LVAD Pulsatility Assesses Cardiac Contractility: *In Vitro* Model Utilizing the Total Artificial Heart and Mock Circulation

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Abstract: There is a need for a consistent, reproducible, and cost-effective method of determining cardiac recovery in patients who receive emerging novel therapeutics for advanced and end-stage heart failure (HF). With the increasing use of ventricular assist devices (VADs) in end-stage HF, objective device diagnostics are available for analysis. Pulsatility, one of the accessible diagnostic measures, is a variable gage of the differential between peak systolic and minimum diastolic flow during a single cardiac cycle. Following implantation of the VAD, HeartWare's HVAD records pulsatility regularly. Thus, we hypothesize that this measurement relates to the contractility of the heart and could be utilized as a metric for determining patient response to various therapeutics. In this study, therefore, we develop a translatable and effective predictive model characterizing pulsatility to determine HF status and potential HF recovery using the SynCardia Total Artificial Heart (TAH) in conjunction with a Donovan Mock Circulation System to create a simulation platform for the collection of pulsatility data. We set the simulation platform to patient conditions ranging from critical heart failure to a normal operating condition through the variation preload, afterload, and left ventricular (LV) pumping force or TAH "contractility." By manipulating these variables, pulsatility was found to accurately indicate significant ($p < 0.05$) improvements in LV contractility at every recorded afterload and preload, suggesting that it is a valuable parameter for the assessment of cardiac recovery in patients. *ASAIO Journal* 2019; 65:580–586.

Key Words: TAH, in vitro model, contractility, pulsatility

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Utilization of stem cells and pharmacological agents are under active investigation as strategies for ventricular remodeling and restoration of contractile function in patients with advanced or end-stage heart failure (HF). In the PROMETHEUS (Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery) and TAC-HFT clinical trials, for instance, mesenchymal stem cell–treated cardiac tissue demonstrated improvement in perfusion and contractile function, along with a reduction in infarct size.[1,2] Other groups have investigated the potential of ventricular assist device (VAD) weaning in conjunction with mesenchymal precursor cells and found that the therapy group tolerated VAD weaning better than nonmesenchymal precursor-treated control group.[3] Generally, investigators studying the efficacy of cardiac remodeling in patients typically utilize expensive and time-consuming methods, *e.g.*, echocardiography or magnetic resonance imaging, to determine the heart's response to therapy.[4,5] Not only are these methods uneconomical and inefficient, they also require a physician to interpret the data. This often leads to inconsistent reporting of the response to therapy across a range of physicians and/or institutions.[6,7] With these drawbacks, there is a need to develop a cost-effective, consistent, and reproducible method of determining cardiac recovery in patients with end-stage HF, which will, in turn, yield more informed medical decisions.

Groups have investigated patients with end-stage HF receiving medication or stem cell therapy for ventricular remodeling in conjunction with VADs.[8–10] Even without specific therapies, LV unloading caused by the implantation of LVADs has demonstrated ventricular remodeling and improvements in contractile function.[11,12] For this reason, evaluation of contractile function in end-stage HF patients with VADs, regardless of treatment regimens, can provide insight on the cardiac status of the patients. Currently available VAD systems collect and record clinically useful pump performance information during normal operation. More specifically, the HVAD records parameters including flow rate, minimum flow, device power, and pulsatility. Herein, we propose that an implanted VAD provides an opportunity to utilize device diagnostic data as a means of determining cardiac function and, thus, as an indicator of cardiac recovery and remodeling over time. The HeartWare HVAD is a continuous-flow device that uses a centrifugal rotor to pump blood. The ADVANCE trial investigated the success of the device through survival, survival to transplantation, or explant of the device for ventricular recovery. It found that the device was successful in 90.1% of patients, making it a viable bridge to transplant option.[13]

The parameter of interest in this study is pulsatility, which is the derivative of the flow calculation, stroke volume and, therefore, may provide important insight on the LV contractility. It is the measure of peak systolic flow velocity minus the minimum

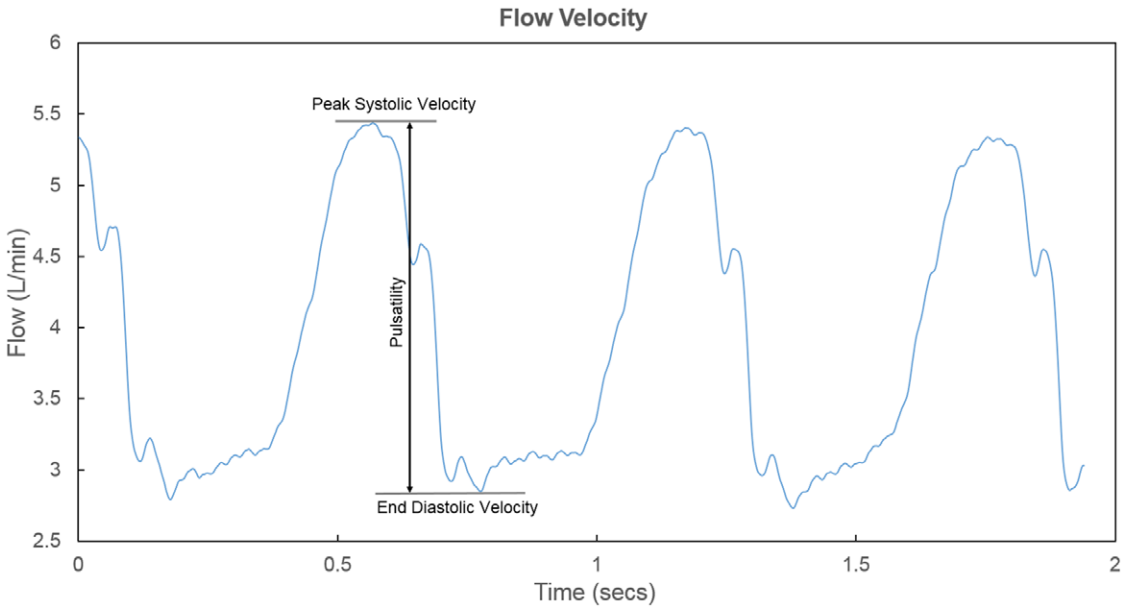

Figure 1. The pulsatility waveform is recorded through the HVAD controller every 15 minutes by calculating the difference in peak systolic flow velocity and end diastolic flow over a single cardiac cycle.

diastolic flow velocity over a single cardiac cycle through the HVAD (**Figure 1**). The device ensures at least one cardiac cycle is captured by calculating pulsatility over a 2 second window, assuming heart rates are greater than 30 beats per minute. Multiple groups have explored using pulsatility as a method of determining cardiac contractility both in animal studies and *in vitro* models. One group analyzed pulsatility through pressure–volume diagrams and H-Q curves by determining the work performed by the heart and the VAD.[14] This provided insight on the level of assistant the VAD provided *versus* the function of the native heart. Another group developed a high-frequency algorithm using the time-dependent derivative of the flow rate (dQ/dt) by varying contractility through changes in ventricular pressures (dP/dt) to determine changes in heart function.[15] Having the ability to record and analyze pulsatility through device diagnostics provides an opportunity to create a clinically translatable model.

Pulsatility provides insight of individual-flow waveforms over time. This can be critical in assessing the long-term status of patients receiving therapies intended for cardiac recovery. The HVAD controller records pulsatility values every 15 minutes from the time of VAD implant, providing 96 data points per day. Trends in this data could potentially provide insight to physicians about patient recovery status simply by analyzing the data recorded by the device.

To understand how changes in pulsatility relate to cardiac status and cardiac recovery, it is important to characterize pulsatility under various conditions. We applied a well-established and characterized model using a SynCardia 70 ml TAH and Donovan Mock Circulation System (DMCS)[16] as a framework for modeling pulsatility through the HVAD. This model has demonstrated the ability of this mock loop to accurately emulate HF and normal operating conditions with the incorporation of a VAD. An established limitation of this mock loop is the differing pressure–volume characteristics compared with the human heart. Because the rigid construction of the TAH, the model does not behave with time-varying elastance, but Frank–Starling behavior remains consistent with physiologic conditions.[16] Cardiac contractility does not vary unless manipulated through the TAH driver. The goal of this study was to model changes in pulsatility under varying degrees of HF by manipulating preload, afterload, and LV pumping force. Preload is the end systolic pressure just before systole, which indicates atrial contractile force, and afterload is the aortic pressure the left ventricle must overcome to eject blood. Variation of these parameters allowed for characterization of pulsatility in relation to cardiac status and how it relates to cardiac recovery. We hypothesized that VAD pulsatility would be proportional to cardiac contractility and increase with LV pumping force or "TAH contractility" and preload when the LV pumping force is sufficient to overcome loading pressures. Because of the insensitivity of the TAH and DMCS to afterload pressures, it is unknown how the HVAD pulsatility algorithm will respond to changes in aortic pressure. These results could validate pulsatility as a valuable indicator of cardiac contractility in patients.

Materials and Methods

The system was constructed similarly to the previously created model[16] with a 70 ml SynCardia TAH and DMCS. The 70 ml pneumatically driven SynCardia TAH was connected to the DMCS with 1 inch tubing. We controlled its pressure through the SynCardia Companion 2 (C2) Driver (SynCardia Systems, LLC, Tucson, AZ). Baseline TAH parameters for normal operating conditions included a LV left drive pressure (LDP) of 180 mm Hg, right ventricular (RV) right drive pressure of 60 mm Hg, left vacuum of −10 mm Hg, right vacuum of −10 mm Hg, 50% systole, and a rate of 100 bpm. The Heartware HVAD (Heartware, Inc., Framingham, MA) was connected between the left ventricle and the aortic (AoP) chamber using T-junctions, circular plastic connector connectors, and flexible 3/16″ thickness polyvinyl chloride tubing (**Figure 2**). The HVAD device

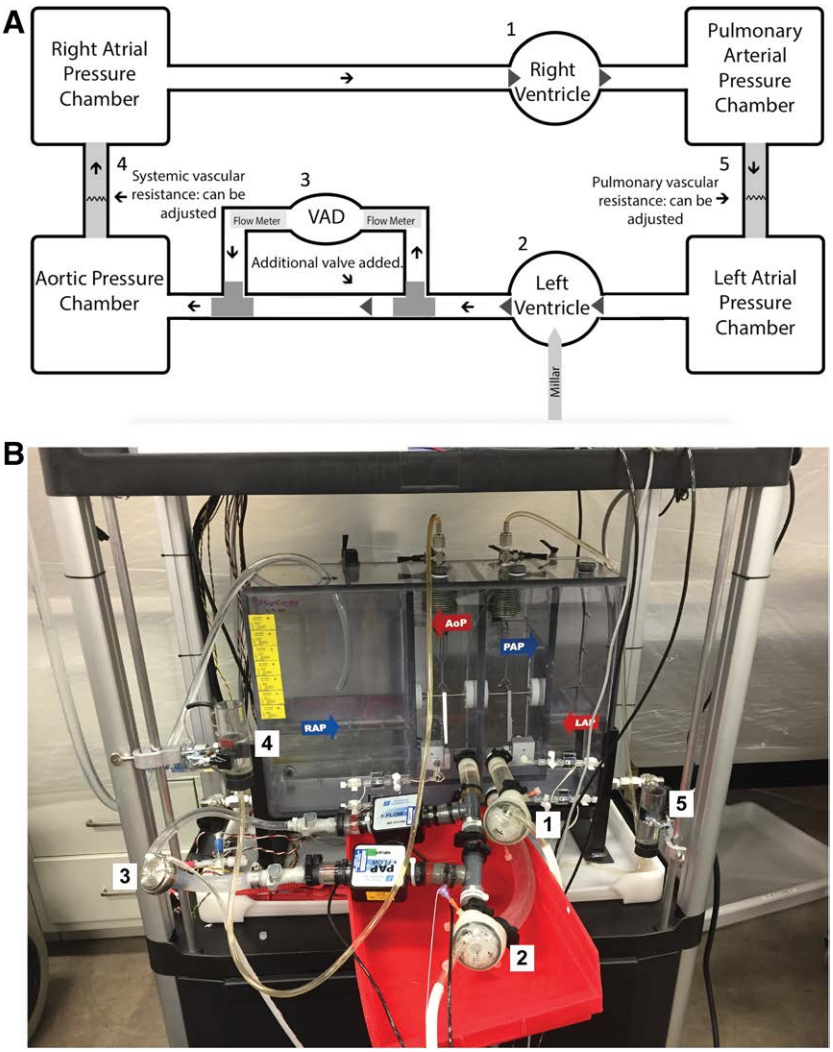

Figure 2. The donovan mock circulation loop **A**: Schematic of mock loop with representation of flow meter and pressure recording positions. The diluted glycerol solution travels though the closed loop emulating the cardiac cycle. The volume of solution in each of the pressure chambers is calibrated to match physiologic pressure gradients. Flow begins in the right atrial pressure chamber to the Total Artificial Heart (TAH) right ventricle (1) where it must overcome the pulmonary vascular resistance (PVR) set using the PVR bellow (5). The preload caused by the RV travels through the left atrial pressure chamber where it is subjected to the TAH left ventricle (2). A Millar catheter placed in the LV records LV pressure. The strength of LV contractions is controlled using the TAH driver as flow continues through the transonic flow meters and HVAD (3) where it must overcome the afterload pressures created in the aortic pressure chamber using the systemic vascular resistance bellow (4). Arrows indicate direction of flow. **B**: Image of TAH and DMC tank with matching numbers 1–5 corresponding to the schematic. DMC, donovan mock circulation loop.

speed was kept constant at 2,700 rpm, and hematocrit was set to 38% to emulate normal blood hematocrit.[17] The DMCS was filled with a 35% glycerol to deionized water ratio to mimic the viscosity of blood. Two transonic flow meters (ME 25 PXN; Transonic Systems, Inc., Ithaca, NY) were connected in line before and after the VAD to record fluid flow rate. Transonic flow meters were calibrated to the predetermined viscosity by Tektronix Calibration Lab. Our team inserted a Millar Catheter (SPR-524; Millar Instruments, Inc., Houston, TX) in the LV to record left ventricular pressure (LVP) and connected it to a pressure control unit (PCU-2000, Millar Instruments, Inc.). Pressure transducers (Abbott, Abbott Park, IL) within each chamber of the DMCS recorded right atrial pressure, pulmonary arterial pressure, left atrial pressure, and aortic pressure (AoP). We sampled all sensors at 1 KHz through a NIDAQ data acquisition board (NI-9219, NI-9211; National Instruments, Austin, TX) by using a custom LabVIEW executable. A separate flow meter (John Ernst Co, Sparta, NJ) recorded total cardiac output (TCO) sampled at 1 Hz to verify flow recorded by the Transonic meters.

Experimental design included varying preload, afterload, and LV contractility. We varied LV preload by adjusting the fill volume of the RV through variation of the TAH right vacuum on the C2 Driver between 0 and −20 mm Hg in 5 mm Hg increments. Afterload between 65 and 115 ± 5 mm Hg in 10 mm Hg increments was varied by adjusting the height of the systemic vascular resistance (SVR bellow) (**Figure 2**, #4) to increase the resistance between the AoP and right atrial pressure chambers.

To ensure the accuracy of the HVAD pulsatility calculation, we recorded six data points at a LV LDP of 120, 140, 160, 180, and 200 mm Hg with a constant baseline preload of 10 mm Hg variation and afterload of 95 ± 5 mm Hg through the HVAD controller at the 15 minute sampling rate. Concurrently, for comparison to the HVAD values, we recorded

Table 1. Comparison of Pulsatility Recorded by the Transonic Flow Meters and the Pulsatility Calculated Through the HVAD Device

LV LDP (mm Hg)	Pulsatility (L/min)	HVAD Pulsatility (L/min)	Delta Pulse (L)	*p* Value
120	2.912 ± 0.022	2.927 ± 0.021	–0.015	0.8636
140	3.564 ± 0.032	3.531 ± 0.029	0.033	0.1909
160	3.906 ± 0.030	3.860 ± 0.036	–0.020	0.3833
180	3.945 ± 0.047	3.973 ± 0.005	–0.028	0.8273
200	3.987 ± 0.029	3.944 ± 0.006	0.043	0.1212

Pulsatility denotes the value recorded via the Transonic flow meter, and HVAD pulsatility denotes the value recorded from the HVAD controller. Delta pulse displays the disparity between the two pulsatility measurements, and the p-value is the result of the statistical comparison of the two measurements.

LV LDP, left ventricular left drive pressure.

10-second data sets of pulsatility through the Transonic flow meters at each LV LDP.

To compare pulsatility between HF (LV LDP 120 mm Hg), medium cardiac conditions (LV LDP 150 mm Hg), and normal operating conditions (LV LDP 180 mm Hg), we recorded six separate 10 second data sets of pulsatility through the Transonic flow meters for each afterload and preload to allow for statistical comparison. We undertook the analysis with a Matlab (Mathworks, Inc., Natick, MA) filtering and peak finder algorithm post data acquisition using the data from the Transonic flow meters. We calculated stroke volume by integrating real-time flow over a 10 second window and divided by the number of contractions using Matlab. All statistical comparisons were performed in Matlab using a nonparametric Mann–Whitney rank-sum test to account for the low sample sizes.

Results

HVAD-Calculated Pulsatility and Real-Time Flow Meter Comparison

As seen in **Table 1**, we observed no significant difference between the true value of pulsatility recorded in real time through the Transonic flow meters and the HVAD calculated pulsatility at any LV TAH pumping force (TAH contractility).

Afterload Variation

Increasing LV TAH contractility resulted in a significant ($p < 0.05$) increase in pulsatility at every measured afterload (AoP) when comparing heart failure and normal operating conditions, and in all but one afterload (75 mm Hg) when comparing heart failure and medium LV TAH contractility (**Figure 3**;

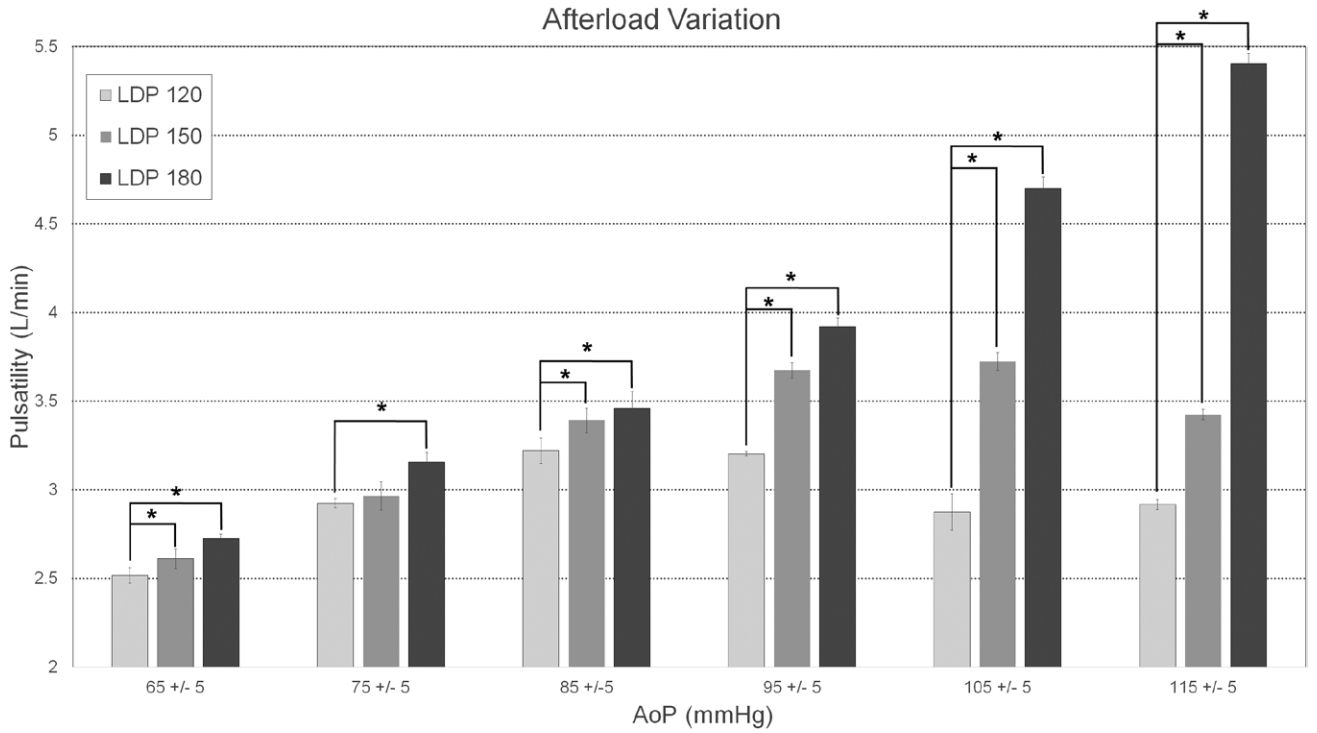

Figure 3. Varying afterload (aortic pressure [AoP]) while recording pulsatility under heart failure Total Artificial Heart (TAH) contractility (left ventricular left drive pressure [LV LDP] of 120 mm Hg), medium TAH contractility (LV LDP of 150 mm Hg), and normal TAH contractility conditions (LV LDP of 180 mm Hg). Significant differences in pulsatility were observed between heart failure and normal LV function at all afterloads and between heart failure and medium LV function at all afterloads but 75 mm Hg.

Table 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A313). Stroke volume remains constant in afterload variation, whereas stroke work and dP/dt increase with an increased afterload.

Average LVP increased with an increased afterload (AoP). More specifically, at a HF LDP (120 mm Hg) and low afterload (65 mm Hg), LVP was 32.47 ± 3.63 mm Hg; at a high afterload (95 mm Hg), LVP was 49.94 ± 2.82 mm Hg; and at the maximum afterload (115 mm Hg), LVP was 61.515 ± 2.48 mm Hg. At a medium drive pressure (150 mm Hg) and low afterload, LVP was 32.32 ± 3.24 mm Hg; at a high afterload, LVP was 51.55 ± 2.94 mm Hg; and at the maximum afterload, LVP was 69.69 ± 3.07 mm Hg. At a normal drive pressure (180 mm Hg) and low afterload, LVP was 29.79 ± 2.88 mm Hg; at a high afterload, LVP was 48.45 ± 2.92 mm Hg; and at the maximum afterload, LVP was 71.667 ± 3.31 mm Hg.

Preload Variation

Increasing LV pumping force resulted in a significant ($p < 0.05$) increase in pulsatility at every measured preload when comparing heart failure TAH contractility to both medium and normal operating conditions (Table 2, Supplemental Digital Content, http://links.lww.com/ASAIO/A313).

Output Evaluation

At a low afterload, TCO is similar in all cardiac status cases. As afterload increased, low and medium cardiac conditions reduced drastically, while normal operating conditions maintained a higher level of TCO throughout the range (Figure 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A313). This is consistent with previous experiments with the TAH and DMCS.[18]

Discussion

In VAD-supported patients, determination of individual patient LV function is vital in the assessment of the efficacy of mechanical circulatory support as well as adjunctive stem cell and/or pharmacologic therapies. The current study establishes the validity of utilizing VAD signal pulsatility as a marker of cardiac contractility and function. Before using the Transonic flow meters to calculate pulsatility, it was necessary to demonstrate that the true flow recorded from the flow meters was equivalent to the pulsatility reported through the HVAD algorithm. This was critical because of the low sampling frequency of the HVAD, which only records data points every 15 minutes. The results in **Table 1** demonstrate the accuracy of the HVAD algorithm.

In the model, the LV LDP of the TAH emulates contractility. To understand how LV LDP reflects physiologic contractility, we must evaluate the function of the TAH. The TAH is a 70 ml, pneumatically driven, pulsatile pump comprised of a rigid outer housing, the "TAH ventricle," with two inner diaphragms. The blood contacting diaphragm fills with blood from the circulatory system while the second diaphragm contacts the pressure-controlled air delivered from the Syncardia C2 driver. Blood fills the diaphragm as air escapes the air-contacting diaphragm during diastole. Next, the designated LDP set on the Syncardia C2 driver is delivered to the air-contacting diaphragm, causing blood to be ejected during systole. The air pressure (LDP) in this case either increases or decreases the ejection volume. The HF LDP (120 mm Hg) will eject less blood, whereas the normal operating condition LDP (180 mm Hg) will fully eject the blood in the blood-contacting diaphragm.[16] Therefore, LDP directly affects the ejection fraction of each contraction similar to physiologic contractility and will be referred to as "TAH contractility."

Contractility in a human heart is dependent on afterload. An increase in afterload will result in an eventual increase in contractility in a healthy heart.[19] Afterload determines the amount of work necessary from the heart to eject blood successfully. We found that at every measured afterload, there was a significant ($p < 0.05$) increase in pulsatility from HF TAH contractility to normal operating conditions. Additionally, there was a significant difference in pulsatility when comparing HF TAH contractility to medium conditions at all afterloads, except 75 mm Hg (**Figure 3**; Table 1, Supplemental Digital Content, http://links.lww.com/ASAIO/A313). Previous models using the TAH and DMCS demonstrated insensitivity to afterload variation in terms of end systolic volume (ESV) and end diastolic volume (EDV) but did show an increase in stroke work and therefore in dP/dt with increased afterload.[16] The results shown here are consistent with previous models demonstrating that as afterload increases, the differential pressure between the inflow and outflow of the VAD increases. HVAD pulsatility accurately indicates improvements in LV contractility regardless of aortic pressure status. Furthermore, even though ESV and EDV remain constant with afterload variation, increases in pulsatility in relationship to TAH LV contractility became more readily apparent at higher afterloads, indicating the pulsatility algorithm's sensitivity to stroke work and dP/dt, independent of stroke volume.

Left ventricular preload was varied by increasing RV output through the variation of the RV vacuum and, therefore, the RV fill volume. An increased preload will result in a higher EDV and stroke volume when contractility is not compromised.[19] Similar to afterload variation, we found that at every measured preload, there was a significant ($p < 0.05$) increase in pulsatility from HF TAH contractility to both medium and normal TAH contractility (**Figure 4**; Table 2, Supplemental Digital Content, http://links.lww.com/ASAIO/A313). These results align with previous evaluation of preload variation, the Frank–Starling behavior of the TAH/DMCS loop, and increases in EDV.[16] This suggests that HVAD pulsatility is sensitive to changes in EDV and can also indicate improvements in LV contractility regardless of RV function or preload pressure status.

These results indicate the HVAD pulsatility algorithm's sensitivity to both preload and afterload, but limitations exist in the model's translation to a clinical setting. Based on the rigid construction of the TAH, changes in pulsatility in relationship to afterload were not the result of increase stroke volume but because of the increase in stroke work. Because the pulsatility varies with preload, stroke work, and LV contractility, it would be necessary to use additional diagnostic tools to determine heart function, such a left heart catheterization or echocardiogram. The combination of multiple LV function markers would provide a stronger overall understanding of the patient's response to various pharmacological approaches. If it is found that pressures have been maintained and an increase in pulsatility is observed,

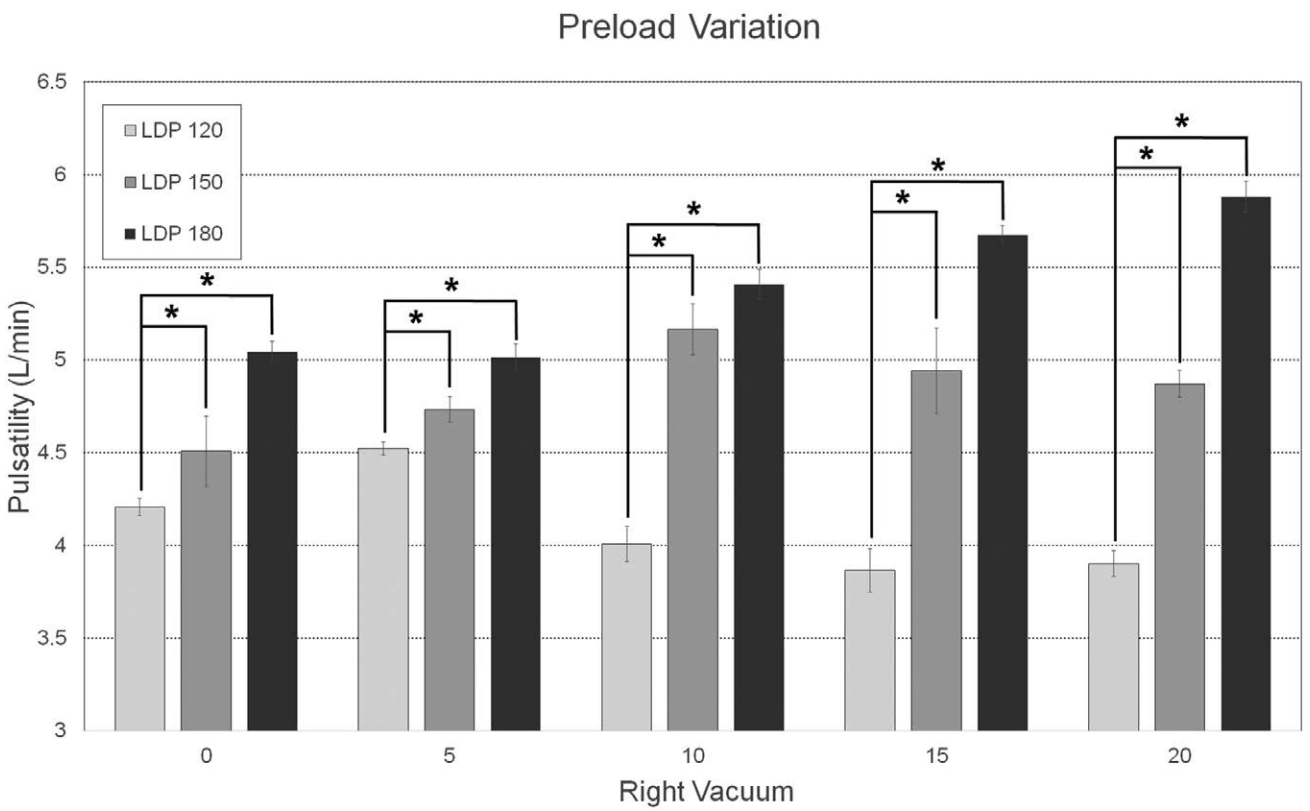

Figure 4. Varying preload by manipulation of the Total Artificial Heart (TAH) right vacuum while recording pulsatility under heart failure conditions (left ventricular left drive pressure [LV LDP] of 120 mm Hg), medium TAH contractility (LV LDP of 150 mm Hg), and normal TAH contractility (LV LDP of 180 mm Hg). Significant differences in pulsatility were observed between heart failure, medium, and normal LV function at all preloads.

then it may be concluded the patient's cardiac contractility has increased. Another limitation within this model is the lack of a flow sensor in the parallel branch measuring flow through the aortic valve to compare waveforms to the meter placed directly after the VAD. Flow meters were instead placed before and after the HVAD to ensure suction did not occur within the system. Although the HVAD controller does display a real-time waveform, this data is not sampled and recorded within device memory. No *in vivo* data is presented within this study, as this model is intended as a framework at analyzing clinical data. Future studies include evaluation of the algorithm *in vivo* with potential methods of increasing cardiac contractility.

The results from both the afterload and preload experiments demonstrate that pulsatility is a dynamic and valuable variable that can be used for translatable diagnostic purposes. It is sensitive to preload variation, increases in LV contractility, and changes in stroke work. It can provide insight into increased cardiac contractility in patients, especially when pressure status is controlled. Translation of this pulsatility model may be used as a framework in identifying patient response to various therapies intended to improve cardiac function, especially in combination with other diagnostic tools. Rather than solely relying on inconsistent or expensive imaging diagnostics, pulsatility provides a low-cost method solely by analyzing the data from the device controller. Longitudinal analysis through the HVAD is both accurate and beneficial for long-term assessment of patient conditions.

References

1. Heldman AW, DiFede DL, Fishman JE, *et al*: Transendocardial mesenchymal stem cells and mononuclear bone marrow cells for ischemic cardiomyopathy: The TAC-HFT randomized trial. *JAMA* 311: 62–73, 2014.
2. Karantalis V, DiFede DL, Gerstenblith G, *et al*: Autologous mesenchymal stem cells produce concordant improvements in regional function, tissue perfusion, and fibrotic burden when administered to patients undergoing coronary artery bypass grafting: The Prospective Randomized Study of Mesenchymal Stem Cell Therapy in Patients Undergoing Cardiac Surgery (PROMETHEUS) trial. *Circ Res* 114: 1302–1310, 2014.
3. Ascheim DD, Gelijns AC, Goldstein D, *et al*: Mesenchymal precursor cells as adjunctive therapy in recipients of contemporary left ventricular assist devices. *Circulation* 129: 2287–2296, 2014.
4. Ait Ali L, Cadoni A, Rossi G, Keilberg P, Passino C, Festa P: Effective cardiac index and systemic-pulmonary collaterals evaluated by cardiac magnetic resonance late after Fontan palliation. *Am J Cardiol* 119: 2069–2072, 2017.
5. Toth GB, Varallyay CG, Horvath A, *et al*: Current and potential imaging applications of ferumoxytol for magnetic resonance imaging. *Kidney Int* 92: 47–66, 2017.
6. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N: Inconsistent grading of aortic valve stenosis by current guidelines: Haemodynamic studies in patients with apparently normal left ventricular function. *Heart* 96: 1463–1468, 2010.
7. Michelena HI, Margaryan E, Miller FA, *et al*: Inconsistent echocardiographic grading of aortic stenosis: Is the left ventricular outflow tract important? *Heart* 99: 921–931, 2013.
8. Ivak P, Pitha J, Wohlfahrt P, *et al*: Biphasic response in number of stem cells and endothelial progenitor cells after left ventricular

assist device implantation: A 6 month follow-up. *Int J Cardiol* 218: 98–103, 2016.
9. Cameli M, Righini FM, Sparla S, *et al*: First evidence of cardiac stem cells from the left ventricular apical tip in patients with left ventricular assist device implantation. *Transplant Proc* 48: 395–398, 2016.
10. Anastasiadis K, Antonitsis P, Argiriadou H, *et al*: Hybrid approach of ventricular assist device and autologous bone marrow stem cells implantation in end-stage ischemic heart failure enhances myocardial reperfusion. *J Transl Med* 9: 12, 2011.
11. Heerdt PM, Holmes JW, Cai B, *et al*: Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in end-stage heart failure. *Circulation* 102: 2713–2719, 2000.
12. Burkhoff D, Klotz S, Mancini DM: LVAD-induced reverse remodeling: basic and clinical implications for myocardial recovery. *J Card Fail* 12: 227–239, 2006.
13. Aaronson KD, Slaughter MS, Miller LW, *et al*; HeartWare Ventricular Assist Device (HVAD) Bridge to Transplant ADVANCE Trial Investigators: Use of an intrapericardial, continuous-flow, centrifugal pump in patients awaiting heart transplantation. *Circulation* 125: 3191–3200, 2012.
14. Yokoyama Y, Kawaguchi O, Kitao T, Kimura T, Steinseifer U, Takatani S: Prediction of the external work of the native heart from the dynamic H-Q curves of the rotary blood pumps during left heart bypass. *Artif Organs* 34: 766–777, 2010.
15. Granegger M, Moscato F, Casas F, Wieselthaler G, Schima H: Development of a pump flow estimator for rotary blood pumps to enhance monitoring of ventricular function. *Artif Organs* 36: 691–699, 2012.
16. Crosby JR, DeCook KJ, Tran PL, *et al*: Physiological characterization of the SynCardia total artificial heart in a mock circulation system. *ASAIO J* 61: 274–281, 2015.
17. Besarab A, Bolton WK, Browne JK, *et al*: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 339: 584–590, 1998.
18. Crosby JR, DeCook KJ, Tran PL, *et al*: A physical heart failure simulation system utilizing the total artificial heart and modified Donovan Mock Circulation. *Artif Organs* 41: E52–E65, 2017.
19. Dong SJ, Hees PS, Huang WM, Buffer SA Jr, Weiss JL, Shapiro EP: Independent effects of preload, afterload, and contractility on left ventricular torsion. *Am J Physiol* 277(3 Pt 2): H1053–H1060, 1999.