

## Platelet activation in juvenile ovines implanted with the Levitronix PediVAS ventricular assist device

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**Statement of purpose:** Ventricular assist devices (VADs) have become increasingly common as a means to bridge patients in end stage heart failure until a donor heart becomes available. For pediatric patients VADs are less commonly applied and few devices are available, although several are under development. 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 pediatric VAD under development, the Levitronix PediVAS. A total of 9 juvenile ovines were implanted with the PediVAS for 30-day periods of support to evaluate the temporal course of platelet activation with two different sets of cannulae.

**Methods:** Flow cytometric assays previously characterized for their ability to quantify circulating activated platelets in ovines were utilized (1). The device evaluated was the Levitronix PediVAS centrifugal pump with polycarbonate blood contacting surfaces. This VAD can generate flows between 0.5-1.7 L/min.

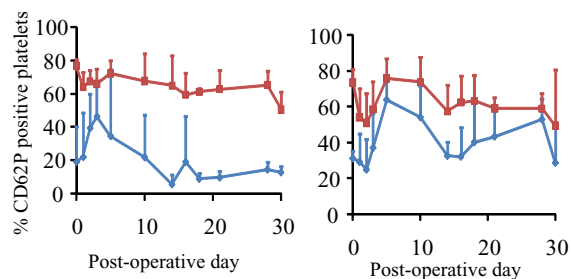
**Implantation:** The PediVAS was implanted as an LVAD in 6 ovines (20-30 kg) using customized Levitronix cannula to connect the pump to the left ventricle and aorta, and 3 ovines using Medtronic Carmeda (heparin) coated cannulae for these connections. Anticoagulation was a combination of heparin and coumadin. At device explant the kidneys and other organs were assessed for evidence of infarcts (putatively related to thromboembolism).

**Blood collection:** Pre-operative blood samples were collected by jugular venipuncture with an 18G 1.5" needle, with the first 3 mL of blood drawn being discarded. Post operative samples were collected from an indwelling carotid arterial catheter. Samples were collected on post-operative days 1, 2 and 3 and then twice weekly for the entire duration of the study. 20 mL of blood was drawn from the arterial catheter, and then 3 mL of blood was collected into 3.8% sodium citrate.

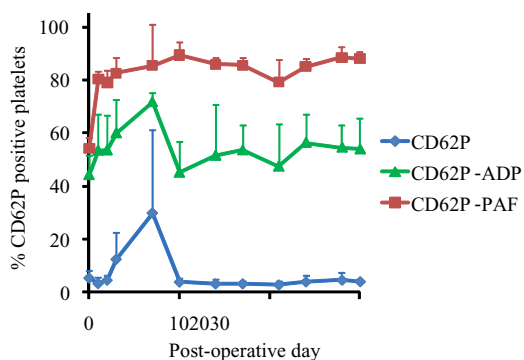
**Platelet Assays:** The % circulating activated platelets was measured using two distinct monoclonal antibodies to detect CD62P expression. The ability of circulating platelets to express CD62P in response to exogenous agonist stimulation (10  $\mu$ M PAF and 20  $\mu$ M ADP) was also measured to evaluate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

**Results:** *Custom Cannula:* In Fig. 1, the temporal platelet activation levels without (blue diamonds) and with PAF stimulation (red squares) is seen for 3 ovines with less than 4 kidney infarcts observed at explantation. Platelet activation returned to basal values by the end of the study. For the other 3 ovines more than 4 kidney

infarcts were observed and the temporal platelet activation was relatively elevated. *Carmeda Coated Cannula:* In Fig. 2 all of the ovines with the Carmeda cannula were found to have minor superficial (< 1% by volume) and fewer kidney infarcts (<3). Circulating platelets also exhibited reduced levels of activation with preserved responsiveness to agonists.



**Fig. 1:** (Left) Three ovines with <4 kidney infarcts at explants exhibit early platelet activation that returns to baseline by study end. (Right) Three ovines with >4 kidney infarcts exhibited a post-operative course characterized by higher levels of platelet activation.  $\blacklozenge$  - Blue diamonds are % CD-62P  $\blacksquare$  - Red Squares are % CD 62P -PAF activated. (Error bars: Standard deviation)



**Fig. 2:** Low levels of platelet activation were observed in three ovines implanted with pumps using heparin-coated cannulae. This was also reflected in a low incidence of kidney infarcts.

**Conclusions:** A pediatric VAD was characterized in terms of temporal platelet activation in an ovine model and demonstrated promising blood biocompatibility, particularly when coupled with heparin-coated cannulae. The results also provided evidence for a relationship between the level of circulating activated platelets over the implant period and the occurrence of kidney infarcts observed at the time of device explantation. This approach appears to have value as a means to evaluate the blood biocompatibility consequences of design decisions prior to the initiation of clinical trials.

**References:** 1. Johnson CA Jr., et al. *Artificial Organs*, 2010.

