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Hemodynamic effects of partial ventricular support in chronic heart failure: Results of simulation validated with in vivo data

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Objective: Current left ventricular assist devices are designed to provide full hemodynamic support for patients with end-stage failing hearts, but their use has been limited by operative risks, low reliability, and device-related morbidity. Such concerns have resulted in minimum use of left ventricular assist devices for destination therapy. We hypothesize that partial circulatory support, which could be achieved with small pumps implanted with less-invasive procedures, might expand the role of circulatory support devices for treatment of heart failure.

Methods: We examine the hemodynamic effects of partial left ventricular support using a previously described computational model of the cardiovascular system. Results from simulations were validated by comparison with an in vivo hemodynamic study.

Results: Simulations demonstrated that partial support (2-3 L/min) increased total cardiac output (left ventricular assist device output plus native heart output) by more than 1 L/min and decreased left ventricular end-diastolic pressure by 7 to 10 mm Hg with moderate-to-severe heart failure. Analyses showed that the hemodynamic benefits of increased cardiac output and decreased left ventricular end-diastolic pressure are greater in less-dilated and less-dysfunctional hearts. Both the relationships between ventricular assist device flow and cardiac output and ventricular assist device flow and left atrial pressure predicted by the model closely approximated the same relationships obtained during hemodynamic study in a bovine heart failure model.

Conclusions: Results suggest that a pump with a flow rate of 2 to 3 L/min could meaningfully affect cardiac output and blood pressure in patients with advanced compensated heart failure. The development of small devices capable of high reliability and minimal complications that can be implanted with less-invasive techniques is supported by these findings.

Commonly used left ventricular assist devices (LVADs) are designed to provide full hemodynamic support for the end-stage failing heart at rest and during exertion.[1] With flow rate capacities ranging from 5 to 10 L/min that adjust to the rate of venous return, these LVADs also provide profound left ventricular pressure and volume unloading, which, during prolonged use, results in structural and functional reverse remodeling.[1,2] However, even modern LVADs are relatively large, require a major surgical procedure for their insertion, and are associated with significant morbidity and mortality, especially during long-term use as an alternative to transplantation (ie, destination therapy).

Clinical experience with approaches such as cardiac resynchronization therapy (CRT)[3,4] and β-blockers[5,6] suggests that a large number of patients with heart failure might derive clinical benefit from partial hemodynamic support. By defini-

Abbreviations and Acronyms

CO = cardiac output
CRT = cardiac resynchronization therapy
EDP = end-diastolic pressure
LA = left atrium
LAP = left atrial pressure
LVAD = left ventricular assist device
LVEDP = left ventricular end-diastolic pressure
VAD = ventricular assist device

tion, partial support could be provided by smaller pumps with lesser flow capacities. Use of smaller pumps could translate into less-invasive insertion procedures, reduced energy requirements, and greater longevity. Such features would facilitate use of LVADs in patients with less-severe heart failure than in current practice. However, little is known about the hemodynamic effects of partial ventricular support in patients with advanced heart failure that do not require full hemodynamic support. Thus knowing which patients might be candidates for partial support, the potential for partial support to induce reverse remodeling, and the anticipated long-term hemodynamic effects of partial support when used as destination therapy are unknown.

We have previously described a computational model of the cardiovascular system[7] that offers the ability to simulate various degrees of heart failure. This model readily lends itself to testing the effects of varying degrees of LVAD support over a range of conditions. The core of this simulation has been used to define important physiologic principles and has been used successfully to prospectively predict the effects of proposed heart failure treatments.[8-12] In the present study we use this simulation to predict the theoretic hemodynamic effects of partial LVAD support with an axial flow pump over a broad range of heart failure states. Initial experiments in animals with chronic heart failure are used to validate the basic aspects of the model.

Materials and Methods

Theoretical Considerations

The hemodynamic effects of partial left ventricular support in heart failure were modeled by using a previously described computational model of the cardiovascular system.[8-12] This model, the parameter values input to the model and basic hemodynamic variables derived from computations under normal conditions, and 3 increasingly severe states of heart failure are detailed in Appendix E1 and Tables E1 and E2. The details of the equations governing flow through a continuous-flow blood pump and how this was interfaced with the cardiovascular system model are also provided in Appendix E1. A similar approach has been used recently to study the effect of weaning an LVAD on the workload on the native heart.[13]

Clinical Simulations

A series of simulated experiments was conducted with the cardiovascular model simulating ventricular assist device (VAD) flow from the left atrium (LA) or left ventricle (LV) to a proximal portion of the arterial tree. Pressure-volume loops were constructed, and left atrial pressure (LAP), aortic flow, and mitral valve flow were determined under conditions of mild, moderate, and severe heart failure before and during LVAD support. Simulations were performed to demonstrate the influence of VAD flow on cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP). Finally, the effects of varying pump preload and afterload on total CO, mean arterial pressure, and LVEDP were analyzed.

In Vivo Comparison

Model simulations were compared with data obtained from an acute bovine experiment conducted to characterize the hemodynamics of partial support in the LA-to-peripheral artery configuration (carotid artery). Cardiac dysfunction was induced in an 85-kg male Jersey breed calf by administration of 20 mg/kg of monensin 8 days before the hemodynamic study.[14] On the day of the operation, anesthesia was induced with isoflurane, followed by a left thoracotomy through the fifth interspace. The animal was instrumented with ultrasonic flow probes (Transonic, Inc, Ithaca, NY) placed on the pulmonary, brachiocephalic, and carotid arteries and on the descending aorta. Pressure was measured in the LA, aorta, and LV with high-fidelity pressure-sensing catheters (Millar Instruments, Houston, Tex). A conductance catheter with a micromanometer tip (Millar Instruments) was introduced retrograde from the aortic arch into the LV.

After instrumentation, a MEDOS DeltaStream DP 1 LT (MEDOS GmbH, Langensebold, Germany) VAD was implanted in an LA-to-left carotid artery bypass configuration with a 30F atrial cannula and an 8-mm graft (Bard Peripheral Vascular, Inc, Tempe, Ariz) for the outflow cannula. Flows generated by the DeltaStream pump were the same as the range of flows possible with the miniature VAD modeled in this study. Thirty-second data collections were performed at baseline and 5, 10, and 15 minutes after attainment of the target flow by adjusting pump speed. The target flow levels evaluated were 1, 2, and 3 L/min. After completion of data collection at each time point at each target flow, data were recorded at 5, 10, and 15 minutes after the pump was turned off, with the LVAD circuit clamped.

After adjusting cardiovascular parameters to match end-systolic and end-diastolic volumes and pressures, CO and LAP obtained from the in vivo experiment in the calf with moderate-to-severe heart failure were plotted against data obtained from the cardiovascular model to demonstrate the validity of model predictions for in vivo results. The animal used in this study received humane care in accordance with the "Guide for care and use of laboratory animals" (National Academy Press, 1996) and the guidelines determined by the Institutional Animal Care and Use Committee of the University of Louisville.

Results

Simulation of Varying Degrees of Compensated Heart Failure

Cardiovascular model parameters were set to simulate normal and mild, moderate, and severe heart failure conditions (Table E2). Note that for each of the increasingly severe

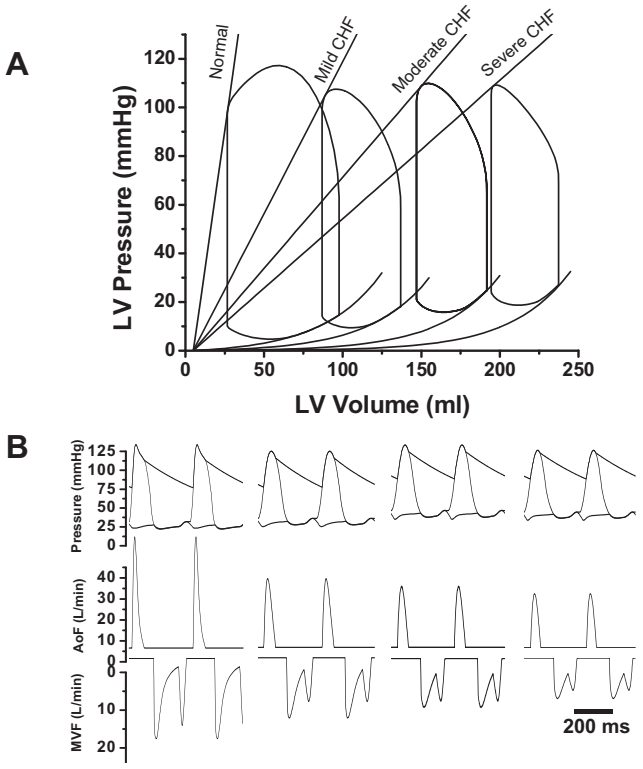

Figure 1. A, Pressure-volume relationships for normal and varying degrees of heart failure conditions. *LV*, Left ventricular; *CHF*, congestive heart failure. B, Pressure and flow tracings for normal and varying degrees of heart failure. *Extreme left* shows tracing in normal condition, with increasing degrees of failure progressing from *left* to *right*. *MVF*, Mitral valve flow; *AoF*, aortic flow.

degree of heart failure, the intent was to simulate well-compensated patients with progressive left ventricular dilatation and loss of contractility. The purpose of the simulations was not to simulate cardiogenic shock.

Pressure-volume loops generated for each of the conditions are shown in Figure 1, *A*. The pressure-volume relationships are typical for progressive heart failure, with the left ventricular end-diastolic pressure-volume relationship exhibiting a progressive shift toward larger volumes, whereas the slope of the end-systolic pressure-volume relationship decreases as the degree of heart failure progresses. The rightward shift of the pressure-volume loop demonstrates the increased dilation of the heart as it fails, and it is this progressive dilation that is the hallmark of left ventricular remodeling. End-diastolic pressure (EDP) increases as the severity of the heart failure state progresses, a consequence of salt and water retention and venoconstriction, which collectively result in an increase of total body stressed blood volume.

The pressures and flow tracings at each of these levels of heart failure are shown in Figure 1, *B*. Compared with normal values, aortic pressure and left ventricular systolic pressure decrease, whereas LAP increases. Because of the decreased contractility of the failing heart, there is a decrease in aortic flow. The reduced CO is of course associated with decreased ventricular filling through the mitral valve, with decreases in both active and passive peak filling velocities. All of these results are consistent with clinically observed changes in hemodynamic signals exhibited by patients with heart failure.

VAD Support

When the simulated VAD is set at 26,000 rpm (set to flow approximately 3 L/min) in an LA-to-aortic bypass configuration modeling partial left ventricular support, there is a leftward shift, narrowing, and increased height (ie, increased peak pressure) of the pressure-volume loop (Figure 2, *A*). This signifies increased aortic and left ventricular peak systolic pressures, with concomitant decreases in LVEDP, left ventricular end-diastolic volume, and LAP. When the pump bypass is from the LV to the proximal portion of the arterial tree, the shape of the loop changes (loss of isovolumic phases because blood is withdrawn continuously), and the degree of unloading (as indexed by the reductions in end-diastolic volume and pressure) is slightly greater (Figure 2, *A*).

With either configuration, flow through the aortic valve decreases during VAD support because the pump is drawing blood from the LA or LV and returning it to the proximal arterial tree, bypassing the left ventricular outflow tract (Figure 2, *B*). With the LV-to-peripheral artery configuration, flow through the aortic valve is very small. Mean flow across the mitral valve is reduced with the VAD withdrawing blood from the LA. In contrast, transmitral flow is increased when the VAD withdraws blood from the LV, a reflection of the overall increase in CO. In both cases native CO was 3.4 L/min, which increased to 4.5 L/min with blood withdrawn from either the LA or LV. Similarly, mean aortic pressure increased from the baseline value of 89 mm Hg to 113 mm Hg during VAD support with either configuration. EDP decreased from 27 mm Hg to 19 and 21 mm Hg with blood withdrawn from the LV and LA, respectively. By comparing the hemodynamic effect of partial support between left ventricular and left atrial blood withdrawal over a wide range of baseline conditions, we confirmed that there are negligible differences in net blood flow or blood pressure and only a 2- to 3-mm Hg effect on LVEDP. Thus because the fundamental effects of partial support on overall cardiovascular function are similar when blood is withdrawn from the ventricle as from the atrium, for simplicity, the remainder of the analysis focuses on withdrawal of blood from the atrium.

Figure 3, *A*, shows how total CO (ie, the sum of VAD flow plus flow from the LV through the aortic valve) varies

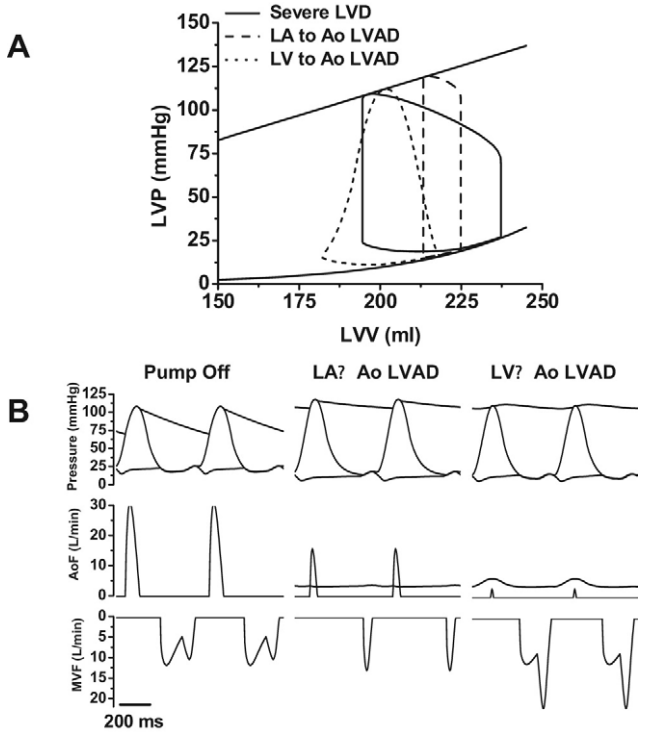

Figure 2. A, Pressure-volume loop at baseline heart failure state *(solid line)*, with pump on (simulation 26,000 rpm, 3 L/min flow) and withdrawing blood from the left atrium *(dashed line)*, and withdrawing blood from the left ventricle *(dotted line)*. *LVD*, left ventricular dysfunction; *LA*, left atrium; *Ao*, aorta; *LVAD*, left ventricular assist device; *LVP*, left ventricular pressure; *LVV*, left ventricular volume. B, Pressure and flow tracings with the pump off and on (approximately 26,000 rpm, 3 L/min flow) in left atrial *(LA)*–aortic *(Ao)* and left ventricular *(LV)*–aortic bypass configuration. *LVAD*, Left ventricular assist device; *MVF*, Mitral valve flow; *AoF*, aortic flow.

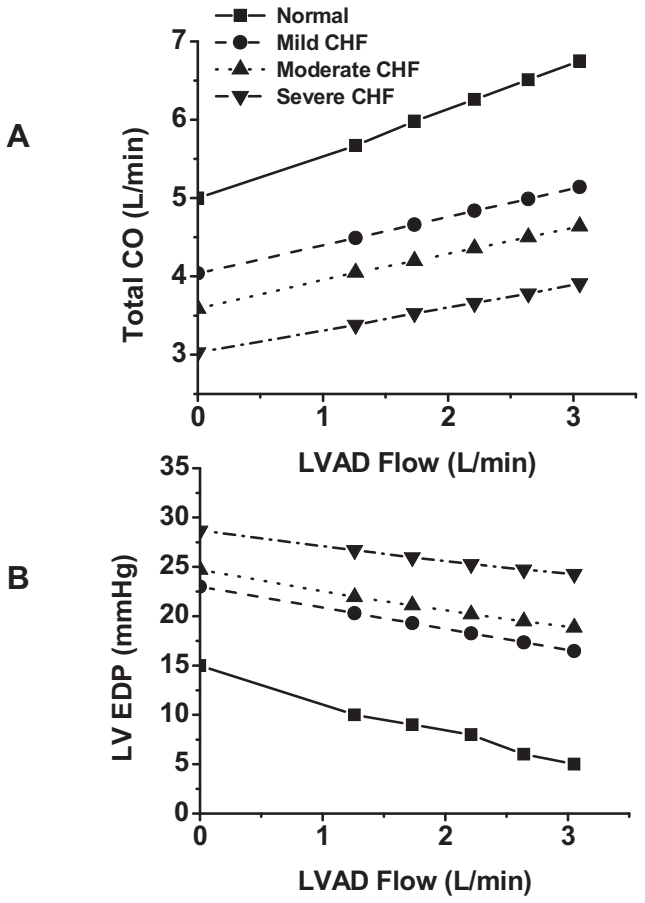

Figure 3. A, Total cardiac output *(CO)* as a function of ventricular assist device flow. The difference in the slope of the relationship for mild and severe heart failure indicates that the effect of partial ventricular assist device support on cardiac output is greater when the heart is less dilated and weak. *CHF*, congestive heart failure; *LVAD*, left ventricular assist device. B, Left ventricular end-diastolic pressure *(LV EDP)* as a function of ventricular assist device flow, further substantiating that this model predicts any degree of partial support to be hemodynamically more effective in states of mild compared with severe heart failure. *CHF*, Congestive heart failure; *LVAD*, left ventricular assist device.

as a function of VAD flow (obtained by progressively increasing VAD speed). The y-axis intercept of these curves represents the CO without any VAD support. The slope of this line was approximately 0.36 (a unitless number) in normal or mild heart failure and decreased to approximately 0.27 in severe heart failure. Thus, for the case of mild heart failure, for every 1 L/min of VAD flow, total CO was increased by 0.36 L/min. The less than 1:1 ratio between change in total CO and VAD flow is because the VAD shunts blood away from the LV; with decreased filling, intrinsic left ventricular output is decreased through the Frank-Starling relationship. The change in slope indicates that the effect of VAD support on total CO is greater when the heart is less dilated and less weak. Furthermore, the increase in total output occurs with the additional benefit of a reduction in LVEDP (a reflection of reduced pulmonary venous pressure). The slope of the relation between VAD flow and EDP (Figure 3, *B*) increased in magnitude from −1.3 in severe heart failure to −2.5 in mild heart failure. Thus with regard to both the increase in total output and reduction in filling pressure, this model predicts that any degree of partial support is hemodynamically more effective in states of mild compared with severe heart failure.

Stressed volume was varied over a wide range, and hemodynamic parameters were recorded with the VAD on (at 26,000 rpm, approximately 3 L/min) or off under conditions simulating mild and severe heart failure (Figure 4) to explore the effect of patient volume status on VAD performance. As shown in Figure 4, *A*, for each setting of cardiac

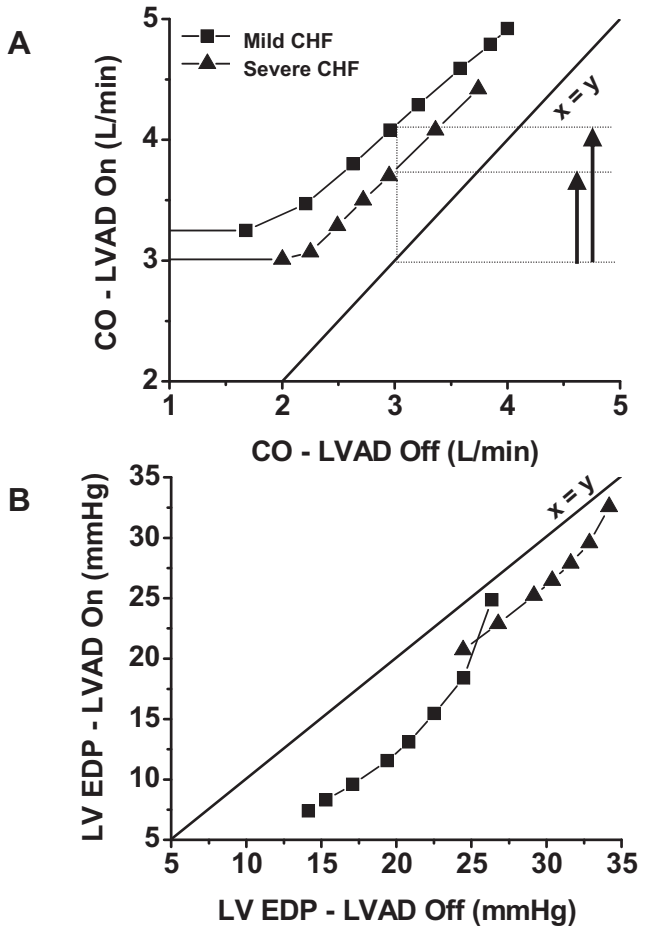

Figure 4. A, Effect of patient volume status on ventricular assist device performance during mild and severe heart failure. At each level of heart failure, partial ventricular assist device support increased total output by the same amount at any given intrinsic cardiac output value. *CO*, Cardiac output; *LVAD*, left ventricular assist device; *CHF*, congestive heart failure. B, Effect of patient volume status on left ventricular end-diastolic pressure *(LV EDP)* with ventricular assist device support during mild and severe heart failure. The effect of partial ventricular assist device support on LV EDP was nonlinear, having a greater effect at lower end-diastolic pressures. *LVAD*, Left ventricular assist device; *CHF*, congestive heart failure.

function, VAD support increased total output by approximately the same amount at any level of intrinsic CO. The proportion of total output assumed by the VAD increased as intrinsic output decreased. Consistent with the results discussed above, the magnitude of the increase was greater in mild compared with severe heart failure. In contrast to the effects on CO, the effect of VAD support on LVEDP was nonlinear, having a greater effect at lower EDPs (Figure 4, *B*).

Optimizing Hemodynamic Effects of VAD Support

As discussed earlier, the addition of partial left ventricular support shifts the pressure-volume loop leftward toward lower volumes, with a decrease in intrinsic CO. Concomitantly, the VAD improves overall circulatory hemodynamics with increases in total CO and mean arterial pressure and a significant decrease in LVEDP. The effects on preload and afterload can be substantial and can be intentionally manipulated in the clinic to optimize the hemodynamic effectiveness of partial hemodynamic support, as shown by the pressure-volume loops shown in Figure 5. The loop shown by the solid line depicts the baseline loop in moderate heart failure. When the VAD is turned on (26,000 rpm), the loop shifts leftward, EDP decreases, and blood pressure increases (dashed line).

The effect on hemodynamic parameters is summarized in Figure 5, *B*. Total CO increases in response to VAD support; the relative contributions of intrinsic left ventricular output and pump flow are shown by the solid and hatched bars, respectively. On institution of afterload reduction (simulated by a decrease in arterial resistance), the loop shifts further leftward (reduced EDP), blood pressure decreases, and the total output increases, with a greater proportion attributable to the pump. Because of the now substantial decrease of EDP, a safe but increased total body fluid status can be tolerated, and an increased EDP is possible (dashed-dotted line), potentially enabling reductions in diuretic dose. Increasing stressed volume to levels at which EDP is still clinically acceptable results in increased total CO, and the pump accounts for a substantial portion of the flow. As a result of optimization of "medical treatment," CO could be increased by approximately 2 L/min, and mean arterial pressure could be increased by 13 mm Hg, whereas EDP is maintained at less than 20 mm Hg in this example. The results presented in Figure 5 thus reveal the mechanisms by which a partial-support VAD allows for optimization of hemodynamic conditions through simple medication adjustments.

In Vivo Comparison

To validate the cardiovascular model, we compared the simulation data with data obtained from an acute in vivo preparation of chronic heart failure. Parameter values for the end-diastolic and end-systolic pressure-volume relations were guided by volume measurements made at baseline in the animal by using the conductance technique, as detailed in the "Methods" section. LVEDP (approximately 25 mm Hg) and left ventricular volume (approximately 223 mL) in the bovine before the initiation of VAD support were similar to values listed in Table E3 for the moderate-to-severe heart failure conditions simulated in the computational model. Pressure and flow measurements were obtained at multiple levels of pump speed, yielding flows up to approx-

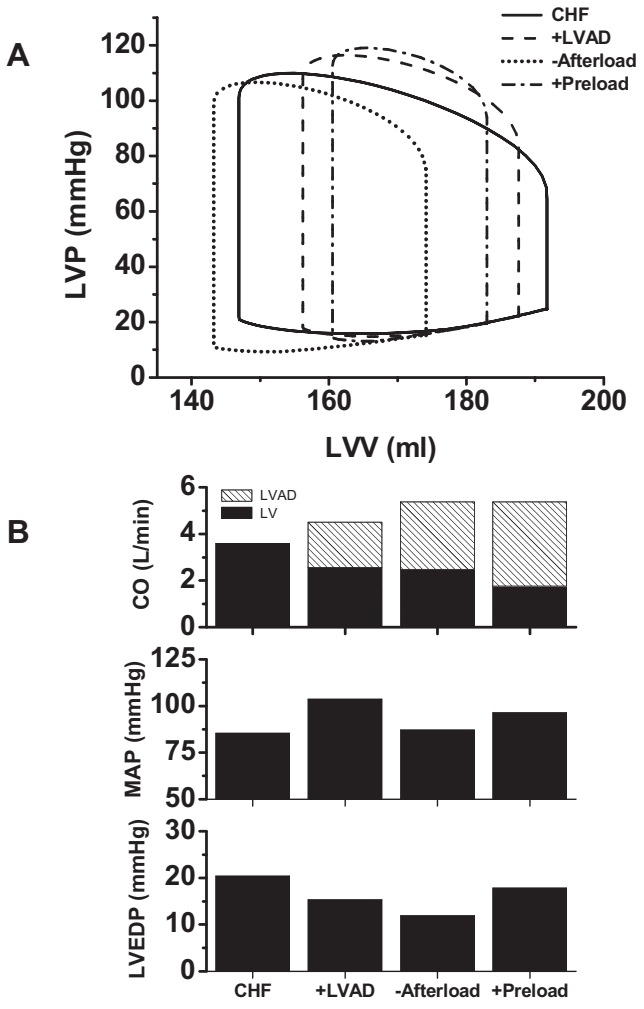

Figure 5. A, Demonstration of the effects of preload and afterload manipulation to optimize the hemodynamic effectiveness of a partial-support ventricular assist device. *LVP*, Left ventricular pressure; *CHF*, congestive heart failure; *LVAD*, left ventricular assist device; *LVV*, left ventricular volume. B, Hemodynamic parameters with varying preload and afterload with and without partial ventricular assist device support. *LV EDP*, Left ventricular end-diastolic pressure; *MAP*, mean arterial pressure; *CO*, cardiac output; *CHF*, congestive heart failure; *LVAD*, left ventricular assist device.

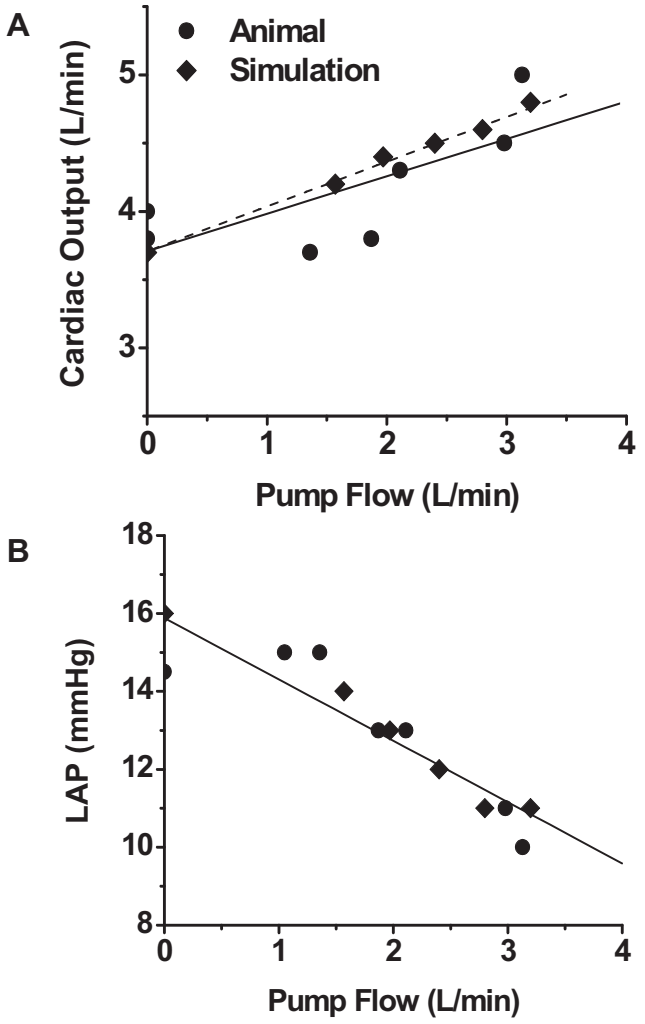

Figure 6. A, In vivo relationship of pump output and total cardiac output. This relationship approximates the same relationship resulting from the simulation. B, In vivo relationship between pump output and left atrial pressure *(LAP)*. Note the similarity of the in vivo relationship to the simulated relationship.

imately 3 L/min. Both the relationship between VAD flow and CO and between VAD flow and LAP predicted by the model closely approximated the same relationships obtained from the in vivo experiment (Figure 6). These findings would therefore justify the underlying assumptions and simplifications intrinsic to the model.

Discussion

Small pumps designed to flow at 2 to 3.5 L/min could potentially be used to provide partial hemodynamic support for patients with heart failure. Some are less than 20 mm in diameter, lending themselves to minimally invasive implantation techniques. The present results demonstrate that flows in the range provided by these small pumps can result in flows sufficient to meaningfully affect CO and blood pressure in patients with advanced compensated heart failure. In the simulations we performed, partial support of approximately 3 L/min increased total CO by more than 1 L/min and decreased LVEDP by 7 to 10 mm Hg in patients with moderate-to-severe heart failure. The effectiveness of this degree of support was further enhanced when afterload and preload were intentionally manipulated in a manner that can be implemented in the clinical setting. In such a condition,

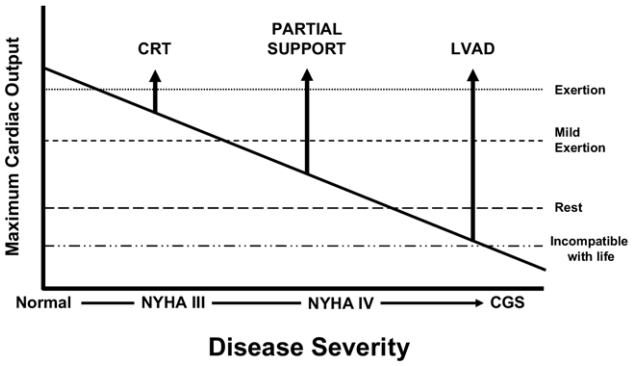

Figure 7. As the severity of disease increases from normal to New York Heart Association class III and IV and ultimately to cardiogenic shock *(CGS)*, the possible maximal cardiac output decreases from that capable of supporting full exertion to that barely necessary to support life. Partial support fills the gap between patients needing small amounts of hemodynamic support to meaningfully enhance exercise tolerance, such as can be provided by cardiac resynchronization therapy *(CRT)*, and those with severe heart failure who require a device that fully assumes the work of the heart. *LVAD*, Left ventricular assist device.

CO could be increased by approximately 2 L/min, mean arterial pressure could be increased by 13 mm Hg, and EDP is maintained at less than 20 mm Hg.

Large-scale studies with β-blockers[5,6] and CRT[3] provide evidence that relatively subtle changes in contractility can result in clinically important benefits, such as increased exercise tolerance and improved quality of life. A mechanical device, such as was modeled in the present study, capable of enhancing CO by more than 3 times the amount provided by CRT could be applied to patients with more severe disease than currently being treated with CRT. The concept of which patients could benefit is shown in Figure 7. There are a large number of patients in whom treatment with optimal medications and devices, such as CRT, fails but who are not sufficiently compromised to receive an LVAD. It is for these patients that a partial-support VAD could be effective and beneficial.

The results of the present modeling study showed that the hemodynamic benefits of partial support are greater in hearts that are less dilated and less dysfunctional. For a given heart structure and function (ie, for specified end-diastolic pressure-volume relationship and end-systolic pressure-volume relationship), a partial-support VAD, such as that characterized by Figure E2, adds a relatively fixed amount of flow over a broad range of native COs (Figure 4). During exercise, intrinsic CO increases, even in patients with heart failure; according to the findings of Figure 4, partial support will add the same fixed amount of flow independent of CO at any particular time or state of exertion. Similarly, patients with different body sizes will have different resting COs, but again the increment in total flow provided by a partial-support VAD is predicted to depend on ventricular characteristics and not on the actual value of intrinsic CO.

In addition to improvement of blood pressure and CO, which improves end-organ perfusion and function, LVAD support induces reverse remodeling, including improvement in intrinsic ventricular function.[1] Reverse remodeling in patients with LVADs is in part a result of pressure and volume unloading of the failing heart and in part a result of the improved neurohormonal milieu (eg, decreased catecholamines, tumor necrosis factor α, and brain natriuretic peptide).[1] Because the results of the present simulation (corroborated by experimental study) demonstrate such unloading, they suggest that partial support might result in reverse remodeling. If this is the case, we hypothesize that as heart structure and function improve, cardiac assistance provided by a partial-support VAD would improve over time as the native heart contribution to flow increases. Such effects could be further enhanced by the introduction and dose optimization of medications known to induce reverse remodeling, such as angiotensin-converting enzyme inhibitors, β-blockers, and aldosterone inhibitors.

There are 2 possible cannulation sites for such pumps: the LV or the LA. As shown in Figure 2, there is a relatively significant difference in the effect of the inflow cannulation site on the shape and position of the resulting pressure-volume loop. With left atrial cannulation, the loops shift toward a slightly lower filling pressure and volume, but peak pressure increases, and the loop is relatively thin (both indicating increased afterload). In contrast, with left ventricular cannulation, there are more significant reductions in filling pressure and volume, peak pressure is relatively constant, and minimum volume attained during the cardiac cycle is also significantly decreased. Because myocardial oxygen consumption is related to the pressure-volume area,[15] it is evident that myocardial oxygen consumption would be decreased more if blood were to be withdrawn from the LV than from the LA. Although the effect on net CO is predicted to be essentially identical between the 2 sites of inflow cannulation, the greater reductions in preload volume, preload pressure, and myocardial oxygen consumption could possibly affect the rate and extent of reverse remodeling achieved during partial support, in which case reverse remodeling would be predicted to be greater with inflow cannulation of the LV.

One limitation of the model used is that no attempt has been made to model a situation in which the pump would cause left atrial collapse and suction. The occurrence of suction and atrial collapse in such settings would reduce flows and create other problems for the pump that are beyond the scope of the present simulation.

In summary, the results of this model analysis suggest that significant hemodynamic benefits can be achieved with partial ventricular support in patients with heart failure. This degree of support is predicted to be more beneficial in hearts that are less dilated and less dysfunctional. These data further suggest that if partial support can induce a degree of reverse remodeling, the effectiveness of partial support might improve over time. Development of small devices that can provide 2 to 3 L/min flow and be implanted with minimally invasive techniques is thus encouraged by these findings. The clinical availability of such devices could result in a risk-reduced and cost-effective way to treat patients with heart failure before they become critically ill.

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Appendix E1

The cardiovascular system was modeled as shown by the electrical analog in Figure E1. The details of this model are provided elsewhere[E1,E2] and will be discussed here in brief. Ventricular and atrial pumping characteristics were represented by modifications of the time-varying elastance (E[t]) theory of chamber contraction, which relates instantaneous ventricular pressure (P[t]) to instantaneous ventricular volume (V[t]). Thus for each chamber,

$$P(t) = P_{ed}(V) + (1 - e(t))P_{es}(V),$$

where

$$P_{ed}(V) = B\,(e^{A(V-Vo)} - 1)$$

$$P_{es}(V) = E_{es}(V - V_o),$$

and

$$e(t) = 1/2\{\sin[(\pi/T_{max})t - \pi/2] + 1\} \quad 0 < t \leq 3/2\ T_{max}$$

$$1/2\ e^{-(t-3/2T_{max})/\tau} \quad t > 3/2\ T_{max},$$

where $P_{ed}(V)$ is end-diastolic pressure as a function of volume, $P_{es}(V)$ is end-systolic pressure as a function of volume, E_{es} is end-systolic elastance, V_o is the volume axis intercept of the end-systolic pressure-volume relationship, A and B are parameters of the end-diastolic pressure-volume relationship, T_{max} is the point of maximal chamber elastance, τ is the time constant of relaxation, and t is the time during the cardiac cycle.

The systemic and pulmonary circuits are each modeled by lumped venous and arterial capacitances (C_v and C_a, respectively); a proximal characteristic resistance (R_c, also commonly called characteristic impedance), which relates to the stiffness of the proximal aorta or pulmonary artery; a lumped arterial resistance (R_a); and a resistance to return of blood from the venous capacitance to the heart (R_v, which is similar, although not identical, to Guyton's resistance to venous return[E3]). The heart valves permit flow in only one direction through the circuit.

The total blood volume (Vol_{tot}) contained within each of the capacitive compartments is divided functionally into 2 pools: the unstressed blood volume (Vol_{unstr}) and the stressed blood volume (Vol_{str}). Vol_{unstr}, sometimes referred to as the dead volume, is defined as the maximum volume of blood that can be placed within a capacitive vessel without increasing its pressure to greater than 0 mm Hg. The blood volume within the capacitive compartment in excess of Vol_{unstr} is Vol_{str}, so that $Vol_{tot} = Vol_{unstr} + Vol_{str}$. The unstressed volume of the entire vascular system is equal to the sum of the Vol_{unstr} of all the capacitive compartments; similarly, the total body stressed volume equals the sum of Vol_{str} for all compartments.[E4] The pressure within the compartment is assumed to increase linearly with Vol_{str} in relation to the compliance (C), as follows:

$$P = Vol_{str}/C$$

The LVAD was modeled as a continuous flow pump with approximately linear pressure-flow characteristics that varied with pump speed, as shown in Figure E2. These data were obtained from a real pump interfaced with a mock circulation using a water-glycerol solution (viscosity, 3.6 cp). The pump is a prototype for a miniature pump designed to be used in a clinical study. As shown, such a pump can generate flows of up to 3.5 L/min with its impeller spinning at 28,000 rpm (pressure head between 100 and 150 mm Hg). As indicated in Figure E1, it could be specified during the simulation whether the LVAD withdrew blood from the LA or the LV. In either case, the blood was pumped to the proximal portion of the arterial system.

The normal value of each parameter of the model was set to be appropriate for a 70- to 75-kg man (body surface area, 1.9 m^2). These values, adapted from values in the literature,[E1,E3-E5] are listed in Table E1. Table E2 shows the parameter values used to simulate varying degrees of heart failure (mild, moderate, and severe). Values shown in Table E1 that do not appear in Table E2 retained the normal parameter values as specified in Table E1.

Table E3 shows the resultant values for hemodynamic parameters at the varying degrees of heart failure defined as mild, moderate, and severe.

References

E1. Santamore WP, Burkhoff D. Hemodynamic consequences of ventricular interaction as assessed by model analysis. *Am J Physiol Heart Circ Physiol.* 1991;260:H146-57.

E2. Burkhoff D, Tyberg JV. Why does pulmonary venous pressure rise following the onset of left ventricular dysfunction: a theoretical analysis. *Am J Physiol Heart Circ Physiol.* 1993;265:H1819-28.

E3. Sagawa K, Maughan WL, Suga H, Sunagawa K. Cardiac contraction and the pressure-volume relationship. Oxford: Oxford University Press; 1988.

E4. Alexander J Jr, Sunagawa K, Chang N, Sagawa K. Instantaneous pressure-volume relation of the ejecting canine left atrium. *Circ Res.* 1987;61:209-19.

E5. Milnor WR. Hemodynamics. Baltimore: Williams and Wilkins; 1982.

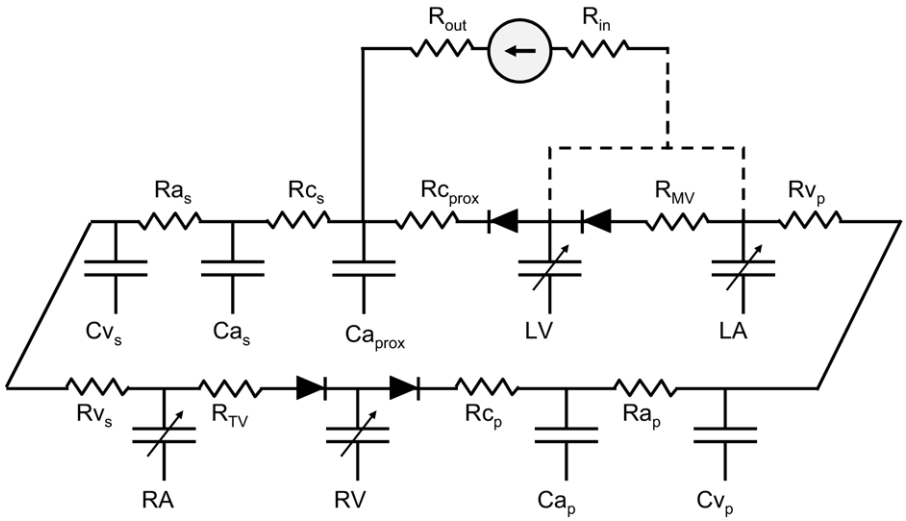

Figure E1. Electrical analog modeling cardiovascular system.

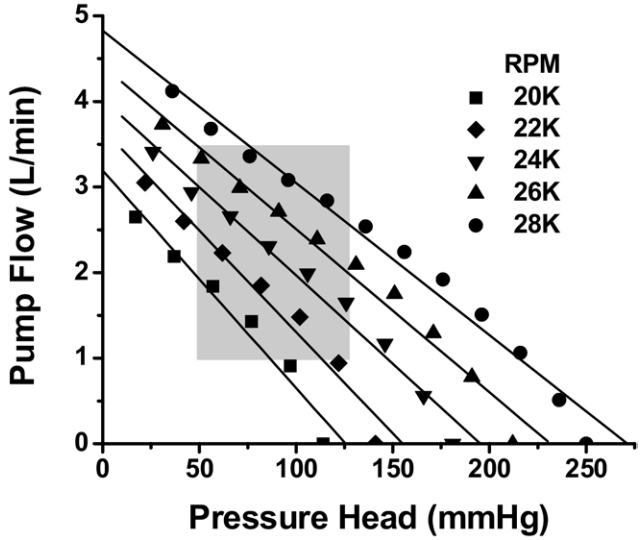

Figure E2. Pressure-flow characteristics of pump modeled. The *gray box* demarcates clinically relevant operating points for the pump.

TABLE E1. Normal parameter values

Parameter group/name	Symbol	Units	Values			
Common parameters						
Heart rate	HR	min^{-1}	70			
AV delay	AVD	ms	160			
Total blood volume	BV_{tot}	mL	5000			
Stressed blood volume	BV_{stress}	mL	950			
Unstressed blood volume	$BV_{unstress}$	mL	4050			
Heart			**RA**	**RV**	**LA**	**LV**
End-systolic elastance	E_{es}	mm Hg/mL	0.45	0.61	0.45	3
Volume axis intercept	V_o	mL	10	5	10	5
Scaling factor for EDPVR	A	mm Hg	0.44	0.35	0.44	1.3
Exponent for EDPVR	B	mL^{-1}	0.049	0.04	0.049	0.027
Time to end-systole	T_{max}	Ms	125	200	125	200
Time constant of relaxation	τ	ms	25	30	25	30
AV valve resistance	R_{av}	mm Hg · s/mL	0.0025		0.0025	
Circulation			**Pulmonary**	**Systemic**		
Characteristic impedance	R_c	mm Hg · s/mL	0.03	0.04		
Arterial resistance	R_a	mm Hg · s/mL	0.03	1.1		
Venous resistance	R_v	mm Hg · s/mL	0.025	0.025		
Arterial compliance	C_a	mL/mm Hg	13	1.5		
Venous compliance	C_v	mL/mm Hg	8	70		

AV, Atrioventricular; *RA*, right atrium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle; *EDPVR*, end-diastolic pressure-volume relationship.

TABLE E2. Parameter values to simulate different degrees of heart failure

	Normal	Mild	Moderate	Severe
HR	70	80	80	80
Stressed blood volume	650	650	1750	1750
RV E_{es}	0.61	0.50	0.42	0.40
RV $_A$	0.35	0.25	0.15	0.10
τ	30	50	70	90
LV E_{es}	4.5	1.25	0.75	0.57
LV $_A$	1.3	0.53	0.16	0.05
Systemic R_c	0.03	0.04	0.04	0.04
Systemic R_a	0.8	1.1	1.2	1.4
Pulmonic R_c	0.03	0.02	0.04	0.02
Pulmonic R_a	0.03	0.02	0.04	0.04
Systemic C_a	1.5	1.0	1.0	1.0

Note that model parameter values not shown in this table retained normal values, as specified in Table E1. See Table E1 for definitions of abbreviations.

TABLE E3. Simulation variables at different degrees of compensated heart failure

Parameter	Units	Normal	Mild	Moderate	Severe
Cardiac output	L/min	5.0	4.0	3.6	3.4
Stroke volume	mL	71.0	50.0	45.0	43.0
Right atrial pressure (mean)	mm Hg	8.0	4.0	10.0	10.0
Pulmonary artery pressure (S/D/M)	mm Hg	27/11 (15)	25/14 (16)	37/22 (25)	39/24 (22)
Left atrial pressure (mean)	mm Hg	8.0	12.0	19.0	22.0
Aortic pressure (S/D/M)	mm Hg	111/57 (82)	109/60 (81)	110/66 (85)	109/71 (89)
RV end-diastolic pressure	mm Hg	13	7	17	17
RV end-diastolic volume	mL	96	91	123	132
RV ejection fraction	%	68	50	36	32
LV end-diastolic pressure	mm Hg	15	18	25	27
LV end-diastolic volume	mL	98	137	192	237
LV ejection fraction	%	73	36	25	18

S/D/M, systolic/diastolic/mean; *RV*, right ventricular; *LV*, left ventricular.