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Preclinical Performance of a Pediatric Mechanical Circulatory Support Device: The PediaFlow® Ventricular Assist Device

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Abstract

Objectives: The PediaFlow® is a miniature, implantable, rotodynamic, fully magnetically levitated, continuous-flow pediatric ventricular assist device (VAD). The 4th generation PediaFlow® (PF4) was evaluated *in vitro* and *in vivo* to characterize performance and biocompatibility.

Methods: Supported by two NHLBI contract initiatives to address the limited options available for pediatric patients with congenital and/or acquired cardiac disease, the PediaFlow® was developed with the intent to provide chronic cardiac support for infants as small as 3 kg. The University of Pittsburgh-led Consortium evaluated PF4 prototypes both *in vitro* and within a preclinical ovine model (n=11). The latter experiments led to multiple redesigns of the inflow cannula and outflow graft resulting in the implantable-design represented in the most recent implants (n=2).

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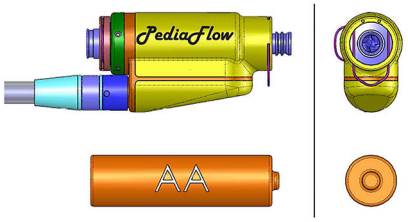
Conflict of Interest Statement

The University of Pittsburgh, Carnegie Mellon University, and LaunchPoint Technologies, LLC are co-inventors of the PediaFlow® technology. The PediaFlow® IP is licensed to HeartWare, Inc., Framingham, MA. The authors have nothing to disclose with regard to commercial support for the work presented herein.

Results: With over a decade of extensive computational and experimental efforts spanning four device iterations, the AA battery-sized PF4 has an operating range of 0.5–1.5 L/min with minimal hemolysis *in vitro* and excellent hemocompatibility (e.g.: minimal hemolysis and platelet activation) *in vivo*. The pump and finalized accompanying implantable components demonstrated pre-clinical hemodynamics suitable for the intended pediatric application for up to 60 days.

Conclusions: Designated a Humanitarian Use Device (HUD) for "mechanical circulatory support in neonates, infants, and toddlers weighing up to 20 kg as a bridge to transplant, a bridge to other therapeutic intervention such as surgery, or as a bridge to recovery" by the FDA, these initial results document the biocompatibility and potential of the PediaFlow® PF4 design to provide chronic pediatric cardiac support.

Graphical Abstract



Central Image: The PediaFlow® pediatric ventricular assist device of this article.

Introduction

Heart Failure in Adults

Heart disease is the leading cause of mortality in adults internationally and domestically, responsible for 1 in every 7 deaths within the United States.[1]. With circulatory assist device development spanning more than five decades for adults, multiple paradigm shifts from pulsatile total artificial hearts, to pulsatile (1st generation) ventricular assist devices (VADs), to continuous-flow (CF) rotary blood pumps (RBPs) have revolutionized the field of mechanical circulatory support (MCS) in adults. Utilizing centrifugal- or axial-flow designs with a single moving impeller, RBPs eliminate the flexible blood membranes, check valves, long cannulas, and tortuous blood paths required in prior pulsatile pumps. This increased simplicity allows for smaller blood-contacting surface area and reduced dead space, thereby reducing thrombosis potential and infection risks, in addition to decreasing the overall device size [2]. Similarly, controller size has been markedly reduced by the elimination of large percutaneous drivelines, compressors, vacuum pumps, solenoids, and large power supplies associated with positive-displacement VADs [3]. Supported by either blood bearings/seals (2nd generation) or suspended by hydrodynamic or electromagnetic forces (3rd generation), RBPs are now the standard for chronic MCS support clinically [3, 4]. With multiple adult CF VADs approved by the Food and Drug Administration (FDA) for bridge-to-transplant or destination therapy applications, these technologies have rescued thousands of adults with refractory end-stage heart failure with additional devices under development or in clinical trials [5].

Pediatric Heart Failure

Within the United States, 25% of all neonates born with a congenital heart defect will require invasive treatment within the first 12 months of life [6]. Nearly 1,800 infants die from congenital heart disease each year while an additional 350 develop cardiomyopathy [7, 8]. Children under 15 kg listed for cardiac transplantation have the highest waiting list mortality rate (17%) in all solid-organ transplantation categories[9]. Cardiac transplantation remains the standard of care for refractory heart failure, but with limited donor availability, only 56% of infants listed received an organ over the last decade [10]. While MCS has successfully decreased waiting list mortality and has been used as a bridge-to-recovery, availability of MCS devices for children remains limited[11, 12].

MCS for Pediatrics

Extracorporeal membrane oxygenation (ECMO) is used extensively for providing temporary cardiac support to children from neonates to adolescents. Although resource intensive, it is cost effective, institutionally available, and rapidly initiated [13]. However, ECMO is indicated only for short durations requiring immobilization, sedation, and has a high complication rate related to bleeding and thromboembolism proportional to support length [14]. For adolescents with sufficient Body Surface Area (BSA), the use of adult-indicated durable CF-VADs is supported by the PediMACs registry with a six month survival rate approaching 90% (n=126) since inception in 2012 [15]. The majority of CF-VADs were implanted in patients 6 years of age or older due to device size, though there is a growing off-label usage of the smaller HeartWare® HVAD typically implanted with an outflow graft constriction or operated at lower speeds (RPM) to maintain pediatric-appropriate flow rates [15–17] in younger patients. Unlike adults however, currently the only FDA approved pediatric-specific bridge-to-transplant MCS device is the Berlin Heart® EXCOR®, a paracorporeal, pneumatically-driven, pulsatile VAD that provides extended support for the pediatric population through the use of varying volume sized pumps coupled to a large pneumatic driver. The potential of the EXCOR® as a life-saving technology for children with heart failure is reflected in our center's experience since 2004 [18]. However the EXCOR® has a substantial risk profile with approximately 80% of patients experiencing at least one significant adverse event, the majority (~50%) from severe bleeding or infection, and is associated with frequent pump exchanges due to device thrombosis around the valve leaflets [19].

Methods

Government Initiatives

While there continues to be a need for next-generation pediatric MCS technology, the small market potential has limited commercial interest. Driven by the lack of progress for this underserved population, the National Heart, Lung, and Blood Institute's (NHLBI) Pediatric Circulatory Support Program (PCSP) awarded over $22 million in 2004 to five separate consortia towards the development of novel pediatric MCS devices [11]. In 2010 NHLBI launched the Pumps for Kids, Infants, and Neonates (PumpKIN) – Pre-Clinical Program and awarded contracts ($24 million) to support four pre-clinical efforts (three for pediatric devices funded under PCSP) to gain Investigational Device Exemption (IDE) from the FDA

[20]. The PediaFlow® Consortium, consisting of the University of Pittsburgh (UoP), Children's Hospital of Pittsburgh, Carnegie Mellon University and LaunchPoint Technologies™ (Goleta, CA), received an award in both NHLBI Programs.

PediaFlow® Development

As a participant in both NHLBI programs, we designed an implantable, mixed flow, fully magnetically levitated (maglev), rotodynamic VAD to support the smallest (BSA <0.5 m^2 with a cardiac index >3.0 L/min/m^2), and consequently most vulnerable, patients, for durations consistent with bridge-to-transplant wait list times, with the objective of minimizing MCS-associated serious adverse events [9, 21]. From the first prototype (PF1) demonstrating the feasibility and biocompatibility of a *de novo*, miniature maglev pump, the developmental evolution and miniaturization of the PediaFlow® pediatric VAD summarized in Figure 1 involved implementation of turbomachinery principles outside of the usual operational ranges [22,23]. Designed to operate at supercritical speeds (RPMs above resonance frequencies), the 3rd generation PediaFlow® (PF3) demonstrated excellent biocompatibility *in vivo* but maglev suspension instabilities limited flow rates to under 1.0 L/min, necessitating further optimization and development [23].

Intended to provide up to six months of circulatory support for patients between 3 to 15 kg at flow rates of 0.3–1.5 L/min, the 4th generation PediaFlow® pediatric VAD (PF4) is the result of over 10 years of biomedical, mechanical, electrical, and computational engineering. Representing the latest pump topology designed to achieve the target flow rates, the PF4's optimized blood-flow path consists of a tapered cylindrical impeller with four blades on the conical inlet face, leading to a single 1.5 mm annular fluid gap region, before passing through a three vane flow straightener machined into the aft-housing upon exit [24]. Integrated 'quick-connect' coupling mechanisms, recessed within the housing, enable direct attachment to the pump inlet and outlet (Figure 1-inset). Approximately the size of AA battery, a decrease in size of almost 75% from the initial PF1 prototype (Figure 2-A), anatomical fit simulations suggest that the PF4 can be fully implanted in infants as small as 5 kg through placement behind the left rectus abdominus muscle with a single percutaneous driveline for electrical power.

In Vitro Assessment

Benchtop evaluation of the PF4 was performed to confirm hemodynamic performance and characterize hemolysis potential. Physiologic flow rate and pressure measurements were simulated in a closed flow loop using a 2.39 centipoise (cP) blood analog glycerol-solution to generate characteristic pump 'H-Q' curves following previously published methods [22]. Using accepted standards, *in vitro* hemolysis testing was performed on several PF4 prototypes prior to *in vivo* implantation using purchased, citrated ovine whole blood (Lampire Inc., Ottsville, PA) with a minimum total plasma protein concentration of 6.0 g/dL within three days of venipuncture[25–28]. The clinically utilized, centrifugal PediMag® (Thoratec®, Pleasanton, CA) pump served as a control for comparison. The Normalized Index of Hemolysis (NIH) was calculated for each pediatric hemodynamic test condition as follows [26]:

$$NIH(g/100L) = \frac{\Delta\ Hb \bullet V \bullet (100 - Ht)/100}{[Q \bullet T]/100}$$

where ΔHb is the measured change in plasma free hemoglobin (g/L), V is the total circuit volume (L), Ht is the blood hematocrit (%), Q is the flow rate (L/min), and T is the test duration (min).

In Vivo Evaluation

Under UoP Institutional Animal Care and Use Committee approved protocols at the McGowan Institute's Center for Preclinical Studies, six PF4 prototypes were implanted in lambs (n=11, 19.0–30.3 kg) without cardiopulmonary bypass to evaluate the chronic *in vivo* hemodynamic performance and biocompatibility of the PediaFlow® and develop the implantable components. Anesthesia, surgical approach, insertion, and post-operative management for the PF4 implants were similar to the 72-day PF3 implant described previously [22, 23]. Three sham studies, in which the aforementioned implant procedure was followed without actual device placement, were performed to serve as complementary 'surgical controls'. Blood samples were drawn at regular intervals during the course of the studies for hematology and biocompatibility assessments, including plasma-free hemoglobin, fibrinogen concentration, and platelet activation and functionality assays, followed by a complete necropsy and pump component examination [22, 29]. Additional/ Further information including an overview of the PF4 pump prototypes, surgical methods for the PF3/sham studies, and a summary of the PF4 animal implants describing the concurrent development of the inflow cannula and outflow graft can be found in the Supplemental Appendix.

PF4 Implantable Design

Detailed here are the most recent PF4 implants (n=2) using he *de novo* designed 5 mm reinforced inflow cannula featuring a parabolic-shaped inlet entrance and detachable sewing ring to unload the left ventricle (Figure 2-B) and a 6 mm Gelweave® (Vascutek® Ltd, Renfrewshire, Scotland, UK) outflow graft with graduated strain relief to return blood to the aorta (Figure 2-C)[30].

Surgical procedure with these implantable components varied only by first attaching the detachable sewing ring to the left ventricle (LV) apex using pledgeted sutures after gaining access. Following full anticoagulation with heparin, the outflow graft was anastomosed to the descending thoracic aorta and back-flushed before mating the graft connector to the pump outlet. The parabolic inflow cannula was inserted through the sewing ring after a cruciate incision without myocardium removal and a wet connection made to the pump inlet by the simultaneous removal of the inflow obturator and partial unclamping of the outflow graft. A perivascular ultrasonic probe (Transonic Systems®, Ithaca, NY) was placed on the outflow graft to measure pump flow rate. Pump support was initiated and cannula depth optimized before thoracotomy closure. Rotational speed was adjusted as needed for a target flow rate of 1.5 L/min.

Results

Hemodynamic Performance In Vitro

The characteristic performance curves of the PF4 highlighted an expanded operating range between 0.3 to 2.0 L/min at physiologically relevant pressure ranges, a marked improvement to PF3 (Figure 3-A). Hemolysis (NIH) varied somewhat among PF4 prototypes but was very low at the three pediatric flow rates tested and comparable to the PediMag® control (Figure 3-B).

Implantation & Operation

The last two implants with the PF4 prototypes and implantable components were unremarkable for a study duration of 14- and 60-days. Pump support was initiated within an hour after first incision, achieving flow rates up to 2.0 L/min before reducing motor speed (RPM) to maintain a target flow rate of 1.5 L/min following chest closure (Figure 4-A). Due to the difficulty of titrating anticoagulation for an activated clotting time (ACT) target of 180–200 s during the previous PF3 study, a continuous infusion of heparin was maintained at 20 UI/kg/hr beginning on post-operative day (POD) 2 and 7 for PF4-S10 (60-day implant) and PF4-S11 (14-day implant), respectively (Figure 4-D).

In Vivo Biocompatibility

During the PediaFlow® implants, hemodynamic performance was within the pediatric physiological range, while serum chemistry, hematology and cellular biocompatibility parameters closely followed the trends observed in the three surgical control sham studies. Plasma-free hemoglobin remained within pre-operative levels and fibrinogen concentration values for the implants and surgical control animals returned to baseline by POD 14 (Figure 5-B, C). Platelet activation, measured by flow cytometry as percent of CD62p+ platelets, had a marked post-surgical response before returning to pre-operative baseline values by POD 10. Throughout the studies, platelets remained responsive to stimulation with platelet activating factor (Figure 4-E).

Necropsy

Examination of the heart, lungs, liver, and spleen for both the PF3 and latest PF4 implants was unremarkable. The inflow cannulae were well healed within the LV apex with no myocardial injury evident, and the blood contacting surfaces of the pump, cannulae and outflow grafts free of adherent thrombus (Figures 5–7). A well-healed, minor cortical infarction on the left kidney of the 72-day PF3 implanted animal was found, most likely from initial surgery (Figure 5-C). No surface lesions or infarcts were found on the kidneys of the two PF4 implants (Figures 6-D,E & 7-G).

Discussion

Implantable pediatric VADs have the potential to expand the number of children in heart failure rescued by MCS [31]. The use of RBPs for the treatment of pediatric heart failure is appealing by reducing the immobilization and in-patient restrictions that are currently associated with the EXCOR®. While the successful miniaturization of CF VADs will impact

pediatric MCS options, the small market size and regulatory process create a significant entry barrier for this technology in the United States. Supported by the bench and pre-clinical findings reported here, the PediaFlow® has the potential to serve as a bridge-to-transplant or bridge-to-recovery device.

Consistent with the program goals for the two NHLBI contracts under which this work was conducted, the primary considerations for the design and development of the PediaFlow® were miniaturization and reduction of serious adverse events by maximizing cellular biocompatibility, as judged on the bench and *in situ* [23, 32, 33]. *In silico* optimization of the rotodynamics, magnetodynamics, heat transfer, and fluid dynamics yielded four successively smaller prototypes that were built and tested both *in vitro* and *in vivo*. Figure 1 displays the marked reduction in profile of the PediaFlow® design in successive generations of prototypes (PF1 – PF4), with the PF4 prototype approximating the size of an AA cell battery (Figure 2-A). By increasing the voice (levitation) coil to motor stator size-ratio to enhance rotor stability and optimizing the pump blading from PF3, flow rates were improved enabling PF4 to reach the target design goals. With an NIH of < 0.02 g/100L for the final PF4 prototypes, the PediaFlow® PF4 device is nonhemolytic (e.g., the NIH for the PF4 approximates that of the maglev PediMag®) and less than published literature values for both adult and pediatric devices [26, 34, 35]. We attribute the absence of hemolysis to the fully magnetically levitated rotor design, the optimized single blood flow path, and relatively large annular gap (1.5 mm), which eliminates the need for bearings or seals, thereby reducing hemolytic potential. As each PF4 pump was hand-built, the variation in NIH among prototypes is likely due to assembly and polishing tolerances.

Another design consideration for the PediaFlow® technology is that pediatric MCS should be rapidly deployable and customizable to support the representative patient population. The use of cardiopulmonary bypass for VAD implantation is expected, however limiting on-pump time remains ideal. Within this context, and for the PediaFlow® inflow cannula, the removable sewing ring provides accurate and unencumbered placement onto the heart apex before allowing insertion and tool-less securement of the inflow body within the LV. The reinforced parabolic-shaped inflow tip (Figure 2-B) eases insertion and serves as a clinical marker for echocardiography peri-operatively to adjust insertion depth and post-operatively when assessing cannula position. Along with the pre-assembled outflow graft and quick connect mechanisms (Figure 2-C), pump support was initiated in the latest studies in under an hour from first incision without the use of cardiopulmonary bypass. Without any evidence of ventricular suction supported by explant analysis in the PF3 and PF4 implant studies, we hypothesize that the additional flow paths provided by the inlet shape geometry render the parabolic-tip resistant to entrapment and less sensitive to positional variations [30].

While *in vivo* analysis is performed in healthy animals and does not necessarily reflect the etiologies in children (i.e.: congenital, dilated, and/or restrictive cardiomyopathies), the results are nonetheless encouraging. The biocompatibility findings *in vivo* (Figure 5) and explant analyses (Figures 6–7) are consistent with the *in vitro* results demonstrating no hemolysis, and neither platelet activation nor platelet dysfunction during implant periods up to 2-months. The lack of documented renal insufficiency or other evidence of thrombogenesis or thromboembolic events with only relatively low-dose heparin and sub-

therapeutic ACTs is especially promising towards the design goal for the PediaFlow® pediatric VAD of solely anti-platelet therapies to minimize bleeding risk clinically [32, 33]. Additional implants using the current PF4 design and components are necessary to demonstrate reproducibility of the preclinical assessment for Investigation Device Exemption (IDE) application.

Conclusion

This report is the culmination of 10-years of NHLBI-supported development of a miniaturized, implantable rotary blood pump for the chronic support of infants/small children with congenital and/or acquired cardiac defects. Over 20 design variations were evaluated and judged based on a multi-component objective function which factored several criteria including anatomic fit, cellular biocompatibility, heat generation and transfer, magnetically levitated suspension robustness, and manufacturability [23]. The design was improved and miniaturized through successive pump prototypes using computational fluid dynamics to minimize flow-induced blood damage via modification of the geometry of the predicted blood flow path [24]. The pump housing was modified to improve surgical fixation and the inflow/outflow attachments optimized to permit ease of insertion according to human factors engineering principles.

The data presented herein document the exceptional biocompatibility and the potential of safely providing chronic mechanical circulatory support to neonates and infants using a miniature, implantable, magnetically levitated, rotodynamic blood pump. As per the requirements of the NHLBI contract programs, the PediaFlow® has been designated by the FDA as a Humanitarian Use Device (HUD) for “mechanical circulatory support in neonates, infants, and toddlers weighing up to 20 kg as a bridge to transplant, a bridge to other therapeutic intervention such as surgery, or as a bridge to recovery.” This important designation provides insight as to the remaining pre-clinical testing (both on the bench and *in vivo*) to be undertaken. While accurate flow estimation has been achieved (Figure A.4), work remains including the final prototyping and testing of a clinical-use controller which is required for the final preclinical studies in anticipation of submitting an IDE application to the FDA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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Glossary:

ACT	activated clotting time
BSA	body surface area
CF	continuous flow
ECMO	extracorporeal membrane oxygenation
FDA	Food and Drug Administration
HUD	humanitarian use device
IDE	investigational device exemption
LV	left ventricle
MCS	mechanical circulatory support
NIH	normalized index of hemolysis
NHLBI	National Heart Lung and Blood Institute
PF3	3rd generation PediaFlow® prototype
PF4	4th generation, final design PediaFlow® prototype
POD	post-operative day
RBP	rotary blood pump
-S*xx*	*in vivo* animal study number
VAD	ventricular assist device

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Central Message:

The PediaFlow® pediatric VAD has the potential to provide long-term cardiac support safely in pediatric patients.

Perspective Message:

Limited options exist, associated with serious neurological and coagulation-related adverse events, for pediatric patients (BSA<1.5 m^2) requiring chronic mechanical circulatory support. The results of our PediaFlow® design highlight the potential to safely provide long-term pediatric cardiac support using a magnetically levitated, fully implantable, continuous-flow rotary blood pump.

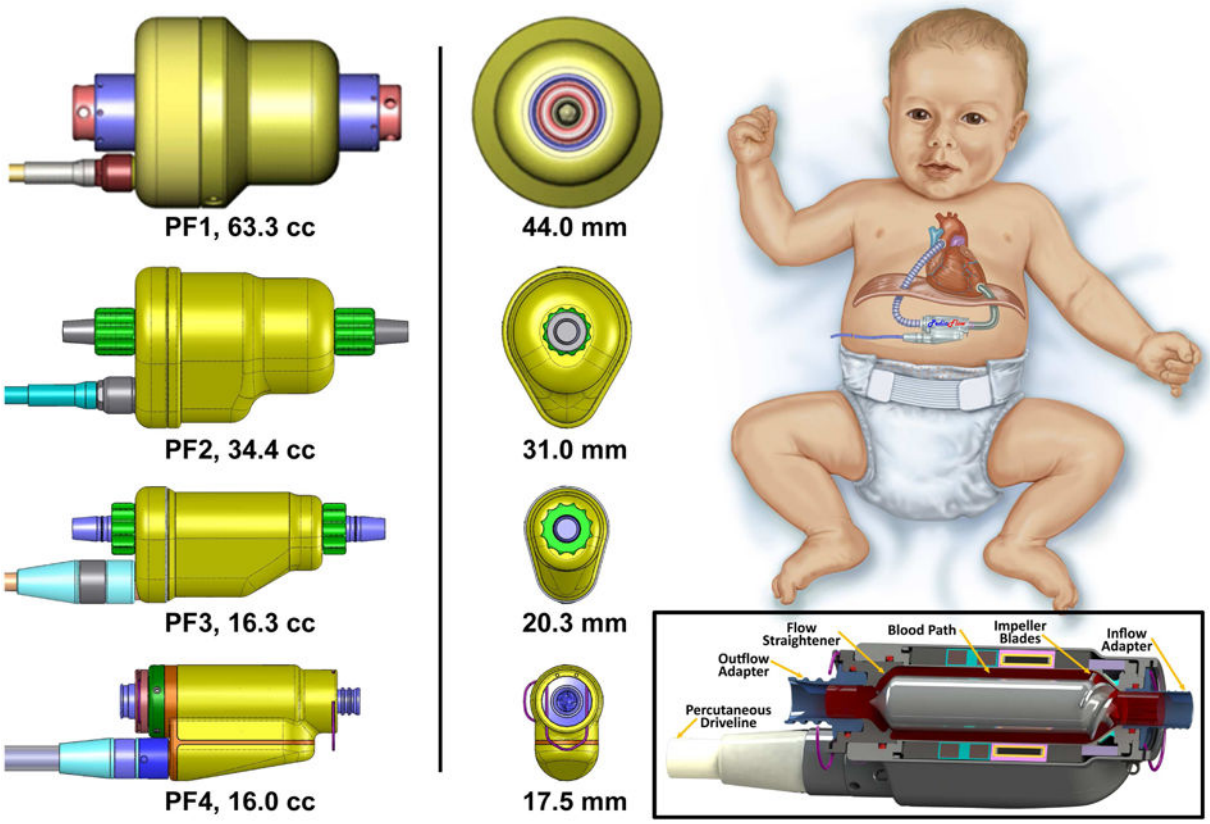

Figure 1:
Evolution and miniaturization of the PediaFlow® from the first prototype (PF1) to the 4th generation (PF4) pediatric VAD and pump topology (**inset**).

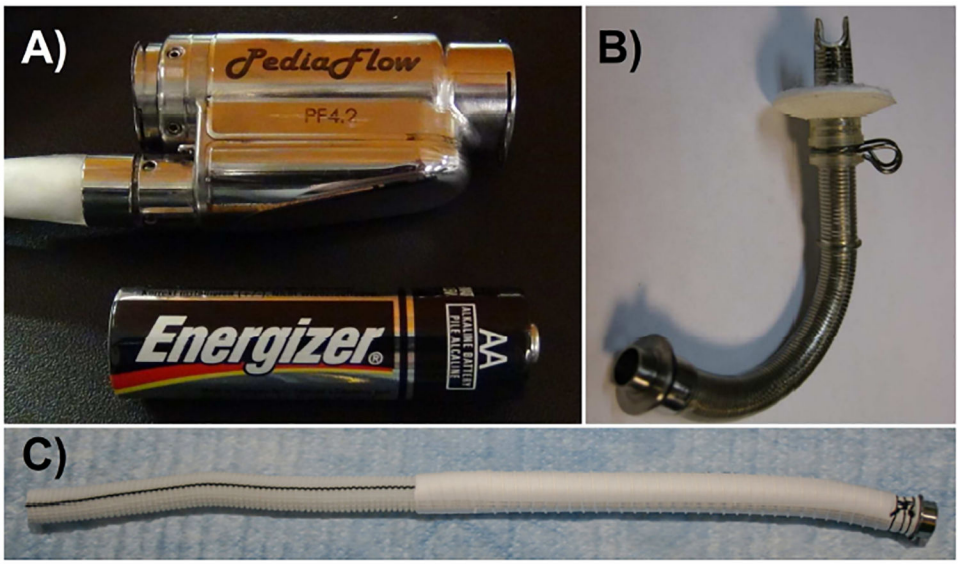

Figure 2:
The PF4 PediaFlow® prototype and implantable components: **A)** the PF4 pump and size comparison (AA battery), **B)** the parabolic-tip inflow cannula with detachable sewing ring, and **C)** the pre-assembled 6 mm outflow graft assembly.

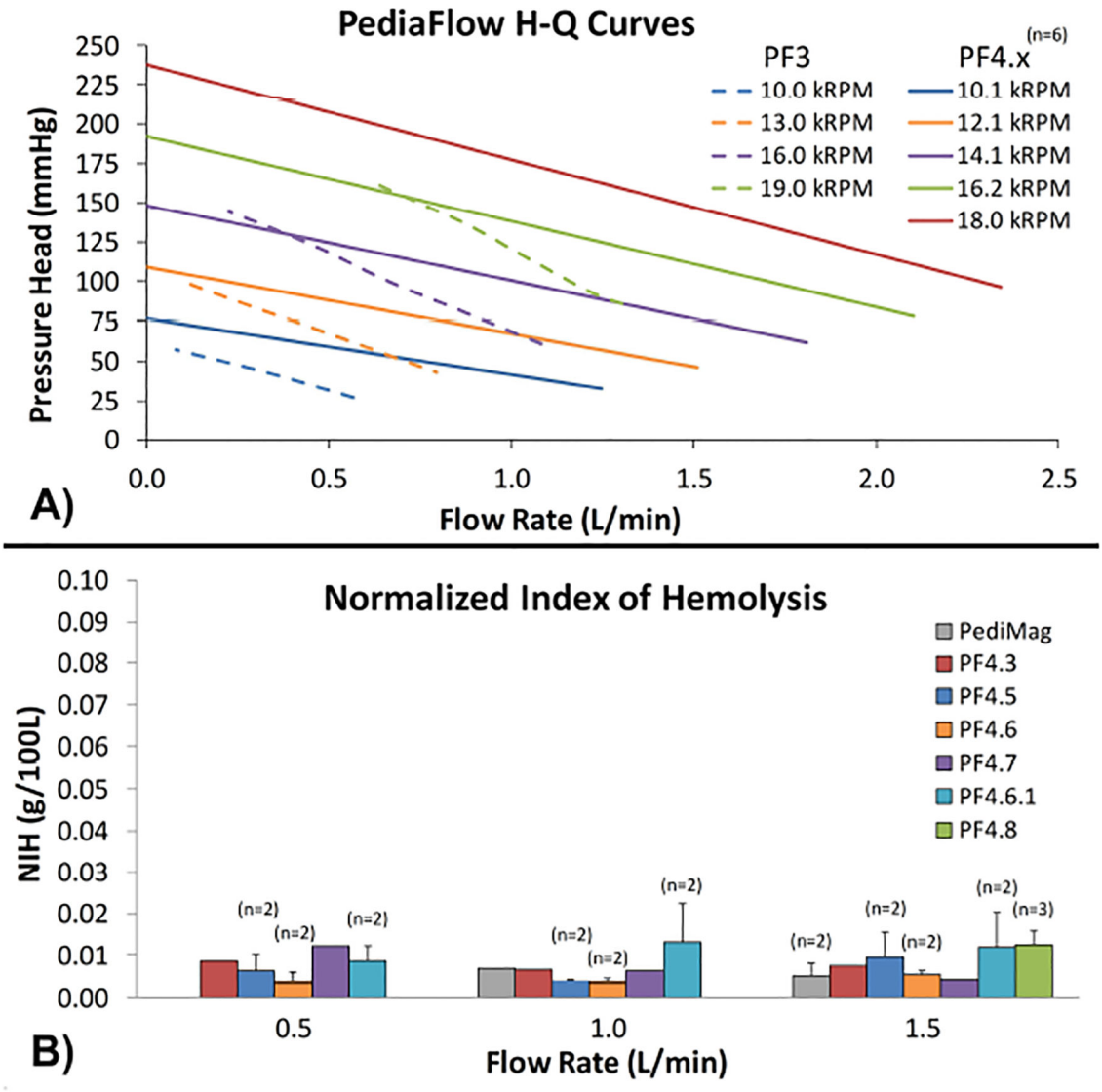

Figure 3:

A) PF4 characteristic H-Q pump curves using a blood analog (viscosity = 2.39 cP) and **B)** the calculated *in vitro* Normalized Index of Hemolysis (NIH) values (mean±SD) for the PF4 prototypes compared with the PediMag® control.

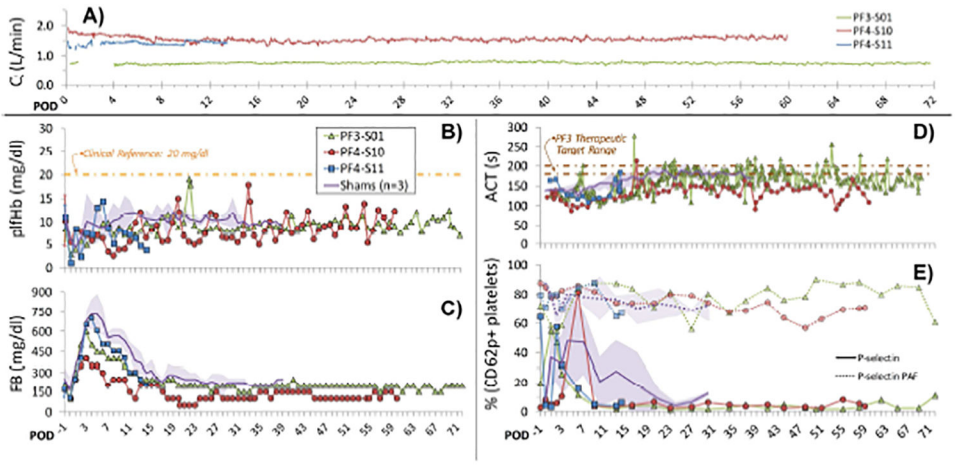

Figure 4:

Results of the two 4th-generation PediaFlow® ovine studies using the current-design cannulae system (PF4-S10, PF4-S11), in comparison to the previous 3rd-gen. chronic implant (PF3-S01) and the non-implanted surgical control 'Shams' (n=3, mean±SD): **A**) Measured pump flow rate (Q) for the implanted animals (gaps indicate durations of signal loss during post-operative acoustic recoupling of the outflow graft probe). Hematological and hemocompatibility measurements including **B)** plasma-free hemoglobin, **C)** fibrinogen, **D)** activated clotting time (ACT), and **E)** platelet biocompatibility as determined by the time course of platelet activation by P-selectin expression and platelet functionality by agonist stimulation using platelet activating factor (PAF).

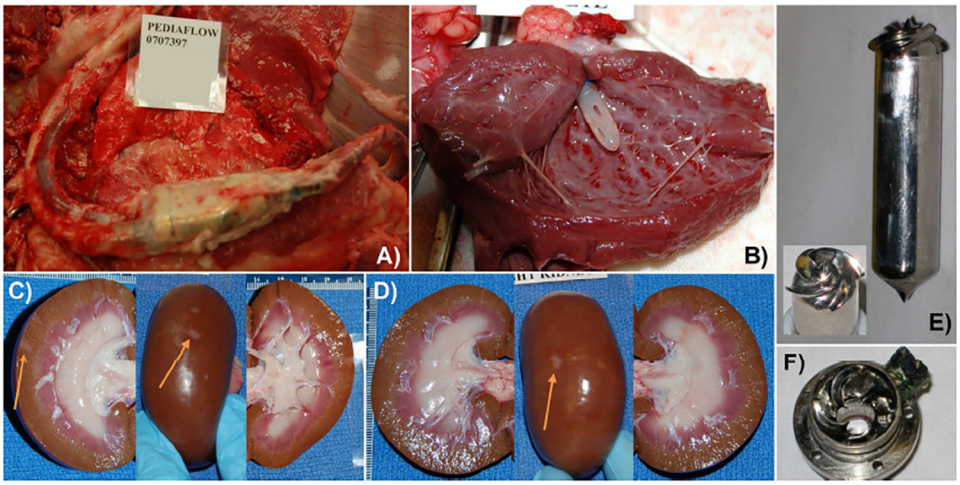

Figure 5:

Necropsy images of the PF3-S01 (72-day) implant: **A)** pump placement *in situ*, **B)** the modified 18Fr fenestrated inflow cannula (Medtronic® DLP, Minneapolis, MN, USA) free of thrombus within the LV, **C)** left kidney with a minor and well-healed cortical infarction, **D)** right kidney with a minor surface infarction that was not visible upon sagittal dissection, **E)** the pump rotor and **F)** stator free of deposition.

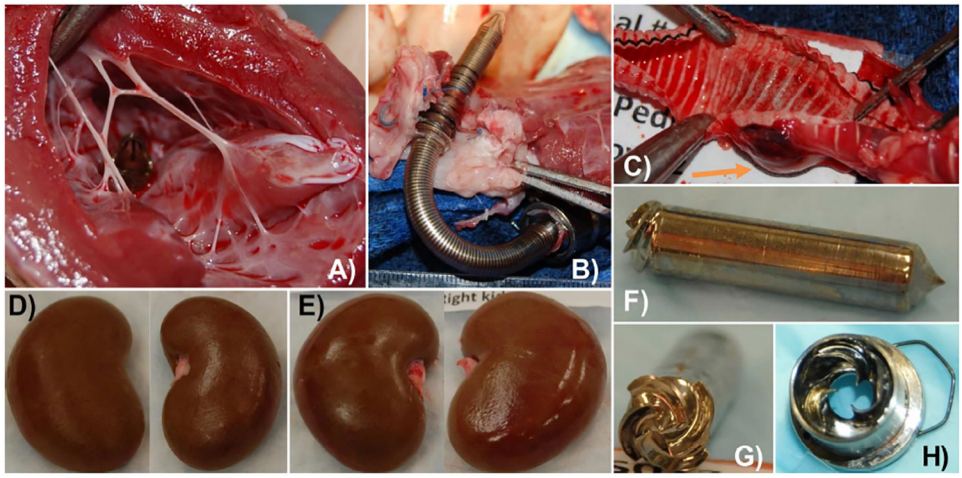

Figure 6:

Necropsy images of PF4-S11 (14-day) implant; **A)** the inflow cannula position *in situ*, **B)** cannula body free of deposition, **C)** adherent thrombus on the exterior of the outflow graft, outside of the blood flow path, possibly from the de-airing needle, **D-E)** kidneys without evidence of infarcts, and **F-H)** rotor, impeller blading, and stator free of deposition.

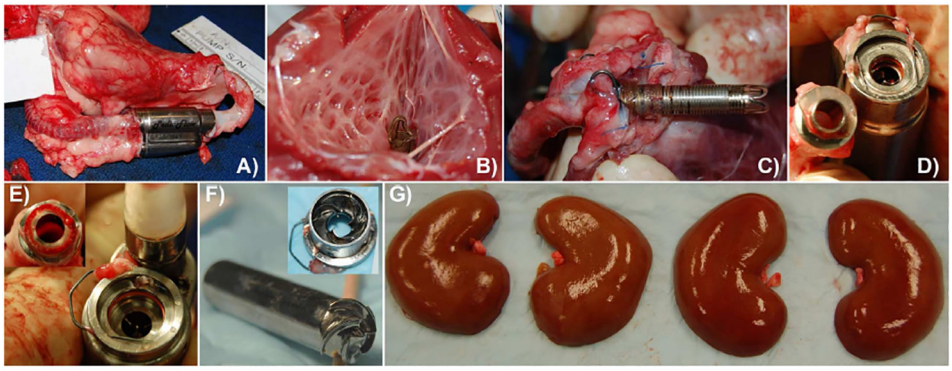

Figure 7:

Explant photos of the PF4-S10 (60-day) implant; **A)** well encapsulated pump *in situ*, **B)** the inflow cannula tip position, **C)** the cannula body, **D)** inflow and **E)** outflow connections free of deposition within the flow path, **F)** the pump rotor and stator **(inset)** free of deposits, **G)** kidneys with no evidence of infarction.