Title:
Prediction of Hemodynamics under Left Ventricular Assist Device

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Running head: Prediction of the impact of LVAD on hemodynamics

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Abstract

Left ventricular assist device (LVAD) saves lives in patients with severe left ventricular (LV) failure. However, predicting how much LVAD boosts total cardiac output (CO) remains difficult. This study aimed to develop a framework to quantitatively predict the impact of LVAD on hemodynamics. We adopted the circulatory equilibrium framework and incorporated LVAD into the integrated CO curve to derive the circulatory equilibrium. In anesthetized dogs, we ligated left coronary arteries to create LV failure and inserted a centrifugal pump as LVAD. Using CO, right (PRA) and left atrial pressure (P LA) measured prior to LVAD support, we predetermined the stressed volume (V) and logarithmic slope of right heart CO curve (Sr). Next, we initiated LVAD at maximum level and then decreased LVAD flow stepwise while monitoring hemodynamic changes. We predicted LVAD-induced CO and PRA for given P LA from the predetermined Sr and V, and compared with those measured experimentally. The predicted CO [r²=0.907, standard error of estimate (SEE)=5.59 mL/min/kg, p<0.001] and PRA [r²=0.967, SEE=0.307 mmHg, p<0.001] matched well with measured values indicating the validity of the proposed framework. We further conducted simulation using the validated framework to analyze the impact of LVAD on PRA under various right ventricular (RV) functions. It indicated that PRA is relatively insensitive to changes in RV end-systolic elastance or pulmonary arterial resistance, but sensitive to changes in V. In conclusion, the circulatory equilibrium framework predicts quantitatively the hemodynamic impact of LVAD. This knowledge would contribute to safe management of patients with LV failure undergoing LVAD implantation.

New & Noteworthy:
Hemodynamic response to left ventricular assist device (LVAD) has not been quantitatively investigated. This is the first report of quantitative prediction of the hemodynamics on LVAD using circulatory equilibrium framework. The validated framework allows us to simulate the impact of LVAD on right atrial pressure under various right ventricular functions.

**Keywords:**
- Left ventricular assist device, hemodynamics, circulatory equilibrium, cardiac output curve, venous return surface

**INTRODUCTION**
Heart failure is one of the most challenging diseases to treat, and long-term survival remains unacceptably poor despite the widespread use of latest guideline-recommended medical therapy (9). Although heart transplantation is the last resort for end-stage decompensated heart failure, the number of donor hearts is never sufficient (2). The advent of left ventricular assist device (LVAD) has saved many lives in patients with end-stage heart failure (1). Because of the remarkable performance of LVAD, its use has expanded rapidly, including destination therapy and bridge to transplant (11). For example, a randomized clinical trial demonstrated that LVAD resulted in marked improvement of quality of life and long-term survival compared with optimal medical therapy (15). Because of these beneficial effects, LVAD has become the first-line treatment for end-stage heart failure.

Despite such outstanding performance of LVAD, it remains difficult to predict how much LVAD improves hemodynamics in each patient. Therefore, the current practice of LVAD is somewhat empirical. Since LVAD-generated cardiac output (CO) cannot exceed venous return and stressed volume determines the amount of venous return, maximum CO under LVAD is limited by the stressed volume. However, currently we have no option to predict LVAD-generated CO before LVAD implantation. Moreover, the presence of right ventricular (RV) failure accompanying left ventricular (LV) failure further complicates the hemodynamic response to LVAD. Systemic congestion and low CO are often observed after LVAD implantation in patients with concomitant RV failure. This indicates that LVAD implantation does not guarantee sufficient total flow unless stressed volume is adequate. Although various indicators of RV failure have been developed, it remains difficult to predict quantitatively the impact of LVAD on systemic congestion (3, 10). Under the current trial-and-error circumstances, we have no reliable indicators to select patients who benefit most from LVAD (12). Therefore, the understanding and prediction of the impact of LVAD on
hemodynamics are crucial in managing patients undergoing LVAD implantation. Nevertheless, no report has been published on the quantitative prediction of hemodynamics after LVAD implantation.

In the 1950s, Guyton (6, 7) proposed the concept of circulatory equilibrium. In this framework, the venous return function is represented by the venous return (VR) curve and cardiac performance by the CO curve, and the circulatory equilibrium is defined as the intersection of the two curves. However, since the CO and VR curves are expressed only as a function of right atrial pressure (P_{RA}), Guyton’s original concept of circulatory equilibrium cannot explicitly take into account the left ventricle and pulmonary vascular system. Sunagawa et al. (22) developed an extended framework consisting of an integrated CO curve and a VR surface as functions of both right and left atrial pressures (P_{LA}) (Fig. 1A) (22). This framework explicitly takes into consideration left ventricle and pulmonary circulation. The intersection between the integrated CO curve and VR surface defines the circulatory equilibrium. Uemura et al. (23, 24) experimentally validated the framework and demonstrated that changes in stressed volume shift the VR surface in response to stressed volume, as anticipated from the framework. This framework allows representation of unilateral as well as bilateral ventricular failure and the redistribution of blood between the systemic and pulmonary vascular systems, and thus is potentially capable of predicting hemodynamics under LVAD support.

The aim of this study was to develop a framework to quantitatively predict the hemodynamic impact of LVAD. We incorporated the effects of LVAD on the left or right heart and the VR surface into the framework of the circulatory equilibrium.

**MATERIALS AND METHODS**
Preparation and procedure

We used six adult mongrel dogs (5 males and 1 female) weighing 16.9–22 kg. Animal care was performed in strict accordance with the Guide for the Care and Use of Laboratory Animals by the United States National Institutes of Health, and experiments were approved by the Committee on Ethics of Animal Experiment, Kyushu University Graduate School of Medical Sciences. Anesthesia was induced by an intravenous injection of pentobarbital sodium (25 mg/kg) and vecuronium bromide (0.2 mg/kg). After endotracheal intubation, mechanical ventilation was started. We continuously infused pentobarbital sodium through a 5-French catheter introduced into the right femoral vein and appropriately maintained the level of anesthesia during the experiment. We bilaterally isolated the carotid sinuses and maintained the intrasinus pressure at 100 mmHg to abolish the baroreflex. We surgically exposed bilateral vagal trunks and sectioned them in the neck region to eliminate other buffering effects. Systemic arterial pressure was measured by a catheter-tipped micromanometer (Model PC-751; Millar Instruments, Houston, TX, USA) via the right common carotid artery. After a median sternotomy, fluid-filled catheters were placed in the left and right atria and connected to pressure transducers (model DX-360; Nihonkohden, Tokyo, Japan) to measure P_{LA} and P_{RA}, respectively. We also placed an ultrasonic flow meter (Model PSB; Transonic, Ithaca, NY, USA) around the ascending aorta to measure LV CO. We ligated the left anterior descending and circumflex artery to create LV failure. We used a centrifugal pump (CBBPX-80; Medtronic, Minneapolis, MN, USA) as LVAD. A systemic perfusion cannula was inserted into the left femoral artery. Two draining cannulas were placed in the left ventricle through the lateral wall and apex. LVAD flow was measured by an in-line electromagnetic flow probe (Model XN; Transonic).
Theoretical Consideration

Impact of LVAD on the integrated CO curve

An integrated CO curve is the composite of left CO (CO_L) and right CO (CO_R) curve.

In severe left heart failure, LV no longer ejects and LVAD support is the sole source of CO_L.

Thus, CO_L is equal to LVAD flow (LVAD_F):

$$CO_L = LVAD_F$$  \hspace{1cm} \text{Eq. 1}

LVAD has no direct impact on RV CO (CO_R). However, the downstream pressure for RV; that is P_LA, is not small enough to be ignored compared to the pulmonary arterial pressure. Furthermore, since LVAD changes P_LA markedly, P_LA has to be taken into consideration in describing CO_R (17). Incorporating P_LA into CO_R (APPENDIX 1) yields the following equation:

$$CO_R = S_R \{\ln(P_{RA})\} - \frac{(1-\text{RVEF_e})P_{LA}}{R_p}$$  \hspace{1cm} \text{Eq. 2}

where S_R is the logarithmic slope of the RV CO curve, RVEF_e is effective RV ejection fraction, and R_p is pulmonary vascular resistance. In this study, we set RVEF_e = 0.6 for normal RV function, and R_p = 0.10 mmHg/mL•min^{-1}•kg^{-1} as reported previously by Shoukas (21). Simultaneous solution of Eqs. 1 and 2 yields the integrated CO curve under LVAD support.

Impact of LVAD on VRS

Although LVAD creates a LV-to-aorta bypass, it does not change the vascular properties or stressed blood volume. Therefore, the VR surface remains unchanged under LVAD support. Thus, we use Eq. 3 for the VR surface similar to Uemura’s report (24) (APPENDIX 2):

$$CO_V = \frac{V}{W} - G_s P_{RA} - G_p P_{LA}$$  \hspace{1cm} \text{Eq. 3}
where COV is the amount of venous return, V represents the total stressed blood volume, and W is the parameter that defines the maximum venous return for a given V (23, 24). G_s and G_p are systemic and pulmonary conductance representing the slope of VR surface with respect to P_RA and P_LA, respectively. We substituted 0.129, 19.61, and 3.49 for W, G_s, and G_p, respectively, because Uemura et al (24) have previously concluded that these values are constant among dogs.

In this study, we numerically derived the intersection of the integrated CO curve and VR surface with LVAD support from Eqs. 1–3 (Fig. 1B). By knowing the values of CO, P_RA, and P_LA before LVAD implantation, we predicted the equilibrium point after LVAD implantation and compared them against the measured values.

**Experimental protocol**

Prior to initiation of LVAD support, we simultaneously recorded CO, P_RA, and P_LA for 1 min. Using those values before LVAD, we predetermined the logarithmic slope of the right heart (S_R) from Eq. 2, and stressed blood volume (V) from Eq. 3. Next, we set LVAD flow at maximum level to empty the left atrium. We then decreased LVAD flow stepwise at 10–15 mL/min/kg per step until LV resumed ejection. Finally, we predicted total CO (=LVAD-generated CO) and P_RA for a given P_LA with the predetermined S_R and V from Eqs. 1–3 and compared them with the measured values. We summarized the procedure used for prediction and comparison in Figure 4.

**Data analysis**

All analog signals were digitized at 200 Hz using a 16-bit analog-to-digital converter (PowerLab 16/35; AD Instruments, Dunedin, New Zealand) using a dedicated laboratory
computer system. We averaged digitized data over 9 s when time series data reached a steady state. Differences between groups were considered significant at P values < 0.05 in paired t test. We calculated the coefficient of determination ($r^2$) for goodness of fit and the standard error of estimate (SEE) for predictive accuracy.

RESULTS

Baseline hemodynamics

Table 1 shows the hemodynamics at baseline and after myocardial infarction (MI). Induction of MI markedly decreased CO ($p=0.035$) and increased $P_{LA}$ ($p=0.000049$) indicating successful creation of severe LV failure. MI did not change arterial pressure (AP) or $P_{RA}$ significantly.

Prediction of circulatory equilibrium for a given $P_{LA}$

Figure 2 shows the time series when maximum LVAD flow was decreased stepwise. Decrease in LVAD flow was accompanied by a decrease in AP, and conversely an increase in $P_{LA}$, while $P_{RA}$ remained virtually unchanged. LV CO remained at zero because the LV did not eject. HR remained unchanged throughout the experiment despite the great changes in AP because the baroreflex was eliminated. Figure 3 illustrates the individual time series of LVAD flow, $P_{RA}$ and $P_{LA}$ of all six dogs. We mark the time points of measured data used for analysis with dotted lines in each panel. Table 2 summarizes $S_R$ and $V$ calculated using the CO, $P_{RA}$, and $P_{LA}$ values obtained before LVAD was started (baseline). Figure 5 demonstrates the relationship between predicted and measured total CO and the relationship between predicted and measured $P_{RA}$ for given $P_{LA}$ using pooled data of all animals. Regression analysis showed
that the predicted total CO ($y = 0.800x + 20.7$, $n = 31$, $r^2 = 0.907$, SEE = 5.59 mL/min/kg, $p <0.001$) and $P_{BA}$ ($y = 1.10x - 0.310$, $n = 31$, $r^2 = 0.967$, SEE = 0.307 mmHg, $p <0.001$) matched well with those measured.
DISCUSSION

The purpose of this investigation was to develop a framework to quantitatively predict the impact of LVAD support on hemodynamics in subjects with end stage LV failure. We showed that the circulatory equilibrium framework is capable of predicting hemodynamic responses to LVAD implantation. Using $S_R$ and stressed volume predetermined from baseline data, the predicted total CO correlated well with those measured. In other words, our results indicate that hemodynamics at various levels of LVAD flow can be predicted. The extended Guyton’s framework allows quantification of the impact of LVAD on each ventricle and the redistribution of blood from pulmonary to systemic circulation, resulting in accurate hemodynamic prediction (Fig. 5). Since LVAD changes $P_{LA}$ markedly, we incorporated $P_{LA}$ as the downstream pressure of pulmonary circulation. The inclusion of $P_{LA}$ renders the RV CO curve dependent on $P_{LA}$ and allows accurate prediction of hemodynamics under LVAD support.

Since LVAD does not change stressed volume, LVAD can only generate sufficient total flow if stressed volume is adequate. Therefore, systemic perfusion is insufficient without enough stressed volume in the pulmonary circulation even though we set LVAD flow to maximum to empty the left atrium. The reason is that stressed volume determines the amount of venous return. This remains true in subjects with normal and impaired RV function. Greater stressed volume is required in RV failure compared to normal RV function. As suggested in our study, the predicted total CO (and $P_{RA}$) provides a practical index of the appropriateness of stressed volume for a given level of RV function. In other words, the proposed framework is capable of identifying patients, before implantation, who will show low output and systemic congestion after LVAD implantation. Considering the fact that we have no practical method to predict hemodynamics after LVAD implantation, such a quantitative prediction
based on the proposed framework is useful in establishing individualized indication for LVAD implantation. This information also allows appropriate management of stressed volume before, during and after LVAD implantation.

There is a great deal of concern about systemic congestion with elevated $P_{RA}$ in many patients under LVAD support. However, Figure 2 illustrates that despite great changes in LVAD flow (50-100 mL/min/kg), $P_{RA}$ remained unchanged, indicating that LVAD flow has little effect on $P_{RA}$. LVAD increases the volume returning to the right atrium because LVAD shifts the volume from pulmonary to systemic circulation. At the same time, the volume ejected from RV increases because LVAD decreases the downstream pressure ($P_{LA}$), which is the afterload of RV; the former increases $P_{RA}$, whereas the latter decreases $P_{RA}$. Therefore, the balance between these antagonizing effects determines how LVAD changes $P_{RA}$. In the present study, we conducted the experiment in subjects with normal RV function and found that LVAD little changed $P_{RA}$. Whether LVAD increases or decreases $P_{RA}$ in RV failure requires further discussions.

To resolve how RV failure alters the relationship between LVAD flow and $P_{RA}$, we conducted a simulation study by simultaneously solving the equations of the circulatory equilibrium framework. We determined how LVAD flow changes $P_{RA}$ under various values of RV contractility and $R_p$ (Fig. 6). We used RV end-systolic elastance ($RVE_{es}$) as a load-insensitive index of contractility. We set the value of $LVEF_e$ at 0.3 for LV failure. Using known empirical constants, we adjusted the stressed volume so that $P_{LA} = 18$ mmHg as baseline condition before LVAD was initiated. We then numerically determined the equilibrium point under each level of LVAD support for various values of $RVE_{es}$ and $R_p$.

Figure 6 demonstrates the relationship between LVAD flow and $P_{RA}$ for given $RVE_{es}$ or $R_p$ at constant stressed volume, because LVAD flow does not change stressed volume.
When \( RVE_{es} \) is the highest (0.14 mmHg/ml/kg), increase in LVAD flow from 0 to 130 mL/min/kg increases \( P_{RA} \) from 2.76 to 3.03 mmHg (Fig. 6A). In contrast, when \( RVE_{es} \) is the lowest (0.04 mmHg/ml/kg), increase in LVAD flow from 0 to 160 mL/min/kg decreases \( P_{RA} \) from 11.3 to 9.92 mmHg (Fig. 6A). Increase in LVAD flow decreases \( P_{RA} \) from 3.94 to 3.42 mmHg at the lowest \( R_p \) (0.05 mmHg/mL•min\(^{-1}\)•kg\(^{-1}\)), but increases \( P_{RA} \) from 13.6 to 15.1 mmHg at the highest \( R_p \) (0.45 mmHg/mL•min\(^{-1}\)•kg\(^{-1}\)) (Fig. 6B).

As shown in Figure 6, whether LVAD flow increases or decreases \( P_{RA} \) depends on the magnitude of \( RVE_{es} \) and \( R_p \). To further clarify these relations, we analytically solved Eqs. 1–3 in the circulatory equilibrium framework and derived the condition in which LVAD increases \( P_{RA} \) as follows (APPENDIX 3).

\[
\frac{1}{G_p} \cdot \frac{1}{T \cdot RVE_{es} + R_p} < 1
\]

Eq. 4

Substituting \( G_p \) by the constant 3.49 mL•min\(^{-1}\)•kg\(^{-1}\)/mmHg (24), and rearranging Eq. 4 yields

\[
T \cdot RVE_{es} + R_p > 0.28
\]

Eq. 5

T is heart period. This equation indicates that LVAD support increases \( P_{RA} \) more when \( RVE_{es} \) or \( R_p \) is higher than normal \( RVE_{es} \) or \( R_p \). It is somewhat counter-intuitive that LVAD increases \( P_{RA} \) more in patients with better RV contractility. In fact, patients with RV failure on LVAD support often develop systemic congestion. Fontan circulation is an extreme case of RV failure in which RV is interpreted to be totally nonfunctioning. Patients with Fontan circulation have poor exercise tolerance associated with elevated central venous pressure (4, 5, 14). However, this is probably not due to increased total flow in Fontan circulation. Assuming \( R_p = 0.1 \) mmHg/mL•min\(^{-1}\)•kg\(^{-1}\) under normal condition (21), Fontan circulation does not satisfy Eq. 5 because \( RVE_{es} \) is zero. This indicates that \( P_{RA} \) does not increase even though exercise increases total flow in Fontan circulation. On the other hand, since exercise apparently increases stressed volume, elevated central venous pressure would be attributable
to increases in stressed volume. Alternatively, $P_{RA}$ increases with increase in total flow at higher $R_p$, which is a significant determinant of changes in $P_{RA}$ after Fontan procedure. In such cases, treatment to decrease $R_p$ would be preferred.

One of the most important findings in this simulation is that at constant stressed volume, LVAD flow has little effect on $P_{RA}$ irrespective of $RVE_{es}$ or $R_p$ level, indicating $P_{RA}$ is insensitive to changes in $RVE_{es}$ or $R_p$. This is a good agreement with our data (Fig. 2). Moreover, this finding suggests that LVAD implantation may not increase $P_{RA}$ even in the case of biventricular failure. In an article on the acute impact of LVAD on RV function, Kukucka et al (8) reported that central venous pressure does not change immediately after LVAD implantation whereas total CO increases significantly. Morgan et al (13) also reported that LVAD support does not worsen RV function or increase $P_{RA}$. Obviously, RV failure is a major clinical problem in patients on LVAD support, who need larger stressed volume to maintain systemic perfusion than those with normal RV function. As shown in Figure 6, lower $RVE_{es}$ or higher $R_p$ requires greater stressed volume than normal $RVE_{es} = 0.07$ mmHg/ml/kg or normal $R_p = 0.1$ mmHg/mL•min^{-1}•kg^{-1} when we make $P_{LA}$ at 18 mmHg before LVAD as an initial condition. Since greater stressed volume increases $P_{RA}$, $P_{RA}$ is sensitive to changes in $V$. In such patients with RV failure, after LVAD generates total CO much enough to maintain systemic perfusion, lowering stressed volume to the level that ensures sufficient preload to LVAD is essential for the management of both systemic congestion and systemic perfusion.

**Limitations**

There are several limitations in this study. First, we conducted the experiments using anesthetized and open-chest dogs. Furthermore, we isolated the bilateral carotid sinuses and cut the vagal trunks. Since the baroreflex and other reflexes via the vagal nerve could alter the
vascular and cardiac properties (18, 19), we eliminated these complex reflexes to understand
the fundamental impact of LVAD on hemodynamics. Second, we assumed RVEF, and R p to
be 0.6 and 0.1 mmHg/mL•min⁻¹, respectively, and the coefficient of downstream pressure for
RV to be 4.0 in Eq. 2. To examine if the assumptions are valid, we changed the coefficient
stepwise from 2.5 to 7.0 and evaluated the goodness of fit (r²). The result indicated that the
coefficient of 4.0 maximized r² at 0.907 as shown in Figure 5. In our study, the experiments
were conducted only under conditions of normal RV function. Although the assumption is
valid under conditions of normal RV function, the coefficient needs to be individualized in
patients. Third, we estimated the RV CO curve from a circulatory equilibrium point before
LVAD implantation for simplicity. Apparently, volume changing methods such as infusing or
withdrawing volume would better describe the CO curve, but these methods are quite invasive
and impractical. There is no question that the accuracy of approximating the RV CO curve
determines the accuracy of prediction. However, this study demonstrated that our method was
good enough and practical to predict the hemodynamics on LVAD. Finally, we utilized
previously reported parameters for the slope of VR surface (24). Those parameters in humans
have yet to be investigated and may differ from dogs. All these limitations may have affected
the results, especially when the method is applied to predict the hemodynamics during LVAD
support in awake and closed-chest humans with intact reflexes. Further studies are required to
examine the application of the proposed framework in clinical settings.

Conclusions

In conclusion, the circulatory equilibrium framework is capable of quantitatively
predicting the hemodynamic impact of LVAD. Simulation studies and analytical solutions
from the circulatory equilibrium framework clarified how LVAD support affects
hemodynamics, especially in the presence of RV dysfunction. This provides physiological insights on the hemodynamics during LVAD support and contributes to safe management of LV failure in patients undergoing LVAD implantation.

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DISCLOSURE:

The authors declare no conflicts of interest, financial or otherwise.

AUTHOR CONTRIBUTIONS:
Authors contributions: T. K., K. S., T. S., T. I., T. K., H. T. and K. S. contributed to the conception and design of research; T. K., K. S., T. S., K. S., T. A. and M. I. performed experiments; T. K., K. S., T. S., K. S., T. I., T. K., H. T. and K. S. analyzed data, and interpreted results of experiments; T. K. wrote the manuscript; K. S., T. S., K. S., T. A., M.I., T.I., T. K., H. T. and K. S. revised the manuscript critically. All authors approved the final version of the manuscript;
Based on the ventricular arterial coupling concept, Uemura et al. (23, 24) previously derived a mathematical model of the cardiac output (CO) curve expressed as a logarithmic function. For further simplicity, we used one parameter logarithmic function to predict the hemodynamics on left ventricular assist device (LVAD) in this study.

\[
CO = S\{ln(P_{AT})\} \quad \text{Eq. 1a}
\]

where \(S\) is a parameter of the heart consisting of diastolic stiffness, heart period (T), end-systolic elastance \((E_s)\) and effective arterial elastance \((E_a)\); and \(P_{AT}\) is atrial pressure. Incorporating the downstream pressure shifts the \(E_a\) line upward and decreases stroke volume (SV) as shown in Figure 7. The reduction in SV (\(\Delta SV\)) is geometrically estimated as follows.

\[
P_d = \Delta SV(E_s + E_a) \quad \text{Eq. 2a}
\]

where \(P_d\) is the downstream pressure. Rearranging Eq. 2a results in the following:

\[
\Delta SV = \frac{P_d}{E_s + E_a} \quad \text{Eq. 3a}
\]

Dividing \(\Delta SV\) by \(T\) yields a decrease in CO (\(\Delta CO\)):

\[
\Delta CO = \frac{1}{T} \cdot \frac{P_d}{E_s + E_a} P_d \quad \text{Eq. 4a}
\]

A previous study showed the following (16, 20).

\[
E_a = \frac{R}{T} \quad \text{and} \quad EF_e = \frac{E_s}{E_s + E_a}
\]

where \(R\) is vascular resistance and \(EF_e\) is effective ejection fraction. Substituting these into Eq. 4a yields:

\[
\Delta CO = \frac{1}{R} \cdot \frac{E_a}{E_s + E_a} P_d = \frac{1-EF_e}{R} P_d \quad \text{Eq. 5a}
\]

Thus, using Eqs. 1a and 5a, CO is expressed as a function of the downstream pressure.

\[
CO = S\{ln(P_{AT})\} - \frac{1-EF_e}{R} P_d \quad \text{Eq. 6a}
\]

Substituting the parameters in Eq. 6a with right ventricular (RV) and pulmonary circulation
parameters yields the RV CO curve as follows.

\[ CO_R = S_R \{ \ln(P_{RA}) \} - \frac{(1-RVEF_e)P_{LA}}{R_p} \]  
Eq. 2

where \( S_R \) is the logarithmic slope of RV CO curve, \( RVEF_e \) is RV effective ejection fraction and \( R_p \) is pulmonary vascular resistance.

APPENDIX 2

Our research group has characterized the vascular system using a distributed resistance-compliance model (17, 18, 22, 23, 24). The stressed blood volume in systemic (\( V_s \)) and pulmonary (\( V_p \)) circulation can be expressed as follows.

\[ V_s = CO_v W_s + P_{RA} C_s \]  
Eq. 7a

\[ V_p = CO_v W_p + P_{LA} C_p \]  
Eq. 8a

where \( CO_v \) is venous return, \( W_s, W_p, C_s \) and \( C_p \) are vascular parameters. Adding Eqs. 7a and 8a, and substituting total stressed volume by \( V \) (=\( V_s + V_p \)) yields

\[ CO_V = \frac{V}{W} - G_s P_{RA} - G_p P_{LA} \]  
Eq. 3

APPENDIX 3

In the circulatory equilibrium framework under LVAD support, analytical solution of Eqs. 1–3 yields the relationship between \( P_{RA} \) and LVAD flow (\( LVAD_F \)) as follows.

\[ S_R \{ \ln(P_{RA}) \} + \frac{G_s}{G_p} \cdot \frac{1}{T \cdot RVE_{es} + R_p} P_{RA} \]

\[ = \frac{1}{G_p} \cdot \frac{1}{T \cdot RVE_{es} + R_p} \cdot \frac{V}{W} + LVAD_F (1 - \frac{1}{G_p} \cdot \frac{1}{T \cdot RVE_{es} + R_p}) \]  
Eq. 9a

Since the left-hand side is a monotonically increasing function of \( P_{RA} \), LVAD flow
increases $P_{RA}$ only when the following condition is met.

$$\frac{1}{\alpha_p} \cdot \frac{1}{T'RVE_{es} + R_p} < 1 \quad \text{Eq. 10a}$$
REFERENCES


10. Matthews JC, Koelling TM, Pagani FD, and Aaronson KD. The right ventricular failure risk score a pre-operative tool for assessing the risk of right ventricular failure in


16. Sagawa K, Maughan WL, Suga H, Sunagawa K. *Cardiac Contraction and Pressure-


**FIGURE LEGENDS**

**Figure 1.** Circulatory equilibrium diagrams (extended Guyton’s model) with left ventricular assist device (LVAD) off (A) and LVAD on (B). Cardiac output (CO), right atrial pressure (P_{RA}), and left atrial pressure (P_{LA}) at equilibrium are given by the intersection between the integrated CO curve (bold black curve) and venous return surface (shaded surface). The integrated CO curve is projected on each CO-P_{LA}, CO-P_{RA} and P_{LA}-P_{RA} planes (thin black lines). LVAD shifts the equilibrium point from the open circle (○) to closed circle (●), illustrating that LVAD increases CO and lowers P_{LA} but has little effect on P_{RA}.

**Figure 2.** Representative time series of hemodynamic changes by step-wise decreases of the flow of left ventricular assist device (LVAD) (LVADF). Left ventricular (LV) cardiac output (CO), arterial pressure (AP), left atrial pressure (P_{LA}), right atrial pressure (P_{RA}), and heart rate (HR) are shown. Because LVAD flow is continuous, LVADF, LV CO and AP are illustrated as raw data. Bold lines in P_{LA} and P_{RA} indicate the average of each time series.

**Figure 3.** Individual time series of data from all six dogs. Each panel shows the flow of left ventricular assist device (LVADF), right atrial pressure (P_{RA}) or left atrial pressure (P_{LA}) in each dog. Data segments enclosed by dotted lines are steady-state data used for analysis.

**Figure 4.** A theoretical and experimental design used in this study to predict total cardiac output (CO) and right atrial pressure (P_{RA}) under left ventricular assist device (LVAD) for given left atrial pressure (P_{LA}). Total CO and P_{RA} for given P_{LA} are predicted using the predetermined logarithmic slope of right heart CO curve (S_{R}) and stressed volume (V) based
on the circulatory equilibrium framework. The predicted total CO and $P_{RA}$ are then compared with those measured. MI, myocardial infarction; LV CO, left ventricular cardiac output; CO$_R$, right heart cardiac output; COV, amount of venous return

Figure 5. Relationship between predicted and measured total cardiac output (CO, A) as well as predicted and measured right atrial pressure ($P_{RA}$, B) for given left atrial pressure. Each graph represents pooled data from 31 data sets (closed circle, ●) from 6 dogs. Predicted total CO [standard error of estimate (SEE)=5.59 mL/min/kg] and $P_{RA}$ [$\text{SEE}=0.307 \text{ mmHg}$] matched well with those measured. Solid line represents the line of identity ($y=x$).

Figure 6. Impact of left ventricular assist device (LVAD) on right atrial pressure ($P_{RA}$). Effects of changes in right ventricular end-systolic elastance (RVE$_{es}$) (A) and pulmonary vascular resistance ($R_p$) (B). Left ventricle ejects in the light gray surface (partial LVAD), and stops ejecting in the dark gray surface (total LVAD). The bold line represents the borderline between partial and total LVAD support. Normal RVE$_{es}$ and $R_p$ are 0.07 mmHg/ml/kg and 0.1 mmHg/mL $\cdot$ min$^{-1}$ $\cdot$ kg$^{-1}$; that is $\text{RVEF}_e = 0.6$, respectively.

Figure 7. Scheme to incorporate downstream pressure ($P_d$) into ventricular arterial coupling. $P_d$ shifts the effective arterial elastance ($E_a$) line upward (dashed to solid line). The intersection between the end-systolic elastance (E$_{es}$) and the $E_a$ changes from the open circle (○) to closed circle (●). The impact of $P_d$ on stroke volume ($\Delta SV$) is graphically illustrated as changes in volume (shaded area).
Table 1: Hemodynamics at baseline and after myocardial infarction (MI) in six dogs

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>after MI</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MAP (mmHg)</td>
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<tr>
<td></td>
<td>HR (/min)</td>
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<tr>
<td></td>
<td>CO (mL/min/kg)</td>
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<td>PLA (mmHg)</td>
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<td>PRA (mmHg)</td>
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<td>84.8, 22.7</td>
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<td>5</td>
<td>88.5, 4.44</td>
<td>60.5, 21.2</td>
</tr>
<tr>
<td>6</td>
<td>98, 2.47</td>
<td>70.2, 1.53</td>
</tr>
</tbody>
</table>

Mean (±SD): 94.3 ± 7.96, 157 ± 4.95, 99.6 ± 8.34, 5.33 ± 1.23, 3.20 ± 0.445, 96.3 ± 22.7, 131* ± 19.6, 75.6* ± 21.2, 14.5* ± 2.47, 4.44 ± 1.53

MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; P_LA, left atrial pressure; P_RA, right atrial pressure; SD, standard deviation. *Significant difference compared with baseline (P < 0.05, paired t test)
Table 2: Calculated $S_R$ using Eq. 2 and $V$ using Eq. 3 (see Methods).

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<tr>
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<td>30.4</td>
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</table>

Mean (±SD) 95.1 (16.7) 27.5 (5.43)

$S_R$, a logarithmic slope of the right ventricular cardiac output curve (APPENDIX 1 shows the constituents of $S_R$); $V$, stressed blood volume; SD, standard deviation
Impact of LVAD on $P_{RA}$

**A**

- $P_{RA}$ (mmHg)
- LVAD$_F$ (ml/min/kg)
- RV $E_{es}$ (mmHg/ml/kg)

**B**

- $P_{RA}$ (mmHg)
- LVAD$_F$ (ml/min/kg)
- $R_P$ (mmHg/ml·min$^{-1}$·kg$^{-1}$)
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