In vitro hemodynamic characterization of HeartMate II at 6000 rpm: Implications for weaning and recovery

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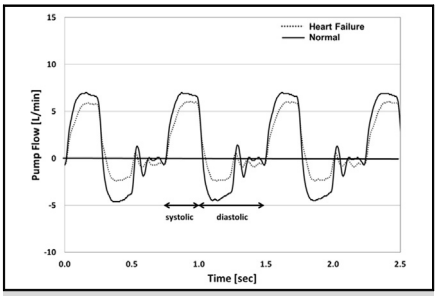
ABSTRACT

Objectives: Pump-off testing to assess left ventricular recovery is not an option for continuous-flow left ventricular assist devices unless measures are taken to prevent pump regurgitation. The purpose of this bench study was to characterize the hemodynamics and pump flow of the HeartMate II (Thoratec Corp, Pleasanton, Calif) left ventricular assist device at 6000 rpm, the speed commonly used clinically to determine left ventricular recovery.

Methods: The HeartMate II device was operated in a mock loop at 3 speeds (6000, 8000, and 10,000 rpm). We acquired pressure-flow curves in each steady state. In pulsatile mode with the pneumatic ventricle (heart simulator) activated, pump flow, total flow, and aortic pressure data were obtained under conditions simulating normal heart function or heart failure.

Results: A large regurgitant flow during diastole was confirmed in normal heart function at 6000 rpm support; however, the net flow was zero, and there were no differences in the mean aortic pressure between 6000 rpm support and no left ventricular assist device support. In contrast, in the heart failure condition, left ventricular assist device flow at 6000 rpm significantly contributed to the mean aortic pressure and total flow because there was less regurgitant flow.

Conclusions: The net pump flow generated by the HeartMate II device at 6000 rpm depends on the degree of residual left ventricular function. In the setting of improved left ventricular function, at 6000 rpm, we noted a large regurgitant flow that reloaded the left ventricle. Although this "marker" can serve as a useful indicator for left ventricular recovery, assessing left ventricular recovery at this speed is flawed unless measures are taken to prevent regurgitant flow. (J Thorac Cardiovasc Surg 2015;150:343-8)



Pump flows at 6000 rpm LVAD support were compared between normal and heart failure conditions.

Central Message

The HeartMate II device (Thoratec Corp, Pleasanton, Calif) at 6000 rpm is a different condition than pump-off with the outflow graft clamped, when the heart has not recovered well.

Perspective

The net pump flow generated by the HeartMate II device (Thoratec Corp, Pleasanton, Calif) at 6000 rpm depends on the degree of residual LV function. In the setting of improved LV function, we noted a large regurgitant flow at 6000 rpm that reloaded the LV. Although this "marker" can serve as a useful indicator for LV recovery, assessing LV recovery at this speed is flawed unless measures are taken to prevent regurgitant flow.

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Left ventricular (LV) recovery sufficient to allow cardiac assist device removal has been reported with the HeartMate II (HMII) (Thoratec Corp, Pleasanton, Calif) left ventricular assist device (LVAD).[1] Although mechanical unloading of the ventricle can lead to many positive geometric, biochemical, and genetic alterations favoring device removal,[2-4] this condition has not translated into clinical success. The sixth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support states that surgeons intended LVADs to be implanted as a bridge to recovery in only 0.9% of cases.[5] Unlike pulsatile devices, in which testing with the pump turned off (pump-off testing) allows assessment of the recovery level of LV function, such testing is not possible with continuous-flow LVADs, because there is no valve to prevent pump regurgitation. In 2010, George and

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This study was supported by internal Cleveland Clinic funding.

Received for publication March 3, 2015; revisions received March 26, 2015; accepted for publication April 3, 2015.

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0022-5223/$36.00

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http://dx.doi.org/10.1016/j.jtcvs.2015.04.015

Abbreviations and Acronyms

AoP = aortic pressure
HMII = HeartMate II
LV = left ventricular
LVAD = left ventricular assist device

colleagues[6] reported a method of assessing myocardial recovery by echocardiography. They suggested that reducing the HMII's pump speed to 6000 rpm (the device's lowest operational setting) was sufficient to exclude the effects of LVAD support on hemodynamics. At most institutions, evaluation of cardiac function for assessing the feasibility of device explantation is performed at 6000 rpm,[1] and this is also currently the speed used in clinical trials of native LV recovery.[7]

In the recently completed clinical trial that showed the safety and efficacy of administration of mesenchymal precursor cells as adjunctive therapy for myocardial recovery in patients with LVADs, the ability to tolerate transient reduction in LVAD speed to 6000 rpm for 30 minutes without signs or symptoms of hypoperfusion was the key efficacy end point, despite the fact that hemodynamic levels at 6000 rpm are still unknown.[8] Because continuous-flow pumps such as the HMII have no valves, reverse flow occurs when the impeller's rotational speed is not high enough to overcome outlet pressure.[6] In vitro pressure-flow data at 6000 to 14,000 rpm in a steady-state condition have been reported.[9,10] The minimum pump flow that can be obtained with a single pump in a steady-state system is zero, and no reverse flow can thereby be generated. Pressure-flow data at 6000 rpm in a pulsatile condition, with the native LV functioning in parallel to the pump, have not been characterized.

Therefore, the purposes of this study were 3-fold: (1) to demonstrate the pressure-flow relationship at a pump speed of 6000 rpm in a mock loop at steady-state versus pulsatile conditions with a mock ventricle; (2) to evaluate pump flow (forward and reverse) and hemodynamics at a pump speed of 6000 rpm connected to a mock ventricle running under normal versus heart failure conditions; and (3) to compare the hemodynamics between when the pump is off and when it is running at 6000 rpm with a mock ventricle under normal versus heart failure conditions.

MATERIALS AND METHODS

The in vitro mock circulatory loop setup we used comprises a modified pneumatic mock ventricle (AB5000; ABIOMED Inc, Danvers, Mass), an adjustable arterial afterload and compliance, and the HMII device with a motor controller capable of varying pump speed (Figure 1). To simulate blood, a mixture of water and glycerin (specific gravity, 1.060) was used as the working fluid. The inflow of the HMII device was connected to an additional outlet of the pneumatic ventricle's blood chamber, and the outflow of the HMII was connected to the aorta distal to the aortic valve. For comparisons, the HMII device was operated at a constant speed of 6000, 8000, or 10,000 rpm. In the pump-off condition, the outflow tubing was clamped to avoid any pump regurgitation. We recorded pump flow and total flow using ultrasonic flow probes and flow meters (20XL, 10XL and T110; Transonic Systems, Inc, Ithaca, NY). Ultrasonic flow probes were clamped onto the ½-inch inner diameter LVAD outflow tubing and on the 1-inch inner diameter loop tubing between the compliance chamber and the reservoir. Pump pressures were monitored with fluid-filled tubing connected to the LVAD pump inlet and outlet; the pneumatic pump pressure was measured on the drive line.

Steady-State Conditions

The pneumatic mock ventricle was not activated for this study. The HMII device was operated at a constant speed of 6000, 8000, or 10,000 rpm. At each pump speed, we manipulated delta pressures (HMII outlet pressure minus HMII inlet pressure) from maximum pump flow (no outlet restriction) to 0 L/min of pump flow (total clamp of the outlet) at increments of 1 L/min. Pressure-flow curves were plotted using the data acquired during static flow testing.

We also estimated the 6000 rpm head curve, which was scaled from published data using the principle of dimensional similitude. Flow was scaled with speed, and pressure was scaled with speed squared (flow $\propto$ pump speed, delta pressure $\propto$ [pump speed]^2). The pressure at negative flow was extrapolated using a third-order polynomial curve fit.

Pulsatile Conditions

The pneumatic mock ventricle as a heart simulator was operated at 80 beats/min. The compliance and resistance of the systemic circulation were adjusted to have 120/80 mm Hg of aortic pressure (AoP) with the pneumatic driving pressure (systolic/diastolic = 170/−44 mm Hg) that generated a cardiac output of approximately 4.0 L/min without activation of the HMII device (simulating normal heart function). The driving pressure was then adjusted (systolic/diastolic = 110/0 mm Hg) to simulate heart failure conditions, in which cardiac output is approximately 1.2 L/min. The dynamic pump flow pattern (instantaneous pump flow), total flow, and AoP were evaluated at each condition.

Data Acquisition and Analysis

All data were recorded at 200 Hz with a PowerLab data acquisition system (ADInstruments Inc, Colorado Springs, Colo), and data were then downloaded into Microsoft Excel (Microsoft Corp, Redmond, Wash) for reduction and analysis. A 7-point average was used for the inlet and outlet pressures to minimize high-frequency noise of the system and to approximate the 30-Hz filter used in the Transonic flow meter; this filter rate is recommended by the manufacturer for heart rates between 60 and 180 beats/min.

RESULTS

Flow-Pressure Curve in Steady-State Conditions

The pressure-flow data at 6000, 8000, and 10,000 rpm are shown in Figure 2. The solid lines are the previously published steady-state data, which range from 8000 to 14,000 rpm.[10] The dashed lines in Figure 2 show the estimated flow-pressure line at 6000 rpm, based on published data. The similarity between our data points and the published data at 8000 and 10,000 rpm reinforces the accuracy of our experimental setup and data acquisition.

Flow-Pressure Curve in Pulsatile Conditions

Figure 3, *A-C*, show the flow-pressure curve at 10,000, 8000, and 6000 rpm of HMII pump speed, respectively.

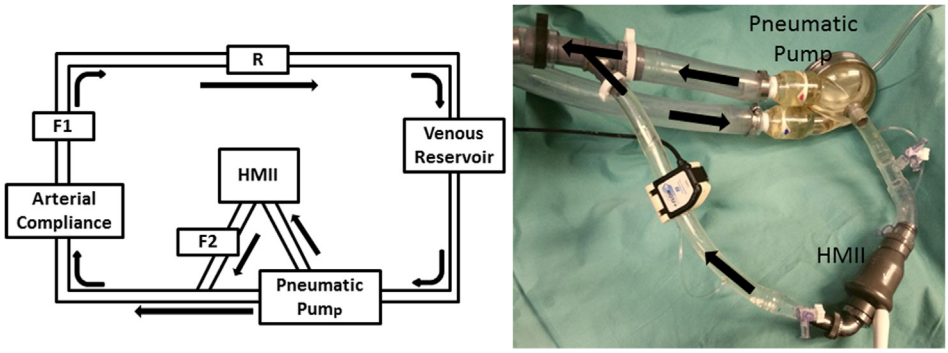


FIGURE 1. Schematic drawing and picture of the HMII device (Thoratec Corp, Pleasanton, Calif) and pneumatic pump circulatory loop used in the in vitro tests. *F1*, Flow probe 1 (total flow); *F2*, flow probe 2 (HMII flow); *HMII*, HeartMate II; *R*, systemic resistor.

The blue markers show the flow-pressure relationship in the normal heart function condition, and the green markers represent the heart failure condition. At 10,000 rpm, there was almost no regurgitant flow in either condition (Figure 3, *A*). The blue and green markers do not appear on the pressure-flow curve (black line) that was obtained under steady-state conditions, showing hysteresis (dependence of the output of a system not only on its current input but also on its history of past inputs) due to compliance and inertia of the mock-loop condition; however, the blue and green curve-fit lines (a third-degree polynomial) followed the steady-state line. At 8000 rpm, regurgitant flow was present (a peak of −3 L/min) in the normal heart condition, but it was small (a peak of −1 L/min) in the heart failure condition (Figure 3, *B*). As with the 10,000 rpm data, curve-fit data, shown as blue and green lines, followed the steady-state line. At 6000 rpm, regurgitant flows were significant in both conditions (Figure 3, *C*). In the normal heart condition, LVAD flow varied between −5 L/min and +7 L/min. In the heart failure condition, it was between −3 L/min and +6 L/min. Curve-fit data in both conditions closely followed the steady-state line.

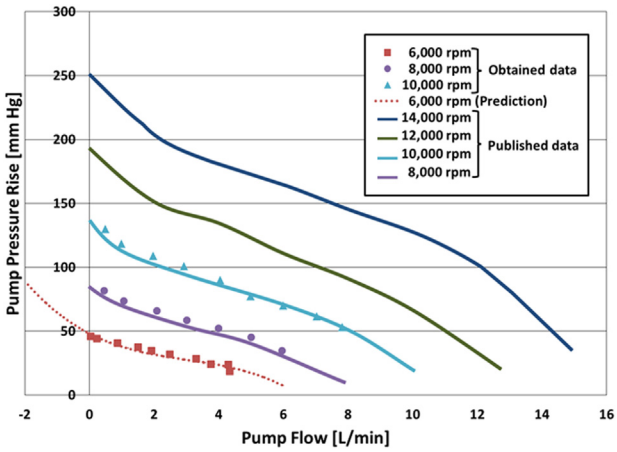


FIGURE 2. Steady-state pressure-flow relationships. These measurements, which include published, estimated (predicted), and obtained data, are shown for the various pump speeds tested.

The pump flow waveforms at 6000 and 10,000 rpm in normal heart function are shown in Figure 4, *A*. There was almost no regurgitant flow at 10,000 rpm support, but obvious regurgitant flow during diastole at 6000 rpm support. The pump flow waveforms at 6000 rpm in normal heart and heart failure conditions are shown in Figure 4, *B*. The regurgitant flow at 6000 rpm in the normal heart condition was greater than that in the heart failure condition. This finding suggests that a large regurgitant flow appearing at 6000 rpm support might be an indicator of good recovery of the native LV.

The AoP waveforms at 6000 rpm support and with no LVAD support (pump off with outlet tubing clamped) in the normal heart function condition are shown in Figure 5, *A*. There was no significant difference in hemodynamics between the 2 conditions, with the exception of higher pulse pressure at 6000 rpm support. The mean AoP and total flow were the same for both conditions. This result suggests that patients who had sufficient recovery might show similar hemodynamics between 6000 rpm support and no LVAD support. The AoP waveforms at 6000 rpm support and no LVAD support in the heart failure condition are shown in Figure 5, *B*. The mean AoP at 6000 rpm support was higher (by ∼10 mm Hg) than that with no LVAD support. Although total flow was the same in both conditions, the LVAD support flow at 6000 rpm accounts for approximately 80% of total flow. Hemodynamic measurements with 6000 rpm support in the heart failure condition were distinctly different from those with no LVAD support.

DISCUSSION

We have shown that the amount of regurgitant LVAD flow at 6000 rpm support depends on how well the native heart can function. Regurgitant flow with the HMII at 6000 rpm in the normal heart condition was greater than

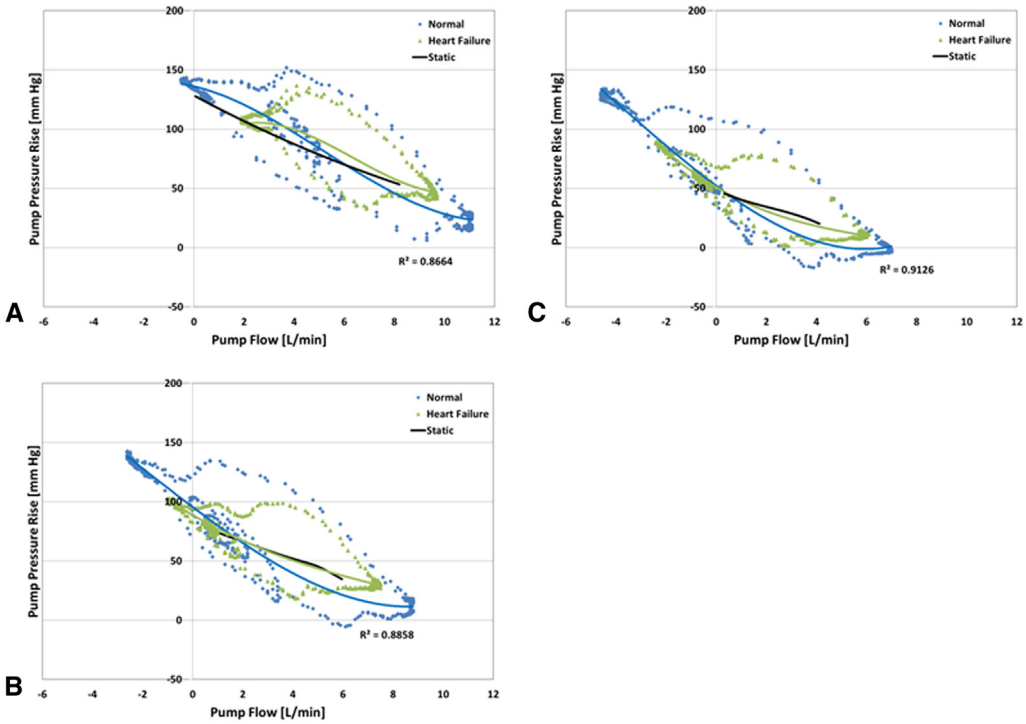


FIGURE 3. Pump flows and pressure increase measurements in a mock loop. Flow and pressure data were compared among steady-state, normal heart function, and heart failure conditions. A, At 10,000 rpm. B, At 8000 rpm. C, At 6000 rpm. R^2, Coefficient of determination.

that in the heart failure condition. Although detection of a large regurgitant flow at 6000 rpm may serve as a marker for adequate LV recovery, it also serves as a significant barrier for truly assessing LV function. Despite prior beliefs that at this speed the net flow is zero, our in vitro characterization suggests that the HMII device makes a significant contribution to total flow because there is less regurgitant flow in the heart failure condition at this speed. George and colleagues[6] reported regurgitant flow at 4000, 5000, and 6000 rpm support in patients and documented no significant differences in regurgitation among the varying conditions. That group's results might have been similar to ours if they had classified the study population in terms of heart function.

In addition, we have shown the differing characteristics of the hemodynamics between 6000 rpm support and no LVAD support. In the normal heart condition, mean AoP and total flow stayed at the same level. However, in the heart failure condition, mean AoP at 6000 rpm support was higher than with no LVAD support. Total flow was the same in both conditions, but LVAD flow made up a considerable part of total flow at 6000 rpm support. This finding suggests that LVAD flow at 6000 rpm in the heart failure condition makes a significant contribution to hemodynamics by providing 1 L/min of pump flow with an increase in the mean AoP of 9 mm Hg.

On the basis of our study's findings, we report the hemodynamics of the HMII device at 6000 rpm differ from those

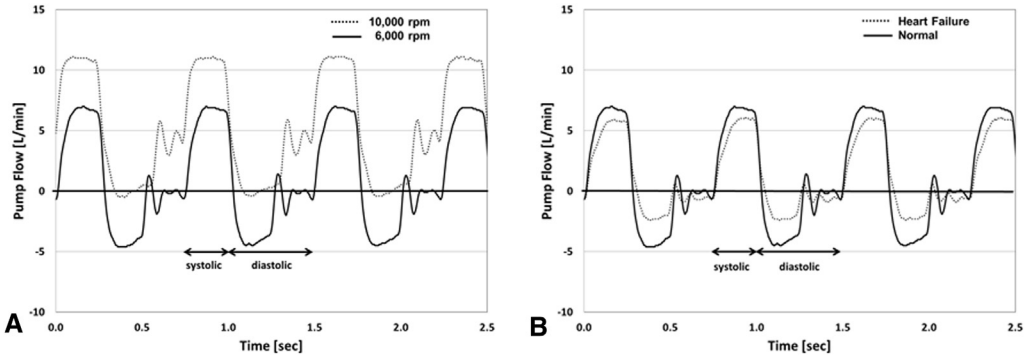
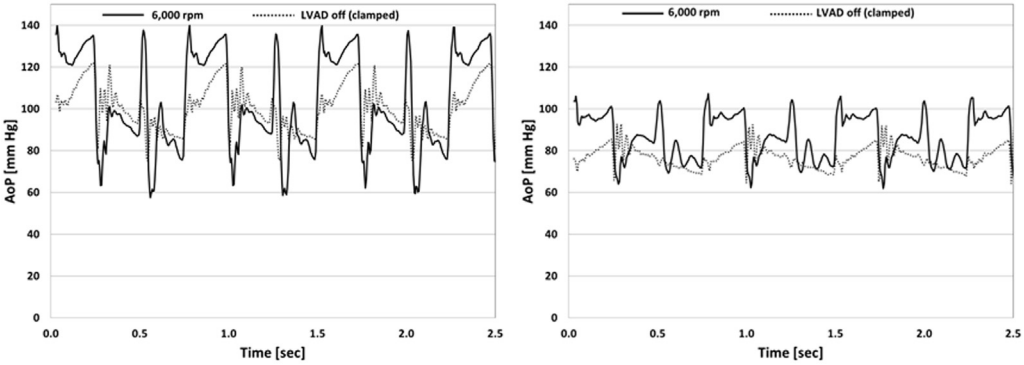


FIGURE 4. Pump flow. A, Pump flows in normal heart function were compared between 6000 rpm LVAD support and 10,000 rpm LVAD support. B, Pump flows at 6000 rpm LVAD support were compared between normal heart function and heart failure conditions.



A

	0 rpm	6,000 rpm
mean AoP [mmHg]	100	102
Pump Flow [L/m]	0	0.76
Total Flow [L/m]	3.96	3.95

B

	0 rpm	6,000 rpm
mean AoP [mmHg]	77	86
Pump Flow [L/m]	0	0.99
Total Flow [L/m]	1.21	1.27

FIGURE 5. Pressure and flow. A, Hemodynamics (AoP and pump flow) in normal heart function were compared between 6000 rpm LVAD support and no LVAD support (LVAD clamped). B, Hemodynamics (AoP and pump flow) in heart failure were compared between 6000 rpm LVAD support and no LVAD support (LVAD clamped). *AoP*, Aortic pressure; *LVAD*, left ventricular assist device.

reported by George and colleagues.[6] Ando and colleagues[11] proposed that an ideal off-test trial condition should be one with both ±0 L/min pump flow and no regurgitant flow at the same time. Their proposed system will be valuable; however, we cannot make similar recommendations at this time. We have demonstrated that the commonly used evaluations of native heart function after LVAD support by reduction of pump speed were significantly different than those from the pump-off condition in a pulsatile environment. If the heart has recovered well, there should be no significant difference between the hemodynamics with LVAD support at 6000 rpm and those with no LVAD support. To determine the conditions of cardiac recovery in the clinical setting, the amount of regurgitation flow should be specifically measured, or a regurgitation percentage may be useful. However, if the heart has not recovered its strong function, the hemodynamics are totally different between those with LVAD support at 6000 rpm and those with no LVAD support. Once again, these data suggest that a true assessment of ventricular recovery should be done with the pump off and the regurgitant flow prevented, perhaps with a percutaneously placed balloon inflated in the outflow graft.

Study Limitations

Because no autoregulatory response mechanism exists in the mock loop that could affect the hemodynamics during LVAD support testing, replication of all in vivo phenomena is not possible. Another limitation of the mock loop includes the restricted end-diastolic volume of the mock ventricle and the hysteresis that occurs because of the distribution of compliance and inertia within the mock-loop system. However, we believe the quantitative changes in hemodynamics induced at 6000 rpm LVAD support in this study are valid, and this study provides the quantification of the reverse flow in LVAD support and of the well-known forward flow in LVAD support.

CONCLUSIONS

Our bench study has shown that the net pump flow generated by the HMII device at 6000 rpm depends on the degree of residual LV function in the native ventricle. In the setting of improved LV function, there was a large regurgitant LVAD flow at 6000 rpm, and the net pump flow was zero. In the heart failure condition, however, there was a significant contribution by the HMII device to total flow because there was less regurgitant flow, which could lead to a false-positive for recovery. Although large regurgitant flow can serve as a useful indicator of native LV recovery, assessing LV recovery at this speed is flawed unless measures are taken to prevent the regurgitant flow.

Conflict of Interest Statement

Dr Starling reports consulting fees from Heartware and Thoratec, as well as grant funding from Thoratec. All other authors have nothing to disclose with regard to commercial support.

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Key Words: Assisted circulation, device removal, heart-assist devices, prosthesis design, risk factors, ventricular function, left

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EDITORIAL COMMENTARY

Mock loop revelations and the calculus for recovery

James K. Kirklin, MD

See related article on pages 343-8.

The clinical application of continuous flow (CF) left ventricular assistance devices (LVAD) evolved from decades of biomedical research to produce mechanical solutions for the chronically failing heart. Durable forms of CF pumps were designed for 5, 10, or more years of support (so-called destination therapy). With the ongoing shortage of available donor hearts, these devices have increasingly been used to support the hearts of patients awaiting heart transplantation (bridge-to-transplant strategy) when rapid cardiac decompensation portends imminent death. The concept of cardiac recovery did not really figure into the original paradigm. Although the possibility that a chronically dilatated, cardiomyopathic heart could recover after LVAD support has been recognized for several decades, actual reports of successful recovery and pump explantation were rare before about 2000.[1]

Early in the new millennium, recovery gained traction as a viable clinical goal. The seminal publication by Birks and colleagues[2] in 2006, for example, reported a remarkable rate of recovery in patients with nonischemic cardiomyopathy with a program of durable LVAD support and administration of clenbuteral, a selective beta 2-adrenergic agonist. As CF technology in North America and Europe developed, additional successful experiences emerged.[3-5]

During the past decade, a flurry of basic science activity has targeted genetic upregulatory responses as they relate to unloading of a maladapted failing left ventricle, which is a requisite for myocardial recovery. Chronic LVAD support in the failing heart has been shown to decrease neurohormone levels, reduce cytokine release, decrease apoptosis, reduce myocyte size, normalize beta adrenergic pathways, and improve calcium handling at the cellular level[6-11]; all of which could contribute to favorable reverse remodeling of the failing ventricle. The fact that chronic heart failure

From the Department of Surgery, University of Alabama in Birmingham, Birmingham, Ala.
Disclosures: Author has nothing to disclose with regard to commercial support.
Received for publication May 6, 2015; accepted for publication May 7, 2015.
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J Thorac Cardiovasc Surg 2015;150:348-9
0022-5223/$36.00
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http://dx.doi.org/10.1016/j.jtcvs.2015.05.031