Donor heart preservation: straight up, or on the rocks?

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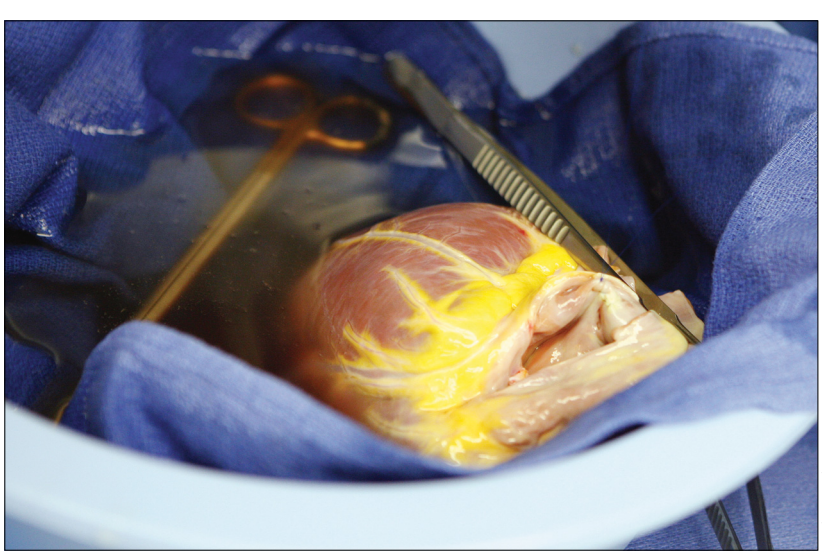
Donor heart preservation using cold static storage is associated with ischaemic injury that restricts the safe preservation interval, contributes to the low utilisation rate of available donor organs, and significantly affects post-transplant survival.[1,2] The pioneering work of Oscar Langendorff,[3] in 1895, led to the realisation that an excised heart could be reanimated and maintained in a beating state with isolated perfusion.[4] Subsequent research has sought to refine the technique of ex-vivo heart perfusion to minimise ischaemic injury, extend the safe preservation interval, optimise organ allocation, resuscitate dysfunctional hearts, and enable viability assessments before transplantation.

In *The Lancet*, Abbas Ardehali and colleagues[5] report findings from their open-label, non-inferiority PROCEED II trial in which 130 heart-transplant patients were randomly assigned to receive a standard-criteria donor heart preserved with either the Organ Care System—an ex-vivo heart perfusion platform that maintains the heart in a warm, beating, and unloaded state—or conventional cold static storage. The primary endpoint of 30 day patient and graft survival in the Organ Care System group (63 [94%] of 67 patients]) was non-inferior to the rate in the cold static storage group (61 [97%] of 63 patients; difference 2·8%, one-sided 95% upper confidence bound 8·8; p=0·45). PROCEED II is the first reported randomised trial assessing the safety of ex-vivo heart perfusion in clinical transplantation, and Ardehali and colleagues should be congratulated on this accomplishment. The trial also represents the first opportunity to scrutinise the Organ Care System method of ex-vivo heart perfusion, and several aspects merit further discussion.

Although the investigators conclude that outcomes in the Organ Care System group were non-inferior to those in the cold static storage group, five donor hearts were deemed unacceptable for transplantation after preservation with the Organ Care System; these hearts were discarded and not included in the analysis, which focused only on recipient outcomes. The discarded hearts all met study inclusion criteria, and were considered suitable for transplantation, irrespective of their subsequent allocation to preservation with either the Organ Care System or cold static storage. Hearts with equivalent risk for graft failure could have been allocated to patients in the cold static storage group and subsequently transplanted. The investigators suggest that the Organ Care System was able to identify pathologically abnormal hearts, and that potential recipients of these hearts were spared exposure to suboptimum organs. Intuitively, patients in the Organ Care System group should have then had superior outcomes by comparison with those in the cold static storage group who did not benefit from Organ Care System screening. The clinical history and echocardiographic measures of all allocated hearts are not presented in sufficient detail to clarify this issue.

Ardehali and colleagues[5] report non-inferiority of the Organ Care System from the recipient perspective. Alternatively, the Organ Care System group might be viewed as inferior if adequacy of myocardial protection and donor heart utilisation was the endpoint, because hearts that were initially deemed acceptable for transplantation were ultimately not implanted. Importantly, the pathological abnormalities identified in these hearts do not necessarily represent non-viability. For example, Quader and colleagues[6] have shown that recipients of cardiac arrest-resuscitated donor hearts do not have inferior post-transplant outcomes. Therefore, if these hearts had been allocated to patients in the cold static storage group they might well have been transplanted with a successful outcome. The overall capacity of the Organ Care System to expand the donor pool might be limited by the non-use of potentially viable donor organs.



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The performance of viability assessments during organ preservation emphasises an important advantage of ex-vivo heart perfusion compared with cold static storage; however, the reliance on use of lactate profiles to accomplish this goal has not been rigorously assessed. Hamed and colleagues[7] identified ending lactate concentration during the preservation of ideal donor hearts as the best predictor of 30-day graft failure (ie, with 63% sensitivity and 98% specificity). These results suggest that a high lactate concentration could accurately identify hearts at risk of post-transplant graft failure; however, a low concentration does not necessarily rule out the possibility of a high-risk heart. For example, Stamp and colleagues[8] described the preservation of an ideal donor heart on the Organ Care System over an 8·4 h period. Despite normal perfusion parameters and lactate concentrations during preservation, the heart became oedematous and primary graft dysfunction occurred after transplantation that required support with extracorporeal membrane oxygenation. This outcome emphasises the value of assessment of myocardial function to confirm organ viability before transplantation, particularly when extended criteria or marginal donor hearts are being preserved.[9]

Ardehali and colleagues[5] report that the Organ Care System reduced the cold ischaemic time but increased total preservation time. Notably, the reduction in cold ischaemic time was not associated with any clinical benefit. This finding suggests that optimum donor heart preservation might be more complicated than simple avoidance of cold ischaemia. Propagation of a proinflammatory state is a known complication of extracorporeal circulation, which might contribute to the development of myocardial oedema during ex-vivo heart perfusion. The addition of steroids to the Organ Care System priming solution is a rational solution to this problem, but the effectiveness of this approach has not been confirmed experimentally. Moreover, little scientific literature exists regarding the best method of preservation of the perfused donor heart from a metabolic and hormonal perspective. The Organ Care System solution includes epinephrine, insulin (about 40 IU/L), and dextrose that would be expected to favour glucose oxidation rather than fatty acid oxidation;[10] however, the effect of this approach on the preservation of myocardial function has not been previously documented.

Will the results of the accompanying trial change clinical practice? Use of the Organ Care System needs additional surgical and technical support, proprietary equipment, and appropriate transport that are inevitably more costly than those needed for cold static storage.[9] At present, preservation of ideal donor hearts with the Organ Care System does not seem to provide sufficient clinical benefit to justify the costs. However, Ardehali and colleagues' findings[5] show that ex-vivo heart perfusion can be used clinically and might hold promise to expand the donor pool.[9] This potential has been exemplified by the successful clinical transplantation of hearts donated after circulatory death in Australia. Through use of pharmacological post-conditioning[11] and avoidance of incremental ischaemic injury with use of the Organ Care System,[12] three successful human transplantations of hearts donated after circulatory death have now been completed.[13] If this technology can be used to increase the number of viable donor organs, the costs of the device might be financially justifiable. Results of the International EXPAND Heart Pivotal Trial (NCT02323321) investigating this potential are eagerly awaited.

Despite decades of research, application of ex-vivo heart perfusion in clinical cardiac transplantation is in its infancy. Ultimately, the hope is that this method will aid the resuscitation and comprehensive assessment of dysfunctional hearts to expand the donor pool.[9] Although many questions remain unanswered, PROCEED II is a seminal study in heart transplantation and could change the approach to donor heart preservation.

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DHF has received non-financial support from XVIVO Perfusion, and has a patent system, compositions, and methods for modulation of calcium ion homoeostasis in harvested transplantable organs pending; a patent apparatus for testing, assessment, and maintenance of harvested hearts for transplantation pending; and a patent system and methods for perfusing and testing organs for transplantation pending. CWW has a patent system, compositions, and methods for modulation of calcium ion homoeostasis in harvested transplantable organs pending.

1 Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult heart transplant report—2009. *J Heart Lung Transplant* 2009; **28:** 1007–22.
2 Khush KK, Menza R, Nguyen J, Zaroff JG, Goldstein BA. Donor predictors of allograft use and recipient outcomes after heart transplantation. *Circ Heart Fail* 2013; **6:** 300–09.
3 Langendorff O. Untersuchungen am überlebenden säugethierherzen. *Pflügers Arch* 1895; **61:** 291–332.
4 Zimmer HG. The isolated perfused heart and its pioneers. *News Physiol Sci* 1998; **13:** 203–10.

5 Ardehali A, Esmailian F, Deng M, et al, for the PROCEED II trial investigators. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet* 2015; published online April 15. http://dx.doi.org/10.1016/S0140-6736(15)60261-6.

6 Quader MA, Wolfe LG, Kasirajan V. Heart transplantation outcomes from cardiac arrest-resuscitated donors. *J Heart Lung Transplant* 2013; **32:** 1090–95.

7 Hamed A, Tsui S, Huber J, Lin R, Poggio EC, 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.

8 Stamp NL, Shah A, Vincent V, et al. Successful heart transplant after ten hours out-of-body time using the TransMedics Organ Care System. *Heart Lung Circ* 2015; published online Feb 5. DOI:10.1016/j.hlc.2015.01.005.

9 Messer S, Ardehali A, Tsui S. Normothermic donor heart perfusion: current clinical experience and the future. *Transpl Int* 2014; published online May 23. DOI:10.1111/tri.12361.

10 Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. *Am J Physiol Endocrinol Metab* 2009; **297:** E578–91.

11 Iyer A, Gao L, Doyle A, et al. Increasing the tolerance of DCD hearts to warm ischemia by pharmacological postconditioning. *Am J Transplant* 2014; **14:** 1744–52.

12 Iyer A, Gao L, Doyle A, et al. Normothermic ex vivo perfusion provides superior organ preservation and enables viability assessment of hearts from DCD donors. *Am J Transplant* 2015; **15:** 371–80.

13 Gallagher J. Surgeons transplant heart that had stopped beating. Oct 24, 2014. http://www.bbc.co.uk/news/health-29751880 (accessed March 9, 2015).