Prediction of circulatory equilibrium in response to changes in stressed blood volume

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Uemura, Kazunori, Toru Kawada, Atsunori Kamiya, Takeshi Aiba, Ichiro Hidaka, Kenji Sunagawa, and Masaru Sugimachi. Prediction of circulatory equilibrium in response to changes in stressed blood volume. Am J Physiol Heart Circ Physiol 289: H301–H307, 2005.—Accurate prediction of cardiac output (CO) and cardiac filling pressures after therapeutic interventions is indispensable for optimal management and improved prognosis of patients with compromised hemodynamics (4, 5, 13, 23). In the 1980s, Sunagawa’s group (20, 27) extended the framework of circulatory equilibrium of Guyton and co-workers (9, 10) to analyze complicated hemodynamic conditions such as left-sided heart failure. The extended framework is composed of a venous return surface representing the venous return of the systemic and pulmonary circulations and an integrated CO curve representing the pumping ability of the left and the right heart (Fig. 1) (27). The intersection point of the venous return surface and the integrated cardiac curve gives the equilibrium CO, left atrial pressure (P_LA), and right atrial pressure (P_RA). Changes in stressed blood volume shift the venous return surface upward or downward, altering the equilibrium point accordingly.

Our previous study (29) experimentally validated that venous return is a linear function of P_LA and P_RA and that this relation is expressed by a flat surface, i.e., the venous return surface (Fig. 1). In addition, because of the small intra- and inter-animal variability in the slope of the surface, only a single set of CO, P_LA, and P_RA values is sufficient to estimate the venous return surface. Furthermore, it is possible to predict how the venous return surface shifts in response to a known amount of change in the stressed blood volume. These findings suggest that if the integrated CO curve can be estimated from a single set of CO, P_LA, and P_RA values, it is possible to predict hemodynamics in response to various therapeutic interventions, which induce changes in loading condition or in the pumping ability of the heart (29). The present study was therefore undertaken to develop a method to estimate the integrated CO curve from a single set of CO, P_LA, and P_RA values and to examine whether intersection of the integrated CO curve and the venous return surface thus estimated predicts hemodynamics in response to extensive changes in the stressed blood volume. Using our model, we were able to estimate the CO curve and predict the hemodynamics in anesthetized, open-chest dogs under conditions of left heart failure as well as normal cardiac function.

METHODS

Integrated CO Curve

In our previous study, we showed that CO is closely related to P_LA or P_RA by a three-parameter logarithmic function (29)

\[
CO = S_L \times \ln (P_LA - F_L) + H_L \tag{1}
\]

\[
CO = S_R \times \ln (P_RA - F_R) + H_R \tag{2}
\]

where S_L, F_L, and H_L and S_R, F_R, and H_R are parameters.

To estimate the integrated CO curve from a single set of CO, P_LA, and P_RA values, we fixed the F and H parameters according to the following rationale. It is well known that the CO curve varies widely with changes in ventricular contractility, heart rate, vascular resistance, and diastolic stiffness (8, 10, 20, 21, 24, 30). As shown in the APPENDIX, these factors are mainly included in the S parameter rather than in the F or H parameters. The S parameter thus comprehensively

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represents the pumping ability of the left or right heart. Therefore, we hypothesized that variations in the CO curve can be explained exclusively by the $S$ parameter. Once standard values of the $F$ and $H$ parameters are determined, we can estimate the integrated CO curve by calculating the $S$ parameter from a single set of CO, PLA, and PRA values.

Animal Preparation

We used 15 adult mongrel dogs of either gender (20–30 kg body wt). Care of the animals was in strict accordance with the “Guiding Principles for the Care and Use of Animals in the Field of Physiological Sciences” approved by the Physiological Society of Japan. Anesthesia was induced with pentobarbital sodium (25 mg/kg), and endotracheal intubation was performed. Isoflurane (1.5%) was continuously inhaled to maintain an appropriate level of anesthesia during the experiment. Catheters (6-Fr) were placed in the right femoral artery and vein for withdrawal of blood and for administration of drugs and fluids. To stabilize autonomic tone, we isolated the carotid sinuses bilaterally and maintained the intrasinus pressure constant at 120 mmHg (22). The cervical vagosympathetic trunks were cut. Systemic arterial pressure was measured by a catheter-tipped micromanometer (model PC-751, Millar Instruments, Houston, TX) placed in the ascending aorta via the right carotid artery. After a median sternotomy, a small pericardial incision was made at the level of the aortic root. An ultrasonic flowmeter (model 20A594, Transonics, Ithaca, NY) was placed around the ascending aorta via the incision to measure CO. Fluid-filled catheters were placed in the left and right atria via the incision to measure $P_{LA}$ and $P_{RA}$, respectively. They were connected to pressure transducers (model DX-200, Nihon Kohden, Tokyo, Japan). The junction between the inferior vena cava and the right atrium was taken as the reference point for zero pressure (22).

Experimental Protocol

Under normal control conditions, we first infused $250 \text{ ml} \times 10\%$ dextran solution via the right femoral vein. We withdrew blood from the femoral artery in steps of $2\text{ ml/kg}$ to a total volume of $16–22\text{ ml/kg}$ (8–11 steps per animal). In each step, after waiting for 1 min, we recorded CO, $P_{LA}$, and $P_{RA}$ for $10\text{ s}$ (Fig. 2). We assumed that this volume reduction alters only the stressed blood volume of the systemic and pulmonary circulation. Because we isolated the baroreceptors, baroreflex-related changes in unstressed blood volume were negligible. We defined the reference values of CO, $P_{LA}$, and $P_{RA}$ when half of the volume reduction was attained.

To create left ventricular failure, we embolized the left circumflex coronary artery with $90-\mu\text{m}$-diameter glass microspheres (28). We adjusted the number of microspheres injected so as to increase $P_{LA}$ by 20 mmHg. We then volume loaded the animals and repeated the protocol described above.

The data were recorded while respiration was temporarily suspended at end expiration. All analog signals were digitized at 200 Hz with a 12-bit analog-to-digital converter (model AD12-16UE, Contec, Osaka, Japan) using a dedicated laboratory computer system (model MA 20V, NEC, Tokyo, Japan) and were stored on a hard disk for subsequent analysis. All the recorded data were averaged over 5 s. All data, except pressure data, were normalized to individual body weight.
Data Analysis

Determination of standard values of F and H parameters. We determined the standard values of the F and H parameters in seven randomly selected dogs (group 1). Using the least-squares method, we fitted the PL_A-CO and PR_A-CO relations obtained under normal conditions to the three-parameter logarithmic functions (Eqs. 1 and 2).

We averaged the F and H values of the left and right heart for the seven animals. The averaged values were used as the standard F and H parameters in subsequent analyses.

Estimation of the integrated CO curve. Using the standard F and H parameters, we examined whether we could estimate the integrated CO curve from a single set of CO, PL_A, and PR_A values. For each animal in group 1, we calculated the S parameter by substituting the reference values of CO, PL_A, and PR_A into Eqs. 1 and 2. This calculation was done under normal and heart failure conditions. After calculation of the S parameter, the PL_A and PR_A measured in each step were substituted into Eq. 1 to estimate CO of the left heart and into Eq. 2 to estimate CO of the right heart. The estimated and measured CO were compared by linear regression analyses.

Prediction of circulatory equilibrium. In the other eight dogs (group 2), we estimated the integrated CO curve and venous return surface. The CO curve was estimated as described above using the standard F and H parameters. Venous return surface was estimated according to our previous work (29) as follows

\[
CO_V = V/0.129 - 19.61PR_A - 3.49PL_A
\]  

(3)

where V is the stressed blood volume, CO_V is the integrated venous return, and 0.129 (min), 19.61 (ml-min⁻¹-kg⁻¹-mmHg⁻¹), and 3.49 (ml-min⁻¹-kg⁻¹-mmHg⁻¹) are standard parameters characterizing the venous return surface (29). The reference CO, PL_A, and PR_A values were used to calculate V, which served as the reference stressed volume.

With altered V (from +8 to −8 ml/kg of the reference value), we numerically determined the intersection of the venous return surface (Eq. 3) and the integrated CO curve (Eqs. 1 and 2) to predict CO, PL_A, and PR_A. The predicted CO, PL_A, and PR_A were compared with the measured values. We considered the change in V (±8 ml/kg) to be substantial relative to the physiological stressed blood volume (±25 ml/kg) (17).

Statistics

Group data are expressed as means (SD). The level of statistical significance was defined as P < 0.05. To test the goodness of fit, the coefficient of determination (r²) and the standard error of estimate (SEE) were calculated.

RESULTS

Determination of the Standard Parameters

Figure 3 shows the measured PL_A-CO and PR_A-CO relations in a representative dog. CO increases in response to increases in PL_A or PR_A by the Frank-Starling mechanisms. These relations could be fitted to the three-parameter logarithmic function as follows: CO = 66.7[ln(PL_A − 2.08)] + 0.1], r² = 0.98, SEE = 5.9 ml-min⁻¹-kg⁻¹ (Fig. 3A) and CO = 112.7[ln(PR_A − 1.39)] + 0.19], r² = 0.98, SEE = 5.5 ml-min⁻¹-kg⁻¹ (Fig. 3B).

Table 1 summarizes the results of the fit in seven dogs. Coefficients of determination were high for the left heart (r² = 0.95–0.99) and the right heart (r² = 0.90–0.99). These results indicated that the logarithmic functions represented the CO curves of the left and right heart with good accuracy. The averaged F and H values (F_L = 2.03 mmHg, H_L = 0.80, F_R = 2.13 mmHg, and H_R = 1.90) for seven animals were used as standard values in subsequent analyses.

Table 1. Fit of CO-PL_A and CO-PR_A relations to three-parameter logarithmic functions

<table>
<thead>
<tr>
<th>Dog</th>
<th>S_L</th>
<th>F_L</th>
<th>H_L</th>
<th>r²</th>
<th>SEE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58.1</td>
<td>1.27</td>
<td>0.61</td>
<td>0.98</td>
<td>4.3</td>
</tr>
<tr>
<td>2</td>
<td>24.4</td>
<td>2.03</td>
<td>2.71</td>
<td>0.95</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>108.4</td>
<td>0.00</td>
<td>0.67</td>
<td>0.95</td>
<td>5.6</td>
</tr>
<tr>
<td>4</td>
<td>66.7</td>
<td>2.08</td>
<td>0.08</td>
<td>0.98</td>
<td>5.9</td>
</tr>
<tr>
<td>5</td>
<td>105.6</td>
<td>2.30</td>
<td>0.02</td>
<td>0.99</td>
<td>5.0</td>
</tr>
<tr>
<td>6</td>
<td>73.5</td>
<td>2.21</td>
<td>0.59</td>
<td>0.99</td>
<td>2.5</td>
</tr>
<tr>
<td>7</td>
<td>42.0</td>
<td>4.32</td>
<td>2.30</td>
<td>0.98</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Mean (SD): 68.4 (30.9), 2.03 (1.29), 0.80 (1.25), 0.97 (4.5)

<table>
<thead>
<tr>
<th>Dog</th>
<th>S_R</th>
<th>F_R</th>
<th>H_R</th>
<th>r²</th>
<th>SEE</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>46.7</td>
<td>2.12</td>
<td>2.34</td>
<td>0.98</td>
<td>4.7</td>
</tr>
<tr>
<td>2</td>
<td>33.9</td>
<td>1.50</td>
<td>2.50</td>
<td>0.96</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>64.1</td>
<td>2.10</td>
<td>2.10</td>
<td>0.90</td>
<td>8.2</td>
</tr>
<tr>
<td>4</td>
<td>112.7</td>
<td>1.39</td>
<td>0.19</td>
<td>0.98</td>
<td>5.5</td>
</tr>
<tr>
<td>5</td>
<td>101.8</td>
<td>1.39</td>
<td>0.92</td>
<td>0.99</td>
<td>4.6</td>
</tr>
<tr>
<td>6</td>
<td>80.6</td>
<td>3.07</td>
<td>1.59</td>
<td>0.99</td>
<td>2.8</td>
</tr>
<tr>
<td>7</td>
<td>37.1</td>
<td>3.33</td>
<td>3.69</td>
<td>0.94</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Mean (SD): 68.1 (31.3), 2.13 (0.8), 1.90 (1.14), 0.96 (5.1)

S_L and S_R (ml-min⁻¹-kg⁻¹), F_L and F_R (mmHg), and H_L and H_R (unitless), parameters of the logarithmic function for left and right hearts, respectively (see METHODS for calculations); r², coefficient of determination; SEE, standard error of the estimate (ml-min⁻¹-kg⁻¹).
Estimation of the Integrated CO Curve

Figure 4 shows the estimated CO curves under normal and heart failure conditions for a single animal. From the reference values, we calculated individual values of the $S$ parameter. Under normal conditions, the estimated CO curve accurately coincided with the measured points in the left and the right heart. A good agreement was also observed under left ventricular failure.

Figure 5 demonstrates the relation between estimated and measured CO of pooled data from seven animals (group 1). The estimated CO agreed with the measured CO in the left and right heart.

Prediction of Circulatory Equilibrium

Figure 6 illustrates the accuracy of prediction of hemodynamics in response to changes in stressed blood volume (8 dogs, group 2). Figure 6A shows the relation between predicted and measured CO. CO was predicted accurately over a wide range of CO values from 30 to 200 ml·min$^{-1}$·kg$^{-1}$. A small intercept value with a slope near unity also indicates the accuracy of prediction. Figure 6B shows the accuracy of the $P_{LA}$ prediction. Although variability increased in the high pressure range (>20 mmHg), the prediction was reasonably accurate. Similarly, $P_{RA}$ was also predicted with reasonable accuracy (Fig. 6C).

DISCUSSION

The results of this study indicate that once a single set of steady-state CO, $P_{LA}$, and $P_{RA}$ values is available, it is possible to predict the changes in hemodynamic variables resulting from a known amount of change in stressed blood volume. This prediction can be very helpful in management of patients under unstable hemodynamic conditions (13, 23).

Estimation of the Integrated CO Curve

We have shown that the integrated CO curve can be estimated with reasonable accuracy under normal and heart failure conditions (Figs. 4 and 5). By fixing the $F$ and $H$ parameters and by ascribing the changes in the CO curve exclusively to the $S$ parameter, we were able to estimate the integrated CO curve from a single set of hemodynamic measurements. As shown in the Appendix, the $F$ and $H$ parameters are mainly related to the end-diastolic pressure-volume relation (Eq. A4). In advanced cardiac disorders seen clinically, the end-diastolic pressure-volume relation may vary drastically (6, 7). Hypertensive or idiopathic cardiomyopathy sometimes induces severe ventricular hypertrophy, thereby significantly altering the diastolic ventricular pressure-volume relation (14). In such cases, it may be desirable not to use fixed values but, rather, to estimate $F$ and $H$ parameters in individual patients. The cardiovascular properties shown in Eq. A4 can be estimated noninvasively under a steady-state hemodynamic condition (3, 12). Integration of these properties into our method may allow independent estimation of the three parameters in individual patients.

The following validations indicate that our mathematical model of the CO curve and its estimation are consistent with previous investigations. First, on the basis of Eq. A4 (see
ular end-diastolic pressure to mean left atrial pressure. Diastolic pressure-volume relation of the left ventricle; the left heart. The values of the cardiovascular properties were calculated the three parameters in the logarithmic function for the left heart in dogs under various cardiac conditions (control, coronary occlusion, and nitroprusside infusion under Table 1). Second, Pouleur et al. (19) examined the CO curve (1.14) were compatible with those obtained in our experiment (Fig. 6). Dashed line, line of identity. Prediction was done by intersecting the venous return surface and the integrated CO curve, both of which were estimated from a set of reference hemodynamic values. Regression analysis (solid line) reveals that predicted CO \((y = 0.93x + 6.5, n = 128, r^2 = 0.96, \text{SEE} = 7.5 \text{ ml min}^{-1} \cdot \text{kg}^{-1})\), \(P_L\) \((y = 0.90x + 0.5, n = 128, r^2 = 0.93, \text{SEE} = 1.4 \text{ mmHg})\), and \(P_R\) \((y = 0.87x + 4, n = 128, r^2 = 0.91, \text{SEE} = 0.4 \text{ mmHg})\) agree reasonably well with measured values.

Clinical Application of the Framework of Circulatory Equilibrium

Cardiac patients frequently receive empirical fluid challenges to treat low CO, unexplained hypotension, and oliguria (1, 32). Such empirical challenges sometimes exert deleterious effects by excessive volume expansion (1, 32). Our framework is free of such problems, because we can accurately estimate the stressed blood volume of the patient and predict hemodynamics resulting from the volume challenge, once we measure a single set of steady-state CO, \(P_L\), and \(P_R\) values with, for example, Swan-Ganz catheters (2).

The outcome of acute or chronic heart failure has been related to the severity of reduced CO and elevated left ventricular filling pressure (4, 5, 13, 23). Several studies, however, indicate that patients with Forrester class IV hemodynamics are not necessarily condemned to a class IV prognosis. Even if the initial hemodynamics are classified as class IV, patients showing reduction in filling pressure after intensive medical therapy have a better prognosis than those without reduction in filling pressure (13, 23). With use of our framework for guidance, proper management of low CO and elevated filling pressures would improve the prognosis of such patients.

In clinical settings, the reference point for zero pressure is related to the severity of reduced CO and elevated left ventricular filling pressure (4, 5, 13, 23). Several studies, however, indicate that patients with Forrester class IV hemodynamics are not necessarily condemned to a class IV prognosis. Even if the initial hemodynamics are classified as class IV, patients showing reduction in filling pressure after intensive medical therapy have a better prognosis than those without reduction in filling pressure (13, 23). With use of our framework for guidance, proper management of low CO and elevated filling pressures would improve the prognosis of such patients.

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Limitations of the Study

All the experiments of this study were conducted in anesthetized, open-chest dogs. Anesthesia and surgical trauma significantly affect the cardiovascular system (31). Whether this equilibrium framework can be applied to conscious, closed-chest animals (including humans) remains to be tested.
We isolated baroreceptors and fixed the autonomic tone in this study. This was necessary, because the baroreflex alters the CO curve and venous return surface through its effects on stressed blood volume, vascular resistance, heart rate, and cardiac contractility (8, 22). How changes in autonomic tone under the closed-loop condition affect the accuracy of hemodynamic prediction remains to be investigated.

**Conclusion**

The integrated CO curve can be estimated on the basis of a single set of hemodynamic measurements (CO, PLa, and PRA). The integrated CO curve thus estimated enables accurate prediction of hemodynamics (CO, PLa, and PRA) after extensive changes in stressed blood volume during heart failure and normal cardiac function.

**APPENDIX**

**Mathematical modeling of the CO curve.** We derived the relation between CO and atrial pressure on the basis of the ventricular pressure-volume relation framework (15, 25) and the ventricular-arterial coupling framework (26) as follows.

The relation between the stroke volume (SV) and the ventricular end-diastolic volume (Ved) has been approximated with reasonable accuracy as

$$SV = \frac{TE_{es}}{TE_{es} + R} \times (V_{ed} - V_{0}) \tag{A1}$$

where $es$ is the slope (elastance), $V_0$ is the volume axis intercept of the ventricular end-systolic-pressure-volume relation, $T$ is the heart period, and $R$ is the arterial resistance (20, 25, 26). Dividing SV by $T$, CO can be expressed as

$$CO = \frac{TE_{es}}{TE_{es} + R} \times (V_{ed} - V_{0}) \tag{A2}$$

$V_{ed}$ can be interrelated with end-diastolic pressure (P_{ed}) by

$$P_{ed} = \alpha V_{ed} + \beta \tag{A3}$$

where $k$, $\alpha$, and $\beta$ are constants (6, 7). If we approximate $P_{ed}$ by a scaled mean atrial pressure (P_{Aa}), $\gamma P_{Aa}$ ($\gamma$ is a proportionality constant), Eq. A2 can be rewritten as

$$CO = \frac{1}{k} \frac{TE_{es}}{TE_{es} + R} \times \left[ \ln \left( \frac{P_{Aa} - \beta}{\gamma} \right) + \ln \left( \frac{\gamma}{\alpha} \right) - kV_{0} \right] \tag{A4}$$

which can be simplified by lumping parameters for cardiovascular system properties into three constants, $S$, $F$, and $H$

$$CO = S \times \left[ \ln (P_{Aa} - F) + H \right] \tag{A5}$$

**GRANTS**

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