Editorial

The impact of technology—use of hypothermic machine perfusion: the next standard of care for controlled donation after circulatory death allograft preservation?

Franklin Rosenfeldt[1#], Silvana Marasco[2#]

[1]Baker Heart and Diabetes Institute, Melbourne, Australia; [2]Department of Cardiothoracic Surgery, Alfred Hospital, Melbourne, Australia
[#]These authors contributed equally to this work.
Correspondence to: Franklin Rosenfeldt, MD, FRACS. Baker Heart and Diabetes Institute, 75 Commercial Rd, Melbourne, Victoria 3004, Australia. Email: rosenfeldt@bigpond.com.

Keywords: Transplantation; cardiac contractility; cardiac procurement; donation after circulatory death; hypothermic machine perfusion (HMP)

Submitted Mar 25, 2024. Accepted for publication Jun 26, 2024. Published online Oct 14, 2024.
doi: 10.21037/acs-2024-dcd-0045
View this article at: https://dx.doi.org/10.21037/acs-2024-dcd-0045

Introduction

Successful heart transplantation from controlled donation after circulatory death (cDCD) hearts procured off-site, was first described in 2015 by the Australian St. Vincent's Hospital group (1). Normothermic perfusion on the Organ Care System (OCS, Transmedics, Massachusetts, USA) was used for resuscitation and assessment of the donor hearts prior to transplantation. The next report of successful cDCD heart transplantation came from Papworth Hospital, England, where normothermic regional perfusion (NRP) of the heart was used to resuscitate and assess the cDCD heart, followed by cold storage or transport using the OCS (2). In 2022, 26% of heart transplants in the United Kingdom were cDCD whereas in the United States, in 2022 cDCD donors comprised only 8.8% of all heart transplants (http://srtr.transplant.hrsa.gov/annual_reports/Default.aspx). Surely a wasted opportunity. But why, and what were the barriers to more widespread uptake?

Current techniques for clinical cDCD heart transplantation

(I) Direct procurement and perfusion (DPP) is used after a period of warm ischaemia, which is ideally less than thirty minutes. Cold crystalloid cardioplegic solution is infused into the cDCD heart. The heart is then explanted and transferred to the OCS primed with donor blood, for rewarming, preservation, assessment and transfer to the implanting hospital.

(II) NRP in the cDCD donor preserves the heart and other organs by placing the donor on extracorporeal membrane oxygenation (with occlusion of the cerebral circulation) for rewarming and, *in situ* assessment of myocardial function (2). If the heart can support the circulation it is arrested with cold crystalloid cardioplegia and prior to transplantation, is preserved by static cold storage or use of the OCS.

Hypothermic machine perfusion (HMP) for cDCD hearts

HMP with crystalloid perfusate has been shown in a canine model of donation after brain death (DBD) heart preservation to provide myocardial preservation superior to cold storage out to twelve hours (3). Recently HMP (XVIVO) has been successfully used clinically for DBD hearts with perfusion times up to nine hours (4). Given these results, it would be logical to use HMP for cDCD heart preservation, especially for long distance transport.

HMP preservation of cDCD hearts using a crystalloid perfusate has been shown in an *ex-vivo* canine model to facilitate aerobic metabolism, resuscitate the cDCD heart and provide functional and metabolic recovery superior to cold storage (5). In a canine study of transplanted cDCD hearts, HMP but not cold storage, preserved cDCD hearts

with 100% survival (6). HMP was also validated in human cDCD hearts, rejected for transplantation, with similarly good recovery of contractility, on an evaluation rig (7).

However, there are several hurdles to be overcome before HMP can be considered as the next clinical standard of care for cDCD heart transplantation. The problem of variable warm ischaemic injury remains an issue in cDCD procurements, and the safe extent of warm ischaemic time is still debated. Cellular viability is preserved for at least 10 minutes after cardiac arrest, but prolonged hypotension prior to or after this point can lead to myocardial damage (8). Given that unavoidable and unpredictable myocardial injury will always exist in cDCD hearts, assessment of heart function prior to transplantation is critical.

NRP resuscitation of the cDCD heart does allow assessment of cardiac contractility. The Transmedics OCS does not assess contractility and so lactate production is used as a marker of preservation, but this has poor concordance with graft function following transplantation (9).

Tissue pH, as well as lactate production and markers of apoptosis from the coronary effluent, can be monitored during HMP to ascertain the adequacy of tissue perfusion. Nevertheless, at this stage of development in the use of HMP for cDCD some additional technology is required to assess heart function before transplantation, something which is not yet commercially available.

Based on our canine and human heart studies (5-7,10), we propose that use of a free-standing warm perfusion rig could allow assessment of function of the cDCD heart after HMP and immediately prior to transplantation as follows. After transport to the implanting hospital, the heart, with its aortic cannula, is transferred from the HMP system to a simple evaluation rig and a balloon is inserted into the left ventricle to measure developed pressure. On the evaluation rig the heart is reperfused with warm donor blood delivered into the aorta from a heart lung machine. After twenty to thirty mins of reperfusion, if contractility as quantified by developed pressure is satisfactory, the recipient can be anesthetised, and the transplant proceed. Meanwhile the heart can be maintained on the rig in a beating, non-working state that is stable for twelve hours or more (10). After unhurried recipient cardiectomy, cold cardioplegia is administered on the rig, the heart is transferred to the operating table and the transplant performed.

Conclusion

Conventional cold static storage is unlikely to play a role in the utilisation of cDCD organs into the future. DPP of off-site cDCD hearts requires the use of the OCS and a dedicated aircraft, altogether an expensive exercise. Normothermic Regional Perfusion of the heart still raises ethical concerns for many surgeons. Successful HMP of cDCD hearts is well validated in the laboratory. The next logical step in the clinical pathway to increase safe utilization of cDCD hearts is to employ the powerful protective effect of HMP. However, confirming the adequacy of cDCD heart function after HMP is still a challenge awaiting a solution. Future directions need to concentrate on assessment of cDCD heart function after HMP to improve the utilisation of this valuable resource.

Acknowledgments

None.

Footnote

Funding: None.

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

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Cite this article as: Rosenfeldt F, Marasco S. The impact of technology—use of hypothermic machine perfusion: the next standard of care for controlled donation after circulatory death allograft preservation? Ann Cardiothorac Surg 2025;14(1):55-57. doi: 10.21037/acs-2024-dcd-0045

