Artificial Organs

A Physical Heart Failure Simulation System Utilizing the Total Artificial Heart and Modified Donovan Mock Circulation

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Abstract: With the growth and diversity of mechanical circulatory support (MCS) systems entering clinical use, a need exists for a robust mock circulation system capable of reliably emulating and reproducing physiologic as well as pathophysiologic states for use in MCS training and interdevice comparison. We report on the development of such a platform utilizing the SynCardia Total Artificial Heart and a modified Donovan Mock Circulation System, capable of being driven at normal and reduced output. With this platform, clinically relevant heart failure hemodynamics could be reliably reproduced as evidenced by elevated left atrial pressure (+112%), reduced aortic flow (−12.6%), blunted Starling-like behavior, and increased afterload sensitivity when compared with normal function. Similarly, pressure-volume relationships demonstrated enhanced sensitivity to afterload and decreased Starling-like behavior in the heart failure model. Lastly, the platform was configured to allow the easy addition of a left ventricular assist device (HeartMate II at 9600 RPM), which upon insertion resulted in improvement of hemodynamics. The present configuration has the potential to serve as a viable system for training and research, aimed at fostering safe and effective MCS device use. **Key Words:** Total artificial heart—Donovan mock circulation—Mechanical circulatory support—Heart failure—Physiologic simulation—Ventricular assist device.

Mechanical circulatory support (MCS) has emerged as the standard-of-care for advanced heart failure (AHA Stage D, NYHA Class IV) (1–4). A range of MCS devices are in clinical use in the United States including implantable ventricular assist device (VAD) systems (Thoratec HeartMate II and HeartWare HVAD), the total artificial heart (SynCardia TAH-t), and a number of percutaneous/extracorporeal short-term devices, with several other systems in development and testing around the world (5). With the growth in MCS use and its increasing technical user base, that is, clinicians, engineers, MCS support staff, nurses, patients, and caregivers, a need exists for an effective, hands-on system for training to the physiology and hemodynamics associated with use of specific MCS devices under simulated physiological real world conditions (5,6). In addition, creating a single physical system, which could be readily used to simulate and assess the performance of a given MCS device under a defined set of clinical conditions prior to in vivo use could ultimately lead to a more personalized, scientifically guided refinement of device parameter settings (i.e., pump speed). Further, such a system would allow for interdevice comparison and provide a means to objectively compare devices under defined hemodynamic conditions.

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To date, a variety of mock circulation systems have been configured to mimic human circulatory physiology and several of these systems have been used for in vitro hemodynamic and hemolysis testing of MCS devices (7–19). However, these mock circulation systems are largely ad hoc setups that are assembled from multiple components for lab use, are not readily available to MCS implanting centers, and are typically not used by clinicians or MCS support staff to train, personalize, or directly compare MCS devices.

Recently we have defined and characterized a full circulatory mock circulation system consisting of the SynCardia TAH in combination with a modified Donovan Mock Circulation System (DMCS) (20). This system is robust, capable of physically reproducing a wide range of hemodynamic parameters, for example, pressure and load extremes, is relatively transportable, and is presently installed in many clinical TAH implanting sites as part of the regulatory-defined training program (21). In a previous report from our group, the physiology of the TAH system was evaluated under normal drive conditions over a wide range of loading parameters. In this study, our group builds upon this work by modifying this system to operate under reduced pumping (systolic and diastolic) conditions, thereby emulating left ventricular failure. Here, we hypothesize that the TAH operating with reduced left ventricular output, in conjunction with the DMCS, will provide a reproducible, robust, physical heart failure model, demonstrating hemodynamics consistent with left ventricular failure. Further, we propose that this configuration could be used as a system to evaluate the functional performance of ventricular assist devices under defined clinical hemodynamic scenarios, for training and research purposes.

In this study, we first define and examine the reproducibility and function of normal and heart failure states with the mock system. Second, we characterize the heart failure model over a range of pre- and afterloads, examining hemodynamics as well as pressure-volume (PV) relationships. Finally, we examine the effect of adding a ventricular assist device to the system as to its ability to modulate hemodynamics.

MATERIALS AND METHODS

The TAH and the hydraulic analog of the circulatory system

A modified Donovan Mock Circulatory System (DMCS) with an affixed 70cc SynCardia TAH (SynCardia Systems, Tucson, AZ, USA) was used for all studies, as fully detailed in our previous report (20; Fig. 1). Briefly, each of the TAH ventricles supports an inner flexible diaphragm assembly separating each ventricle into two compartments, an air compartment and a blood compartment. The diaphragm assembly is mobilized via pulses of air supplied by an external pneumatic driver. Air in from the driver causes an upward mobilization of the diaphragm assembly, which in turn forces blood out of the ventricle during systole, resulting in forward, pulsatile flow (22). Diastole occurs with air evacuation from the ventricle, allowing the diaphragm assembly to move outward from the blood chamber, creating space in the blood side of the ventricle thus allowing it to fill with blood. The external pneumatic driver allows for the control of drive pressure and vacuum for each ventricle, percent systole, and beat rate (22). The SynCardia TAH as used in normal, clinical use is driven using the partial fill, full eject principle (i.e., the ventricles are partially filled during diastole and fully ejected during systole—all fluid filled during diastole is ejected each cardiac cycle). Operating the TAH in partial fill conditions ensures that there is always reserve volume in the ventricle to accommodate for additional venous return from the body (creating a Starling-like effect). In clinical use, the TAH driver is always set to provide enough driving pressure on the diaphragm to eject all fluid in the ventricle (i.e., ensuring afterload can be overcome [22]).

A DMCS (SynCardia Systems) was used to simulate the systemic and pulmonary portions of the human vasculature for all experiments (21). The DMCS contains four chambers representative of the following domains: right atrium, pulmonary artery, left atrium, and aorta, with the ability to control the flow resistance between aorta and right atrium via a bellows-operated valve (simulating systemic vascular resistance) and pulmonary artery and left atrium via a bellows-operated valve (simulating pulmonary vascular resistance). Vascular compliance is manipulated via control of the volume of air within each of the chambers representing the four vascular domains (21). The system was filled with a 35% (v/v) glycerin/deionized water solution, with a viscosity of 3.5 cps at 24°C, as a functional blood equivalent.

Experimental configuration and baseline normal operating conditions

All chambers of the DMCS were fitted with pressure transducers (Abbott, Abbott Park, IL, USA) allowing pressure determination for each chamber: aortic pressure (AoP), left atrial pressure (LAP),

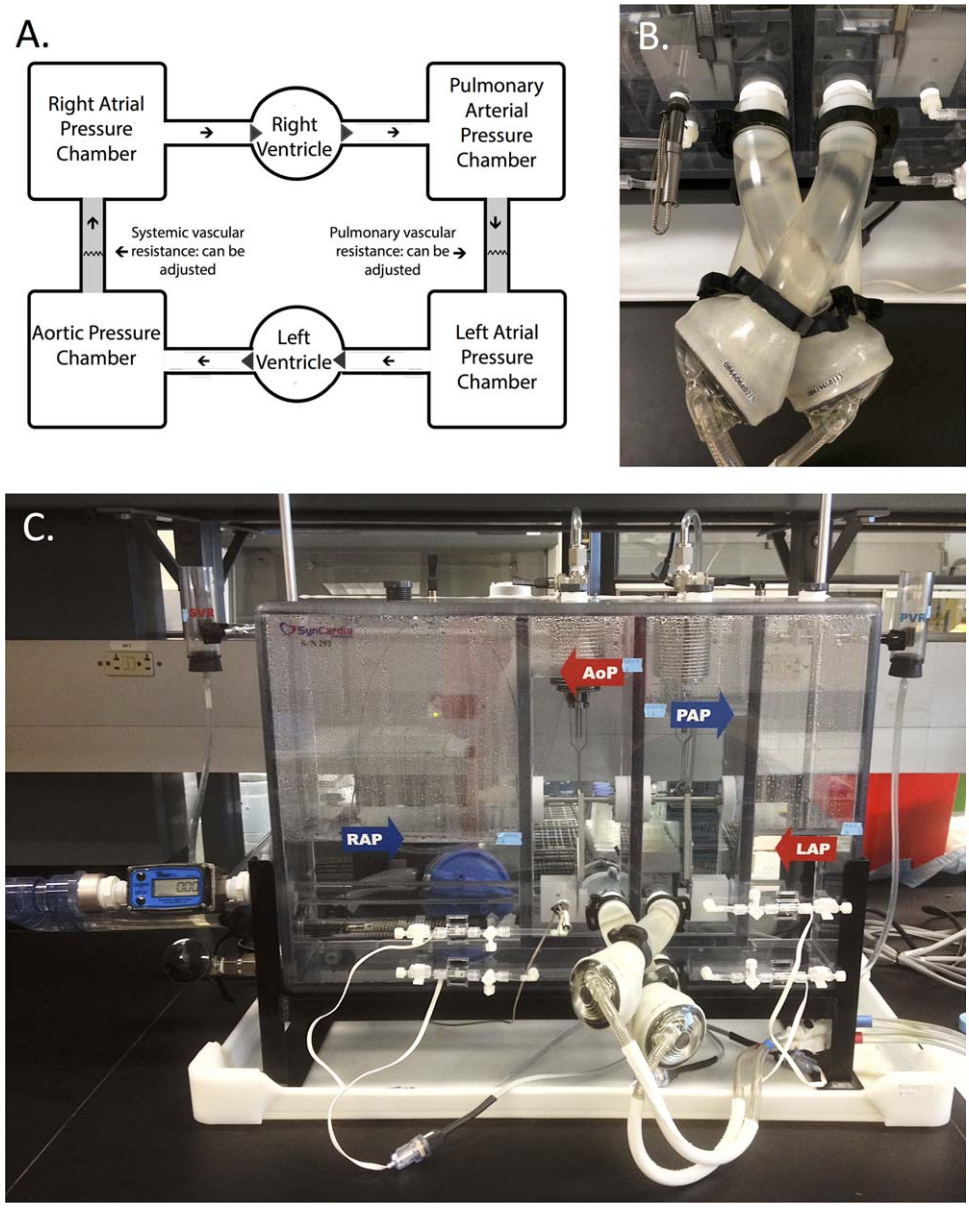

FIG. 1. The donovan mock circulation system (unmodified). A: Fluid flow through the TAH (right and left ventricle) and Donovan Mock Circulation System (four chambers). The triangles within the ventricles represent valves of the TAH. B: Close-up of the left and right ventricles of the TAH attached to the DMCS. C: The DMCS with attached TAH.

right atrial pressure (RAP), and pulmonary artery pressure. Four high-fidelity strain gage pressure catheters (SPR-524, Millar Instruments, Houston, TX, USA) connected to a pressure control unit (PCU-2000, Millar Instruments) were used to monitor continuous AoP, left ventricular pressure, right ventricular pressure, and left-atrial pressure. Three flow meters (ME 25 PXN, Transonic Systems, Ithaca, NY, USA) were placed throughout the system to measure fluid flow rates of left ventricular inflow, left ventricular outflow, and VAD outflow (Fig. 8). Data from all sensors were acquired at 200 Hz with a compact data acquisition board (NI-9219, NI-9211, and two NI-9205, National Instruments, Austin, TX, USA) interfaced with a custom LabVIEW executable.

The TAH was driven by the Companion 2 pneumatic driver (SynCardia Systems). Baseline normal driver conditions were: left drive pressure 180 mm Hg, left vacuum −10 mm Hg, right drive pressure 60 mm Hg, right vacuum −10 mm Hg, heart rate 100 beats per minute, and 50% systole. Once baseline parameters were set on the driver, the DMCS was set to "normotensive" patient conditions: right atrial mean pressure 6 ± 5 mm Hg, pulmonary arterial mean pressure 20 ± 5 mm Hg, left atrial mean pressure 10 ± 5 mm Hg, and aortic mean pressure 95 ± 5 mm Hg.

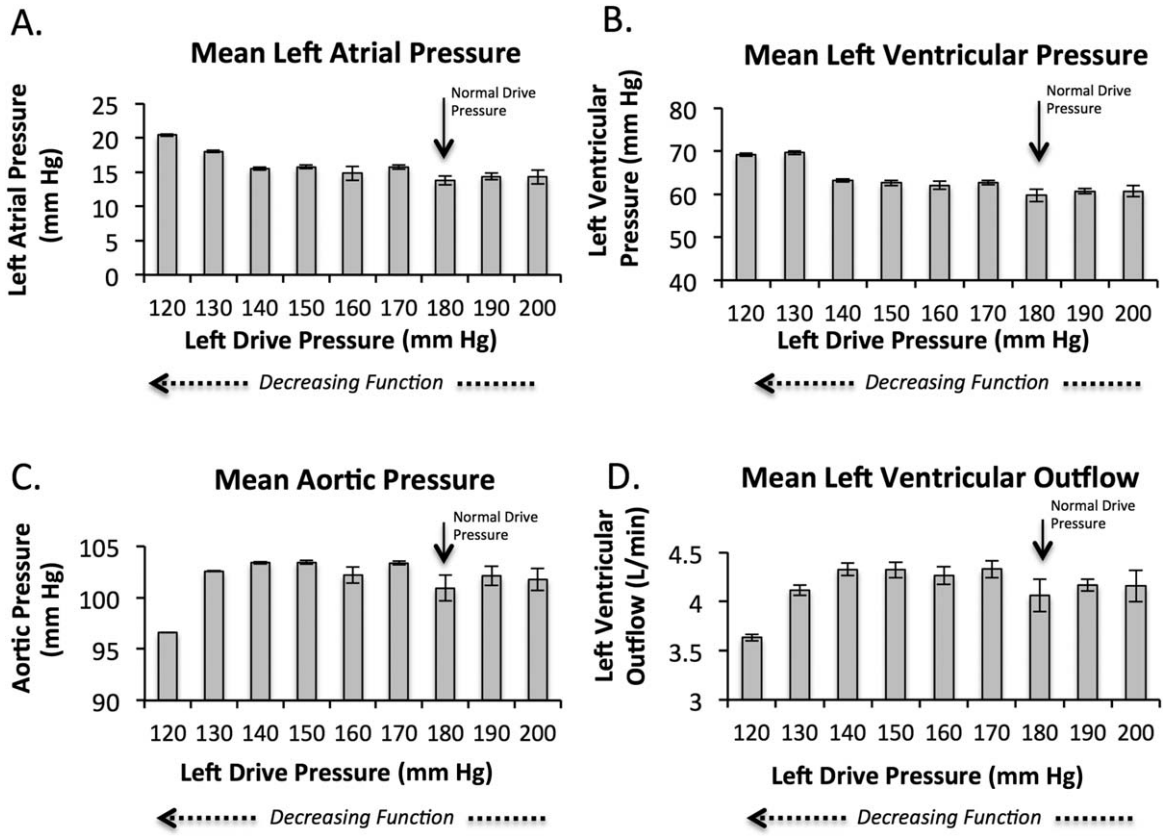

FIG. 2. Effect of progressive "Failure" (decreasing left drive pressure) on TAH and systemic pressures. A–D: Average LAP, left ventricular pressure, AoP, and left ventricular outflow are shown over a range of left drive pressures. The arrow over 180 mm Hg indicates the normal left drive pressure typically used clinically. No driveline vacuum was applied with the driver to further decrease function of the TAH to mimic reduced function.

Emulation of left ventricular failure with the DMCS and TAH

To mimic the hemodynamics of left ventricular failure, two parameters were varied on the Companion 2 TAH driver system: left ventricular driving pressure (affecting ventricular systole) and left ventricular vacuum (affecting ventricular diastole). During characterization of the system in reduced output "heart failure" conditions, the DMCS was set to normal operating conditions (settings provided above) as a baseline. The TAH pneumatic driver (Companion 2) left vacuum was then set to 0 mm Hg and the left driving pressure was varied between 200 and 120 mm Hg in increments of 10 mm Hg; 120 mm Hg is the minimum achievable left driving pressure on the Companion 2 Driver (180–200 mm Hg is the typical left drive pressure used clinically). Following each incremental adjustment, the DMCS was allowed to equilibrate and stabilize for 2 min, following which data from all channels were recorded at 200 Hz for 10 s and completed three times. Pressure, flow, and percent ventricular emptying were measured as endpoint variables for all protocols completed. (The term "ejection fraction" was avoided in this report—reserving this for a tissue ventricle, as the TAH with a plastic ventricle does not dilate, lacks time varying elastance and is purposely under-filled during clinical use to allow for a Starling-like effect of partial fill, full eject, increasing output based on increasing venous return.)

Effect of varying afterload and preload on heart failure model hemodynamics

The system's response to an increase in afterload was assessed with the TAH operating under reduced drive conditions, left ventricular drive pressure of 120 mm Hg and left ventricular vacuum of 0 mm Hg. These reduced output settings were used for heart failure conditions throughout the study. The mean AoP (afterload) was raised in 5 mm Hg increments from 95 to 110 mm Hg. Similarly, the system's response to a change in preload was assessed during reduced driver conditions through variations in the right ventricular vacuum, which in turn varied left ventricular end-diastolic volume

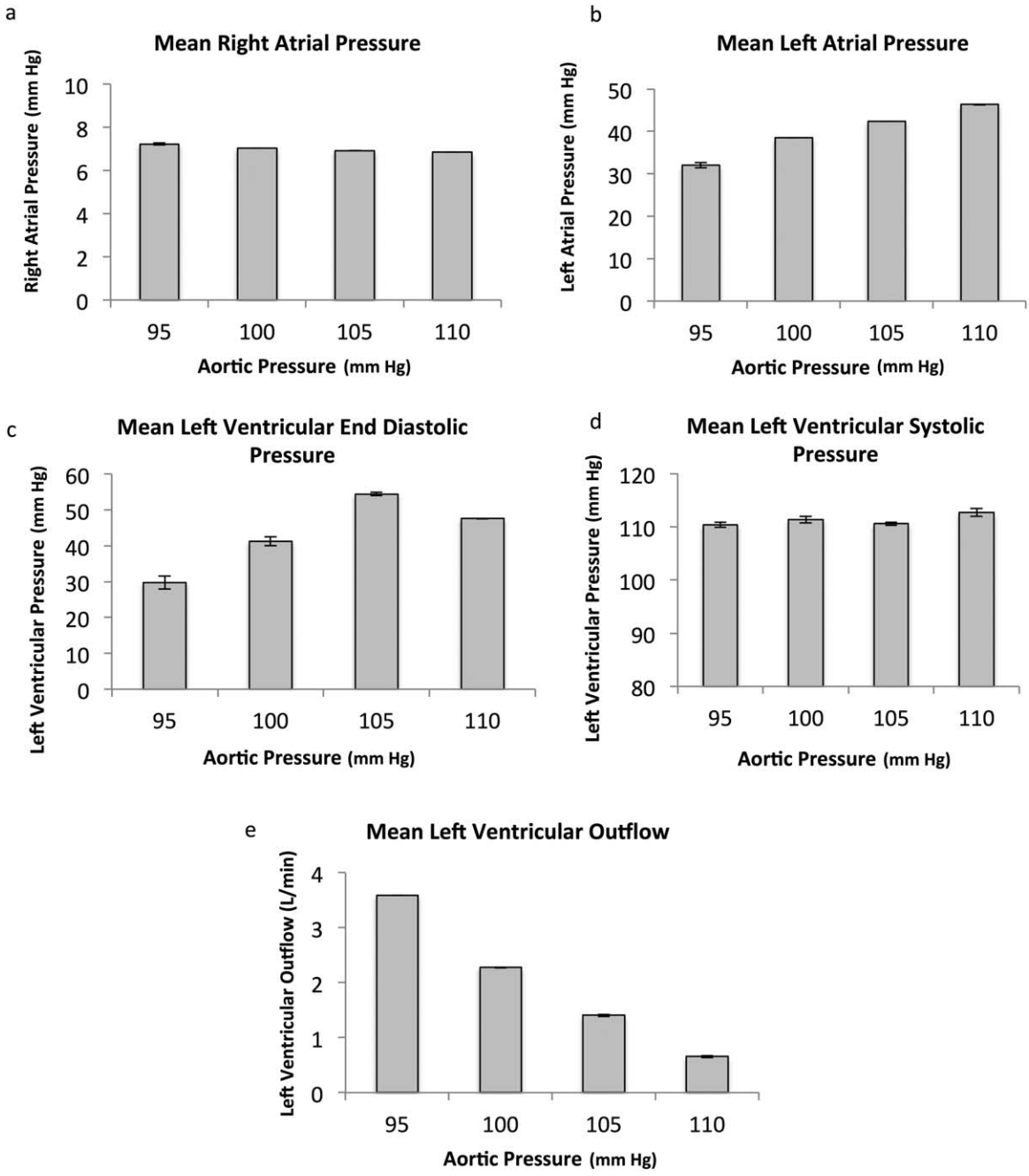

FIG. 3. Effect of afterload alterations in heart failure conditions. A–D: Plots of mean RAP, LAP, left ventricular end diastolic pressure, left ventricular systolic pressure, and left ventricular outflow over a range of mean AoPs (afterloads). The afterload was varied using the bellows operated valve in the DMCS.

(EDV). The right vacuum was varied from 0 to 20 mm Hg (10 mm Hg being the normal vacuum value used clinically) so that the EDV of the left ventricle ranged from 48 to 73 mL. Following each incremental adjustment, the tank was allowed a 2-min interval to reach steady state, following which data from all channels was recorded at 200 Hz for 10 s. Each test condition was repeated three times.

Addition of a ventricular assist device to the mock system

The DMCS with attached TAH was altered to allow for incorporation of various MCS devices via modification of the left ventricular outflow tubing. Two T-junctions, separated by a one-way bi-leaflet Open Pivot artificial heart valve (Medtronic, Minneapolis, MN, USA), were placed between the

outflow of the left ventricle and the inflow to the aortic (AoP) chamber of the DMCS. This system alteration (i.e., T-junctions with additional valve) essentially "extends" the left ventricle such that the inflow of any LVAD could be incorporated within the mock vasculature loop without damaging the ventricle of the TAH. This additional valve acts as the primary aortic valve when the LVAD is in use (the TAH's native aortic valve will remain open when the LVAD is in place). Note that the limitation of incorporation of the MCS device in this manner limits the ability of the user to simulate severe suck-down events that could occur in a native ventricle. A flow sensor (ME 25 PXN, Transonic Systems) was placed immediately distal to the MCS insertion site to measure device outflow.

Effect of VAD pump speed on heart failure model physiology

With the system set to heart failure mode (66% of baseline left drive pressure) a HeartMate II LVAD was added to the circuit and set to operate over a range of speeds (7000–11000 RPM, in increments of 200 RPM). Following each incremental adjustment, the system was allowed a two-minute interval to reach steady state, following which data from all channels was recorded at 200 Hz for 10 s. Each test condition was repeated three times.

RESULTS

Defining the heart failure model

Incremental decreases in the left pneumatic drive pressure, with the vacuum at 0 mm Hg, led to a reduction of TAH filling and ejection. As left drive pressure was decreased with vacuum removed (Fig. 2), an effective decline in pumping action, or "model inotropy," was observed. Reduction of left drive pressures from 200 to 120 mm Hg resulted in a progressive reduction in mean AoP from 89.7 ± 1.8 to 84.8 ± 0.1 mm Hg (-5.4%), and left ventricular output from 4.15 ± 0.2 to 3.6 ± 0.1 L/min (-12.6%), accompanied by an increase in LAP from 16.2 ± 1.3 to 34.4 ± 0.1 mm Hg ($+112\%$).

When reducing drive pressure, once full eject conditions are not met, stoke volume will decrease with each decrease of drive pressure. However, note that when full-eject conditions are met, changes in drive pressure will not vary pumping characteristics to a large degree as long as full ejection is occurring. As shown in the presented data, Fig. 2, full eject was lost once the drive pressure was reduced to 130 mm Hg—this can be observed by a slight increase in LAP (A), increase in mean left ventricular pressure

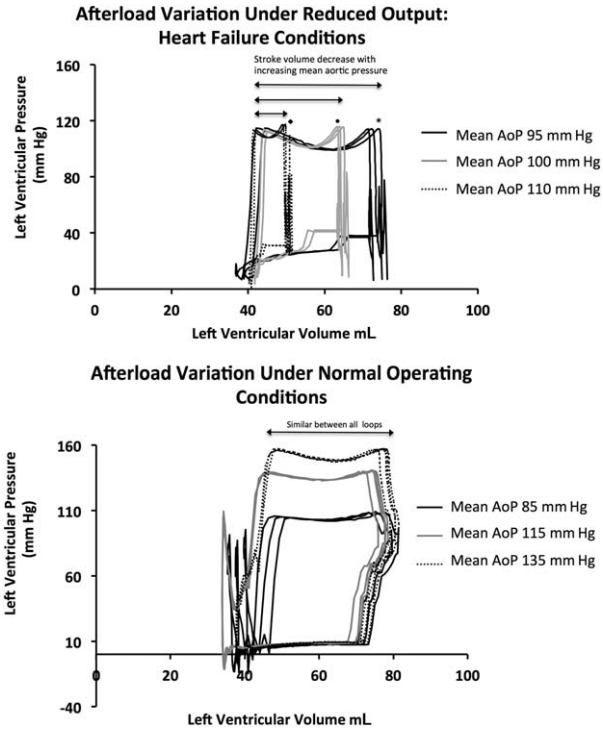

FIG. 4. PV loops with varying afterloads in heart failure and normal conditions. A: PV loops with 95, 100, and 110 mm Hg mean AoPs, corresponding to systolic pressures of 111, 112, and 114 mm Hg respectively. B: PV loops with 85,115, and 135 mm Hg mean AoPs. Notice the difference in loop trends over the varying afterloads. Stroke volume (loop width) decreases with increased afterload whereas in normal operating conditions stroke volume remains the same over varying afterloads. Normal condition pressure volume loops (Crosby et al., 2014). In heart failure conditions, PV loops with a mean AoP of up to 135 mm Hg (as was tested under normal conditions) was not achievable because flow through the system would cease at higher AoPs.

(B) increased fluid remaining in the ventricle causing increase in the mean pressure, reduction in AoP (C) and reduction of mean left ventricular outflow (D) at 130 mm Hg when comparing to the higher drive pressures. In addition, all these effects are exaggerated when the drive pressure is reduced to 120 mm Hg.

Emulation of the most severe, that is, worst case, heart failure hemodynamics obtainable with the TAH + DMCS configuration, as tested, was governed by the maximum degree of drive pressure reduction achievable with the affixed driver. In this case, using the Companion 2 driver, which has an internally designed reduction limit based on clinical use, this was 120 mm Hg. Under these conditions, the DMCS had a mean RAP of 7.1 ± 0.1 mm Hg, mean left ventricular pressure of 69.2 ± 0.7 mm Hg, mean AoP of 84.8 ± 0.1 mm Hg, mean LAP of 34.4 ± 0.1 mm Hg, and left ventricular outflow of 3.6 ± 0.1 L/min. It was these parameters that were used as a baseline "heart failure" condition for the

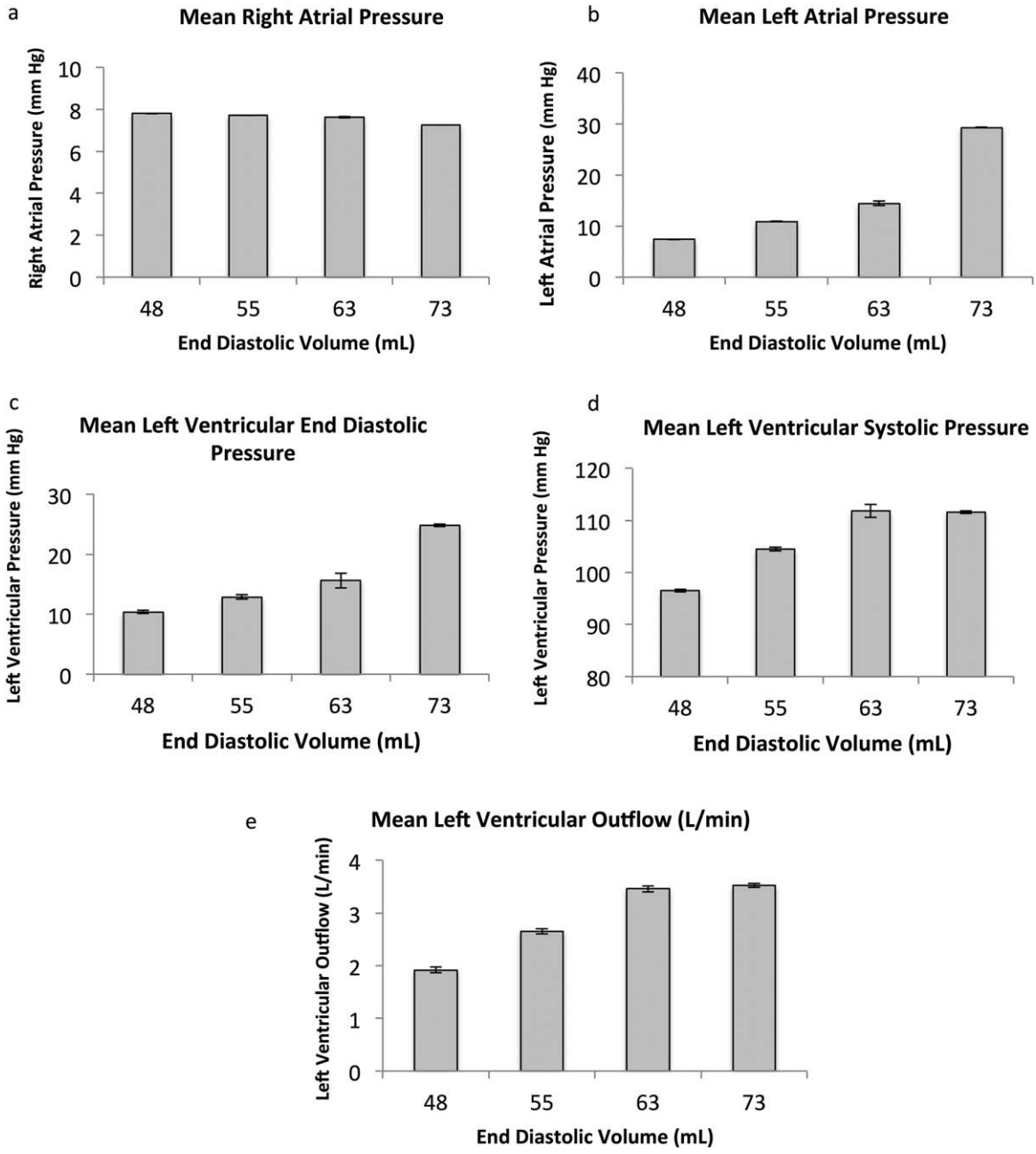

FIG. 5. Varying the preload. Preloads were acquired through variations in the right ventricular vacuum pressure. A–D: Plots of mean RAP, LAP, left ventricular end diastolic pressure, left ventricular systolic pressure, and left ventricular outflow over a range of preloads.

remainder of studies outlined. Of note, standard deviations above and throughout this report represent standard deviation between mean values of each collected data set. The small standard deviation values highlight the reproducibility of the model.

Effect of afterload variation on heart failure model hemodynamics

Afterload was increased in the DMCS by manipulating the bellows-operated valve to restrict flow between the AoP chamber and RAP chamber. Figure 3a–e displays mean RAP (a), mean RAP (b), mean LAP (c), mean left ventricular end diastolic pressure (d), mean left ventricular systolic pressure, and (e) mean left ventricular outflow over a 10-s acquisition period with varying mean AoPs. As mean AoP was increased from 95 to 110 mm Hg, mean RAP exhibited a 5.2% reduction, from 7.2 to 6.9 mm Hg (Fig. 3a), average LAP increased by 30.7%, from 35.4 to 46.3 mm Hg (Fig. 3b), and

mean left ventricular end diastolic pressure increased from 29.7 to 54.4 mm Hg (Fig. 3c). At 110 mm Hg, there is a reduction in end diastolic pressure because the ventricle is not filling as quickly once afterload is increased to 110 mm Hg, notice that mean cardiac output is <1 L/min at this level of afterload. This decreased filling will attribute to the lower LVP at 110 mm Hg in comparison to 105 mm Hg. Mean left ventricular systolic pressure remained fairly consistent, between 110.3 and 112.6 mm Hg over the range of afterloads tested (Fig. 3d). Left ventricular outflow decreased significantly, from an average of 3.59 to 0.66 L/min, an 81% reduction (Fig. 3e).

Effect of afterload variation on heart failure model PV relationships

PV loops obtained under heart failure conditions at varying afterloads are shown in Fig. 4. For ease of interpretation, pressure spikes (artifact) caused by closure of the mitral valve were removed from the pressure tracing in the heart failure model (Fig. 4a). Afterload variation under normal operating conditions is shown in Fig. 4b. Under heart failure conditions, as afterload was increased, a prominent reduction in stroke volume (width of the PV loop) was noted, with the smallest stroke volume detected at an AoP of 110 mm Hg. This trend correlated with results shown in Fig. 3; as afterload increased, output decreased. Additionally, ventricular end systolic volume was between 40 and 50 mL. The ventricle inherently has a residual volume of near 30 mL during full ejection, that is, when the diaphragm assembly has reached its maximum extended position. In reduced output mode, the end systolic volume was consistently higher than 30 mL, indicating that the ventricle was not fully ejecting the end diastolic volume (EDV). Compared with the afterload variations observed under normal operating conditions (Fig. 4b), which reveal a consistent stroke volume over varying afterloads, the PV loops in heart failure conditions (Fig. 4a) show that the TAH operating under reduced output conditions is sensitive to afterload. The increase in concavity of the loops during systole (top of the loop) in Fig. 4a compared to the loops in Fig. 4b is likely due to a "lagging" of diaphragm movement under heart failure conditions, as drive pressure is significantly lower than normal operating conditions.

Effect of preload variation on the heart failure model

Venous return and preload were altered through adjustment of the right ventricle vacuum pressure.

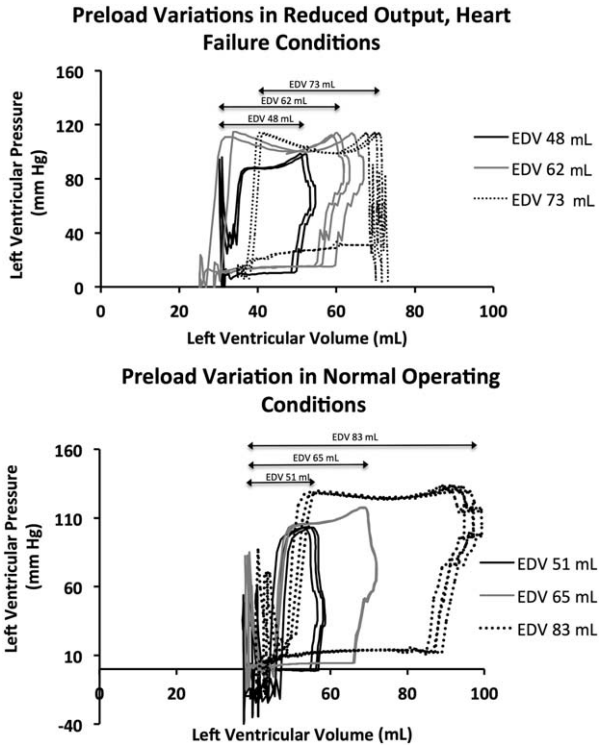

FIG. 6. PV loops with varying preloads. PV loops with variations in left ventricular preload. A: With reduced output "heart failure" conditions. B: Under normal operating conditions. Notice the difference in stroke volume (loop width) between heart failure and normal operating conditions. In normal operating conditions, an increase in stroke volume is obvious with increased EDV whereas, in heart failure conditions, increased EDV does not elicit as high of a change in stroke volume.

Vacuum was varied between 0 and −20 mm Hg (normal operation being −10 mm Hg), resulting in changes in achieved left ventricular EDV. However, no change was seen in left ventricular EDV with right vacuum parameters >−12 mm Hg, thus, only data from 0 to −12 mm Hg vacuum are presented. The effects of preload variation on mean LAP (a), left ventricular pressure (b), left ventricular outflow (c), and AoP (d) are shown in Fig. 5a–d. As EDV was increased from 48 to 73 mL, mean RAP remained relatively constant (Fig. 5a), LAP increased as end diastolic pressure increased, with a 106% increase in LAP, rising from a mean of 8.8 mm Hg at an EDV of 48 mL to a mean of 18.5 at an EDV of 73 mL (Fig. 5b). Mean left ventricular pressure similarly increased, +46%, from 45 to 66 mm Hg (Fig. 5b) as preload was increased. Accordingly left ventricular end diastolic pressure increased, +41%, from 10.3 to 24.86 mm Hg with augmented preload (Fig. 5c) as well as left ventricular systolic pressure, +15.5% from 96.4 to 111.5 mm Hg (Fig. 5d), and left ventricular outflow as

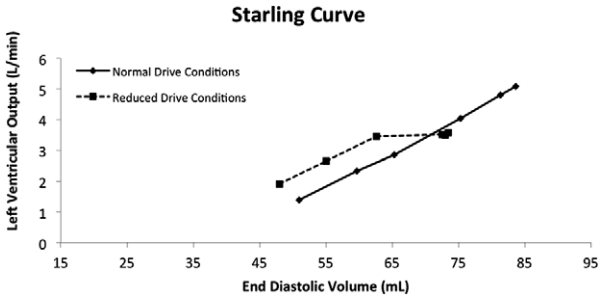

FIG. 7. Starling Curve. Left ventricular output versus left EDV (fill volume). Variations in preload were achieved by manipulating the right vacuum. Comparison between normal (solid) and reduced drive pressures (dotted).

well, revealing a significant increase of 86%, from 1.92 to 3.58 L/min, with increasing EDV (Fig. 5e).

Effect of preload variation on heart failure model PV relationships

PV loops under various preload conditions are shown in Fig. 6. As EDV was increased in heart failure mode (Fig. 6a), increases in stroke volume (loop width) between an EDV of 48–62 mL were detected. Stroke volume increases between an EDV of 62 and 73 mL were minimal and the end systolic pressure between these two preloads remained similar, though greater than the end systolic pressure generated with an EDV of 48 mL. Figure 6b shows PV loops generated under normal operating conditions, which demonstrate incremental increases in stroke volume with increasing EDV.

A Starling Curve for the variations in preload is presented in Fig. 7, comparing normal left ventricular drive conditions to the reduced drive conditions (20). Under normal drive conditions a higher EDV was achieved when the right ventricular vacuum was set at −20 mm Hg, reaching an EDV of 84 mL for normal conditions compared to 73 mL at heart failure conditions. In addition, heart failure conditions produced little increase in left ventricular output once an EDV of 63 mL was reached. At an EDV of 63 mL, left ventricular output averaged 3.45 ± 0.1 L/min across all test runs, while at an EDV of 73 mL, left ventricular output was 3.5 ± 0.1 L/min, $P = 0.6$. As in the human heart, the TAH demonstrates increased stroke volume and increased (left) ventricular pressure during systole with increases in EDV. However, in the heart failure model a threshold left ventricular EDV is reached, above which preload augmentation does not increase left ventricular output, as the pump has inadequate pumping force to eject fluid out of the ventricle; this action being similar to a failing heart. Further, the TAH, with a physically set, non-dilatable ventricle, cannot continue to benefit from dilatation and volume augmentation as in the human ventricle.

Addition of a VAD to the model system: Effect of LVAD pump speed alteration on heart failure model hemodynamics

A HeartMate II LVAD was successfully added to the circulatory loop via the addition of two T-junctions and one heart valve; a flow diagram of the configuration is shown in Fig. 8. Following establishment of baseline heart failure conditions as above, HeartMate II speed was adjusted from 7000 to 11 000 RPM, in 200 RPM increments (Fig. 9). As LVAD speed was increased the following were

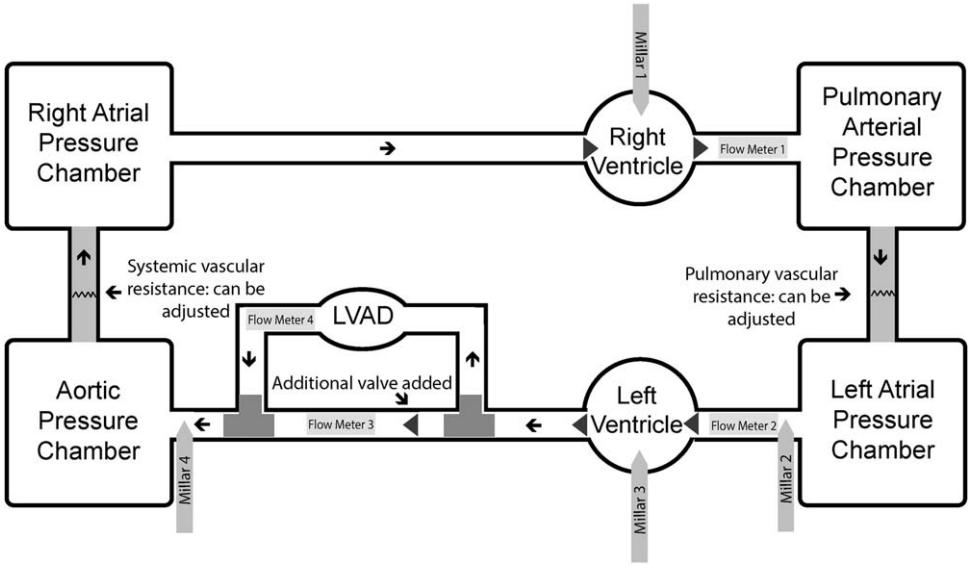

FIG. 8. The incorporation of a ventricular assist device. A ventricular assist device was incorporated into the loop via the addition of two T-junctions and the addition of a valve that acts as the aortic valve when the VAD is powered on, essentially extending the volume of the left ventricle. This allows for the addition of a VAD into the system without damaging or altering the TAH. The triangles represent valves. All sensor and flow meter placements are depicted. When the VAD is on, the aortic valve remains open.

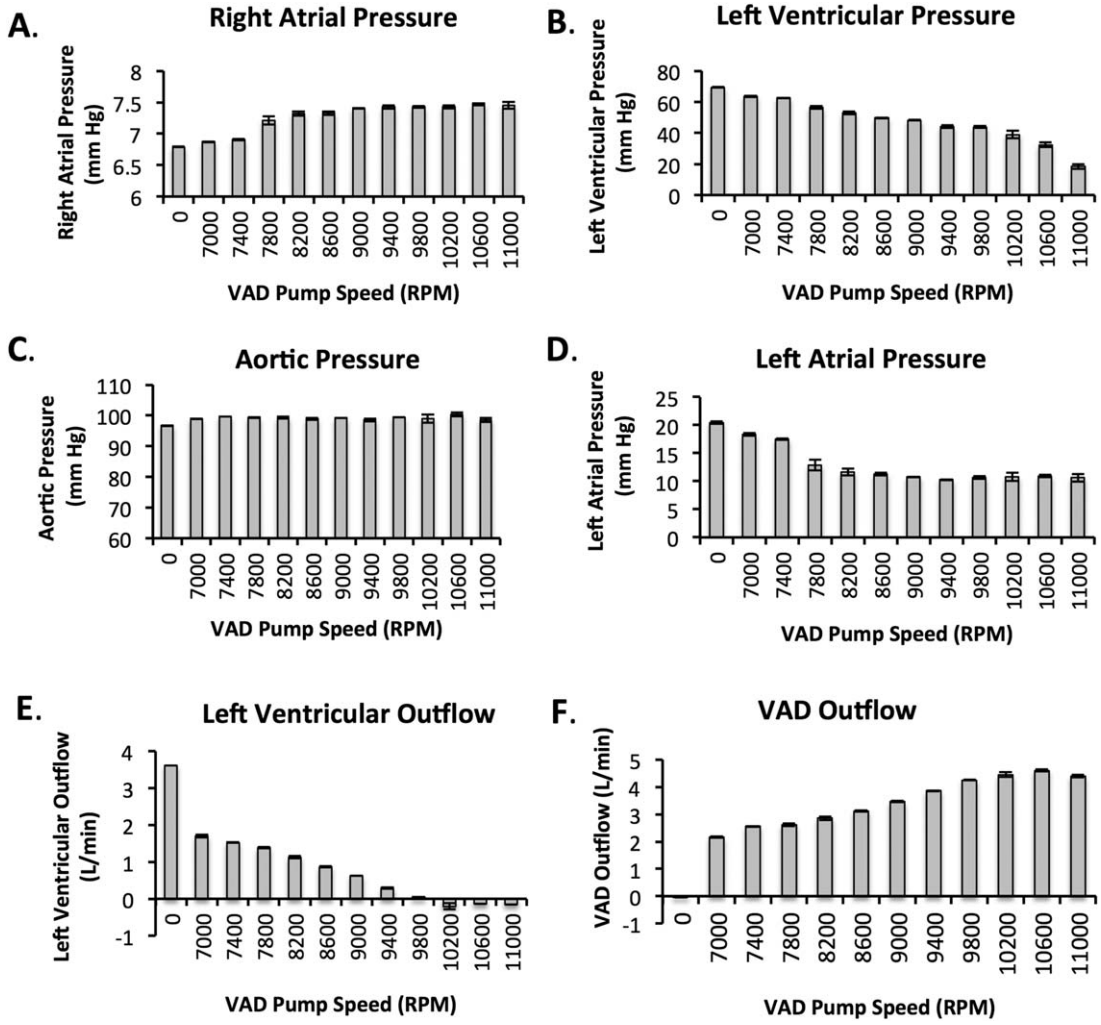

FIG. 9. HearMate II operation at varying speeds. Figures A–F display RAP, left ventricular pressure, AoP, LAP, left ventricular outflow, and VAD outflow as the HeartMate II ventricular assist device was placed in-line with our heart failure model. Note the reductions in HF conditions as RPM is increased. At speeds above 9800 RPM, suction is occurring within the left ventricle, which is why left ventricular flow becomes negative.

observed: an 8% increase in mean RAP from 6.9 to 7.5 mm Hg, a 68% decrease in mean left ventricular pressure from 62 to 20 mm Hg, limited variation in AoP, a 56% decrease in LAP from 18 to 10 mm Hg, a 108% decrease in left ventricular outflow 1.7 to −0.15 L/min, yet a significant 204% increase in LVAD outflow from 2.16 to 4.4 L/min. The negative left ventricular outflow observed at higher pump speeds is attributable to LVAD pump suction, as fluid in the ventricle is being diverted from left ventricle ejection via pump suction at high pump speeds; small leakage occurs across the aortic valve, that is, the additional valve added into our system (from the aorta to the left ventricle). Leakage of the aortic valve does happen with LVAD patients, overtime if the pump speed is too high, creating too low a pressure in the ventricle during diastole. Our mock system actually mimics this occurrence.

DISCUSSION

In this study, we build upon our prior work of characterizing the physiology of the TAH integrated with a modified Donovan Mock Circulatory System to further define and assess the performance of this configuration as a robust mock circulation system, capable of operating and reproducing both normal and heart failure hemodynamics. Herein, via modifying pump drive parameters, a reproducible left ventricular heart failure model has been demonstrated and physiologically characterized. The value of the platform lies in its biventricular pulsatile heart, hands-on robustness, and its conduit

designs, allowing for the physical addition and interchange of MCS devices. As such, this offers an interactive training tool, affording the ability to examine hemodynamic effects and consequences of pressure and volume variations encountered in patients with heart failure and MCS devices. Further, this system may be used for inter-device comparative studies and research, which is largely impossible in man due to the invasive nature of MCS device implantation, not to mention prohibitive cost and ethical issues. While herein we report only on the system as a model of left ventricular failure, from ongoing studies by our group it is clear that the system can physically emulate right ventricular failure as well as biventricular failure, allowing similar characterization to be performed, training to be accomplished as well as interdevice add-on comparative studies to be undertaken. Reports on these expanded uses will be forthcoming in the future.

A wide variety of physical circulation models and mimics of heart failure hemodynamics have been developed over the years, but most are limited due to either being overly simple—for example, inability to accurately vary load, inotropy or pulsatility; or overly complex—that is, with multiple physical elements patched together which pose challenges as to transportability, or ease of use (10,12,13,17). This system offers a distinct set of advantages when compared with these earlier systems. The present system affords reproducible vascular loading, resistances, and hemodynamic variation of loading via simple mechanical means—without the need for computer or servo control. Use of the TAH allows for true pulsatility with defined impulse wave and dp/dt characteristics, as well as variable "model inotropy." Being a physically contained unit constructed of polycarbonate, flexible yet robust tubing, and the affixed TAH, the system is durable and transportable. As a set system that has been used extensively in the lab, by our group and others, with defined standard operating instructions, it allows for ease of use and reproducibility of hemodynamics. Further, as the system is an element of required training for TAH centers, significant availability already exists at numerous medical centers. Additionally, with defined, simple conduit modifications as in this study, the system allows for addition and interchange of a wide range of augmentative or alternative MCS devices into the circuit, which provides a valuable model system for training and research.

While various physical models of heart failure have been developed (9,10,12,13,15,17), only one other group to date (Senage et al.) has incorporated a pulsatile artificial heart within a mock system. Though these investigators used a TAH, they did not fully characterize the physiology of the heart failure model under normal and heart failure operating conditions nor use a clinically relevant pulsatile drive system to pump the paired TAH ventricles. Further, in their study LVAD inflow ports were placed upstream from the left ventricle thus limiting ventricular filling. Herein, that gap is closed through use of a defined, pulsatile, clinical TAH system; characterization of the heart failure model prior to device testing; incorporation of present day LVADs in a more clinically relevant circulation location followed by examination of this addition as to physiologic impact on hemodynamic performance (16). As such, parameters defined and characterized in our study can be used to replicate and establish easy-to-use heart failure models widely, particularly in those centers already in possession of the TAH and DMCS.

As shown in this study under heart failure conditions the TAH demonstrates Starling-like behavior, although to a lesser degree as compared with non-heart failure conditions, with a reduction seen in the relationship between output and preload, as exists in the failing human heart (23–25). The Starling-like characteristics of the heart failure model are shown to respond to increases in preload, but only at lower EDV, with output plateauing at higher EDV, as the ventricle cannot fully eject large volumes during heart failure operation and cannot continue to dilate for further augmentation. The system also exhibits afterload sensitivity, with ventricular output and left ventricular ejection decreasing dramatically with increased afterload, thus leading to increased LAP. The afterload response of the heart failure model thus closely mimics the human heart in failure, which demonstrates a reduction in stroke volume when subjected to increased afterload.

There are clear variations in the shape of PV loops in the TAH compared with PV loops of the human heart (26,27). Under normal operating conditions, the TAH has been shown to be afterload insensitive (20). However, with the TAH operating in reduced drive heart failure mode, the left ventricle is not always capable of overcoming the afterload and fully ejecting all volume that enters the ventricle during diastole. Reduction in stroke volume, that is, width of the PV loop, is seen even with a 5 mm Hg increase from baseline mean AoP, with flow decreasing to under 1 L/min at a mean AoP of 110 mm Hg.

During preload variation, a left ventricular EDV greater than 74 mL was not achieved by right vacuum manipulations. With the left vacuum turned off in the described heart failure model, the diaphragm is incapable of rapidly mobilizing to its "down or fully withdrawn position," to allow additional filling even with increased preload applied. In a sense, this behavior exhibits an element of diastolic dysfunction, with reduced ability to fill. In addition, during preload variations, left ventricular output failed to rise with increasing preload at EDV-greater than 63 mL, due to the reduction in pumping power of the left ventricle as occurs in the failing human heart. Despite these "boundary" limitations, this system is able to mimic many, if not most of the important characteristics of the hemodynamics of the heart failure patient (26,28,29).

With an LVAD connected to the heart failure model system, a clear improvement in hemodynamics occurred. When LVAD speed was increased, elevated atrial pressure and mean left ventricular pressure were reduced and total cardiac output (LVAD + left ventricular outflow) increased. Additionally, back flow was observed with excessive LVAD speed. The determination of best operating LVAD pump speed, when the device is first implanted into a patient, is essential. As the TAH is a biventricular system and has pulsatile pumping action, LVAD displays will show waveforms and values that are typical of what is observed clinically (30–32). Thus, this system may be utilized as a training tool to mimic various patient parameters and situations that are clinically relevant to the LVAD operating team, allowing training for optimized device performance as well as management of various suboptimal and failure clinical scenarios. For example, in this platform, aortic line variations can be visualized to determine aortic valve opening hemodynamics, flow to or from the device can be completely or partially occluded, device waveforms and pulsatility indices can be visualized, and vascular resistance can be easily be modified, all vital and relevant for real world use. Studies are presently underway examining the comparative effectiveness of differing VAD systems under defined, identical heart failure conditions utilizing this platform.

Clinical impact

With the rise in use of a wide variety of MCS devices, the clinical management personnel involved continue to become increasingly diverse. Presently in addition to physicians, VAD coordinators, nurses, nurse practitioners/physician assistants, engineers, and emergency personnel participate in aspects of patient care. As such the present system is well adapted to train these groups. As with all technical systems, it has been clearly shown that increased simulation-based training ultimately increases operative skill and management of failure scenarios (33). To date the unmodified SynCardia Mock system has been utilized to train more than 100 medical center groups in the USA and around the world on proper driver operation of the SynCardia TAH-t. Multiple clinical training scenarios are completed during this training.

In addition to TAH training, the present system, with the modifications discussed in this article, has been used as a model of heart failure alone as a general pathophysiology training tool and simulator for the impact of therapeutic (pharmacologic) manipulation (34).

Further, with the growing variety of commercially available MCS devices, in or newly entering the market, the present platform is well suited to allow training and research as to the relative performance of a given MCS device under defined hemodynamic conditions, which cannot be completed in patients and is difficult in animal models.

Reproducibility

Under all settings and conditions evaluated, normal and heart failure, the system provided reproducible results, as can be observed through the low reported standard deviations. Additionally, no significant drift was observed over time throughout testing. As such, the described configuration represents a robust mock circulation system, capable of operating and consistently reproducing both normal and heart failure hemodynamics.

Limitations

The lowest achievable driving pressure of the Companion II driver (120 mm Hg) is also a limitation of the described model. Heart failure severity could be increased in this model if a lower drive pressure was utilized, as is achievable with the original SynCardia TAH driver, the CSS Console (35). The CSS Console allows for left drive pressure adjustments between 0 and 300 mm Hg, whereas the Companion II is limited between 120 and 280 mm Hg. In prior and ongoing work by our group it is clear that the envelope of performance of the present described system can be expanded, if need be, through use of a pulsatile pneumatic driver with wider operating range.

CONCLUSION

A robust, physiologically defined, user-friendly physical left ventricular heart failure model has been developed and characterized using the Donovan Mock Circulation System and the SynCardia Total Artificial Heart. This construct provides physiologically relevant, reproducible pressures and flows representative of clinical left heart failure hemodynamics. The ability to readily manipulate patient parameters on the DMCS and the straightforwardness in adjusting pumping parameters on the TAH driver provides a versatile system capable of simulating and modeling a multitude of clinical scenarios. The ability to rapidly interpose a wide variety of MCS devices in the flow circuit makes this platform an effective tool for comparative assessment of MCS device performance. Widespread availability of the DMCS and TAH already within the TAH user community further enhances the value of the described system for use as both a hands-on training tool and a research platform, ultimately aimed at enhancing the care and outcomes of patients with MCS devices.

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