The World's First Pig-to-human Heart Xenotransplant: Where is this Going?

Written by: James K. Kirklin, MD

The seminal genetically engineered pig-to-human heart xenotransplant by Dr. Bart Griffith on 7 January 2022, will be officially recognized not only as the first such heart transplant, but the first such genetically engineered transplant of any kind into a living human patient. This will rank up there with the Baby Fae neonatal heart transplant from a baboon to a baby with hypoplastic left heart syndrome (HLHS), performed by Dr. Leonard Bailey in October of 1984. Were he alive, Dr. Bailey would be thrilled that his early vision of xenotransplantation will now become a clinical reality. The immense scientific and industry investment in this xenotransplant construct will undoubtedly pave the way for large scale application of this model, and without the angry backlash of some groups against the Baby Fae experiment. After all, pigs are a routine source of food as well as biologic valves for human implants. Following this initial adventure, the clinical platform will likely rapidly turn toward a methodical clinical trial of pig-to-human kidney transplants using this same genetic model of approximately 10 modified genes.

So, what does this mean for the pediatric community? I must confess that I was stunned that the first human heart xenotransplant would be in an adult, since ventricular assist devices and the total artificial heart are readily available. At any rate, the FDA did approve this historic operation on a compassionate use basis, indicating that no other viable option was available for this patient. Going forward, perhaps the most likely patients will reside in the pediatric community. Although Bailey's amazing episode ignited the field of infant heart transplantation, the severe shortage of infant heart donors was rapidly appreciated, and infant heart transplantation settled into the realm of a highly successful but infrequently utilized therapy. Indeed, by 2000, almost no pediatric centers were routinely listing HLHS babies for primary heart transplantation; instead, the Norwood operation rapidly became standard therapy, despite the superior long-term outcomes with intial neonatal heart transplantation. [1]

From an immunologic perspective, the most important human antibodies against pig tissues bind to a galactose epitope on the surface of all pig endothelial surfaces, which is absent in humans, apes, and baboons. These "natural" anti-Gal antibodies in humans against this galactose epitope likely develop during the neonatal period when viruses and other microorganisms that express Gal enter through the gastrointestinal tract. Through genetic engineering, pigs can be bred in which the 3 known carbohydrate xeno-antigens are deleted (knock-out), thus avoiding immediate attack by the human immune complexes. In addition, up to 8 additional human complement-regulatory, coagulation-regulatory, and anti-inflammatory proteins have been incorporated into the pig genome. These genetic manipulations have effectively eliminated hyperacute rejection in the pig-to -primate models. Rejection is much more likely to manifest as antibody-mediated rather than cellular rejection, although t-cells are often seen in the grafts. [2]

Now, after more than 2 decades of orderly scientific investigations using genetically engineered pigs, the experience with so-called triple knock-out (TKO) pig to primate heart transplants suggest a high likelihood of short to mid-term survival in humans. Although essentially non-working heterotopic models with abdominal implants have been extensively studied to understand the immunologic response by primates to TKO pig hearts, the real test of clinical utility is complete replacement of the recipient heart with the pig heart (orthotopic heart transplant). The early success of McGregor at the Mayo Clinic and more recently the Munich group with pig-to-primate orthotopic heart transplantation has produced survivors out to 6 months or more . Of considerable importance is the unique susceptibility of the pig heart to ischemic/reperfusion injury following transplantation,[3] *resulting in transient myocardial edema and reversible depressed cardiac function4. This led investigators to propose unorthodox solutions for myocardial preservation that continue to pose important barriers to achieving prompt excellent graft function* [4]*. Investigators at the University of Alabama at Birmingham have reported success with standard Del Nido cardioplegia solution as used in standard cardiac surgery (personal communication, David Cleveland, September, 2021), and Griffith's team used continuous ex-vivo perfusion of the explanted pig heart in their human case.*

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When clinical trials are considered for heart xenotransplants, pediatric patients are a likely target, since durable mechanical circulatory support devices as a bridge to transplantation are much less effective in infants and small children compared to adolescents and adults. The pediatric patient groups most likely to be considered are those with difficult anatomy for ventricular assist device implant, highly sensitized patients unlikely to get a suitable donor match, and small patients who are unlikely to survive the extended period needed to find a suitable donor. In this context, pediatric xenotransplantation might be considered in a "bridge-to-transplant" trial. The following are possible examples of patient groups for such a hypothetical trial:[5]

1. *Primary therapy for HLHS with contraindications for the Norwood procedure, particularly with unstable hemodynamics.*
2. *Early post-transplant graft failure in infants and children and potentially older pediatric patients.*
3. *Conditions with high waitlist mortality, such as infants with Ebstein's malformation and hemodynamic compromise and single ventricle palliation with poor ventricular function or severe AV valve insufficiency.*
4. *Congenital heart disease with prior cardiac surgery, poor hemodynamics, and sensitization with high titers of pre-formed antibodies*
5. *Patient groups at high risk with standard mechanical circulatory support, such as those with single ventricle physiology*

Whatever the specific trial design, the path is now much clearer for real, large scale application of pediatric heart xenotransplantation. Once babies and children can be thoroughly studied for their immune response to the pig heart, the hemodynamic response related to growth and possible restrictive physiology, and possible susceptibility to side effects of potentially new immunosuppressive regimens, the role of this incredible therapy as a bridge to a human heart or long term therapy will become much clearer. So, buckle up and enjoy what will certainly be an amazing era in pediatric heart transplantation.

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