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EDITOR'S PAGE

When Pigs Fly What Will the Future of Heart Failure Therapeutics Look Like?

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"The time has come" the Walrus said,
"To talk of many things:
Of shoes—and ships—and sealing wax—
Of cabbages—and kings—
And why the sea is boiling hot—
And whether pigs have wings."
From the narrative poem
The Walrus and the Carpenter by Lewis Carroll
published in *Through the Looking-Glass*[1]

The expression "when pigs fly" is an adynaton (figure of speech) that refers to something so hyperbolic that it is extremely unlikely to ever happen. This phrase is often used to mock efforts that are overly ambitious. In this issue of *JACC: Basic to Translational Science*, Boulet et al[2] provide a comprehensive State-of-the-Art Review on "Cardiac Xenotransplantation: Challenges, Evolution, and Advances." This article is accompanied by an insightful commentary by Eugene Braunwald, entitled "Cardiac Xenotransplantation: Another Historic First?"[3] In reading these articles, I am reminded of the comments by the late Stanford cardiac surgeon and pioneer in transplantation, Norman Shumway, who famously opined that: "Xenotransplantation is the future, and always will be." I wonder now as I write this Editor's Page whether Dr Shumway ever read Lewis Carroll when he was a child.

The field of cardiac xenotransplantation represents the good, the bad, and the ugly aspects of cardiovascular translational medicine writ large. The good aspects of cardiac xenotransplantation, as described brilliantly in the review by Boulet et al,[2] are that xenotransplantation represents the exciting synergy between CRISPR/Cas9 genome editing technology and immunology, and thus is a remarkable example of how advances in basic science can be applied to overcoming problems that are encountered in clinical medicine. The bad and ugly parts of xenotransplantation are that, if and when xenotransplantation becomes available, it will likely be extremely expensive and will therefore raise questions about how societies choose to spend their health care dollars. This in turn will raise significant ethical issues about whether this technology will be available to everyone who might benefit from it, or whether it will be restricted to those who can afford it. The journal Nature reported that each porcine transplant into a baboon costs approximately $500,000, which will make this an extremely expensive technology to develop and perfect before proceeding to clinical trials.[4] At time of this writing, it is unclear what the cost will be to transplant a porcine heart into a human. As noted by Boulet et al,[2] the actual cost of cardiac xenotransplantation is imponderable at present, because the competing costs of developing the therapy will need to be weighed against the economic and social costs of reducing the burden of heart failure in wait-listed patients and those patients who never make it to the wait-list.

The good, bad, and ugly aspects of xenotransplantation notwithstanding, the aspect of cardiac xenotransplantation translation that I find most intriguing is how to identify a viable path forward to develop this approach as a practical therapy for patients with advanced heart failure. These patients currently have the option(s) of being treated with drugs, devices, or undergoing a cardiac transplantation. Each of these therapies is relatively mature and certainly likely to be less expensive than a cardiac xenotransplant. So, is there a translation path forward for cardiac xenotransplantation? Before addressing this question, it is useful to review what is known about current outcomes for patients with advanced heart failure.

At present, the evidence base for the use of medical therapy among patients with heart failure with a reduced ejection and advanced symptoms is limited,

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insofar as it is often difficult to achieve the dose(s) of neurohormonal antagonist recommended in clinical trials in these patients because of dose-limiting symptomatic hypotension, worsening renal function, or both. Although the U.S. Food and Drug Administration recently approved 4 drugs for the treatment of patients with a reduced ejection fraction with New York Heart Association functional class II to IV symptoms, astoundingly, <3% of the patients in the trials that led to regulatory approval had New York Heart Association functional class IV symptoms. Perhaps not surprisingly, this has resulted in difficulties in reproducing some of the results of various Phase III trials in subsequent Phase IV studies that are enriched for patients with advanced heart failure.[5] Because there are so few patients with advanced heart failure with a reduced ejection fraction enrolled in Phase III clinical trials, contemporary guidelines for these patients have focused instead on cardiac transplantation, mechanical circulatory support, or palliative care. As discussed by Dr Mandeep Mehra in his overview of the first 50 years of the field of cardiac transplantation,[6] the translational path forward for transplantation was based on anecdotal outcomes and single-center registries that ultimately led to remarkably improved clinical outcomes for adults undergoing cardiac transplantation. Currently, adult cardiac transplant patients have a ~90% 1-year survival rate and a remarkable 80% survival rate at 5 years. In contrast to transplantation, the translational path forward for left ventricular assist devices (LVADs) was more conventional and consisted of randomized trials that assessed hard clinical outcomes for patients with advanced heart failure randomized to receive optimal medical therapy compared with patients randomized to receive pulsatile-flow LVAD support in patients ineligible for heart transplantation. With continual advances in continuous flow LVAD technologies, current 1-year survival rates are 82% and are now approaching 80% at 2 years.[7]

Given the tremendous successes and outcomes with the management of advanced heart failure, it is hard to imagine how any Institutional Review Board would ever sign off on a clinical trial design that randomized patients to receive a pig heart that may cost upward of $500,000 per heart vs randomizing patients to treatment arms that cost far less and have 80% 5-year survival rates. In their State-of-the-Art Review, Boulet et al[2] remark presciently: "As the history of evolution of cardiac allotransplantation or mechanical circulatory support attests, advances occur incrementally rather than in a transformative manner." We currently have a shortage of suitable cardiac allografts for transplantation for the patients who need them, and there are patients who do not qualify for or who are not good candidates for LVADs or cardiac transplantation. As Dr Braunwald aptly notes in his commentary, "Advanced heart failure is not going away."[3] To move forward, the heart failure community will need to develop clinical equipoise around the questions raised in the thoughtful review by Boulet et al[2] as we try balance the tremendous excitement and promise of a shiny new technology against the ethical and moral imperatives of maintaining patient safety and the good of the public. My take is that we are not there yet, but we will get there, as we always have, when faced with the challenge of improving the clinical outcomes for heart failure patients. As always, I would like to hear your thoughts on this topic, either through social media (#JACC:BTS) or by e-mail (JACC@acc.org).

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