Maintaining heart function in donors declared 'dead by circulatory criteria' could improve access to transplantation

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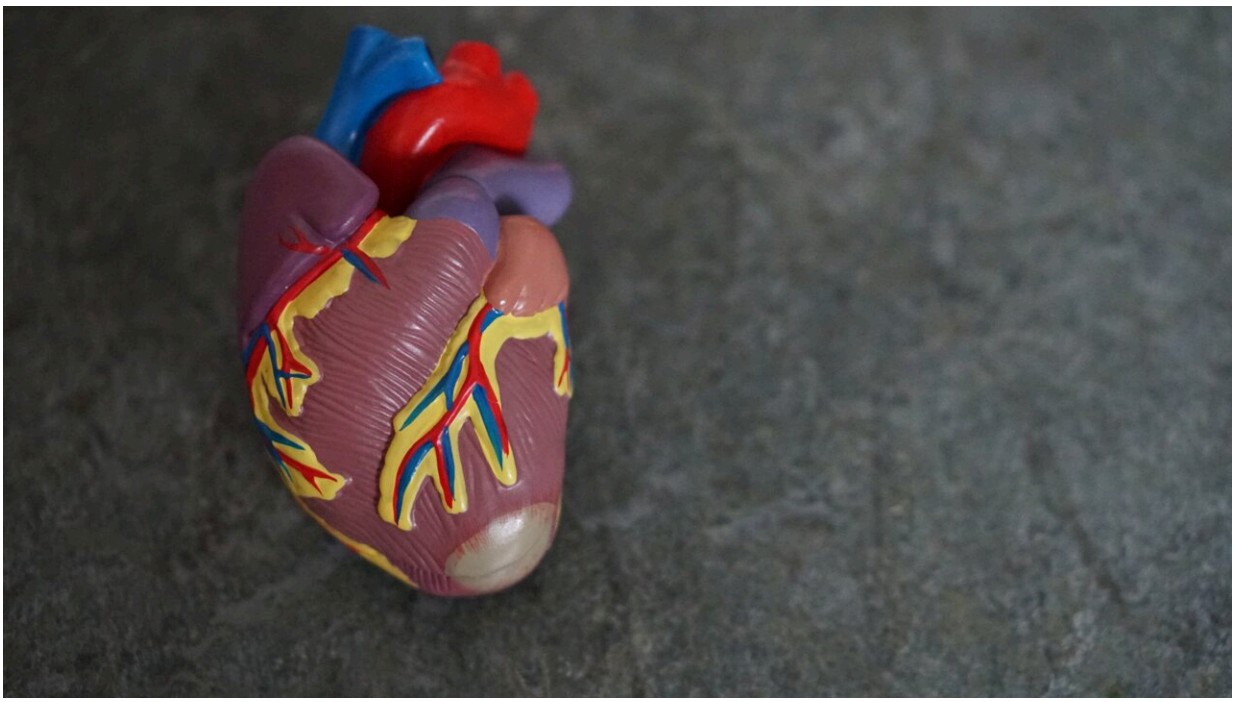

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More donated hearts could be suitable for transplantation if they are kept functioning within the body for a short time following the death of the donor, new research has concluded.

The organs are kept functioning by restarting local circulation to the heart, lungs and abdominal organs—but, crucially, not to the brain—of patients whose hearts have stopped beating for five minutes or longer and have been declared dead by circulatory criteria (donation after circulatory death, or DCD).

It is hoped that this technique could increase the number of usable donated hearts by as much as 30% in the future, helping address the shortage of transplant organs. In 2021, 8,409 heart transplants were reported to the Global Observatory on Donation and Transplantation (GODT) by 54 countries. This activity is in contrast with the 21,935 patients who were on a heart waiting list during the year 2021, of whom 1,511 died while waiting and many others became too sick to receive a transplant.

John Louca, a final year medical student at Gonville & Caius College, University of Cambridge, and the study's first author, said, "Heart transplants are the last bastion for patients with end-stage heart failure. They are successful—patients who receive a transplant live on average a further 13 to 16 years. The biggest problem they face is actually getting access to a donated heart: many patients will die before an organ becomes available. That's why we urgently need to find ways to increase the suitability of donor organs."

Though the first heart transplant performed at the Groote Schuur Hospital in Cape Town (South Africa) in 1967 was obtained from a DCD donor, this technique was abandoned and replaced by heart transplants obtained from donors confirmed dead using neurological criteria (donation after brain death, or DBD)—in other words, their brain has stopped functioning entirely.

Until recently, heart transplants worldwide were still performed only with organs obtained from DBD donors. However, in recent years, heart

transplants from DCD donors have become a clinical reality worldwide thanks to years of research carried out in Cambridge.

DCD is the donation of organs by patients who tragically have a non-survivable illness. These patients are typically unconscious in intensive care in hospital and dependent on ventilation. Detailed discussions between doctors, specialist nurses and the patient's family take place and if the family agree to organ donation, the process starts.

After treatment is withdrawn, the heart stops beating and it begins to sustain damage to its tissues. After 30 minutes, it is thought that this damage becomes irreversible and the heart unusable. To prevent this damage, at the time of death these non-beating hearts are transferred to a portable machine known as the Organ Care System (OCS) where the organ is perfused with oxygenated blood and assessed to see whether it is suitable for transplantation.

This technique was pioneered by Royal Papworth Hospital NHS Foundation Trust in Cambridge, whose transplant team carried out the first DCD heart transplant in Europe in 2015. Royal Papworth has since become the largest and most experienced DCD heart transplant centre in the world.

DCD heart transplantation started simultaneously in Australia, followed by Belgium, The Netherlands, Spain and U.S.. According to the GODT, 295 DCD heart transplants were performed in these six countries in 2021.

Organ Care Systems are expensive, costing around US$400,000 per machine plus an additional $75,000 for consumables for each perfused organ. An alternative, and much more cost-effective approach, is known as thoraco-abdominal normothermic reperfusion (taNRP). This involves perfusing the organ *in situ* in the donor's body and is estimated to cost

around $3,000. Its use was first reported in 2016 by a team at Royal Papworth Hospital.

In a study published in *eClinical Medicine*, an international team of clinical scientists and heart specialists from 15 major transplant centres worldwide, including the UK, Spain, the U.S. and Belgium, looked at clinical outcomes of 157 DCD donor hearts recovered and transplanted from donors undergoing taNRP. They compared these with the outcomes from 673 DBD heart transplants, which represents the 'gold-standard'.

The team found that overall, the use of taNRP increased the donor pool significantly, increasing the number of heart transplantations performed by 23%.

Mr. Stephen Large, Consultant Cardiothoracic Surgeon at Royal Papworth Hospital and chief investigator, said, "Withdrawing life support from a patient is a difficult decision for both the families and medical staff involved and we have a duty to honour the wishes of the donor as best we can. At present, one in ten retrieved hearts is turned down, but restoring function of the heart in situ could help us ensure more donor hearts find a recipient."

Survival rates were comparable between DCD and DBD heart transplantation, with 97% of patients surviving for more than 30 days following taNRP DCD heart transplant, 93% for more than a year and 84% of patients still alive after five years.

Professor Filip Rega, Head of Clinic at the Department of Cardiac Surgery, UZ Leuven, Belgium, said, "This promising new approach will allow us to offer heart transplantation, a last resort treatment, to many more patients in need of a new heart."

The researchers say that some of the benefits from taNRP are likely thanks to the reduced amount of time the heart was not receiving oxygenated blood, known as its warm ischaemic time, when compared to direct procurement (that is, when the heart is removed immediately for transplant, and perfused outside the body). The median average time was 16.7 minutes, significantly less than the 30 minutes associated with permanent damage to the heart cells.

An added benefit to this approach is that it allows medical teams to simultaneously preserve several organs, such as the liver, pancreas and kidneys, without the need of several organ-specific external machine perfusion devices. This decreases complexity and costs.

Professor Ashish Shah, Head of the Department of Cardiac Surgery at Vanderbilt University Hospitals, Nashville, U.S., said, "Heart transplantation has been and always will be a uniquely international effort. The current study is another example of effective international collaboration and opens a new frontier, not just in transplantation, but in our basic understanding of how all hearts can be rescued."

Dr. Beatriz Domínguez-Gil, Director General of the National Organisation of Transplantation in Spain, said, "The results of this collaborative study bring hope to thousands of patients in need for a heart transplant every year throughout the world. Its findings reveal that DCD heart transplantation based on taNRP can lead to results at least similar to the gold standard and increase hearts available for transplantation in a manner that contributes to the sustainability of health-care systems."

More information: John Louca et al, The international experience of in-situ recovery of the DCD heart: a multicentre retrospective observational study, *eClinicalMedicine* (2023). DOI: 10.1016/j.eclinm.2023.101887

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