A New Perspective in Baboon Cardiac Xeno Transplantation

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Abstract

End-stage heart failure is prevalent in the industrial world and there is a long waiting list for heart and other organs, yet the pool of donors are limited to less than 10% of all brain death cases coming out of traffic accidents. The National Highway Safety Administration of the United States reports that only 2,800 transplant organs were harvested out of a total of 56,000 road accident deaths in 2016. In China, it is expected to have a record number of transplants this year mainly harvested from executed prisoners, (world number two in execution after Iran), despite a new ban applied this year (South China Morning Post).

One of the most exciting potential donor pools which is also very close genetically to Human beings is the baboon, in which we will try to re-ignite interest in research and development for farming and harvesting of their organs for use in people in need of Xenotransplantation. The same has been done from pig farming.

There is also an opportunity to use them as a Xeno-bridging to all transplantation.

Key words: baboon, xenotransplant; Papio, concordant, discordant, Cyclosporine, total lymphoid irradiation

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Introduction

Cardiac Xenotransplantation (Xeno-from Greek meaning “Foreign”), is the transplantation of living organs from one species to another (2).

With contrast to all transplantation (from another individual of the same species), they both offer a potential treatment for end-stage organ-failure which is prevalent in the industrial world. It also raises many novel medical, legal and ethical issues, especially harvesting from animals (3). Also a continuing concern is that many animals, such as the baboon, have a shorter lifespan than humans, meaning that their tissues age at a quicker rate (4).

An increasing shortage of transplant donor hearts currently results in an escalating number of preventable Human deaths.

At present 65% of patients on transplant waiting lists will not be able to receive a heart by the end of one year. 22 people die every day on the organ transplant waiting list (12).

It is a sad situation which could be alleviated by somehow increasing the pool of available donor hearts.

Xenocardiac transplantation, the use of animal hearts for transplantation for human beings is now and will be in near future the golden opportunity in developing countries with lesser rigid laws for animal protections. It may be medicine’s most viable answer to the urgent and insurmountable human heart scarcity.

As we know, heart transplantation is a cultural phenomenon/a procedure engaging both physical and symbolic manipulation of human and non-human bodies, therefore transforming its corporeality, identity, and culture. Due to obscured issues of Cardiac Xenograft related to non-human animals namely chimpanzees and baboons and that could also be stressful to human heart recipients, revealing that the cardiac Xenograft may not be widely embraced, yet its culture could soon be changed, therefore providing a way forward for those in need of cardiac transplantation (5).

For pig-to primate xenotransplantation, a significant number of barriers have been identified and potential solutions generated, however, the survival rates remain modest at best with longest heterotopic heart transplant surviving only 99 days and the longest functioning orthotopic heart transplant surviving only 39 days (6).

In the late 20th century organ replacement surgery has been presented, both in medical texts and in media, as a miracle of modern medicine (Birke, 1996). Heart transplantation is one of medicine's most flamboyant symbols. The replacement of diseased vital organs with healthy cadaveric organs is now a routine therapy that not only extends life, "but also improves its quality and is not particularly expensive" as compared to L.VAD (Nuffield council on bioethics (NCB), 1996, P2).

For Biomedicine, the continuing success of heart replacement technologies is now hampered by deficits in "natural" resources: hearts available for transplantation. As each year passes, the shortfall in heart supply increases, resulting in unnecessary patient morbidity and mortality (Caplan, 1992; Calne, 1993; NCB, 1996). According to a report by the United States, National Highway Safety Administration, out of 55,000 road mortalities only 2,800 hearts were harvested and used for transplantation (National Procurement Agency, 2016, yearly report). Remaining rigidly unresponsive to alternatives, health education strategists [Bulletin of Medical Ethics] (BME), 1991; Caplan, 1992], or changes in the diagnosis of death (Ohnuki-Tierney, 1994; Singer, 1994), heart scarcity now constitutes one of medicine's fastest growing problems (Concas, 1994). The answer to the human heart shortage is now seen to lie in the resurrection of the Xenocardiac transplantation, a trans-species of which extensive animal farms can be established. The use of animal products and parts is already routine in human medicine. As yet unfamiliar, and more ambitious, is the proposal of whole organ, namely heart from healthy transgenic animals into humans with end-stage heart failure.

"Concordant xenotransplantation" means transplant between more genetically related species versus "Discordant xenotransplantation" which occurs between more distantly related species, were analyzed. At the turn of century the first cardiac Xenograft involved using heart from pigs, dogs, sheep, monkey and goat into Humans and took place in Europe.

The surgeons were unaware that such a diversity with distantly related species, would cause such a fierce rejection from recipient immune systems, that imminent massive graft failures were evident. So more closely related species such as chimpanzee and baboon (Papio Papio) with more genetic similarity with humans were selected with good results.

Chimpanzee, due to their protected semi-extinct status, were placed on protected list and were eliminated from the donor list. On the other hand, the baboon is considered by proponents a well breeding and overflous species in nature and even produced commercially in some farms in subcontinent India for the purpose of export for research and development.

It is believed to be the future selection of scarcity of Xenocardiac transplantation. Guinea baboon from African continent (also called Savanna Baboon) has a life spam of 35-45 years with a body mass of 15-40 kg. Their gestation period is about 6 months and the nursing period is also about 6 months. Their colony has about 200 individuals. They eat almost anything including small mammals . They are very communicative animals by using a variety of vocalization and physical interactions. This species also has used its vocal communications to be received and interpreted by predators.

Animal Ethics and religion

One of the most vocal and strongest organization for animal rights is People for the Ethical Treatment of Animals (PETA).

They enjoy very strong and powerful support from every NGO.

They receive some funds and their members are willing to sacrifice on controversial issues to challenge it even at the level of physical altercations. The latest occurred in 2009, when a group of 50 individuals from PETA entered a section of research and development of Minnesota Mining and Manufacturing (3M) in St. Paul.

Now with this incident, that place has turned into a fortress rivaling place neighboring Fort Knox in Kentucky!

The PETA group have repeatedly stated that they are "opposed to the use of animals and animal tissues for experimentation, medical training, and clinical treatments(9). They are opposed to the idea of xenotransplantation because they maintain that humans do not have the right to breed and use other animals for their own needs. Religious views and organ transplant in Islam and Judaism forbid use of pig products (porcine), yet in dire situations when a human life might be saved, it allows exception .

Buddhits regard organ donation as a personal matter which should be left to an individual's conscience. A Hindu tenet is that the body must remain as a whole in order to pass into eternal life, therefore transplantation is not condemned except for the use of cows which are regarded as sacred, so a Hindu can donate or accept an organ without prohibition and can use animal organs to alleviate his sufferings.

Also it's notable that in Hindu Mythology, lord Ganesh (Lord's Shiva's son) received a xenograft from an elephant head after lord Shiva inadvertently severed his Son's head.

Experimental Xeno Transplantation in Discordant Vs. Concordant Xenotransplantation:

The idea of transplantation across discordant xenogenic barriers in an orthotopic newborn pig-to-juvenile baboon model was first explored at Loma Linda labs in California in early 1990's. Because of hyper-acute rejection as a first stage, it was important to eliminate or reduce Baboon's preformed xenoantibody by exposing them to Swine Sugar Antigens (8,9). Also by Matsumiya et al (10) splenectomy was omitted, and the baboon recipients were preoperatively immunosuppressed one month using Cyclosporine and Methotrexate. Total lymphoid Irradiation (TLI) was administered for one week.

All animals survived the transplantation procedure. Nearly complete adsorption of anti-pig xenoantibody was documented, and no sign of hyper acute rejection was observed. Delayed rejection occurred almost uniformly between post operative days 10 and 14. Rejection was successfully reversed in two animals using massive doses of methylprednisolone , but the two animals succumbed to exacerbation of delayed xenograft rejection at 19 and 24 days. Cellular infiltrates included macrophages and T-Cell Killers, suggestive that delayed discordant xenograft rejection occurs by mechanism other than classic allograft cellular or humeral pathways.

While the idea of xenograft as a bridge to cardiac allografting is still developing, the core decision on Human neonatal cross-species transplantation has slowed down due to lack of donors.

One of the important questions was whether the antibody response to the xenografted heart would develop and later would be cross reactive and cause reaction to the allografted heart. So sensitization of this nature might preclude successful secondary allotransplantation. This question was initially explored by Alonso de Begona(11), who employed a model in which African green monkey hearts were transplanted into the neck of five immunosuppressed Juvenile Baboons using a technique previously shown by the Columbia University Group (CUG).

These grafts were rejected over a period of 5 to 65 days. Lymphotoxic Xenoantibody was identified in recipient blood samples. The rejected xenografts were removed, and the recipient circulating xenoantibody titers were observed to peak over 24 to 48 hours. Using cardiopulmonary bypass primed without blood, the immature Baboon recipients then underwent orthotopic cardiac allotransplantation. All survived the secondary heart allotransplant procedure without evidence of hyper acute, Antibody mediated rejection. They were immunosuppressed to varying degrees using a cyclosporine (CSA) protocol (Table 1) (Figures 1-5).(23)

Table 1: Survival of xenografts and allografts and host therapy employed in a xenograft bridge to allograft model using an immature baboon recipient

	Cardiac heterotopic xenograft (African green monkey)		Cardiac orthotopic allograft (Common olive baboon)		
Experiment	Therapy[a]	Survival (days)	Therapy[a]	Survival (days)	Allograft rejection
1	A	11	A	10	Severe
2	A	5	A: B^{rescue}	58	Moderate to severe
3	A	6	A: B^{rescue}	65	Moderate to severe
4	A; B+ C^{rescue}	13	A; B+ C^{rescue}	198[b]	Non
5	A+B+C	65	A; $B^{induction}$	164[b]	None

Fig. 1. Max, an immature baboon recipient of an orthotopic cardiac xenotransplant acquired from a donor rhesus monkey. He was an active, growing, healthy baboon photographed 1 year after transplantation. He went on to live 502 days and died of cytomegalovirus disease. His xenograft was free of rejection, but coronary disease was in evidence at autopsy.

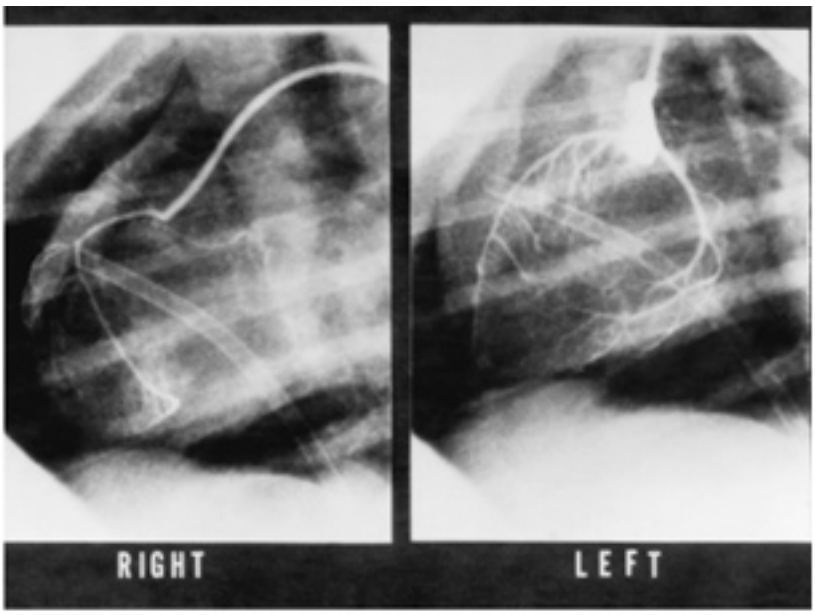

Fig. 3. Coronary arteriograms (CAG) obtained on routine evaluation o Max, an immature baboon recipient of a rhesus monkey heart orthotopi cally implanted 1 year prior to these contrast studies. Coronary arterie appear normal in size and distribution.

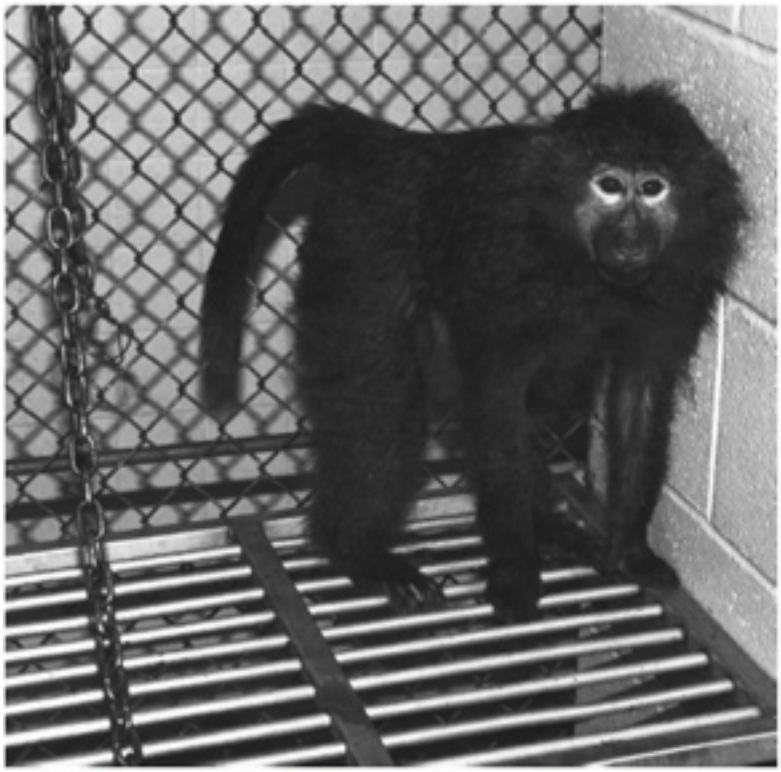

Fig. 4. Baboon recipient of orthotopic rhesus monkey cardiac xenotransplantation. This recipient lived 515 days on a maintenance immunosuppressive regimen of cyclosporine and methotrexate. The animal required treatment with methylprednisolone boluses for only two episodes of graft rejection. She grew and developed well. She ultimately died of right coronary artery obstruction and selective right ventricular fibrosis.

Fig. 5. Vigorous, healthy juvenile baboon recipient of orthotopically implanted piglet heart photographed 10 days after transplantation. She went on to live 16 days, dying suddenly of delayed xenograft rejection.

Recently researchers at the National Institute of Health (NIH) reported that they were able to have a pig's heart beating inside the abdomen of a baboon for more than 500 days (13).

Matsumiya et al (14-16) developed a similar species of six xenotransplanted baboons in which the concept of pre-transplant immune suppression was utilized and splenectomy was omitted. The cyclosporine and Methotraxate were administered comparable to Loma Linda University. Three recipients survived for a year with the longest for a total of 515 days.

Most morbidity and mortality were related to viral infection. By use of OKT3 for acute myocarditis (Ali Sadeghi et al) (17) the ejection fraction improved from 10-20% all the way to 50-70% (18, 19).

Again long term survival in 3 groups of baboon that underwent orthotopic concordant cardiac xenotransplantation of up to 300 days was reported by Asano, et al (20) for effects of immunosuppressive regimens with total irradiation of lymphoid tissues pre-transplant and use of cyclosporine, methotrexate, and antithymocyte globulin. This regimen leads to suppression of the interleukin2 pathway and xenoantibody production.

Dr. Smith reviewed the cardiac Xenotransplantation (21) which had an account of the immunological basis presented followed by an overview of approaches under study to overcome rejection and so he concluded that at present there are insufficient scientific data on which to base clinical cardiopulmonary xenotransplantation.

Conclusion

There is an irony that investigators are trying to mimic an experimental procedure to cover up the sponsor's interest in clinical trails of cardiac xenotransplantation. The accusation lies in using "The guise of bridge-to-transplantation" to appear acceptable to institutional and peer's review or ethics boards.

From time to time, the FDA publishes guidance documents to assist sponsors and investigators interested in conducting clinical trials of cardiac xenotransplantation. Such final documents can be accessed on internet at http://www.fda.gov/cber/guidelines.

It is well known that xenotransplantation and its byproducts come under direct FDA regulations. In 1997, FDA formed xenotransplantation subcommittee of the BRMAC as an open discussion and ongoing mechanism for the scientific, medical, social, ethical and public health issues raised by specific ongoing and proposed protocols.

Some data from experimental labs at Loma Linda university and elsewhere indicate the momentum toward clinical xenotransplantation are both timely and justified. Federal Agencies are taking this work very seriously with plenty of research funds. Each proposal or protocol to initiate additional clinical trials of cardiac xenotransplantation will be reviewed by these agencies with an eye to scientific and benefits to public health and protection of experimental subjects. Keeping in mind the daily loss of human life due to lack of donor hearts and lack of any commercially

producing animal farms away from watchful eye of animal rights groups and institutional review boards and federal oversight agencies whose mandate is to first protect and ensure that patient and public benefit clearly outweigh the potential risks will surely justify and direct the necessary funds and resources to the bright future of these animal farms. Clearly a baboon with a mass of 40 to 50kg can be used as a donor heart for xenotransplantation of small human adults and definitely in pediatric transplant coming directly from a farmed baboon.

However, the use of cardiac xenografts solely as bridges to allotransplantation does not increase the donor pool; therefore, successful, permanent cardiac xenotransplantation must itself be viewed as the target of future clinical investigations so the pool of donor hearts would expand to the benefit of waiting needy patients. In the future, clinical heart xenotransplantation may accomplish its intended goal of achieving prolonged graft survival by diverting huge research funds and other resources by both public and private sectors. But we should be aware of the unintentional task of pressure groups namely the powerful animal rights groups to further hinder any scientific achievements by ignoring the need of that section of population in need of a new heart. We must remember that clinical transplantation is the only effective therapy for end-stage organ failure (22).

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