2011;50:940-950.
7. Sutherland FJ, Shattock MJ, Baker KE, Hearse DJ. Mouse isolated perfused heart: characteristics and cautions. *Clin Exp Pharmacol Physiol*. 2003;30:867-878.
8. Curtis MJ, Macleod BA, Tabrizchi R, Walker MJ. An improved perfusion apparatus for small animal hearts. *J Pharmacol Methods*. 1986;15:87-94.
9. Duignan T, Guariento A, Doulamis IP, et al. A multi-mode system for myocardial functional and physiological assessment during ex situ heart perfusion. *J Extra Corpor Technol*. 2020;52:303-313.
10. Guariento A, Doulamis IP, Duignan T, et al. Mitochondrial transplantation for myocardial protection in ex-situ−perfused hearts donated after circulatory death. *J Heart Lung Transplant*. 2020;39:1279-1288.
11. Kadowaki S, Siraj MA, Chen W, et al. Cardioprotective actions of a glucagon-like peptide-1 receptor agonist on hearts donated after circulatory death. *J Am Heart Assoc*. 2023;12:e027163.
12. Bolli R. Mechanism of myocardial "stunning". *Circulation*. 1990;82:723-738.
13. Wijns W, Serruys PW, Slager CJ, et al. Effect of coronary occlusion during percutaneous transluminal angioplasty in humans on left ventricular chamber stiffness and regional diastolic pressure-radius relations. *J Am Coll Cardiol*. 1986;7:455-463.
14. Suga H, Hisano R, Hirata S, Hayashi T, Ninomiya I. Mechanism of higher oxygen consumption rate: pressure-loaded vs. volume-loaded heart. *Am J Physiol*. 1982;242:H942-H948.
15. Suga H. Ventricular energetics. *Physiol Rev*. 1990;70:247-277.
16. Sagawa K. The ventricular pressure-volume diagram revisited. *Circ Res*. 1978;43:677-687.
17. Lewis BS, Gotsman MS. Current concepts of left ventricular relaxation and compliance. *Am Heart J*. 1980;99:101-112.
18. Schweiger M, Everitt MD, Chen S, et al. Review of the discard and/or refusal rate of offered donor hearts to pediatric waitlisted candidates. *Pediatr Transplant*. 2020;24:e13674.
19. Bailey LL, Razzouk AJ, Hasaniya NW, Chinnock RE. Pediatric transplantation using hearts refused on the basis of donor quality. *Ann Thorac Surg*. 2009;87:1902-1908; discussion 1908-1909.

20. Morrison AK, Gowda C, Tumin D, et al. Pediatric marginal donor hearts: trends in US national use, 2005-2014. *Pediatr Transplant*. 2018;22: e13216.

21. Paul JJ, Tani LY, Shaddy RE, Minich LL. Spectrum of left ventricular dysfunction in potential pediatric heart transplant donors. *J Heart Lung Transplant*. 2003;22:548-552.

22. Smith JW, O'Brien KD, Dardas T, et al. Systematic donor selection review process improves cardiac transplant volumes and outcomes. *J Thorac Cardiovasc Surg*. 2016;151:238-243.

23. Israni AK, Zaun D, Rosendale JD, et al. OPTN/SRTR 2016 annual data report: deceased organ donation. *Am J Transplant*. 2018;18(suppl 1): 434-463.

APPENDIX E1. DONATION AFTER CIRCULATORY DEATH (DCD) HEART MODEL

In this section, methods to create the DCD heart model and the process to safely switch to working mode are summarized. Detailed descriptions of the DCD heart model using juvenile pigs are provided in our previous report.[E1] Warm ischemic time of the DCD hearts is defined as the time period from mechanical ventilation withdrawal to cardioplegia infusion. Cardioplegia solution is administrated 15 minutes after cardiac arrest to mimic the clinical setting, consisting of five-minute "no touch" period plus 10 minutes for sternotomy/cannulation. A total of 500 mL of cardioplegia solution (34.95 mL of dextrose 70%, 5 mL of KCL 2-mmol/L, 3.37 mL of NaCl 4-mmol/L, 0.38 mL of Mg_2SO_4 2-mmol/L, 456.30 mL of water, supplemented with 1000 U of erythropoietin and 50 mg of nitroglycerin) is given antegrade into the aortic root. The heart is then excised and placed onto the ex-vivo heart perfusion circuit, where the heart is reperfused with oxygenated whole blood (10 mL/kg/min) at 36.5 °C via the innominate arterial cannula. When switching to working mode from ex-vivo perfusion mode, the left atrial cannula is opened while maintaining arterial blood flow through the innominate arterial cannula at the same time. This ensures coronary perfusion via the blood flow from the innominate arterial cannula even if the left ventricle struggles to pump blood into the aortic root. Furthermore, this allows the heart to adapt to the loaded condition, and also enables the heart to deair inside the left ventricle with less concern for air embolism in the coronary arteries. When the left ventricle successfully pumps blood to maintain coronary perfusion, the innominate arterial line is clamped. These careful approaches are helpful for a smooth transition to working mode while maintaining coronary perfusion.

ASSESSMENT OF HEMODYNAMIC FUNCTION OF DCD HEARTS

Baseline hemodynamic function was assessed before ischemia and in working mode. Echocardiography was performed with a Vivid S6 ultrasound transducer (GE Healthcare). Left ventricular ejection fraction was measured by the modified Simpson method. Peak early diastolic tissue (e′) velocity was measured at the lateral and septal mitral annulus from tissue Doppler in the apical 4-chamber view.

Data obtained by the pressure-volume catheter (VSL, Transonic Inc) connected to an ADV500 Combo PV Foundation System (version 5.0; Transonic Inc) was processed and recorded by LabChart 8 (ADInstruments Inc).

METABOLIC VARIABLES

Arterial blood was obtained from an arterial line post-oxygenator. Venous blood was collected from the coronary sinus via a cannula in the pulmonary artery. Both arterial and venous blood sampling were performed every 30 minutes during reperfusion and working mode. At each time point, blood gas analysis was performed with an iSTAT analyzer (Abbott Inc) to calculate myocardial oxygen consumption, arterial oxygen content, venous oxygen content and coronary vascular resistance. Formulas to calculate these parameters are provided in our previous report.[E1]

E-Reference

E1. Kadowaki S, Siraj MA, Chen W, et al. Cardioprotective actions of a glucagon-like peptide-1 receptor agonist on hearts donated after circulatory death. *J Am Heart Assoc*. 2023;12:e027163.
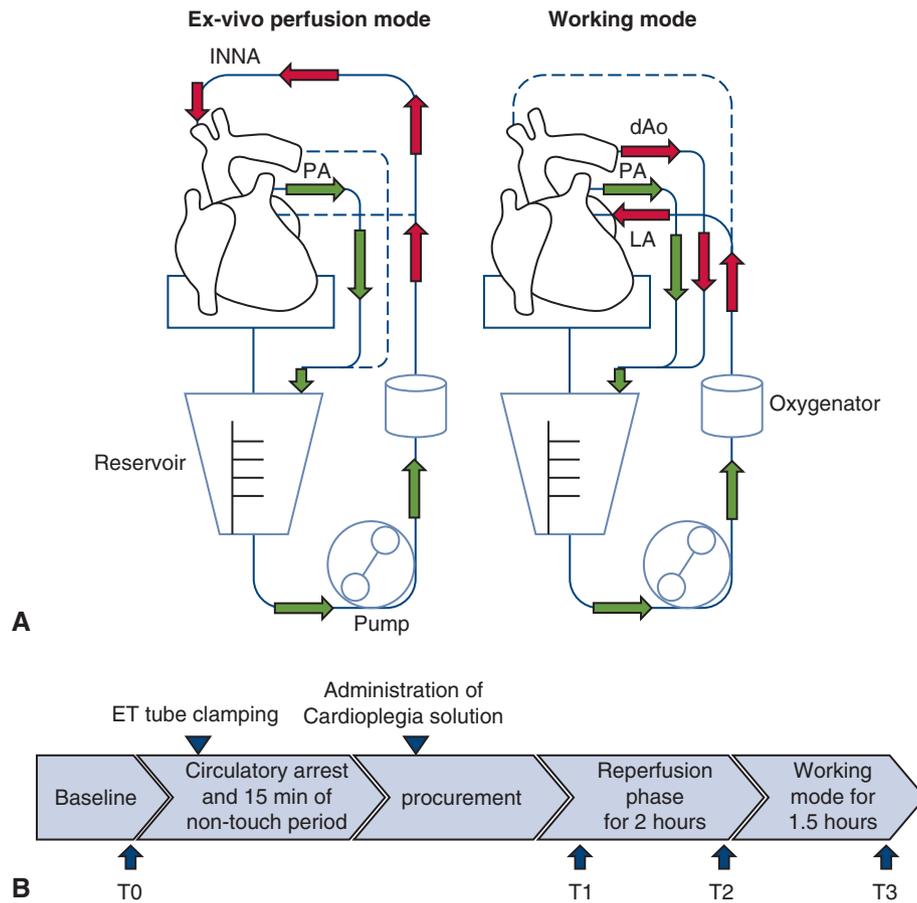
FIGURE E1. Perfusion methods and experimental protocol. All donations after circulatory death (DCD) hearts were reperfused on the EVHP for 2 hours, and then switched to the working mode to assess functional recovery. During the working mode, DCD hearts were preloaded and allowed to eject 120% of cardiac output. A, Ex vivo perfusion mode (*left*) and working mode (*right*) are shown. *Dotted lines* indicate clamped and not used. *Arrows* show flow directions, and *red* and *purple* indicate arterial and venous blood, respectively. B, Experimental protocol. Circulatory arrest was induced via clamping an endotracheal tube, and then DCD hearts were procured after 15 minutes of non-touch period. There are 4 designated time points to get blood samples: T0, before ischemia; T1, immediate after reperfusion; T2, 2 hours after reperfusion; and T3, at the end of the working mode. *INNA*, Innominate artery; *dAo*, Descending aorta; *PA*, pulmonary artery; *LA*, left atrium; *ET*, endotracheal tube.[1]
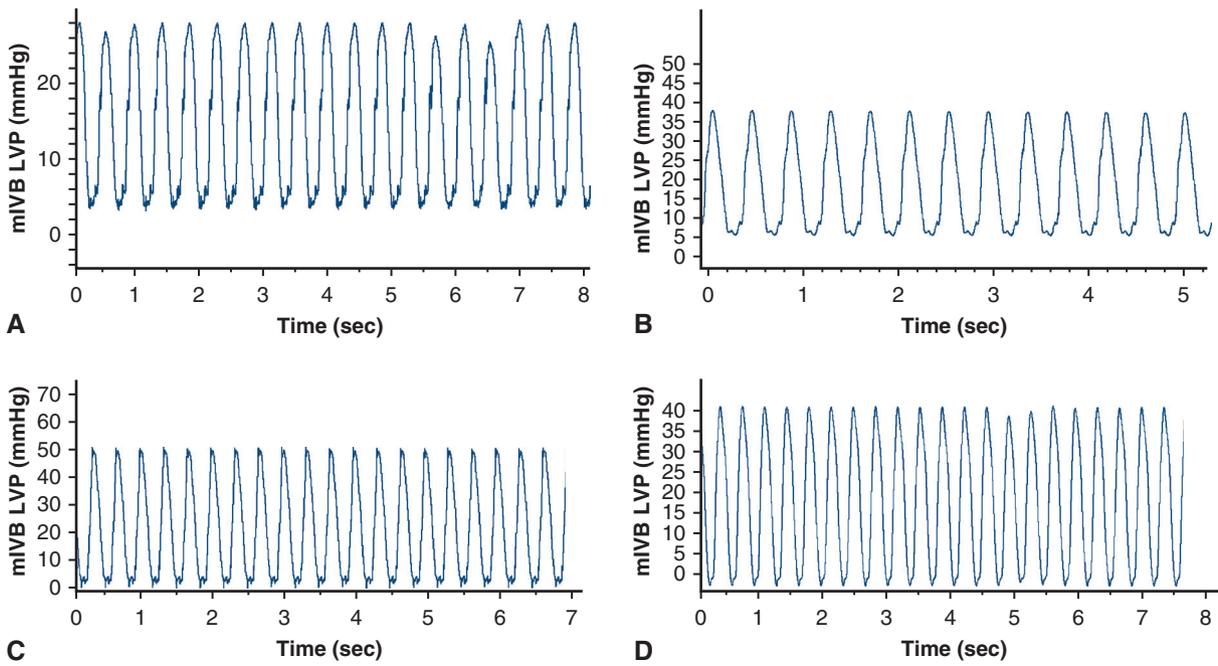
FIGURE E2. Representative figures of inaccurate left ventricular pressure waveforms. A-C, Damping wave forms, requiring fully unfolding the balloon. D, Negative minimum pressure of the left ventricle, suggesting saline leakage from the balloon, requiring changing it to a new balloon. *mIVB*, Modified intraventricular balloon; *LVP*, left ventricular pressure.
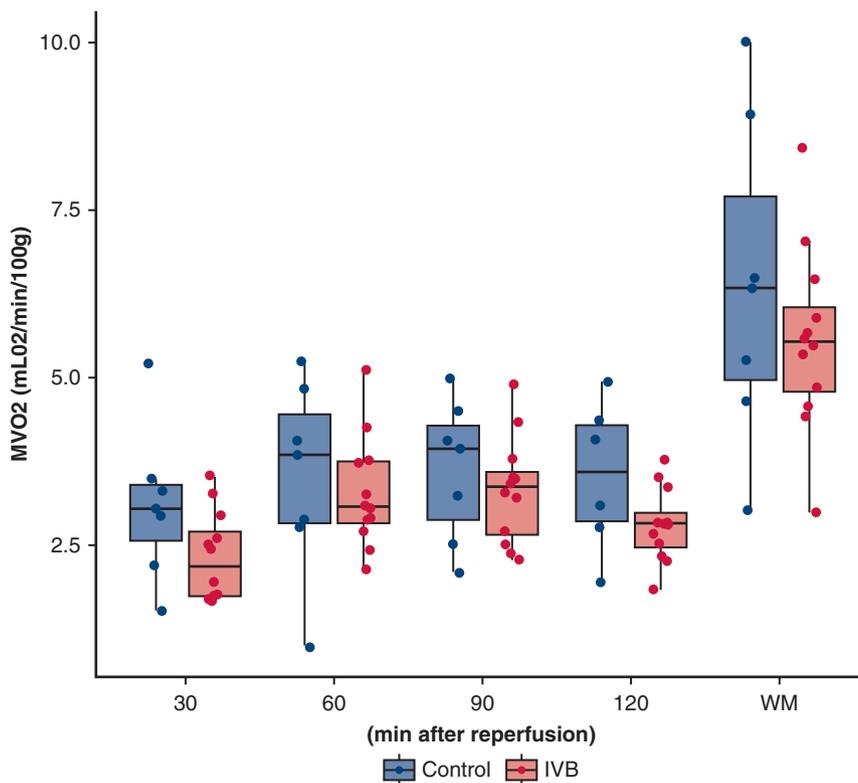
FIGURE E3. MVO$_2$ of donation after circulatory death hearts with (n = 12) versus without the modified intraventricular balloon (n = 6) during reperfusion phase. $P > .1$ at all time points. *MVO$_2$*, Myocardial oxygen consumption; *IVB*, intraventricular balloon.