Continuous-Flow Cardiac Assistance: Effects on Aortic Valve Function in a Mock Loop

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Background. As the use of left ventricular assist devices (LVADs) to treat end-stage heart failure has become more widespread, leaflet fusion—with resultant aortic regurgitation—has been observed more frequently. To quantitatively assess the effects of nonpulsatile flow on aortic valve function, we tested a continuous-flow LVAD in a mock circulatory system (MCS) with an interposed valve.

Materials and Methods. To mimic the hemodynamic characteristics of LVAD patients, we utilized an MCS in which a Jarvik 2000 LVAD was positioned at the base of a servomotor-operated piston pump (left ventricular chamber). We operated the LVAD at 8000 to 12,000 rpm, changing the speed in 1000-rpm increments. At each speed, we first varied the outflow resistance at a constant stroke volume, then varied the stroke volume at a constant outflow resistance. We measured the left ventricular pressure, aortic pressure, pump flow, and total flow, and used these values to compute the change, if any, in the aortic duty cycle (aortic valve open time) and transvalvular aortic pressure loads.

Results. Validation of the MCS was demonstrated by the simulation of physiologic pressure and flow waveforms. At increasing LVAD speeds, the mean aortic pressure load steadily increased, while the aortic duty cycle steadily decreased. Changes were consistent for each MCS experimental setting, despite variations in stroke volume and outflow resistance.

Conclusions. Increased LVAD flow results in an impaired aortic valve-open time due to a pressure overload above the aortic valve. Such an overload may initiate structural changes, causing aortic leaflet fusion and/or regurgitation. © 2010 Elsevier Inc. All rights reserved.

Key Words: left ventricular assist device; continuous flow; aortic valve; mock circulation.

INTRODUCTION

Aortic valve commissural fusion and resultant insufficiency have recently begun to be considered complications of the prolonged use of left ventricular assist devices (LVADs), whether they produce pulsatile or nonpulsatile flow [1, 2]. Previous reporters have suggested that these complications result from certain local hemodynamic forces that affect aortic valve function during LVAD support [1–3]. To date, no detailed flow analyses or hemodynamic assessments have been available concerning the effects of reduced or nonpulsatile flow on aortic valve function during the cardiac cycle. We believe that the increased pressure load above the aortic valve due to increased LVAD flow may result in reduced aortic valve-open times and, consequently, may lead to aortic valve complications. The objective of the present study was to quantitatively assess the complex interaction between reduced or nonpulsatile aortic flow and aortic valve function in a mock-loop circulation using a nonpulsatile LVAD. The assessment was undertaken to calculate the aortic valve’s average mechanical load, open time, and transvalvular flow at different pump-flow settings and to determine the correlation between LVAD flow and aortic valve function.

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MATERIALS AND METHODS

Mock Circulation Setup

The "systemic" mock circulation (Fig. 1A) comprised a left ventricle, an aortic valve, an aortic tube model, and a Windkessel system that provided peripheral impedance (HemoLab BV, Eindhoven, The Netherlands). The system was primed with water and 0.5 g/L of xanthan gum solution, which has a viscosity of 3.71 mPa, equal to the viscosity of blood with a hematocrit of 34%.

The left ventricle was a servomotor-operated piston pump that could be programmed to deliver a cardiac output of $10 \text{ L/min}$ at a heart rate of $120 \text{ bpm}$. The shape of the output-flow curve was freely programmable. For this study, we used a symmetric systolic output flow that lasted for 35% of a heartbeat. The left ventricle ejected the test solution through a 21-mm standard bileaflet mechanical aortic valve (CarboMedics Inc., Austin, TX) into a flexible polyurethane tube that had the mechanical characteristics of the human aorta, ensuring proper pressure-wave propagation and reflection. The aortic tube terminated in a three-element hydraulic Windkessel system that mimicked total arterial resistance and compliance. The Windkessel's resistance was adjustable with a clamp. From the Windkessel, the test solution returned to an open storage container mounted directly onto the left ventricle. The liquid returned to the left ventricle via a second mechanical heart valve.

The following properties were measured simultaneously at a 1-kHz data rate with pressure transducers (Gould Instrument Systems, Valley View, OH) and flow probes (Transonic Systems Inc., Ithaca, NY): left ventricular pressure, aortic pressure, aortic flow, and pump flow.

To mimic the hemodynamic properties of an ejecting left ventricle as closely as possible (thereby ensuring minimal deviation from physiologic hemodynamic conditions in an LVAD recipient), we used the above-mentioned 21-mm CarboMedics standard bileaflet mechanical aortic valve. To ensure proper filling of the left ventricle, we used a 25-mm CarboMedics prosthesis as a mitral valve substitute.

The LVAD used in this study was the Jarvik 2000 intraventricular assist device (Jarvik Heart, Inc., New York, NY) [4], which features five constant speeds of operation, ranging from 8000 to 12,000 rpm.

The data measured by the pressure and flow sensors were received and recorded in the HemoLab software program. Figure 1B is a schematic representation of the above-described system components.

Study Design

At each LVAD speed, the mock loop simulated a different clinical hemodynamic state. Initially, we used a stroke volume of 60 mL and adjusted the clamp to vary the aortic pressure from 80/50 to 120/80 and then 140/100 mmHg. Without changing the Windkessel settings, we lowered the stroke volume to 40 mL at each setting, resulting in lower aortic pressures. Subsequently, with the Windkessel set to an aortic pressure of 120/80 mmHg and a stroke volume of 60 mL, we changed the stroke volume to 32 and then 48 mL. Finally, with the Windkessel adjusted to yield an aortic pressure of 120/80 mmHg, we tested the mock loop again at stroke volumes of 32 and 48 mL. All experiments were conducted at a heart rate of 60 bpm. Table 1 summarizes the settings used. At each combined LVAD setting (speed, heart rate, cardiac output, and afterload), the total and pump flows were measured along with the left ventricular and aortic pressures. Measurements were taken during 50 consecutive heartbeats at a data rate of 1 kHz.

![FIG. 1. (A) Photograph of the cardiovascular mock circulation system and (B) schematic representation of the data-acquisition-system components.](image)

**TABLE 1**

<table>
<thead>
<tr>
<th>Experiment</th>
<th>SV (mL)</th>
<th>BP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>60/40</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>120/80</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>80/60</td>
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<td>4</td>
<td>60</td>
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<td>8</td>
<td>60</td>
<td>140/90</td>
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<td>9</td>
<td>32</td>
<td>40/25</td>
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<td>11</td>
<td>32</td>
<td>120/80</td>
</tr>
<tr>
<td>12</td>
<td>48</td>
<td>120/80</td>
</tr>
</tbody>
</table>

SV = stroke volume; BP = blood pressure.
For reference, the aortic valve flow was determined by subtracting the pump flow from the total flow.

All statistical tests were performed by using Microsoft Office Excel software (Microsoft Corp., Redmond, WA) on a personal computer. Analysis of variance (ANOVA) was used to compare continuous variables. \( P \) values of < 0.05 were considered significant.

RESULTS

Twelve sets of experiments were performed, each at all five possible pump settings for the Jarvik 2000 LVAD. In each of the twelve experiments, despite different pressure and stroke volume settings, the trends for the changes in the pump flow, pressure difference over the aortic valve, and valve duty cycle were all uniform. Therefore, at each of the five pump settings, we averaged the data for the twelve experiments, and then graphed the resulting five data points to easily visualize these changes. Figure 2 shows the mean pump flow at increasing pump speeds. Figure 3 shows typical pressure and flow waveforms, which indicate the functionality of the mock loop and the validity of the acquired data. The data in Figure 3 were taken from the 120/80-mmHg experiments involving a normal ventricular stroke volume. The mock circulatory system was operating under these settings with the LVAD outlet clamped just below the ventricle-pump connection, so that normal blood flow patterns could be simulated. Correlation of these waveforms with standard physiologic pressure and flow waveforms indicated the functionality of the mock loop and LVAD and the validity of the acquired data. Figure 4 shows the pressure difference over the aortic valve, which was averaged for each experiment. In all cases, the average pressure load on the aortic valve increased with increasing pump speeds in comparison to baseline. Only with the pump connected and switched off was the transvalvular pressure lower.

The increase in the pressure load directly affected the aortic valve’s duty cycle (Fig. 5). In all cases, the duty cycle decreased at increasing pump speeds, reflecting a shorter valve-open time during each heartbeat. In half of the cases (experiments 2, 7, 8, 10, 11, and 12), the duty cycle was reduced to almost zero at higher pump speeds; in the rest of the cases, it stayed at

FIG. 2. Mean pump flow at increasing pump speeds (\( *P < 0.05 \) versus baseline). Baseline = pump off and outflow graft clamped; 0 = pump off and outflow graft unclamped.

FIG. 3. (A) Typical aortic (gray) and left ventricular (black) pressure waveforms. (B) Typical aortic-flow waveform.

FIG. 4. Mean aortic valve pressure load (\( *P < 0.05 \) versus baseline). Baseline = pump off and outflow graft clamped; 0 = pump off and outflow graft unclamped.
15%. Under normal conditions, the duty cycle is around 30%, but the valve remained closed most of the time at high pump speeds. In this set of experiments, the duty cycle was a function of pump speed. The reduced open time (Fig. 5) was also reflected in the reduced aortic flow (Fig. 6).

DISCUSSION

In this mock circulation study, we demonstrated that the mean aortic pressure load on the aortic valve gradually increases with increasing LVAD speeds and flows, while the aortic duty cycle decreases sharply. The validity of the mock circulatory system was initially confirmed by our ability to produce physiologic pressure and flow waveforms for normal heart function with no functioning LVAD support. Once the system was validated, we incorporated LVAD function into the model at increasing pump speeds, which correlated with clinically used pump settings. We were able to demonstrate that as the pump speed increased, the flow through the pump also increased, reflecting greater flow through the aorta. At the same time, flow through the aortic valve decreased, especially when the cardiac stroke volume was low, as in a failing ventricle. The failure-mode experiments (numbers 1, 3, 5, 7, and 9–12) also resulted in higher pump flows than the nonfailure-mode experiments, likely due to the lower pressure increase needed to generate net forward flow. Whereas most of the test fluid continued “downstream” to the Windkessel compliance system, which represented systemic compliance in our model, there was also a small amount of retrograde flow towards the aortic valve. The augmentation of total flow at increasingly high pump speeds increased the aortic pressure load on the aortic valve, as characterized by elevated pressure differences across the valve.

With the growing aortic pressure load on the aortic valve, the total valve-open time was reduced, because an increasingly smaller portion of left ventricular systole involved a pressure that surpassed the aortic pressure—a necessary condition for valve opening. Furthermore, total flow through the valve was reduced with increasing LVAD support. This resulted not only in shorter valve-open times but also in a less than fully open valve configuration at peak systole. The aortic valve used in this study was a mechanical one. Although the deformation of such a valve is not comparable to that of a natural valve, the varying pressure-flow relationship and its resultant impact on aortic valve opening should reflect the same physiologic phenomena observed in natural valves [4]. Because the valve’s hemodynamic boundary conditions were kept as physiologic as possible, the valve itself was not expected to significantly influence the total aortic flow and pressure in the mock system.

Over their lifetime, aortic valve leaflets are exposed to considerable cyclical stresses. The leaflets are subjected to flexural deformations during valve opening (systole) and closing (diastole), shear stress while open, and planar tension while closed [5]. During diastole, the aortic valve withstands a transvalvular pressure of around 80 mmHg, causing the aortic leaflet tissue to undergo an average stress of nearly 250–400 kPa. Under physiologic conditions, the loading time is so brief that the effects of viscoelasticity on leaflet interstitial cell deformation are negligible and no cellular strain-rate effects occur. On the other hand, experimentally increasing the diastolic time results in time-dependent deformation of the interstitial cells when the aortic valve is closed [6]. Zamarripa-Garcia and coworkers [3] have shown that the aortic valve load increases in the presence of a continuous-flow LVAD. While the valve is closed, it can
bear a pressure load, so the average transvalvular pressure may be higher at low duty cycles. Our data indicate not only that the absolute value of the average load increases by almost 25% but also (possibly of equal importance) that the time span in which the load is applied is approximately 20% longer than it would be under normal, physiologic conditions.

Thubrikar and associates [7] have reported that the radial length of the aortic leaflets does not change significantly during systolic aortic flow; however, when the leaflets close and coapt under increasing pressure, the radial length increases during diastole. Moreover, Weston and Yoganathan [8] have reported that porcine aortic leaflets exposed to either constant shear stress or a constant static pressure do not maintain the aortic valve interstitial cells’ contractile phenotype after 48 h. The function of these cells is believed to be crucial for the long-term integrity of the aortic valve’s surrounding extracellular matrix and for its continual renewal and repair.

In case of a continuous pressure overload above the aortic valve, as seen in our study, the radial length of the aortic leaflets is likely to increase further over time and result in a remodeled aortic valve, leading to regurgitation and annular deformation. Accordingly, the impaired opening time and concomitant regurgitation may result in further altered flow conditions, including longer leaflet exposure to blood components due to blood stagnation above the aortic valve. These changes may increase the likelihood of hemolysis, thrombosis, and/ or fusion of the aortic valve leaflets [9, 10].

In the light of previous reports regarding an increasing rate of aortic valve regurgitation and fusion after LVAD implantation [1–3], our results may suggest the impact of impaired aortic valve mechanics on the development of this complication.

CONCLUSION

Continuous-flow LVAD support results in an increased average pressure load on the aortic valve, not only because of an increased diastolic blood pressure but also because of an increased valve-closure time. In a clinical situation, it is likely that the reduced valve-open time and, more importantly, reduced forward flow through the valve would lead to incomplete opening of the valve during peak systolic flow, causing permanent deformation of the aortic leaflets and, thus, insufficiency of the valve. Additional in vivo and in vitro studies are ongoing at our institutions to further investigate the mechanisms of aortic valve regurgitation after LVAD implantation.

REFERENCES