Platelet activation in juvenile ovines implanted with the PediaFlow® 4th generation pediatric ventricular assist device

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Statement of purpose: Ventricular assist devices (VADs) have become increasingly common as a bridge to transplant in patients with end stage heart failure. For pediatric patients VADs are less commonly utilized due to the absence of approved devices. While VAD support generally has positive outcomes, morbidity associated with thromboembolism remains of concern, likely related to the artificial surfaces and blood flow patterns associated with these devices.

In this study we evaluated the blood biocompatibility of a miniature-sized (AA cell battery) pediatric VAD under development via NHLBI funding, the PediaFlow® 4th generation device. This VAD has Ti6Al4V blood contacting surfaces with blood flow achieved by a magnetically suspended and controlled rotor spinning at ~ 15,000 RPM. A total of 7 juvenile ovines were implanted with 4th generation PediaFlow VADs to evaluate the temporal course of platelet activation, as one index of blood biocompatibility.

Methods: *Implantation:* The PediaFlow was implanted in 7 ovines (20-30 kg) designated as S#, depending on the study #. Anticoagulation was a combination of heparin and coumadin. At device explant the kidneys and other organs were examined for evidence of infarcts (putatively related to thromboembolism).

Blood collection: Pre-operative blood samples were collected by jugular venipuncture, with the first 3 mL of drawn blood discarded. Post operative samples were collected from an indwelling carotid arterial catheter on post-operative day (POD) 1, 2 and 3 and then twice weekly for study duration.

Platelet Assays: The % circulating activated platelets was measured using two distinct monoclonal antibodies to detect CD62P (1). The ability of circulating platelets to express CD62P in response to exogenous agonist stimulation (10 µM PAF and 20 µM ADP) was also measured to evaluate preserved platelet function.

Results: Circulating platelet CD62P expression **(Figure 1)** was found to be low in all pre-operative samples except for animals S017 and S044, which was attributed to animal stress during blood collection. Animals S017, S026, S018 and S044 showed an increase in platelet activation during the first post-operative week. S033 and S034, which were terminated by POD 3, had lower platelet activation (~5-10 %). S009, the animal which survived for 27 days, had very low platelet activation throughout the study. The higher levels of platelet activation observed in S026 and S018 (40-75% on POD3) are consistent with pathology reports indicating the presence of mild to moderate kidney infarcts.

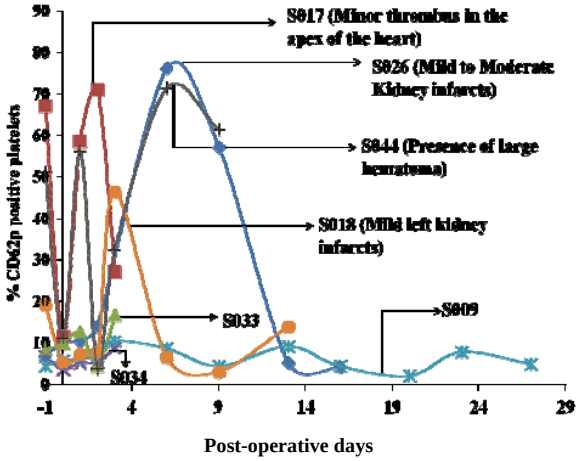

Fig. 1: *A substantial increase from the pre-operative platelet activation values is seen immediately post-operatively, with return over time toward pre-operative values. -1 indicates a pre-operative sample.*

The elevated levels of platelet activation in S017 are likely due to the presence of minor thrombus in the apex of the heart, and S044 presented at autopsy with a hematoma in the left thoracic cavity and infectious pericarditis. Most of the animals (except S033 and S034) demonstrated an increased response to ADP and PAF after POD 5 versus the day of PediaFlow implant. Response to these agonists stabilized after week one (in S018, S009 and S026). The difference between stimulated and unstimulated activation levels was diminished early in the postoperative period compared to later days indicating reduced functionality during the initial post-operative period.

Conclusion: A miniaturized pediatric VAD was characterized in terms of temporal platelet activation in an ovine model and demonstrated promising blood biocompatibility in that platelet activation markers in all animals tended to recover to pre-implant values following surgery, and the platelets were responsive to agonists. Elevated platelet activation was found in ovines where pathology reports indicated hemostatic-related incidents such as kidney infarction, thrombus in the heart and hematoma. Assessing platelet activation appears to have value as a minimally invasive means to temporally evaluate blood biocompatibility in this pediatric blood pump and can provide evidence of biocompatibility prior to the initiation of clinical trials.

Ref: 1. Johnson CA Jr, et al. *Artif Organs. 32:136-45 (2008).*