Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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EDITORIAL COMMENT

Heart Transplant

Challenge Accepted*

David A. Baran, MD

Heart transplantation has been an improbable success story. The audacious idea that a human heart could be transferred from a dead person to someone who is facing terminal heart disease was shocking in 1965 when a heart transplant was first accomplished by Barnard.[1] Enthusiasm was short-lived because of a lack of understanding of the immune processes involved in allograft rejection,[2,3] but some investigators, such as Caves et al[4] and Griepp et al,[5] continued to work through the challenges, although the odds were against them.[4,5]

In the United States, the demand for heart transplantation has remained quite strong, with the supply of organ donors persistently outstripped by the number of patients on the waiting list. Alternative modalities such as left ventricular assist devices evolved in parallel and arguably represent a compelling alternative for some patients with survival at 5 years approaching that of transplantation.[6]

Now as we fast forward more than 50 years, heart transplantation has become almost a commodity item, with quality scrutinized and little tolerance for variation, with the expectation that outcomes will be universally positive. Regulatory oversight by the U.S. federal government through the Organ Procurement and Transplantation Network and their designated contractor, the United Network for Organ Sharing, has led to the expectation that most centers will achieve 90% 1-year post-transplant survival, which is an admirable goal. However, there are many issues which may prevent this from being a reality, including donor, recipient, and systems issues.

Donor issues are inherent in the process of heart transplantation. We have limited information in most cases because the source of truth (the donor) cannot speak, and we are left with history from charts and grieving families, as well as very heterogeneous levels of testing and evaluation processes. Even simple tests such as echocardiography and coronary angiography are not always available, and when they are obtained, transmission of high-fidelity images often remains a challenge.

This situation is compounded by issues with infection, as well as concern that the donor organ could transmit diseases to the recipient, especially in the setting of high immunosuppression. Beyond chronic diseases such as hepatitis B and C and cytomegalovirus infection, other pathogens and diseases such as Zika virus, Chagas disease, and West Nile virus have presented concerns, and where necessary, screening pathways have been modified to exclude such donors. None of these pathogens or diseases is as widespread as COVID-19, which has led to worldwide morbidity and mortality as a pandemic.

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With the development of various treatments and the general improved understanding of infection, there has been increasing experience with accepting cardiac donors with evidence of recent or current COVID-19 infection.[7-11] In this issue of the *Journal of the American College of Cardiology,* Madan et al[12] on an analysis from the United Network for Organ Sharing registry that looked at specific testing (nucleic acid testing [NAT]) for adult organ donors in the United States from May 2020 to June 2022. There were a total of 27,862 donors (any organ) over the

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From the Section of Heart Failure, Transplant, and Mechanical Circulatory Support, Cleveland Clinic Heart Vascular and Thoracic Institute, Cleveland Clinic Florida, Weston, Florida, USA.
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approximately 2-year time period, and 1,445 (5.2 %) of these donors had a positive COVID-19 test result. Of these donors, 1,017 (70.4 %) were deemed to have active COVID-19 (positive NAT result before donor procurement), and 428 (29.6 %) had negative repeat NAT results before procurement (deemed recently recovered). Consistent with previous reports, only 21.4 % of these donors (309 of 1,445) were used for heart transplants (190 with active COVID-19 and 119 recently recovered).

Madan et al[12] examined mortality post-transplant and compared COVID-19 donors with non-COVID-19 donors as well as the subgroups of COVID-19 donors, including recently recovered and active COVID-19 infection. They also performed propensity matching to compare the small number of COVID-19 donors with a pool of matched non-COVID-19 donors. They found that post-transplant survival was significantly worse if an active COVID-19 donor was used as compared with a non-COVID-19 or recently recovered COVID-19 donor. The difference was marginal at 6 months but significant at 1 year and persisted despite statistical adjustment for a variety of factors known to influence post-heart transplant survival. Madan et al[12] advise caution regarding the use of COVID-19-positive donors for heart transplantation.

Although the results of the study by Madan et al[12] are provocative, there are major limitations. First, the follow-up period post-transplant is quite short, with a median follow-up for the overall group of 11.2 months (IQR: 5.4-12.3 months) and 5.7 months (IQR: 1.5-6.5 months) for the COVID-19 group. The Kaplan-Meier survival curves comparing COVID-19 groups and non-COVID-19 groups (Figures 2 and 3 in Madan et al[12]) are superimposable until 3 months post-transplant, which also coincides with fewer patients with adequate observation time. The difference between recently recovered COVID-19 and active COVID-19 is also problematic, with the median number of days from a positive test result to donation being 6 and 2 days, respectively. It is hard to fathom that a difference of 4 days in the time to positive viral testing is sufficient to make a biologic difference, particularly beyond 90 days post-transplant.

The study by Madan et al[12] gives a current snapshot of transplant activity in the United States. The use of offered heart donors (COVID-19 and otherwise) remains quite low. The increases noted in heart transplantation volume in recent years result from an increase in the number of donors and actually not from the use of offered donors, which appears to be dropping.[13] Accepted COVID-19 donors were highly selected, and they represent the minority of donors accepted. Madan et al[12] did not show a clear correlation with the cause of post-transplant death and donor COVID-19. It is unclear whether this reflects the limitations of registry data or the lack of a true correlation of donor COVID-19 status and survival. Reporting 6-month outcomes when less than one-half of patients have 6-month survival data is problematic regardless of the *P* value. At most, the current study should motivate longer longitudinal studies but should not dissuade clinicians from using carefully selected donors.

What is the way forward when dealing with increasingly complex patients and donors? I would propose consideration of the following points.

- Heart transplantation always requires a continuous evaluation of the risk-benefit equation. There will always be insufficient information, whether related to the limitations of donor hospitals that are often not equipped to perform tertiary testing, the difficulties of transmitting imaging, or the lack of clear guidance on evolving situations such as that of COVID-19.
- We must always be cognizant of the risk of rejecting the donor that is offered in the hopes of finding a subsequent, more desirable one. We are not guaranteed to see tomorrow, nor are patients always likely to receive a “better offer.”
- The landscape of COVID-19 is shifting as well, with increasing numbers of donors and recipients having experienced multiple episodes of vaccination and/or infection. The COVID-19 virus is also continuing to mutate, and mortality continues to decrease, perhaps as a result of therapeutics and improved approaches to care.
- When it comes to matters of transplantation, we must not stop rising to new challenges! The success of transplantation relies on many things, but repetition, team dynamics, and sufficient volume are all critical. Poor outcomes during the years post-transplant can occur for reasons wholly unrelated to the transplant procedure, yet there is no allowance for this in regulatory frameworks. Only by maintaining a sufficiently large program can a team “afford to take risks.” The risks of today become the standard protocols of tomorrow.

Todays’ challenge is whether to use COVID-19 donors, but this is just one in a long series of obstacles that have been successfully surmounted in the last 50 years. Heart transplantation clinicians and teams continually innovate and find new solutions to problems. In the future, perhaps we will find ways to use even more organs, human or otherwise, to deliver the promise of heart transplantation to more critically ill patients.

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ADDRESS FOR CORRESPONDENCE: Dr David A. Baran, Section of Heart Failure, Transplant, and MCS, Cleveland Clinic Heart Vascular and Thoracic Institute, 2950 Cleveland Clinic Boulevard, Weston, Florida 33331, USA. E-mail: barand@ccf.org. Twitter: @davebaran.

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