Also, it would be of interest (as has been indicated by the authors in their response to reviewers but not mentioned in the manuscript text) to conduct proteomic/metabolomic assessment of the infused plasma composition in comparison with the extracted plasma composition over the time of the perfusion; this might give more indication of the donor heart physiology during this perfusion period.

In conclusion, this pilot study represents a potentially very promising advance toward extending the viability of donor hearts for transplantation but, like most studies, leads to many more avenues that need exploring before it can be incorporated into the clinical armamentarium.

See Article page 128.

Commentary: Getting better with every beat. Extending the clock with ex vivo perfusion for heart transplantation

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Donor heart supply remains the fundamental limiter to heart transplantation. Despite a growing need for organs, only 1 in 3 hearts from organ donors are used for transplantation.¹ To reduce the growing gap between organ supply versus need, expanded donor selection criteria, such as increased donor age and even donation after cardiac death, have emerged. The acceptance of more “marginal” donors must be balanced by the need to ensure appropriate organ quality. Furthermore, the 6-hour cold ischemic time window

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CENTRAL MESSAGE

Ex vivo heart perfusion is possible using continuous plasma exchange for a duration of 24 hours, potentially expanding time windows for evaluating candidate organs for heart transplantation.

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remains a geographic and logistical hurdle for transplantation. Ex vivo organ perfusion systems have promise to overcome these challenges. The TransMedics Organ Care System has been used in heart transplantation and shown to be safe with normothermic perfusion times of less than 4 hours.²

In this study, Tchouta and colleagues³ from the University of Michigan push the clock even further, demonstrating good explanted heart function 24 hours after explanation in pig hearts using normothermic ex vivo perfusion. This same

group has previously demonstrated good heart function up to 3 days after explantation using a paracorporeal animal.⁴ Informed by their previous work, Tchouta and colleagues engineered an ex vivo system that allows continuous exchange of donor plasma from the organ circulation with pooled porcine plasma. This continuous plasma exchange enables the removal of toxins while maintaining oncotic pressure and possibly other beneficial proteins found within plasma, similar to what might occur with a paracorporeal animal.

Although this study represents an innovative step toward increasing the clinical utility of vivo organ perfusion systems, some important limitations remain. First, the impact of donor brain death upon the donor heart is not accounted for in this study yet is an important factor clinically. Brain death impairs donor heart function both in the donor and, potentially, in the recipient and activates apoptotic and inflammatory pathways.⁵ Second, ex vivo heart assessment was limited to the left ventricle and only at a fixed volume using a balloon transduction system. True left ventricle performance would be better assessed using pressure–volume analysis at different loading conditions.⁶ Furthermore, as the authors point out, cardiac functional assessment after a second cold ischemic insult and implantation was not assessed and thus unknown. Finally, the perfusate may have an important impact on heart inflammation and immune activation after transplantation. Although donor blood offers the obvious advantage of oxygen carrying red blood cells, donor immune cells could promote inflammation. The addition of pooled plasma from multiple donors may further amplify inflammation and merits further investigation.

Further innovation and development of ex vivo heart perfusion is necessary to expand the availability of heart transplantation. By increasing the time window, surgeons can better assess more marginal hearts and potentially intervene using novel therapies, such as gene- and cell-based therapies to reduce ischemia–reperfusion injury and graft rejection.⁷ Hearts that are currently being discarded may be found to be getting better with every beat and instead transplanted. As the authors describe, realization of this goal may one day make heart transplantation an “elective” procedure and more widely available to patients with advanced heart failure.

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