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Surgical and Nonsurgical Complications of a Pig to Baboon Heterotopic Heart Transplantation Model

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Abstract

A modified immunosuppressive regimen, developed at the National Institutes of Health, has been employed in a large animal model of heterotopic cardiac xenotransplantation. Graft survival has been prolonged, but despite this, our recipients have succumbed to various surgical or nonsurgical complications. Herein, we have described different complications and management strategies. The most common complication was hyperco-agulability (HC) after transplantation, causing thrombosis of both small and large vasculature, ultimately leading to graft loss. While managing this complication we discovered that there was a delicate balance between HC and consumptive coagulopathy (CC). CC encountered in some recipient baboons was not able to be reversed by stopping anticoagulation and administering multiple blood transfusions.

Some complications had iatrogenic components. To monitor the animals, a solid state left ventricular telemetry probe was placed directly into the transplanted heart via the apex. Induction of hypocoagulable states by continuous heparin infusion led to uncontrollable intra-abdominal bleeding in 1 baboon from this apical site. This occurrence necessitated securing the probe more tightly with multiple purse strings and 4-quadrant pledgeted stay sutures. One instance of cardiac rupture originated from a lateral wall infarction site. Earlier studies have shown infections to be uniformly fatal in this transplant model. However, owing to the telemetry placement, infections were identified early by temperature spikes that were treated promptly with antibiotics.

We had several cases of wound dehiscence due to recipients picking at the sutures. These complications were promptly resolved by either re-approximating the wound or finding distractions for the baboon. A few of the most common problems we faced in our earlier experiments were related to the jacket, tether, and infusion pumps. It was difficult to keep the jackets on some baboons and the tether had to be modified several times before we assured long-term success. Infusion catheter replacement resulted in transplant heart venous obstruction and thrombosis from a right common femoral venous line. Homeostatic perturbations such as HC and CC and baboon-induced wound complications comprised most complications. Major bleeding and death due to telemetry implantation and infarct rupture occurred in 2 baboons. Despite the variety of complications, we achieved significant graft prolongation in this model.

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Heterotopic transplantation of cardiac xenografts from a pig into a baboon is a commonly used model to study rejection and the effects of various immunosuppressive and immunomodulating agents. Unfortunately due to the genetic disparity and to the requirement for significant immuno-suppression, many complications have been recorded,[1–3] including disseminated intravascular coagulopathy (DIC) and other coagulopathies.[4–7] In addition to drug side effects, several other complications occur in this model due to need for central intravenous lines; requiring restraining jackets and tethers. Herein we have described the complications encountered among 20 transplantations and the remedies that we applied to avoid them in the future.

MATERIALS AND METHODS

Animal

Fifteen healthy baboons weighing from 6 to 15 kg were used as recipients. The same number of piglets weighing from 4 to 10 kg were used as the heart donors. Using an NIH Animal Care and Use Committee (ACUC)-approved protocol, we performed heterotopic heart transplantations, as described in detail elsewhere.[8] Briefly, the pig heart aorta was anastomosed to the baboon abdominal aorta and the pig heart pulmonary artery to the baboon inferior vena cava.

Immunosuppression Regimen

The regimen is described in Table 1.

RESULTS

Complications are described in Table 2. Some animals experienced >1 complication therefore the total *n* in Table 2 is greater than the number of experimental animals ($n = 15$). A wide spectrum of complications were observed during this experiment. Most were recognized early and corrected. Some baboons showing life-threatening complications were euthanized as mandated by NIH ACUC regulations. In a few cases, the complications led to death of the recipient baboon; most deaths were unexpected and could not have been prevented. Despite these complications, rejection was not observed in the transplanted pig hearts.

DISCUSSION

A valuable lesson was learned from our initial experiments where most of the complications, especially ones categorized as nonsurgical, occurred during the initial experiments. Several modifications were made to strengthen and secure the jackets and to rectify the mechanical problems with the tether that carried the intravenous line needed for injections and infusions.

In the initial experiments, owing to unavailability of sufficient donor blood for transfusions, anemia caused by bleeding complications could not be corrected. In later experiments, multiple infusions of packed red blood cells were available to help overcome this potentially lethal complication.

Infections have been reported to be one of the major causes of morbidity and mortality.[3] Fortunately, owing to early detection of infections with the help of telemetry, we aggressively treated them at the earliest sign of a fever spike. Thus, this complication was easily averted in our experiments.

In most experiments, the transplanted graft was functional at the time of euthanasia or baboon death. Proper management of complications significantly prolongs the survival of cardiac xenografts and recipients.

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Table 1

Immunosuppressive Regimen

Drugs	Dose	Timing
Induction		
Anti CD20	19 mg/kg	Preop days −7 and 0
ATG	40–50 mg/kg	Preop days −2 and −1
Anti CD154	25 mg/kg	Preop days −1 and 0
CVF	50–100 U/kg	Preop days −1 and 0
Maintenance		
Anti CD20	19 mg/kg	Postop days 7 and 14
Anti CD154	25 mg/kg	Postop days 3, 7, 10, 14, and 19, q weekly
CVF	50 U/kg	Postop day 1
MMF	20 mg/kg/2 hr IV infusion	BID daily
Steroids	2 mg/kg	BID, tapered off in 7 weeks
Aspirin	81 mg	Daily
Heparin	Maintain ACT 2× baseline	Continuous infusion
Supportive		
Ganciclovir	5 mg/kg/d	Daily
Cefazolin	250 mg	BID for 7 days
Epogen	200 U/kg	Daily from day −7 to 7, then weekly
Ketorolac	15 mg	Just before anti-CD154

Table 2

Complications

	n	Description	Remedy	Graft Dysfunction	Recipient Mortality
Nonsurgical					
Jacket	5	Torn, unzipped, chewed	Jacket modifications	No	No
Tether	5	Swivel mechanism dysfunction, detachment	Modifications	No	No
Catheter	6	Thrombosis, nonfunctional	Increased anticoagulation	Yes	No
Surgical/post surgical					
Bleeding	4	Mostly from implant site in transplanted heart or from rupture of mesenteric vessels	Telemetry implant properly secured	No	Yes
Infection	3	Early detection due to telemetry	Easily controlled with antibiotics	No	No
Adhesions	2	Mostly mesenteric/bowl adhesions to the transplanted heart	None	No	No
Gastric bleeding	1	From the gastric ulcers	Treatment of gastric ulcers and decreased use of aspirin	No	Yes
Anemia	3	Due to unknown cause or bleeding	Packed RBC transfusion	Yes	Yes
Intestinal obstruction	2	Due to adhesion and fecal impaction	Surgical exploration to relieve the obstruction	No	Yes
Aspiration Pneumonia	1	Due to bowl obstruction and vomiting	Related to above complication	No	Yes
Sudden death	4	Bleeding or unknown causes	Partially by securing the LVP telemetry probe	No	Yes
Rupture of intestine	1	Due to adhesions	Did not recur	No	Yes
Coagulopathy	1	Thrombocytopenia, consumption of clotting factors	Heparin hiatus, blood transfusions	No	Yes
Cardiac rupture	1	Improper healing of myocardial infarct	Making sure that the heart is properly perfused	Yes	Yes