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Concordant VS. Discordant Xeno Cardiac Transplantation; The past, present and future trends

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Abstract: There is a huge waiting list for recipient of heart for people in need of, yet the pool of donors is limited to less than 10% of all brain death cases coming out of road accidents. NHSA reports 2700 Transplants were harvested out of 55000 road accident brain deaths in 2014. A country (China) expects a record number of transplants this year mainly harvested from executed prisoners (world number one in execution followed by IRAN), despite a new ban applied this year (The south China Morning Post). So, one of the most exciting donor pool which also is very close genetically to Human being is Baboon, in which we will try to reignite interest in research and development for farming and harvesting their organs for use in people in need of Cardiac Transplant.

Key words: concordant; discordant; xenotransplant; Baboon; Papio; cyclosporine;

Introduction

An increasing shortage of transplant donor hearts currently results in an escalating number of preventable human deaths. It can be alleviated by somehow increasing the pool of available donor hearts. Xeno heart transplantation, the use of animal heart for transplantation into humans is now and will be in near future heralded as medicine's most viable answer to the urgent and insurmountable human heart scarcity. Heart xenotransplantation will be a cultural phenomenon-a procedure engaging both physical and symbolic manipulating of human and non-human bodies, thereby transforming corporeality, identity and culture. Due to obscured issues of heart xenografts related to nonhuman animals namely Chimpanzee and Baboons and also that could be distressful to human heart recipients, revealing that the Xenograft heart may not be widely embraced, yet its culture could be changed soon, therefore to have the way forward for those in need of heart transplantations [10].

Heart transplantation is one of medicine's most flamboyant symbols. In late 20th century organ replacement surgery has been presented, both in media and medical text, as a miracle of modern medicine (Birke, 1996). The replacement of diseased vital organs with healthy cadaveric organs is now routine-a therapy that not only extends life, "but also improve(s) its quality (and) is not particularly expensive". (Nuffield Council on Bioethics (NCB), 1996, P.2). For Biomedicine, the continuing success of heart replacement technology is now hampered only 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 National Highway Safety Administration, U. S. Department of Transportation each year in U.S. alone there are about 5500 deaths reported, of which only 2700 hearts are harvested and used for transplantation (National Procurement Agency, 2014, yearly report, NHSA 2014). Remaining tenaciously unresponsive to alternative procurement policies, health education strategies [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 lay in the resurrection of the heart Xenograft 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 proposed transplantation of whole heart from healthy transgenic animals into humans with end-stage heart failure.

At the turn of century transplanting first heart xenograft involved from Pigs, dog, sheep, monkey and goat into humans and took place in Europe. The surgeons were unaware that "discordant

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xenotransplantation" between such distantly related species, would cause the immune system to mount a much fiercer rejection than "concordant xenotransplantation" between more closely related species of which Chimpanzee and Baboon (PapioPapio) share with human beings.

Due to its protected semi-stinct species, Chimpanzee will not be used for this process, yet Baboon is a well preserved and even produced at commercial farms in Asia (especially in subcontinent India) and is the future solution for scarcity of concordant heart xenotransplantation. Guinea Baboon also called Savanna Baboon from old world monkey family has a life span of 35-45 years with mass of 13 to 40Kg. Gestation period is about 6 months and nursing is also 6 months. They live in a group of up to 200 individuals. They eat everything including small mammals.

They are very communicative animals. They communicate by using a variety of vocalization and physical interactions. This animal also has vocal communications apparently intended to be received and interpreted by predators. The concept of rights for donor animals is controversial. Nonhuman primates such as Chimpanzees or Baboons have complex social behaviors, and various ethical concerns exist regarding their use. One of the strongest and most vocal groups of animal rights groups, is People for the Ethical Treatment of Animals (PETA). They have repeatedly stated that they were "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 right to breed and use other animals for their own needs. Religious views on heart xenotransplantation in Islam or Judaism forbid use of Pig organs, yet in dire situation, it allows exceptions especially where a human life might be saved. Buddism regard organs donation as a matter that should be left to an individual's conscience. A Hindu tenet is that the body must remain whole in order to pass into eternal life, therefore transplantation is not condemned except cows which are sacred, and so a Hindu can donate or accept an organ without prohibition and can use animal organs to alleviate his human sufferings. It's notable that in Hindu Mythology lord Ganesh (Lord Shiva's son) received a xenograft of an elephant head after lord Shiva inadvertently severed his Son's head.

Concordant Xenotransplantation:

Human neonatal cross-species transplantation evolved around the idea of xenograft as a bridge to cardiac allografting. The important question was whether the antibody response to xenografted heart would develop and later would be cross reactive and cause reaction to allografted heart. So, sensitization of this nature might preclude successful secondary allo-transplantation. This question was initially explored by Alonso de Begona[1], 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.

These grafts 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 xeno-antibody titers were observed to peak over 24 to 48 hours. Using cardiopulmonary bypass primed without blood, the immature Baboon recipients then underwent orthotropic cardiac all transplantation. 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).

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

Experiment	Cardiac heterotopic xenograft (African green monkey)		Cardiac orthotopic allograft (Common olive baboon)		Allograft rejection
	Therapy [a]	Survival (days)	Therapy [a]	Survival (days)	
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

[a]Immuno-suppression. A: cyclosporine + azathioprine + solumedrol; B: goat anti-human T Cell IgG; C: monoclonal antibody; rescue: therapy for acute rejection; induction: therapy for induction only

[b]Electively euthanized

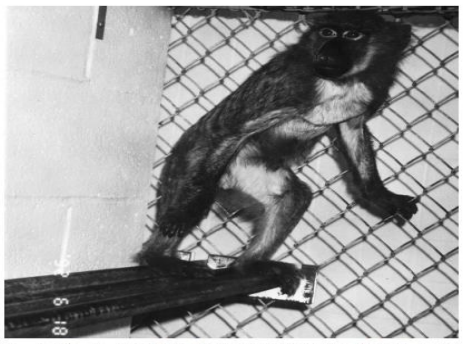

Fig. 1. Max, an immature baboon recipient of an orthotopic cardiac xenotransplant acquired from a donor rhesus monkey. He was an active, growing, healthy baboon photographed 1 year after transplantation. He went on to live 502 days and died of cytomegalovirus disease. His xenograft was free of rejection,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

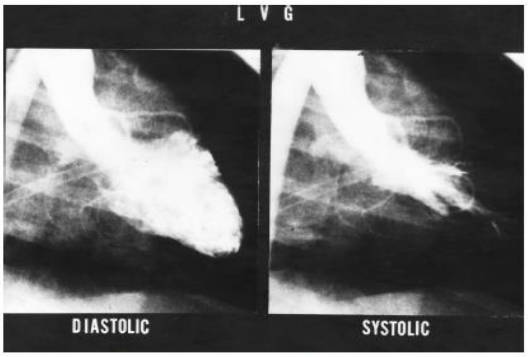

Fig. 2. Contrast left ventriculograms (LVG) obtained on routine evaluation of Max, an immature baboon recipient of a rhesus monkey heart. Systolic ejection and diastolic compliance were normal in the xenograft 1 year after orthotopic transplantation.

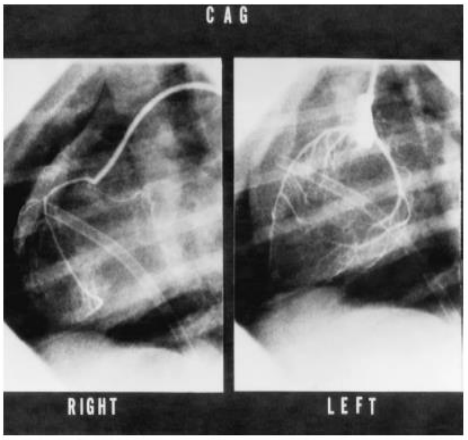

Fig. 3. Coronary arteriograms (CAG) obtained on routine evaluation of Max, an immature baboon recipient of a rhesus monkey heart orthotopically implanted 1 year prior to these contrast studies. Coronary arteries appear normal in size and distribution.

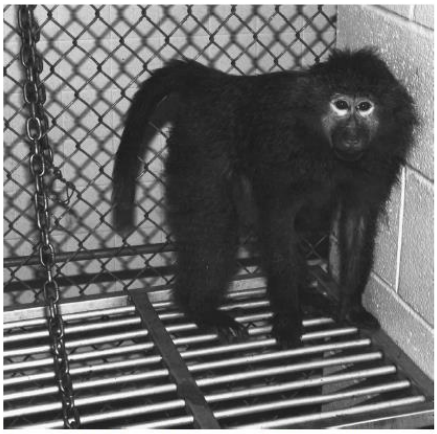

Fig. 4. Baboon recipient of orthotopic rhesus monkey cardiac xenotransplantation. This recipient lived 515 days on a maintenance immunosuppressive regimen of cyclosporine and methotrexate. The animal required treatment with methylprednisolone boluses for only two episodes of graft rejection. She grew 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.

Matsumiya *et al.,* [2-4] developed a similar species of six xenotransplanted Baboons in which the concept of pre-transplant immunosuppressant was utilized and splenectomy was omitted. Cyclosporine and methotrexate were administered comparable to Loma Linda University. Three recipients survived for a year with longest in 515 days.

Most morbidity and mortality were related to viral infection. By use of OKT3 for acute myocarditis (Ali Sadeghi *et al.*,) [5] the ejection fraction improved from 10-20% all the way to 50-70%[13, 14]. Again, a long-term survival in 3 groups of Baboon whom underwent orthotopic concordant cardiac xenotransplantation of up to 300 days were reported by Asano, *et al.,* [15] for effects of immunosuppressive regimens which the one with total irradiation of lymphoid tissues pre- transplant

and use of cyclosporine, methotrexate, and anti-thymocyte globulin. This regimen leads to suppression of the interleukin2 pathway and xeno-antibody production. Dr. Smith had reviewed the cardiac xenotransplantation [16] which had an account of the immunological basis was 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.

Discordant Xenotransplantation:
The idea of transplanting across discordant xenogeneic barriers in orthotropic newborn Pig-to-Juvenile Baboon model was first explored at Loma Linda labs in early 1990's. Because of hyper acute rejection as a first stage, it was important to eliminate or reduce Baboon performed xeno-antibody by exposing them to Swine Sugar Antigens [6,7]. Also by Matsumiya *et al.,* [8] 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 xeno-antibody was documented, and no sign of hyper acute rejection were observed. Delayed xenograft rejection occurred almost uniformly between postoperative 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 monocellular such as macrophages and natural killer cells, suggesting that delayed discordant xenograft rejection occurs by mechanism other than classic allograft cellular or humeral pathways.

Conclusion

Data from experimental labs of Loma Lina University and elsewhere indicate the momentum toward clinical cardiac xenotransplantation is both timely and justified. Federal Agencies are taking the research seriously. 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 the waiting time for that human donor hearts, the institution poised to commence or recommence clinical trials of heart xenotransplantation by watchful institutional review boards and federal oversight agencies whose mandate is to first protect and ensure that patient and public benefit clearly outweigh potential risks. Clearly Baboon with a mass of up to 80 to 100 pounds can be used as a donor heart for concordant xenotransplantation of small human adults and definitely in pediatric transplant coming directly from a farmed animal.

Current Status and Future Directions:
Xenotransplantation and xenotransplantation products come under the FDA regulations. In 1997, FDA formed xenotransplantation subcommittee of the BRMAC as an open discussions and ongoing mechanism for the scientific, medical, social, ethical and public health issues raised by specific ongoing and proposed protocols. 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 the internet at http://www.fda.gov/cber/guidelines; Although clearly an experimental procedure, investigators in clinical cardiac xenotransplantation have been accused of using "the guise of bride-to-transplantation" to appear acceptable to institutional review or ethics boards.

However, the use of cardiac xenografts solely as bridges to allo-transplantation 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 be enlarged to the benefit of needy patients. In the future, clinical heart xenotransplantation may accomplish its intended goal of achieving prolonged graft survival by allocating funds and extensive resources to research and developments by both private and public sectors.

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