After the First Pig-to-Human Heart Transplant, Scientists Look to the Future of Cardiac Xenotransplantation

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In December 2021, 57-year-old David Bennett was fighting for his life. His heart was failing despite a potent cocktail of intravenous drugs and a balloon pump that had been placed in his aorta to improve his heart function. He was being kept alive with extracorporeal life support, and his only hope was a heart transplant.

But according to a published report Bennett had a history of not sticking to medical treatment plans, a characteristic that made him ineligible to receive a donor heart. Four heart transplant programs denied his request for an organ. That was when a team of clinical researchers at the University of Maryland began to evaluate the merits of an experimental procedure through which Bennett could receive a genetically modified pig heart instead of a human one.

“He understood this wasn’t a proven treatment, and it could go either way,” cardiac surgeon and scientist Muhammad Mohiuddin, MBBS, director of the cardiac xenotransplantation program at the University of Maryland School of Medicine, told JAMA in an interview.

Bennett consented, and the modified pig heart was transplanted into his body early this January. It was the first clinical cardiac transplant to use a pig heart. But attempts to transfer organs from one species to another—with the goal of treating human disease—date back more than a century.

“The idea for various types of organ xenotransplants has been around for a long time, mainly because the availability of human organs has been so limited,” Jeffrey Platt, MD, a professor of surgery, microbiology, and immunology at the University of Michigan, said in an interview.

“With ventricular assist devices, which work like implantable pumps to treat end-stage heart failure, animal organs could be produced at a large scale, eliminating the long wait for a human donor organ. Many ethical concerns—some of them long-standing—will need to be resolved first. Oversight and guidance must span the animal and human experiments that are necessary to bring the procedure to wider clinical use,” Platt said.

Previous attempts at xenotransplantation have failed for various reasons, prime among them is the body’s strong immune response to an organ identified as foreign. In addition to daunting immunological barriers, a transplanted animal organ must also be able to perform its normal physiological and metabolic functions in the human recipient. A transplanted pig heart, for example, must adapt its activity when a person climbs a flight of stairs or lies down for a nap.

Infections that can transmit from the donor animal to the human recipient—or from the recipient to the donor organ—have also posed a significant bottleneck to advancing the potentially lifesaving science.

Meanwhile, there’s an urgent need for more donor organs: most years several hundred people in the US die while waiting for a new heart. As with ventricular assist devices, which work like implantable pumps to treat end-stage heart failure, animal organs could be produced at a large scale, eliminating the long wait for a human donor organ.

Many ethical concerns—some of them long-standing—will need to be resolved first. Oversight and guidance must span the animal and human experiments that are necessary to bring the procedure to wider clinical use, noted L. Syd M. Johnson, PhD, bioethicist at the State University of New York Upstate Medical University.

“Of Primates and Pigs
Human cardiac xenotransplants have been attempted 4 times with nonhuman primate hearts. In fact, the first ever heart transplant, in 1964, used a chimpanzee—not a human—donor heart. With this and the next 2 attempts, in the late 1970s, the patients died within a matter of hours. Then, in 1984, an infant born with a fatal heart condition who was publicly known as Baby Fae died 20 days after receiving a baboon heart.

The highly publicized and controversial...
procedure was the last clinical cardiac xenotransplant until this year.

The first patient to receive another person’s heart only survived 18 days after the 1967 procedure. In recent decades, progress with human-to-human heart transplants has offered a foundation for researchers to study cardiac xenotransplants. Still, Platt said, “The lessons we’ve learned from transplanting human hearts are not by themselves sufficient [for an] enduring transplant of an animal organ.”

To move the science forward, researchers in the mid-2000s began to transplant organs from genetically modified pigs into nonhuman primates such as baboons.

Mohiuddin and his colleagues removed parts of pig cell surface proteins that triggered immune rejection and inserted human genes to tamp down inflammatory responses. Even so, the primates’ immune systems frequently rejected the pig grafts, Mohiuddin said.

In 2012, his team reported having kept genetically modified pig hearts alive for up to 8 months in baboons, thanks to a modified regimen of immune-suppressing drugs. Unlike in human organ transplants, the researchers found that depleting the baboons’ B cells in addition to suppressing their T-cell responses was critical to the xenografts’ long-term survival.

“This really showed the importance of B-cell immunity in delayed rejection of grafts,” Mohiuddin said. “That was a major breakthrough.”

They reported further improvements—up to 900 days of survival—in a 2016 publication. In both studies, however, they placed the pig hearts into the baboons’ abdomens. Although the organs did not perform their circulatory functions, the experiments revealed the immune mechanisms and genetic modifications necessary for a pig heart’s survival in a different species. “These served as a proof of concept that we could avoid the rejection of a pig heart in primates,” Mohiuddin said of the studies. “The next natural step was to test if this heart could sustain life.”

There the group encountered new challenges. When they transplanted modified pig hearts into baboons’ cardiovascular systems, “the heart failed within 2 or 3 days—not due to rejection but because the pig heart kind of runs out of steam,” Mohiuddin said.

A recently developed method for preserving donor hearts with cold nonischemic continuous perfusion instead of standard cold static storage helped overcome this problem and led to longer-term survival for baboons, the researchers reported this March.

Other hurdles along the way—such as pig hearts that swelled unexpectedly in animal recipients—have helped the team refine the genetic modifications. The heart that Bennett eventually received had 10 edits, made using CRISPR (clustered regularly interspaced palindromic repeats) gene editing: 4 pig genes that code for cell surface antigens and growth hormone were removed, and 6 human genes were inserted to improve compatibility.

Preclinical studies “revived the field of xenotransplantation,” Mohiuddin said. “But we still needed to understand more in nonhuman primate models before entering human clinical trials.”

A Pioneering Patient

Despite this, as Bennett ran out of options, Mohiuddin’s team began to wonder whether he would be a suitable candidate for a pig heart transplant under the US Food and Drug Administration (FDA) Expanded Access Program. A person facing a life-threatening condition may be offered an experimental drug or procedure through the program if no other treatments exist.

Over the 2021 holiday season, regulators and clinicians worked around the clock to evaluate Bennett’s case. He underwent 4 psychiatric assessments to ensure that he understood the experimental transplant’s risks. Explaining the many unknowns that Bennett would face was challenging, Mohiuddin recalls. “It was a difficult conversation to have, but he had already been told by other physicians that the machine he was on was the only life support they could offer him,” he said. “But he was very positive and said, ‘Even if I don’t survive, you will learn a lot.’”

The FDA approved the request on New Year’s Eve, and Bennett received his new heart about a week later. His health began to improve after the surgery. He was weaned off life support, and for the first time in 109 days, he sat in a chair by his bed and waved to caregivers. He watched the Super Bowl and felt so much better that he asked why he was still in the intensive care unit, Mohiuddin said.

The team considered moving him to a regular room in the hospital, but on the 49th day after the transplant, the experimental heart began to swell and started to fail. Life support was restarted, and Bennett died 11 days later when it was compassionately withdrawn.

According to a report Mohiuddin and colleagues published in July, there was no sign of organ rejection. Tests hinted that a latent porcine viral infection may have played a role. The patient’s poor health before the procedure was also a factor, Mohiuddin said, because it meant that the team couldn’t suppress his immune system as much as they had in animal experiments.

The procedure yielded information that couldn’t have emerged from animal studies, Mohiuddin said: “For instance, we learned that certain immunoglobulin drugs used routinely in human-to-human transplants might not be ideal for xenotransplants, because they include antibodies that can act against the pig heart.”

Bennett’s willingness to participate in the research brought xenotransplantation closer to something that can be studied and pursued in clinical settings, said Platt, who was not involved with the case. “It’s taken decades and an abundance of experience to optimize human-to-human transplants,” he said. “It’s going to take a while, and a lot of effort, to optimize [animal-to-human] transplants.”

Not Ready for Prime Time

This June and July, as part of a unique study, surgeons at New York University (NYU) transplanted pig hearts with the same 10 genetic modifications as Bennett’s donor heart into 2 recently deceased patients. The patients’ physiological and immune responses were then observed for 72 hours. “When we designed this trial, the idea was that we’d replicate everything that we do clinically in a regular transplant procedure,” Nader Moazami, MD, a cardiothoracic surgeon and surgical director for heart transplantation at the NYU Langone Transplant Institute, said in an interview.

The researchers saw no signs of immune rejection or infection. They were most interested in whether the transplanted hearts could support circulatory functions in the patients, who had been declared brain dead. With the first patient, Moazami said, the pig heart was too small to do so sufficiently. The second patient’s donor organ was a better fit size-wise, allowing the procedure to go more smoothly.

Matching a pig heart’s size to a human recipient in future transplants will require
more research into the gene changes, Moazami said. One of the edits knocks out the porcine growth hormone gene to prevent the swelling that posed problems in baboons. But it’s not yet known how much this change alters the organ’s baseline size. “We don’t know the discrepancy in the size of the heart in a 100-kilogram pig with and without this gene knockout,” he said. “We need to start understanding the effects of the gene modifications better.”

Researchers aim to understand how the genetic modifications necessary for xenotransplants affect the donor animals. Pigs usually give birth to about 10 piglets in a litter, but only about half of genetically modified piglets survive, according to Mohiuddin. “There is some evidence of attrition with all these gene modifications,” he said, “but the technology is improving.”

Consistent, long-term survival also requires more preclinical study. In Mohiuddin’s recent animal experiments, the baboons lived up to 9 months with functioning heart xenotransplants, eventually dying of unrelated lung infections, he said.

Overall, the current data suggest that some barriers have been resolved, Moazami said, “but by no means does this mean we’re ready for human xenotransplants.”

**Ethics and Unknowns**

Xenotransplantation research navigates thorny ethical terrain, not least of which is the need to study the procedure in people who require new organs to survive. Researchers also must grapple with animal welfare concerns and regulations around experiments involving patients with brain death, Johnson said.

Typically, experimental drugs or devices permitted by the FDA for compassionate use have undergone more extensive preclinical research or even early clinical trials.

“That’s a different scenario than xenotransplantation, where we’re not out of the preclinical phase yet,” Johnson said. “Any time we have a brand-new type of research, there’s the possibility that we don’t have the regulatory and ethical framework in place to do it the right way.”

Still, the research could prove particularly significant for certain populations, such as children with congenital heart conditions who need transplants. Most left ventricular assist devices and other technologies that support heart function cannot be implanted in children. End-stage interventions can mean months on end in the hospital, waiting until a donor organ becomes available, according to David Cleveland, MD, MBA, a pediatric cardiovascular surgeon at the University of Alabama at Birmingham.

“The waiting list for infants in need of a heart is highest for any solid organ transplant,” Cleveland said in an interview.

He and colleagues are working on transplanting pig hearts into infant baboons in the hope of achieving long-term survival. How long the organs would function in young human patients is an important consideration—a pig’s lifespan is typically only 20 years. Could animal hearts serve as a long-term solution, or will they act as a temporary bridge that keeps children alive until a human organ becomes available? “Theoretically, children could go home and be with their parents while they wait for a transplant,” Cleveland said.

Many unknowns must be resolved before that becomes reality—if it even does. “We don’t know yet whether xenotransplants will ever become clinically relevant,” Moazami said. “But unless we look and try to answer some of these questions, we will never know.”

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**Note:** Source references are available through embedded hyperlinks in the article text online.