Assessment of Cardiac Function During Axial-flow Left Ventricular Assist Device Support Using a Left Ventricular Pressure–derived Relationship: Comparison With Pre-load Recruitable Stroke Work

Patrick I. McConnell, MD,[a] Carlos L. Del Rio, MS,[b] Pawel Kwiatkowski, MD,[a] David J. Farrar, PhD,[c] and Benjamin C. Sun, MD[a]

Background: In this study we evaluate load-independent ventricular function during left ventricular assist device (LVAD) support based solely on telemetered measurements of left ventricular (LV) pressure, which has not been reported previously.

Methods: Adult sheep underwent placement of an axial-flow LVAD, a telemetered LV pressure manometer and instruments for pressure–volume analysis. In unsedated sheep, the simultaneous determination of both stroke work/end-diastolic volume (SW/EDP [PRSW]; slope: M_W) and LV triple-product (TP = LVSP · dP/dt · HR) vs LV end-diastolic pressure (TP/EDP; slope: M_{TP}) were performed before and then after β_1-blockade using the LVAD to acutely unload the ventricle.

Results: LVAD support (4.5 ± 0.31 liters/min) was maintained for 1 week. During LV unloading "runs," the LVAD flow (Q_V) increased (up to 5.8 ± 0.71 liters/min), although there were decreases in SW (3,061 ± 747 to 1,556 ± 410 mm Hg ml^{-1}), LV TP (3,127 ± 397 to 1,019 ± 335 × 10^5) and LV EDP (18.2 ± 1.2 to 9.7 ± 1.8 mm Hg). The TP/EDP and SW/EDV relationships established during the unloading runs were highly linear (R^2 up to 0.95) and their slopes were reduced by β-adrenergic blockade ($p < 0.001$).

Conclusions: The TP/EDP relationship established during LVAD unloading of the LV was load-independent and sensitive to changes in cardiac inotropy, and correlated with PRSW. J Heart Lung Transplant 2007; 26:159–66. Copyright © 2007 by the International Society for Heart and Lung Transplantation.

There has been growing acceptance in the belief that long-term left ventricular (LV) volume unloading with a left ventricular assist device (LVAD) can allow recovery of cardiac function and reverse cardiac remodeling and thus permit device explantation—the so-called "bridge to recovery."[1–3] Despite favorable alterations reported in cardiac remodeling,[4–6] calcium handling,[7,8] β-adrenergic function and other molecular and cellular signaling pathways in heart failure,[9–12] very few patients on LVAD support (e.g, <5% of chronic heart failure patients[1,13]) demonstrate sufficient improvement to allow for long-term device removal.[14] Nonetheless, the clinical and scientific communities agree that with better diagnostic capabilities aimed to direct device operation and/or concomitant therapy,[15,16] improved success rates for "recovery" will be achieved. The Working Group on Recovery from Heart Failure with Circulatory Assist of the National Heart, Lung and Blood Institute,[17] have recommended: (1) serial determination of anatomic structure and functional parameters aimed at proper assessment of recovery; (2) identification of markers and predictive factors of "recoverable" hearts; and (3) design of mechanical assist devices and systems specifically for cardiac recovery. Likewise, the VALAD trial began enrolling patients in Germany to evaluate a transmyocardially placed telemetered LV pressure manometer (LVP1000; Transoma Medical, St. Paul, MN) during LVAD support.

If easier methods existed for evaluating LV function during LVAD support,[18–22] permitting greater frequency or even automated assessments, it is likely that improvements in device operation and "weaning" strategies could be realized. However, to date, no specific method exists for the determination of cardiac function in patients supported with a continuous-flow LVAD based on hemodynamic signals alone (e.g., LV pressure). We propose a method to assess pre-load recruitable function (contractility) of the LV during axial-

From the [a]Division of Cardiothoracic Surgery and [b]Department of Computer and Electrical Engineering, The Ohio State University Medical Center, Columbus, Ohio; and [c]Thoratec Corporation, Pleasanton, California.

Submitted March 30, 2006; revised October 9, 2006; accepted November 13, 2006.

Supported in part by a post-doctoral fellowship from the American Heart Association, Ohio Valley Affiliate (to P.I.M.).

Reprint requests: Patrick I. McConnell, MD, Department of Surgery, University of Utah, 636 East Browning Avenue, Salt Lake City, UT 84105. Telephone (cell): 801-703-3491. Fax: 614-293-8153. E-mail: pimcconnell@msn.com

 1053-2498/07/$–see front matter. doi:10.1016/j.healun.2006.11.010

flow LVAD support based solely on telemetered LV pressure.

METHODS

The present studies were approved by the Institutional Laboratory Animal Care and Use Committee (ILACUC) at The Ohio State University, and adhered to the statutes of the Animal Welfare Act and the guidelines of the Public Health Service.

LVAD Placement and Instrumentation

Adult sheep ($N = 6$, 78 ± 3 kg) underwent axial-flow LVAD (HeartMate II, Thoratec Corp., Pleasanton, CA) placement through a left thoracotomy. The LVAD inflow cannula was positioned through the LV apex and the outflow graft (16 mm) was sewn to the proximal descending thoracic aorta.

Fluid-filled catheters (Tygon) were secured into the descending thoracic aorta and left atrial appendage. In 4 of 6 animals ($N = 4$), two pairs of piezoelectric crystals (2 mm, Sonometrics, Inc., New London, ON, Canada) were placed endocardially at the mid-papillary level (short axis, SA) and at the LV base and near the LV apex (long axis, LA) for calculation of LV volumes. Telemetered manometers (TL11M3-D70-PCP; Data Sciences International [DSI], St. Paul, MN) were secured within the right ventricle (RV, $N = 5$) and the LV chamber. An ultrasonic transit-time flow probe (16 mm, Transonic, Inc., Ithaca, NY) was secured around the LVAD outflow graft. Animals were allowed to recover for at least 1 week although the LVAD was operated continuously at approximately 9,000 rpm (partial support).

Data Acquisition

Aortic and left atrial fluid-filled catheters were connected to calibrated Statham pressure transducers (Model P23XL; Biggo-Spectramed, Oxnard, CA) and amplified (Gould, Valley, OH) for their respective pressures. The telemetered pressure waveforms were acquired through a receiver (Model UA-10; DSI) and electronically calibrated while adjusting for atmospheric conditions; the accuracy of LV pressure was confirmed against calibrated aortic and left atrial pressure signals. The outflow graft blood flow signal (Q_v) was amplified and calibrated before each experiment.

All waveforms and their derivatives were collected (1 kHz) and analyzed by a 16-channel data acquisition software system (IOX, version 1.7; EMKA Technologies, Falls Church, VA). Hemodynamic waveforms were analyzed through software (IOX) and mean data (2-second averages) were output to tab delimited files and accessed using standard spreadsheet software (EXCEL; Microsoft, Inc., Redmond, WA).

Calculated Parameters

The following parameters were obtained:

- LV volume (ml) was derived from the endocardially positioned sonomicrometers using the equation: $(SA^2 \cdot LA \cdot \pi/6) \cdot 1{,}000$.
- LV triple-product (TP) was extracted on a per-beat basis using the equation: $LVSP \cdot dP/dt_{max} \cdot HR$.
- LV stroke work (SW): $\int LVP \cdot dLV\ volume$.

Study Designs

Baseline data ("on support") were collected from awake, unrestrained animals while standing and "on support" (~9,000 ± 400 rpm). LV unloading with the axial-flow LVAD (HeartMate II) was performed after the pump speed was reduced to 6,000 rpm and the animals were allowed to stabilize for 2 minutes. The LVAD was then programmed to increase speed (100 rpm/s) until LVSP was less than the mean arterial pressure (MAP; aortic valve not opening) or to approximately 11,000 rpm—a "run." The TP/EDP relationship and the PRSW were derived from the same run.

Responses to Esmolol

The responses of TP/EDP and PRSW to changes in inotropy were evaluated after β_1-adrenergic blockade with esmolol hydrochloride. After a baseline run (on the same day), animals were given an intravenous (IV) bolus of esmolol (25 mg) followed by IV esmolol infusion (5 mg/kg/min) and the run was repeated.

Responses to Phenylephrine

After-load independence of the TP/EDP relationship was assessed in a single animal on 3 separate days. Before each study, autonomic blockade was produced with atropine (0.1 mg/kg IV) and metoprolol (5 mg IV) to minimize baroreflex activation during phenylephrine (PE) infusion (0.01, 0.1 and 0.25 μg/kg/min).

Statistics

Data are presented as mean ± SEM and were collected during a single experimental period or day. Therefore, comparisons of hemodynamic values after autonomic blockade and PE doses and between time-points (i.e., "on support," 6,000 rpm and 11,000 rpm within groups, and at 6,000 rpm before and after esmolol) were made using 1-way analysis of variance (ANOVA) with a repeated-measures design (SIGMASTAT v2.03, Systat Software, Inc., Point Richmond, CA). If the F-ratio was found to exceed a critical value ($\alpha < 0.05$), the post hoc Bonferroni method was applied to undertake pairwise comparisons. The slopes of the SW/EDV (M_W) and TP/EDP (M_{TP}) relationships were derived from least-squares linear regression analysis of plots (2-second

averages) for the SW/EDV and for the TP/EDP relationships (respectively). Multiple linear regression analysis (MINITAB v14.2. Minitab, Inc., State College PA) was used to compare M_{TP} and M_W before and after esmolol infusion and also to compare M_{TP} after autonomic blockade and PE infusion. All of the investigators had full access to the data and take responsibility for its integrity and have read and agreed to this article as written.

RESULTS

Animals ($N = 6$) were partially supported with the LVAD for 13 days (range 8 to 17 days). A typical run progressed from 6,000 to 10,880 ± 120 rpm. Representative hemodynamic tracings during an LVAD unloading "run" are shown in Figure 1. Corresponding sets of pressure–volume (P-V) loops generated before and after esmolol are displayed in Figure 2A and B. The PRSW and TP/EDP relationships before and after esmolol are shown in Figure 2C and D, respectively. Esmolol reduced M_{TP} from 159 ± 23.8 to 71 ± 15.1 mm Hg s^{-1} ($N = 6$; $p < 0.001$) and M_W from 117 ± 15.8 to 72 ± 9.4 mm Hg ($N = 4$; $p < 0.001$). Right ventricular dP/dt_{max} was reduced after esmolol, although the remaining right-sided hemodynamics were not significantly altered by the LVAD unloading runs. Additional hemodynamic data from runs before and after esmolol infusion are presented in Table 1.

Outflow graft blood flow (Q_V) was not different before or after esmolol (Figure 3A). LVAD blood flow increased linearly with LVAD speed until reaching a plateau. Each component of the LV TP (i.e., dP/dt_{max}, LVSP and HR) relative to Q_V during a run is shown in Figure 3B–D. The predominant effect of esmolol on the TP/EDP slope was reduced LV contraction velocity (dP/dT_{max}; Figure 3B). Linear regression (Figure 4) demonstrated a good correlation between TP and SW before or after esmolol during LVAD unloading: $y = 1.03x + 227.9$ ($R^2 = 0.74$; $p < 0.001$).

Selected data after autonomic blockade and PE infusion are presented in Table 2. Infusion of 0.01, 0.1 and 0.25 μg/kg/min of PE after autonomic blockade (on 3 separate days) increased LVSP by 10.2 ± 2.56, 20.7 ± 1.51 and 27.2 ± 0.93 mm Hg, respectively ($p < 0.007$). As shown in Figure 5, a clustering of points or plateau was noted at higher filling pressures during PE infusions. However, below a certain LVEDP, here denoted as a "flex point," the TP/EDP relationship (M_{TP}) was observed to be linear (Figure 5, inset). Although the TP/EDP relationship shifted to the right during PE infusions (increased pre-load), no differences were observed in M_{TP} for each dose of PE (varying after-load) when compared with complete autonomic blockade (Figure 5 and inset). Accounting for PE dose and day, variability in TP and M_{TP} were 33.4 ± 4.7% (673 ± 92.6 × 10^{-5} mm Hg^2 s^{-1}) and 7.0 ± 1.17% (4.59 ± 0.68 mm Hg s^{-1}), respectively.

DISCUSSION

P–V Analysis During Axial-flow LV Unloading: ESPVR vs PRSW

A proof-of-concept comparison was made of a potential LV pressure- derived index of cardiac contractility, TP/EDP, to the PRSW (SW/EDV) in sheep supported by an axial-flow LVAD. Likewise, Ferrari and colleagues[18] recently reported on monitoring the load-independent cardiac function of 2 patients at implant and explant of an axial-flow LVAD. They used offline P–V analysis

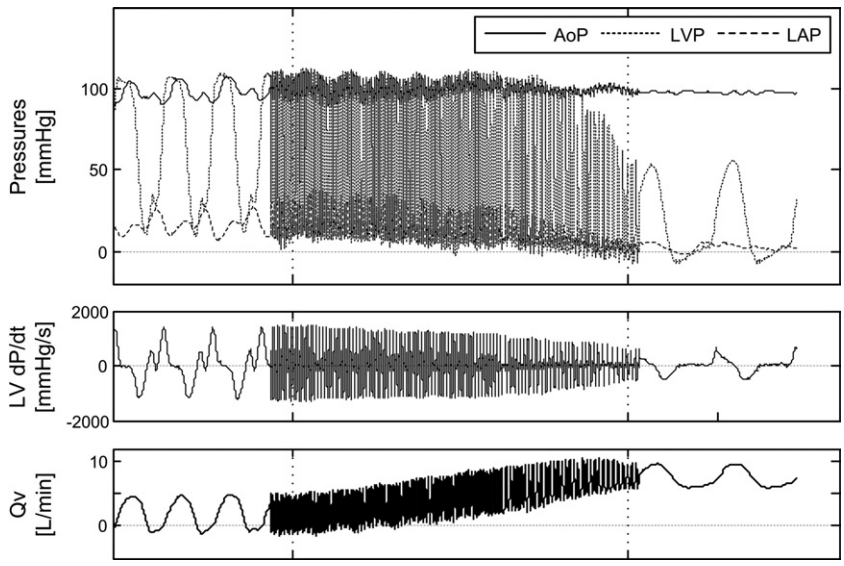

Figure 1. Simultaneous hemodynamic traces of aortic, left ventricular and left atrial pressures (top panel); left ventricular derivative of pressure vs time (middle panel); and ventricular assist device blood flow (bottom panel) during an LV unloading "run" with axial-flow LVAD.

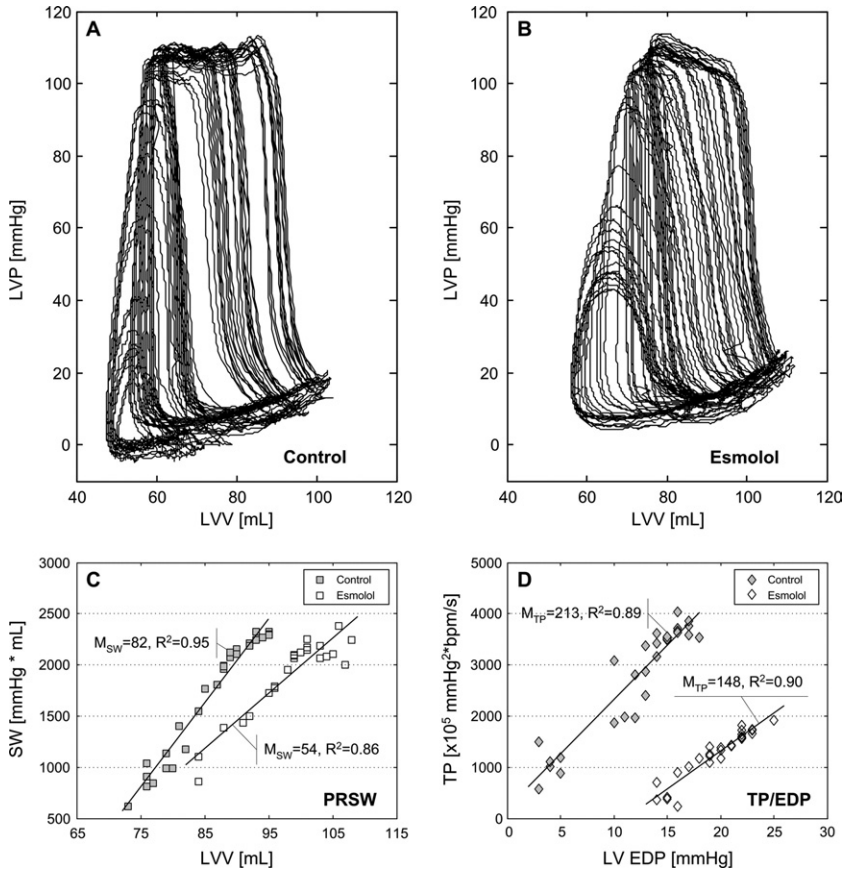

Figure 2. Influence of cardiac contractility on pressure–volume loops generated during left ventricular assist device unloading (6,000 to ~11,000 rpm) before (A) and after (B) esmolol. Plots of pre-load recruitable stroke work (M_W) (C) and left ventricular triple-product vs end-diastolic pressure (M_{TP}) (D) were derived simultaneously before and after esmolol.

derived from catheter-acquired LV pressure signals and echocardiographically derived LV volumes. They also established end-systolic pressure–volume relationships (ESPVRs) in a novel way by using the LVAD to acutely unload the LV. Nevertheless, theoretical and technical issues related to axial-flow LV unloading limit the interpretation of ESPVR or end-systolic elastance.[23,24]

For example, the systemic circulation is supported and prevents significant changes in the end-systolic pressures (Figure 2A and B), although the axial flow device unloads the LV until that point where LV volumes are insufficient to allow for aortic ejection (LVSP < MAP; Figure 1). The ESPVR (slope: E_{es}) relies on the coupling of LV end-systolic pressure with end-systolic volume,[25] a prerequisite confounded by axial-flow LV unloading due to the maintained end-systolic pressures despite a decrease in LV volume. Therefore, optimism for E_{es} as an index sensitive to cardiac function during continuous-flow LVAD support[18,24] may be limited given these circumstances.

Pre-load recruitable stroke work (PRSW), like the ESPVR, is a P–V-derived and load-independent index of cardiac contractility.[26,27] However, unlike the E_{es}, the slope of the PRSW (M_W) remains sensitive to cardiac contractility during axial-flow LV unloading because both SW and EDV vary with the degree of support yet independently of each other. Moreover, the PRSW is linear over a greater range of LV volumes,[28] a condition we have specifically demonstrated for an axial-flow LVAD.[23] Clinically, neither PRSW nor ESPVR can be generated in real time.[18]

Components of the LV TP

In this study, the LV TP was intended to provide a surrogate for SW as derived solely from systolic pressure, heart rate and the maximal time-derivative of LV pressure (dP/dt_{max} − contractility). The dP/dt_{max} is traditionally considered a poor measure of cardiac contractility because it is altered by changes in heart rate and LV-developed pressure (i.e., pre- and after-load dependent). Therefore, any method used to create a pre-load–sensitive index relying on dP/dt must maintain LV-developed pressure nearly constant while LV pre-load varies—as occurs with axial-flow LV unloading (Figures 1 and 3B). Although no previous studies have

Table 1. Axial-flow Left Ventricular Unloading "Runs" Before and After β_1-adrenergic Blockade

	On support	Baseline		Esmolol (5 mg/kg/min)	
	(~9,000 rpm)	6,000 rpm	~10,880 rpm	6,000 rpm	~10,880 rpm
Arterial					
HR (bpm)	119 ± 7.1	131 ± 9.9	77 ± 8.6[c]	118 ± 7.9	66 ± 14.2[c]
Q_v (liters/min)	4.5 ± 0.31	1.2 ± 0.25[a]	5.8 ± 0.71[c]	1.7 ± 0.21[d]	5.5 ± 0.53[c]
SBP (mm Hg)	106 ± 2.4	118 ± 4.1[a]	110 ± 4.4	105 ± 6.4[d]	106 ± 5.3
DBP (mm Hg)	89 ± 5.1	90 ± 4.4	103 ± 4.4[b]	85 ± 5.5	100 ± 4.7[c]
MAP (mm Hg)	97 ± 4.2	103 ± 4.7	104 ± 4.6	95 ± 5.7	101 ± 5.0
aBP (mm Hg)	14.5 ± 0.98	28.3 ± 2.18[a]	6.3 ± 1.04[c]	20.3 ± 2.72[d]	6.36 ± 0.91[c]
Left ventricular					
LV SP (mm Hg)	108 ± 3.3	116 ± 5.2	79 ± 8.1[c]	105 ± 6.4[d]	79 ± 10.4
LV EDP (mm Hg)	13.2 ± 1.50	18.2 ± 1.17[a]	9.7 ± 1.75[c]	24.4 ± 2.18[d]	15.3 ± 1.83[c]
LV dP/dt_{max} (mm Hg s^{-1})	2,182 ± 231	2,286 ± 236	1,431 ± 282[b]	1,567 ± 194[d]	1,184 ± 207
LV dP/dt_{min} (mm Hg)	−2,053 ± 128	−2,219 ± 79	−1,155 ± 182[b]	−1,688 ± 147	1,081 ± 173
Tau	30.6 ± 2.22	34.0 ± 2.87	19.3 ± 2.39[c]	46.2 ± 5.38[d]	40.3 ± 6.71
TP (mm Hg^2 s^{-1} × 10^5)	2,970 ± 299	3,127 ± 397	1,019 ± 335[c]	1,847 ± 314[d]	947 ± 245[b]
SW ($N = 4$), (mm Hg ml^{-1})	2,216 ± 423	2,455 ± 451	1,302 ± 189[c]	1,646 ± 388[d]	1,093 ± 344
Right ventricular ($N = 5$)					
RV SP (mm Hg)	29.1 ± 3.10	32.4 ± 4.43	29.4 ± 4.00	33.6 ± 3.89	29.2 ± 3.23
RV mDP (mm Hg)	4.63 ± 2.08	5.70 ± 2.46	4.73 ± 2.44	8.04 ± 1.98	6.63 ± 2.25
RV dP/dt_{max} (mm Hg/s^{-1})	1,084 ± 213	1,123 ± 225	895 ± 92	750 ± 121[d]	763 ± 115
RV dP/dt_{min} (mm Hg/s^{-1})	−733 ± 89	−829 ± 139	−728 ± 88	−702 ± 81	−561 ± 40

All data expressed as mean ± SEM ($N = 6$). Comparisons were done by ANOVA with repeated measures.

LV, left ventricle; RV, right ventricle; HR, heart rate; Q_v, assist device blood flow; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; aBP, aortic beat pressure; SP, systolic pressure; EDP, end-diastolic pressure; mDP, mean diastolic pressure; Tau, time constant of LV relaxation (Weiss method); TP, triple product; SW, LV stroke work.

[a] $p < 0.05$ from "on support" vs 6,000 rpm.

[b] $p < 0.05$ from 6,000 rpm within groups.

[c] $p < 0.01$ from 6,000 rpm within groups.

[d] $p < 0.05$ baseline vs esmolol at 6,000 rpm.

linked TP to EDP as an index of cardiac function, the dP/dt_{max} has been effectively compared with EDV during vena cava occlusions.[29]

The reduction of LV TP during an LVAD unloading "run" was also partially accounted for by a decrease in heart rate. This progressive bradycardia is not likely mediated by autonomic reflexes, as neither atropine nor β_1-adrenergic receptor blockade prevented the response (Figure 3C). Moreover, the mechanism dictating this unloading-related bradycardia is difficult to explain, given that both the changes in left atrial pressures (decreasing) and the concomitant loss of pulsatility within the aorta should have acted autonomically to produce instead a reflex tachycardia. Nonetheless, the observed progressive decrease in HR was consistent with previously reported changes in SW and myocardial oxygen consumption (MVO_2) during LVAD unloading.[30]

Linearity of TP/EDP and PRSW During Axial-flow LV Unloading

Both TP/EDP and the SW/EDP were observed to be linear during continuous-flow LVAD-assisted unloading. This linearity is in apparent opposition to the curvilinear relationship historically reported for SW/EDP (Frank–Starling relationship) during isolated heart preparations.[31] Several possible explanations exist for the observed linearity of TP/EDP. Foremost, the TP/EDP does not rely on a geometric/volumetric assessment of the LV for calculation, and presumably would be less sensitive to artifacts created by LV volume estimation.[32,33] Furthermore, unlike P–V determinations during an inferior vena cava (IVC) occlusion or in an isolated heart preparation,[31] where right-sided filling pressures are unsupported, continuous-flow LV unloading supports the right-heart filling pressures (Table 1). Therefore, little septal bulging (toward the right ventricle) would have resulted during LV unloading, thus avoiding an artifact (curvilinear) altering the Frank–Starling relationship.[32]

Under nearly all experimental conditions the TP/EDP was observed to be linear over the full range of LV volumes. The significance of the plateau in the TP/EDP observed after PE infusion remains unclear as it could be simply an artifact of maintaining high LV pressures despite early LV unloading. The relevance of this observation is also not completely clear, as the TP/EDP relationship was linear below the so-called

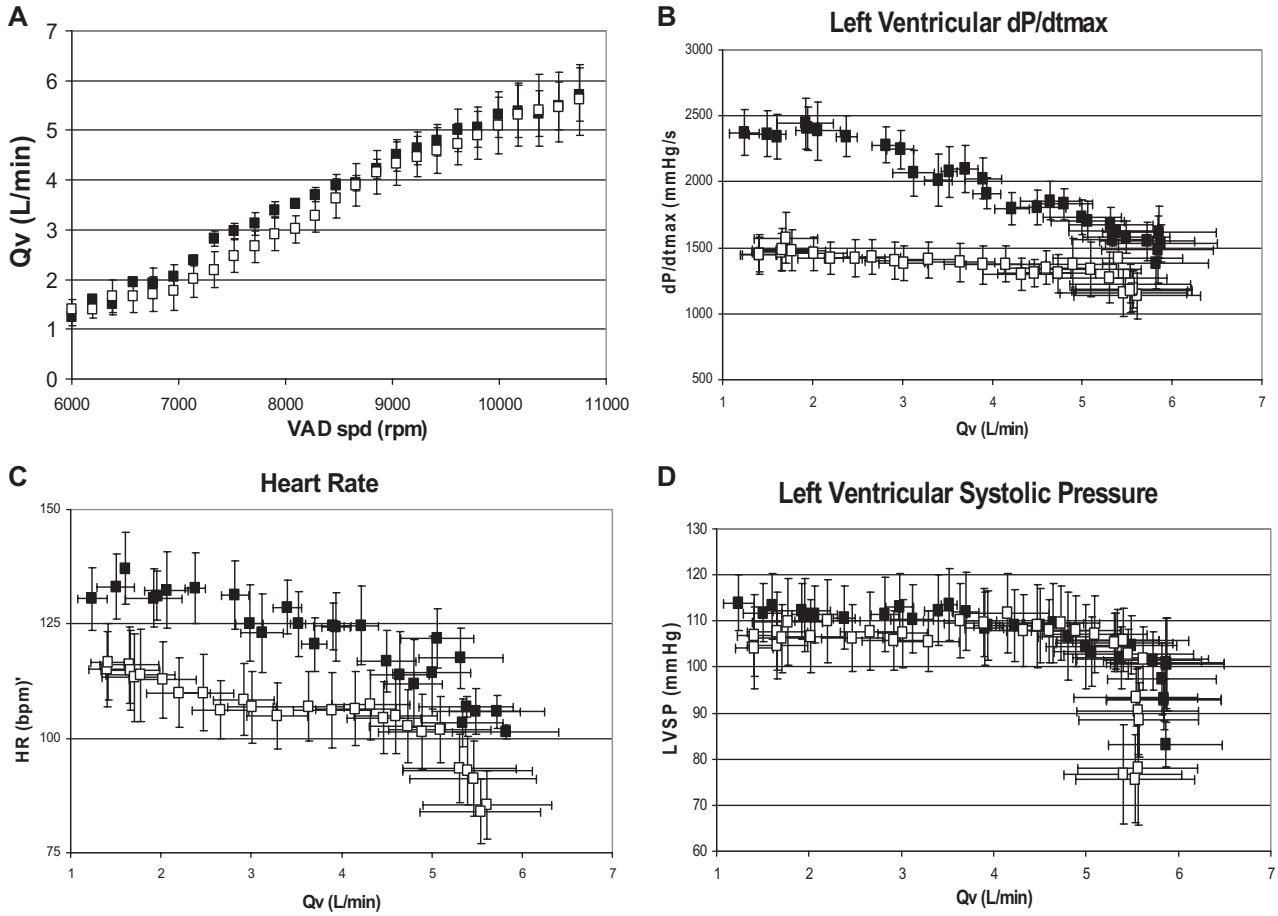

Figure 3. The effect of axial-flow left ventricular unloading on LVAD outflow graft blood flow (Q_V) compared with LVAD speed (A) and individual parameters (B–D) comprising the left ventricular triple-product ($N = 6$, 2-second averages ± SEM) during a baseline "run" (■) and after esmolol (□) relative to LVAD blood flow.

"flex point" and the variability of the M_{TP} was very low (7%) between days and doses of PE (Figure 5 and inset). If TP/EDP was observed to be non-linear in clinical patients with LVAD support (heart failure), then perhaps the operational point where TP assumes a linear relationship with EDP might provide valuable diagnostic information. A flex point might identify a filling pressure (and corresponding level of LVAD support) where the LV resumes a more normal Frank–Starling relationship (negative slope) and thus a guide for a physiologic operating point during LVAD support.

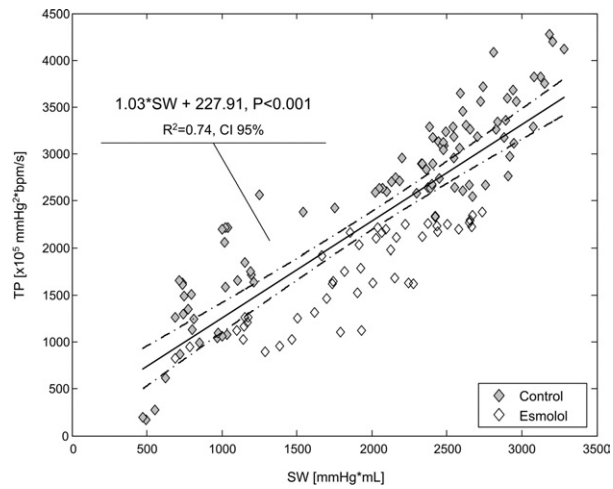

Figure 4. Comparison of left ventricular triple-product (TP) and stroke work (SW) before (♦) and after esmolol (◇) during left ventricular unloading with an axial-flow LVAD in sheep ($N = 4$).

Reflex Activation

Foremost among potential confounding factors related to LVAD unloading could be autonomic reflex activation by alterations in right-sided and systemic hemodynamics. Very little change was apparent in right ventricular (RV) pressures during LVAD unloading runs (Table 1). Therefore, it is unlikely that altered venous filling pressures would have contributed in any substantial way to alter autonomic tone. Left atrial baroreflex activation (Bainbridge reflex) on reloading of the atria was evident (increased heart rate) and could have affected the TP/EDP relationship.[34] Both esmolol ($N =$

Table 2. Responses to Phenylephrine (PE) after Autonomic Blockade[a]

	LV SP (mm Hg) (p-value)[b]	LV EDP (mm Hg) (p-value)[b]	dP/dt_{max} (mm Hg s^{-1}) (p-value)[b]	HR (bpm) (p-value)[b]	TP (mm Hg^2 s^{-1} $\times$ 10^5) (p-value)[b]	M_{TP} (mm Hg s^{-1} · bpm) (p-value)[b]	P_{TP} (M_{TP} x-intercept) (p-value)[b]
Baseline	114.4 ± 4.6 (0.088)	36.4 ± 2.6 (1.00)	2,078 ± 150 (0.012)	144 ± 4.6 (0.064)	3,242 ± 364 (0.025)	120.2 ± 16.3 (0.05)	6.9 ± 3.1 (1.00)
Autonomic blockade	107.8 ± 5.2	42.5 ± 2.9	1,530 ± 142	131 ± 1.6	2,085 ± 293	69.0 ± 7.3	5.4 ± 3.4
PE 0.01[c]	118.0 ± 2.7 (0.007)	43.6 ± 5.5 (1.00)	1,801 ± 230 (0.415)	135 ± 1.5 (1.00)	2,705 ± 419 (0.492)	72.4 ± 7.8 (1.00)	13.9 ± 4.8 (1.00)
PE 0.10[c]	128.5 ± 5.5 (<0.001)	50.0 ± 3.5 (0.780)	1,904 ± 170 (0.103)	136 ± 0.5 (0.343)	3,143 ± 398 (0.042)	71.8 ± 9.4 (1.00)	13.7 ± 1.8 (1.00)
PE 0.25[c]	135.0 ± 4.6 (<0.001)	56.3 ± 3.9[a] (0.059)	1,899 ± 180 (0.109)	137 ± 1.9 (0.391)	3,301 ± 380 (0.019)	75.0 ± 5.6 (1.00)	12.3 ± 6.1 (1.00)

Data expressed as mean ± SEM, with pump at 6,000 rpm (N = 3 days).

LV SP, left ventricular systolic pressure; EDP, end-distolic pressure; dP/dt_{max}, maximum derivative of pressure vs time; HR, heart rate; TP, triple product; M_{TP}, slope of TP/EDP; P_{TP}, pressure at zero TP (x-intercept).

[a]Atropine (0.1 mg/kg) and metoprolol (5 mg).

[b]ANOVA repeated measures vs autonomic blockade.

[c]In micrograms per kilogram per minute.

6 animals) and complete autonomic blockade tended to reduce the observed increase in HR on acute cardiac reloading, supporting the idea that at least some sympathetic activation may have been present before a "run" (Tables 1 and 2). Vagal withdrawal, also associated with the Bainbridge reflex, was evident because atropine administration did not further increase the heart rate after LV reloading. Therefore, reflex activation, and perhaps its subsequent reversal (unloading), could alter TP/EDP.

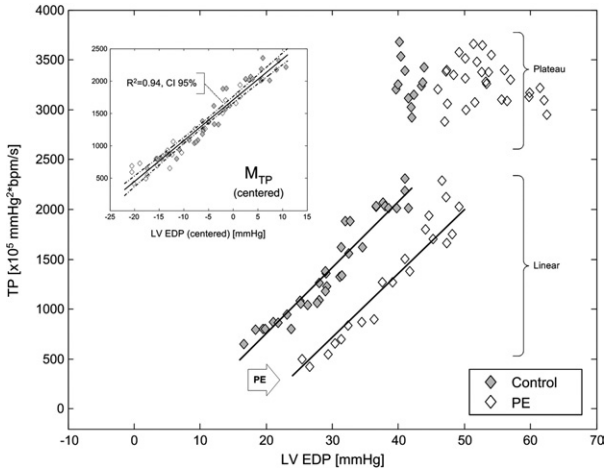

Figure 5. Effect of after-load variation on the relationship of left ventricular triple-product vs end-diastolic pressure (TP/EDP; slope: M_{TP}) during left ventricular unloading with an axial flow LVAD before (♦) and after (◇) phenylephrine (PE) infusion. Despite a considerable increase in LV filling pressures with PE infusion (rightward shift), the relationship of TP/EDP was linear and nearly identical before and after PE (inset). A plateau or clustering of points was evident at the highest left ventricular filling pressures, below which (i.e., "flex point") the TP/EDP was linear irrespective of after-load (see Table 2).

Study Limitations

The current experiments were carried out on a limited number of animals with normal cardiac function at the time of LVAD implantation; therefore, the observed TP/EDP relationships may not apply to clinical heart failure. Although we have shown that the relationship of TP/EDP was maintained after pharmacologic alterations of cardiac function mimicking heart failure (esmolol), further validation in diseased hearts is required. Similarly, LV unloading was to the descending thoracic aorta and differences may exist when the LVAD outflow is to the ascending aorta. Furthermore, the linear and pre-load–dependent reduction in TP was a consequence of continuous-flow support of the systemic circulation while unloading the LV, allowing for linear variation of the TP vs the pre-load. Pulsatile ventricular assist devices would not provide the same graduated beat-to-beat LV pre-load reduction as continuous-flow LVADs; therefore, the TP/EDP would not be applicable in patients supported with a pulsatile LVAD.

In conclusion, the ability to quantify myocardial performance is essential for the development of strategies aimed to effectively improve the utilization of LV assist devices as a "bridge to recovery," transplantation and/or as destination. Up to now, the limited availability of functional, metabolic, histologic and/or molecular data has provided little new insight into optimal strategies for LVAD operation targeting recovery. Furthermore, beyond the mere assessment of LV hemodynamics, frequent and reliable evaluation of cardiac function will likely be required for directing concomitant therapy and for the potential institution of a closed loop between heart and device. LV pressure alone and pressure-derived indices, like the TP/EDP relationship,

could improve care among patients with mechanical circulatory support—especially for cases in which device "weaning" criteria are critical.

The authors thank Laine Kathary and Angela Phillips for their expert technical assistance in completing these studies.

REFERENCES

1. Farrar DJ, Holman WR, McBride LR, et al. Long-term follow-up of Thoratec ventricular assist device bridge-to-recovery patients successfully removed from support after recovery of ventricular function. J Heart Lung Transplant 2002;21:516–21.
2. Hetzer R, Mueller J, Weng Y, Wallukat G, Spiegelsberger S, Loebe M. Cardiac recovery in dilated cardiomyopathy by unloading with a left ventricular assist device. Ann Thorac Surg 1999;68:742–9.
3. Nakatani T, Sasako Y, Kobayashi J, et al. Long-term circulatory support to promote recovery from profound heart failure. ASAIO J 1995;41:526–30.
4. Bruckner BA, Stetson SJ, Perez-Verdia A, et al. Regression of fibrosis and hypertrophy in failing myocardium following mechanical circulatory support. J Heart Lung Transplant 2001;20: 457–64.
5. Levin H, Oz M, Chen J, Packer M, Rose E, Burkhoff D. Reversal of chronic ventricular dilation in patients with end-stage cardiomyopathy by prolonged mechanical unloading. Circulation 1995;91: 2717–20.
6. Zafeiridis A, Jeevanandam V, Houser SR, Margulies KB. Regression of cellular hypertrophy after left ventricular assist device support. Circulation 1998;98:656–62.
7. Chen X, Piacentino V III, Furukawa S, Goldman B, Margulies KB, Houser SR. L-type Ca^{2+} channel density and regulation are altered in failing human ventricular myocytes and recover after support with mechanical assist devices. Circ Res 2002;91:517–24.
8. Heerdt PM, Holmes JW, Cai B, et al. Chronic unloading by left ventricular assist device reverses contractile dysfunction and alters gene expression in endstage heart failure. Circulation 2000;102:2713–9.
9. Dipla K, Mattiello JA, Jeevanandam V, Houser SR, Margulies KB. Myocyte recovery after mechanical circulatory support in humans with end-stage heart failure. Circulation 1998;97:2316–22.
10. Margulies KB, Matiwala S, Cornejo C, Olsen H, Craven WA, Bednarik D. Mixed messages transcription patterns in failing and recovering human myocardium. Circ Res 2005;96:592–9.
11. Torre-Amione G, Stetson SJ, Youker KA, et al. Decreased expression of tumor necrosis factor-alpha in failing human myocardium after mechanical circulatory support: a potential mechanism for cardiac recovery. Circulation 1999;100:1189–93.
12. Wolff MR, Buck SH, Stoker SW, Greaser ML, Mentzer RM. Myofibrillar calcium sensitivity of isometric tension is increased in human dilated cardiomyopathies: role of altered beta adrenergically mediated protein phosphorylation. J Clin Invest 1996;98:167–76.
13. Mancini DM, Beniaminovitz A, Levin H, et al. Low incidence of myocardial recovery after left ventricular assist device implantation in patients with chronic heart failure. Circulation 1998;98: 2383–9.
14. Helman DN, Maybaum SW, Morales DLS, et al. Recurrent remodeling after ventricular assistance: is long-term myocardial recovery attainable? Ann Thorac Surg 2000;70:1255–8.
15. Hon KFJ, Yacoub MH. Bridge to recovery with the use of left ventricular assist device and clenbuterol. Ann Thorac Surg 2003; 75(suppl):S36–41.
16. Yacoub M. A novel strategy to maximize the efficacy of left ventricular assist devices as a bridge to recovery. Eur Heart J 2001;22:534–40.
17. Reinlib L, Abraham W. Recovery from heart failure with circulatory assist: a working group of the National Heart, Lung and Blood Institute. J Card Fail 2003;9:459–63.
18. Ferrari M, Kadipasaoglu KA, Croitoru M, et al. Evaluation of myocardial function in patients with end-stage heart failure during support with the Jarvik 2000 left ventricular assist device. J Heart Lung Transplant 2005;24:226–8.
19. Gorcsan J III, Severyn D, Murali S, Kormos RL. Non-invasive assessment of myocardial recovery on chronic left ventricular assist device: results associated with successful device removal. J Heart Lung Transplant 2003;22:1304–13.
20. Khan T, Delgado RM, Radovancevic B, et al. Dobutamine stress echocardiography predicts myocardial improvement in patients supported by left ventricular assist devices (LVADs): hemodynamic and histologic evidence of improvement before LVAD explantation. J Heart Lung Transplant 2003;22:137–46.
21. Hetzer R, Muller JH, Weng Y, Meyer R, Dandel M. Bridging-to-recovery. Ann Thorac Surg 2001;71(suppl):S109–13.
22. Slaughter MS, Silver MA, Farrar DJ, et al. A new method of monitoring recovery and weaning the Thoratec left ventricular assist device. Ann Thorac Surg 2001;71:215–8.
23. McConnell PI, Sun BC. Pressure–volume analysis during axial flow VAD support. J Heart Lung Transplant 2005;25:256–7.
24. Sakamoto T. Evaluation of native left ventricular function during mechanical circulatory support: theoretical basis and clinical limitations. Ann Thorac Cardiovasc Surg 2002;8:1–6.
25. Sagawa K. The end-systolic pressure–volume relation of the ventricle: definition, modifications and clinical use. Circulation 1981;63:1223–7.
26. Glower DD, Spratt JA, Snow ID, et al. Linearity of the Frank–Starling relationship in the intact heart: the concept of preload recruitable stroke work. Circulation 1985;71:994–1009.
27. Krukenkamp IB, Silverman NA, Kollmorgen TA, Levitsky S. Correlation between the linearized Frank–Starling relationship and myocardial energetics in the ejecting heart: effect of protected and unprotected global ischemia. J Thorac Cardiovasc Surg 1988;95:455–64.
28. Takaoka H, Suga H, Goto Y, Hata K, Takeuchi M. Cardiodynamic conditions for the linearity of the preload recruitable stroke work. Heart Vessels 1995;10:57–68.
29. Little WC, Cheng CP, Peterson T, Vinten-Johansen J. Response of the left ventricular end-systolic pressure volume relation in conscious dogs to a wide range of contractile states. Circulation 1988;78:736–45.
30. Goldstein AH, Monreal G, Kambara A, et al. Partial support with a centrifugal left ventricular assist device reduces myocardial oxygen consumption in chronic, ischemic heart failure. J Card Fail 2005;11:142–51.
31. Sarnoff SJ, Berglund E. Ventricular function I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. Circulation 1954;9:706–18.
32. Olsen CO, Tyson GS, Maier GW, Spratt JA, Davis JW, Rankin JS. Dynamic ventricular interaction in the conscious dog. Circ Res 1983;52:85.
33. Tyson GS, Maier GW, Olsen CO, Davis JW, Rankin JS. Pericardial influences on ventricular filling in the conscious dog: an analysis based on pericardial pressure. Circ Res 1984;54:173.
34. Hajdu MA, Cornish KG, Pazenbeck MJ, Zucker IH. The interaction of the Bainbridge and Bezold–Jarish reflexes in the conscious dog. Basic Res Cardiol 1991;86:175–85.