Supporting Information for

Quantification of Pulsed Operation of Rotary Left Ventricular Assist Devices with Wave Intensity Analysis

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Animal Preparation

The Yale University Institutional Animal Care and Use Committee granted approval of all experimental protocols, which are consistent with the “Position of the American Heart Association on Research Animal Use”. Four Yorkshire pigs (44 – 60 kg; mean 51 kg) were prepared based on a refined protocol that successfully provided anesthetic effects during entire period of experiments without loss of heart function, for example resulting in ventricular fibrillation\textsuperscript{18}.

Surgery and Instrumentation

A median sternotomy was used for the surgical approach. The pericardium was opened and was not reapproximated after LVAD implantation. Antiarrhythmic drugs (lidocaine 7 mg/kg and amiodarone 450 mg total) were administered following the refined protocol\textsuperscript{18} in preparation for insertion of the inflow cannula into the LV of the heart. The outflow was attached to the ascending aorta. In two animals, a centrifugal LVAD was used (HVAD; HeartWare, Framingham, MA) and in other two animals an axial LVAD was used (HMII; Thoratec, Pleasanton, CA). Pressure, flow, and electrocardiogram (ECG) were measured during the experiment. Detailed measurement procedures are provided in Supplementary information.

Pressure was measured in the ascending aorta, pulmonary artery, left atrium, and left and right ventricles. The 5F aortic catheter (Transonic Scisense Inc., London, Ontario, Canada) was inserted through the carotid artery and advanced to the ascending aorta. The high-fidelity catheter-tip transducer was referenced via its fluid-filled lumen to an external pressure transducer (ADInstruments, Colorado Springs, CO) connected to a four-channel bridge amplifier (ADInstruments). Zero pressure was defined as the midlevel plane of the heart with the animal in the supine position. A Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA) was inserted in the jugular vein and advanced to the pulmonary
artery. The distal port of the Swan-Ganz catheter was connected to an external pressure transducer. The left atrium was accessed by directly inserting a 3F catheter (Transonic Scisense Inc.) through the left atrial appendage. The left and right ventricles were accessed by directly inserting cannulas (20 Gauge Arterial Catheterization Set, Arrow International Inc., Reading, PA) through the anterior wall of the respective ventricle. Each ventricular cannula was attached to fluid-filled lines connected to external pressure transducers.

Flow was measured in the ascending aorta, pulmonary artery, and the LVAD outflow cannula. The 18 mm flow probes were placed (Confidence-series probes and flowmeter model TS420; Transonic Systems Inc., Ithaca, NY) on the main pulmonary artery (immediately downstream of the tip of the pulmonary artery catheter) and on the aorta (immediately upstream of the tip of the aortic catheter). An external clamp-on type flow sensor (8PXL-series; Transonic Systems Inc.) was used to measure flow in the LVAD outflow cannula.

A 3-limb lead ECG was also recorded using an animal biological amplifier and needle electrodes (ADInstruments). Electronic signals were sampled at 400 Hz with data acquisition hardware (PowerLab Model 16/35; ADInstruments) and LabChart Pro software (ADInstruments). Data were filtered post hoc at 50 Hz using zero-phase digital filtering in Matlab (Mathworks Inc., Natick, MA).

**Dynamic VAD Control**

Controller was configured to enable both continuous and pulsatile VAD operation. In order to realize the physiological advantages of a pulsatile flow VAD, surgeons were allowed to control the continuous flow pump speed or switch to pulsatile mode in which the systolic and diastolic pump speed, heart rate, and systolic duration can all be set and wirelessly programmed. As a further improvement, the controller also can operate in an ECG synchronization mode. In this mode, three electrodes are used to measure the
ECG of the animal in real time. A time delay can be implemented to synchronize the pulsatility of the VAD with the natural pulsatility of the animal’s heart. Optimizing the synchronization between the heart’s natural ECG and VAD pulsatility is part of ongoing work. A Python-based graphical user interface (GUI) has been developed to allow the surgeon to easily control the speed and pulsatility of the VAD. The GUI also recorded all of the data associated with the wireless power transfer, as well as the motor controller characteristics including pump speed, power, and flow rate. Data logging occurred at a rate of 160Hz.

Wave Intensity Analysis (WIA)

Waves created incremental changes in pressure and flow and net wave intensity (dI) and wave energy (I) were calculated as follows:

\[ dI = dPdU \]  
\[ I = \int_{t_{\text{start}}}^{t_{\text{end}}} dI \, dt \]  

Equation 1

Equation 2

Net wave intensity (i.e., Equation 1) has units of W/m² and net wave energy (i.e., Equation 2) was used to quantify wave energy during a period of interest (i.e. from t_start to t_end) and has units of J/m². dP and dU are the incremental changes in pressure and velocity respectively. Velocity was determined by dividing flow by the cross-sectional area of the blood vessel; the diameter of which was estimated by the size of flow probe used to measure flow.

Forward waves were defined as originating upstream and were caused by the contracting and relaxing heart. Backward waves were defined as originating downstream and were caused by wave reflections in normal physiological conditions and potentially by the aortic outflow graft site in the LVAD physiology examined in the experimental conditions created in these experiments. Positive or
negative wave intensity only indicates whether forward- or backward-going waves dominate at any particular time during the cardiac cycle. However, it is possible to determine the magnitude and type of wave if the local wave speed is known.

Single-point wave speed (c) was calculated using the linear regression method\textsuperscript{19}, where it was assumed that only one wave is present during the upstroke of systole and the density of blood (\(\rho\)) is 1040 kg/m\(^3\). The linear relationship of pressure and velocity during this period was used to determine the wave speed and decompose wave intensity, pressure, and velocity into forward-going (+) and backward-going (−) wave components as follows\textsuperscript{8}:

\[
\begin{align*}
\text{Equation 3} \\
\text{Equation 4} \\
\text{Equation 5}
\end{align*}
\]

\[
dP_{\pm} = \pm \frac{1}{2} (dP \pm \rho cdU) \\
dU_{\pm} = \pm \frac{1}{2} (dU \pm \frac{dP}{\rho c}) \\
dI_{\pm} = \pm \frac{1}{4\rho c} (dP \pm \rho cdU)^2
\]

**Comparative WIA among physiological interventions**

The effects that increased afterload and preload had on LV generated wave intensity patterns are shown in Figure 5C. Afterload was increased with norepinephrine, which created peripheral vasoconstriction through the alpha-adrenergic effect and increased contractility through inotropic effects\textsuperscript{26}. Although the vasopressor effects of norepinephrine are greater than dobutamine\textsuperscript{27}, the large increase in FCW intensity and greater wave energy created by norepinephrine in this study are consistent with other studies showing the similar effect with dobutamine\textsuperscript{12, 21}. This suggests that the inotropic effect of norepinephrine increases the intensity of forward waves and outweighs any vasopressor effects that would otherwise serve to depress the intensity of forward waves\textsuperscript{12}.
Preload was increased with an acute infusion of fluid used to increase LV end-diastolic pressure. The greater force of contraction caused by the Frank-Starling mechanism is manifested by a larger FCW intensity and greater wave energy compared to baseline. This response was expected as the pericardium was not closed after LVAD implantation and the additional fluid volume did not compress the LV chamber as a result of a possible leftward septal shift caused by increased right ventricular end-diastolic volume. Therefore, one can speculate that the increase of LV wave energy with volume loading may not occur in congestive or right ventricle heart failure conditions.

**Clinical implications**

Measurement of wave intensity and performing WIA can be accomplished in LVAD patients when simultaneous measurements of blood pressure and velocity are made with a LV catheter capable of making these measurements in the aorta or LVAD outflow. Alternatively, pressure measurements can be combined post hoc with echocardiographic measurements of Doppler velocity. Compared to prior methodologies, WIA provides a straightforward method to robustly quantify the wave energy provided by the heart and/or LVAD and evaluate heart and pump function.

**Limitations**

This study focused on measuring the effects of continuous versus pulsed LVAD operation and differences between centrifugal and axial LVADs. This study did not compare different continuous pump speeds or different ranges of speed modulation. It could be hypothesized that higher pump pulsatility would have greater effects on the LV. However, the range of pulsed operation is limited by an upper speed limit that will cause ventricular suction and a lower speed limit that allows back flow.
through the LVAD. Nevertheless, future studies could be designed to investigate other ranges of speed modulated pulsatility.

Periods of co- and counter-pulsation were identified post-hoc by the pattern created by LVAD outflow (see Figure 4). The asynchronous pulsed LVAD operation used in this study may be different from synchronous pulsed LVAD operation. In this study, asynchronous LVAD pulsation was used primarily for technical reasons related to triggering the pump with the ECG signal in real time and the natural changes in intrinsic heart rate from beat to beat. While synchronous pulsatility in either co- or counter-pulsation mode has the potential to have greater repeatability, this study used at least 5 minutes of data collection during asynchronous pulsation to obtain enough individual cardiac cycles related to co- and counter-pulsation.