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Chronic *In Vivo* Testing of the Penn State Infant Ventricular Assist Device

William J. Weiss[*], **Elizabeth L. Carney**[†], **J. Brian Clark**[‡], **Rebecca Peterson**[*], **Timothy K. Cooper**[†,§], **Thomas P. Nifong**[§], **Christopher A Siedlecki**[*], **Dennis Hicks**[*], **Bradley Doxtater**[*], **Branka Lukic**[*], **Eric Yeager**[*], **John Reibson**[*], **Joshua Cysyk**[*], **Gerson Rosenberg**[*], and **William S. Pierce**[*]

[*]Department of Surgery, Penn State College of Medicine and Penn State Children's Hospital, Hershey, Pennsylvania, USA

[†]Department of Comparative Medicine, Penn State College of Medicine and Penn State Children's Hospital, Hershey, Pennsylvania, USA

[‡]Department of Pediatrics, Penn State College of Medicine and Penn State Children's Hospital, Hershey, Pennsylvania, USA

[§]Department of Pathology, Penn State College of Medicine and Penn State Children's Hospital, Hershey, Pennsylvania, USA

Abstract

The Penn State Infant Ventricular Assist Device is a 12-14 ml stroke volume pneumatically actuated pump, with custom Björk-Shiley monostrut valves, developed under the National Heart, Lung, and Blood Institute (NHLBI) Pediatric Circulatory Support program. In this report we describe the 7 most recent chronic animal studies of the Infant VAD in the juvenile ovine model, with a mean body weight of 23.5 +/- 4.1 kg. The goal of 4-6 weeks survival was achieved in 5 of 7 studies, with support duration ranging from 5 to 41 days; mean 26.1 days. Anticoagulation was accomplished using unfractionated heparin, and study animals were divided into 2 protocol groups: the first based on a target activated partial thromboplastin time of 1.5 to 2 times normal, and a second group using a target thromboelastography R-time of 2 times normal. The second group required significantly less heparin, which was verified by barely detectable heparin activity (anti-Xa). In both groups, there was no evidence of thromboembolism except in one animal with a chronic infection and fever. Device thrombi were minimal, and were further reduced by introduction of the custom valve. These results are consistent with results of adult VAD testing in animals, and are encouraging given the extremely low levels of anticoagulation in the second group.

Keywords

Ventricular assist device; pediatric heart failure; animal testing

Corresponding Author: William J. Weiss, PhD, Howard E. Morgan Professor of Surgery and Bioengineering, Penn State Milton S. Hershey Medical Center, Mail Code H151, Room C4864, Hershey, PA 17033, Tel: 717-531-6228, Fax: 717-531-4464, bweiss@psu.edu.

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Introduction

Mechanical circulatory support devices are now a viable therapeutic option in advanced heart failure in adults. However, this technology has been slow to develop for pediatrics, in part due to the smaller number of pediatric patients requiring support, and in part due to the technical challenges in downsizing adult devices. The only VAD currently available for infants and small children, and capable of support durations of months, is the Berlin Heart EXCOR® (Berlin Heart GmbH, Berlin, Germany). The EXCOR has resulted in survival rates similar to those in adults, and has stimulated awareness of VAD support in pediatrics where prior experience was limited to extracorporeal membrane oxygenation. However, thromboembolic events are reported in 38-63% of pediatric patients in North America[1-3], compared to 18% in adults[4], and the event rate (per patient-month) of stroke and neurologic dysfunction is an order of magnitude higher than in adult VADs.

Penn State, in collaboration with Minnetronix, Inc. (St. Paul, MN) has developed a VAD for use in infants, under the NHLBI Pediatric Circulatory Support Program [5,6]. Our approach has been to scale a proven adult VAD technology to pediatric size, while focusing on device safety by minimizing thrombus formation. This paper describes the most recent series of 7 chronic animal studies performed under that program. The primary objective of these studies was to assess the device performance and biocompatibility, leading to formal pre-clinical studies. A secondary objective was to improve our understanding of thrombogenicity testing in animal models, through multi-component measurements of the coagulation system. An important goal in designing pre-clinical studies for circulatory support devices has been selecting an anticoagulation regimen in the animal model that is consistent with the thrombogenic sensitivity in humans, under expected clinical anticoagulation therapy. Because of species differences in platelet function and coagulation pathways, the direct application of human anticoagulation therapeutic ranges, such as equivalent activated clotting time (ACT) or activated partial thromboplastin time (aPTT) ranges, may or may not result in equivalent levels of device-related thrombus formation and embolization in animals.

Materials and Methods

Device Description

The Penn State Infant VAD (Figure 1) has a stroke volume of 12-14 ml. The design is based on the adult Thoratec® PVAD™ which was developed at Penn State as the Pierce-Donachy VAD [7]. The Infant VAD utilizes 17mm Björk-Shiley monostrut (BSM) Delrin disk valves with mounting flanges that are custom designed to fit this pump, and which are manufactured in house. This valve type is used in adult devices including the Thoratec® PVAD™, Arrow LionHeart™, and Penn State Total Artificial Heart. The large orifice of the tilitng disk inlet valve results in high inflow velocities that produce a sustained rotational flow in the pump and effective washing of the sac surface, without recirculation regions where thrombus can form[8].

The maximum VAD output is 1.6 l/min, which fully supports infants with a body surface area up to 0.5 m^2. The pump may be implanted in children where ambulation and long term support are anticipated, but is expected to be para-corporeal in infants. The device is designed to function for durations in excess of one year, and may be utilized for left (LVAD), right (RVAD), or bi-ventricular (BiVAD) support.

Automatic control of pump beat rate in response to preload pressure is accomplished by operating in a full-to-empty mode and detecting the pump-full condition from the driveline airflow. This automatic preload sensitivity allows maximum flow and ventricular unloading

to be achieved while limiting excessive inlet suction. Inlet suction may cause collapse of the ventricular chamber, leading to thrombus formation, irritation of the myocardium, and arrhythmias. LVAD preload sensitivity also provides safe left atrial pressure control during BiVAD support.

Pre-operative, surgical, and post-operative protocols

All animal studies were approved by the Institutional Animal Care and Use Committee at Penn State College of Medicine. The animals were housed in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, and veterinary care adhered to *The Guide for the Care and Use of Laboratory Animals*[9].

Purpose-bred Dorset-Finn lambs were used in this series with a mean body weight of 23.5 +/- 4.1 kg at surgery. Our implantation and analgesia protocol are described in detail by Carney et al [10]. Briefly, the VAD was implanted in the left preperitoneal space, with the inflow cannula (15 cm length) from the left ventricular apex and the outflow cannula (25-30 cm length) to the descending thoracic aorta. Cannulae for animal testing are 6 mm internal diameter tapering to 3/8 inch internal diameter at the pump. The inlet cannula is segmented polyurethane, and the outlet is segmented polyurethane and ePTFE. Cardiopulmonary bypass was not used for implantation. Epicardial echocardiography was used to visualize the position of the apical cannula in the left ventricle. The pneumatic driveline was tunneled to a paraspinous exit site. A right external jugular catheter was placed at least 2 weeks before surgery to allow platelet function to stabilize, so that the pre-operative measurements reflected normal baseline conditions.

Overall, in this program, a total of 15 chronic animal studies were performed using the Infant VAD as an LVAD, in 11 lambs and 4 goats. In addition, we completed 1 acute study, 3 surgical shams, and 4 hematologic control studies. Survival was limited in the early studies due to atelectasis and respiratory failure, not related to VAD function. The protocol was revised [11] and healthy survival was demonstrated in the final 7 animals, which are described in this paper (Identification (ID) numbers nos. 12-18). The planned duration of the chronic studies was 4-6 weeks, which was achieved in 5 of the 7 studies (range 5 to 41 days; mean 26.1 days).

Activated partial thromboplastin time (aPTT) and antithrombin III (ATIII) levels were measured on a CA1500 coagulation analyzer (Dade Behring, Newark, DE) using functional clot-based assays. Heparin levels were measured on the CA1500 using a chromogenic anti-Xa assay[12]. The anti-Xa assay is considered a more reliable measure of heparin activity than aPTT, especially at low heparin levels. Since we had not previously established the sensitivity of the anti-Xa assay in ovine blood, we first determined calibration factors for anti-Xa and aPTT *in vitro* with ovine plasma using spiked unfractionated heparin (UFH) concentrations ranging from 0.2 to 1.0 U/ml. The resulting correlation between anti-Xa and aPTT was used to determine the aPTT therapeutic range, consistent with current practice [13].

Thomboelastography (TEG) was used to measure the global coagulation kinetics and clot strength [14]. Whole blood (native, non-citrated) was collected in a 3 cc syringe directly fitted to a jugular catheter. After mixing 1 cc of blood with kaolin activator, 360 microliter aliquots of the blood/kaolin mixture were pipetted into 2 cups on the TEG analyzer (Thrombelastograph Haemostasis Analyzer 5000); one cup was free of additives and the other cup contained 2.0 International Units (IU) of lyophilized Heparinase I (an amount sufficient to reverse 6.0 IU of heparin/ml of blood). The time from blood draw to analysis was under 1 minute.

Platelet aggregation was measured using whole-blood impedance platelet lumi-aggregometry (Chrono-log Whole-Blood Lumi-Aggregometer 560-CA with AGGRO/LINK® 5.1, Chrono-log Corp, Haverton, PA, USA). Activation agonists were adenosine diphosphate (ADP) (10μM) and collagen (1 μg/ml), based on previous work by Soloviev et al[15]. Impedance was recorded 6 minutes after the addition of agonist. By manufacturer's protocol, luciferase should be added simultaneously with an agonist at the start of each test. However, whenever the luminescence reagent was added at the same time as our agonists (collagen and ADP) we experienced premature aggregation. Therefore, our protocol was changed to add luciferase to the sample after aggregation was complete.

We evaluated the cross-reactivity of commercially available clinical assays for the detection of D-dimer and fibrin degradation products. None of the methods were able to detect D-dimer or fibrin degradation products in a positive control preparation using ovine or bovine plasma samples.

Anticoagulation

The anticoagulation regimen was based on protocols generally used with pediatric VADs in infants[2,16-18]. Unfractionated heparin is usually started when hemostasis has been established, with a target aPTT of 60-70 secs. The heparin may be transitioned to low molecular weight heparin with anti-Xa monitoring. ATIII is given if levels fall below 70%. In older children, heparin may be transitioned to warfarin, with a target international normalized ratio of 3-3.5. Platelet agents may include aspirin, dipyridamole, and clopidogrel. Platelet therapy may be based on TEG, platelet aggregation, or other platelet function assays.

In our animal studies with the pediatric VAD, we utilized unfractionated heparin without platelet inhibitors. The method of heparin dosing has evolved. In earlier animal studies, we based the heparin infusion on ACT, as commonly used in circulatory support device testing [19], in part due to the low cost and availability of point-of-care ACT devices. However, recommendations for chronic heparin therapy in humans are based on actual heparin activity, most commonly measured via anti-Xa, with a therapeutic range of 0.35 – 0.70 U/ml, or a corresponding aPTT range determined by the individual center [13].

Two different heparin anticoagulation protocols were used in this most recent series of animals. In the “aPTT group” (n=4, IDs 12, 13, 14, 18), heparin was titrated to achieve a target aPTT of 1.5-2 times the normal (pre-op) mean of 27.1 +/- 2.7 secs). This target range of 40-54 secs was found to be equivalent to an anti-Xa level of 0.39 -0.56 U/ml. We subsequently observed in the aPTT group that TEG indicated hypo-coagulability despite a therapeutic aPTT. We therefore initiated a second series (“TEG group”, n=3, IDs 15-17) in which heparin was titrated to achieve a target TEG R-time of 2 times normal, which required significantly lower levels of heparin.

LVAD Operation

The Infant VAD was operated in automatic full-to-empty mode in all cases, using the air flow fill detection system. The automatic mode was set for an end-diastolic delay of 30 msecs, which was found in previous *in vitro* studies to minimize hemolysis related to inlet valve closing[20]. The diastolic drive pressure (vacuum) was adjusted to give a mean VAD flow rate of 0.8 – 1.2 liters/min. A fixed systolic drive pressure of 250 mmHg was used and the systolic duration was adjusted as needed for complete ejection with an end-systolic delay of 10-30 msecs.

Pathology

A complete gross necropsy (except gross examination of the brain) was performed in all animals. Any gross evidence of infarction was noted and collected for histology. The aorta and carotid, pulmonary, renal, and iliac arteries, as well as the jugular veins, were grossly dissected and examined for evidence of thromboembolism. Because of the device routing with the outlet cannula attached to the descending thoracic aorta, combined with their high relative blood flow and endarterial circulation, kidneys were thoroughly sampled for histology in all 7 lambs to look for evidence of thromboembolism/cortical infarction. Additionally, liver and lung were examined for thromboembolism/infarction in all 7 lambs. The following organs were also examined by histology: Spleen (6/7), heart (2/7), gastrointestinal tract (2/7), and brain (1/7), and any evidence of thromboembolism or infarction was noted.

Results

VAD parameters were consistent and are summarized in Table 1. Note that the average diastolic pressure required to fill the VAD was no greater than 6 mmHg vacuum, indicating low hemodynamic resistance of the 6 mm inlet cannulae and the absence of tip occlusion in the left ventricle. These values of diastolic pressure also are the most negative pressures possible at the inlet tip, demonstrating the lack of inlet suction.

There was no evidence of end organ dysfunction. Creatinine, lactate dehydrogenase (LDH), total bilirubin, blood urea nitrogen (BUN), alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT) were within the normal range for surgical sham animals following a 2 week post-surgical period. The plasma free hemoglobin after the 2^{nd} week was 10.6 +/- 6.3 mg/dl, which was not significantly different from the pre-operative level of 10.2 +/- 7.5 mg.dl. Hematocrit was significantly reduced post-operatively (28.0 +/- 3.9 % versus 30.4 +/- 3.0 %, $p < .005$), presumably due to the sample volume required for blood studies. Fibrinogen levels (Figure 2) displayed an acute phase response with peak levels occurring at days 6-7 and returning to normal on day 14. Platelet and white blood cell counts required approximately 4 weeks to return to normal (Figure 2).

Figure 3 summarizes anticoagulation for the 7 most recent studies. The aPTT group required a higher heparin dose throughout the study. Heparin requirements in the TEG group were highest during the first week, but were then reduced to 15-20 units/kg/hr. The aPTT was similar in both groups during the first week; thereafter, in the aPTT group, the aPTT averaged 1.74 times the pre-operative mean (target range was 2 times normal), while in the TEG group, aPTT was not significantly different from pre-op values ($p < .00001$). Heparin activity, as measured by anti-Xa, averaged 0.40 +/- 0.19 U/ml in the aPTT group and 0.011 +/- 0.027 U/ml in the TEG group. Based on the aPTT and anti-Xa measures, the animals in the TEG group showed no evidence of heparin activity after the first post-operative week. ATIII was significantly lower ($p<.001$) in the aPTT group than in the TEG group.

The TEG data is summarized in Figure 4 for the two anticoagulation groups. Differences between the groups were significant ($p < .001$) after day 14 in the R time, K time, Angle, and Coagulation Index (CI), with the TEG group showing significantly less anticoagulation. The CI (a weighted combination of R, K, Angle, and MA) was calculated using the equation for native whole human blood as provided by the manufacturer[21]. In humans, a range of -3 to +3 is considered normal coagulation, and the pre-operative, normal coagulation data for the lambs falls within this range. R, K, Angle, and CI with heparinase (not shown) found no difference between pre- and post-operative coagulation, nor differences between the two anticoagulation groups. Therefore, the anticoagulation effects in Figure 4 are due to heparin, rather than a coagulopathy related to the VAD or other underlying causes. The maximum

amplitude (MA) is a measure of clot strength, affected primarily by platelet function, platelet count, and fibrinogen. MA does not differ significantly between the two groups, nor is it affected by heparinase. MA generally follows the trend of fibrinogen, platelet count, and platelet aggregation.

Platelet aggregation data are shown in Figure 5, which compares the VAD animals to surgical shams (identical surgical procedure, no VAD implanted, and heparin dose equivalent to the aPTT group) and to control animals (no surgery, but heparin dose equivalent to the aPTT group). ADP aggregation post-operatively was higher in the VAD group than in the surgical sham or control group, but did return to the pre-operative normal range for that group at 3-4 weeks. Collagen aggregation showed a similar, but noisier, trend. Collagen aggregation was suppressed in the sham and control animals after heparin was started on day zero. Adenosine triphosphate release was measured for both agonists, but results were variable and there were no clear trends or significant differences among groups.

Complications

The most serious complications in this series were related to infection: cecal abscess and weight loss (ID 12), bronchopneumonia of undetermined etiology (ID 14), *Mycoplasma ovipneuminae* bronchopneumonia (ID 15), and *Staphylococcus aureus* infection via the thoracotomy site presumably due to inadequate pre-operative skin preparation (ID 17). As a prophylaxis for *Mycoplasma ovipneumoniae* infection, 3 animals received an antibiotic regimen of florfenicol intramuscular during the quarantine (one week) and/or pre-operative period (two weeks).

Device problems were encountered in 3 studies (IDs 12,14,15). Air leaks occurred at the purge seal (ID 12) and at the diaphragm seal (ID 14). There were 2 blood sac failures (ID 14, 15). The blood sac design was later changed from a symmetric design to an asymmetric design to reduce stresses in the polymer sac during flexing. The new design has demonstrated no evidence of wear during 3 month *in vitro* durability studies.

Necropsy and Explant Analysis

There have been no strokes or evidence of end organ dysfunction in either the aPTT or TEG groups. There were no significant differences between the groups in renal infarcts or attached thrombi, though the number of animals is small. The kidneys were grossly normal in 4 of 7 cases (IDs 14,15,17,18). In 2 cases (IDs 13,16) there were cortical depressions and fibrosis consistent with old infarcts. The only case of a significant, recent renal infarct was found in ID 12, in which there was persistent infection (cecal abscess), weight loss, and elevated platelet aggregation. Therefore, in the absence of significant infection, chronic embolization does not appear to be occurring with this device.

Typical cannulation sites are shown in Figure 6. Macroscopic adherent thrombi were found in the outlet graft, anastomosis, or inlet cannulae in one case (ID 17): – *S. aureus* operative contamination, with significant thrombi found on nearly all device surfaces. Minor kinks in the outlet cannulae were noted in 2 cases (IDs 13, 14) 2-3 cm from the pump connector. The outlet cannulae–to-graft junction was clean except for a small fibrin deposit in ID 13 and microscopic nodules in ID 16. The LV apical inlet cannulae were free of obstruction except for partial tip occlusion in IDs 14 and 16.

IDs 12-17 utilized a standard BSM clinical valve with a polyurethane washer mount. A thin fibrin ring was frequently found at the valve-washer and valve-connector junction. The most recent animal (ID 18) used the new tube valve (Figure 7). The fibrin ring was eliminated with the new design, although there was a thrombus at the valve-sac junction associated with a sac surface defect and gap between the valve and sac surface. In 3 cases, a thin red

translucent deposit was found at the junction of the inlet cannula and pump connector. There was no evidence of wear or cavitation damage on the valve disks or flanges.

The blood sac surfaces have been free of macroscopic thrombi except for an occasional isolated strand of white fibrin, and macroscopic deposits in the flex zone in 3 cases (IDs 14, 16, 18) usually leading into the outlet port region (Figure 7).

Discussion

A significant challenge in the development of pediatric circulatory support devices has been minimizing thromboembolic risk. At the lower Reynolds numbers found in pediatric devices, relative to adult VADs, viscous boundary layers result in lower wall shear rates and less turbulent mixing, leading to an increased propensity for platelet adhesion and thrombus formation. Our previous experience with the predecessor to our current pulsatile pediatric VAD showed significant thrombus formation in animals. The Berlin Heart EXCOR has also been prone to thrombus formation. In these cases, the valve designs (ball valve and polymer trileaflet, respectively) have been of primary concern. Therefore, we now utilize the BSM tilting disk valve, based on extensive measurements of flow velocities[8] and previous success with this valve in adult blood pumps.

Although the pneumatic VAD is not a new technology, there have been significant refinements to the design, manufacturing, and testing that distinguish this VAD from previous generation pulsatile VADs. Three-dimensional solid modeling and computer numerical controlled machining have been used to produce a device with blended contours to enhance smooth blood flow with minimal stasis, and close tolerances in the critical mating parts. We have also undertaken comparative studies of segmented polyurethanes and the effect of fabrication process variables on the quality of the blood contacting surfaces. The surface finish specification on the pump blood contacting surfaces is Rq (root mean squared surface roughness) less than 25 nm (1 μ-inch); which is monitored using optical profilometry. Taken together, these incremental improvements are critical for minimizing clot formation.

The animal results have confirmed that thrombogenicity is now on the order of that seen during pre-clinical testing of successful adult VADs. This is especially encouraging given the low levels of anticoagulation, especially in the TEG group, and in spite of the complications of infection and device malfunction. In the entire group of 15 chronic studies, there was clinical evidence of device thromboembolism in only one case (stroke in ID 11) in which an intraventricular thrombus was found at necropsy due to improper placement of the cannula.

The monitoring of the coagulation system in these studies has been useful for understanding variability and temporal changes in the animals. For example, in animal ID 12 with a persistent fever and cecal abscess, platelet aggregation and TEG maximum amplitude were elevated. Since thromboembolism was not evident in that animal (and the animal was not treated with platelet inhibitors), the platelet function data supported the conclusion that the VAD and cannulae are fairly resistant to platelet adhesion. We have also noted that animals exhibit significant platelet activation when moved to the animal facility, and we therefore now use a 2 week pre-operative period for acclimation and normalization of platelet function.

The ability to perform measurements at frequent, regular intervals has provided data regarding temporal changes. We have noted a consistent acute phase response, evident in the fibrinogen levels peaking at 6 days post-operatively. Platelet count and white blood cell count peak slightly later, during the second post-operative week, and show a slower return to

normal. This data supports the need for frequent monitoring and more aggressive anticoagulation in patients during the 1-2 week post-operative period. The elevated platelet count and fibrinogen correlate with the increased clot strength as measured by TEG MA.

In the first post-operative week, the heparin dose and aPTT were similar whether using the TEG or aPTT target ranges. Thereafter, the TEG protocol (2 times normal R time) called for a significantly lower heparin dose. The aPTT protocol (1.5-2 times normal aPTT) led to increasing heparin dose, higher heparin activity, and lower antithrombin III levels. The TEG and aPTT groups diverged markedly after day 14, with the aPTT group showing increasing hypocoagulability in the TEG parameters, while the aPTT was conversely decreasing. The reason for the discrepancy between aPTT and TEG measures may be due to other coagulation factors and/or platelet interactions, which are detected by TEG but not aPTT.

Platelet aggregation was not significantly different in the aPTT and TEG groups (which differed only in the heparin levels). The 10 μM ADP agonist gave the most repeatable results, showing maximum aggregation at day 6 and return to normal in the third post-operative week, for VAD and sham animals, but showing no change for control animals. Aggregation with 1 μg/ml collagen agonist was more variable. It is possible that a higher collagen concentration (4-5 μg/ml) may be required [22]. In some clinical protocols, platelet inhibitors would be added in response to the increased platelet activity. In these studies, the post-operative rise in platelet aggregation was monitored but not treated, and this period of time is most likely a thrombogenic challenge to the device.

Interestingly, collagen-induced aggregation was suppressed, coinciding with the start of heparin, in the control and sham animals, but not the VAD animals. Heparin has been shown to suppress collagen-induced platelet aggregation in humans[23]. This platelet inhibition may be offset by device-related activation in the VAD animals, resulting in no apparent change in post-operative collagen–induced aggregation in that group.

The use of platelet inhibitors, with or without anticoagulants, during pre-clinical animal testing of circulatory support devices using ovines, varies among groups. On one hand, normal ovine platelet counts are higher than in humans (475K/μl +/- 191 vs. 261K/μl +/- 48, respectively) [24]. However, in a study of platelet interactions with cardiovascular biomaterials[25], sheep platelets were found to attach and spread to a lesser extent than human platelets. We undertook these studies with the option of using clopidogrel if needed[26] but did not find it necessary, even at the lowest heparin doses. Flow cytometric measurements of platelet activity by P-selectin immunolabeling were performed in one animal in this series, and may be an important addition in the future.

Additional studies are needed to evaluate the correlation between animals and humans in terms of their coagulation response to VADs (biomaterials and shear exposure), as well as their response to anticoagulants and platelet inhibitors. Our results suggest that heparin dosing in ovines based solely on aPTT may be excessive, and may fail to detect a hypocoagulable state after the first 2-3 weeks post-operatively. Excessive use of inhibitors of coagulation and platelet function in animals would under-predict thromboembolism in humans. Similarly, the ACT is not recommended for monitoring low level heparin therapy. We had previously explored using ACT by developing a correlation between ACT and aPTT [26,27] in lambs, but later found the correlation to be inconsistent at low levels of heparin.

TEG provided a sensitive measure of global coagulation, which guided our assessment of appropriate therapeutic ranges for anticoagulation in the lamb. A similar approach may be useful in other species. However, TEG does require careful control of blood sampling, handling, and time-to-measurement. TEG-based protocols for heparin management in

circulatory support patients are used with success in some centers[28]. Improved coagulation monitoring should result in less variability in animal study results, provide data for assessing the effect of complications such as infection and device malfunction on study outcomes, and provide guidance for clinical anticoagulation strategies.

Conclusion

Chronic animal testing of the Penn State Infant VAD was performed in the juvenile ovine model. Heparin anticoagulation protocols were based on either aPTT or TEG targets, with the TEG protocol resulting in negligible levels of heparin activity. Thromboembolism and device thrombi were minimal, even in the presence of infection or device malfunction.

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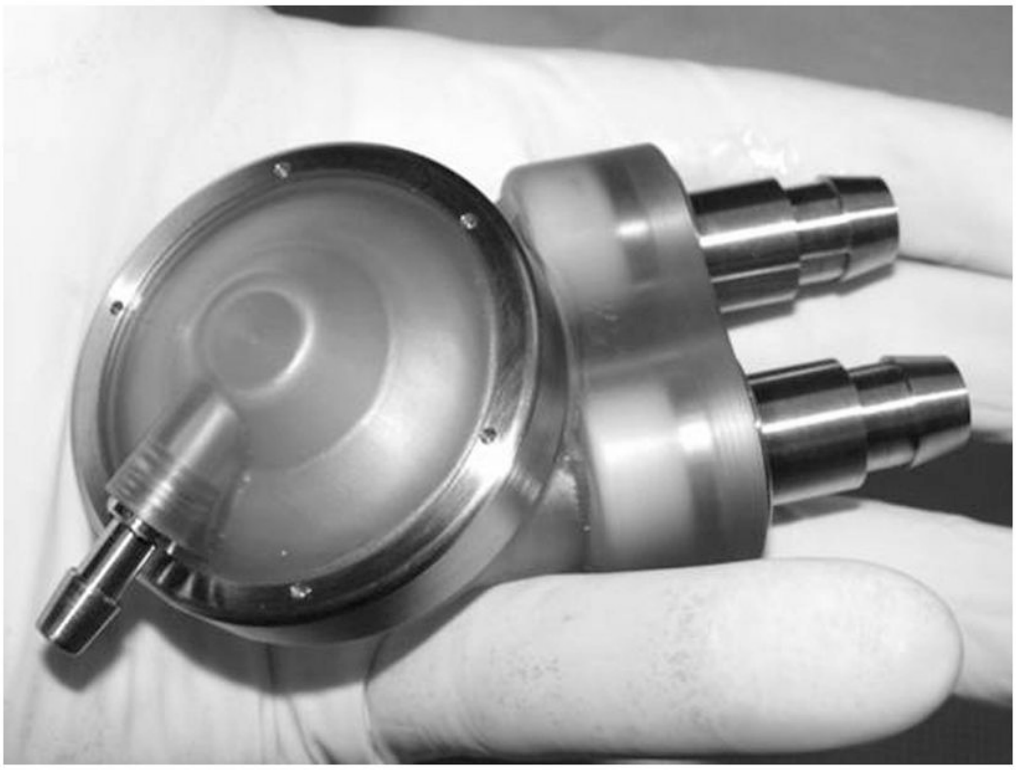

Figure 1.
The Penn State Infant VAD has a stroke volume of 12-14 ml and utilizes a custom Bjork-Shiley Monostrut valve.

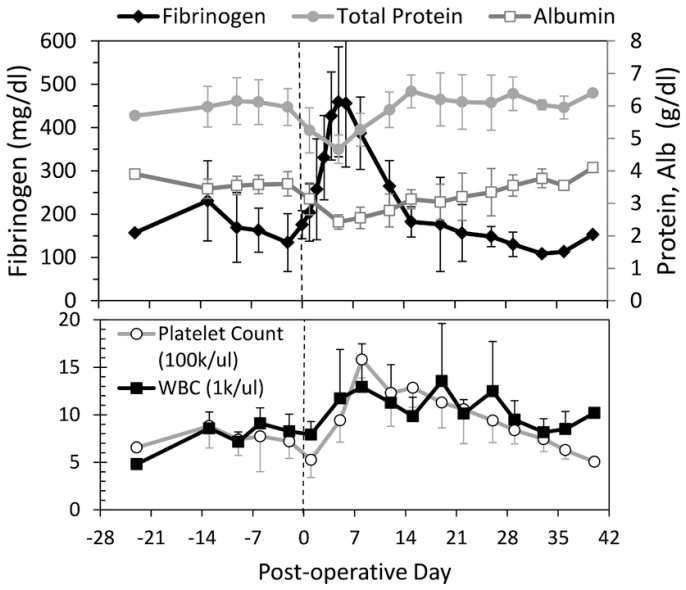

Figure 2.

Fibrinogen, total protein, and albumin (upper) demonstrating an acute phase response. Platelet and white blood cell count (lower) exhibited a more gradual return to normal.

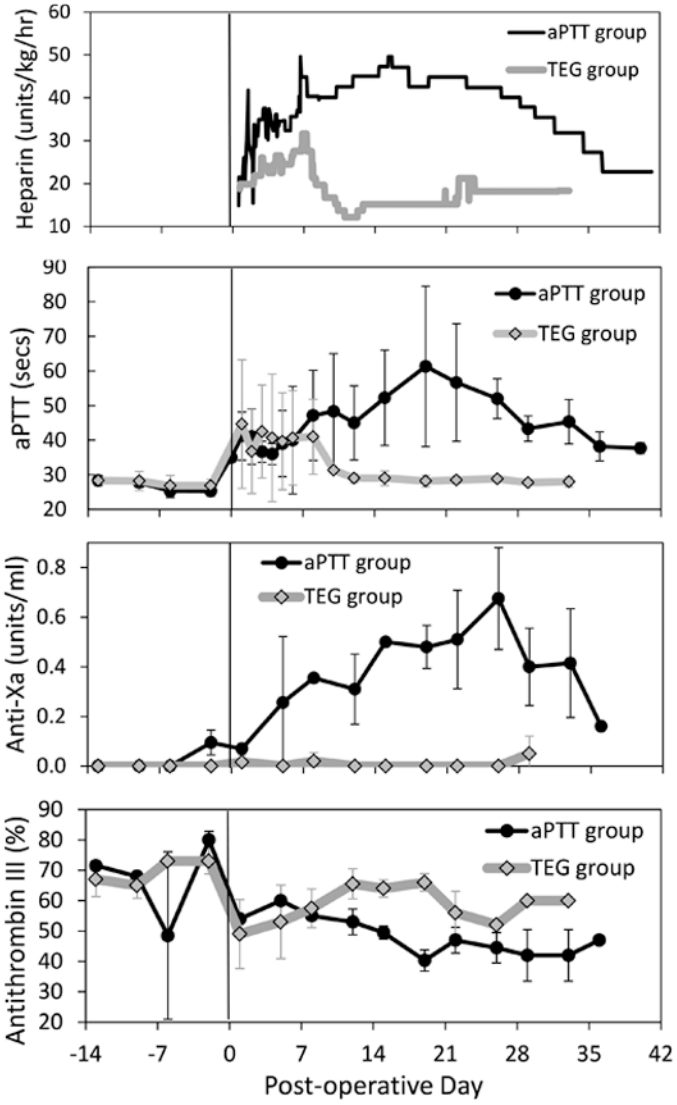

Figure 3.
Anticoagulation data for the aPTT group and TEG group.

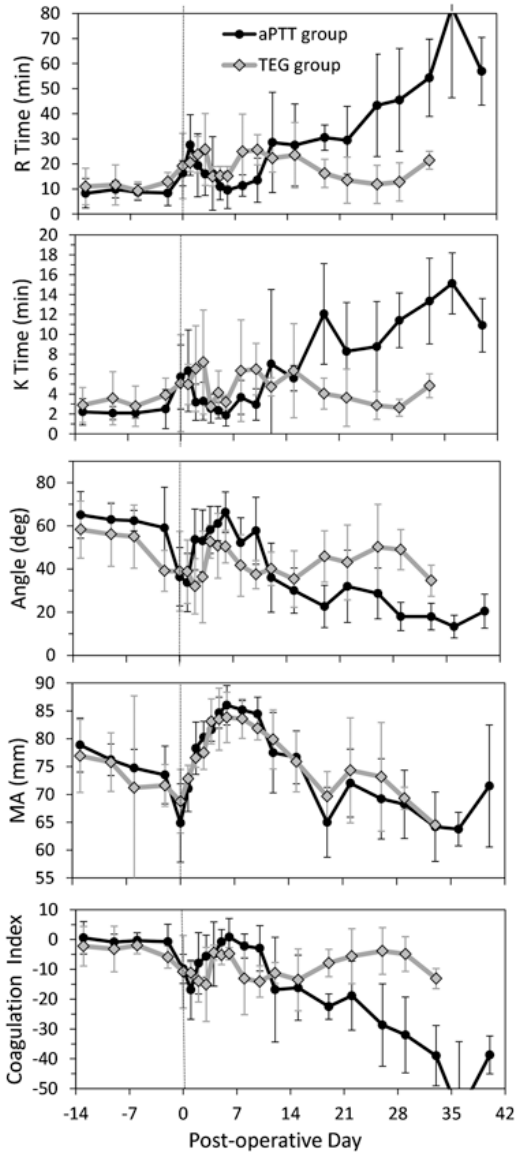

Figure 4.
TEG data for the aPTT group and TEG group.

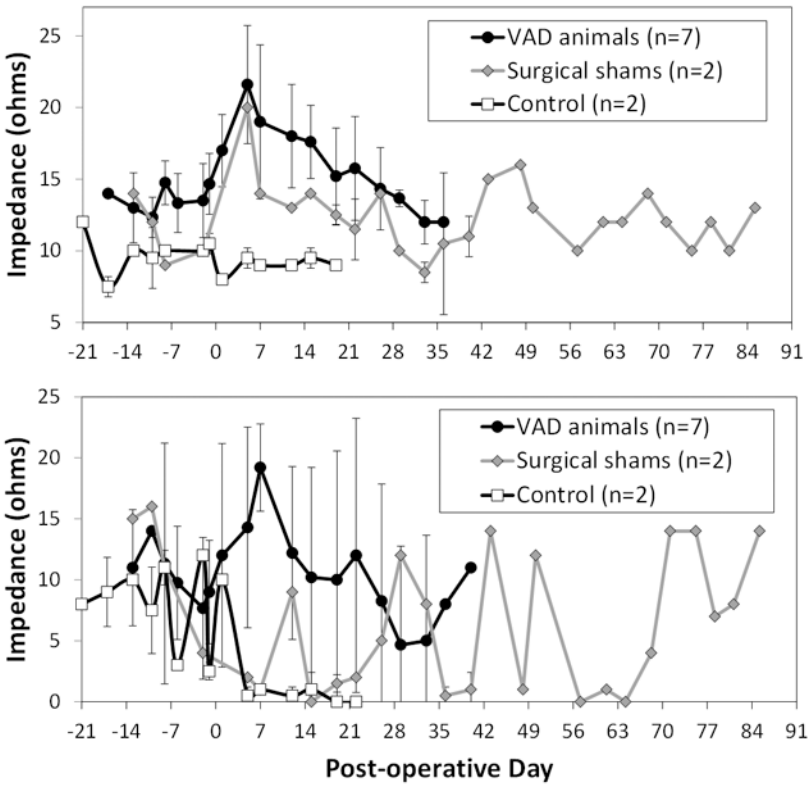

Figure 5.

Platelet aggregation with agonists of 10 μM ADP (upper graph) and 1 μg/ml collagen (lower graph). The TEG and aPTT groups were not statistically different and are shown combined (VAD animals). The post-operative values for ADP and collagen aggregation were statistically different from both shams and controls ($p < .05$).

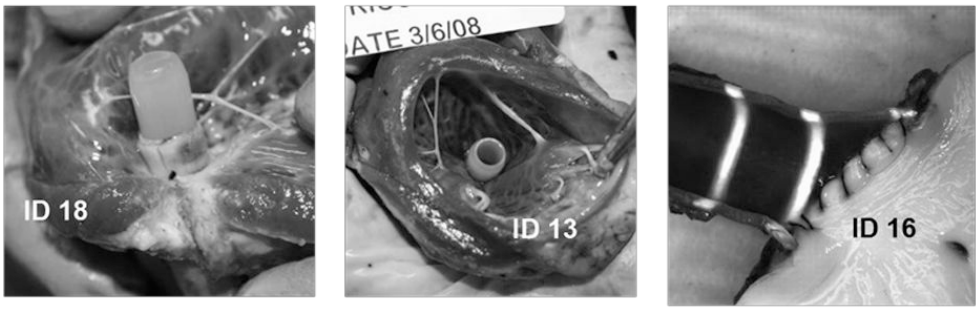

Figure 6.
(a) Inlet cannula tip from ID 18 (35 days), showing the textured cuff and the lack of organized thrombus; (b) Inlet cannula tip from ID 13 (41 days), with the cannula tip centrally aligned in the ventricle and no endocardial lesions due to abrasion from the cannula tip (c) Outlet graft anastomosis from ID 16 (33 days).

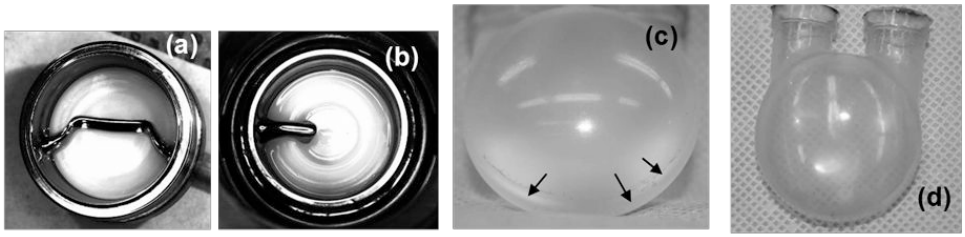

Figure 7.
(a). Outlet valve-sac junction from ID 18 (35 days) with the custom BSM valve, (b) Outlet valve-connector junction from ID 18. (c) Blood sac from ID 18 (35 days) showing only minor deposits in the flex zone. (d) Blood sac from ID 11 (41 days) showing no macroscopic deposits.

Table 1

In vivo VAD parameters. Systolic drive pressure was 250 mmHg. Estimated flowrate at 80 bpm is 1.1 liters/min.

ID	Diastolic Pressure (mmHg)	Systolic Duration (msec)	VAD Rate (bpm)
12	-6 ± 7	317 ± 9	75 ± 7
13	-2 ± 8	293 ± 8	82 ± 8
14	-6 ± 5	306 ± 15	57 ± 5
15	0 ± 10	300 ± 18	76 ± 10
16	-4 ± 0	315 ± 14	72 ± 7
17	-2 ± 1	336 ± 30	76 ± 8
18	-5 ± 0	281 ± 10	84 ± 7