Modified pig-to-human heart transplant had unexpected changes in heart's conduction system

October 31 2022

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Heart rhythm measures in the electrocardiograms of the first pig-to-human heart transplant found unexpected differences in the electrical

conduction system of the genetically modified pig heart compared to an unmodified pig heart, according to preliminary research to be presented at the American Heart Association's Scientific Sessions 2022. The meeting, held in person in Chicago and virtually, Nov. 5-7, 2022, is a premier global exchange of the latest scientific advancements, research and evidence-based clinical practice updates in cardiovascular science.

Xenotransplantation—the process of implanting an organ from one animal species to another—took a leap forward in January 2022, when a 57-year-old man with terminal heart disease received the first-ever transplant of a genetically modified pig heart. The patient lived for 61 days.

Researchers have been working on this new pig-to-human transplantation technique for over 30 years. If successful, harvesting hearts from genetically modified pigs, whose genes have been altered so that they can be safely transplanted to humans, may one day be a reality.

"There are several potential challenges for transplanting a pig heart into a human. With any transplant including this one, there is always the risk of rejection, the potential risk of infection and a third one is abnormal heart rhythms, and that is where the electrocardiogram (ECG) comes in," said Timm Dickfeld, M.D., Ph.D., a professor of medicine and director of electrophysiology research at the University of Maryland School of Medicine in Baltimore. "It's truly a novel finding that the ECG parameters of the pig heart after transplantation into a human were so different compared to the commonly found ECG parameters for native pig hearts."

Monitoring the heart with ECG after transplantation is one way to assess the electrical conduction system after a heart transplant. A 12-lead ECG measures the electrical conduction in 12 different electrical angles of the heart.

Specifically, researchers reviewed two ECG measures: the PR interval/QRS complex and the QT interval. The PR interval and QRS complex measure the time it takes electricity to travel from the top to the bottom chamber and across the bottom chambers, thus, pumping blood through the heart. The QT interval measures the time it takes the lower chambers of the heart to go through a full electrical cycle associated with a heartbeat.

For this study, the ECG data of the transplant patient were collected usually once a day after the transplant. Prior research demonstrated that ECG parameters of the pig heart in a pig body had a short PR interval (50 to 120 milliseconds), short QRS (70 to 90 milliseconds) and short QT (260 to 380 milliseconds).

"In contrast, the first-ever ECG of a genetically modified heart xenotransplant found a longer PR interval of 190 milliseconds, QRS duration of 138 milliseconds and QT of 538 milliseconds, which is longer than what would be expected from a pig heart in a pig body," Dickfeld said.

"In a human heart, when those parameters get longer, this can indicate signs of electrical or myocardial disease," he said. "The pig heart ECG parameters were extended to what we see in a human heart and often the measures even extended beyond what we consider normal in a human heart."

Additionally, the continual ECG measures indicate that prolonged PR intervals remained stable after the transplant, averaging about 210 milliseconds. QRS duration remained prolonged with about 145 milliseconds, however, these shortened later during the 61-day post-transplant period.

"The QRS duration may prolong when, for example, the muscle and the

electrical system itself is diseased, and that is why it takes a long time for electricity to travel from cell to cell and travel from one side of the heart to the other," Dickfeld said. "In general, we would prefer for this QRS measure not to prolong too much."

Finally, the study revealed an increased QT duration averaging about 509 milliseconds with dynamic fluctuations. The lowest QT duration was observed on day 14. "In the human heart, the QT duration is correlated with an increased risk of abnormal heart rhythms," Dickfeld said. "In our patient, it was concerning that the QT measure was prolonged. While we saw some fluctuations, the QT measure remained prolonged during the whole 61 days."

The researchers believe these findings provide a foundation for future research to better understand the effects of xenotransplantation on the heart's electrical system and to better prepare for future cases of xenotransplantation.

In 2020 (the most recent data available), the United States recorded the highest number of heart transplants at 3,658 transplantations performed, according to the American Heart Association's 2022 Heart Disease and Stroke Statistical Update. As of February 2021, 3,515 people were on the waiting list for a heart transplant, and 49 people were on the waiting list for a heart and lung transplant, also according to the update.

"The ultimate goal is that if someone needs a heart, xenotransplantation may be an option," Dickfeld said. "We need to make xenotransplantation safer and more doable in these challenging areas: rejection, infection, pumping problems and certainly in the area of abnormal electrical signals and heart rhythms."

The major limitation is that this study is a first-of-its kind in a single patient. Future research will have a better foundation of knowledge on

which to build.

"This was a true milestone for research on xenotransplantation, the transplantation of organs from one species to another, in this case from pigs to human. There were a number of key steps that will be fundamental to the success of these operations largely centered around genetic manipulation to reduce organ rejection. Solving the problem of rejection may ultimately lead to use of this method to help numerous patients with advanced heart failure," said Paul J. Wang, M.D., FAHA, who was not involved in the study, director of the Stanford Cardiac Arrhythmia Service and a professor of medicine and bioengineering at Stanford University, and editor-in-chief of the American Heart Association's journal *Circulation: Arrhythmia and Electrophysiology*.

"It will be extremely interesting to understand the factors that affect the changes in the parameters observed comparing the pig-in-pig values vs. the pig-in-human values. We will want to look at factors such as how they reflect rejection and hemodynamic status," Wang said. "Further analysis of the electrocardiogram including ST-T wave abnormalities may also provide unique insights."

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Provided by American Heart Association