Nature Reviews Cardiology **12**, 317 (2015); published online 5 May 2015; doi:10.1038/nrcardio.2015.69

TRANSPLANTATION

Ex vivo perfusion of human hearts—implications for donor organ availability

Preservation of hearts between harvesting from a donor and implantation into a recipient is a limitation to transplantation. Currently, hearts are temporarily kept in cold ischaemic storage, which leads to time-dependent ischaemic and reperfusion injuries, and can impair cardiac function after transplantation. A possible solution to this challenge is use of the Organ Care System (TransMedics, USA), an *ex vivo* heart perfusion platform that can be used to maintain hearts in a warm, beating state.

In the PROCEED II trial, use of the Organ Care System was compared with standard cold storage for preservation of donor hearts. The trial was a prospective, open-label study performed in 10 transplantation centres in Europe and the USA. Between June 2010 and September 2013, 130 patients were randomly allocated to receive hearts stored using the Organ Care System ($n=67$) or standard cold storage ($n=63$). In the intention-to-treat population, the primary end point (30-day patient and graft survival) was 94% and 97% in each group, respectively ($P=0.45$), indicating noninferiority of the Organ Care System. The rates of cardiac-related serious adverse events, severe rejection, and length of stay in the intensive care unit did not differ significantly between the two groups.

The total time during which a heart was out of the body was, on average, longer with the Organ Care System than with cold storage (324 min versus 195 min). However, the mean duration of cold ischaemia was shorter with the Organ Care System (113 min versus 195 min). The researchers believe that "in addition to reducing cold ischaemia time, Organ Care System technology can conceivably allow longer preservation time, which could improve organ sharing and matching". However, in an associated commentary article published in *The Lancet*, Darren Freed and Christopher White point out that

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"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."

The majority of donor hearts come from individuals after confirmation of brain-stem death. An alternative definition of death is 'circulatory death'—an irreversible cessation of mechanical or electrical activity of the heart. Harvesting of kidneys, lungs, and livers after declaration of circulatory death has increased the numbers of these organs available for transplantation. However, successful transplantation of hearts distantly procured from donors after circulatory death has not been described. These hearts are subjected to a period of warm ischaemia during withdrawal of life support, they need to be preserved during transportation to the recipient hospital, and their viability needs to be assessed before transplantation.

In a second paper published in *The Lancet*, Kumud Dhital and colleagues describe a series of three patients at St Vincent's Hospital in Sydney, Australia who successfully underwent cardiac transplantation using hearts donated after declaration of circulatory death and subsequently preserved using the Organ Care System. The warm ischaemic time ranged from 22 min to 28 min, and the hearts were perfused using the Organ Care System for 245–260 min. After surgery, two patients required temporary mechanical support, but all three had normal cardiac function within 1 week of transplantation.

Dhital explains that "increased resilience to the inevitable period of warm ischaemia ... [was achieved] through the addition of post-conditioning agents to the cardioplegia used for myocardial protection". The Organ Care System "meant that we had a platform for instrumenting the donor heart and reanimating it on the machine with subsequent support, reconditioning, and functional assessment". Commenting on the article in *The Lancet*, Magdi Yacoub raises the dilemma of "balancing protection and sensitivity to donors with the need to increase the availability of viable donor hearts for transplantation". Yacoub believes that ensuing discussions "should revisit a consensus position on the definition of death itself". Bruno Reichart, who was not involved in these studies, suggests that the high cost and staffing requirements of the Organ Care System might diminish its role in routine heart preservation, but believes that "the true value of the system might be for use with hearts harvested after declaration of circulatory death, if the ethical concerns surrounding this definition can be resolved by society".

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Original articles Ardehali, A. *et al*. Ex-vivo perfusion of donor hearts for human heart transplantation (PROCEED II): a prospective, open-label, multicentre, randomised non-inferiority trial. *Lancet* 10.1016/S0140-6736(15)60261-6 | Dhital, K. K. *et al*. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. *Lancet* doi:10.1016/S0140-6736(15)60038-1