Editorial

Heart Xenotransplantation: Current Issues and Perspectives

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Cardiac surgery rapidly gained much publicity following its establishment in the late 50s. Nonetheless, subsequent advances in percutaneous techniques in the domain of cardiovascular diseases overshadowed cardiac surgery for a substantial period until a recent project rekindled interest, among scientists and patients, in cardiac surgery.

The project in question was the xenotransplantation of a pig heart to a human, performed on January 7th, 2022. The patient survived for approximately 2 months with satisfactory hemodynamics and without mechanical and pharmaceutical support. The cause of his death has yet to be fully elucidated, although a pig virus seems to be the likely culprit.

While it was the first transplantation of a pig heart to a human, by no means was it the first heart xenotransplantation. Indeed, the first transplantation ever was the xenotransplantation of a chimpanzee heart to a human performed by Hardy[1] in 1964. The outcome was, however, disappointing, with Hardy facing many problems in the following years due to his perceived "unethical" procedure. He was even expelled from the American Medical Association for a while. All this led to the abandonment of such techniques for about 50 years, although the science has evolved greatly since then, with parts of animals such as swine pericardium being widely used in common practice.

The recent project was pioneered by Griffith on the strength of advances in immunosuppression. For instance, xenotransplantation from a pig heart to a non-human heart was investigated, and the results showed that cardiac xenotransplantation was feasible in the midterm.[2] A landmark in this field was the publication of a study in 2018 in which modified pig hearts were transplanted in chimpanzees, and the survival exceeded 195 days in 4 out of 5 recipients.[3] The results of that study raised the interest in heart xenotransplantation among scientists. Pierson[4] claimed that such results, on condition of reproducibility, could pave the way toward further clinical heart xenotransplantation trials. Still, Reichart[5] opined that a more acceptable costimulation blockade was required for future human applications and safe donor animals that would not cause harmful infectious diseases in human recipients.

From a technical perspective, pig heart donor grafts offer such advantages as similarity with the human heart, relatively

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swift breeding, cost-efficiency, and fewer ethical barriers.[6] The construction of a modified donor heart is complicated, with the principal goal being the creation of chimeric animals. More specifically, gene-editing technologies combined with cross-breeding are employed to produce personalized organ generation. The generated organ in tandem with immunosuppression and gene reprogramming constitutes the step preceding xenotransplantation.[7] In the technical field, the formidable barriers to overcome are as follows:

a) hyperacute rejection and acute humoral xenograft rejection, happening from minutes to hours post-transplantation;

b) initial cellular xenograft dysfunction, presenting from minutes to hours post-transplantation; and

c) acute humoral rejection, attributed to coagulation dysregulation and elicited antibody immunity, presenting from days to weeks post-transplantation.[8, 9]

Nonetheless, even the supporters of cardiac xenotransplantation admit that this method is indicated in selected cases. Pierson et al[10] defined the criteria for cardiac xenotransplantation consisting of 4 principal categories: the risk of allograft failure due to immunologic factors, contraindications for the ventricular assist device, adult congenital heart diseases, and severe biventricular failure without established end-organ failure.

Indubitably, the enthusiasm for new methods that could offer solutions in the treatment of end-stage cardiac failure is elevated. Nevertheless, the technical barriers notwithstanding, ethical parameters should be considered. First and foremost, the transmission of zoonotic viral diseases is a complication that cannot be neglected, especially after the disastrous experience of the COVID-19 pandemic worldwide. In other words, are we ready to take the risk of performing xenotransplantation even though the risk of a new pandemic may arise? Is it ethical to risk the creation of new zoonotic diseases in order to treat cardiac failure in some patients? Can we risk public health for a group of people in despair? These are some crucial concerns that need to be delineated, and of course a definite regulation is required. Moreover, a matter of debate is whether it is worth using economic and human resources for the development of this technique or whether these resources could be more beneficial in the improvement of other methods.[11] Thankfully, the most common religions (Christianity, Judaism, and Islam) worldwide are not opposed to xenotransplantation as it is a method for life prolongation, and the value of life is above all.[12]

Cardiac xenotransplantation is a burning issue among the scientific community. The need for solutions regarding end-stage cardiac failure is undoubtedly well understood as 250 000 patients die due to this entity annually.

To sum up, the pros and cons of xenotransplantation should be examined meticulously at scientific level from all aspects so as to make appropriate decisions, avoid possibly lethal consequences, and devise a “wise” plan (Figure 1).

All the procedures were performed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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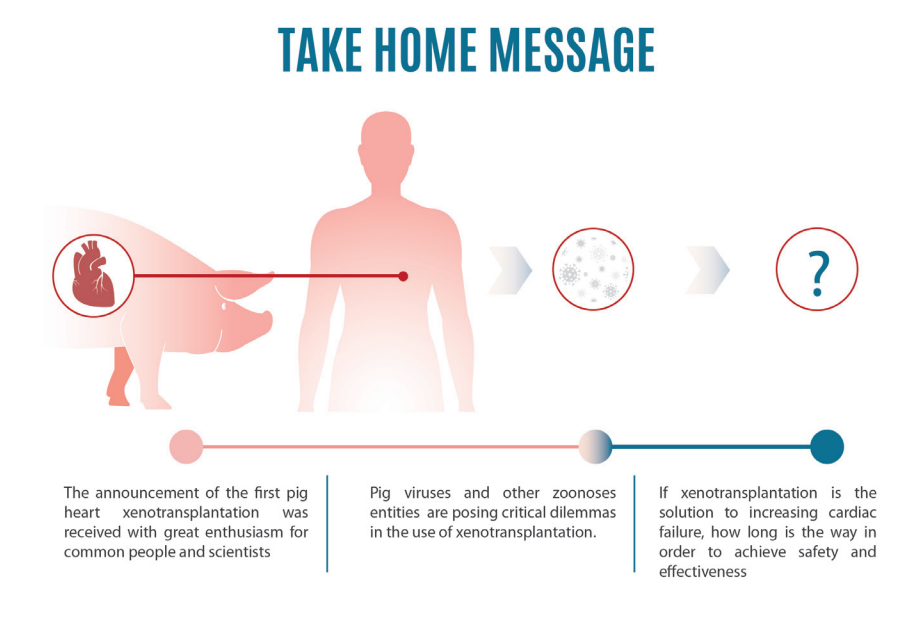

Figure 1. Diagram summarizing the concerns and the questions regarding cardiac xenotransplantation from pig to human.

the graphics for this editorial.

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