

Cardiac function unchanged following reanimation with normothermic regional perfusion in donation after circulatory death



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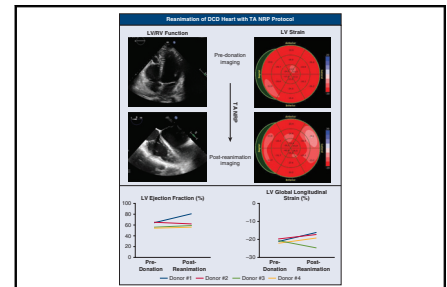
ABSTRACT

Objectives: To determine whether hearts reanimated with normothermic regional perfusion (NRP) have clinically detectable changes in function using echocardiography comparing the prearrest and post-NRP imaging. As heart transplantation from donation after circulatory death (DCD) continues to increase, preliminary results suggest outcomes comparable with donation after brain death. It is unknown whether the obligatory period of warm ischemia experienced during DCD withdrawal process causes immediate changes in cardiac allograft function following in situ reanimation.

Methods: We retrospectively reviewed and compared predonation with postreanimation echocardiographic findings in all DCD donors at our institution from January to October 2021. All DCD donor organs were reanimated with in situ thoracoabdominal NRP after circulatory death. Echocardiographic assessment included (1) 2-dimensional and speckle-tracking measures of chamber size and function; (2) ejection fraction; (3) fractional area change; and (4) global longitudinal strain.

Results: Altogether, 4 DCD heart donations were performed during the study period. Basic demographics and withdrawal ischemic time periods are reported. There were no changes in left ventricular ejection fraction and right ventricular fractional area change when comparing the predonation and the postreanimation echocardiogram. There was a minimal, nonstatistically significant decrease in left ventricular global longitudinal strain and right ventricular free-wall systolic strain in 3 of the 4 donors following reanimation.

Conclusions: DCD cardiac allografts reanimated with NRP demonstrated no change in echocardiographic parameters used for a standard predonation donor heart evaluation. Findings suggest cardiac function of DCD allografts reanimated with thoracoabdominal NRP is not adversely impacted by limited period of warm ischemia following circulatory arrest. (*JTCVS Techniques* 2022;15:136-43)



Predonation echocardiographic evaluation to the postreanimation echocardiographic images.

CENTRAL MESSAGE

Thoracoabdominal normothermic regional perfusion (NRP) permits in situ cardiac evaluation after death. Predonation versus post-reanimation echoes showed preserved left ventricular ejection fraction.

PERSPECTIVE

This study evaluated structure and functional assessment of 4 donors undergoing thoracoabdominal normothermic regional perfusion (TA-NRP) in the setting of donation after circulatory death. In situ evaluation permits the reanimated heart to be assessed before procurement for transplantation. We found that postreanimation cardiac size and biventricular function was not statistically different.

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Abbreviations and Acronyms

DCD	= donation after cardiac death
GLS	= global longitudinal strain
LV	= left ventricle
NRP	= normothermic regional perfusion
RV	= right ventricle/ventricular
TA	= thoracoabdominal
TEE	= transesophageal echocardiography
TTE	= transthoracic echocardiography

Heart transplantation using donation after circulatory death (DCD) has the potential to significantly increase the number of available donor organs over the standard donation after brain death donor pool.¹ DCD donation is unlike donation after brain death in that donor organs are perfused normally until dissection is complete. Then, a crossclamp is applied and cardioprotective measures delivered. In contrast, DCD organs undergo warm ischemia between circulatory arrest and graft procurement. Successful recovery of a heart for transplantation is based on expeditious in situ reperfusion with oxygenated blood after circulatory arrest and an obligatory no-touch 5-minute period. Through cannulae placed in the ascending aorta and right atrium, the circulation is restarted artificially with venoarterial extracorporeal membrane oxygenation after excluding head and neck vessels to prevent blood flow to the brain.¹ Cardiac allograft evaluation in donation after circulatory death is particularly critical, given the variable and potentially damaging conditions to which grafts are exposed before donation.

There are 2 significant events between the predonation evaluation of a potential DCD heart and the implantation of the graft into the recipient: hypoxic circulatory arrest followed by procurement reperfusion (warm ischemia) and the period of cold storage for transport from donor hospital to a recipient institution (cold ischemia). The impact of the warm ischemia on the performance of the donor can be evaluated using the thoracoabdominal (TA) normothermic regional perfusion (NRP) protocol, permitting the evaluation of donor heart performance before the administration of organ-preservation solution, procurement, and the placement on static cold-storage.

Preclinical animal studies regarding DCD cardiac donor organ performance demonstrate that hypoxia-specific cardiac arrest is associated with increased right ventricular (RV) strain as a hemodynamic consequence of rapid elevation in pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction.²⁻⁴ This may be concerning for the potential impact on the posttransplantation function of the DCD cardiac allograft, particularly in recipients with pretransplantation pulmonary hypertension. Messer and

colleagues⁵ demonstrated the feasibility of functional graft assessment of DCD grafts with transesophageal echocardiography (TEE) after weaning the donor from extracorporeal mechanical support during TA-NRP donor heart recovery. However, there is paucity of data with regards to specific echocardiographic indices used for functional evaluation of DCD allografts reanimated with NRP after cardiac arrest. Here donor cardiac assessment was evaluated using standard 2-dimensional echocardiography methodology as well as 2-dimensional strain to evaluate and compare donor cardiac function as determined during predonation evaluation and following reanimation.

METHODS

Following approval by the institutional review board on May 19, 2021 (0315-21-EP), donor echocardiograms of Maastricht Category 3 DCD donors⁶ at the University of Nebraska Medical Center during the period of January 2021 to November 2021 were evaluated. Predonation evaluation echocardiograms were compared to echocardiograms performed following reanimation using our institutional TA-NRP protocol.

DCD TA-NRP Protocol

All potential DCD hearts were evaluated with transthoracic echocardiography (TTE)/TEE to assess predonation function and rule out structural abnormalities. Organs were recovered in accordance with our study protocol (NCT04626284) approved by the institutional review board on October 28, 2020 (0460-20-FB) using TA-NRP. In short, after circulatory arrest and a mandatory 5-minute no-touch period, the donor chest was opened through median sternotomy, the head and neck vessels were divided, and flow was re-established through arterial cannula placed in the ascending aorta and venous cannula positioned in the right atrium. Vasopressin and phenylephrine infusions were used to maintain an adequate blood pressure; no inotropic medications were used. Following resuscitation and optimization, the donor was separated from extracorporeal mechanical support, allowing the donor heart to provide full circulatory support. Details of the withdrawal process and timeline of the TA-NRP related interventions are depicted in Figure 1.

Graft Functional Evaluation

The donor hearts underwent functional assessment with TEE (Philips CVx machine and X8-2t TEE probe; Philips Healthcare). Standard linear measurements denoting cardiac chamber size and function were performed.⁷ Global longitudinal strain (GLS) of the left ventricle (LV) and free wall strain of the RV were performed on both the predonation and post-reanimation echocardiograms (TOMTEC-ARENA TTA2.40.00; TOMTEC) on images with a framerate of 40 to 60 Hz. GLS was determined using the AutoStrain package using 4-chamber, 2-chamber, and long-axis (3-chamber) views of their respective echocardiograms. RV free wall strain was performed from a 4-chamber view to evaluate the free-wall of the RV. There was incomplete data regarding transmitral flow and other parameters of diastolic function to incorporate into the evaluation.

Statistical Analysis

Continuous variables are presented as median with 25th and 75th percentile intervals and compared with Wilcoxon signed ranks test for 2 related samples. Statistics 26 (IBM Corp) was used for statistical analyses.

RESULTS

Our team attended 11 DCD heart recoveries during the study period, of which 5 were located at our institution,

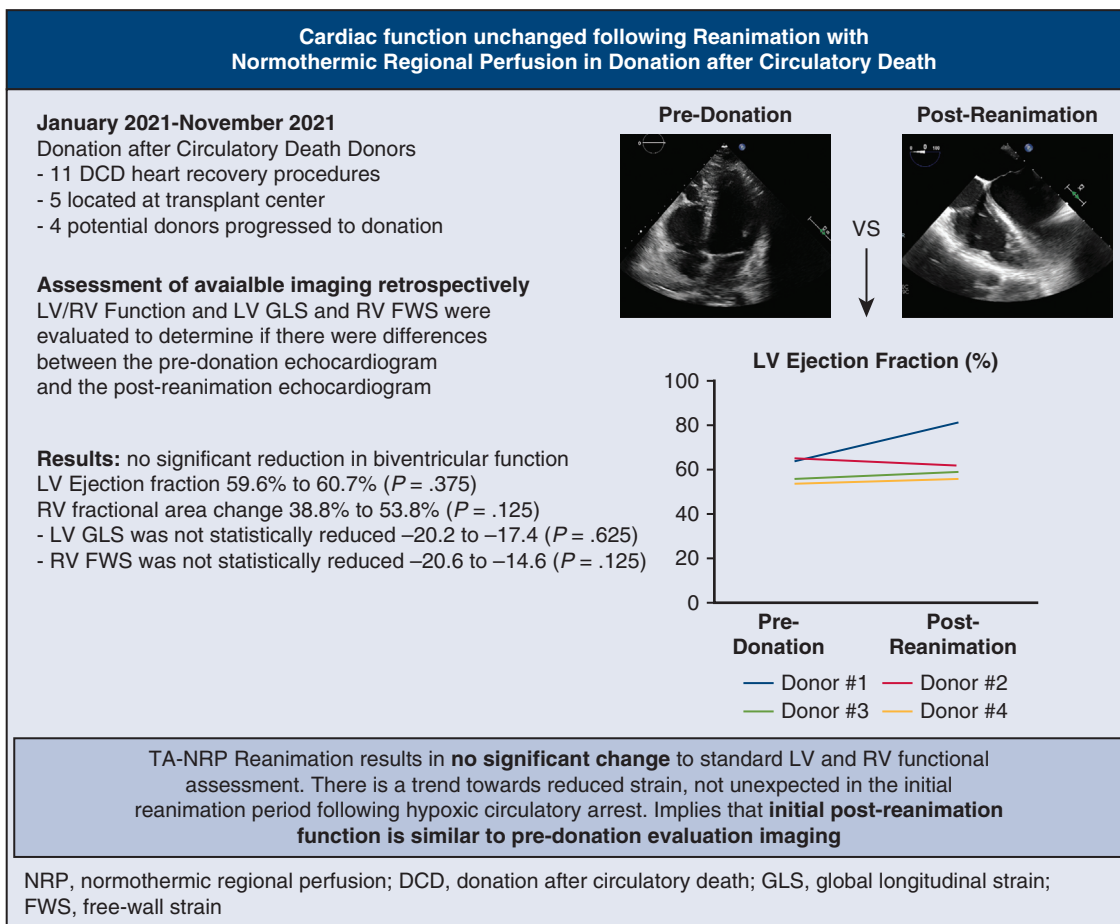


FIGURE 1. Graphical summary timeline of the events and steps that occur during the DCD TA-NRP protocol. The steps undertaken by the surgical team are indicated as *boxes* above the timeline. Steps performed by the anesthesiology team. The timeline is broken down by color into 6 distinct periods from the withdrawal of life-sustaining therapies until the donor organs are procured. *DCD*, Donation after circulatory death; *TA-NRP*, thoracoabdominal normothermic regional perfusion; *LV*, left ventricular; *RV*, right ventricular; *GLS*, global longitudinal strain; *FWS*, free-wall strain; *SBP*, systolic blood pressure.

and 4 progressed to death and underwent the TA-NRP protocol along with TEE imaging for in situ assessment. All 4 hearts were successfully reanimated and separated from extracorporeal mechanical support. Three of the 4 donor hearts were procured and transplanted. One heart was not used due to concern with the length of warm ischemia for the kidney, in a recipient needing dual organ (heart–kidney) transplantation. The flowchart of donor selection for the study is summarized in Figure 2.

Donor demographics and withdrawal ischemic time periods are presented in Table 1. In all cases, the target functional warm ischemic time of less than 30 minutes was maintained. Paired measurements obtained from the predonation and post-NRP echocardiograms are shown in Table 2. These paired measurements demonstrate similar values for biventricular size and measures of systolic function. As well, the GLS for the LV and the free wall strain for the RV are demonstrated. Comparisons and statistical

evaluation between predonation and postreanimation measurements are depicted in Table 3.

The statistical evaluation demonstrated nonsignificant differences between the predonation evaluation and the postreanimation imaging following TA-NRP protocol. There is no significant difference in measures of LV and RV size and systolic function using biplane ejection fraction or fractional area change, respectively. Although we did not detect any statistically significant difference, there was a tendency toward a reduction in both LV and RV strain. Graphical representation of these changes between predonation imaging and postreanimation imaging is shown in Figure 3.

For reference, a normal expected value for both LV GLS and RV free-wall strain would be less than -20% , with a more negative number indicative of better performance of strain and a less negative number (closer to zero) indicative of worse systolic performance as measured by strain.⁷ Of

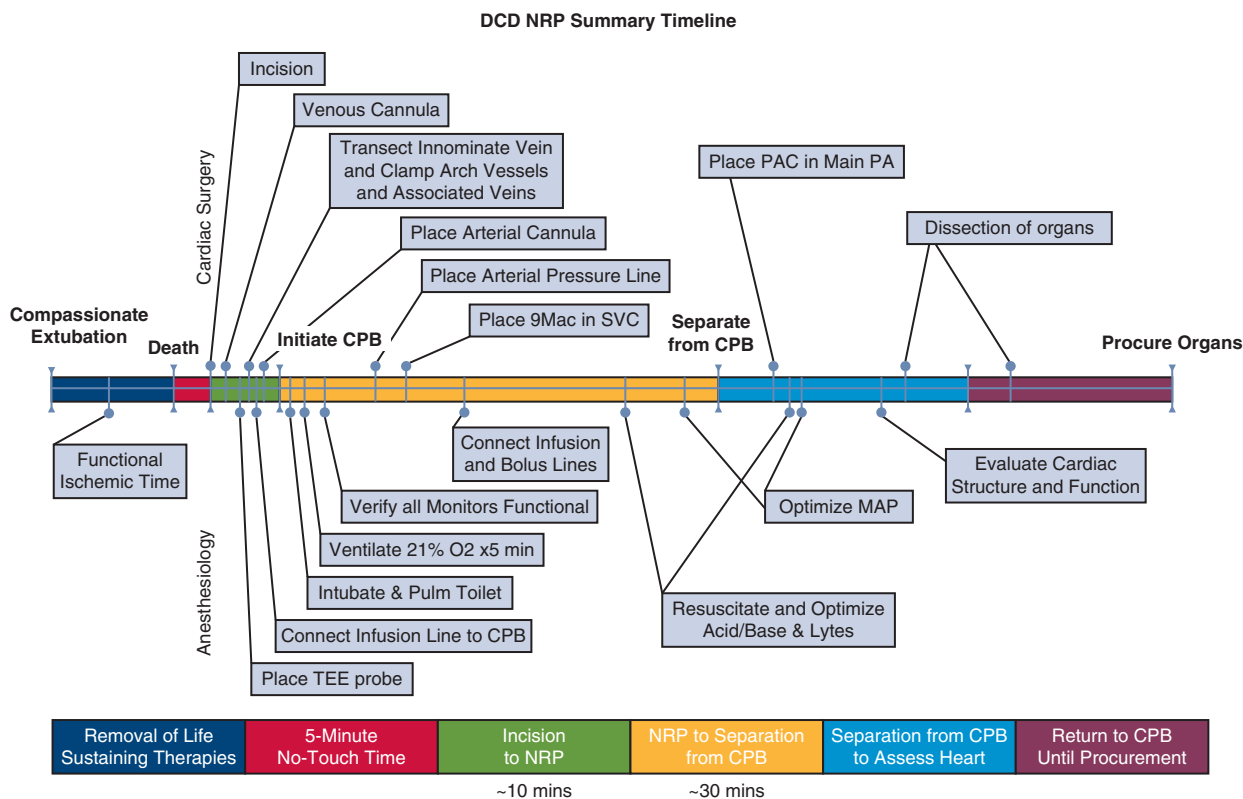


FIGURE 2. Flowchart demonstrating the potential DCD donors during the period reviewed and the outcome of these donors. *DCD*, Donation after circulatory death; *9MAC*, 14-French multiple lumen introducer catheter with a 9-French internal lumen; *SVC*, superior vena cava; *CPB*, cardiopulmonary bypass; *TEE*, transesophageal echocardiography; *PAC*, pulmonary arterial catheter; *PA*, pulmonary artery; *MAP*, mean arterial pressure; *NRP*, normothermic regional perfusion.

the strain values recorded, it is of note that 2 of the 3 donor hearts demonstrated a small reduction that may be of clinically relevance in both LV GLS and RV free-wall strain measures, going from -21.4% to -18.4% in one patient and -20.4% to -15.1% in the other and -19% to -16.3% in the third. The same was true for RV free-wall strain,

showing values of -24.7% to -16.4%, -18.4% to -12.8%, and -16.9% to -11.2%, respectively. These changes, although not statistically significant, may be sub-clinical changes detected by strain and not seen by traditional evaluation metrics. The other donor showed improvement in the LV GLS and no change in the RV strain

TABLE 1. Demographic data and time periods associated with circulatory death and initiation of normothermic regional perfusion

	Donor #1	Donor #2	Donor #3	Donor #4
Demographics				
Age, y	23	26	27	17
Sex	M	M	M	M
Body surface area, m ²	2.1	1.9	2.1	2.1
Reason for admission	Injury/trauma	Injury/trauma	Drug overdose/hypoxia	Injury/trauma
Time intervals				
Agonal phase*	18 min	63 min	41 min	9 min
Acirculatory phase†	15 min	13 min	14 min	12 min
WIT‡	33 min	76 min	55 min	21 min
fWIT§	16 min	22 min	25 min	12 min
Other organs procured	Liver, kidney	Kidney	Liver, lung, kidney	Liver, kidney

WIT, Warm ischemia time; fWIT, functional warm ischemic time. *Period from withdrawal of life sustaining therapies to mechanical asystole. †Period from mechanical asystole to the start of in situ organ reperfusion (includes 5 minutes of no-touch). ‡Period from withdrawal of life sustaining therapies to the start of in-situ organ reperfusion (includes 5 minutes of no-touch). §Period from donor systolic blood pressure less than 50 mm Hg to the start of in situ organ reperfusion (includes 5 minutes of no-touch).

TABLE 2. Parameters obtained of the 4 donors from predonation imaging and postreanimation echocardiography during in situ evaluation following separation from mechanical circulatory support

Modality	Donor #1		Donor #2		Donor #3		Donor #4	
	TTE*	TEE†	TTE*	TEE†	TTE*	TEE†	TTE*	TEE†
LV parameters								
LVIDd, cm	5.0	4.9	3.7	3.6	4.6	4.2	4.9	4.6
LVIDs, cm	3.5	3.4	2.3	2.6	2.8	2.2	3.3	3.3
LV EF	54%	56%	56%	59%	64%	81%	65%	62%
RV parameters								
RVIDd, cm	3.3	3.3	3.9	4.1	4.1	3.6	3.5	2.9
FAC	38%	49%	40%	45%	48%	59%	35%	59%
Strain parameters								
LV GLS	-21.4%	-18.4%	-20.4%	-15.1%	-20.0%	-24.1%	-19%	-16.3%
RV free-wall	-24.7%	-16.4%	-18.4%	-12.8%	-22.9%	-22.4%	-16.9%	-11.2%

TTE, Transthoracic echocardiography; TEE, transesophageal echocardiography; LV, left ventricle; LVIDd, left ventricular internal dimension in diastole; LVIDs, left ventricular internal dimension in systole; LV EF, left ventricular ejection fraction (as determined by Simpson's biplane method of discs); RV, right ventricle; RVIDd, right ventricular internal dimension in diastole (as measured in the RV₁ position); FAC, fractional area change; GLS, global longitudinal strain. *Predonation measurements. †Postheart reanimation measurements.

values. No clinical differences were seen in wall thickness and LV outflow tract dimensions. There was no difference in valvular function when comparing the paired studies.

DISCUSSION

The main finding of our study is that standard echocardiography measurements of ventricular size and function did not show any significant difference between the predonation and postreanimation echocardiogram in any donor. DCD heart transplantation is associated with donor hypoxic circulatory arrest followed by variable period of warm ischemia before organ recovery, leading to potential short- and long-term impacts on graft function. Short-term performance by echocardiographic imaging suggests that these organs are similar in size and function to the predonation imaging study. Although there were minor differences (<2 mm) in some of the linear dimensions used to quantify LV and RV structure, this falls within normal variation. These data correspond to the current understanding that reanimated donor hearts using TA-NRP have normal function. Our results did not confirm previous observation from preclinical studies suggesting compromised RV

function because of hypoxic pulmonary vasoconstriction during the withdrawal process.

We used strain measurement in addition to standard clinical echocardiography indices employed in donor cardiac allograft pretransplantation evaluation. Previous evidence suggests that strain echocardiography is associated with little interobserver variability and has similar reference ranges for both sex and age.⁸ Strain is also a sensitive method to detect subclinical changes in cardiac function. We postulate that the combination of LV ejection fraction and LV GLS measurement is superior modality to detect subclinical cardiac dysfunction, specifically if the same vendor-specific software is used to analyze the predonation and postreanimation with NRP images.^{9,10} We termed these changes "subclinical" to emphasize that the changes measured are not seen in commonly used measures of size and function, namely chamber dimension and systolic performance characteristics. Significant changes must be present in structure and function to have measurable differences in linear measurements. Strain has demonstrated its ability to detect subclinical changes in various population, such as hypertension and cardiotoxic medications.¹¹

TABLE 3. Comparisons between predonation and postreanimation measurements taken with echocardiography

	Pre-WLST	Post-TA-NRP	P value*
LVIDd, cm	4.73 (0.57 IQR)	4.4 (0.62 IQR)	.125
LVEF, %	59.6 (0.86% IQR)	60.7 (0.0% IQR)	.375
LVGLS	-20.2 (-0.9 IQR)	-17.4 (3.83 IQR)	.625
RVIDd, mm	3.7 (0.49 IQR)	3.45 (0.54 IQR)	.375
RVFAC, %	38.8 (4.6% IQR)	53.8 (10.7% IQR)	.125
RVFWS	-20.6 (5.33 IQR)	-14.6 (5.45 IQR)	.125

WLST, Withdrawal of life-supporting therapies; TA-NRP, thoracoabdominal normothermic regional perfusion; LVIDd, left ventricular internal dimension in diastole; IQR, interquartile range; LVEF, left ventricular ejection fraction; LVGLS, left ventricular global longitudinal strain; RVIDd, right ventricular internal dimension in diastole (as measured in the RV₁ position); RVFAC, right ventricular fractional area change; RVFWS, right ventricular free-wall strain. *Wilcoxon signed rank test for 2 related samples.

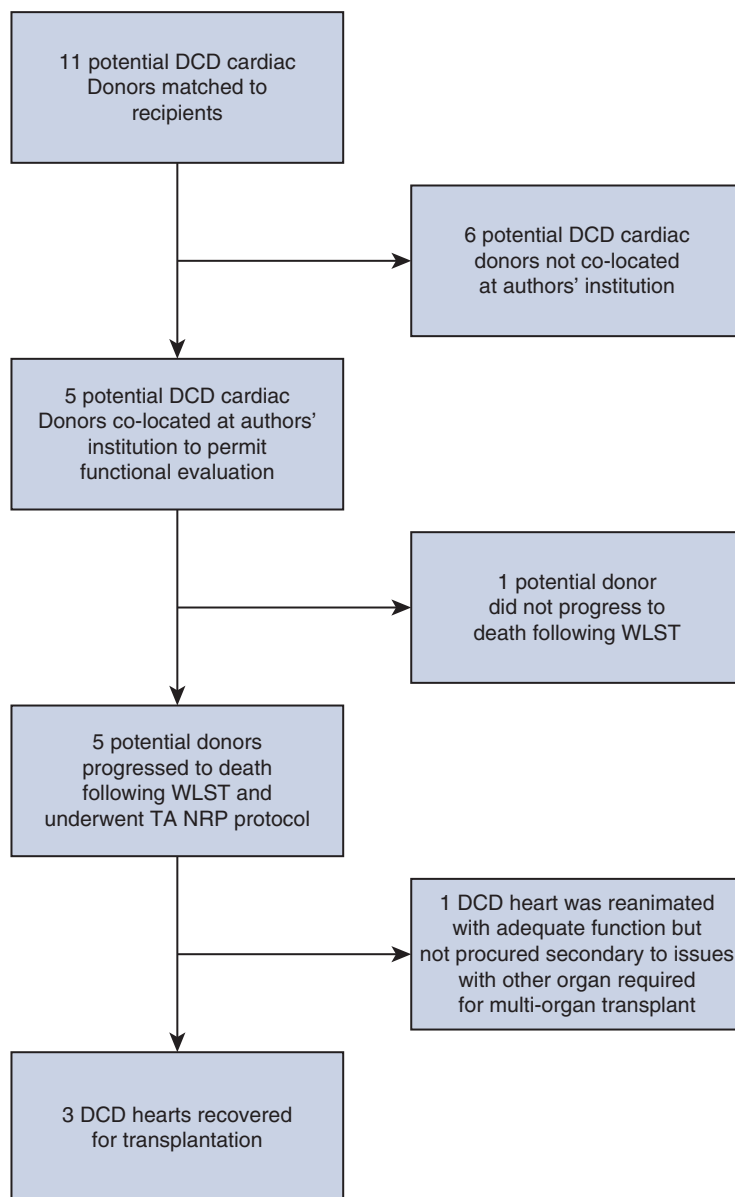


FIGURE 3. Summary of the findings from comparing predonation echocardiographic evaluation with the postreanimation echocardiographic images. Two-dimensional images to evaluate cardiac function before potential DCD donation were compared with the findings after reanimation using the TA-NRP protocol. There were no statistically significant differences seen in both LV ejection fraction and in LV global longitudinal strain, although there was trend towards reduced LV GLS following reanimation. *DCD*, Donation after circulatory death; *TA-NRP*, thoracoabdominal normothermic regional perfusion; *LV*, left ventricle; *GLS*, global longitudinal strain.

Longitudinal comparison of strain results over time is best accomplished using the same modality, but in this case, TTE was compared with TEE in 3 of the 4 cases. Studies evaluating the similarities and differences in TTE and TEE show that TTE strain is often slightly higher (more negative) values for strain when compared with TEE, suggesting that the TTE strain is better than the TEE for the same subject in comparison.¹²⁻¹⁴ While the absolute values are not identical, the 2 modalities demonstrate excellent agreement when comparing GLS;

segmental analysis does not demonstrate such agreement.¹³ This may be from differences in imaging plane orientation or other factors. While strain was done off-line and retrospectively in this setting, it could be a potentially helpful metric for biventricular function after TA-NRP, especially if the predonation LV GLS was known before in situ functional assessment.

In this series, 2 donors demonstrated no change in the overall size and systolic function measured by LV ejection fraction and RV fractional area change when predonation

and post-TA-NRP echocardiograms were compared. However, the same 2 donors had a reduction in LV and RV strain. The other 2 donors demonstrated reduced LV and RV size parameters between the predonation TTE and the postreanimation TEE. Other, less rapidly changing measurements appear to be within the margin of measurement error for echocardiography showing no change in overall structure, suggesting that measured differences in chamber size/volume and evaluation of systolic function is the result of either the hypoxic arrest after withdrawal of life-supporting therapies or alterations to vascular resistance following reanimation. Regarding these linear measurements, it is possible that overall performance following reanimation was improved when compared with cardiac function at the time of evaluation for potential donation. As the hemodynamic state of the donor is not controlled for, it is possible that the changes are reflective of different afterload states in the systemic and pulmonary vasculature.

Regarding the 6 recoveries that were omitted, the recovery team was not able to perform a formal TEE examination. The logistic and financial burdens associated with distant TA-NRP are substantial, and there are limitations with regards to the number of personnel and equipment the recovery team can deploy. To avoid dependence on local resources (availability of a trained anesthesiologist and TEE machine) our institution has adopted Fick-based cardiac output calculations and epicardial echocardiography as a means of post-TA-NRP graft assessment in lieu of TEE.

A concern based on preclinical animal studies has been raised about the potential for hypoxia-related RV dysfunction in a DCD setting. Animal models demonstrated that hypoxia-specific cardiac arrest is associated with an elevated pulmonary vascular resistance and increase of the RV size, which is concerning for the potential impact on the function of the DCD donor heart.^{3,4} In addition, there was demonstrable decrement in LV cardiac function in those animals that underwent a hypoxic cardiac arrest compared with animals that underwent an exsanguination cardiac arrest.² The impact on the RV from the period of hypoxia and the biventricular dysfunction recognized as the result hypoxic circulatory arrest as reported in animal studies has not been demonstrated in our findings nor reported in clinical DCD heart transplantation experiences elsewhere.^{1,5,15}

As the volume of DCD hearts transplantation continues to expand, recognizing the potential impact of cardiac arrest to impair both short-term and long-term transplantation outcomes requires continued vigilance and functional graft assessment when possible.¹⁶ The minimizing of functional ischemic time and restoration of oxygenated blood flow via the TA NRP protocol not only reanimates cardiac function but improves perfusion of other organs.¹⁷ Our experience

suggests that DCD hearts reanimated after a relatively short functional warm ischemic time and without need for inotropic support demonstrate donor cardiac function not clinically different from the predonation echocardiogram, although there is identifiable reduction in strain in a subset of cases.

Limitations/Summary/Future Inquires

Our study has several limitations inherent to the nature of a single-center observational study. The major limitation of our analysis is the small sample size that predisposes the study to the risk of a type II error. It is possible that the lack of statistical difference would not bear out in a larger sample population. This series of 4 DCD heart donors undergoing TA NRP at one institution is far too small to make wide sweeping assumptions on the overall performance of all hearts procured in this manner. Despite the limitations, we believe our results refute concerns presented that DCD hearts that undergo circulatory arrest (as Category 3 DCD donors experience) does not preclude their use secondary to irreversible RV dysfunction and injury. The “hypoxic-ischemic” arrest experienced in these cases is different from the “hypoxia-only” arrest as described in animal models does provide uncertainty on whether other organs may be impacted.²⁻⁴ Future evaluation and comparison will further the understanding on maximally tolerated functional ischemic time limits and characteristics seen during the reanimation process during TA-NRP and the separation from mechanical circulatory support that supports adequate functional capacity for the donor heart. This experience suggests that in DCD hearts reanimated after a relatively short functional ischemic time and without need for inotropic support, donor cardiac function following reanimation is not clinically different from the predonation echocardiogram, although there is identifiable reduction in strain.

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.

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Key Words: donation after circulatory death, heart transplantation, strain, echocardiography