Heart Xenotransplantation: Historical Background, Experimental Progress, and Clinical Prospects

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If pig hearts could be transplanted successfully into patients with end-stage cardiac failure, the critical shortage of hearts from deceased human donors would be overcome. The several attempts at cardiac xenotransplantation carried out in the 20th century, usually with hearts from nonhuman primates (NHPs), are reviewed, as are the surgical techniques used in experimental heart transplantation in animals. For a number of reasons, the pig has been selected as the potential source of organs for clinical transplantation. The major pathobiological barriers that the pig presents, and progress in overcoming these barriers either by genetic engineering of the pig or by the administration of novel immunosuppressive agents, are described. Currently, non–life-supporting pig heterotopic heart transplantation in NHPs has extended to more than 2 years in 1 case, with life-supporting orthotopic heart transplantation of almost 2 months. Future approaches to resolve the remaining problems and the selection of patients for the initial clinical trials are briefly discussed.

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> Clinical xenotransplantation is just around the corner—but it may be a very long corner.–Sir Roy Calne, 1995

> Xenotransplantation is the future of transplantation, and always will be.–Randy Morris

It is estimated that in the United States 4 to 5 million individuals experience heart failure, and approximately 400,000 new cases are added to this pool every year [1]. Thus tens of thousands of patients per year might benefit from heart transplantation, yet fewer than 3,000 heart transplant procedures are performed annually in the United States (Fig 1). Eurotransplant reports that 17.7% of patients waiting for a heart transplant died in 2011 [2]. Unless there are breakthroughs in other fields of medicine, the shortage in the availability of suitable donor hearts will almost certainly increase in the future. The limitation in organ availability has renewed interest in the potential of xenotransplantation (cross-species transplantation, eg, from pig to human) [3].

Interest in this field continued sporadically throughout the late 20th century. In the majority of cases, hearts from nonhuman primates (NHPs) were selected, with a minority using hearts from other mammals (Table 1) [4].

James Hardy (Fig 2A), who had been investigating heart allotransplantation in the experimental laboratory and was planning the first clinical attempt, acquired some chimpanzees as potential donors in the event he could not identify a deceased human donor. His proposed recipient was, by today's criteria, less than ideal because he had extensive peripheral vascular disease, for which he had undergone bilateral amputations, and was semicomatose [5]. Because he was deteriorating rapidly, Hardy decided to implant a chimpanzee heart. This proved not to be large enough to support the circulation, and the patient died within 2 hours. Subsequent histopathologic examination by Rose [6] suggested that antibody-mediated rejection contributed to the failure of the graft. Interestingly, the brief consent form for the procedure was signed by a relative of the semicomatose patient, and although it did state that no heart transplantation had been performed previously, it made no mention that an animal heart might be used. There was an adverse response from both the medical profession and the public to this operation, dissuading Hardy from carrying out any further clinical heart transplantation at that time.

Based on the experimental studies of Demikhov, Brock, and Shumway [7], clinical orthotopic heart allotransplantation was first performed by Christiaan Barnard in 1967 in Cape Town (Fig 2B) [8]. He later developed a technique of heterotopic heart transplantation, which had some advantages in those early days when graft failure from ischemic injury or from acute rejection was not uncommon [9, 10]. In 1977, he used this technique in an attempt to support (with xenografts) 2 patients in postcardiotomy shock who could not be weaned from cardiopulmonary bypass after routine cardiac surgical procedures [11]. A baboon heart failed rapidly, but a chimpanzee heart supported the patient for 4 days until it was rejected before the patient's own heart had recovered.

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Abbreviations and Acronyms

CRP = complement regulatory protein
Gal = galactose-α1,3-galactose
GTKO = α1,3-galactosyltransferase gene knockout
NeuGc = N-glycolylneuraminic acid
NHP = nonhuman primate
TBM = thrombomodulin

In 1984, pediatric cardiac surgeon Leonard Bailey (Fig 2C) transplanted a baboon heart orthotopically into an infant girl, known as Baby Fae, who had been born with hypoplastic left heart syndrome [12]. At that time, it was almost impossible to obtain donor organs for infants. The operation was technically successful, but the graft underwent rejection and the patient died 20 days later. Even though the relatively new and more potent immunosuppressive agent cyclosporine was administered, this proved to be inadequate to prevent rejection across the species barrier. Furthermore the graft was ABO-incompatible because the O blood type is essentially not seen in baboons. Baby Fae's transplant did little to advance xenotransplantation, but it drew the attention of the medical community and the public to the dearth of deceased human organs available for infants. As a result, pediatric cardiac allotransplantation received a considerable boost.

In the enthusiastic flush of heart transplantations that followed soon after Barnard's first allotransplantation, 2 well-known cardiac surgeons, Donald Ross (Fig 2D) and Denton Cooley (Fig 2E), transplanted pig and sheep hearts, respectively, in patients who were about to die [13–15]. Ross preempted Barnard in performing a heterotopic transplantation in the hope that his patient's native heart would recover good function, but hyperacute rejection occurred within minutes. In a second patient on the same day, he carried out a test by perfusing a pig heart with blood from the heart-lung machine, with the same result of hyperacute rejection, and so did not carry out the transplantation. Cooley's sheep heart suffered a similar fate. There were 2 further reports of pig hearts being transplanted (1 in Poland [16] and 1 in India [17]), but details of the latter case were scarce and mainly through the lay press (Table 1).

From these early experiences, it was clear that the immune response to a nonprimate mammalian heart was much stronger than to an NHP heart. However, for a number of reasons, recent experimental studies have concentrated attention on pigs as potential sources of organs (Table 2).

Materials and Methods

Surgical Techniques of Experimental Heart Transplantation

The early development of surgical techniques in the laboratory has been reviewed previously [7]. Heterotopic transplantation indicates placing the heart in an ectopic position without removing the native heart. Heterotopic techniques can be categorized as "working" or "nonworking" models.

In nonworking models the donor heart is perfused and beats forcefully but does not contribute support to the recipient's circulation, so these models have been largely applied for the study of the immunopathologic features of graft rejection and the efficacy of immunosuppressive therapies. These models proved valuable in the early research into allotransplantation (when graft survival was often short, ie, days) and have proved equally valuable in xenotransplantation (when graft survival initially proved to be very short, ie, minutes rather than hours or days). If the site of the graft is in the abdomen or neck, the

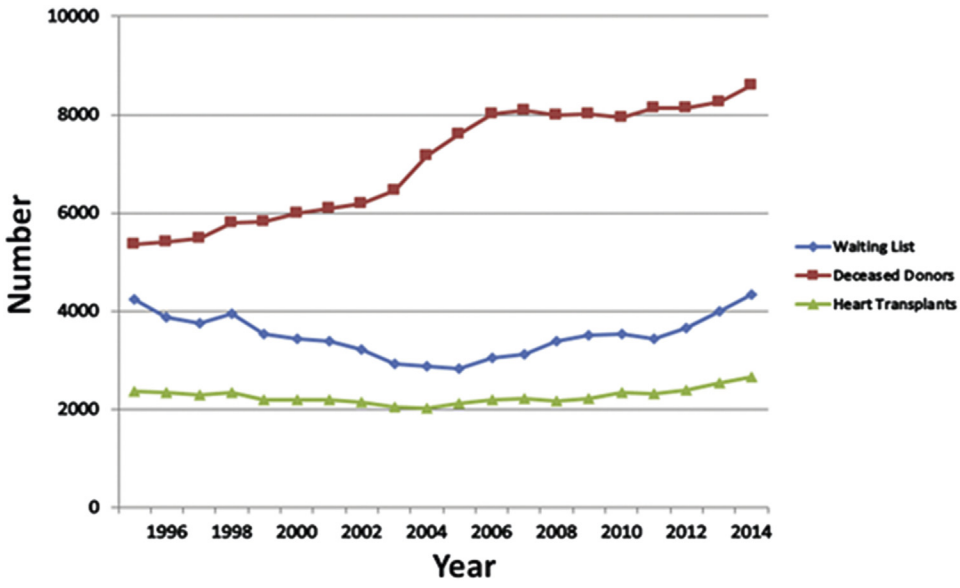

Fig 1. Number of patients awaiting heart transplantation, number of deceased donors that became available, and number of heart transplants carried out in United States annually from 1990–2014. (Courtesy of United Network for Organ Sharing/Organ Procurement and Transplantation Network [UNOS/OPTN] http://optn.transplant.hrsa.gov/converge/latestData/step2.asp.)