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EXTRACORPOREAL MEMBRANE OXYGENATION vs. COUNTERPULSATILE, PULSATILE, AND CONTINUOUS LEFT VENTRICULAR UNLOADING FOR PEDIATRIC MECHANICAL CIRCULATORY SUPPORT

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Abstract

OBJECTIVE—Despite progress with adult ventricular assist devices (VADs), limited options exist to support pediatric patients with life-threatening heart disease. Extracorporeal membrane oxygenation (ECMO) remains the clinical standard. To characterize (patho)physiologic responses to different modes of mechanical unloading of the failing pediatric heart, ECMO was compared to either intraaortic balloon pump (IABP), pulsatile-flow (PF)VAD, or continuous-flow (CF)VAD support in a pediatric heart failure model.

DESIGN—Experimental.

SETTING—Large animal laboratory operating room.

SUBJECTS—Yorkshire piglets (n=47, 11.7±2.6 kg).

INTERVENTIONS—In piglets with coronary ligation-induced cardiac dysfunction, mechanical circulatory support devices were implanted and studied during maximum support.

MEASUREMENTS and MAIN RESULTS—Left ventricular, right ventricular, coronary, carotid, systemic arterial, and pulmonary arterial hemodynamics were measured with pressure and flow transducers. Myocardial oxygen consumption and total-body oxygen consumption (VO₂) were calculated from arterial, venous, and coronary sinus blood sampling. Blood flow was measured in 17 organs with microspheres. Paired student t-tests compared baseline and heart failure conditions. One-way repeated-measures ANOVA compared heart failure, device support mode(s), and ECMO. Statistically significant (p<0.05) findings included: 1) improved left ventricular blood supply/demand ratio during PFVAD, CFVAD, and ECMO but not IABP support, 2) improved global myocardial blood supply/demand ratio during PFVAD, and CFVAD

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but not IABP or ECMO support, and 3) diminished pulsatility during ECMO and CFVAD but not IABP and PFVAD support. A profile of systems-based responses was established for each type of support.

CONCLUSIONS—Each type of pediatric VAD provided hemodynamic support by unloading the heart with a different mechanism that created a unique profile of physiological changes. These data contribute novel, clinically relevant insight into pediatric mechanical circulatory support and establish an important resource for pediatric device development and patient selection.

Keywords

pediatric heart failure; ventricular assist device; mechanical circulatory support; extracorporeal membrane oxygenation; intra-aortic balloon pump; counterpulsation; continuous flow; pulsatile flow

Introduction

Over the past two decades, mechanical circulatory support has evolved into a standard therapy for adults with advanced heart failure. Multiple devices are commercially available or poised for clinical trials[1]. Yet pediatric mechanical circulatory support has not progressed at the same pace. Venoarterial extracorporeal membrane oxygenation (ECMO) remains the clinical standard to support pediatric patients with heart failure, even if pulmonary pathology is absent. Despite wide implementation of ECMO at tertiary care centers, mortality rates that range from 38 to 73% [2-6] for cardiac-specific indications signify an urgent need to improve this technology or to develop alternative therapies.

To address the paucity of mechanical circulatory support options for pediatric patients, in 2004 the National Heart, Lung, and Blood Institute (NHLBI) sponsored a program to develop novel pediatric VADs[7]. Five contracts were awarded to develop a family of mechanical systems to support infants and children with congenital or acquired heart disease. These included an apically-implantable mixed flow device[8], an apically-implantable continuous-flow device[9], an intravascular mixed flow device[10], a compact extracorporeal cardiopulmonary assist system[11], and an implantable pulsatile device[12]. Preclinical evaluation of four of these devices is underway as part of the NHLBI Pumps for Kids, Infants, and Neonates (PumpKINs) program[13] with clinical trials planned to begin in 2014.

The anticipated arrival of novel pediatric devices raises important clinical questions. ECMO, counterpulsatile, pulsatile-flow, and continuous-flow devices each unload the ventricle(s) by a distinctive mechanism. A better understanding of the pediatric response to different methods of support and a direct comparison to ECMO, the current clinical standard, will help to optimize patient selection and improve clinical outcomes.

With these goals in mind, we characterized (patho)physiological responses to multiple circulatory support strategies in a pediatric model of heart failure. In piglets with acute, ischemic left ventricular dysfunction, ECMO (without atrial septostomy) was compared to either an intra-aortic balloon pump (IABP), a pulsatile-flow (PF)VAD, or a continuous-flow (CF)VAD during maximum support. The primary objective was to establish a systems-based profile of physiological responses for each type of pediatric mechanical circulatory support. The entirety of the data, which include clinical, engineering, and physiological parameters, are presented as a resource to facilitate pediatric device development and patient selection.

Materials and Methods

Study Overview

All animals received humane care and were handled in accordance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). Experimental procedures followed animal study protocols approved by the University of Louisville Institutional Animal Care and Use Committee.

Experimental Design

Yorkshire piglets ($n=47$, 11.7 ± 2.6 kg) were surgically instrumented to determine left ventricular, right ventricular, coronary, carotid, systemic arterial, and pulmonary arterial hemodynamics, MVO_2 , and VO_2 , and end-organ blood flow with neutron-activated $15\ \mu\text{m}$ microspheres. Sequential coronary ligation was performed to induce acute, ischemic left ventricular dysfunction. In each animal, an ECMO circuit and either an IABP, PFVAD, or CFVAD were implanted. Group 1 animals underwent ECMO vs. IABP support. Group 2 animals underwent ECMO vs. PFVAD support. Group 3 animals underwent ECMO vs. CFVAD support. The experimental timeline is outlined in Figure 1.

In each animal, hemodynamics (15 second epochs), blood gas, and end-organ blood flows were measured at steady-state conditions during normal baseline (prior to coronary ligation), heart failure, VAD support (IABP or PFVAD or CFVAD), and ECMO support without atrial septostomy or an atrial drain. The ECMO circuit was operated at maximum support achieved without causing collapse of the inflow bladder bag. As such, the experimental setup most closely simulated ECMO placement in an emergent setting. In animals with an IABP, measurements were recorded during 1:1 counterpulsation. Balloon inflation and deflation were timed to maximize aortic diastolic pressure augmentation and minimize aortic end-diastolic pressure. In animals with a PFVAD, measurements were recorded during asynchronous and synchronous 1:1 support. In animals with a PFVAD or CFVAD, measurements were recorded during maximum support without causing atrial collapse and suction events.

Surgical Preparation

Animals were fasted, preanesthetized with intramuscular ketamine (30 mg/kg) and acepromazine (0.2 mg/kg) and anesthetized with isoflurane (1.5 to 3%) and room air. A left lateral thoracotomy was performed and the right carotid artery and jugular vein were exposed through a neck incision. Single-tip, high-fidelity micromanometer catheters (Millar Instruments, Houston, TX) were placed in the pulmonary artery and left atrium. A dual-tip, high-fidelity micromanometer catheter (Millar Instruments, Houston, TX) was advanced retrograde from the aorta into the left ventricle. Transit-time ultrasonic flow probes (Transonics, Ithaca, NY) were placed around the left anterior descending (LAD) coronary artery, left carotid artery, aortic root, and pulmonary artery to measure volumetric blood flows. Blood sampling catheters were introduced into the right carotid artery, pulmonary artery, and coronary sinus to sample blood and measure blood gases. An infusion catheter was introduced into the left atrium for serial injections of microspheres to determine end-organ blood flows. A blood-sampling catheter was introduced into the femoral artery for simultaneous withdrawal of a microsphere reference blood-flow sample.

The animal was anticoagulated with a bolus injection of heparin (300 units/kg) and subsequent small boluses of heparin to maintain an ACT greater than 300 seconds. An ECMO circuit (CAPIOX SX 10 Oxygenator, Terumo, Somerset, NJ) as well as either an IABP (Group 1, IABP, $n=19$, 12.6 ± 1.7 kg), a PFVAD (Group 2, $n=18$, 9.5 ± 2.3 kg), or a CFVAD (Group 3, $n=12$, 13.0 ± 2.1 kg) were connected to each animal. Figure 2A-C

demonstrates the surgical configuration in each group. For ECMO support, an inflow cannula (10, 12, or 14 French, Biomedicus, Medtronic, Minneapolis, MN) was introduced via the right external jugular vein into the right atrium. A 5 or 7 cc IABP (Datascope, Fairfield, NJ) was introduced via the right femoral artery into the descending thoracic aorta. Balloon inflation and deflation timing were manually adjusted based on the high-fidelity aortic-root waveform displayed on the IABP console (System 97, Datascope, Fairfield, NJ). A PFVAD (University of Utah Infant Ventricular Assist Device, Artificial Heart Research Laboratory, Salt Lake City, UT) with an 18 or 20 Fr inflow cannula (Research Medical, Edwards Lifesciences, Midvale UT) was introduced into the left atrium. A CFVAD (BP-50 Bio-Pump®, Biomedicus, Medtronic, Minneapolis, MN) with an 18 or 20 Fr inflow cannula (Research Medical, Edwards Lifesciences, Midvale UT) was introduced into the left atrium. An outflow cannula (14 or 16 Fr, Research Medical, Edwards Lifesciences, Midvale UT) was inserted into the descending aorta and used for ECMO as well as PFVAD or CFVAD outflow return to the systemic circulation. A transit-time ultrasonic flow probe (Transonics, Ithaca, NY) was placed around the outflow cannula to measure flow through each device.

Induction of Heart Failure

Intravenous lidocaine (20 mg bolus, 20 mg/hour infusion) and esmolol (5 mg/kg bolus, 50 µg/kg/min infusion) were administered to prevent arrhythmia. Sequential coronary ligation (3.8 ± 1.8 ligations, range 1 to 8 ligations) of branches of the left anterior descending (LAD) coronary artery induced acute, ischemic left ventricular failure. Target cardiac dysfunction was achieved when three of four criteria were met: approximate reduction of 1) left ventricular cardiac output by 25%, 2) mean aortic pressure by 10 mmHg, 3) mixed venous O₂ saturation by 10%, and/or 4) an elevation of left atrial pressure (LAP) by 5 mmHg. Animals with life-threatening hypotension were supported with boluses of intravenous normal saline and continuous infusion of phenylephrine and/or epinephrine to effect.

End-Organ Blood Flow Measurements

During each experimental condition, a separate color (isotope label) of 15 µm neutron-activated microspheres (Biopal, Worcester, MA) was injected into the left atrium, and a reference blood sample was simultaneously withdrawn from the femoral arterial line. The microsphere technique enabled the precise measurement of regional end-organ blood flow. During microsphere injection, a reference blood-flow sample was withdrawn from the femoral artery at a rate of 4 ml/min for 60 seconds with a calibrated syringe pump (Harvard Apparatus, Holliston, MA) in order to determine organ specific flows in milliliters per minute per gram of tissue (ml/min/g) as previously described[14].

Blood Gas Analysis

During each experimental condition, blood samples were simultaneously withdrawn from the right carotid artery, pulmonary artery, and coronary sinus. Samples were processed with a blood gas analyzer (IRMA_{SL} Blood Analysis System, Diametrics Medical, Roseville, MN) to measure hemoglobin content ([Hb] g/dL) and hemoglobin oxygen saturation (% O₂ Sat). Oxygen content ([O₂]) was calculated for each blood sample:

$$[O_2] = \frac{\%O_2\text{Sat} \times [Hb] \times O_2\text{capacity of Hb (1.34 ml O}_2\text{/g)}}{100} = [\text{ml O}_2\text{/100 ml}]$$

Total myocardial oxygen consumption (MVO₂) was calculated as:

$$MVO_2 = ([O_2]_a) - ([O_2]_{cs}) \times MBF = [ml\ O_2/min/100g]$$

$[O_2]_a$ =arterial oxygen content, $[O_2]_{cs}$ =coronary sinus oxygen content, and MBF=total myocardial blood flow as determined by the microsphere method

Whole body oxygen consumption (VO_2) was calculated as:

$$VO_2 = ([O_2]_a) - ([O_2]_v) \times (LVCO + VADF) = [ml\ O_2/min]$$

$[O_2]_a$ =arterial oxygen content, $[O_2]_v$ =mixed venous oxygen content, LVCO=left ventricular cardiac output, VADF=ventricular assist device flow (VADF=0 during baseline, heart failure, and IABP conditions)

Necropsy and Microsphere Analysis

After completion of the experimental protocol, animals were euthanized. The heart, lungs, kidneys, brain, pancreas, liver, spleen, and adrenal glands were harvested and weighed. Tissue and reference blood samples were sent to BioPAL, Inc. (Worcester, MA) for radioactive assay and automated calculation of blood flow in ml/min/g for each vascular bed during each experimental condition.

Instrumentation, Data Reduction, and Statistics

All transducers were pre- and post-calibrated against known physical standards to ensure measurement accuracy. Collected data were signal conditioned and A/D converted at a sampling rate of 400 Hz for digital analysis using our GLP compliant data acquisition system[15].

Hemodynamic parameters were calculated on a beat-to-beat basis for each 15 second data set with the Hemodynamic Evaluation and Assessment Research Tool (HEART) program[16] developed in Matlab (Version 6.5, MathWorks, Natick, MA). All analyzed beats in each data set (approximately 20 to 30 beats) were averaged to obtain a single representative mean value for each calculated parameter.

Pressure and flow waveforms were used to derive the following hemodynamic parameters: heart rate (HR), left ventricular (LV) stroke volume (SV), LV cardiac output (LVCO), LV pressure (LVP), LV $\pm dP/dt$, left ventricular external work (LVEW), aortic pressure (AoP), left atrial pressure (LAP), LAD flow (LADF), aortic flow (AoF), systemic vascular resistance (SVR), carotid artery flow (CarotidF), VAD flow (VADF), right ventricular (RV) SV, RV cardiac output (RVCO), pulmonary artery pressure (PAP), pulmonary vascular resistance (PVR). Rate-pressure product, an index of cardiac metabolic demand[17], was calculated as the product of HR and $LVP_{peak-systolic}$. Total arterial flow during VAD and ECMO support was calculated as the sum of LVCO and $VADF_{mean}$. $LADF_{mean}$ normalized to LVEW was used as an index of the left ventricular blood supply/demand relationship[18]. Total myocardial blood flow (MBF_{total}, as determined by microspheres) normalized to MVO_2 was used as an index of the global myocardial oxygen supply/demand relationship. Additional measured parameters were included in Supplemental Tables 1-3.

Prism version 4.00 (GraphPad, La Jolla, CA) was used to perform statistical analyses and to plot data. To verify the induction of a clinically relevant state of heart failure, two-tailed paired student t-tests were used to compare baseline and heart failure conditions. One-way repeated measures ANOVA with Tukey post-test for comparison of means were performed to compare heart failure, VAD support mode(s), and ECMO for each parameter within each

of the three groups of animals. A $p < 0.05$ (95% confidence) was considered statistically significant. All data were presented as mean $\pm$ standard error.

Results

Model of Pediatric Heart Failure

Of the 47 piglets studied, 26 (Group 1 $n=10$, Group 2 $n=10$, Group 3 $n=6$) completed the experimental protocol. In these animals, LAD ligation produced ischemic cardiac dysfunction with many phenotypic similarities to clinical heart failure. In aggregate, animals exhibited an approximate reduction in LADF_{mean} by 40% (21 ± 1 to 13 ± 1 ml/min, $p < 0.0001$), LVCO by 25% (1.94 ± 0.13 to 1.43 ± 0.12 L/min, $p < 0.0001$), AoP_{mean} by 10 mmHg (65 ± 2 to 54 ± 2 mmHg, $p < 0.0001$), mixed venous O₂ saturation by 20% (84 ± 2 to $67 \pm 3\%$, $p < 0.0001$), renal blood flow by 40% (left kidney: 1.47 ± 0.21 to 0.89 ± 0.09 ml/min/100g, $p < 0.01$; right kidney: 1.51 ± 0.19 to 0.90 ± 0.10 ml/min/100g, $p < 0.01$), and an increased LAP_{mean} by approximately 3 mmHg (9 ± 1 to 12 ± 1 , $p < 0.0001$). The remaining 21 animals died prior to completion of the protocol, typically from intractable arrhythmia. Data from animals that did not complete the experimental protocol were not included in the analysis.

IABP vs. ECMO

IABP support produced significant ($p < 0.05$) suprasystolic diastolic augmentation (Figure 2F, G) but did not improve arterial flows, left ventricular filling pressures, or left ventricular workload (Table 1, Table 2). LADF normalized to LVEW, an index of the left ventricular blood supply/demand relationship, did not change (Table 1). Similarly, MBF_{total} normalized to MVO₂, an index of the global blood supply/demand relationship throughout the heart, did not change. In contrast, ECMO support restored arterial flows to near baseline values and significantly reduced left ventricular filling pressures and left ventricular workload (Table 1, Table 2). Although LADF did not return to baseline values, LADF normalized to LVEW increased significantly (Table 1). However, with ECMO support MVO₂ increased to a greater extent than MBF_{total}, which resulted in an unchanged global myocardial oxygen supply/demand relationship. A significant increase in HR was observed during ECMO but not IABP support.

IABP support did not change RVCO, PVR, or PAPs (Table 2). In contrast, the significant decrease in RVCO during ECMO support resulted in significant increases in PAP_{mean} and PAP_{diastolic} via a dramatic, significant increase in PVR (Table 2).

IABP support did not change AoP_{mean} or AoP_{systolic} but significantly reduced AoP_{diastolic} and restored a normal AoP_{pulse}. In contrast, ECMO support significantly increased AoP_{diastolic} but not AoP_{mean}, AoP_{systolic}, or AoP_{pulse} (Table 3).

IABP support did not change CarotidF_{mean}. However, CarotidF_{pulse} was significantly greater during IABP support than during heart failure or ECMO support. In contrast, ECMO support restored CarotidF_{mean} to baseline values. However, CarotidF_{pulse} was significantly and dramatically reduced and indicated a near continuous-flow blood flow pattern to the head. Importantly, during IABP but not ECMO support, carotid steal[19], a brief flow reversal, was noted in the carotid artery and was likely due to the large reduction in AoP_{diastolic} caused by rapid deflation of the IABP (Supplemental Table 3).

IABP support significantly improved cerebral, cerebellar, and pulmonary blood flow versus ECMO. In contrast, during ECMO support, significant reductions in cerebellar and pulmonary blood flow were noted. Neither IABP nor ECMO support altered VO₂ (Table 4).

PFVAD vs. ECMO

Asynchronous and synchronous 1:1 PFVAD support significantly reduced LV filling pressures and left ventricular workload to a similar degree as during ECMO support (Table 1, Table 2). Significant improvements were also noted for LADF normalized to LVEW during PFVAD and ECMO support (Table 1). Importantly, asynchronous and 1:1 synchronous PFVAD support significantly improved MBF_{total}/MVO₂ (Table 1). In contrast, during ECMO support MBF_{total}/MVO₂ did not change. A significant increase in HR was observed during ECMO support, whereas HR did not change during PFVAD support.

Asynchronous and synchronous 1:1 PFVAD support significantly improved RVCO over ECMO, and did not affect PVR, or PAPs (Table 2). In contrast, the significant decrease in RVCO during ECMO support resulted in significant increases in PAP_{mean} and PAP_{diastolic} via a dramatic, significant increase in PVR (Table 2).

Neither asynchronous nor synchronous 1:1 PFVAD support changed AoP_{mean}, AoP_{systolic}, or AoP_{diastolic}. However, a near normal AoP_{pulse} was maintained. In contrast, ECMO support significantly increased AoP_{diastolic} but not AoP_{mean} or AoP_{systolic}. During ECMO support, AoP_{pulse} was significantly reduced from heart failure values (Table 3).

Asynchronous and synchronous 1:1 PFVAD support and ECMO improved CarotidF_{mean} to baseline values. CarotidF_{pulse} did not change from baseline during PFVAD support. In contrast, during ECMO support CarotidF_{pulse} significantly and dramatically decreased (Table 3).

Asynchronous and synchronous 1:1 PFVAD support did not change end-organ blood flow. During asynchronous support, cerebellar and pulmonary blood flow were significantly greater than during ECMO support. Neither PFVAD nor ECMO support altered VO₂ (Table 4).

CFVAD vs. ECMO

CFVAD support increased arterial flows above baseline and significantly reduced LV filling pressures and left ventricular workload greater than during ECMO support (Table 1, Table 2). A large but non-significant increase that may have been due to the small sample size was noted for LADF normalized to LVEW during CFVAD and ECMO support (Table 1). Importantly, CFVAD support restored MBF_{total}/MVO₂ to baseline values (Table 1). In contrast, ECMO did not change MBF/MVO₂. A significant increase in HR was observed during ECMO support, whereas HR did not change during CFVAD support.

CFVAD support did not change RVCO. PVR and PAPs did not change versus heart failure but were significant versus ECMO (Table 2). In contrast, the significant decrease in RVCO during ECMO support resulted in significant increases in PAP_{mean} and PAP_{diastolic} via a dramatic and significant increase in PVR (Table 2).

CFVAD support significantly improved AoP_{diastolic}. However, AoP_{systolic} decreased, and AoP_{mean} did not change. As a result, the AoP_{pulse} was significantly reduced. In contrast, ECMO support significantly improved AoP_{diastolic} but not AoP_{mean} or AoP_{systolic}. AoP_{pulse} was not reduced to the same degree as during CFVAD support (Table 3).

Neither CFVAD nor ECMO support changed CarotidF_{mean}. However, CarotidF_{pulse} was significantly reduced during CFVAD and ECMO support (Table 3).

Neither CFVAD support nor ECMO changed end-organ blood flow or VO₂ (Table 4).

Discussion

These data represent the most comprehensive experimental evaluation of pediatric VADs to date. We measured cardiac and systemic physiological parameters during ECMO, IABP, PFVAD, and CFVAD support in a piglet model of ischemic, left ventricular failure. In comparison to heart failure, the most notable and statistically significant findings included: 1) improved left ventricular blood supply/demand ratio during PFVAD, CFVAD, and ECMO but not IABP support, 2) improved global myocardial blood supply/demand ratio during PFVAD, and CFVAD but not IABP or ECMO support, and 3) diminished pulsatility during ECMO and CFVAD but not IABP and PFVAD support. Each method of support unloaded the heart by a different mechanism that created unique physiological changes. We speculate that a unique profile of physiological changes associated with each device-type has important implications for device development, control algorithms, patient selection, patient management, and clinical outcomes. The following discussion highlights the advantages and disadvantages of each mechanism of support as indicated by this investigation.

ECMO Support

Venoarterial ECMO bypasses the heart and lungs and provides non-pulsatile, volumetric unloading of both ventricles while oxygenating the blood. Clinically, blood is removed from the right atrium, oxygenated, and returned to the aorta. In this study, the major benefits were a significantly improved left ventricular blood supply/demand relationship and increased systemic blood flows. Limitations included an invasive mode of support, diminished pulsatility, increased PVR, and pulmonary hypertension. Importantly, the global myocardial blood supply/demand relationship, which included right ventricular blood flow and oxygen consumption, did not improve because of significantly increased right ventricular myocardial metabolic demands. Intentional left atrial decompression was not performed. Although LAP increased significantly after coronary ligation, LAP did not reach critical values (~18 mmHg) that would meet the clinical criteria for left atrial septostomy or an atrial drain, common strategies to relieve elevated filling pressures during pediatric ECMO support. As such, increased right ventricular afterload likely was not responsible for elevated myocardial metabolic demands during ECMO support, which may have instead been the consequence of an elevated heart rate, elevated left ventricular peak systolic pressure, and elevated aortic systolic pressure.

Of note, ECMO support significantly increased PVR and PAPs. In most tissues, hypoperfusion triggers hypoxic vasodilation to improve flow. However, in the lungs, paradoxical hypoxic *vasoconstriction* occurs to reroute blood to ventilated regions of lung. Our data demonstrated that during ECMO support, right atrial unloading decreased right ventricular preload and significantly reduced pulmonary arterial flow, which may have triggered hypoxic vasoconstriction and elevated PVR and PAPs. This finding may have important implications for the clinical management of cardio-respiratory failure, especially in patients with pulmonary hypertension.

Nevertheless, ECMO remains the most common approach to salvage the failing pediatric cardiopulmonary system. Yet ECMO is only suitable for days to weeks of support, and only 50% of patients survive to hospital discharge[5]. An ECMO circuit precludes ambulatory therapy, and the large artificial surface area of the oxygenator predisposes to bleeding, thromboembolic, and immune-related complications. As a result, the waiting time for a pediatric cardiac allograft often exceeds the useful duration of ECMO support. Consequently, ECMO may be appropriate as a bridge to decision, but alternative pediatric mechanical circulatory support options are urgently needed for long-term therapy.

IABP Support

In adults, IABP counterpulsation reduces aortic afterload and increases myocardial blood flow by augmenting diastolic blood pressure. In this study, benefits included a minimally invasive approach, diastolic augmentation, afterload reduction, and preservation of native pulsatility. The major limitation was that IABP counterpulsation is a partial-support modality that is insufficient for life-threatening circulatory decompensation or prolonged support.

Pediatric IABPs (2.5 to 20 ml) are clinically available[20]. Timing of an IABP in pediatric patients is extremely important and is best accomplished with M-mode echocardiography[21]. A recent meta-analysis reported 68% survival to discharge with pediatric IABP support[20]. Importantly, IABP implantation does not require major surgery. However, the patient must remain supine and sedated during support and is thereby susceptible to numerous complications. As a result, when IABP therapy is employed for greater than 20 days, vascular complications, bleeding, and infection occur frequently and are associated with increased mortality[22].

Pulsatile-Flow Support

PFVADs mimic native heart function with alternating systole and diastole to provide volumetric unloading of the failing left ventricle while maintaining pulsatile blood flow. In this study, benefits included a greatly improved left ventricular and global myocardial blood supply/demand relationship, preservation of pulsatility, and improved end-organ blood flow in select vascular beds. The major limitation was an invasive mode of support. Of note, significant differences were not observed between asynchronous and synchronous 1:1 support modes, which may simplify device management in patients with arrhythmia in whom an electrocardiographic trigger is unreliable.

The Berlin Heart EXCOR Pediatric VAD (Berlin Heart AG, Berlin, Germany), an pneumatically-driven extracorporeal PFVAD, is clinically available in the United States. Survival was recently reported at 88% vs 75% for ECMO support[23], which further supports the use of VAD therapy over ECMO in pediatric patients.

Continuous-Flow Support

CFVADs provide continuous, volumetric unloading of the failing ventricle. In this study, benefits included an improved left ventricular and global myocardial blood supply/demand relationship and significantly reduced pulmonary arterial and left ventricular filling pressures. Limitations included an invasive mode of support, severely diminished arterial pulsatility, and reduced end-organ blood flow.

The DeBakey VAD Child (MicroMed Technology, Inc. Houston, TX), an axial-flow CFVAD, is clinically available under a Humanitarian Device Exemption as a bridge to cardiac transplantation in children (body surface area 0.7 to 1.5 m²)[24]. More recently, the HeartWare HVAD (HeartWare, Miami, FL), a compact adult centrifugal-flow VAD, was successfully implanted in seven children (6 to 16 years old) as a bridge to transplant[25]. However, a CFVAD for infants and small children is not yet available.

The clinical relevance of pulsatility during mechanical circulatory support is unclear[26, 27]. Studies have demonstrated the superiority of pulsatile over non-pulsatile flow during cardiopulmonary bypass in pediatric patients[28, 29] and pediatric animal models[28, 30]. Despite the abundance of evidence in favor of pulsatile perfusion, a debate over which mode of support is better still exists. Indeed, separate investigators have reported no difference between continuous and pulsatile blood flow in pediatric patients[27, 31]. It remains to be

determined whether pulsatile flow is physiologically superior to continuous flow in pediatric patients during prolonged support.

Clinical Implications

Reliable long-term circulatory support for children remains a major unmet need in pediatric cardiology. Prior to 2000, pediatric-specific VADs were not used in North America as a bridge to cardiac transplantation[32]. The field consisted of a few small case series of oversized, adult devices in adolescent patients[33]. More recently, the field of pediatric VADs has expanded[4, 32]. Between 2003 and 2006, the number of compassionate appeals to the FDA for permission to use the Berlin Heart increased by 1,667%[13]. During this period, it was shown that mechanical circulatory support decreased cardiac transplant waiting-list mortality and improved organ utilization in children[34]. Significant federal resources were allocated to the development of pediatric devices. In 2004, the NHLBI awarded 5 contracts for a total of \$22.4 million to develop pediatric devices. In 2010, the PumpKIN program was established to conduct the clinical evaluation of these devices[13].

In parallel, reports have demonstrated better outcomes with VAD support versus ECMO in pediatric patients[23, 35-37]. Support with a VAD provides inherent advantages that include early extubation and ambulation, oral feeding, easier transportation, less anticoagulation and consumption of blood products[38], and reduced risk of infection and patient sensitization[39]. Furthermore, the plasticity of the pediatric heart may promote a higher rate of myocardial recovery than in adults, and potential for recovered patient-years is high[40].

Improved outcomes and the federal commitment to the development of novel pediatric VADs herald multiple mechanical options to manage pediatric heart failure. Each device entails unique surgical and physiological considerations and offers benefits and drawbacks for the patient and the physician. As the field advances, it becomes important to consider how device implantation, mechanism of action, organ-specific responses, hemocompatibility, potential for myocardial recovery, as well as human factors such as quality of life during support contribute to long-term outcomes. Preclinical studies that examine the *chronic* effects of mechanical unloading of the failing pediatric heart may be an appropriate next step.

Limitations

These experiments were not designed to directly compare the effects between IABP, PFVAD, and CFVAD support but rather each support mode versus ECMO. The severity of heart failure and responses to different types of support were variable between animals and groups. Variable responses may have been related to the complexity of the experimental and clinical presentation of pediatric heart failure as well as the different surgical configuration of each type of support—the intraaortic position of the IABP, the left atrial inflow of the PFVAD and CFVAD, and the right atrial inflow of the ECMO circuit. The experimental setup simulated mechanical circulatory support in an emergent setting, not during chronic support. As such, these data reflect fundamental changes that may occur during the initiation of support and may only be extrapolated to prolonged support with caution. Our model also did not recreate the unique hemodynamic imbalances observed with complex congenital heart defects. As such, our results are most relevant for hemodynamic impairment with a failing four-chambered heart as occurs in Kawasaki's cardiomyopathy, viral myocarditis, or anthracycline cardio-toxicity.

A potential limitation was the small number of animals in the CFVAD vs. ECMO analysis (n=6). When few animals are studied, there is a risk that observed effects could be driven by chance findings in one or two animals (type I statistical error). Encouragingly, all animals

demonstrated consistent and highly statistically significant changes. Nonetheless, due to the small sample size, we may have failed to detect important effects (type II statistical error). Multiple borderline statistically significant p-values from this analysis suggested that this was the case.

Limitations notwithstanding, this study contained major strengths that included a clinically relevant animal model, numerous overlapping measurements, and investigation of multiple pediatric mechanical circulatory support strategies.

Conclusions

Reliable long-term circulatory support for children remains a major unmet need in pediatric cardiology. To date, these data represent the most comprehensive experimental evaluation of mechanical circulatory support in a pediatric model of cardiac failure and establish an important resource for clinicians, investigators, government agencies, and industry for further pediatric device development and patient selection. Strengths and weaknesses of each circulatory support technique were identified. Additional preclinical studies are needed to further refine the clinical utility of long-term pediatric mechanical circulatory support.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

The timeline of each experimental protocol is outlined. IABP, intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; PFVAD, pulsatile-flow ventricular assist device; CFVAD, continuous-flow ventricular assist device. Coronary ligation produced acute ischemic left ventricular dysfunction prior to evaluation of different modes of pediatric mechanical circulatory support.

Figure 2.

A-C: Schematic illustrations demonstrate the surgical configuration for each experimental comparison between an (A) intraaortic balloon pump (IABP), a (B) pulsatile-flow ventricular assist device (PFVAD), or a (C) continuous-flow ventricular assist device (CFVAD), and extracorporeal membrane oxygenation (ECMO) in a piglet model of acute, ischemic heart failure. In Group 1 (IABP vs. ECMO), the IABP was introduced via the femoral artery and advanced into the descending thoracic aorta. In Group 2 (PFVAD vs. ECMO) and group 3 (CFVAD vs. ECMO), the VAD inflow cannula was implanted in the left atrium and the outflow cannula was implanted in the descending thoracic aorta. In groups 1, 2, and 3, the ECMO inflow cannula was inserted into the jugular vein and advanced into the right atrium, and the outflow went to the cannula in the descending thoracic aorta. **D-K:** Example waveforms of aortic pressure (AoP), aortic flow (AoF), carotid flow (CarotidF), left anterior descending coronary artery flow (LADF), and VAD flow (VADF) are shown at baseline, during heart failure, and during each mode of support.

Cardiac Mechanoenergetics

Table 1

	LAF (ml/min/g)	RAF (ml/min/g)	RVF (ml/min/g)	LVF (ml/min/g)	MBF _{total} (ml/min/g)	LAD _F mean (ml/min)	LVEW (mmHg-ml)	HRxLVP _{peak} - systolic (bpm-mmHg)	MVO ₂ (ml O ₂ /min/100g)	LAD _F mean/LVEW (ml/min/mmHg-ml)	MBF _{total} /MVO ₂ (ml/min/100g/ml O ₂ /min)
n=8						n=10	n=10	n=9			
ANOVA p-value	p<0.05	p<0.05	p<0.01	p<0.05	p<0.05	p=0.23	p=0.18	p=0.08	p=0.07	p<0.01	p=0.32
Baseline	0.79±0.17	0.75±0.17	0.91±0.14	0.93±0.15	0.92±0.13	26±4	1.558±157	8.694±617	1.58±0.29	0.0166±0.0018	0.64±0.11
Heart Failure	0.32±0.07 [*]	0.38±0.05 [*]	0.59±0.05 [*]	0.41±0.04 [*]	0.58±0.13	16±3 [*]	858±117 [*]	6.540±573 [*]	1.65±0.38	0.0194±0.0023	0.38±0.05 [*]
1:1 IABP	0.39±0.09	0.52±0.08	0.72±0.11 [‡]	0.51±0.09	0.64±0.12	19±3	899±130	6.652±517	1.68±0.32	0.0230±0.0036 [‡]	0.44±0.08
ECMO	0.66±0.22 [‡]	1.20±0.39 [‡]	1.75±0.41 [‡]	0.87±0.24 [‡]	1.08±0.25	19±3	696±182	7.883±814	3.72±1.08	0.0350±0.0050 [‡]	0.33±0.03
n=9						n=10	n=9				
ANOVA p-value	p<0.05	p<0.05	p<0.01	p<0.001	p<0.001	p=0.10	p<0.0001	p<0.0001	p<0.01	p<0.01	p<0.01
Baseline	0.68±0.14	0.68±0.18	0.64±0.12	0.55±0.10	1.32±0.69	16±2	852±65	7.996±510	2.59±0.70	0.0191±0.0044	0.30±0.03
Heart Failure	0.42±0.08 [*]	0.59±0.14	0.46±0.08	0.39±0.07 [*]	0.44±0.07	9±2 [*]	574±61 [*]	5.968±495 [*]	2.03±0.42	0.0152±0.0028	0.28±0.04
Asynchronous	0.63±0.17	0.59±0.15	0.58±0.11 [‡]	0.44±0.08 [‡]	0.57±0.11 [‡]	11±2	263±60 [‡]	5.634±749 [‡]	1.48±0.39 [‡]	0.0346±0.0085 [‡]	0.45±0.08 [‡]
1:1 Synchronous	0.51±0.12	0.64±0.17	0.53±0.08 [‡]	0.39±0.07 [‡]	0.47±0.06 [‡]	12±2	237±53 [‡]	5.089±719 [‡]	1.25±0.25 [‡]	0.0410±0.0099 [‡]	0.49±0.07 [‡]
ECMO	1.05±0.36 [‡]	1.57±0.61	1.34±0.32 [‡]	0.98±0.21 [‡]	1.54±0.35 [‡]	13±3	314±91 [‡]	8.050±833 [‡]	4.27±1.15 [‡]	0.0400±0.0071 [‡]	0.38±0.07
n=6						n=6	n=6	n=6			
ANOVA p-value	p=0.22	p=0.11	p<0.05	p<0.05	p<0.05	p=0.73	p=0.05	p<0.05	p=0.07	p=0.29	p=0.16
Baseline	0.44±0.07	0.33±0.07	0.73±0.15	0.64±0.04	0.66±0.05	24±4	1.518±146	8.470±351	1.60±0.44	0.0145±0.0023	0.53±0.10
Heart Failure	0.35±0.14	0.54±0.21	0.83±0.17	0.51±0.08	0.58±0.10	13±4 [*]	1.057±267	7.053±535	2.93±0.93	0.0120±0.0027	0.25±0.04 [*]
Continuous Flow	0.25±0.06	0.43±0.06	0.48±0.10 [‡]	0.27±0.05 [‡]	0.31±0.06 [‡]	11±3	288±127 [‡]	5.700±506 [‡]	1.07±0.34	0.0626±0.0400	0.50±0.18
ECMO	0.77±0.36	1.78±0.75	2.7±0.95	1.33±0.42	1.64±0.53	12±3	550±161	8.859±963	10.39±5.15	0.0266±0.0076	0.27±0.05

IABP, intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; LAF, left atrial flow; RAF, right atrial flow; RVF, right ventricular flow; LVF, left ventricular flow; LAD_F, left anterior descending (coronary artery) flow; LVEW, left ventricular external work; HR, heart rate; LVP, left ventricular pressure; MVO₂, total myocardial oxygen consumption.

^{*} p<0.05, heart failure vs. baseline;

[‡] p<0.05, support mode vs. heart failure;

[‡] p<0.05, support mode vs. ECMO.

Cardiac Hemodynamics

Table 2

n=10														
ANOVA p-value	LCO (L/min)	VADF _{mean} (L/min)	VADF _{mean} +LYCO (L/min)	LYSV (ml)	HR (bpm)	LAP _{mean} (mmHg)	LVP _{end-diastolic} (mmHg)	LVP _{peak} systolic (mmHg)	+dP/dt (mmHg/s)	-dP/dt (mmHg/s)	RVCO (L/min)	RVSV (ml)	PVR (dyne-s/cm ⁵)	PAP _{mean} (mmHg)
	p=0.08	---	p=0.08	p<0.01	p<0.00	p<0.01	p<0.01	p=0.41	p=0.37	p=0.68	p<0.001	p<0.0001	p<0.001	p=0.07
Baseline	2.39±0.18	---	2.39±0.19	22±1	107±4	9±1	9±1	81±4	947±91	1445±97	2.51±0.24	23±2	830±118	23±1
Heart Failure	1.75±0.16*	---	1.75±0.16*	17±1*	104±3	12±1*	14±1*	62±4*	716±83*	934±93*	1.65±0.13*	16±1*	1,271±126*	23±2
1:1 IABP	1.78±0.17	---	1.78±0.17	17±1 [‡]	107±3 [‡]	11±1	13±2	62±4	792±80	-969±98	1.86±0.20 [‡]	17±2 [‡]	1,107±102 [‡]	24±1 [‡]
ECMO	1.30±0.32	0.91±0.06	2.22±0.33	11±3 [‡]	116±3 [‡]	8±1 [‡]	8±2 [‡]	68±6	682±117	-1021±138	0.97±0.21 [‡]	9±2 [‡]	3,913±846 [‡]	37±3
														30±2 [‡]
														24±2 [‡]
														5±1
n=9														
ANOVA p-value	p<0.0001	p=0.07	p=0.08	p<0.000	p<0.00	p<0.000	p<0.05	p<0.01	p=0.15	p<0.0001	p<0.000	p<0.05	p=0.10	p=0.87
Baseline	1.56±0.10	---	1.36±0.10	14±1	99±5	9±1	81±4	860±57	1290±73	1.43±0.13	14±1	517±59	17±1	4±1
Heart Failure	0.96±0.08*	---	0.96±0.08*	11±±1*	87±5	12±2	69±5*	624±41*	978±97*	0.99±0.09*	11±1*	713±47*	18±2	5±1
Asynchronous ₈	0.48±0.11 [‡]	0.67±0.03	1.14±0.13	5±1 [‡]	92±5 [‡]	5±1 [‡]	61±8	484±48 [‡]	805±133	1.21±0.14 [‡]	13±1 [‡]	580±47 [‡]	15±2	5±1
1:1 Synchronous	0.45±0.09 [‡]	0.72±0.05	1.17±0.12	5±1 [‡]	93±5 [‡]	4±1 [‡]	56±8 [‡]	467±38 [‡]	845±150	1.22±0.15 [‡]	13±2 [‡]	698±180	16±2	4±1
ECMO	0.52±0.15 [‡]	0.60±0.06	1.14±0.16	5±1 [‡]	112±8 [‡]	7±2 [‡]	73±7	687±83	975±149	0.55±0.15 [‡]	5±1 [‡]	3,153±1,319	23±4	4±1
														21±6
n=6														
ANOVA p-value	p=0.17	---	p=0.50	p=0.11	p<0.01	p=0.07	p=0.05	p<0.05	p<0.01	p<0.01	p<0.01	p<0.0001	p<0.0001	p=0.23
Baseline	2.14±0.23	---	2.14±0.23	22±2	98±4	11±1	13±4	885±48	1340±83	2.14±0.20	885±203	22±2	32±2	5±1
Heart Failure	1.70±0.29	---	1.69±0.29	18±3*	96±4	13±2*	15±3	707±89	1037±83	1.71±0.28	1044±51	21±2	29±3	5±1

n=6																	
n=6	ANOVA p-value	p=0.17	---	p=0.50	p=0.11	p<0.01	p=0.07	p<0.05	p=0.05	p<0.05	p<0.01	p<0.01	p<0.01	p<0.001	p<0.001	p=0.23	
Continuous Flow		0.96±0.53	1.39±0.26	2.36±0.73	9±5	99±44 [‡]	6±1	6±3 [‡]	58±5 [‡]	390±54 [†] [‡]	576±77 [†] [‡]	1.72±0.23 [‡]	17±2 [‡]	18±2 [‡]	27±2 [‡]	10±2 [‡]	4±1
ECMO		0.87±0.19	1.16±0.06	2.03±0.23	8±2	108±3 [‡]	11±3	12±3	81±7	734±113	1050±106	0.80±0.14 [‡]	7±1 [†]	33±4 [†]	41±5 [†]	26±4 [†]	6±1

IABP, intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVCO, left ventricular cardiac output; VADF, ventricular assist device flow; HR, heart rate; LVSV, left ventricular stroke volume; LAP, left atrial pressure; LVP, left ventricular pressure; RVCO, right ventricular cardiac output; PVR, pulmonary vascular resistance; PAP, pulmonary artery pressure; CVP, central venous pressure.

* p<0.05, heart failure vs. baseline;
[†] p<0.05, support mode vs. heart failure;
[‡] p<0.05, support mode vs. ECMO.

Table 3

Arterial Hemodynamics

	LVCO (L/min)	SVR (dyne-s/cm ⁵)	AoP _{mean} (mmHg)	AoP _{systolic} (mmHg)	AoP _{diastolic} (mmHg)	AoP _{pulse} (mmHg)	AoP _{diastolic- augmentation} (mmHg)	CarotidF _{mean} (ml/min)	CarotidF _{pulse} (ml/min)
n=10									
ANOVA p-value	p=0.08	p=0.66	p=0.33	p=0.31	p<0.0001	p<0.01	---	p<0.05	p<0.0001
Baseline	2.39±0.18	2,451±196	67±3	83±4	51±3	32±2	---	184±18	361±33
Heart Failure	1.75±0.16*	2,627±145	53±3*	66±4*	41±2*	24±2*	---	142±19*	368±31
1:1 IABP	1.78±0.17	2,507±132	56±3	64±4	33±3 [‡]	32±1 [‡]	20±1	150±20	578±38 [‡]
ECMO	1.30±0.32	2,739±250	59±5	72±6	50±3 [‡]	22±3	---	183±24 [‡]	23±9 [‡]
n=10									
ANOVA p-value	p<0.0001	p=0.31	p=0.09	p=0.78	p<0.01	p<0.01	---	p<0.05	p<0.0001
Baseline	1.36±0.10	3,927±408	62±3	80±3	45±3	35±3	---	121±13	342±52
Heart Failure	0.96±0.08*	4,671±462*	53±5*	70±5*	40±4	29±2*	---	104±11	337±40
Asynchronous	0.48±0.11 [‡]	5,661±1275	54±5	70±5	43±5 [‡]	27±2 [‡]	---	127±14	363±35 [‡]
1:1 Synchronous	0.45±0.09 [‡]	4,332±657	55±6	68±6	46±6	22±2	---	134±15 [‡]	357±43 [‡]
ECMO	0.52±0.15 [‡]	6,403±1,474	63±6	73±7	56±5 [‡]	17±3 [‡]	---	125±18	188±38 [‡]
n=6									
ANOVA p-value	p=0.17	p=0.99	p=0.17	p=0.12	p<0.01	p<0.001	---	p=0.18	p<0.001
Baseline	2.14±0.23	2,678±401	66±3	87±4	48±3	39±4	---	146±12	384±57
Heart Failure	1.70±0.29	2,918±268	57±4	75±5	42±3	33±3	---	124±17	371±43
Continuous Flow	0.96±0.53	2,876±411	59±4	65±4	57±4 [‡]	9±3 [‡]	---	131±12	76±24 [‡]
ECMO	0.87±0.19	2,928±172	68±8	82±8	58±7 [‡]	24±2	---	163±21	158±43 [‡]

IABP, intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; LVCO, left ventricular cardiac output; SVR, systemic vascular resistance; AoP, aortic pressure; CarotidF, carotid flow.
* p<0.05, heart failure vs. baseline;

[†] p<0.05, support mode vs. heart failure;

[‡] p<0.05, support mode vs. ECMO.

End-Organ Blood Flow

Table 4

n=9	VO ₂ (ml O ₂ /min)	n=8	L Cerebrum (ml/min/g)	R Cerebrum (ml/min/g)	Cerebellum (ml/min/g)	Brainstem (ml/min/g)	L Lung (ml/min/g)	R Lung (ml/min/g)	L Kidney (ml/min/g)	R Kidney (ml/min/g)	Pancreas (ml/min/g)	Liver (ml/min/g)	Spleen (ml/min/g)	L Adrenal (ml/min/g)	R Adrenal (ml/min/g)
ANOVA p-value	p=0.15		p=0.12	p<0.05	p<0.01	p=0.45	p<0.01	p<0.001	p=0.60	p=0.48	p=0.39	p=0.40	p=0.69	p=0.16	p<0.05
Baseline	22.3±4.0		0.31±0.08	0.28±0.07	0.62±0.08	0.42±0.10	1.99±0.48	2.51±0.76	1.69±0.31	2.13±0.45	0.29±0.08	0.52±0.20	1.14±0.22	0.88±0.33	0.83±0.35
Heart Failure	36.2±4.0 *		0.26±0.05	0.24±0.04	0.35±0.03 *	0.39±0.08	0.96±0.20 *	0.98±0.21 *	0.90±0.13 *	1.02±0.18 *	0.22±0.05	0.21±0.06	0.41±0.07 *	0.41±0.04	0.39±0.08
1:1 IABP	35.7±7.6		0.33±0.07	0.30±0.06 ‡	0.43±0.06 ‡	0.38±0.11	1.16±0.24 ‡	1.14±0.23 ‡	1.01±0.15	1.20±0.18	0.19±0.04	0.36±0.08	0.54±0.09	0.62±0.14	0.63±0.13
ECMO	59.0±12.5		0.18±0.06	0.12±0.05	0.18±0.05 †	0.27±0.09	0.27±0.13 †	0.17±0.09 †	0.84±0.17	0.96±0.19	0.31±0.13	0.30±0.13	0.43±0.14	0.97±0.28	1.12±0.25 †

n=9	n=8														
ANOVA p-value	p=0.36	p=0.42	p=0.45	p<0.0001	p=0.48	p<0.05	p<0.05	p=0.76	p=0.20	p=0.15	p=0.23	p=0.32	p=0.09	p=0.19	p<0.05
Baseline	25.6±5.8	0.30±0.10	0.34±0.07	0.63±0.17	0.49±0.12	1.09±0.18	1.43±0.30	1.45±0.50	1.21±0.21	0.18±0.05	0.44±0.15	1.71±0.56	0.85±0.19	0.72±0.17	
Heart Failure	32.1±5.7	0.42±0.09	0.30±0.04	0.51±0.06	0.58±0.12	0.91±0.20	0.93±0.20 *	0.73±0.17	0.70±0.13 *	0.18±0.06	0.30±0.07	0.78±0.21	0.58±0.12	0.58±0.06	
Asynchronous	28.5±5.4	0.56±0.16	0.52±0.09	0.75±0.12 ‡	0.62±0.16	1.21±0.42 ‡	1.55±0.60 ‡	0.87±0.26	0.95±0.22	0.28±0.06	0.44±0.12	1.71±0.61	0.79±0.15	0.69±0.08 ‡	
1:1 Synchronous	29.9±6.2	0.53±0.17	0.45±0.09	0.64±0.10 ‡	0.64±0.15	1.04±0.29	1.31±0.34	0.85±0.21	0.81±0.16	0.23±0.04	0.32±0.05	1.38±0.40	0.95±0.28	0.80±0.11	
ECMO	33.8±7.7	0.42±0.11	0.37±0.17	0.21±0.08 †	0.40±0.21	0.35±0.14	0.39±0.16	0.76±0.18	0.75±0.21	0.32±0.09	0.43±0.09	0.74±0.25	1.55±0.53	1.72±0.48 †	

n=6	n=6														
ANOVA p-value	p=0.98	p=0.38	p=0.49	p=0.63	p=0.46	p=0.51	p=0.76	p=0.20	p=0.15	p=0.23	p=0.32	p=0.24	p=0.69		
Baseline	51.8±10.7	0.21±0.07	0.24±0.07	0.34±0.07	0.26±0.09	1.17±0.39	1.00±0.28	1.20±0.18	1.12±0.17	0.16±0.06	0.30±0.10	0.87±0.39	0.33±0.07	0.28±0.14	
Heart Failure	64.7±21.8	0.45±0.13	0.45±0.14	0.65±0.17	0.48±0.16	0.75±0.21	0.55±0.16	1.10±0.21	1.04±0.27	0.21±0.06	0.17±0.06	0.43±0.15	0.63±0.20	0.54±0.19	
Continuous Flow	60.4±21.3	0.23±0.04	0.24±0.04	0.42±0.05	0.31±0.03	0.43±0.08	0.50±0.19	0.81±0.13	0.67±0.16	0.11±0.04	0.25±0.08	0.28±0.10	0.39±0.07	0.51±0.16	
ECMO	63.4±12.6	0.44±0.26	0.40±0.27	0.48±0.34	0.37±0.18	0.95±0.64	0.42±0.25	1.74±0.66	1.58±0.68	0.30±0.12	0.49±0.30	1.04±0.65	1.09±0.53	0.84±0.56	

IABP, intraaortic balloon pump; ECMO, extracorporeal membrane oxygenation; VO₂, total body oxygen consumption; L, left; R, right.

^{*} p<0.05, heart failure vs. baseline;

[‡] p<0.05, support mode vs. heart failure;

[‡] p<0.05, support mode vs. ECMO.