Biomedical Engineering

Effective Ventricular Unloading by Left Ventricular Assist Device Varies With Stage of Heart Failure: Cardiac Simulator Study

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Although the use of left ventricular assist devices (LVADs) as a bridge-to-recovery (BTR) has shown promise, clinical success has been limited due to the lack of understanding the timing of implantation, acute/chronic device setting, and explantation. This study investigated the effective ventricular unloading at different heart conditions by using a mock circulatory system (MCS) to provide a tool for pump parameter adjustments. We tested the hypothesis that effective unloading by LVAD at a given speed varies with the stage of heart failure. By using a MCS, systematic depression of cardiac performance was obtained. Five different stages of heart failure from control were achieved by adjusting the pneumatic systolic/diastolic pressure, filling pressure, and systemic resistance. The Heart Mate II® (Thoratec Corp., Pleasanton, CA) was used for volumetric and pressure unloading at different heart conditions over a given LVAD speed. The effective unloading at a given LVAD speed was greater in more depressed heart condition. The rate of unloading over LVAD speed was also greater in more depressed heart condition. In conclusion, to get continuous and optimal cardiac recovery, timely increase in LVAD speed over a period of support is needed while avoiding the akinesis of aortic valve. *ASAIO Journal* 2011; 57:407–413.

Left ventricular assist devices (LVADs) are used as a surgical unloading therapy to treat end-stage heart failure (HF). The primary use of LVADs is a bridge-to-transplant (BTT)[1–3] and destination therapy (DT).[4–6] Recently, there have been an increasing number of studies investigating the use of LVADs as a bridge-to-recovery (BTR), ultimately resulting in pump explantation in some cases.[7–9] As the availability of donor hearts is limited, BTR is a promising therapy for patients with advanced HF. However, to achieve this goal, a protocol is required for optimal LVAD parameter settings at the time of implant (*i.e.*, acute setting) and adjustment of the device over time (*i.e.*, chronic adjustment) to promote patient-specific cardiac recovery. Continuous-flow LVADs have become increasingly popular due to their small size and reduced thrombogenicity.[10] The speed setting for these devices is a critical factor that governs the amount of unloading of left ventricle (LV) and is, in general, determined based on clinical experience and patient's current cardiac condition. It is a great challenge to obtain a preset optimal setting that encourages and/or enhances the recovery because the amount of unloading at a given pump speed may vary with the stage of HF. It is likely that insufficient unloading may limit the incidence of recovery. Conversely, excessive unloading may cause aortic fusion and atrophy which may lead to further deterioration of cardiac performance before recovery.[7,11] In addition, excessive pump speeds may generate negative pressure in the cavity of LV, resulting in ventricular suction that can lead to severe arrhythmias.[12] This suggests that there may be appropriate compromise between the degree of LV unloading and operation of the LVAD within optimal physiological ranges to promote recovery. Thus, discreet setting of LVADs at the time of implant and chronic adjustment may be crucial for acquiring the optimal amount of unloading that enhances cardiac recovery. In fact, quantification of effective unloading by LVADs at systematically varying stage of HF is not trivial due to clinical difficulties. Although there have been diverse animal models of HF suggested serving well for better understanding and treatment of the disease, the stability and reproducibility of the models are still vulnerable even for one condition.[13] Efficacy of time, technique, and cost-effectiveness for creating a model is also a crucial factor.[14]

The mock circulatory system (MCS) as a cardiac simulator has been used extensively to aid device development and benchmark the capability of the LVADs and artificial hearts.[15–19] A pneumatically driven artificial ventricle added to the MCS enables hemodynamic and hydrodynamics simulation of HF.[20,21] In vitro testing of artificial hearts and LVADs provides the insight into in vivo performance of LVADs and cardiac response of failing hearts. This study investigated the effective LV unloading at different stages of HF over LVAD speed by using the MCS. The overall hypothesis of the study is that the effective unloading by LVAD at a given speed varies with the stage of HF.[22]

Materials and Methods

Adult MCS

The MCS developed by the Penn State University[23] was utilized to perform the study (**Figure 1**). Briefly, the MCS consists of two spring-loaded, rolling diaphragm-type piston cylinders that simulate the venous compliance and systemic

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Submitted for consideration December 2010; accepted for publication in revised form June 2011.

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DOI: 10.1097/MAT.0b013e318229ca8d

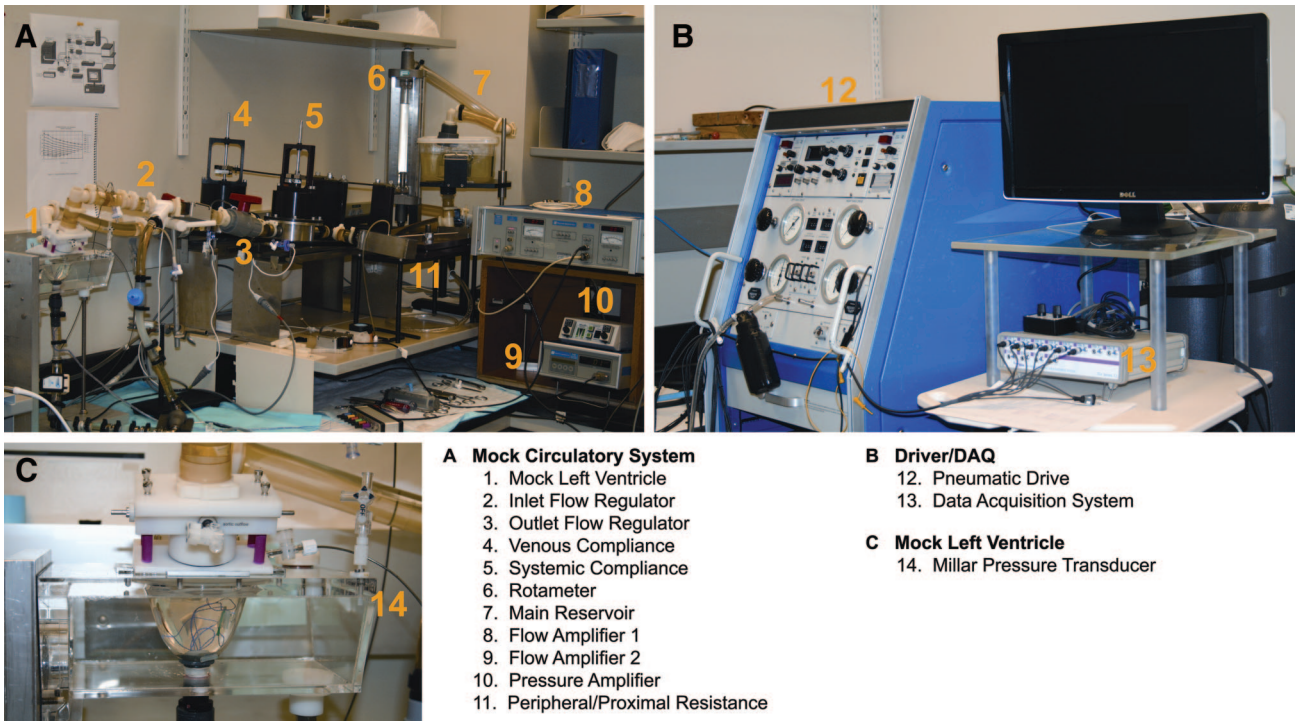

Figure 1. A: The MCS developed by the Penn State University. **B:** Pneumatic driver and Sonometric data acquisition system. **C:** The mock left ventricle. MCS, mock circulatory system.

arterial compliance and an adjustable systemic resistance. A compressible, transparent silicone mock LV (ViVitro Labs Inc., Victoria, Canada) that mimics the shape and motion of ventricular contraction is connected to a pneumatic driver (Sarns/3M Inc., Ann Arbor, MI). The Heart Mate II (Thoratec Corp., Pleasanton, CA) axial-flow LVAD was connected to the apex of the mock ventricle and operated at fixed speed using a custom motor controller developed on the ARM Cortex-M3 embedded platform (ST Microelectronics, Geneva, Switzerland).[24]

Heart Failure

Systematic variation of HF was achieved by adjusting the pneumatic systolic/diastolic driveline pressure. The following pneumatic driveline pressures (systole/diastole) were used to simulate normal left ventricular function and five stages of HF: 300/−28 mm Hg (Control), 250/−12 mm Hg (HF 1), 210/−4 mm Hg (HF 2), 175/2 mm Hg (HF 3), 140/9 mm Hg (HF 4), and 110/17 mm Hg (HF 5). Note that the pneumatic driveline pressure and the LV pressure in the MCS are not necessarily the same. Heart rate (HR) and systolic time duration (T_{sys}) were fixed at 80 bpm and 250 milliseconds for all stages of HF. The venous compliance and systemic arterial compliance were maintained constant for all heart conditions as well. The systemic resistance was gradually increased as the heart condition was depressed, and thus, the dilated LV was obtained. Hemodynamic parameters at each heart condition were acquired at LVAD speed of 8000, 8400, 8800, 9200, and 9600 RPM. Data for the baseline (BL) (*i.e.*, with no LVAD) of each heart condition were acquired while clamping the inlet and outlet of the cannula connected to the LVAD.

Pressure-Volume Measurement

The volume of the LV was assessed using six sonomicrometry crystals (2 mm, 34 AWG, Cu) (Sonometrics Inc., Ontario, Canada) anchored to inner surface of the LV (two in apical and basal planes and four in anterior, posterior, free and septal

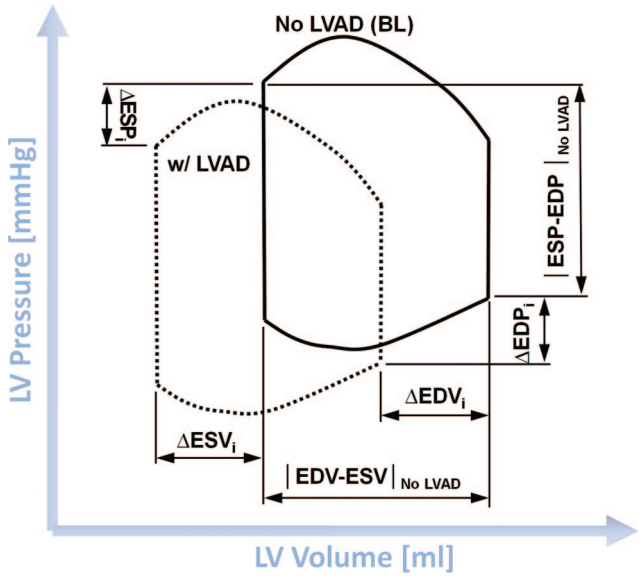

Figure 2. Schematic for calculation of normalized effective unloading on ventricular volume and pressure at end-diastole and end-systole. LVAD, left ventricular assist device; BL, baseline; ESP, end-systolic pressure; ESV, end-systolic volume; EDP, end-diastolic pressure.

Table 1. Hemodynamic Parameters for Control and Failing Hearts (HF1–HF5) Corresponding to the Mock Loop Driver Setting

Physiological Parameter	Control	HF1	HF2	HF3	HF4	HF5
EDV (ml)	82.7	88.9	95.5	101.7	108.0	113.6
ESV (ml)	39.5	54.3	67.1	75.9	87.2	97.7
EDP (mm Hg)	−7.3	−3.2	1.2	5.7	10.0	19.1
ESP (mm Hg)	116.6	109.7	102.9	92.6	83.9	71.6
SV (ml)	43.2	34.6	28.4	25.8	20.9	15.9
EF	0.52	0.39	0.30	0.25	0.19	0.14
SW (mm Hg · ml)	6537.6	5007.7	3759.1	2773.3	1943.3	1092.9
dP/dt_{max}	1862.0	1326.7	1119.4	1080.6	890.2	718.7
E_{ES} (mm Hg/ml)	2.02	1.30	0.99	0.68	0.46	0.37
V_0 (ml)	−18.6	−30.4	−38.0	−61.5	−96.5	−95.7
Aop_{max} (mm Hg)	90	88	85	79	74	71
CVP_{mean} (mm Hg)	31	35	38	42	45	49
CO (LPM)	3.5	2.8	2.3	2.0	1.7	1.3

EDV, end-diastolic volume; ESV, end-systolic volume; EDP, end-diastolic pressure; ESP, end-systolic pressure; SV, stroke volume; EF, ejection fraction; SW, stroke work; dP/dt_{max}, maximum time rate change of left ventricular pressure; E_{ES}, end-systolic elastance; V_0, ventricular volume intercept; Aop_{max}, maximum aortic pressure; CVP_{mean}, mean central venous pressure; CO, cardiac output.

wall). The LV pressure was monitored by a Millar Mikro-Tip Catheter Pressure Transducer (Millar Instrument Inc., Houston, TX) placed in the LV cavity. Composite pressure-volume loops were generated by averaging LV pressure and LV volume over approximately 10 cardiac cycles. The end-systolic (ESPVR) and end-diastolic pressure-volume relationships (EDPVR) were determined by occluding the inlet flow mimicking the caval occlusion. The slope of ESPVR and EDPVR were acquired with linear least-squares fitting of end-systolic and end-diastolic pressure-volume points, respectively, when afterload and preload were reduced with occlusion.

Measure of Volumetric and Pressure Unloading

As the depression of heart condition in general is coupled with both the diastole and systole, end-diastolic and end-systolic volume unloading at each pump speed over the heart condition was quantified by normalizing the volumetric drops (*i.e.*, $|\Delta EDV|_i$ and $|\Delta ESV|_i$) from the BL by the magnitude of the BL volume difference at end-diastole (ED) and end-systole (ES) (*i.e.*, $|EDV - ESV|_{BL}$) which is same as stroke volume of the BL. Likewise, end-diastolic and end-systolic pressure unloading at each LVAD speed over the heart condition was quantified by normalizing the pressure drops from the BL (*i.e.*, $|\Delta EDP|_i$ and $|\Delta ESP|_i$) by the magnitude of the pressure difference of the BL at ED and ES (*i.e.*, $|ESP - EDP|_{BL}$). **Figure 2** shows a schematic for calculating the normalized volumetric and pressure unloading at ED and ES. For example, to obtain the normalized volumetric and pressure unloading at ED,

$$[\text{Normalized EDV Unloading}]_i = |\Delta EDV|_i / |EDV - ESV|_{BL},$$

where $|\Delta EDV|_i = |EDV_i - EDV_{BL}|$

$$[\text{Normalized EDP Unloading}]_i = |\Delta EDP|_i / |ESP - EDP|_{BL},$$

where $|\Delta EDP|_i = |EDP_i - EDP_{BL}|$

with i = 8000, 8400, 8800, 9200, and 9600 RPM. Normalized volumetric and pressure unloading at ES can be understood likewise.

Data Acquisition and Analysis

Pressure and volume of the LV were recorded continuously by the Sonometrics Data Acquisition System (Sonometrics Inc., Ontario, Canada). Data analysis was performed using Sonosoft software (Sonometrics Inc, Ontario, Canada) and a custom program developed in Matlab (Mathworks, Natick, MA).

Results

Hemodynamics

Hemodynamic parameters for control and each stage of HF are shown in **Table 1**. All the physiological parameters clearly represent the depression of heart condition. **Figure 3A** shows the pressure-volume loops of control and depressed heart conditions. The Starling's response by the MCS was also able to be described reasonably well, and decreased stroke work was obvious as the heart condition got more depressed. **Figure 3B** shows a series of pressure-volume loops for control and ESPVRs of all heart conditions. The slopes of ESPVR at each condition were acquired with linear least-squares fitting ($r > 0.90$ for all conditions) of end-systolic pressure-volume points when afterload and preload were reduced with occlusion. Reduced end-systolic contractility (E_{ES}) was observed in depressed heart condition (see the slopes of ESPVRs). Change in heart condition was characterized by the stroke work and end-systolic elastance (**Figure 3C**). With a systematic variation of heart condition, stroke work changes in linear fashion, whereas the contractility changes in rather nonlinear fashion.

Measure of Ventricular Unloading

Pressure-Volume Loop. Under all heart conditions, increased LVAD speed resulted in a leftward and downward shift of pressure-volume loops. The amount of shift was differed by heart condition and greater in more depressed heart condition (**Figure 4**).

Pump Speed vs. Volumetric and Pressure Drop. At a given LVAD speed, nominal volumetric drop at ED and ES was greater in more depressed heart condition (**Figures 5**, **A** and **B**). The volumetric drop over LVAD speed showed a linear relationship, *i.e.*, LV volume was linearly decreased with linear increase in LVAD speed. The pressure drop at ED over LVAD speed also showed linearity; however, the difference in nominal pressure drop at each heart condition was not significant (**Figure 5C**). There were multiple interesting features in nomi-

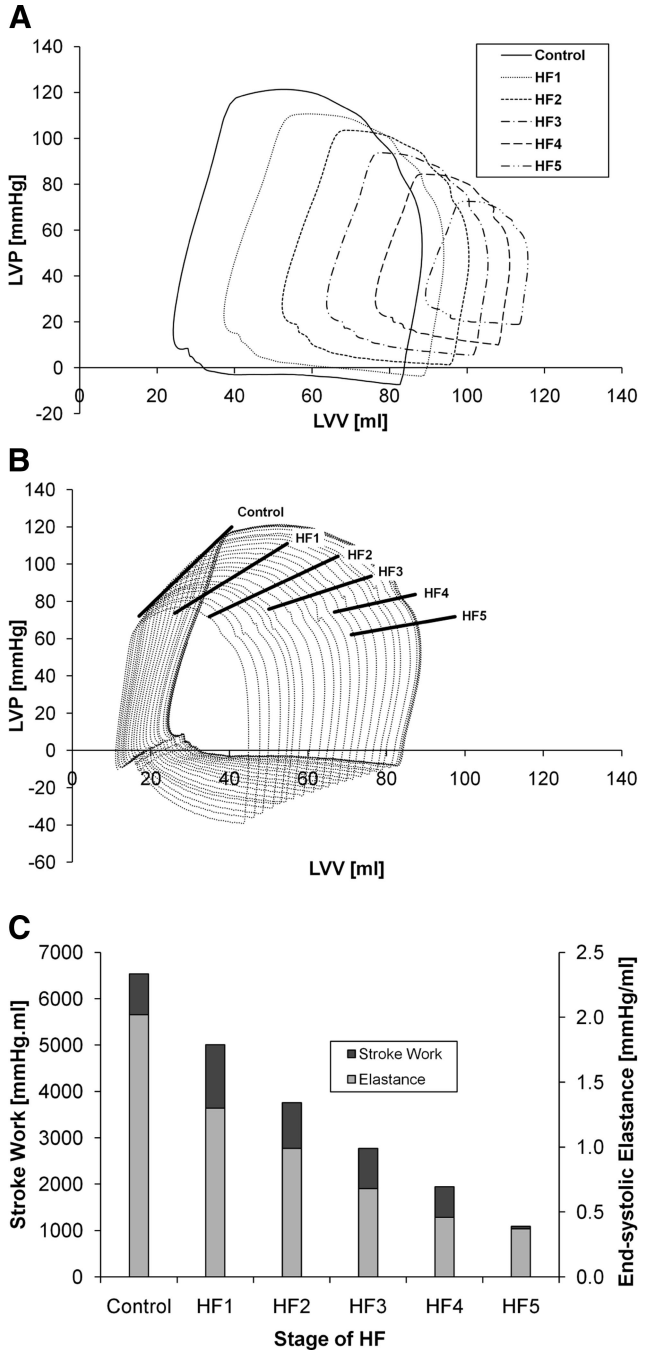

Figure 3. Pressure-volume loops of control and heart failures (**A**) and a series of pressure-volume loops for control and ESPVRs of all heart conditions ($r > 0.90$ for all conditions) (**B**). The conditions of control and failing hearts were characterized in term of stroke work and end-systolic elastance (**C**).

nal pressure drop at ES (**Figure 5D**): the pressure drop at ES seemed to be highly related to both the heart condition and kinematics of aortic valve (*i.e.*, valve opening and closing). The pressure drop was widely varied over the heart condition; however, the rate of pressure drop over LVAD speed at control, HF1, and HF2 was nearly plateau (see the slopes of control, HF1, and HF2). Knowing that the motion of aortic valve at HF3 became inert with LVAD on, and fully closed at HF5 by any given LVAD speed, the rate of pressure drop over LVAD speed started to increase (see the slopes HF3, HF4, and HF5) and was stiffer in more depressed heart condition.

Volumetric and Pressure Unloading. **Figure 6** shows the volumetric unloading and pressure unloading at ED and ES. Note that the effective unloading on LV volume and pressure varies over the stage of HF. At a given LVAD speed, the effective volumetric and pressure unloading was greater in more depressed heart condition. In addition, the rate of unloading over LVAD speed appeared to be greater at more depressed heart condition (see the slopes of bar graphs at each heart condition). The amount of volumetric unloading at ED and ES was similar for all heart conditions. The effective pressure unloading at ED was nonlinearly increased over the heart condition. As presented in **Figure 5D**, the rate of pressure unloading at ES kept nearly constant over LVAD speed until the aortic valve becomes inert. In case of normal aortic valve opening, the effective pressure unloading at ES was decreased over the depression of heart condition; however, when the aortic valve remained closed, the effective pressure unloading at ES started to follow the same fashion as other parameters, *i.e.*, nonlinear increasing of effective unloading over the heart condition with greater rate of unloading over LVAD speed.

Conclusions

This study examined the effective unloading by mechanical circulatory assist device at different heart conditions with a given LVAD speed. The primary finding of this study is that the effective ventricular unloading varies with the stage of HF at a given LVAD speed: the effectiveness of hemo-/hydrodynamic and mechanical unloading is more significant in more advanced HF.[25] This suggests that a "smart adjustment" may be needed during the mechanical circulatory support. For example, if a patient's heart condition has improved from HF5 to HF4, the amount of unloading would be reduced by 30% provided no speed adjustment was made. Thus, to get equivalent amount of unloading and continuous cardiac recovery, LVAD speed may need to be increased. The significance of this discovery is that it provides the insight to aid the patient-specific optimal setting of the LVADs at the time of implant and long-term adjustment.[26]

Despite frequent signs of cardiac recovery by the LVADs have been reported, there are still more questions than answers for this promising phenomenon. In fact, definitive answer for the duration of the LVADs implantation is currently unavailable. It is reported that long-term unloading by LVADs leads to deterioration of cardiac performance mainly due to depression of myocyte contractility.[27–30] However, Brinks *et al*[31] reported that contractility is preserved in the long-term unloaded heart. Besides, the effect of mechanical unloading seems to be also influenced by the patient's heart condition.[22] Therefore, understanding the amount of ventricular unloading while controlling the degree of ventricular atrophy associated with myocyte contractility seems very important for both the time of LVAD implantation and during LVAD support. This in turn suggests the significance of the optimal amount of unloading, period of support, and weaning time as for a way of BTR.[7]

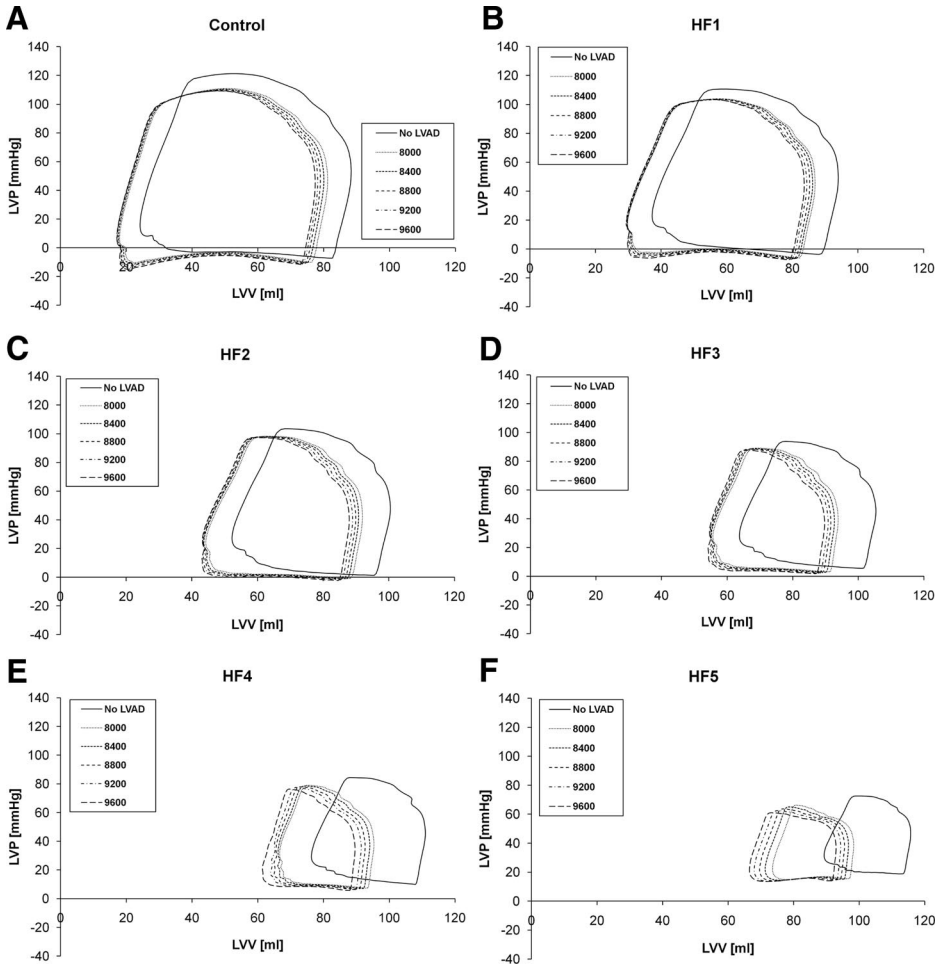

Figure 4. Shift of pressure-volume loops by LVAD for control (**A**), HF1 (**B**), HF2 (**C**), HF3 (**D**), HF4 (**E**), and HF5 (**F**). LVAD, left ventricular assist device.

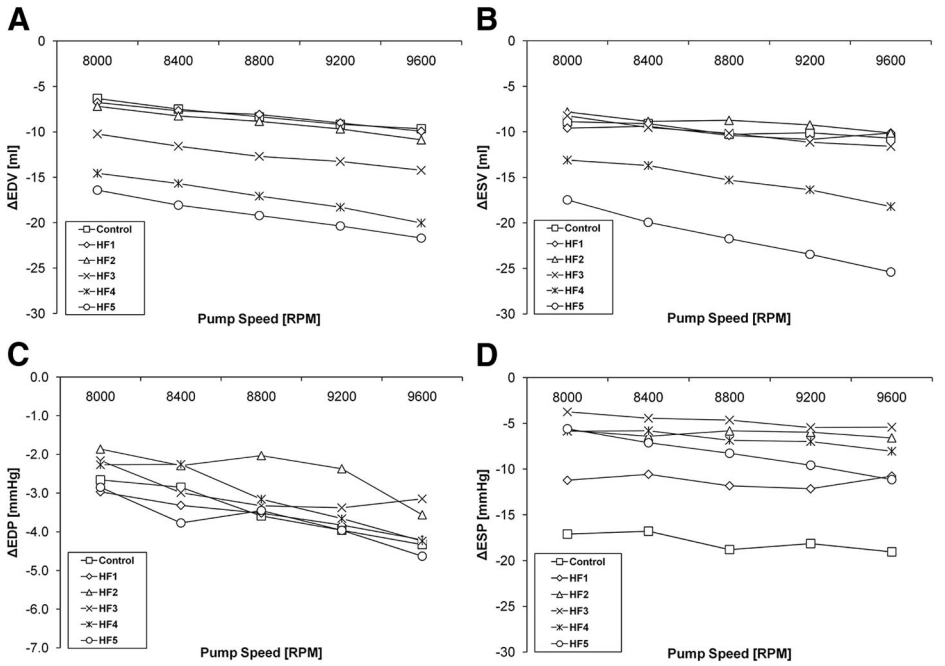

Figure 5. Nominal drop of EDV (**A**), ESV (**B**), EDP (**C**), and ESP (**D**). EDV, end-diastolic volume; ESV, end-systolic volume; EDP, end-diastolic pressure; ESP, end-systolic pressure.

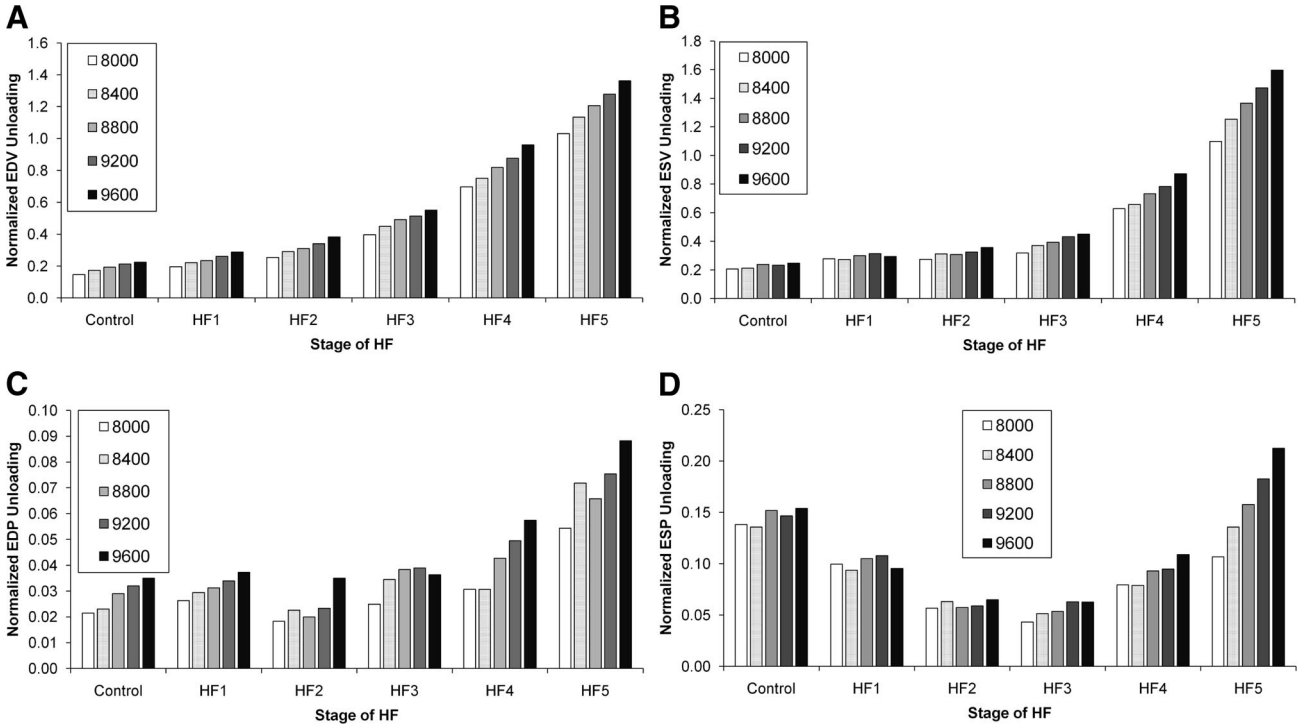

Figure 6. Normalized effective unloading on EDV (**A**), ESV (**B**), EDP (**C**), and ESP (**D**). EDV, end-diastolic volume; ESV, end-systolic volume; EDP, end-diastolic pressure; ESP, end-systolic pressure.

Limitations

As Koenig *et al*[20] pointed out appropriately, the utility of the MCS is limited solely by hemo-/hydrodynamics. Replication of all in vivo phenomena by the MCS is not possible despite its preferred feasibility of duplication on hemo-/hydrodynamic characteristics shown in in vivo setting. Thus, there might be incomparable results between in vivo and in vitro mock circulatory testing. Besides, in vivo utility of LVAD at different stages of HF may lead to many changes at the cellular, molecular, and organ levels that this study is not capable of. Due to the limited setup (*i.e.,* no pulmonary circulation) of our MCS and circulatory characteristic of LVADs, this study only focused on the LV unloading. However, understanding rigorous interaction between left and right ventricular function is crucial because right ventricular failure can be developed by long-term mechanical circulatory support[32] and LVAD filling affects right ventricular ejection rate and stroke work.[33] It is also known that LVAD support leads to a decrease in right ventricular afterload, increased compliance, and decreased contractility with these effects being predominant in depressed heart condition.[34] This may suggest that biventricular support may be required in severely depressed heart to avoid potential multiorgan failure. This study is not capable of quantifying the interaction between left and right ventricular functions induced by LVAD support; however, the utility of the MCS provides the insight to design and quantification of unloading of failing hearts with LVAD which still provides a way to quantify the cardiac response and performance of advanced failing hearts with LVAD.

Summary

In summary, this study provides an insight for LVAD treatment as a BTR to a patient-specific optimal setting of LVAD at the time of implantation and long-term adjustment to encourage and enhance cardiac recovery. Due to unique characteristic of each stage of HF, ideal operation range of LVAD at the time of device implantation is currently unknown and subjective. As we are confronting the reality of severe limitation of available organs, it is certain that a BTR for patients with advanced HF is an attractive modality that is still in need of understanding the relationship between device setting (acute, chronic) and current condition of the patient which potentially helps with establishing the universally accepted weaning protocol.

Acknowledgment

The authors thank Drs. Gerson Rosenberg and William Weiss for their assistance in developing the mock circulatory system.

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