In vivo Biocompatibility Assessment of a Pediatric Ventricular Assist Device

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Introduction: One to two thousand children a year could benefit from prolonged mechanical circulatory support. The only current options are extracorporeal membrane oxygenation (ECMO) and cardiac transplantation. ECMO support duration is limited due to high complication rates, especially bleeding and thrombosis. Cardiac transplant waiting times are extended stemming from limited organ availability and the wide size range of harvested organs. To address this need, a pediatric ventricular assist device (VAD) is being developed to provide cardiac support until recovery occurs, or a transplant becomes available. In this study several flow cytometric assay previously applied in bovines and humans were adapted to ovines and applied to assess device biocompatibility.

Methods: The device undergoing testing was based on the adult CentriMag VAD, which has supported over 40 patients in Europe and has begun clinical trials in the US. The pediatric centrifugal pump, constructed from molded polycarbonate, can generate flow rates of 0.3-2.5 liters per min (LPM) utilizing a magnetically suspended rotor. The device was placed extracorporeally in a drive console, which generates the impeller rotation and maintains the impeller position.

Implantation: The prototype pediatric VADs were implanted in 3 juvenile sheep weighing 10 to 30 kg. The device interfaced with the circulation through a 16 Fr MLP cannula (Medtronic, Minneapolis, MN) placed in the jugular vein (1st 2 implants) or a custom 34 Fr PVC cannula placed in the left ventricle, connected to surgical grade Tygon® tubing, and attached to the pump inlet. The pump outflow was connected to the Tygon®, then attached to a 12 Fr MLP cannula (Medtronic, 1st 2 implants) or a custom PVC 24 Fr arterial cannula, and placed in a carotid artery. Heparin was administered to achieve an activated clotting time (ACT) exceeding 400 secs during the implant and 180-200 secs afterwards.

Blood collection: Blood samples for biocompatibility studies were collected pre-operatively (pre-op) and then twice weekly. 20 mL of blood was drawn through an arterial line, then 1.4 mL of blood was collected 1:10 into tubes (Sarstedt, Newton, NC) containing 3.8% trisodium citrate. The 20 mL of blood were then re-infused. The pre-op sample was collected via jugular venipuncture with an 18G 1.5" needle, with the first 5 mL of blood drawn being discarded before sample collection.

Biocompatibility Assays: Flow cytometric assays were performed to measure platelet CD62P expression, using two polyclonal antibodies (Becton Dickinson, LaJolla, CA and Fitzgerald Industries, Concord, MA), and annexin V (BD/Pharmingen, La Jolla, CA) binding. GB20A antibody (VMRD, Pullman, WA) identified ovine platelets. Leukocytes were indicated with anti-ovine CD45 (Serotec, Raleigh, NC). Platelet microaggregates (PMAs), the percent of GB20A+/CD45- events larger than single platelets, and platelet-leukocyte aggregates (PLAs), CD45+/GB20A+ events, were also quantified.

Results / Discussion: The first two studies were electively terminated on post-operative day (POD) 8; the first due to low flows (0.1-0.4 LPM) attributed to cannula position. The second animal displaced the outflow cannula by kicking it, causing excessive bleeding. The third animal successfully completed the 33-day study, although it required 2 transfusions post-operatively for bleeding. Results from 3 flow cytometric assays from the 3rd implant are shown in the **Figure**.

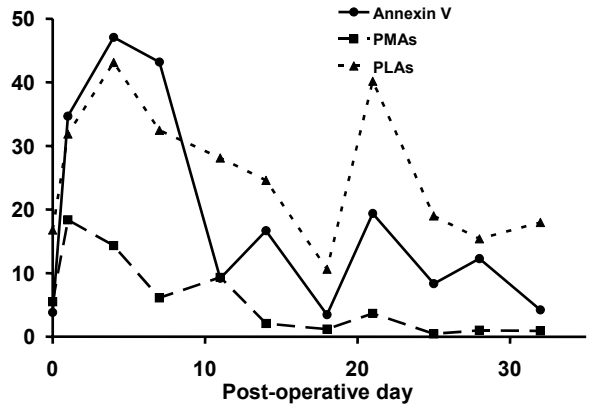

***Figure**. Percent of circulating platelets binding annexin V and PMAs and PLAs, increased after implant, then trended downward to return to pre-op levels on day 32.*

Single platelet CD62P levels were usually less than 2%, although PMAs expressed high levels of CD62P. Ring thrombi were present at tubing connections and the distal tip of the outflow cannula of the first study. A few small thrombi adhered to the impeller of the first device, while the other devices were free of thrombus. No end organ infarcts were found.

Conclusions: Flow cytometric assays to measure ovine biocompatibility demonstrated platelet activation and aggregation occurred following the implant procedure. However, in the longest study, assay levels returned to pre-op levels in spite of the large amount of foreign surface material in contact with the blood These preliminary results are encouraging, suggesting that the Levitronix pediatric pump possesses acceptable biocompatibility as long as the cannulation challenges can be adequately addressed.