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***In Vitro* and *In Vivo* Performance Evaluation of the Second Developmental Version of the PediaFlow Pediatric Ventricular Assist Device**

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Abstract

Ventricular assist devices (VADs) have significantly impacted the treatment of adult cardiac failure, but few options exist for pediatric patients. This has motivated our group to develop an implantable magnetically levitated rotodynamic VAD (PediaFlow®) for 3–20 kg patients. The second prototype design of the PediaFlow (PF2) is 56% smaller than earlier prototypes, and achieves 0.5–1.5 L/min blood flow rates. *In vitro* hemodynamic performance and hemolysis testing were performed with analog blood and whole ovine blood, respectively. *In vivo* evaluation was performed in an ovine model to evaluate hemocompatibility and end-organ function. The *in vitro* normalized index of hemolysis was 0.05–0.14 g/L over the specified operating range. *In vivo* performance was satisfactory for two of the three implanted animals. A mechanical defect caused early termination at 17 days of the first *in vivo* study, but two subsequent implants proceeded without complication and electively terminated at 30 and 70 days. Serum chemistries and plasma free hemoglobin were within normal limits. Gross necropsy revealed small, subclinical infarctions in the kidneys of the 30 and 70 day animals (confirmed by histopathology). The results of these experiments, particularly the biocompatibility demonstrated *in vivo* encourage further development of a miniature magnetically levitated VAD for the pediatric population. Ongoing work including further reduction of size will lead to a design freeze in preparation for of clinical trials.

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Keywords

Pediatric; Mechanical circulatory support; Ventricular assist device; Pre-clinical study; *In vivo*

INTRODUCTION

Neonatal patients experiencing severe heart failure comprise >65% of the pediatric cardiac transplant waiting list.¹⁹ Although significant advances have been made in adult circulatory support with ventricular assist devices (VADs), extracorporeal membrane oxygenation (ECMO) has been the standard of care for children <25 kg with severe heart failure. Data gathered from patients at Children's Hospital of Pittsburgh of UPMC (our clinical collaborators on this project) indicates that pediatric VAD patients have better survival (90%) vs. ECMO (66%) for cardiac support (Table 1). Nevertheless, both ECMO and VAD patients experienced similar rates of bleeding, infection, and neurologic events that are found in adult VAD recipients.^{12,16} Analysis of these data demonstrates that, prior to the start of the Berlin Heart clinical trial, all patients treated with VADs were larger (BSA > 1.2 m²) with a primary diagnosis of cardiomyopathy. Clearly, there exists a prevailing need for pediatric VADs to support bridge-to-transplant and bridge-to-recovery in pediatric heart failure. This provided the motivation of our group to develop an implantable pediatric VAD, the PediaFlow®, suitable for long-term (≥60 days) support for the smallest pediatric patients (3–20 kg). The associated hemodynamic design requirements include 0.3–1.5 L/min blood flow against up to 80–140 mmHg (peak systolic pressure). In the worst case scenario 1.5 L/min would provide a life-sustaining cardiac index of 1.8 L/min/m² for a 20 kg patient. However, without supplemental native cardiac function, physical activity would be limited. These hemodynamic requirements, indicated in Fig. 1, evolved from the physical characteristics of the patient population at Children's Hospital of Pittsburgh in consideration of pressure losses in cannula, native cardiac function and physical activity.¹⁹ In addition to flow capability, a paramount requirement of any VAD is excellent biocompatibility, defined by negligible hemolysis and platelet activation, comparable to sham surgery.

The PediaFlow VAD is a mixed flow rotodynamic blood pump incorporating a magnetically levitated impeller which eliminates the need for bearings and seals. The first-generation PediaFlow (PF1) has undergone preliminary testing *in vivo*.⁶ The low hemolysis and platelet activation in the PF1 prototype were very encouraging, but the flow rate was limited to less than 1 L/min flow rate due to constraints on the operating motor speed. The current report presents further refinements leading to a second-generation version (PF2) that is 56% smaller (Fig. 2) and features a redesigned motor for increased efficiency and higher operating speeds to meet the flow demands. The continued miniaturization of the pump was made possible through supercritical operation of the rotor, meaning that the operating speed range of the magnetically suspended rotor (which drives the fluid flow) lies above the natural resonant frequencies of the rotor and magnetic bearings. Further miniaturization based on this discovery is anticipated to ensure that the PediaFlow will be implantable in our smallest target patients. We describe here the *in vitro* and pre-clinical *in vivo* testing of two independent productions of PediaFlow PF2 prototype (PF2.1 and PF2.2). *In vivo* testing focused on measures of hemocompatibility and preservation of normal organ function in healthy animals.

MATERIALS AND METHODS

In Vitro Testing

The pressure and flow rate characteristics (H-Q) of PF2.1 were tested *in vitro* using a blood analog solution of 2.3 cP glycerol-saline (corresponding to the viscosity of ovine blood with a hematocrit of 25% at 37 °C) in a closed fluid circuit. The viscosity of the glycerol-saline solution was measured with standard capillary viscometry techniques. This viscosity was chosen to represent the hematocrit in the test animals, which would be a worst-case-scenario for the magnetic stability of the pump that occurs in low viscosity fluids. The pressure rise (ΔP) and flow produced by the pump (H-Q) were recorded over a range of impeller speeds (5–18 kRPM) under varying afterload. These data were used to assure satisfactory pump capacity and performance, and provided the basis for flow estimation *in vivo*. An electronic microphone was positioned adjacent to the pump housing to detect potential intermittent contact of the (magnetically levitated) rotor with the housing walls.

In addition to the H-Q test, PF2.1 was subjected to *in vitro* hemolysis tests using established methods.^{6,7} The hemolysis testing was performed in a mock circulatory loop consisting of a reservoir bag, PVC tubing, polycarbonate connectors and reducers, and the pump. The mock loop was filled with 300–400 mL of fresh citrated ovine blood collected from donor sheep housed at the University of Pittsburgh under an existing IACUC protocol. The blood hematocrit (Ht) for each test was adjusted to 30% prior to filling the loop by addition or removal of plasma.¹⁴ Total blood hemoglobin concentration (tHb) was measured by an OSM3 hemoximeter (Radiometer American Inc., West Lake, OH).

The loop was operated for 2 h at each of three flow rates sequentially (0.5 L/min, 1 L/min, and 1.5 L/min) in two experiments. An additional 2 h study was conducted at 1 L/min. Pressure, flow rate, and temperature were recorded throughout each experiment. Samples of blood (2 mL) were obtained within 5 min of flow initiation to establish the baseline plasma free hemoglobin after adequate mixing. Additional samples were taken each half-hour thereafter for each study duration. Samples were centrifuged (Jouan CR412, Jouan, Inc., Winchester, VA) at 2800×g for 15 min at room temperature to remove the bulk of the cellular components of the blood. The separated plasma was transferred to 1.5 cc microcentrifuge tubes and centrifuged again (Eppendorf 5417R, Hamburg, Germany) at 20,800×g for 20 min to remove any remaining cells or cellular debris from the previous step. Plasma free hemoglobin (plfHb) was measured by absorbance at 540 nm using a spectrophotometer (Spectronic® GENESYS5™, Spectronic Instruments, Inc., Rochester, NY, USA).²³ The plfHb values (g/L) were used to calculate the normalized index of hemolysis (NIH) according to

$$\text{NIH (g/100 L)} = \frac{\Delta \text{PlfHb} \times V \times \frac{(100 - \text{Ht})}{100}}{Q \times T} \times 100$$

where ΔPlfHb is difference in plfHb between the current time point and the baseline for that flow rate, V is the loop volume (L), Q is the flow rate (L/min), and T is the test time (min) at that flow rate.

In Vivo Evaluation

Three pre-clinical *in vivo* studies were conducted on 40–60 kg Cheviot breed lambs. Two studies had intended durations of 30 days and one study had an intended duration of 70 days. All animal studies were performed under a protocol approved by the Institutional Animal Care and Use Committee of the University of Pittsburgh. Prior to device implantation, each

animal received endotracheal (ET) intubation and was maintained under anesthesia with 2% Isoflurane in oxygen and medical air. Ventilation was closely monitored, and tidal volume, respiratory frequency, and peak end expiratory pressures (PEEP) were supported to nominal arterial blood gas requirements. Venous and arterial lines were placed in the jugular vein and left external carotid artery, respectively. Both arterial and venous lines were tunneled to exit through the dorsal portion of the neck and secured in place.

A left, fourth interspace thoracotomy was performed to expose the left ventricular apex and descending thoracic aorta (used as surrogate for the very short and inaccessible ascending aorta/brachiocephalic trunk). Amiodarone (150 mg) was administered for cardiac support to limit any arrhythmias caused by cardiac manipulation. The heart was elevated, and a custom-fabricated sewing ring attached to the LV apex using large, pledgeted mattress-type sutures. Anticoagulation was initiated with a loading dose of sodium heparin to produce activated clotting times (ACT) greater than 400 s. The pump outflow cannula (modified 20fr EOPA arterial cannula, Biomedicus) was inserted into the descending thoracic aorta. The inflow cannula (modified 18fr DLP® venous cannula, Biomedicus) was inserted through the apex of the left ventricle via a stab-incision, and secured to the sewing ring with umbilical tape. The PediaFlow VAD (PF2 prototype) was then connected to its appropriate inflow and outflow graft, de-aired, and flow initiated. The pump was placed caudal to the heart, between the sixth and seventh ribs and the diaphragm. The thoracotomy was closed in four layers after placing a chest drainage tube to evacuate accumulation of serous fluid and post-operative bleeding. The animal was extubated and transferred to a critical care suite in the animal facility. A similar surgical procedure was performed on three “sham” animals not receiving a VAD to provide baseline data over 30 days.

All animals received post-operative critical care including: Flunixin Meglumine (1 mg/kg IV q8-12 h), for the first 7 days post-surgery and then as needed thereafter; cefazolin (IV q8hrs) for 12-days; Reglan (metoclopramide, IV, q12) for up to 3-days or until gastric motility is normalized. All animals received anticoagulation with sodium heparin and I.V. Coumadin (warfarin sodium; Bristol-Meyers, Devens, MA) to maintain the ACT 180–200 s and INR: 2.0–3.0. A data acquisition system (DATAQ, DI-710, Akron, OH), recorded the speed and position of the rotor position, motor coil currents, and blood pressure. Hemorheological assays (plfHb, Ht, and fibrinogen⁷) and serum biochemistry were monitored throughout each study.

A complete necropsy examination was performed by the implanting surgeon at each study termination. Systemic heparinization (400 IU/kg) followed by thiopental (50 mg/kg) was used to initiate cardiac arrest. After confirmation of cardiac arrest, an injection of 50 mL of potassium chloride was given to limit agonal contractions expediting pump extraction. These methods for euthanasia are accepted by the *Panel on Euthanasia of the American Veterinary Medical Association*. The animal was then exsanguinated, and the left lateral chest wall was removed to expose the thoracic organs. The PediaFlow VAD and cannulae were disassembled into component parts (inflow cannula, pump, and outflow cannula) and visually examined for the presence of any abnormalities. Any thrombus or other abnormalities were described and photographed. Vital organs of interest (lungs, heart, kidneys, liver, and spleen) were removed, examined, and sectioned. Any gross changes were described and photographed. All organ sections were preserved in 10% buffered neutral formalin for histopathologic analysis by a veterinary pathologist in the University of Pittsburgh Division of Laboratory Animal Research. Finally, the pump was disassembled, photographed, and inspected for damage to the percutaneous cable, motor, magnets, and impeller.

RESULTS

In Vitro Performance

The steep family of performance curves for the PF2.1 pump indicated a relatively strong dependence on hemodynamic after-load with no evidence of rotor instability (Fig. 1). The normalized index of hemolysis (NIH) increased with flow rate (Fig. 3), but remained within acceptable limits over the intended operating range (0.5–1.5 L/min).⁶

In Vivo Performance

Data presented in Table 2 summarizes the parameters from the *in vivo* studies. The implant of the first PF2 prototype (PF2.1) was terminated at 17 days due to mechanical instability (manufacturer's defect in the percutaneous cable). The percutaneous cable was repaired, and the subsequent implantation of PF2.1 reached the intended 30 days without incident. A second build of the PF2 prototype (PF2.2) was implanted for 70 days and concluded without incident; postmortem examination revealed three small holes in the percutaneous cable and evidence of fluid penetrating the outer housing.

Mean arterial pressure, heart rate, and serum chemistries demonstrated no clinically relevant changes resulting from VAD operation (See Table 2). Similarly, plfHb and Hct remained near baseline for all VAD and "sham" studies (See Fig. 4a). Fibrinogen concentrations rose postoperatively and returned to baseline for all VAD and "sham" studies (Fig. 4b). Anticoagulation was difficult in these animals. The warfarin dose ranged between 10 mg and 20 mg per day, which is relatively high compared to human dosage (0.09–0.33 mg/kg/day for pediatrics, and 2–10 mg/day for adults). Because the INR values remained below 2.5 for a large portion of the implant time, a continuous infusion of heparin was required in our studies.

Pump Operation In Vivo

Figure 5 demonstrates the hourly averaged pump parameters. Motor speed fluctuations for the first PF2.1 study resulted from repeated pump stoppages due to the fractured wire. Variations in axial position for the second (30-day) PF2.1 study were found like-wise to be an artifact of fatigue in the axial position sensor following the first PF2.1 study. Prolonged drift in PF2.2 axial position resulted from thermal failure in the controller electronics. Nonetheless, the pump operated stably because of its robust, virtual zero power control.¹⁵ The different motor current, motor speed and estimated flow rates represent the pre-determined set points for each implant.

Necropsy

Gross examination of the heart, lungs, liver, and spleen were unremarkable in all studies. No surface kidney lesions were found for PF2.1 (17-day). For PF2.1 (30-day) and PF2.2 (70-day), surface infarctions on one or both of the kidneys were found (See Figs. 6b–6c). The histopathology findings in the kidneys reported by the veterinary pathologist described mild interstitial fibrosis in wedge-shaped areas of healing tissue representative of an early insult (See Figs. 6d–6e). The apex of the heart displayed typical granulomatous epicarditis with foreign body structures consistent with residual suture material, but no gross lesions related to the presence of the inflow cannula. Lung tissue in two of the animals showed some minor pulmonary fibrosis and edema related to handling during the thoracotomy. The spleen and liver were described as relatively unremarkable with no apparent pathologies. The blood-contacting surfaces of the pump and the inflow and outflow cannulae were free of adherent thrombus, despite surface scratches caused by several touchdown episodes in the PF2.1 (17-day) animal and pre-operatively in the PF2.1 (30-day) and PF2.2 (70-day) animals (see Fig. 7).

DISCUSSION

The development of miniaturized, biocompatible pediatric VADs is likely to result in broader utilization of mechanical circulatory support for mortally ill children.²² The results of the present studies are encouraging that the PediaFlow could potentially achieve this objective.

Small clearances in the flow path (~0.50 mm) resulted in steeper performance curves compared to other continuous flow blood pumps.^{20,21} Nevertheless, the NIH values remained in an acceptable range (0.05–0.2 g/100 L) compared to other axial pumps tested at a similar hematocrit.¹⁴ These results are attributable to the magnetically suspended rotor, which obviates blood trauma associated with traditional bearings and seals. The moderate increase in NIH with flow rate can be explained by the axial migration of the rotor towards the outlet portion of the housing, creating a smaller gap between the spinning rotor and the stationary stator vanes that redirect the flow in the axial direction. The migration of the rotor at higher speeds was verified at 10% rotor travel (~25 μ m) and is a normal consequence of the force-balances generated on the rotor by the magnetic bearings which offset the force created by the moving fluid and creates a condition where virtually zero power (VZP control algorithm) is required to maintain levitation.

Although small cortical infarctions were noted on the kidneys, all were considered to be superficial and did not impact renal function. Such observations have been reported for other investigational devices in ovine models.^{8,11,18} The histopathologic findings suggested that these infarctions were well-healed, and occurred early in the post-operative period. A potential cause may have been heightened inflammatory response and platelet activation, such as evidenced by elevated and variable neutrophil counts in PF2.2 from a confirmed fecal culture for whipworm. However, it is possible that unstable thrombi were generated (in either the cannula or pump) due to inadequate anticoagulation (INR < 2.0). Irrespective of the source of these microemboli, we are encouraged that pfHb values for all animals in the study were less than 15 mg/dL and within reported ranges for other continuous flow VADs, in a similar animal model,^{4,8,9,18} and are within the limits of haptoglobin binding capacity (<50 mg/dL).¹⁷ Although there are few studies of plfHb in clinical patients, pediatric VAD patients have plfHb values that can range from 5 mg/dL to 40 mg/dL depending on device type (centrifugal, axial, or bi-VAD).⁵ Additionally, a retrospective study in Michigan by Gbadegesin et al.³ has demonstrated the average peak plfHb value of pediatric patients surviving ECMO was 48.4 mg/dL ($n = 68$) while the non-survival group had an average peak plfHb of 93.6 mg/dL ($n = 36$).

The mechanical failures for this study centered on the percutaneous cable and sensor wires, and have been reported for numerous other devices.¹⁰ Steps have been taken to provide more rigorous component testing prior to the final fabrication and implantation. Specifically, a thicker, more resistant jacket material will be used for the percutaneous cable to minimize the possibility of damage to conductors due to lacerations of the cable jacket, and larger, more robust co-axial cables will be used to replace the micro co-axial cable in the existing PF2 percutaneous cable in order to increase the durability of the cable and minimize the chance of any fatigue related failures.

The reduction in size from the PF1 (63.3 cm³ total volume) to PF2 (35.3 cm³ total volume) was necessary for moving towards our target patient population of 3–20 kg pediatric patients in heart failure. We desire a fully implantable system that can be used for up to 6 months of continuous support, which is well within the median time for transplantation of this patient population¹³ or potentially to wean the patient from the device in instances such as viral myocarditis or myocardial stun following cardiomyotomy. With the development of more

biocompatible and user-friendly pediatric VADs, it is anticipated that the potential patient population who could benefit from such technology will in fact grow from the current estimates as more cardiology centers have access to this technology.²² Despite the reduction in size achieved by PF2, it is still too large for full implantation in the smallest patients <15 kg.² We are utilizing multidisciplinary physics and computational approaches to reduce size further. The third-generation PediaFlow (PF3) occupies just 16.6 cm³ total volume (approximate size of a AA battery).¹ This is achieved, in part, taking advantage of larger gaps with smaller components—without sacrificing the upper limits of flow rate (1.5 L/min).

In summary, the second generation PediaFlow (PF2) represents significant progress towards an implantable VAD to serve the 3–20 kg pediatric patient population. Our goal is to freeze the design to permit an IDE application to be submitted to the FDA by 2012.

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FIGURE 1.

PF2 performance curves for 2.5 cP (gray) and 3.5 cP (black) blood analog solutions. The dashed design envelope indicates the physiologic conditions (peak systolic pressure and flow) under which the PediaFlow pump would be expected to perform.

FIGURE 2.

The PediaFlow PF2 prototype is 56% smaller than the previous design; moving closer to the goal of being implantable in a newborn.

FIGURE 3.
Calculated Normalized Index of Hemolysis in vitro.

FIGURE 4.

(a) pIffHb, Ht and (b) Fibrinogen sham [$n = 3$] and PF2 [$n = 3$] studies. Values are mean $\pm$ standard deviation for POD ≤ 30 .

FIGURE 5. Pump parameters recorded in vivo. (a) Axial position, (b) Motor current, (c) Motor speed, (d) Estimated flow.

FIGURE 6. Necropsy findings for VAD studies; (a, d) PF2.1 (17 days); (b, e) PF2.1 (30 days); (c, f) PF2.2 (70 days); (a–c) gross and (d–e) Histopathology results.

FIGURE 7. Disassembled pump photographs (a–c) PF2.1 17 (days); (d–f) PF2.1 (30 days); (g–h) PF2.2 (70 days). Despite rotor surface scratches (lower images), no thrombus or platelet deposition was found.

TABLE 1

Characteristics of pediatric patients treated with VAD or ECMO at CHP of UPMC.

	VAD	ECMO
Demographics		
Number of pts	29	59
Age (yrs)	8.9 ± 6.5 (0–18)	2.3 ± 4.7 (0–17.83)
BSA (m ²)	1.1 ± 0.7 (0.2–2.3)	0.4 ± 0.4 (0.1–1.8)
Support Duration (days)	37.7 ± 46.9 (0–175)	4.5 ± 3.7 (0.1–21.5)
Cause of heart failure		
CHD	6	36
Cardiomyopathy	19	9
Cardiogenic Shock	0	8
Cardiac Arrest	0	3
Post-transplant	1	2
Myocarditis	3	1
Survival statistics		
MCS survival	26 (90%)	39 (66%)
Survival to discharge	23 (79%)	29 (49%)
Complications rates		
Bleeding	8 (28%)	13 (22%)
Device Change	4 (14%)	7 (12%)
Neurologic	6 (21%)	7 (12%)
Renal	3 (10%)	29 (49%)
Cardiovascular	7 (24%)	22 (37%)

Patients treated between January 2005 and January 2009. Demographic data is presented as mean ± standard deviation with the range in parenthesis. Survival and Complication Data presented as total number with percentage in parenthesis. MCS = Mechanical Circulatory Support; CHD = Congenital Heart Defect.

TABLE 2

Study parameters and serum chemistry.

Pump and duration	PF2.1 17/30 days	PF2.1 30/30 days	PF2.2 70/70 days	Reference Ranges
Weight (kg)	60	45	40	
Flow rate (L/min)	1.2	1.5	0.5	
Mean arterial pressure (mmHg)	93 ± 8.8 (96)	83 ± 9.5 (76)	82 ± 10.6 (86)	80–100
Heart rate (bpm)	92 ± 13 (75)	95 ± 15 (74)	93 ± 14 (75)	60–120
WBC (×1000/mm ³)	6.4 ± 1.5 (5.0)	6.6 ± 1.4 (4.3)	8.1 ± 1.7 (7.3)	4–12
Platelets (×1000/mm ³)	647 ± 202 (494)	462 ± 109 (495)	666 ± 348 (596)	250–750
Neutrophils (×1000/mm ³)	3.6 ± 1.4 (2.0)	2.8 ± 0.9 (1.5)	2.7 ± 0.8 (2.0)	0.7–6.0
Lymphocytes (×1000/mm ³)	2.4 ± 0.82 (2.4)	3.5 ± 1.7 (2.6)	5.0 ± 1.9 (4.7)	2–9
Hb (g/dL)	9.8 ± 0.7 (11.8)	8.2 ± 0.8 (9.9)	11.4 ± 1.2 (9.9)	9–15
HCT (%)	24.8 ± 2.1 (29.3)	23.8 ± 2.6 (28.3)	33.5 ± 3.8 (29.9)	27–45
INR	1.1 ± 1.1 (1.32)	1.1 ± 0.8 (1.7)	1.9 ± 3.7 (1.1)	N/A
PTT (s)	41.7 ± 13.1 (30.3)	46.7 ± 10.3 (33.3)	56.7 ± 13 (37.3)	N/A
Fibrinogen (mg/dL)	398 ± 136 (250)	308 ± 135 (230)	228 ± 89 (133)	100–500
plfHb (mg/dL)	7.4 ± 2.1 (10.6)	11.6 ± 4.1 (16.6)	11.3 ± 2.7 (13.6)	<50*
BUN (mg/dL)	11.8 ± 2.6 (18.0)	11.6 ± 6.6 (21)	11.1 ± 3.7 (19)	10.3–26
Glucose (mg/dL)	80.6 ± 8.5 (81)	91 ± 3.7 (79)	83.6 ± 6.4 (84)	44–81.2
Creatinine (mg/dL)	0.7 ± 0.1 (0.6)	0.7 ± 0.2 (0.6)	0.5 ± 0.1 (0.5)	0.9–2.0
Ca (mg/dL)	9.1 ± 0.8 (9.2)	9 ± 1 (8.7)	9.8 ± 0.7 (10.4)	9.3–11.7
Cl (mmol/L)	109 ± 6 (108.0)	113 ± 4.3 (103)	108 ± 4 (109)	100.8–113.0
K (mmol/L)	4.5 ± 0.6 (3.9)	4.7 ± 1.6 (3.3)	4.8 ± 0.9 (4.7)	4.3–6.3
Na (mmol/L)	145.4 ± 4.7 (144.0)	148.5 ± 6.1 (147)	145 ± 3 (145)	141.6–159.6
ALT (IU/L)	21.2 ± 14.9 (13.0)	28.3 ± 18.2 (29)	10.8 ± 6.8 (17)	14.8–43.8
AST (IU/L)	150 ± 81 (65)	164 ± 133 (143)	74.9 ± 46.5 (92)	49.0–123.0
Albumin (g/dL)	2.5 ± 0.2 (2.7)	3 ± 0.3 (2.7)	2.9 ± 0.4 (2.7)	2.4–3.0
Tot. bilirubin (mg/dL)	0.12 ± 0.04 (0.1)	0.1 ± 0.1 (0.1)	0.1 ± 0 (0.1)	0.1–0.5
GGT (IU/L)	44 ± 9 (43)	41.3 ± 10 (35)	49.7 ± 7.6 (52)	10–118
Cholesterol (mg/dL)	46.6 ± 23.4 (31.0)	71 ± 20.2 (54)	53.6 ± 16.3 (29)	44.1–90.1
ALP (IU/L)	144.6 ± 52 (203)	70.7 ± 14.6 (89)	178 ± 56 (267)	26.9–156.1

Pump and duration	PF2.1 17/30 days	PF2.1 30/30 days	PF2.2 70/70 days	Reference Ranges
Total protein (g/dL)	6.0 ± 0.2 (6.8)	6.1 ± 0.3 (6.1)	5.8 ± 0.3 (5.5)	5.9–7.8

Data presented as mean ± standard deviation with baseline in parenthesis. Reference ranges derived from The Merck Veterinary Handbook (9th Edition, 2008) unless otherwise noted.

* Acceptable level of plfHb defined as <50 mg/dL based on haptoglobin binding capacity of haptoglobin.⁹