Heart transplant advances: Ex vivo organ-preservation systems

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Feature Editor Note—*In the accompanying article, the team from Duke presents the underlying concepts and early data surrounding the implementation of ex vivo organ preservation in heart transplantation. Cold storage is currently the standard practice in donor-heart preservation, yet with this approach, prolonged ischemic times lead to greater rates of primary graft dysfunction. The goal of ex vivo heart preservation is to minimize ischemic damage during storage, facilitate longer periods of storage, and allow opportunity for detailed evaluation of marginal donor hearts prior to transplantation. Currently, one device, the TransMedics Organ Care System, or "heart-in-a-box," has received the CE mark of approval in Europe and is undergoing review for Food and Drug Administration approval in the United States. The authors review the theory of operation of the device and discuss how knowledge gaps regarding its best use may be addressed in the future.*

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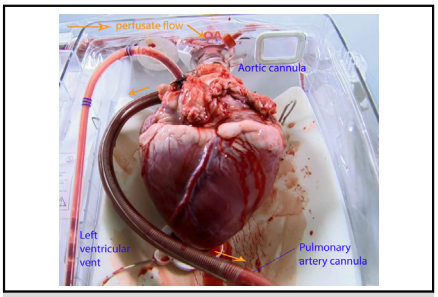

A donor heart undergoing ex vivo perfusion on the TransMedics Organ Care System.

CENTRAL MESSAGE

Ex vivo heart perfusion enables expansion of the donor pool and to date shows comparable outcomes to the standard of care.

BACKGROUND: COLD STORAGE AND ITS SHORTCOMINGS

Traditional storage of donated hearts has built on strategies for cardioplegia used during cardiac surgery, as well as preservation solutions used in the transplantation of other solid organs. While cold storage has supported heart transplantation for decades and allowed it to expand, the process of cold storage results in ischemic damage. Ischemic time is correlated with primary graft dysfunction (PGD) and 1-year post-transplant survival in a nearly linear manner.[1] Unlike other solid organs, hearts are sensitive to ischemic times longer than 4 hours. This relationship varies with donor age, but heart donation is persistently limited by this narrow time frame.[2] This limits the effective range across which donor hearts can be transported and the overall number of donors whose hearts are actually used for transplantation. This in turn contributes to longer waiting times for heart transplantation, greater waitlist mortality, and presumably lower listing rates because recipients may be assumed to have a prohibitively long wait time ahead of them. The new heart-allocation system promotes greater organ sharing overall but with the disadvantage of greater overall mean ischemic time.[3]

ADVANTAGES OF EX VIVO PERFUSION

Ex vivo organ preservation may enable the expansion of the overall number of heart transplants and lower rates of early graft dysfunction. These are realized through (1) safe extension of the time between procurement and transplantation and (2) ex vivo assessment of extended criteria hearts.

Ex vivo perfusion has also facilitated donation of hearts after circulatory determination of death (DCD), allowing the inclusion of heart transplantation with that of other solid organs in that avenue of donation. The theoretical challenges of DCD heart transplantation are similar to those associated with expanded-criteria or long-distance cold storage transplantation (increased ischemia–reperfusion injury) but also include the lack of opportunity to inspect the heart before arrest and uncertainty surrounding the variable "agonal" period while the donor is hypotensive and hypoxemic but has not yet progressed to asystole. Pulmonary vasoconstriction, increased pulmonary wedge

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pressure, and a catecholamine surge contribute to right ventricular distention during this period.[4,5] Ex vivo perfusion enables a period of recovery and evaluation before the final decision to transplant the organ.

CLINICAL EXPERIENCE WITH EX VIVO PERFUSION

While multiple competing platforms have been introduced for ex vivo perfusion of liver and lung allografts, the only platform that has achieved clinical success for ex vivo heart perfusion is the Organ Care System (OCS; TransMedics, Andover, Mass) (Figure 1). This platform was first examined in the PROTECT I trial (Prospective Multi-Center European Trial To Evaluate the Safety and Performance of the Organ Care System for Heart Transplants), a single-arm study done in 4 centers in England and Germany, which demonstrated safety among 20 hearts transplanted out of 25 hearts instrumented on OCS from 2006 to 2007.[6] The PROTECT II trial followed in 2007-2008, although results have not been formally published. The OCS has subsequently been CE marked for use in the European Union. The US-based PROCEED II (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation) trial demonstrated noninferiority of outcomes for 67 transplants transported with the OCS platform relative to 63 cold static storage control cases.[7] The US trial was a randomized trial limited to low-risk heart transplant cases. Both of PROCEED II trials reported comparable short-term outcomes. Further analysis of a subset of the PROCEED II participants showed no significant difference in outcomes with OCS at 2 years.[8]

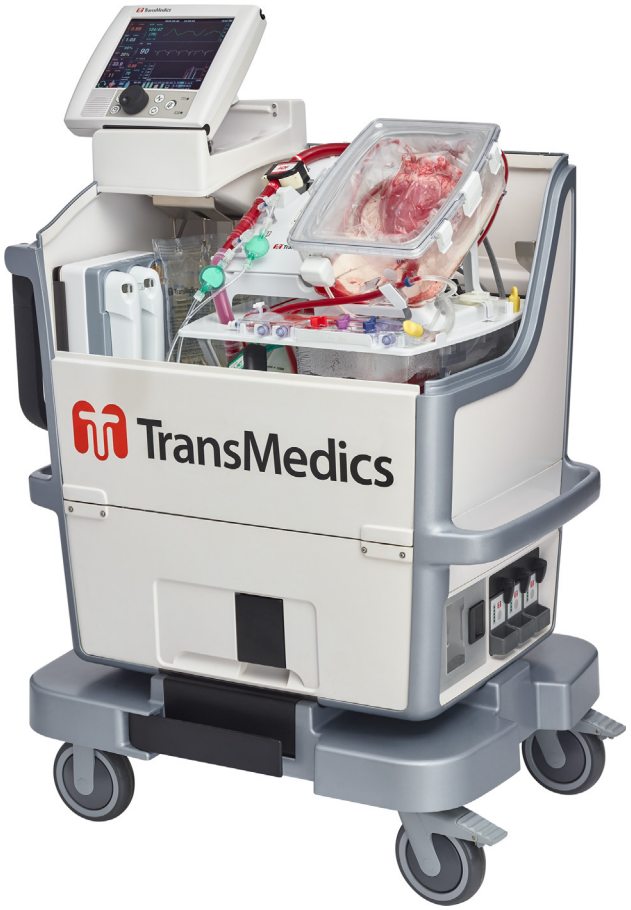

FIGURE 1. The TransMedics Organ Care System is the only platform for ex vivo heart perfusion that has been used for human transplantation.

Further clinical testing was performed in the US-based EXPAND (International Trial to Evaluate the Safety and Effectiveness of The Portable Organ Care System Heart For Preserving and Assessing Expanded Criteria Donor Hearts for Transplantation) trial, which analyzed high-risk transplants with anticipated prolonged ischemic times (>4 hours) or marginal donor heart features (left ventricular hypertrophy, ejection fraction of 40%-50%, donor downtime >20 minutes, donor age >55 years). The short-term results of the EXPAND trial were presented in 2019, showing excellent short-term outcomes in 75 patients transplanted from a total of 93 hearts recovered and perfused on OCS.[9] Full results were expected to follow at the 2020 International Society for Heart and Lung Transplantation meeting (canceled because of the coronavirus disease 2019 [COVID-19] pandemic). The primary end point in EXPAND was freedom from death or severe primary graft dysfunction; the study cohort exceeded a predetermined historical performance measure to demonstrate noninferiority. The device remains investigational in the United States at this time.

The use of OCS for transplantation of DCD hearts was first reported in 2015 by the St Vincent's (Sydney) group, who used OCS for 3 recipients.[10] The ongoing US Donation after Circulatory Death Heart OCS Trial randomizes three-quarters of patients to the experimental arm in which DCD transplantation is possible, although participants may undergo standard-of-care transplant if that becomes available first. To ensure enough participants are in the control arm, one-quarter are randomized to only receive a standard-of-care heart.

The main potential advantage of ex vivo heart perfusion is the expansion of the donor pool by the use of hearts not previously considered for transplantation. This may be due to marginal characteristics of the heart or remote location of the donor that would otherwise lead to a prohibitively long ischemic time. Expanding the donor pool allows recipients to receive better size- and immunologically-matched hearts. Ex vivo perfusion allows for greater flexibility and safety margin in the explant of the recipient's native heart in the case of multiple previous sternotomies or congenital abnormalities. Other reviews have outlined these and other theoretical benefits of ex vivo perfusion.[11,12]

TRANSMEDICS OCS

The TransMedics OCS works on a Langendorff model, in which perfusate is delivered via an external pump into the aortic root (retrograde), closing the aortic valve, and directing perfusate into the coronary arteries (as opposed to circulation powered by the ventricles themselves in which blood would flow across the aortic valve).[13] This model allows for consistent delivery of perfusate and measurement of flow.

Recovery

Recovery of the heart from a donor who has been declared dead proceeds similarly to a cold-storage recovery but with an additional step: just before crossclamp is applied, a large cannula is inserted into the right atrium and 1200 cc of donor blood is rapidly collected. This blood is emptied into the OCS reservoir along with additives while the donor heart is clamped, flushed with cold preservation solution, topically cooled with ice, and explanted.

Preparation for Perfusion

Instrumentation consists of (1) insertion of an aortic cannula: this cannula is the point of suspension of the heart on the device and the route for delivery of perfusate; (2) insertion of a pulmonary artery cannula; (3) insertion of a left ventricular vent to avoid air entrapment and distention of the LV; (4) closing of the inferior vena cava and superior vena cava so most of the coronary perfusate is directed from the coronary sinus to the pulmonary artery cannula; and (5) insertion of temporary pacing wires in the ventricular muscle. The heart is then attached to the OCS machine and perfusion is begun (Figure 2). The heart is quickly warmed to 34°C, defibrillation is performed if needed, and the heart is paced.

Management of the Heart on OCS

Assessment of the function of the heart is limited since the heart is not loaded (an inherent feature of the Langendorff model). The heart is paced but not loaded with volume in either ventricle, so ejection fraction cannot be easily measured or approximated. (The Papworth group has described the modification of the OCS to allow pressure–volume loop measurement using Millar catheters, although this has not been used clinically.[14]) The heart is not in the same anatomic position where it is evaluated during procurement (it rests on the right ventricle and is suspended from the ascending aorta only), limiting direct visualization of function somewhat. The platform does allow access to the coronary ostia for catheterization, when prerecovery angiography is not available.[15] Flow is controlled by altering the force of each linear pump stroke (frequency can be altered by synchronizing pump strokes with the QRS complex). Pressures are measured in the aortic root and in the pulmonary artery cannula (also the sites of perfusate sampling).

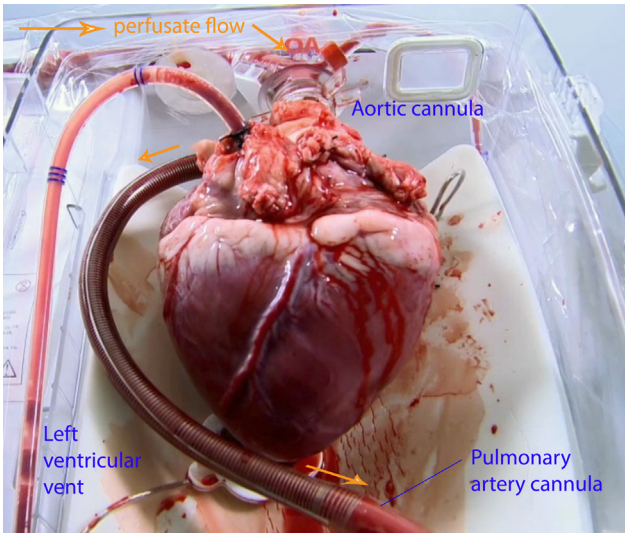

FIGURE 2. A donor heart undergoing perfusion on the TransMedics Organ Care System. (Wires for myocardial pacing have not yet been placed.)

Perfusion Management and Evaluation

The main mode of evaluation of hearts is biochemical. Trends in perfusate lactate have been obtained and recorded for all the trials of the OCS, as lactate has been shown to correlate with post-transplant outcomes.[16] Baseline lactate is measured in the donor serum before arrest. Lactate levels are measured in samples of the perfusate being pumped to the aorta and from the perfusate returning to the reservoir from the pulmonary artery; the values are trended as well as the differential which indicates whether the heart is absorbing or secreting lactate.

While lactate is the end point and best proxy of viability, parameters measured during heart perfusion include flow delivered to the aorta, flow through the pulmonary artery reflecting coronary artery flow, temperature, oxygen saturation, hematocrit, and pulmonary artery pressure. The pressure in the aortic root is measured and controlled with infusion of a solution containing adenosine, causing coronary dilation, effectively reducing the outflow resistance of the pump. In our experience, myocardial edema develops quickly when the coronaries see excessive perfusate flow. Indeed, we believe myocardial edema is the factor that pushes us to minimize the total amount of perfusion time. We have found that providing the lowest amount of aortic flow that allows us to keep lactate levels low minimizes edema and reduces primary graft dysfunction. Stable lactate levels have been a criterion for heart acceptance in all trials evaluating OCS, but other (admittedly more qualitative) factors go into that decision as well. Just as with a cold-storage heart, consideration of recipient and donor factors

(eg, height and weight match, severity of the recipient's illness, immunologic matching, etc) and subjective assessment of the heart are important factors in determining whether to use a heart after perfusion for transplantation. In our experience no one factor has been highly predictive of primary graft dysfunction: While a donor heart that exhibits a rising lactate, visibly increasing edema and high root pressure despite high amounts of adenosine infusion may be at obviously high risk of PGD, the presence of only one of these factors usually does not indicate high PGD risk (and does not indicate that the heart should be discarded). Further research is needed to identify other metabolites (or a panel of compounds) that helps predict post-transplant function. Based on our experience, the degree of myocardial edema during perfusion would likely correlate with primary graft dysfunction; however, an objective and "real-time" measure would need to be developed to operationalize this relationship.

CONCLUSIONS/FUTURE DIRECTIONS

The financial impact of this technology has been difficult to assess. The Ontario provincial health authority was unable to draw any strong conclusions about the theoretical economic impact of OCS for DCD transplantation despite a thorough review.[17] The cost of the machine as well as that of the disposables presents a barrier to entry for lower-volume transplant programs, whereas larger programs may be able to amortize that cost over a significant increase in the number of transplants that can be performed. At our center, we have noted substantially decreased wait times in trial participants; we theorize that this leads to decreased need for temporary mechanical circulatory support and lower waitlist mortality, which helps justify the costs. We also believe that ex vivo perfusion leads to less PGD than would be seen in cold storage of donor hearts when ischemic times would be prolonged by long travel time and unpredictable time requirements for explanting a durable left ventricular assist device. This reduction in PGD, while not yet quantified, would support cost-effectiveness of ex vivo perfusion.

Ex vivo perfusion has considerable potential as a platform for interventions on the donor heart: these could include gene therapy or other treatments to modify the immune profile of the graft and reduce rejection.[18] This may be of importance, since there is evidence that ex vivo perfusion induces inflammatory responses during perfusion. Ex vivo perfusion is an appealing platform since therapeutic substances can be administered directly to the coronaries and without the absorptive capacity of other organs.

Our emerging understanding of the physiology of ex vivo heart perfusion may prompt us to revisit some of the concepts surrounding preservation solution and initial flushing that have been carried over from the cold static storage model.[19] Finally, a durable "working-mode" perfusion platform has been elusive but would offer more direct assessment of function during perfusion, as well as potentially reducing some of the inflammatory response seen in Langendorff retrograde aortic perfusion.[20]

In conclusion, ex vivo heart perfusion has already enabled significant expansion of the donor pool, the use of hearts that would otherwise have been excluded due to geographic or donor-related factors, and to date shows comparable outcomes with the standard of care.

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. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report. Focus Theme: allograft ischemic time. *J Heart Lung Transplant*. 2017;36:1037-46.
2. Russo MJ, Chen JM, Sorabella RA, Martens TP, Garrido M, Davies RR, et al. The effect of ischemic time on survival after heart transplantation varies by donor age: an analysis of the United Network for Organ Sharing database. *J Thorac Cardiovasc Surg*. 2007;133:554-9.
3. Goff RR, Uccellini K, Lindblad K, Hall S, Davies R, Farr M, et al. A change of heart: preliminary results of the US 2018 adult heart allocation revision. *Am J Transplant*. 2020;20:2781-90.
4. White CW, Lillico R, Sandha J, Hasanally D, Wang F, Ambrose E, et al. Physiologic changes in the heart following cessation of mechanical ventilation in a porcine model of donation after circulatory death: implications for cardiac transplantation. *Am J Transplant*. 2016;16:783-93.
5. Iyer A, Chew HC, Gao L, Villanueva J, Hicks M, Doyle A, et al. Pathophysiological trends during withdrawal of life support: implications for organ donation after circulatory death. *Transplantation*. 2016;100:2621-9.
6. Tenderich G, Tsui S, El-Banayosy A, Dhital K, Schulte-Eistrup S, Schulz U, et al. 293: The 1-year follow-up results of the PROTECT patient population using the Organ Care System. *J Heart Lung Transplant*. 2008;27:S166.
7. Ardehali A, Esmailian F, Deng M, Soltesz E, Hsich E, Naka Y, et al. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet*. 2015;385:2577-84.
8. Chan JL, Kobashigawa JA, Reich HJ, Ramzy D, Thottam MM, Yu Z, et al. Intermediate outcomes with ex-vivo allograft perfusion for heart transplantation. *J Heart Lung Transplant*. 2017;36:258-63.
9. Schroder JN, D'Alessandro D, Esmailian F, Boeve T, Tang P, Liao K, et al. Successful utilization of extended criteria donor (ECD) hearts for transplantation—results of the OCS™ Heart EXPAND trial to evaluate the effectiveness and safety of the OCS heart system to preserve and assess ECD hearts for transplantation. *J Heart Lung Transplant*. 2019;38:S42.
10. Dhital KK, Iyer A, Connellan M, Chew HC, Gao L, Doyle A, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet*. 2015;385:2585-91.
11. Ragalie WS, Ardehali A. Current status of normothermic ex-vivo perfusion of cardiac allografts. *Curr Opin Organ Transpl*. 2020;25:237-40.
12. Messer S, Ardehali A, Tsui S. Normothermic donor heart perfusion: current clinical experience and the future. *Transpl Int*. 2015;28:634-42.
13. Bell RM, Mocanu MM, Yellon DM. Retrograde heart perfusion: the Langendorff technique of isolated heart perfusion. *J Mol Cell Cardiol*. 2011;50:940-50.
14. Messer SJ, Axell RG, Colah S, White PA, Ryan M, Page AA, et al. Functional assessment and transplantation of the donor heart after circulatory death. *J Heart Lung Transplant*. 2016;35:1443-52.

15. Ghodsizad A, Bordel V, Ungerer M, Karck M, Bekeredjian R, Ruhparwar A. Ex vivo coronary angiography of a donor heart in the Organ Care System. *Heart Surg Forum*. 2012;15:E161-3.
16. Hamed A, Tsui S, Huber J, Lin R, Poggio E, Ardehali A. Serum lactate is a highly sensitive and specific predictor of post cardiac transplant outcomes using the Organ Care System. *J Heart Lung Transplant*. 2009;28:S71.
17. Ontario Health (Quality). Portable normothermic cardiac perfusion system in donation after cardiocirculatory death: a health technology assessment. *Ont Health Technol Assess Ser*. 2020;20:1-90.
18. Bishawi M, Roan J-N, Milano CA, Daneshmand MA, Schroder JN, Chiang Y, et al. A normothermic ex vivo organ perfusion delivery method for cardiac transplantation gene therapy. *Sci Rep*. 2019;9:8029.
19. White CW, Ali A, Hasanally D, Xiang B, Li Y, Mundt P, et al. A cardioprotective preservation strategy employing ex vivo heart perfusion facilitates successful transplant of donor hearts after cardiocirculatory death. *J Heart Lung Transplant*. 2013;32:734-43.
20. Hatami S, White CW, Qi X, Buchko M, Ondrus M, Kinnear A, et al. Immunity and stress responses are induced during ex situ heart perfusion. *Circ Heart Fail*. 2020;13:e006552.

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