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Comparison of Vascular Pulsatility in the Native Beating Heart versus Direct Mechanical Ventricular Actuation Support of the Fibrillating Heart

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COMPARISON OF VASCULAR PULSATILITY IN THE NATIVE BEATING
HEART VERSUS DIRECT MECHANICAL VENTRICULAR ACTUATION
SUPPORT OF THE FIBRILLATING HEART

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I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY <u>Nathan Victor Wright</u> ENTITLED <u>Comparison of Vascular Pulsatility in the Native Beating Heart Versus Direct Mechanical Ventricular Actuation Support of the Fibrillating Heart</u> BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF <u>Master of Science in Biomedical Engineering</u>.

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ABSTRACT

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   Most conventional cardiac assist devices today employ continuous flow blood pumps to supplement function in the dysfunctional heart. Continuous flow pumps are predominantly preferred to the original pulsatile pumps due to the smaller size (greater implantability) and higher efficiency they achieve. However, interest in the impact of vascular pulsatility on human health has arisen from the growing evidence of higher complications with nonpulsatile devices compared to pulsatile devices. Direct cardiac compression (DCC) offers a unique solution to the pulsatility issue through the application of force directly to the heart's surface. It is believed that employing the existing pump architecture of the heart better produces natural pulsatility than blood pumps in series with the heart. The purpose of this study was to determine if external cardiac compression by direct mechanical ventricular actuation (DMVA), produces arterial pulsatile quality to that of the naturally beating heart. This concept was tested using DMVA, a non-blood contacting DCC device capable of actively augmenting diastole, on an acute fibrillating model in nine large animals (seven canine and two swine). Hearts, being fibrillated in order to eliminate the heart's natural function to generate pulsatile blood flow, were supported by the DMVA device. Progressive

myocardial weakening and acute failure throughout the experiment resulted from repeated cycles of fibrillation and defibrillation. Aortic pressures and flows were recorded periodically in ten second captures. Conventional measures of pulsatility (pulse pressure, energy equivalent pressure, surplus hemodynamic energy, frequency pulsatility index) were computed from these captures for comparison of arterial pulsatility between the naturally beating heart and the fibrillating heart supported by DMVA. Pulsatility in the naturally beating heart was measured from both the healthy normal heart and the weakened heart. Mean aortic flows and pressures were equivalent between DMVA condition and unsupported weakened heart condition. The results suggests pulsatile similarity between DMVA support for the fibrillating heart and the unsupported naturally beating heart. No index of arterial pulsatility was significantly lower from DMVA support heart compared to the unsupported beating heart at the same level of cardiac output ($p > 0.05$). DMVA proved able to restore arterial blood flow pulsatility in the fibrillating heart compared to the naturally beating heart.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AI – Aortic Insufficiency

AVM – Arteriovenous Malformations

CPB – Cardiopulmonary Bypass

CSF – Cerebrospinal Fluid

DCC – Direct Cardiac Compression

DMVA – Direct Mechanical Ventricular Actuation

ECLS – Extra-corporeal Life Support

EEP – Energy Equivalent Pressure

FFT – Fast Fourier Transform

GI – Gastrointestinal

LVAD – Left Ventricular Assist Device(s)

MAP – Mean Arterial Pressure

MCS – Mechanical Circulatory Support

PI – Pulsatility Index

PI_{freq} – Frequency Pulsatility Index

PowIdx – Power Index

PP – Pulse Pressure

SHE – Surplus Hemodynamic Energy

THE – Total Hemodynamic Energy

VEGF – Vascular Endothelial Growth Factor

VFIB – Ventricular Fibrillation

I. INTRODUCTION

Heart disease is the leading cause of death in the United States in the twenty-first century, responsible for twenty-five percent of all deaths according to the Centers for Disease Control and Prevention [1]. Given the limitations inherent to drug therapies and cardiac transplantation, cardiac assist devices have seen increasing prevalence in the past few decades for their utility in unloading the heart. Though first generation assist devices employed physiologic pulsatile blood pumps, nonpulsatile or continuous flow pumps which use impellers to continuously circulate blood are now the standard. Their smaller size, energy efficiency, and durability (fewer moving parts) allow for better implantability compared to the bulkier, percutaneous pulsatile devices. However, interest in physiologic pulsatile devices has been renewed because complications in nonpulsatile devices have been seen over time (see Table 1 for a summary of the following comparisons).

CONSEQUENCES OF NONPULSATILE CIRCULATION

BARORECEPTORS

The performance of vascular baroreceptors are linked to the pressure and flow characteristics in blood circulation. Vascular baroreceptors participate in the regulation of blood pressure by altering vascular tone. Renal baroreceptors, sensitive of pressure drops, activate the renin-angiotensin cycle to contract or dilate vessels as needed for suitable renal perfusion [2]. Baroreceptors are also sensitive to vascular pulsatility,

indicated by higher glomerular filtration rates with increased pulsatility and higher flow rates. Mandelbaum and Burns demonstrated that arterial pressure elevates in nonpulsatile perfusion compared to pulsatile perfusion at equivalent levels of cardiac outputs. When canines on cardiopulmonary bypass (CPB) were subjected to similar mean flow rates for both pulsatile and nonpulsatile perfusion, the arterial pressure increased significantly in the nonpulsatile group [3]. Continuous flow devices must compensate for the absence of pulsatility by increasing pump speeds, leading to many adverse hematological concerns discussed in subsequent sections. Sympathetic nervous activity in the carotid sinus, which is regulated by baroreception, has been observed to reduce during nonpulsatile circulation, suggesting an element of electrical dysfunction [4-5].

HEMATOLOGY

Several studies have shown that nonpulsatile perfusion is associated with gastrointestinal (GI) bleeding compared to pulsatile perfusion [6-11]. Increased bleeding, particularly in the brain and GI tract, is likely the result of anticoagulation necessary for any blood pump; however, the discrepancy in incidences of bleeding between nonpulsatile and pulsatile devices suggests another mechanism involved. Pulsatility may influence blood clotting pathways via endothelial release of von Willebrand factor. This was recognized due to the higher observed incidence of acquired von Willebrand disease. Unusually higher shear stresses in nonpulsatile pumps can result in the loss of high molecular weight multimers of von Willebrand factors which are responsible for binding collagen to platelets for clotting [6-7,10,12].

Arteriovenous malformations (AVM) tend to form in the GI tract because of insufficient perfusion of intestinal mucosa during nonpulsatile circulation. Decreased

2

pulse pressure and malperfusion cause mucosal ischemia and reconstruction of mucosal vascular network. Shear-induced upregulation of vascular endothelial growth factor (VEGF) may also be responsible for increased angiogenesis. The formation of these AVM intensifies GI bleeding [10,13-14] since the new vessel walls are thinner and less durable than the preexisting vessels. It also has been shown that incidences of hemolysis are significant in patients with nonpulsatile cardiac support devices [15-16], mostly occurring in proximity to the impeller.

RENAL FUNCTION

Kidney circulation and kidney metabolism has been found inferior for nonpulsatile circulation. In canine experiments comparing pulsatile CPB to continuous flow CPB, renal function decreased in the nonpulsatile group. This group experienced higher excess lactate levels, higher renal arteriovenous lactate differences, and higher peripheral vascular resistance [17]. Similar clinical studies, measuring the renal function in terms of biomarkers, have confirmed adverse kidney response. One study of patients above the age of seventy evaluated the effect of CPB flow on the renal function, and concluded that nonpulsatile perfusion during was inferior to pulsatile perfusion. At three days post-operation, the nonpulsatile group had significantly higher levels of cystatin C and creatinine (biomarkers of renal health) and higher blood urea nitrogen levels. Likewise, the nonpulsatile group had significantly lower urine output and more incidences of acute kidney injury [18]. Two meta-analyses have investigated large scale the comparisons of continuous circulation's effect on kidney function. The first meta-analysis compiled the data of ten studies that included 477 patients on nonpulsatile CPB and 708 patients on pulsatile CPB. These patients were considered for this meta-analysis because they met

the following criteria: research was prospective in nature, trial on human subjects, baseline demographics were recorded, and that outcome data included renal function biomarkers. The second meta-analysis considered the data of nine studies, with 674 on pulsatile CPB and 798 patients on nonpulsatile CPB. This second meta-analysis investigated renal function biomarkers and renal malfunctions. Both meta-analyses concluded that nonpulsatile perfusion during CPB was disadvantageous to pulsatile perfusion for post-operative renal function based on significant differences in creatinine clearances, serum lactate levels, serum creatinine and greater incidences of acute renal insufficiency in nonpulsatile perfusion [19-20].

LYMPHATIC FLOW

Lymphatic formation and circulation were shown to diminish in the presence of nonpulsatile arterial circulation, but were normal and similar to physiological levels in the presence of artificially generated pulsatile circulation. This was first discovered in experiments on rabbit ears. Continuous perfusion corresponded to a reduction in lymph formation and circulation while pulsatile perfusion corresponded to lymph formation and circulation [21]. With similar experiments on rabbit ears, it was also shown that interstitial fluid movement is promoted by pulsatile perfusion. Edema in the interstitial space increased, when the ears were subject to nonpulsatile arterial circulation. But pulsatile perfusion caused immediate fluid movement in the interstitial space [22]. It has been shown that reduction in arterial pulsatility suppresses the formation and flow of cerebral spinal fluid (CSF) likewise. During nonpulsatile blood circulation, once lymphatic or CSF flow has been diminished, pressure increases in interstitial space. The pressure gradient between the interstitial space and the capillaries then decreases,

reducing osmosis through the capillaries. High oncotic pressure may further increase the interstitial fluid pressure. If the interstitial fluid pressure surpasses the pressure in the capillaries, the capillaries may collapse [23].

NEUROLOGICAL

Neurologic recovery following cardiac arrest was shown to improve with pulsatile resuscitation through direct cardiac compression compared to nonpulsatile CPB; canines were arrested and then reperfused with either pulsatile biventricular cardiac massage or nonpulsatile CPB and later evaluated for neurological recovery after the animals were deceased. Nonpulsatile perfusion resulted in more severe loss of CA1 pyramidal neurons, and higher incidences of ischemic changes in caudate nucleus and water shed regions of the cerebral cortex [24]. In a similar study of canines on CPB, acute cell swelling and early ischemic cell change were seen in the canines subject nonpulsatile perfusion but not in the pulsatile group [23].

VASCULAR

In a study of patients on CPB that were high risk for cardiac surgery, microcirculation deteriorated in the patients on nonpulsatile CPB compared to pulsatile CPB; O'Neil, et al., found that a lower proportion of normally perfused micro-vessels occurred during nonpulsatile CPB. They also found an increase in leukocyte activation in the microcirculation from nonpulsatile circulation [25]. In left ventricular assist devices (LVAD), nonpulsatile pumps are more likely to cause aortic insufficiency (AI) than pulsatile pumps [26-28 44-46]. Higher blood flow velocities and shear stress of the nonpulsatile circulation intensify the blood flow dynamics. The aortic medial layer experiences thinning from the higher stresses because of a replacement of normal smooth

muscle tissue with atrophic smooth muscle cells, resulting in aortic root dilation and AI

[28]. Commissural fusion, which was shown to be more common in nonpulsatile LVAD

than in pulsatile flow LVAD, could contribute to AI [29]. Hatano, et al., showed that

patients on nonpulsatile LVAD were at higher risk of aortic insufficiency than the [27].

Overall, strong evidence has shown the superiority of pulsatile circulation to

nonpulsatile circulation. A large-scale study, comparing pulsatile CPB to nonpulsatile

CPB, found significant risks from nonpulsatile circulation. Of 350 patients on CPB,

evenly distributed between pulsatile and nonpulsatile, total mortality, the number of

deaths attributed to post-perfusion low cardiac output, and the necessity of intra-aortic

balloon or drug circulation support were significantly higher in the nonpulsatile group

while the increase in hemolysis, postoperative bleeding complications, and blood cell

depletion were not associated with pulsatile group [30]. A summary of health issues

associated with nonpulsatile flow is shown in Table 1.

Table 1 – Summary of issues associated with vascular blood flow non-pulsatility from cardiac assist devices. While continuous flow devices offer greater implantability, nonpulsatile devices have been associated with greater incidence of adverse health outcomes compared to pulsatile devices.

Summary of Problems with Nonpulsatile Circulation	
Area	Effect
Baroreceptors	-Sensitivity to nonpulsatile circulation (renin-angiotensin dysfunction)
Hematological	-Acquired von Willebrand Syndrome (reduced clotting ability) -AV Malformations (VEGF dysfunction promotes abnormal angiogenesis) -Increased hemolysis
Clotting	-Greater incidence of bleeding or thrombosis (anticoagulants or flow-based platelet dysfunction)
Renal Function	-Altered renal blood flow regulation and low perfusion
Lymphatic	-Decreased lymph flow, increased interstitial fluid retention
Immune Dysfunction	-Increased leukocyte activation and inflammation -Greater evidence of infection
Vascular Dysfunction	-Reduced microcirculatory perfusion and vascular bed patency -Shear-based endothelial dysfunction

DIRECT MECHANICAL VENTRICULAR ACTUATION

As discussed, most cardiac assist devices are blood pumps. However, direct cardiac compression (DCC) devices, which augment pump function by directly applying force to the surface of the heart, have been increasingly considered as alternative to blood pumps. DCC devices have included cups, cuffs, and skeletal muscle (cardiomyoplasty) [31]. Our lab has been working on a form of DCC called direct mechanical ventricular actuation (DMVA), comprising a contoured polymer cup placed over the ventricles which is driven by a percutaneous drive system. The cup has a hard outer housing and a flexible inner diaphragm bonded together at the rim and apex (Figure 1). The drive system generates support by inflating and deflating the sealed extradiaphragmatic space between the housing and diaphragm, facilitating systole and diastole respectively. A continuous apical vacuum prevents the heart from being ejected during support and maintains good contact between the epicardium and diaphragm [32]. The significant difference between DMVA and other DCC devices is the ability to augment diastolic function. Most DCC are merely heart compression devices and depend on passive filling for diastolic function.

Though most cardiac assist devices require tedious and highly controlled procedures for implantation and application, DMVA is advantageous for a resuscitative role due to its rapid installation. The relative simplicity of providing surgical access to the heart (which can be done by a general surgeon), without need for cannulation, allows for documented installation times of less than five minutes in both animal [33-34] and clinical [32, 35-36] studies. With respect to long-term device applications, DMVA has considerable benefits to blood pump devices. Most notably is the lack of blood contact. In order to prevent thrombosis from the blood pumps, anticoagulants must be provided for

the duration of support, causing bleeding risks. The invasiveness of blood contact also produces greater risk for infections compared to devices operating external to the heart. DMVA is also naturally biventricular, which helps to balance output from both sides of the heart.

DMVA has been shown to return cardiac hemodynamic output to near normal levels in animal hearts following fibrillation from circulatory arrest [32-43]. Cardiac and cerebral resuscitation are significantly improved by DMVA compared to closed-chest compression [32], open-chest cardiac massage [33], and CPB [37-40]. In canine comparisons between DMVA and CPB support for cardiac arrest, neurological recovery was significantly better in the canines supported by DMVA based on levels of cerebral oxygen consumption, loss of neurons, and ischemic changes [37, 40]. DMVA proved applicable as bridge-to-transport in clinical trials, without inducing significant myocardial trauma [35, 41]. In studies of canines supported by CPB or DMVA following coronary artery bypass grafting, subjects supported by DMVA had better graft integrity with no anastomotic disruption [42-43]. Cadaver kidney preservation has also been successfully performed through DMVA use [44].

In addition to supplementing blood pumping ability, direct actuation of cardiac tissue may provide additional benefits in preventing atrophy and unloading heart and modulating cellular stretch signaling. Since DMVA makes use of existing cardiac structure, it has been suggested that the cup may be able to generate the pulsatile flow and pressure characteristics similar to those generated by the physiologically contracting heart.
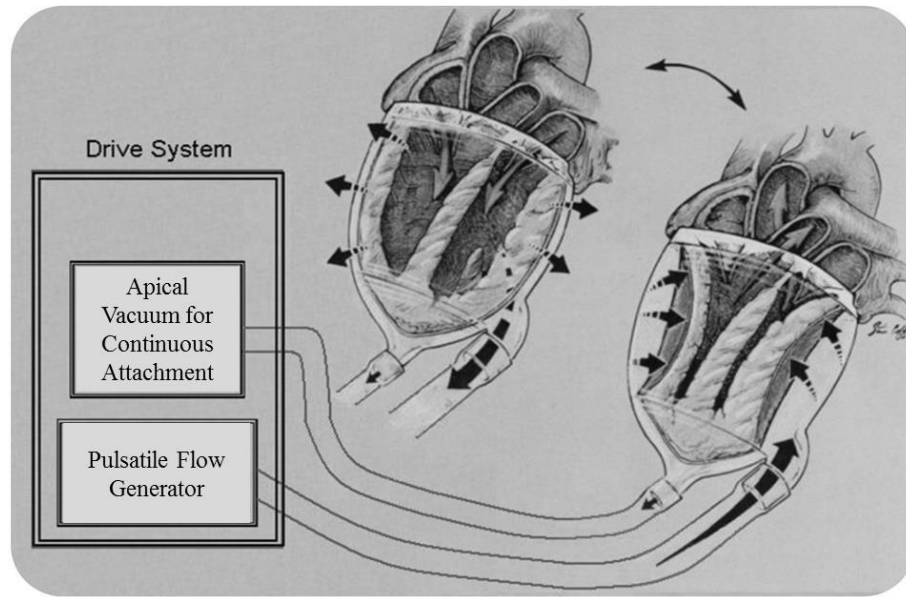
Figure 1. DMVA is a non-blood contacting form of direct cardiac compression. DMVA consists of a polymer cup composed of a hard outer shell enclosing a flexible polymer diaphragm. The ventricles are positioned against the diaphragm up to the AV groove. The isolated space between the shell and diaphragm is expanded and retracted using a pneumatic piston to augment both systolic contraction and diastolic relaxation. These forces are translated to the ventricular surface after proper device attachment. Attachment is achieved by a continuous low vacuum delivered via an apical port. This vacuum both prevents expulsion of the heart during systolic compression and allows better contact between the diaphragm and epicardium. Inflation of extradiaphragmatic space contracts the ventricular myocardium introduce systolic function, and deflation of the space relaxes the ventricular myocardium to introduce diastolic function.

PURPOSE

The purpose of this study was to determine if external cardiac compression by DMVA produces arterial flow and pressure pulsatile characteristics similar to the native beating heart. This was assessed using an acute fibrillating heart model to evaluate pulsatility due to DMVA support alone.

Hypothesis: DMVA support of the fibrillating heart restores arterial hemodynamic pulsatility to that of the beating heart.

This thesis is accomplished by the following specific aims:

1. Determine if conventional measures of vascular pulsatility (pulse pressure, frequency pulsatility index, energy equivalent pressure, surplus hemodynamic energy) are equivalent between the non-beating DMVA-supported heart and the unsupported beating heart.

2. Determine if differences in mean arterial pressures and flows affect pulsatility comparisons between the non-beating DMVA-supported heart and the unsupported beating heart.

QUANTIFYING PULSATILITY

A major challenge to the research of pulsatility is inconsistency in defining or quantifying pulsatile character. After over sixty years of investigating pulsatility, no standard criteria or definition has been established for what qualifies pulsatile circulation [45]. Much literature from the past has considered only extremes in the blood pressure as the quality of pulsatility. This approach fails to recognize the hemodynamics quality of the blood flow and inadequately disregards flow rate pulses. Pulsatile circulation is polymorphic with a hemodynamic energy gradient; physiologic pulsatility is evidenced in its flow patterns and hemodynamic energy levels [46]. Pulsatile flow is generated from energy gradients, not pressure gradients. Continuous flow pumps, such as roller pumps, have been modified to introduce an essence of pulsatility in their circulation based on a pressure-defined pulsatility [47]. When such pseudo-pulsatile pump are implemented into mechanical circulatory support and labeled as pulsatile, their conclusions might be suspect because their flow characteristics are much different than physiologic pulsatility [48-49]. Though the pseudo-pulsatile pumps generate flow with equivalent mean and extreme pressures to physiologic flow, they generate significantly different flow patterns and hemodynamic energy levels [46]. Research that disclaims the advantages of pulsatile perfusion to nonpulsatile perfusion may be inadequate because their definition of pulsatility ignores flow hemodynamics [48-49]. To legitimize research, pulsatility should be quantified based on hemodynamic flow patterns and energy levels in addition to pulses in pressure.

PULSE PRESSURE

Metrics of pulsatility have been based upon a number of factors including pressure, flow velocity, flow harmonics, and hemodynamic energy levels in arterial flow. Pulse pressure (PP), the most rudimentary measure, quantifies pulsatility as the difference between systolic pressure (P_{sys}) and diastolic pressure (P_{dia}) [50].

$$PP = P_{sys} - P_{dia} \qquad (1)$$

As defined by PP, blood flow becomes nonpulsatile when PP has been diminished; mechanical circulatory support devices are considered nonpulsatile when PP is less than 15 mmHg, and pulsatile when PP is greater than 15mmHg [45, 51]. Safar, et al., investigated the relation between PP and end-stage renal disease and concluded that the reduction of aortic-brachial PP amplification was a significant predictor of all-cause mortality in patients with end-stage renal disease. They also found that carotid PP was a better predictor of overall mortality than brachial PP [50]. Myers, et al., investigated the correlation of PP to pump speed of continuous flow LVAD. They found that smaller PP resulted in the inability of aortic valve to open normally, increasing risk of complications [52]. PP is not the most efficient measure of blood flow pulsatility because it does not recognize hemodynamic properties of the flow. LVAD or CPB can generate similar PPs to that of the beating heart, but differ greatly from physiologic circulation in their flow profiles and energy levels [46].

PULSATILITY INDEX

Pulsatility index (PI) quantifies pulsatile circulation based on variations in flow velocities; it is the difference between maximum systolic velocity (V_{sys}) and minimum diastolic velocity (V_{dia}) over the mean flow velocity (V_{mean}) in a vessel [53-54].

$$PI = \frac{V_{sys} - V_{dia}}{V_{mean}} \tag{2}$$

PI is applicable for the calculation of pulsatility in cerebral vessels, and is measured

based on transcranial Doppler. PI has been found to correlate with intracranial pressure

[55-56]. Soehle, et al., investigated the relationship between vital conditions including PI

to mortality and morbidity of patients who had subarachnoid hemorrhages. They only

concluded that higher PIs, or higher cerebral blood pulsatility, were predictive of negative

outcomes [57]. PI has not been found to compare pulsatile and nonpulsatile perfusion.

FREQUENCY PULSATILITY INDEX

Pulsatility can be quantified in terms of the frequency harmonics of the pulsatile blood

flow [58-60]. The heart's pump function by nature generates cyclic frequency in the flow.

Every periodic curve can be transformed into a series of sine curves or harmonics on the

frequency domain (Figure 2). The flow frequency in arterial circulation is driven by the

beating heart, while continuous or nonpulsatile flow has no cyclic frequency. Pulsatility

based on flow frequency can be quantified as the frequency pulsatility index (PI_{freq}).

PI_{freq} is calculated by transforming the flow into its frequency spectrum with the Fast

Fourier transform (FFT) and analyzing the harmonic amplitudes. The equation is

$$PI_{freq} = \frac{\Sigma(A_i^2)}{A_0^2} \tag{3}$$

where A_i is the amplitude of each harmonic and A_0 is the amplitude of mean flow. PI_{freq}

is dependent on wave frequency (heart beat or systolic duration) and flow magnitude.

PI_{freq} has been analyzed for optimization of end organ health, for comparison between

pulsatile and nonpulsatile cardiac support, and for relationship with vascular resistance
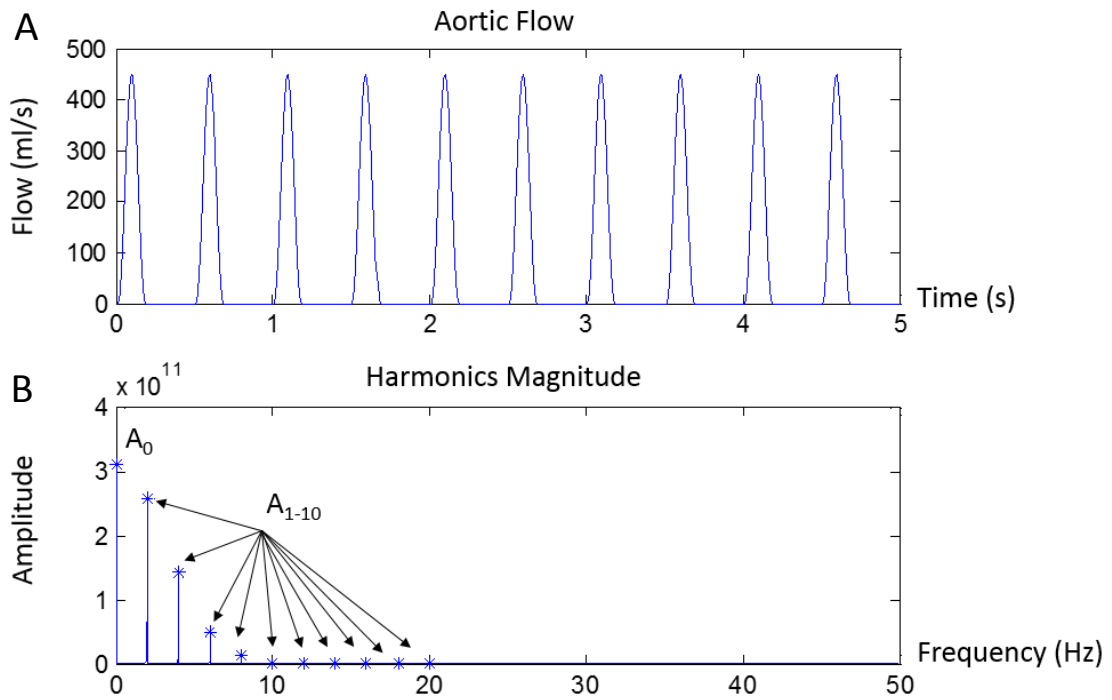
[58-61].

Figure 2. (A) Example of aortic flow waveform. (B) Fourier transform of flow waveform. The FFT is a set of sinusoid waves that model the flow on the frequency domain. PI_{freq} is calculated from the harmonic amplitudes. The harmonics (A_{1-10}) are squared and summed, and divided by the square of the mean flow (A_0).

ENERGY EQUIVALENT PRESSURE

Because pulsatile circulation is dependent on energy gradients rather than pressure gradients and pulsatile flow is quite different than continuous flow in levels of hemodynamic energy, pulsatility has been quantified as an energy equivalent pressure (EEP) which is the ratio between the hemodynamic energy and the flow volume during a specific time period (the area under the hemodynamic power curve to the area under the flow curve) [62-63].

$$EEP = \frac{\int flow * pressure\ dt}{\int flow\ dt} \tag{4}$$

Intrinsic to fluid motion is the energy present in the blood flow. The pulsatile energy is the excess energy in the pulsatile flow above what a continuous flow at the same mean rate possesses; the quantity of pulsatile energy is the difference between EEP and mean arterial pressure (MAP) [49]. Continuous flow, which has no pulsatile energy, has an EEP equal to its MAP; surplus hemodynamic energy (SHE) is the difference between EEP and MAP in energy per volume units. Total hemodynamic energy (THE) is the conversion of EEP to energy per volume units [63].

$$SHE = 1332 * (EEP - MAP)\ [ergs/cm^3] \tag{5}$$

$$THE = 1332 * EEP\ [ergs/cm^3] \tag{6}$$

SHE and THE can be converted to the SI units of J/m^3 by dividing by 10. The loss in pulsatile energy by nonpulsatile circulation is observed by the decrease in the difference between EEP and MAP. A pump's ability to generate hemodynamic energy similar to that the beating heart can be evidences by this difference. The normal human heart has a ten percent difference between EEP and MAP [47]. In experimental studies, physiologic pulsatile pumps generated a ten to twelve percent difference in experiments on pigs,

pseudo-pulsatile pumps (nonpulsatile pumps that are manipulated to generate a pulse pressure) generated a three to five percent difference, and nonpulsatile pumps generated a zero to one percent difference between EEP and MAP [64].

Even when CPB might employ pulsatile pumps, the energy in the blood flow can be dissipated in the CPB system before reaching the patient's body. Lim, et al., analyzed the system settings and configuration of CPB and extra-corporeal life support (ECLS) to maximize the human arterial pulsatility levels, in terms of EEP, SHE, and THE [46]. Lee, et al., performed similar experiments on the configuration of the ECLS circuit to optimize arterial pulsatility in terms of EEP, SHE, and THE [65]. Undar, et al., investigated the pulsatility of CPB on neonatal pig hearts and found that physiologic pulsatile pumps generate higher hemodynamic energy levels than other kinds of pumps [66]. Bartoli, et al., compared arterial EEP of LVAD supported bovine hearts between pulsatile and continuous flow pumps. EEP, SHE, and their percent difference were significantly lower in the nonpulsatile devices compared to the pulsatile devices and compared to the native heart. The volume-pressure relationship in the nonpulsatile group diminished, and the opening aortic valve was restricted [67]. Travis, et al., compared the correlation of EEP to vasculature impedance and compliance for pulsatile and nonpulsatile LVAD at high and low support. Pulsatility, based on hemodynamic energy, decreased in nonpulsatile LVAD group but was restored to baseline levels in pulsatile LVAD group. Their results showed that vascular impedance immediately increased with nonpulsatile LVAD and decreased with pulsatile LVAD, though this was not indicative of impedance for long term support [63].

POWER

Because metrics such as EEP and SHE quantify pulsatility essentially as a pressure, attempts have been made to quantity pulsatile flow by power components [68-69]. The hydraulic power from the left ventricle delivered through the blood flow to the systemic circulation consists of a potential power derived from pressure, a minimal kinetic power, and a negligible gravitational potential power. This pressure potential power is the product of instantaneous aortic flow and pressure

$$\dot{W}(t) = p(t) * f(t) \tag{7}$$

where $\dot{W}(t)$ is the potential power, and p(t) and f(t) are the Fourier transforms of the instantaneous aortic pressure and flow waves respectively. When the flow and pressure transforms are multiplied together and rearranged, the active power can be equated as

$$\dot{W}_{act} = \dot{W}_{sdty} + \dot{W}_{puls} = P_o Q_o + \frac{1}{2}\sum_{n=1}^{N} P_n Q_n \cos(\phi_n - \theta_n) \tag{8}$$

Where P_o is mean pressure, Q_o is mean flow, P_n is the nth pressure harmonic, Q_n is the nth flow harmonic, and $\phi_n - \theta_n$ is the phase difference between flow and pressure [69]. The active power has a steady flow power ($\dot{W}_{sdty}$), which is the minimum power required to deliver blood flow to systemic circulation, and a pulsatile power ($\dot{W}_{puls}$), which is the power delivered into the pulses and not contributing to forward flow. The pulsatility portion of active power provides a metric of pulsatility. Studies have been performed to link the pulsatility components of power to arterial resistance and elasticity [69]. Both pressure and flow are accounted for in this metric of power units, while EEP and SHE cancel out the flow to be in pressure units.

SHEAR STRESS

Consequent of the blood flow is the shearing of endothelium which actively regulates many physiological blood vessel responses. Increase in shear stress can stimulate arteriogenesis, formation of new arteries. The rise in shear stress from the increase of the continuous flow rate to maintain pressure levels can promote endothelial cell migration, and thus arteriogenesis [70]. Assistance in vascular defense is also a role of shear stress. Nitric oxide (NO), an important protective molecule in the vasculature, is produced in a process called endothelial nitric oxide synthase (eNOS). The increase in shear stress stimulates eNOS activity [71-72]. Shear stress is a function of shear rate, and shear rate is a function of flow rate. Normal arterial values of shear stress range between ten and forty dyne/cm^2. But because arterial flow is pulsatile and due to meandering of vessels, the flow is at times disturbed, and the shear stress can become negative or exceed normal values. Likewise, non-physiologic conditions can raise the levels of shear stress [70].

II. METHODS

The Wright State University Lab Animal Care and Use Committee approved the experimental protocol, and all animals were treated in compliance with the Guide for the Care and Use of Laboratory Animals, published by the National Institutes of Health, revised 1996.

SURGICAL PROTOCOL AND EXPERIMENTAL TIMELINE

This study consisted of nine large animal models, seven canines and two swine. Both canines and swine were considered to represent various cardiac sizes. Swine hearts represent larger human hearts, and canine hearts represent smaller human hearts. The subjects were pre-anesthetized with Telazol (6 mg/kg), Xylazine (3 mg/kg), and Atropine (0.02 mg/kg). After which, the subjects were treated with tracheal intubation and mechanical ventilation. Drug infusion was administered by vascular access through bilateral femoral cutdowns. Anesthesia was maintained with 1-2% isoflurane, and arterial pressure was regulated with phenylephrine. Median sternotomy and pericardiotomy were performed to fit the cup to the animal hearts. The subjects were monitored for left ventricular, aortic, and central venous pressures with Spectramed P23xl pressure transducers. A median sternotomy and a pericardiotomy were performed on the subjects. A COfidence ultrasound flow probe with a TS420 perivascular module was inserted about the ascending aorta for monitoring cardiac output. A computer acquisition system monitored hemodynamics, pulse oximetry, end-tidal dioxide, and rectal temperature. DMVA drive systems were instrumented to measure pulsatile and continuous vacuum

pneumatic pressure and pulsatile flow. The schematic of instrumentation setup is in Figure 3.

The experimental timeline began with the pre-experimental condition. The pre-experiment condition provided a baseline to measure the pulsatility of the healthy beating heart. The experiment consisted of ventricular fibrillation, a period of DMVA support, defibrillation, and a period of beating without support. Post-sternotomy baseline data was recorded. To induce ventricular fibrillation (V-FIB), a 9-volt battery shocked the ventricles through the epicardium. V-FIB continued for a five minute period, after which DMVA support was given for fifteen minutes. The hearts were then defibrillated after the period of DMVA support. If defibrillation failed to restore normal cardiac rhythm or if severe failure was present (cardiac output $\leq$ 60% baseline), DMVA support was reapplied for an additional fifteen minutes; but if defibrillation successfully restored the heart to its normal cardiac rhythms, the heart would remain unsupported for fifteen minutes of recovery. After the recovery or supported failure, the heart was again fibrillated and the cycle was repeated. This cycle was repeated for approximately two hours (Figure 4).
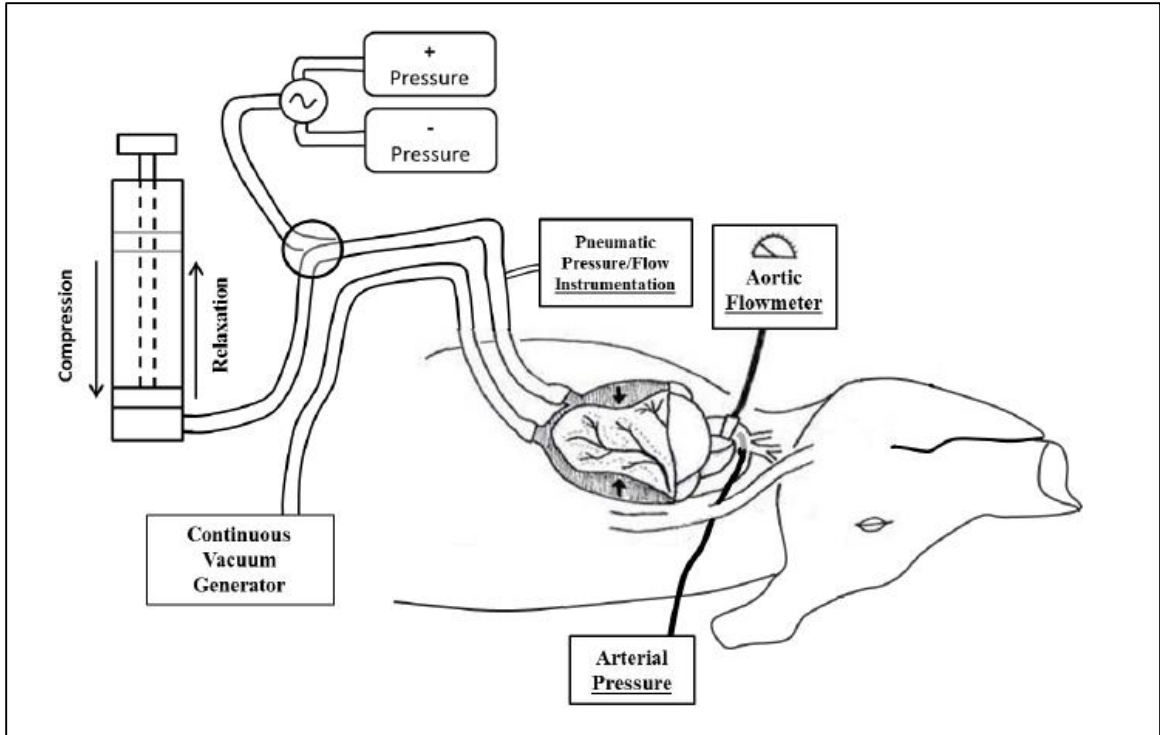
Figure 3. Schematic of experimental setup for data collection. Data collection instrumentation included aortic flow meter, aortic pressure transducer, pneumatic pressure transducer and flow meter, and drive system. Animals were instrumented for flow and pressure readings at the ascending aorta.
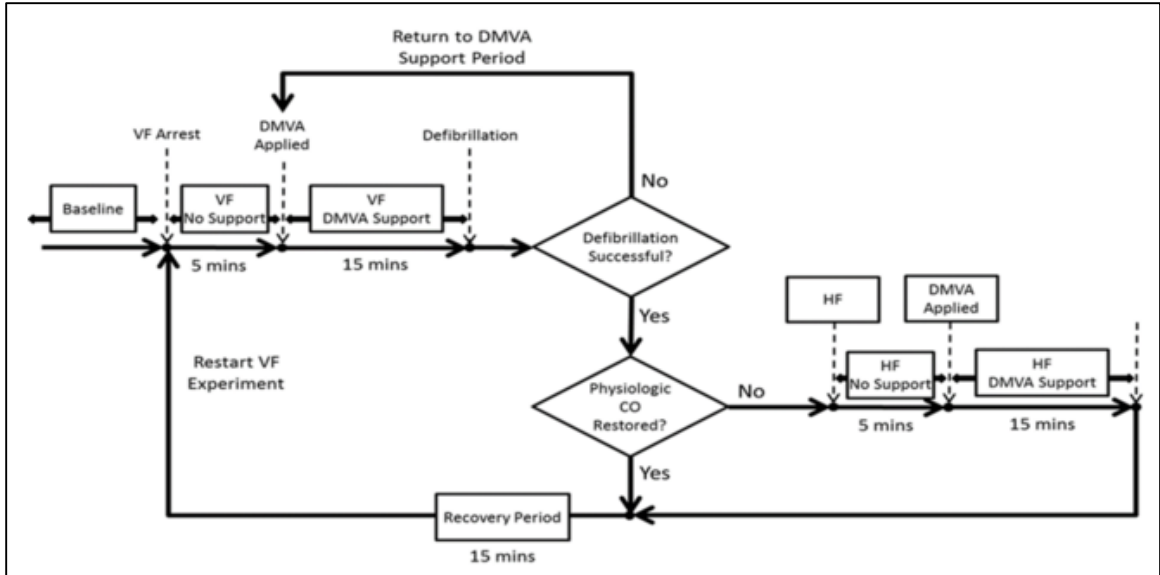
Figure 4. Experimental timeline used for this study. After taking physiologic baseline measurements (following medial sternotomy and instrumenting animal for pressure and flow readings), ventricular fibrillation was generated using a direct current shock to the heart surface. After five minutes of fibrillation without support, DMVA was applied to the fibrillating heart. Following the fifteen minute period of DMVA support, the cup was removed and the heart was defibrillated. If successful, the beating hearts were commonly in failure. After a DMVA support period for the failing heart, the cycle was started again. In this way different levels of cardiac health were assessed as the animal became more dysfunctional with repeated cycles.

Ascending aorta pressure and flow data was recorded throughout the experiment over several hundred ten-second captures at 800 Hz. For comparison between DMVA and the naturally beating heart, the data was categorized into the experimental conditions. After which, the data captures of aortic flow and pressure were analyzed for calculation of arterial pulsatility. Captures from support during failure, captures without pressure and flow data, and captures during periods of inadequate DMVA support were excluded. (For the rest of this paper, "support" refers exclusively to support during fibrillation.)

Experimental conditions were divided into (1) the pre-experiment beating heart, (2) DMVA support during fibrillation at normal physiologic cardiac output (output greater than 60% of the baseline output), and (3) the unsupported beating heart following defibrillation at normal physiologic levels. The conditions of DMVA support and post-arrest beating heart had equivalent levels of mean arterial pressure and aortic flow, providing similar conditions of the pulsatility comparison. Baseline arterial flow and pressure was higher than post-arrest and DMVA supported arterial flow and pressure. Table 2 describes experimental conditions.

Table 2. This experiment compared pulsatility as generated by DMVA during fibrillation to the pulsatility generated from the naturally beating heart. Experimental conditions were classified as DMVA support and beating heart pre-experiment or beating heart post-arrest. Mean aortic flow and MAP was not significant between supported heart and post-arrest beating heart. Arterial pulsatility from DMVA could be compared to the beating heart at similar conditions and to the baseline healthy beating heart.

Experimental Condition	Sample Size	CO (L/min)	MAP (mmHg)	Description
Pre-Experiment Beating Heart	35	3.08 ± 0.06	94.20 ± 4.03	Baseline post-sternotomy condition of unsupported heart before experiment
DMVA Support for Fibrillating Heart	47	2.71 ± 0.05*	77.33 ± 4.24*	Condition during experiment when heart was fibrillating and supported by DMVA and cardiac output was at normal levels (CO > 60% baseline CO)
Post-Arrest Beating Heart	87	2.70 ± .05*	83.60 ± 3.63*	Condition during experiment when heart was beating without support following defibrillation (CO > 60% baseline CO)

Values expressed as Mean ± SEM; * $p < 0.05$ vs Baseline

ANALYTIC MEASURES

Pulse pressure (PP), as defined in Equation 1, accounts for variance between systolic and diastolic pressure. In the data captures, instantaneous pressure waveforms were recorded, from which systole and diastole were measured. Pulse pressure was calculated from these pressure wave forms as the difference between the systolic pressure and the diastolic pressure. PP was calculated for comparison between the supported heart and the beating heart from 131 data captures. Traces with poor signal resolution were excluded.

The frequency pulsatility index (PI_{freq}), quantifies pulsatility based on the frequency harmonics in the blood flow. Equation 3 defines PI_{freq} as the ratio of the sum of flow harmonics squared to the mean flow squared. This index requires flow to be transformed to frequency spectrum by FFT to measure the harmonic amplitudes. The flow wave forms from 169 data captures was transformed by FFT to the frequency spectrum from which PI_{freq} was calculated.

Based on hemodynamic energy, pulsatility is quantified as energy equivalent pressure (EEP) and total hemodynamic energy (THE) and accounts for both pressure and flow qualities in the blood flow. This measures hemodynamic energy in units of pressure and energy per volume and is defined in Equations 4 and 6 as the amount of hemodynamic energy per flow volume for a given period. Surplus hemodynamic energy (SHE), the difference between EEP and MAP in terms of energy per volume, is defined in Equation 5. EEP, SHE, and THE were calculated from the flow and pressure wave forms from 169 captures during the experiment. To compare pulsatile energy when arterial pressure differs among conditions, the ratio of EEP to MAP was calculated for relative pulsatility.

EEP already calculates the hemodynamic energy in its numerator, but divides the hemodynamic energy by the flow volume. EEP, therefore, cancels the flow out of its index and remains only as a pressure. A power term could be calculated through dividing the hemodynamic energy by the time period of the capture.

$$PowIdx = \frac{\int (flow*pressure)dt}{time} \tag{9}$$

This power index would have terms of pressure and flow and account for both the flow and pressure qualities of pulsatile flow. This metric was calculated from 169 data captures for comparison of DMVA to beating heart. Power index calculation was converted to watts.

One of the effects of the blood flow is the shearing of endothelium. Instantaneous aortic flow was recorded throughout the entire experiment, from which maximum shear stress was approximated for each capture during baseline flow and during each experimental condition. Shear rate for Poiseuille or laminar flow is defined by Equation 7 as a function of flow rate, and shear stress is defined by Equation 8 as function of shear rate [73].

$$\dot{\gamma} = \frac{32Q}{\pi D^3} \tag{10}$$

$$\tau = \mu\dot{\gamma} \tag{11}$$

In Equations 7 and 8, Q is the maximum flow rate for each capture, D is the inner diameter of the vessel, and μ is the dynamic viscosity of blood. The pulsatile flow cannot be assumed as purely laminar. But approximation of shear stress with Equation 8 provides a proportional comparison of shear stress from DMVA compared to beating heart. In this study, the internal diameter of the ascending aorta in canines was

approximated to 1.5 cm [74]. Dynamic viscosity was approximated with the dynamic viscosity of human blood at 37°C to 0.0032 N*s/m^2 [75]. Maximum shear stress was calculated from about flow data captures from the canines.

Based on all these metrics, arterial pulsatility was compared between DMVA support for fibrillation and the naturally beating heart. Student's t-tests were performed between experimental conditions. P-values below 0.05 indicated index significance between conditions. These tests determined if pulsatility was restored by DMVA to that of the naturally beating heart.

Table 3. Metrics of Pulsatility. Each of these measures were calculated as a means to quantify pulsatility. Pulsatility was compared between supported heart and beating heart based on these measures.

Calculation	Equation	
Pulse Pressure	$PP = P_{sys} - P_{dia}$	[mmHg]
Frequency Pulsatility Index	$PI_{freq} = \dfrac{\Sigma(A_i^2)}{A_0^2}$	[dimensionless]
Energy Equivalent Pressure	$EEP = \dfrac{\int flow * pressure\ dt}{\int flow\ dt}$	[mmHg]
Surplus Hemodynamic Energy	$SHE = EEP - MAP$ $SHE = 1332 * (EEP - MAP)$	[mmHg] [erg/cm3]
Total Hemodynamic Energy	$THE = 1332 * EEP$	[erg/cm3]
Power Index	$PowIdx = 0.0022\dfrac{\int (f * p)dt}{time}$	[m3/s*Pa or W]
Shear Stress	$\tau = \mu\dot{\gamma}$	[dyne/cm2]

III. RESULTS

AIM I: METRICS OF PULSATILITY

In execution of the first aim of this experiment, the conventional measures of pulsatile quantification were performed for each experimental condition on all the flow and pressure data captures. Statistical analysis was performed on each pulsatility metric for comparison of arterial pulsatility between DMVA support and the unsupported beating heart. Not all animals produced all experimental conditions for comparison between beating and fibrillating supported heart. The following results are shown as mean ± standard error.

PULSE PRESSURE

PP results from arterial blood flow were as follows: 68.95 ± 4.79 mmHg for baseline beating heart, 70.57 ± 4.25 mmHg for DMVA support, and 39.71 ± 3.44 mmHg for unsupported beating heart post-arrest. PP was significantly higher from DMVA support compared to beating heart at the same cardiac output but had equivalent PP to baseline healthy heart (Figure 5). Systolic pressure was found to be higher for fibrillation support than for the beating the heart while diastolic pressure remained relatively constant between supported and beating heart. The rise in PP of the supported heart was thus caused by the rise in systolic pressure. When considering the animals individually, PP in every animal was either not significant between supported and beating hearts, or higher in the supported heart.

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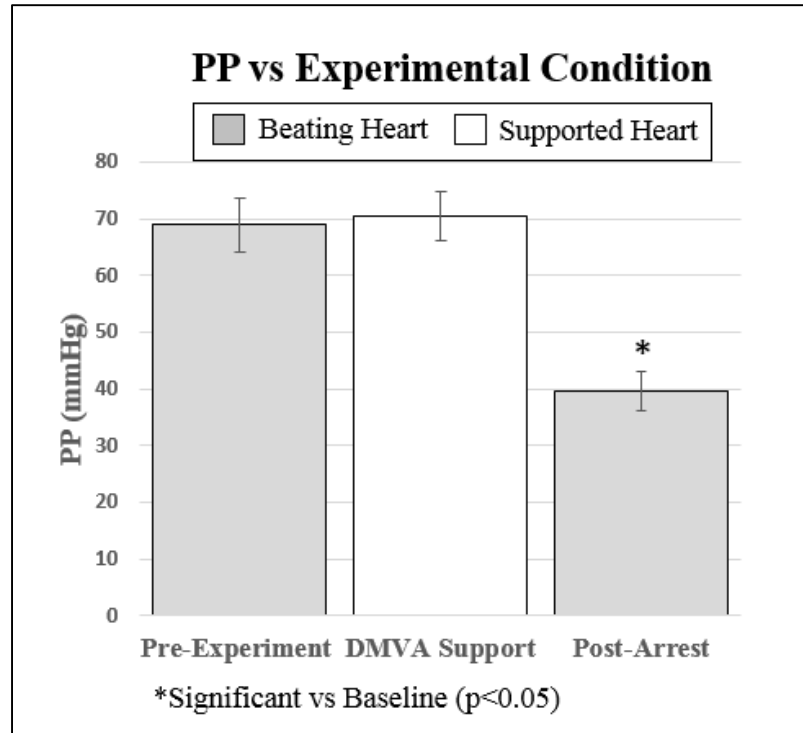
Figure 5. Comparison of pulse pressure (mean and standard error) between the fibrillating

supported heart and the beating heart. PP was significantly higher during fibrillation

support than PP for beating heart at the same cardiac output. The beating heart was

progressively weakening, and the dysfunctional myocardium was unable to maintain

pulse pressure compared to DMVA support. Due to mechanisms of DMVA compression,

the systolic portion of the pressure wave was larger from the supported heart than from

the beating heart. DMVA's PP was equivalent to the pre-experiment PP.

FREQUENCY PULSATILITY INDEX

PI_{freq} results from arterial blood flow were as follows: 0.72 ± 0.05 for baseline beating heart, 0.82 ± 0.04 for DMVA support, and 0.68 ± 0.04 for unsupported beating heart post-arrest. Based on the frequency harmonics, DMVA's PI_{freq} was significantly higher than PI_{freq} of the post-arrest beating heart (Figure 6). Compared to the pre-experiment beating heart, DMVA had no significance in terms of frequency harmonics. When considering the animals individually, PI_{freq} had no significant differences between beating heart and fibrillating heart in most cases. When PI_{freq} was significantly different, it was higher in the fibrillating heart than in the beating heart.
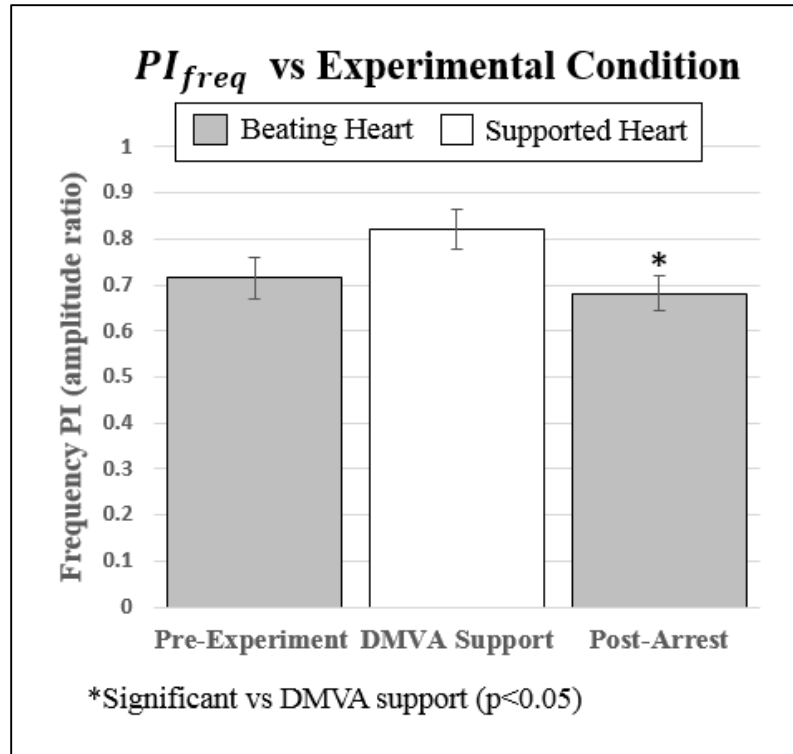
Figure 6. Comparison of PI$_{freq}$ (mean and standard error) between supported heart and beating heart. PI$_{freq}$ was significantly higher support compared to the beating heart at the same outputs. PI$_{freq}$ was dependent on wave frequency and mean flow volume. Because of myocardial dysfunction, the post-arrest beating heart may have experienced inconsistency in flow wave frequency though flow was maintained, causing this measure of pulsatility to be dropped for beating heart compared to supported heart.

ENERGY EQUIVALENT PRESSURE

EEP results from arterial blood flow were as follows: 112.35 ± 4.21 mmHg for baseline beating heart, 96.23 ± 4.43 mmHg for DMVA support, and 96.18 ± 3.79 mmHg for unsupported beating heart post-arrest. According to the data of all animals combined, EEP levels were not significantly different between the beating heart and the supported fibrillating heart at the same cardiac output. EEP significantly decreased from pre-experiment condition to DMVA and post-arrest beating heart conditions because flow and pressure were at lower levels (Figure 7). These results were represented when considering the animals individually. EEP was similar between the post-arrest beating heart and the supported heart in almost all cases. Total hemodynamic energy results were identical to EEP results because THE is the energy per volume conversion of EEP. Thus, THE was not significant between the native beating heart and the fibrillating supported heart.
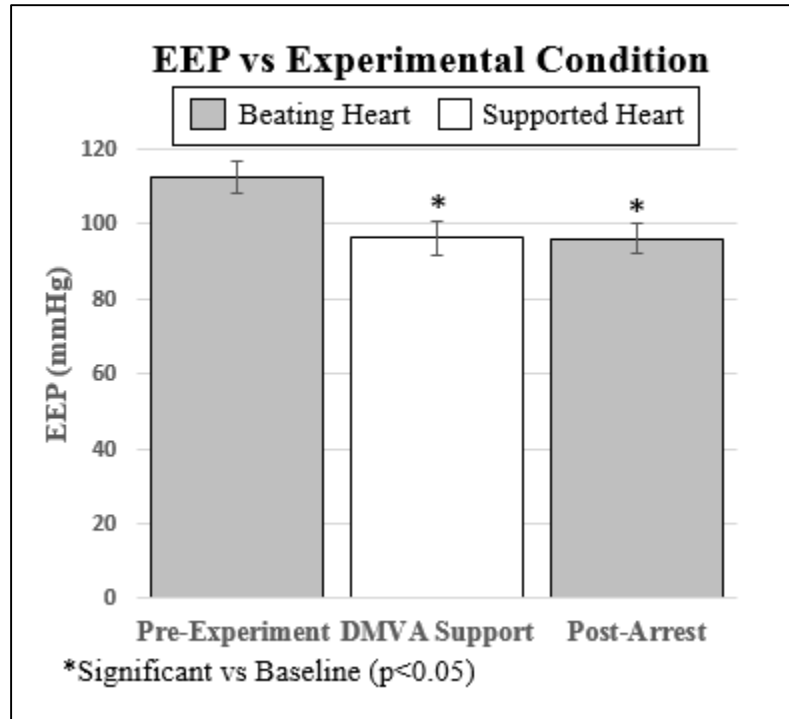
Figure 7. Comparison of EEP (mean and standard error) between supported and beating heart at each experimental condition. EEP was not significant between beating heart and supported heart at same output level. EEP dropped significantly as output level dropped. Application of DMVA for the fibrillating heart restored hemodynamic energy to that of a beating heart, relative to flow. However, EEP or hemodynamic energy was lower in DMVA support than pre-experiment baseline because flow and pressure were lower during DMVA support.

Though EEP is a function of flow and pressure, EEP was plotted versus both to see their effect on EEP (Figure 8). EEP appeared to grow fairly proportionally to mean aortic flow. This relationship was dependent upon animal, however. The rate of EEP growth with respect to flow varied among animals causing the fanning of data in the plot of EEP versus flow. EEP had a strong linear relationship with MAP ($R^2 = 0.8$), independent of animal. Because the slope was less than 1.0, the change in MAP was greater than the change in EEP between two captures; the difference between EEP and MAP decreased as arterial blood pressure increases. These relationships did not appear to be affected by whether the heart was beating on its own or the fibrillating heart was being supported by the cup (Figure 9).
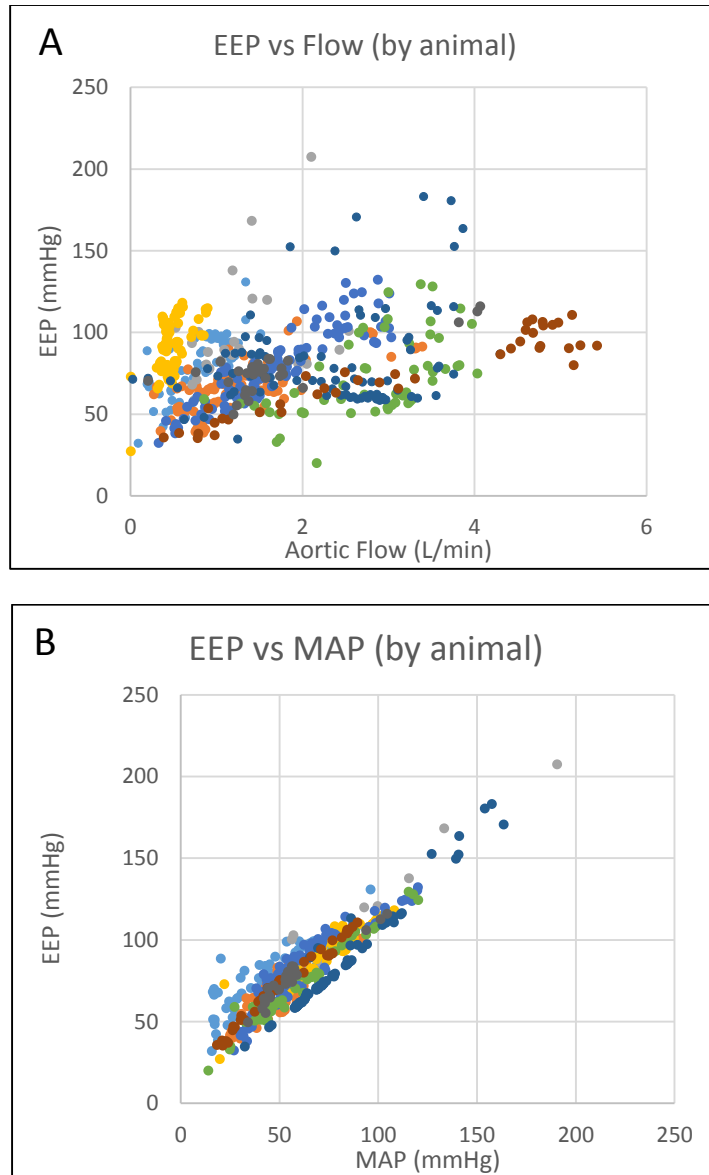
Figure 8. Comparison of EEP to aortic flow (A) and to MAP (B). EEP seemed to increase with aortic flow, when considering the data as a whole. But for animals individually, there appeared to be a more linear relationship between EEP and flow. The rate of change between EEP and flow varied in each animal causing the fanning of the data. There was a strong linear relationship between EEP and mean arterial pressure ($R^2 = 0.80$).

Figure 9. Comparison between beating heart and supported heart of EEP to aortic flow relationship (A) and of EEP to MAP relationship (B). Neither relationship seemed to be affected by whether or not the heart was naturally beating or was supported during fibrillation.

Because EEP was proportionally dependent on MAP which varied among experimental conditions and animals, and because the presenc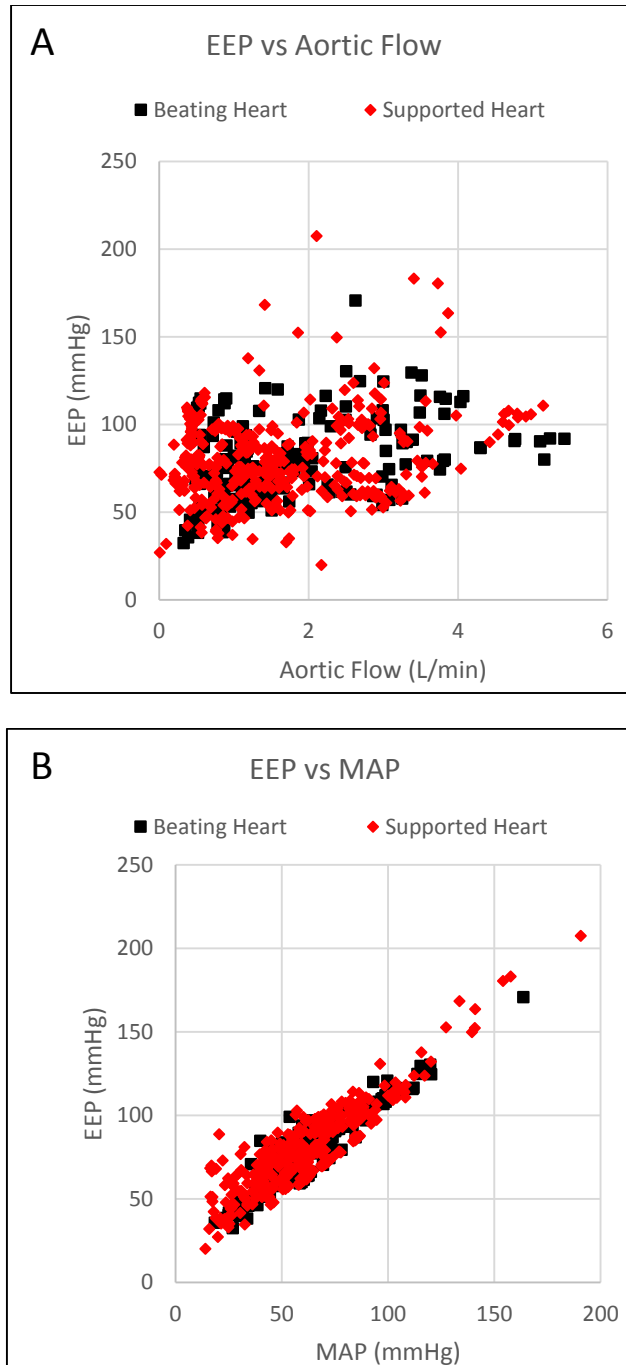e of pulsatility was quantified in the difference between EEP and MAP, the ratio between EEP and MAP provided an effective measure of pulsatility relative to pressure. The EEP to MAP ratio results from arterial blood flow were as follows: 1.22 ± 0.02 for baseline beating heart, 1.26 ± 0.02 for DMVA support, and 1.16 ± 0.02 for unsupported beating heart post-arrest. According to the data of all the animals combined, the EEP to MAP ratio was significantly higher from DMVA support compared to post-arrest beating heart, but the EEP to MAP ratio had no significance between DMVA support and pre-experiment beating heart (Figure 10). DMVA restored hemodynamic energy relative to mean pressure in the fibrillating heart to that of the naturally beating heart.
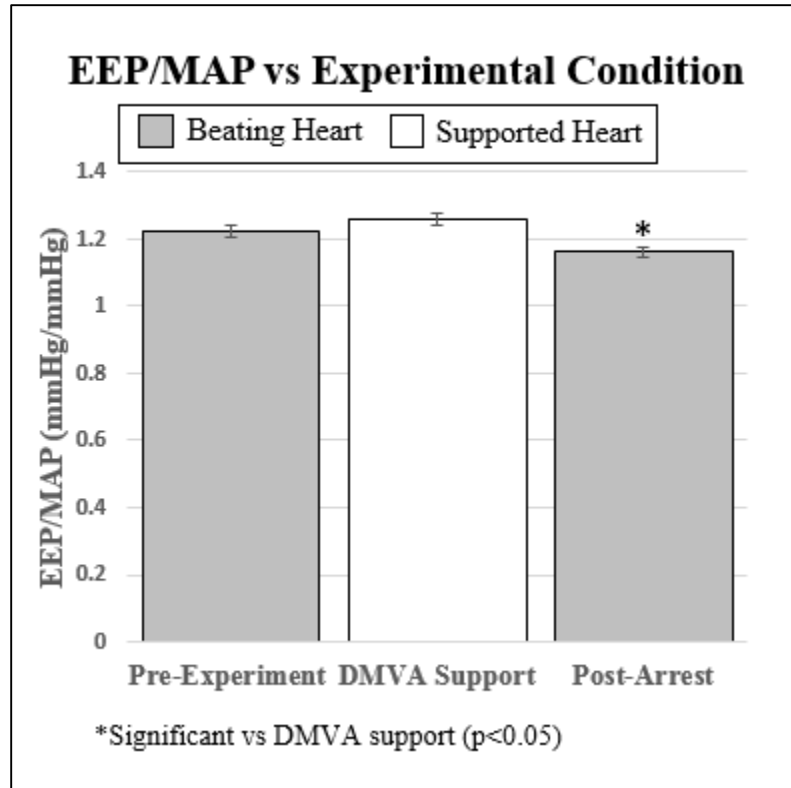
Figure 12. Comparison of EEP/MAP to experimental conditions. EEP/MAP had no significance between the supported heart and the pre-experiment beating heart. DMVA had a higher EEP/MAP ratio than beating heart at same cardiac output. Though hemodynamic energy relative to flow was similar between the two conditions, DMVA offered higher hemodynamic energy relative to mean pressure than the beating heart. This may have been due to some myocardial dysfunction from repeated fibrillation and defibrillation.

SURPLUS HEMODYNAMIC ENERGY

Surplus hemodynamic energy, the difference between EEP and MAP in terms of energy per volume, quantifies the pulsatile energy present in pulsatile circulation. SHE results from arterial blood flow were as follows: 18.15 ± 1.09 mmHg for baseline beating heart, 18.94 ± 1.15 mmHg for DMVA support, and 12.59 ± 0.98 mmHg for unsupported beating heart post-arrest. According to the data of all animals combined, SHE was significantly higher for fibrillation support than for the naturally beating heart at the same cardiac output (Figure 11). When compared to pre-experiment beating heart, SHE had no significant difference. For the animals individually, SHE was not significant between beating heart and fibrillating supported heart in most cases. SHE also had mostly no significant between the pre-experiment heart and DMVA support. In cases of significance, SHE was higher for support. DMVA support during fibrillation restored pulsatility in terms of SHE to that of the naturally beating heart.
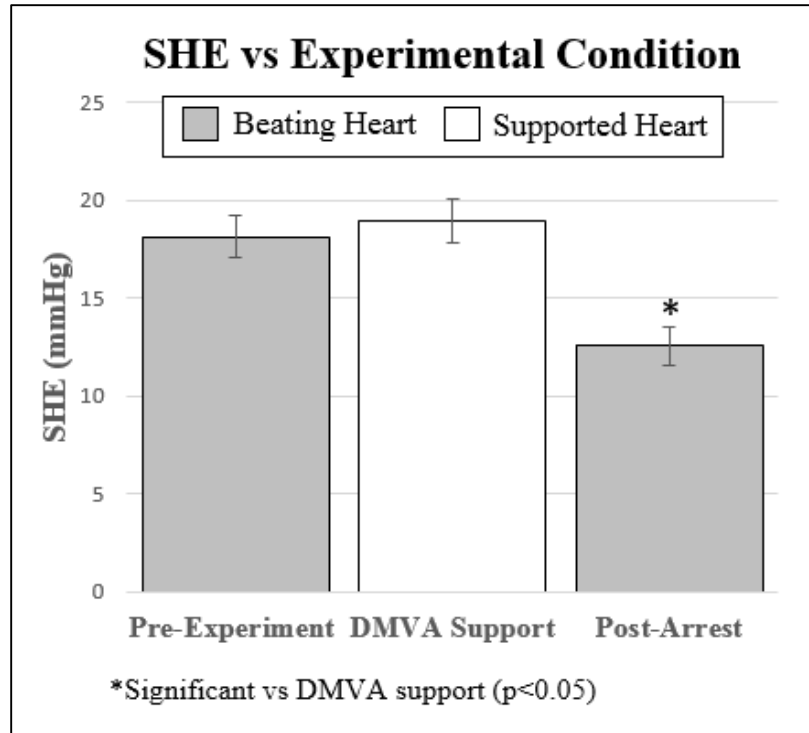
Figure 11. Comparison of SHE (Mean and standard error) between supported heart and beating heart. SHE was larger for supported heart compared to post-arrest beating heart at the same cardiac output. DMVA had no significance in SHE with pre-experiment beating heart. Significance may be due to a translation of energy to pulsatile form from cup mechanics. Pulsatility in terms of SHE was restored by DMVA support of the fibrillating heart to that of the naturally beating heart at similar flows.

POWER INDEX

PowIdx, a measure for the amount of hemodynamic energy in the flow over the time of the data capture, was calculated from flow and pressure data. PowIdx results from arterial blood flow were as follows: 0.73 ± 0.03 W for baseline beating heart, 0.53 ± 0.03 W for DMVA support, and 0.53 ± 0.3 W for unsupported beating heart post-arrest. According to the data of all animals combined, DMVA had no significance in terms of PowIdx with the unsupported beating heart at the same cardiac output level. Though DMVA had equivalent PowIdx as the beating heart at the same output level, DMVA had a significantly lower PowIdx than the pre-experiment beating heart (Figure 12).
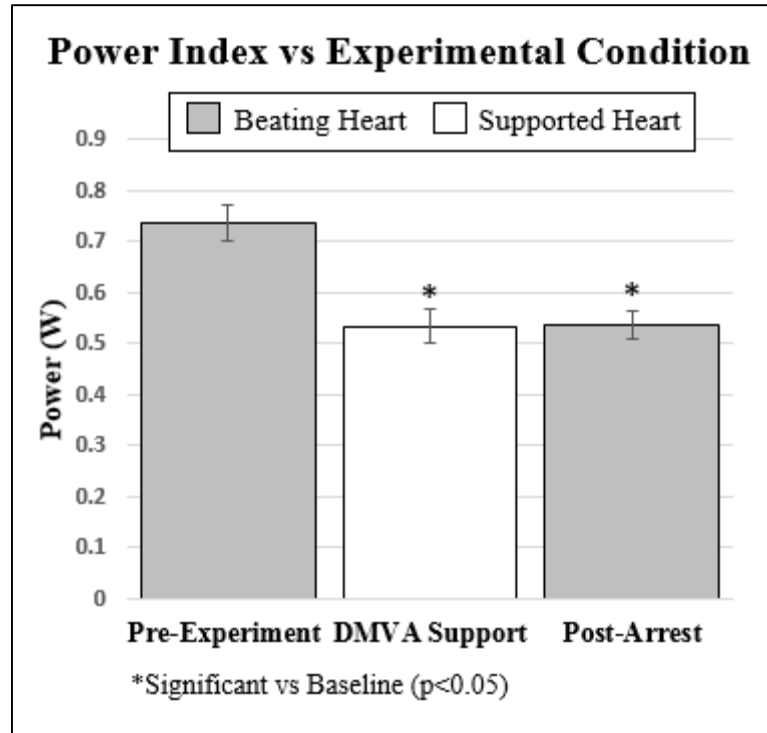
Figure 12. Comparison of PowIdx (Mean and standard error) between supported heart and beating heart. PowIdx was equivalent between supported heart compared and post-arrest beating heart at the same cardiac output. DMVA's PowIdx was significantly lower than PowIdx of pre-experiment beating heart. Significance is because the pre-experiment condition was at higher cardiac output, and higher hemodynamic energy levels. When DMVA generated normal output levels, its PowIdx was equivalent to the beating heart at the same output levels.

SHEAR STRESS

Maximum endothelial shear stress results from arterial blood flow were as follows: 19.38 ± 0.91 dyne/cm^2 for baseline beating heart, 22.21 ± 0.78 dyne/cm^2 for DMVA support, and 18.17 ± 0.72 dyne/cm^2 for unsupported beating heart post-arrest. When the heart was in fibrillation and supported by DMVA, levels of maximum endothelial shear stress in the ascending aorta did not decrease compared to when the heart was naturally beating (Figure 13). According to the data of all the animals combined, the maximum shear stress was significantly higher from DMVA compared to the post-arrest beating heart. Maximum shear stresses from DMVA were also significantly higher than those from the pre-experiment beating heart.
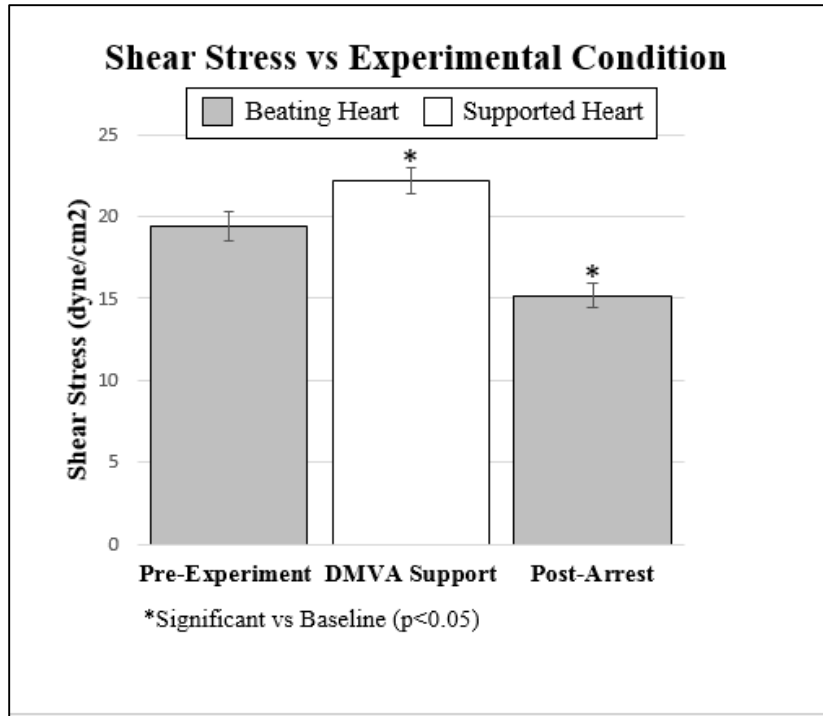
Figure 13. Comparison of endothelial shear stress (mean and standard error) in the ascending aorta between beating and supported heart. Shear stress was significantly higher for the supported heart than for the beating heart at both baseline condition and post-arrest condition. Maximum shear stress decreased in beating heart from baseline to post-arrest because flow rate had dropped.

AIM II: EFFECTS OF AORTIC FLOW AND PRESSURE

In execution of the second aim, each metric of pulsatility was compared to mean aortic flow and to mean aortic pressure to evaluate how those metrics were. MAP appeared to have a positive correlation with flow rate (Figure 14). This relationship varied from animal to animal, causing the data as a whole to be scattered; but for individual animals, the correlation between pressure and flow was strong for a majority of animals ($R^2>0.5$). This relationship was not affected by whether or not the heart was beating or supported during fibrillation (Figure 14.B). The association between pressure and flow was important for analyzing pulsatility of this experiment because flow and pressure varied among animals.

When comparing PP to either aortic flow or MAP, PP showed no apparent relationship with either (Figure 15). These plots show that PP from the supported heart was generally higher than PP from the beating heart. It was previously shown that PP was significantly higher in the supported heart than in the beating heart at the same cardiac output. Though pressure and flow level did not seem to affect PP, DMVA support did generate higher PP than the beating heart. And this was shown to be the result of higher relative systoles in the supported heart from the cup mechanism.

PI_{freq}, a function of flow frequency harmonics, seemed to rise as flow and pressure drop (Figure 16). In the beating heart pressure and flow have little effect on PI_{freq}. However, when the heart is supported, PI_{freq} seems to increase when both pressure and flow decrease.

When comparing SHE to aortic flow and MAP, SHE seemed to decrease somewhat as both increased, but with no strong correlation (Figure 17). This relationship did not seem

to be affected by whether the heart was naturally beating or was being supported during fibrillation.

Maximum shear stress, a function of maximum flow rate, had strong correlation with cardiac output or mean aortic flow (Figure 18). In most animals, the coefficient of determination (R^2) between maximum shear stress and mean aortic flow was greater than 0.7. The comparison of maximum shear stress to MAP showed less correlation. Based on these plots, shear stress did not seem to be affected by whether or not the flow was generated by DMVA or by the beating heart.
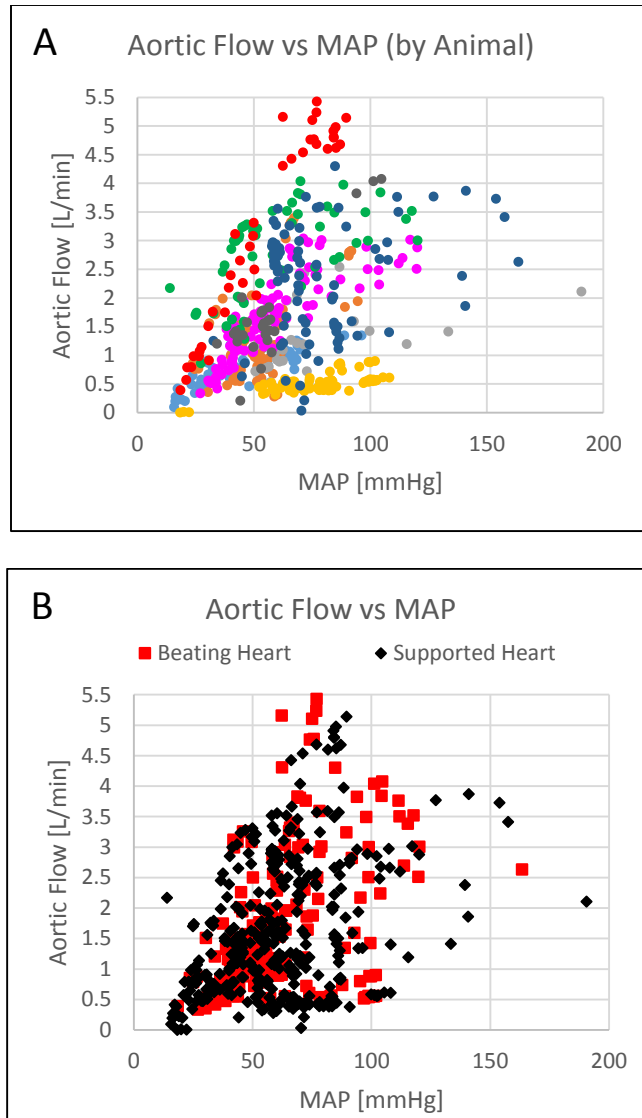
Figure 14. Comparison between MAP and aortic flow in all animals (A) and based on

flow generation (B). MAP appeared to increase as flow rate increased. In the majority of

animals, there was a fairly linear relationship between MAP and flow ($R^2 > 0.5$). This

relationship was dependent on animal; the slope varies from animal to animal causing the

data as a whole to fan. The correlation between pressure and flow was not affected by

whether the flow is generated by the beating heart or by DMVA support of the fibrillating

heart. Because pressure and flow varied among animals, this relationship may have been

important for the pulsatile metrics.
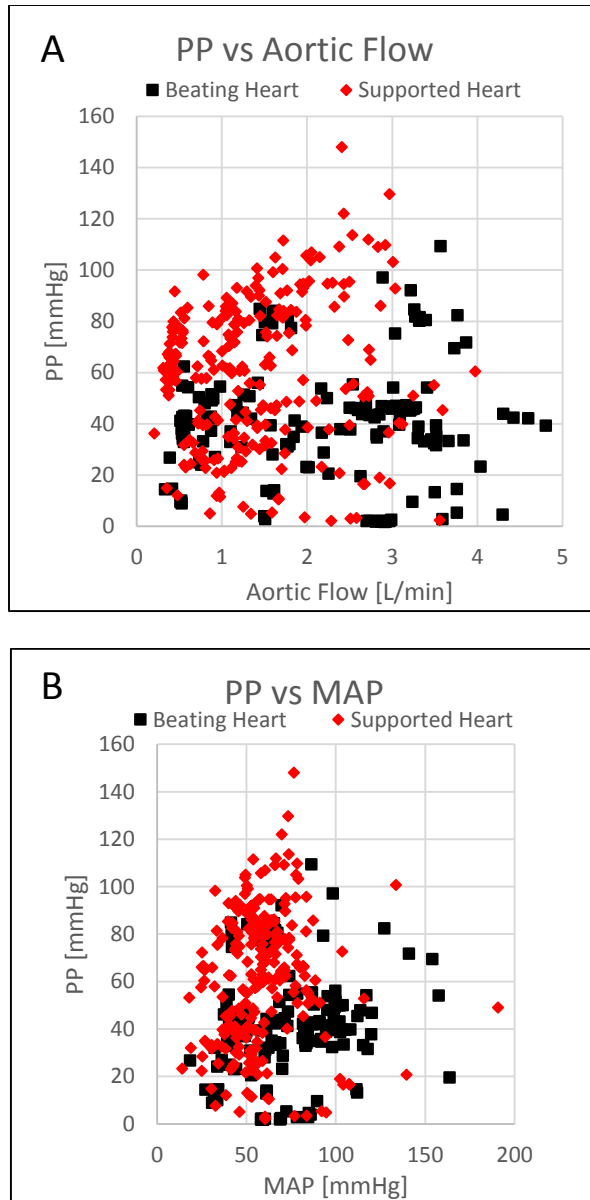
Figure 15. Comparison of PP to aortic flow (A) and mean arterial pressure (B). PP had no apparent correlation to pressure or to flow. PP seemed to be higher in the supported heart than in beating in both these plots. As already shown at the same output, PP was significantly higher in the supported heart than in the beating heart. PP was not apparently affected by magnitude of flow or pressure but was dependent upon source of flow, whether from beating heart or DMVA supported heart.
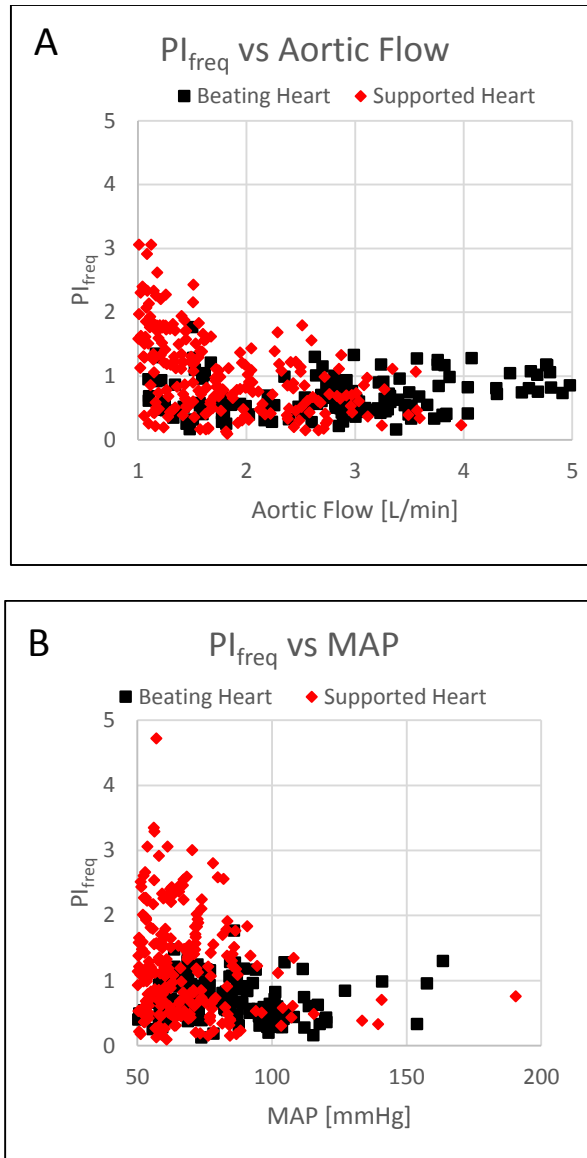
Figure 16. Comparison of PI$_{freq}$ to aortic flow (A) and pressure (B). PI$_{freq}$ seemed to increase as both pressure and flow decreasd for the supported heart but not for the beating heart. Because PI$_{freq}$ quantifies pulsatility as the amount of wave frequency over the flow magnitude, DMVA maintains wave frequency at lower volumes causing this index to increase at lower outputs.
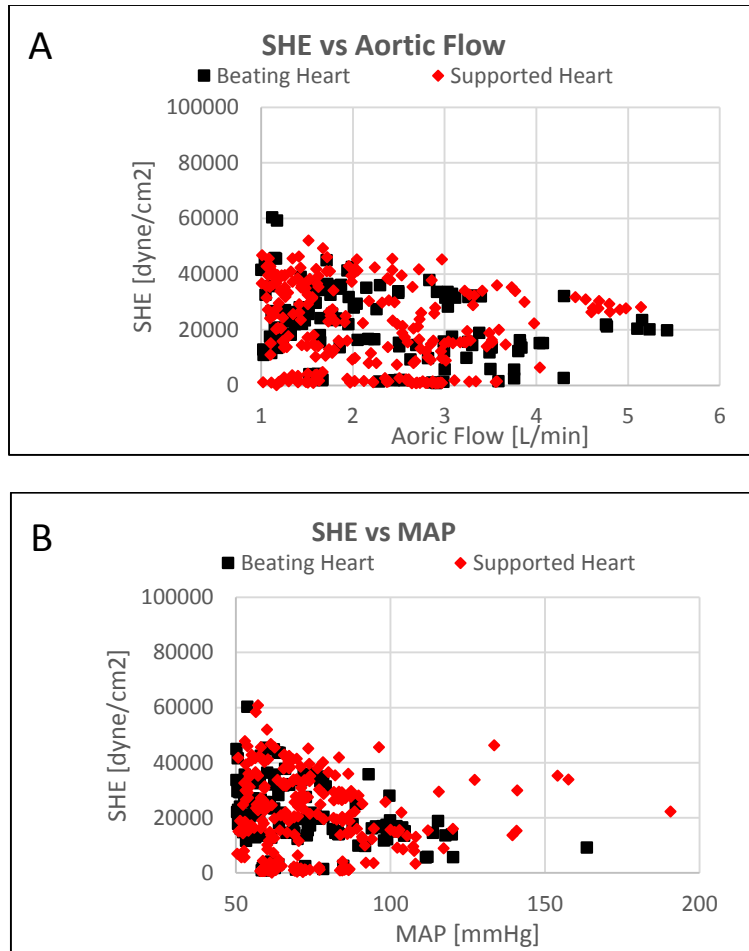
Figure 17. Comparison of SHE to aortic flow (A) and to MAP (B). SHE seemed to

decrease as both increase but without strong correlation. SHE is the difference between

EEP and MAP. EEP and MAP were already shown to be linearly related, with MAP

growing faster than EEP. The decrease in MAP was faster than the decrease in EEP at the

lower flows and pressures, causing the difference between them to rise at the lower flows

and pressures; thus, SHE increased as MAP decreases. SHE's relationship with pressure

and flow did not seem to be affected by whether or not the flow was generated by the

beating heart or by DMVA.
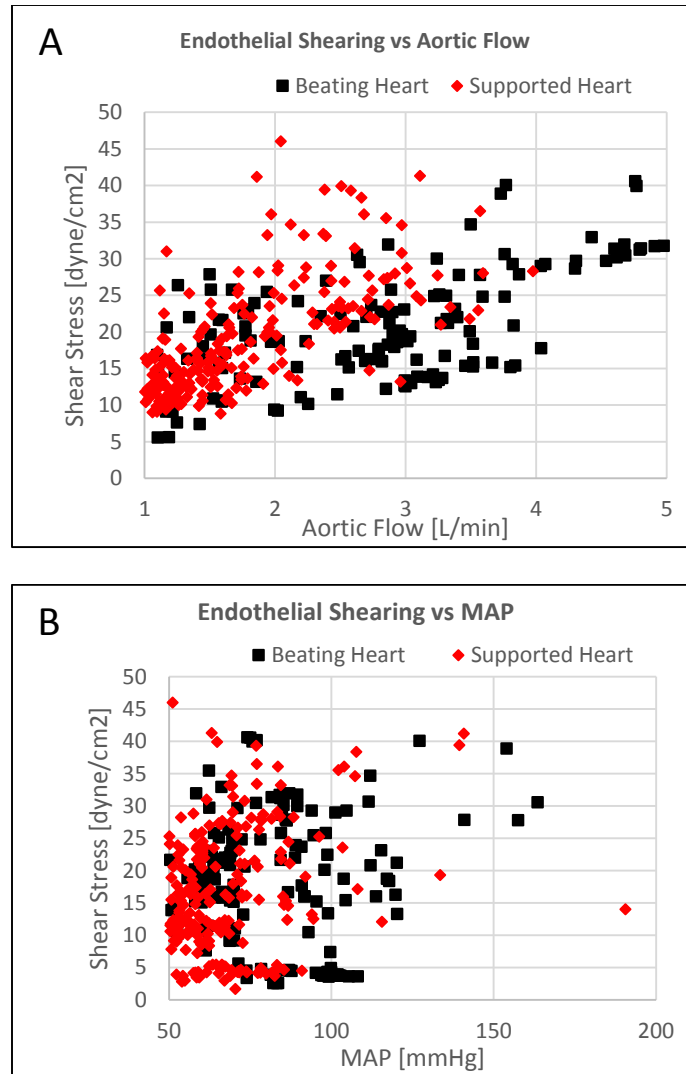
Figure 18. Comparison of maximum aortic endothelial shear stress to aortic flow (A) and
to MAP (B). Maximum shear stress had strong linear relationship with aortic flow
(R^2>0.7 in most animals). As mean flow rate in pulsatile flow increased, the maximum
flow rate would intuitively increase. Because shear stress is a function of flow rate,
maximum shear stress increased with flow rate. Shear stress had less correlation with
MAP, but did seem to increase with the rise in MAP. Shear stress did not seem to be
affected by whether the flow was generated by the beating heart or by DMVA.

IV. DISCUSSSION

Given the lack of a standard measure for pulsatility, pulsatile quantification has been somewhat inconsistent across the literature, though EEP seems to be the most represented index in current literature. All of the measures included in this study derive their quantification of pulsatility from flows and or pressure waveforms. Though both canine and swine models were used, physiologic differences between canines and swine do not confound these results since the comparison are normalized to each animal specifically. Likewise, having both species provided representation of larger and smaller hearts. Pulsatility could be directly compared between DMVA and the beating heart because mean flows were normalized between subjects with minimal significance in aortic flows and pressures.

Pulse pressure is the most basic method to quantify pulsatility, only representing the extremes of the pressure signal. DMVA appeared to produce significantly higher pulse pressures than the naturally beating heart at the same cardiac output. This increase was largely due to significant increases in systolic pressure observed during DMVA support while diastolic pressures remained relatively consistent. The rise in systolic pressure may have been due to the mechanisms of the cup air pressure. Nonpulsatile flow pumps can be manipulated to generate pulse pressures by varying pump impeller speed throughout the cardiac cycle. However, the flow dynamics from these pumps differ from those of physiologic pulsatile flow.

Frequency analysis provides a measure of pulsatility based on the properties of the Fourier transform. The Fourier transform fits a series of sinusoids in the frequency-domain plot from the flow data. A continuous flow signal shows up simply as the DC component in a frequency-domain plot since no sinusoid can be fitted to a flat line. Introducing pulsatility or flow frequency into the flow signal produces greater amplitudes (harmonics) of the non-DC frequency values. Given this relationship, pulsatility can reasonably be measured with the PI_{freq} which quantifies pulsatility as ratio of cycle frequency to flow magnitude. Continuous flow has a PI_{freq} of zero because it lacks flow frequency and has zero harmonics in its Fourier transform. The higher PI_{freq} from DMVA support compared to the post-arrest beating heart can be explained by possible loss of flow wave frequency when the heart was in failure. The dysfunctional myocardium could alter the consistency of wave frequency or the numerator of this term at this condition dropping its PI_{freq} below that of the supported heart. DMVA restored pulsatility in terms of frequency harmonics to that of the pre-experiment beating heart.

Pulse pressure has been largely replaced by EEP to measure pulsatility because EEP accounts for both pressure and flow and accounts for the entirety (integration) of both signals rather than just the extremes. EEP is a measure of the total hemodynamic energy per volume of blood flow in pressure terms. The difference between EEP and MAP (SHE) provides a measure of pulsatility energy. There was no significant differences in the EEP values between the supported heart and the beating hearts at the same cardiac output. However, EEP from DMVA was lower than the EEP of the pre-experiment state which was hyper-dynamic and possessing more energy per volume. SHE from DMVA support was equivalent to the SHE of the pre-experiment beating heart, and was

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significantly higher than the SHE of the post-arrest beating heart at the same cardiac output. Though DMVA was at the same energy per volume level (EEP) as the post-arrest beating heart, this energy was translated into a pulsatile form since SHE was higher for DMVA. Normalizing EEP relative to MAP provided the comparison of pulsatile energy between flows at different mean pressures. A nonpulsatile flow has an EEP/MAP ratio equal to 1.0; EEP/MAP of healthy human hearts was found to be about 1.1 [47]. The average EEP/MAP from these animals was about 1.2. This ratio had no significant difference between DMVA support and the pre-experiment beating heart.

The current methods to quantify pulsatility are not without concern, however. Pulsatility in the blood is an effect that is present in both the pressure and flow dynamics. Pulse pressure quantifies the pulsatility essentially as a pressure. And though EEP (along with SHE) quantifies pulsatility based on hemodynamic energy, it characterizes pulsatility ultimately as a pressure. To quantify pulsatile flow as a pressure fails essentially disregards its flow dynamics. PI_{freq} quantifies pulsatility as a ratio of wave frequency to flow volume; but this flow is dimensionless. Pulsatility, which has a physical presence in pressure and flow, cannot validly be measured without dimensions. Power analysis might more suitably quantify pulsatility because power is the product of flow and pressure. Pulsatility studies using hemodynamic power as a metric are not prevalent but have been attempted.

Relevant to pulsatile flow is the shear stresses from the flow to the endothelium. Endothelial signaling is often impaired via altered stress profiles during mechanical circulatory support. Continuous flow at the same mean rate as pulsatile flow would decrease the maximum shear stress levels by over fifty percent of the maximum shearing

of pulsatile flow. When continuous flow is increased for pressure regulation, maximum shear stress could be at abnormal levels. Altered shear stresses in continuous flow systems result in dysfunctional endothelial signaling (such as changes in reactive oxygen and nitrogen species and abnormal angiogenesis). While the analysis in this study was limited by assumptions of laminar flow, constant viscosity, and vessel diameter, the results should be considered proportional in comparing continuous and pulsatile flow systems with the similar flows. The pulsatile system is able to maintain transient shear values far above a continuous system which may facilitate abnormal endothelial signaling. Normal human values of arterial shear stress range between 10 and 40 dyne/cm^2 [68]. In our animal tests, aortic maximum shear stresses were close to 20 dyne/cm^2 for the beating heart and DMVA support.

Also of interest is the impact of mean aortic flow and pressures to the pulsatile indices. Correlations between aortic flow and pressure were observed. When plotted against each other, MAP appeared linearly proportional to flow from animal to animal ($R^2 > 0.5$ in most animals). The link between flow and pressure might have had some effect on the quantification of pulsatility. With the exception of pulse pressure, all indices appeared to have some impact by flow and pressure. EEP had strong linear correlation with MAP ($R^2 = 0.8$). This correlation was explained because hemodynamic energy (and pulsatility based on hemodynamic energy levels) increased with higher flow and pressure levels. Endothelial shear stress appeared to have a slight proportional relationship with flow and pressure, but with poor correlation. Shear stress, a function of flow rate, would be theoretically related to mean flow rate, but this shear stress is calculated from peak flow rates which can vary at a given mean flow. PI_{freq} and SHE seem to increase as

pressure and flow levels drop; these correlations are weak as well. A drop in mean aortic flow in the presence of maintained flow frequency from the cup could drive the PI_{freq} up during DMVA support at lower outputs. MAP decreased more quickly than the hemodynamic energy dropped at low outputs causing DMVA's rise in SHE. Because only EEP had a strong correlation with MAP, EEP could be normalized by it. No other metric could be normalized by flow or pressure.

For this comparison of pulsatility between DMVA and the beating heart, support at normal cardiac outputs is the only condition that is valuable. DMVA at lower cardiac outputs was due to improper settings in the device such as wrong cup size or wrong pressure input, and these results disregarded. Adequate consideration of DMVA's ability to restore arterial pulsatility required attention to DMVA at normal physiologic outputs.

Of ultimate importance is that pulsatility was restored by the DMVA support to the baseline physiologic levels and equivalent to or higher than that of the unsupported beating heart at the same output. Only EEP and PowIdx had significance between DMVA and beating heart because DMVA was at a lower cardiac output and possessed less energy than the hyper-dynamic condition. But with terms of relative pulsatility such as EEP/MAP and SHE, DMVA was equivalent to the pre-experiment baseline. Since the heart is fibrillating during support, the DMVA cup provided essentially all the heart function. Significance in arterial pulsatility between DMVA support and the beating heart at the same cardiac output occurred when the heart was weakened and essentially in a failure state following defibrillation.

Future studies on DMVA might consider redefining pulsatility based on power which is the product of flow and pressure so to truly represent both elements. Pulsatility has yet

58

to be actually quantified by both flow and pressure, since its indices essentially become pressure or dimensionless from the conventional metrics. A power analysis would be more robust and better account for the presents of pulsatility in the arterial flow and pressure. Perhaps simply a root-mean-square of the instantaneous power could represent the pulsatility, or even a more complex calculation of power such as those already attempted in literature could better quantify pulsatility. However, to effectively compare pulsatile flow, a better means of quantifying pulsatility than the conventional measures is essential.

Other possible studies on DMVA could consider pulsatility in other ways. DMVA supports both ventricles simultaneous from the cup; the pulmonary pulsatility likely is effected by the device. Effects to pulmonary pulsatility may be of interest. And while my current study has analyzed pulsatility of DMVA support during fibrillation, the pulsatility may respond differently to DMVA's interaction with a weakly beating heart. These sorts of studies on DMVA's affect to pulsatility should be considered.

The absence of natural functionality in the fibrillating heart provided an ideal model to determine the impact of DMVA mechanics since the heart's function came almost entirely from the device. DCC devices have been considered advantageous in generating physiologic pulsatile flow compared to many blood pumps. By definition, DCC devices better replicate pump dynamics than blood-contacting devices because DCC is directly pumping by myocardial contractility. However, it was not known whether this external pumping motion truly generated arterial pulsatile flow equivalent to the intrinsic pulsatility from the heart's contractility. This study suggests that external compression of

the heart by DMVA can indeed restore pulsatility to physiologic levels; a summary of results is in Table 4.

Table 4. Summary of results. Pulsatile characteristics in arterial blood flow were restored by DMVA support for the fibrillating heart. All pulsatile metrics from DMVA support were equivalent to or higher than those of the unsupported beating heart at the same cardiac output. DMVA's arterial pulsatility was equivalent to that of the pre-experiment baseline heart in all terms except EEP and PowIdx at which the baseline had a higher cardiac output and thus higher hemodynamic energy levels. However, in terms of relative hemodynamic energy such as EEP/MAP or SHE, pulsatility from DMVA was equivalent to the pre-experiment baseline beating heart.

Experimental Condition	Sample Size	CO (L/min)	MAP (mmHg)	Measures of Pulsatility					
				PP (mmHg)	Freq PI	EEP (mmHg)	EEP/MAP	SHE (mmHg)	PowIdx (W)
Baseline Beating Heart	35	3.08 ± 0.06	94.20 ± 4.03	68.95 ± 4.79	0.72 ± 0.05	112.35 ± 4.21	1.22 ± 0.02	18.15 ± 1.09	0.74 ± 0.03
DMVA Support for Fibrillating Heart	47	2.71 ± 0.05*	77.33 ± 4.24*	70.56 ± 4.25	0.82 ± 0.04	96.23 ± 4.26*	1.26 ± 0.02	18.94 ± 1.15	0.53 ± 0.03*
Unsupported Failing Heart	87	2.70 ± .05*	83.60 ± 3.63*	39.71 ± 3.44*^	0.68 ± 0.04^	96.18 ± 3.79*	1.16 ± 0.02*^	12.59 ± 0.98*^	0.53 ± 0.03*

Values expressed as Mean ± SEM; * $p<0.05$ vs Baseline; ^ $p<0.05$ vs DMVA

CO = cardiac output; MAP = mean arterial pressure; PP = pulse pressure; Freq PI = frequency pulsatility index; EEP = energy equivalent pressure; SHE = surplus hemodynamic energy; PowIdx = power index

V. CONCLUSION

This study compared pulsatility in arterial blood flow between DMVA support of the fibrillating heart and the naturally beating heart and suggested the equivalency of arterial flow pulsatility between DMVA and the naturally beating heart. In the present state of cardiac support devices in which most devices generate nonpulsatile flow by convention, DMVA provides non-blood contacting pulsatile flow support. Pulsatility was quantified based on pressure dynamics, frequency harmonics, and hemodynamic energy and was shown to be similar between DMVA support and the pre-experiment beating heart. The levels of pulsatility from DMVA support were similar to those of the post-arrest beating heart at the same cardiac output. Based on lack of significance, this study suggests that DMVA restores pulsatile characteristics in arterial flow in a fibrillating heart to that of the native beating heart.

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