A novel framework of circulatory equilibrium

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A novel framework of circulatory equilibrium. Am J Physiol Heart Circ Physiol 286: H2376–H2385, 2004. First published February 5, 2004; 10.1152/ajpheart.00654.2003.—A novel framework of circulatory equilibrium was developed by extending Guyton’s original concept. In this framework, venous return (COv) for a given stressed volume (V) was characterized by a flat surface as a function of right atrial pressure (P RA ) and left atrial pressure (P LA ) as follows: COv = V/W – GSPRA – GPPLA, where W, GS, and GP denote linear parameters. In seven dogs under total heart bypass, COv, P RA, P LA, and V were varied to determine the three parameters in each animal with use of multivariate analysis. The coefficient of determination (r² = 0.92–0.99) indicated the flatness of the venous return surface. The averaged surface was COv = V/0.129 – 19.61P RA – 3.49P LA. To examine the invariability of the surface parameters among animals, we predicted the circulatory equilibrium in response to changes in stressed volume in another 12 dogs under normal and heart failure conditions. This was achieved by equating the standard surface with the individually measured cardiac output (CO) curve. In this way, we could predict CO [y = 0.90x + 5.6, r² = 0.95, standard error of the estimate (SEE) = 8.7 ml·min⁻¹·kg⁻¹], P RA (y = 0.96x, r² = 0.98, SEE = 0.2 mmHg), and P LA (y = 0.89x + 0.5, r² = 0.98, SEE = 0.8 mmHg) reasonably well. We conclude that the venous return surface accurately represents the venous return properties of the systemic and pulmonary circulations. The characteristics of the venous return surface are invariant enough among animals, making it possible to predict circulatory equilibrium, even if those characteristics are unknown in individual animals.

venous return; cardiac output; hemodynamics

THE FRAMEWORK FOR CIRCULATORY EQUILIBRIUM was pioneered by Guyton and associates in the 1950s (14–17). They characterized the venous return properties of the systemic vein by the venous return curve and the apparent pumping function of the cardiothoracic compartment by the cardiac output (CO) curve (Fig. 1A). The intersection of the two curves determines equilibrium CO and right atrial pressure (P RA ) (14). This concept clearly defined the circulatory equilibrium under rather simple pathophysiological conditions, such as hemorrhage and exercise, and deepened our understanding of control mechanisms of CO. However, because the original framework lumped various subsystem components, such as the right ventricle, pulmonary vascular system, and left ventricle, into a single cardiothoracic compartment, the lack of consideration of the venous return properties of the pulmonary circulation and the pumping ability of the individual ventricles makes it difficult to define the circulatory equilibrium under more complex conditions such as unilateral ventricular failures, which are often seen in clinical settings (2). In other words, redistribution of blood between the systemic and pulmonary circulations cannot be defined by their original framework.

To deal with the blood redistribution, Guyton et al. (15) modified the original framework and developed a two-compartment model. However, the analysis of hemodynamics by this two-compartment model is rather complex. In this model, left ventricular CO is determined as the equilibrium between left ventricular CO and pulmonary venous return. Similarly, right ventricular CO is determined as the equilibrium between right ventricular CO and systemic venous return. They derived equilibrium CO of the total circulation by iteratively redistributing stressed blood volume between the two compartments until the CO of the two compartments matched (15). The complexity of the analysis makes application to hemodynamic analysis impractical in the clinical setting.

To overcome the limitation of the framework of Guyton et al., Sunagawa et al. (24, 30) proposed a novel framework of circulatory equilibrium. In the framework of Sunagawa et al., the venous return properties of the systemic and pulmonary circulations are integrated to deal with blood volume redistribution between the two circulations. A mathematical analysis using a simple linearized model (see APPENDIX ) indicated that venous return (COv) for a given stressed volume (V) forms a flat surface (venous return surface) as a function of P RA and left atrial pressure (P LA ; Fig. 1B). This is formulated as follows

COv = V/W – GSPRA – GPPLA

where W denotes the parameter that defines the maximum venous return for the given stressed volume and GS and GP are slopes of venous return with respect to P RA and P LA, respectively. As we show in the APPENDIX , these three linear parameters reflect vascular compliance and resistance. The circulatory equilibrium is given as the intersection of the venous return surface and the integrated CO curve, defined as a function of P RA and P LA, thereby representing bilateral ventricular function (24, 30). Changes in V shift the venous return surface upward and downward, thereby altering the equilibrium point accordingly.

This extended framework of Guyton et al. allows us to predict circulatory equilibrium, even in the presence of unilateral ventricular dysfunction, making it useful in clinical settings where complex pathophysiologies must be interpreted. With this framework for guidance, proper management of low CO and/or pulmonary congestion should improve the prognosis of cardiac patients (10, 21). However, the characteristics of...
the venous return surface have never been experimentally studied. Therefore, it is not known whether the simple flat surface represents the integrated venous return of the pulmonary and systemic circulations.

The purpose of this investigation was to experimentally validate the concept of the venous return surface (24, 30). To examine the characteristics of the venous return surface, we determined $W$, $G_s$, and $G_p$ using a total heart bypass preparation. To examine the invariability of the characteristics of the venous return surface under a range of stressed volumes among animals, we predicted the circulatory equilibrium from the intersection of the measured integrated CO curve and the venous return surface, as defined by the standard set of parameters. The results indicated that the venous return surface was indeed remarkably flat. Its parameter values were invariable enough among animals that circulatory equilibrium for a given integrated CO curve could be predicted under unilateral heart failure as well as during normal cardiac function.

METHODS

Preparation

Care of the animals was in strict accordance with the guiding principles of the Physiological Society of Japan. We used seven adult male mongrel dogs ($26.3 \pm 2.4$ kg) for examination of the venous return surface and another 12 male dogs ($26.1 \pm 3.2$ kg) for measurement of the integrated CO curve to predict circulatory equilibrium.

Dogs were anesthetized with pentobarbital sodium (25 mg/kg) and intubated endotracheally. Urethane (250 mg/ml) and $\alpha$-chlooralose (40 mg/ml) were continuously infused (0.3 ml·kg$^{-1}$·h$^{-1}$) to maintain an appropriate level of anesthesia during the experiments. A 5F catheter was placed in the right femoral vein for administration and withdrawal of blood, fluids, and drugs. To stabilize autonomic tone, we isolated the carotid sinus bilaterally and kept the intrasinus pressure constant (120 mmHg) (27). The cervical vagosympathetic trunks were cut to eliminate their buffering effects. Systemic arterial pressure was measured through a fluid-filled catheter placed in the thoracic aorta via the left common carotid artery and connected to a pressure transducer (model DX-200, Nihon Kohden). After a median sternotomy, the heart was suspended in a pericardial cradle. Fluid-filled catheters were placed in the right and left atrium and in the main trunk of the pulmonary artery for measurement of $P_{RA}$, $P_{LA}$, and pulmonary arterial pressure, respectively. The junction of the vena cava and the right atrium was taken as the reference point for zero pressure.

To examine the venous return surface, we performed a total heart bypass (Fig. 2). The perfusion system was initially primed with ~200 ml of heparinized blood from another dog. Two roller pumps (MERA) were used to control systemic and pulmonary flows. A systemic perfusion cannula was placed in the right common carotid artery. A draining cannula for the pulmonary circulation was introduced into the right ventricle through the right atrium. A pulmonary perfusion cannula was placed in the right common carotid artery. A draining cannula for the pulmonary circulation was inserted into the right ventricle through its free wall. A pulmonary perfusion cannula was placed in the pulmonary artery through the right ventricle. A draining cannula for the pulmonary circulation was introduced into the left ventricle via the apex. The flow rates of both pumps were measured by in-line electromagnetic flow probes (model MFV-2100, Nihon Kohden). The two probes were simultaneously calibrated using a graduated cylinder. Both pumps began with an initial flow rate of 80 ml·min$^{-1}$·kg$^{-1}$. Finally, umbilical tape was placed around the pulmonary artery to hold the pulmonary cannula was tightened, and the ascending aorta was clamped, thus switching to the total heart bypass. Ligation of the coronary arteries arrested the heart.

Figures 2. Schematic representation of experimental setup used to characterize the venous return surface. Systemic and pulmonary circulations are perfused by pumps 1 and 2, respectively. Venous outflow is drawn directly into the pumps without passing through a reservoir.
Experimental Protocol

Characterization of the venous return surface. After a stable condition was obtained, the flow rates of both pumps were varied stepwise from 40 to 100 ml min⁻¹ kg⁻¹ in 20 ml min⁻¹ kg⁻¹ increments (Fig. 3). At flow rates of 60 and 80 ml min⁻¹ kg⁻¹, we varied the blood volume distribution between the pulmonary and systemic circuits by transiently unbalancing the flow rates of the two pumps. Steady state was attained in each flow rate within 50 s. In each step, we measured pump flow rate and bilateral atrial pressure during temporary suspension of ventilation at end expiration. We obtained a total of six recordings in each dog. To estimate W, we removed or added blood volume by 5 to 4 ml/kg, which was assumed to alter only the stressed blood volume. Because we isolated the baroreceptors, baroreflex-related changes in unstressed volume were negligible. We then repeated the same protocol.

Measurement of the integrated CO curve for prediction of circulatory equilibrium. In six dogs, to alter CO over a wide range, we first infused ~200 ml of whole blood. We then withdrew blood in 2 ml/kg steps up to a total of 10–22 ml/kg (5–11 steps for a single animal) while measuring CO and bilateral atrial pressures (Fig. 4). As in the first protocol, we assumed that this volume reduction altered only the stressed blood volume of the systemic and pulmonary circulation. We defined the reference stressed volume when half of the infused blood was withdrawn. This reference was used when stressed volume was changed to predict circulatory equilibrium. In six other dogs, left ventricular failure was induced by embolization of the left circumflex coronary artery with glass microspheres (90 μm diameter) (35). We adjusted the number of microspheres to increase P LA by 20 mmHg. We then volume loaded the animals and repeated the same protocol.

Data Analysis

All analog signals were digitized at 200 Hz with a 12-bit analog-to-digital converter (Contec, Osaka, Japan) using a dedicated laboratory computer system; the data were then stored on a hard disk for subsequent analysis. All the recorded data were averaged over 5 s and expressed as means ± SD. All data, excluding pressure data, were normalized to individual body weight. The level of statistical significance was defined as P < 0.05.

Derivation of parameters of the venous return surface. We used the algebraic mean of the flow rates of pumps 1 and 2 as CO V. A multivariate linear regression was performed on a set of six recordings, with Eq. 1 used to derive G S and G P in each dog. We repeated the same analysis when the stressed volume was changed. Because changes in the stressed volume did not significantly affect G S or G P, we derived W as the ratio of changes in stressed volume to the amount of parallel shift of the venous return surface (see APPENDIX). To test the
goodness of fit of the multivariate regression equation as a representation of the venous return surface, the multiple coefficient of determination ($r^2$) and the standard error of estimate (SEE) were calculated. To estimate the error relative to the average value of the respective parameters, we derived coefficients of variation for $G_S$, $G_P$, and $W$.

**Prediction of Circulatory Equilibrium**

To characterize the CO curve for each animal as a function of $P_{RA}$ and $P_{LA}$, we fitted CO as a function of $P_{RA}$ using a three-parameter logarithmic curve

$$CO = a_R \ln (P_{RA} - \beta_R) + \gamma_R$$

and CO as a function of $P_{LA}$ using

$$CO = a_L \ln (P_{LA} - \beta_L) + \gamma_L$$

Coefficients of fitted logarithmic functions, $a_R$, $\beta_R$, and $\gamma_R$ and $a_L$, $\beta_L$, and $\gamma_L$, characterized the CO curve of the right and left heart, respectively. They were determined by the least-squares method (Fig. 5A).

To predict the equilibrium points for each animal, we used the standard set of parameters of the venous return surface derived from the first protocol to determine the venous return surface for a given change in stressed volume. We then numerically estimated the intersection of the venous return surface and the integrated CO curve given by Eqs. 2 and 3 (Fig. 5B). This was achieved by simultaneously solving Eqs. 1–3 for CO, $P_{LA}$, and $P_{RA}$. The predicted CO, $P_{RA}$, and $P_{LA}$ were compared with measured CO, $P_{RA}$, and $P_{LA}$.

**RESULTS**

**Venous Return Surface**

Figure 6 shows a representative venous return surface as a function of $P_{RA}$ and $P_{LA}$. All six points measured are aligned on a unique flat surface. The alignment is even clearer if the data points are viewed from a direction parallel to the surface (Fig. 6, inset). The six points obtained from each animal were closely aligned on a flat surface (Fig. 7). Table 1 summarizes the parameter values obtained from seven dogs. The fact that the multiple correlation of determination was close to unity ($r^2 = 0.92–0.99$), with a small SEE relative to the amount of venous return, suggested that the approximation of venous return by a flat surface was reasonably accurate.

Parameter values defining the venous return surface did not differ markedly among animals. Coefficients of variation of $W$, $G_S$, and $G_P$ were 38, 11, and 17%, respectively. From these data, we defined the standard venous return surface as follows:

$$CO_V = V/0.129 - 19.61P_{RA} - 3.49P_{LA}$$

With different animals, this standard venous return surface was used to predict circulatory equilibrium under a variety of stressed volumes and cardiac functions in the second protocol.

**Prediction of CO, $P_{RA}$, and $P_{LA}$**

Table 2 shows a summary of the approximation of the integrated CO curve using a three-parameter logarithmic curve. In each animal, the coefficient of determination was high for the CO curve of the right ventricle ($r^2 = 0.96–0.99$) and the left ventricle ($r^2 = 0.89–0.99$) under normal cardiac conditions. In other words, the logarithmic curves represented the integrated CO curve with reasonable accuracy. The logarithmic function remained a good approximation under the condition of unilateral heart failure, as evidenced by the high coefficients of determination: $r^2 = 0.73–0.99$ and 0.84–0.99 for the CO curves of the right and left ventricles, respectively.

Using the standard venous return surface, we predicted circulatory equilibrium by determining the intersection of the venous return surface and the integrated CO curve under a variety of stressed volumes and cardiac functions. Figure 8A

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**Fig. 6.** Venous return (CO$_V$) plotted against simultaneously obtained $P_{RA}$ and $P_{LA}$ in a representative case. A venous return surface determined by a set of 6 recordings is superimposed. Inset: 6 points and surface are viewed from a direction parallel to the surface. The 6 points are aligned closely along a single line and lie on a single surface, i.e., venous return surface.

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shows the relations between predicted and measured CO. CO was predicted with reasonable accuracy ($y = 0.90x + 5.6, n = 104, r^2 = 0.95, \text{SEE} = 8.7 \text{ml min}^{-1} \text{kg}^{-1}$), despite large changes in CO: from 40 to 220 ml min$^{-1}$ kg$^{-1}$. The ratio of \text{SEE} to the mean of the predicted CO was 0.090, indicating small variability around the regression line. A small intercept value with near unity slope also indicates the accuracy of prediction. Thus it is fair to say that this framework predicted CO reasonably well, irrespective of cardiac conditions, i.e., normal or left heart failure.

$P_{RA}$ was also predicted accurately, regardless of stressed volume and cardiac function ($y = 0.96x, n = 104, r^2 = 0.98, \text{SEE} = 0.2 \text{mmHg}$; Fig. 8B). The ratio of \text{SEE} to the mean of the predicted $P_{RA}$ was 0.069. From as low as 1 mmHg to as high as 8 mmHg, $P_{RA}$ could be predicted accurately.

Predicted $P_{LA}$, as a whole, agreed reasonably well with $P_{LA}$ measured over a wide range ($y = 0.89x + 0.5, n = 104, r^2 = 0.98, \text{SEE} = 0.8 \text{mmHg}$; Fig. 8C). The ratio of \text{SEE} to the mean of the predicted $P_{LA}$ was 0.087.

### DISCUSSION

We have shown that a linear model of venous return, i.e., the venous return surface, characterizes the venous return properties of the systemic and pulmonary circulations with reasonable accuracy. The surface was, in fact, remarkably flat. When the venous return surface, with standard parameters, was equated with the integrated CO curves of different animals under a variety of stressed volumes and cardiac functions, the predicted CO, $P_{RA}$, and $P_{LA}$ agreed well with measured values. These results strongly support the validity of the venous return surface concept (24, 30) and suggest its usefulness in the clinical setting.

### Characteristics of the Venous Return Surface

The venous return surface was remarkably flat. Its flatness is attributable to the constant nature of $W$, $G_S$, and $G_P$ during changes in loading conditions. Because these parameters are a complex function of vascular resistance and compliance and

Table 1. Parameter values characterizing the venous return surface

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>$G_S$</th>
<th>$G_P$</th>
<th>$W$</th>
<th>$r^2$</th>
<th>\text{SEE}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19.77</td>
<td>3.83</td>
<td>0.154</td>
<td>0.99</td>
<td>1.9</td>
</tr>
<tr>
<td>2</td>
<td>23.30</td>
<td>3.39</td>
<td>0.232</td>
<td>0.92</td>
<td>7.4</td>
</tr>
<tr>
<td>3</td>
<td>20.99</td>
<td>4.04</td>
<td>0.099</td>
<td>0.97</td>
<td>3.7</td>
</tr>
<tr>
<td>4</td>
<td>17.60</td>
<td>2.92</td>
<td>0.088</td>
<td>0.99</td>
<td>1.3</td>
</tr>
<tr>
<td>5</td>
<td>16.17</td>
<td>3.46</td>
<td>0.092</td>
<td>0.92</td>
<td>6.5</td>
</tr>
<tr>
<td>6</td>
<td>19.01</td>
<td>4.26</td>
<td>0.107</td>
<td>0.99</td>
<td>1.5</td>
</tr>
<tr>
<td>7</td>
<td>20.44</td>
<td>2.55</td>
<td>0.132</td>
<td>0.99</td>
<td>1.2</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>19.61 ± 2.33</td>
<td>3.49 ± 0.61</td>
<td>0.129 ± 0.051</td>
<td>0.97</td>
<td>3.4 ± 2.6</td>
</tr>
</tbody>
</table>

$G_S$ (ml·min$^{-1}$·mmHg$^{-1}$·kg$^{-1}$), $G_P$ (ml·min$^{-1}$·mmHg$^{-1}$·kg$^{-1}$), and W (min) are parameters characterizing venous return surface. See METHODS for calculations. $r^2$, coefficient of determination; \text{SEE}, standard error of the estimate (ml·min$^{-1}$·kg$^{-1}$).
Table 2. Accuracy of fit to a three-parameter logarithmic function

<table>
<thead>
<tr>
<th>Dog</th>
<th>Right Ventricle</th>
<th>Left Ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r^2 )</td>
<td>SEE</td>
</tr>
<tr>
<td>1</td>
<td>0.99</td>
<td>5.3</td>
</tr>
<tr>
<td>2</td>
<td>0.96</td>
<td>7.2</td>
</tr>
<tr>
<td>3</td>
<td>0.96</td>
<td>11.4</td>
</tr>
<tr>
<td>4</td>
<td>0.96</td>
<td>6.9</td>
</tr>
<tr>
<td>5</td>
<td>0.96</td>
<td>6.6</td>
</tr>
<tr>
<td>6</td>
<td>0.97</td>
<td>7.7</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.97</td>
<td>7.5 ± 2.1</td>
</tr>
</tbody>
</table>

Integrated CO Curve

We measured the CO curves of both ventricles by changing the stressed blood volume (25, 28). The mean slopes of the right and left CO curves under normal cardiac conditions were 55.6 ± 18.7 and 27.2 ± 12.3 ml·min\(^{-1} \cdot \)mmHg\(^{-1} \cdot \)kg\(^{-1}\), respectively, which are reasonably close to those found in the previous study (28).

A three-parameter logarithmic function approximated the CO curves well. According to the framework of ventricular-arterial coupling using the volume-elastance concept, CO, or stroke volume under a constant contractility, arterial resistance and heart rate depend linearly on end-diastolic volume (24, 29).

Fig. 8. Relations between values predicted and actually measured for CO (A), \( P_{RA} \) (B), and \( P_{LA} \) (C) for 104 steps pooled over 12 output curves. ●, Normal cardiac function; ○, left heart failure; dashed lines, lines of identity. Regression analysis (solid lines) revealed that predicted CO (\( y = 0.39x + 5.6, n = 104, r^2 = 0.95, \text{SEE} = 8.7 \text{ ml·min}^{-1} \cdot \text{kg}^{-1} \)), \( P_{RA} \) (\( y = 0.96x, n = 104, r^2 = 0.98, \text{SEE} = 0.2 \text{ mmHg} \)), and \( P_{LA} \) (\( y = 0.89x + 0.5, n = 104, r^2 = 0.98, \text{SEE} = 0.8 \text{ mmHg} \)) agreed reasonably well with measured values.
between end-diastolic volume and filling pressure. This is indeed reasonable, because the pressure-volume relation of the diastolic ventricle is known to be exponential; therefore, the volume-pressure relation should be the inverse of exponential, i.e., logarithmic (12).

Mechanical parameters such as ventricular systolic and diastolic elastance, heart rate, ventricular interdependence, and arterial resistance have been shown to affect CO (22, 24). To clarify therapeutic targets in the management of cardiac patients, it is crucial to relate those mechanical parameters to the CO curve, as we have done with the venous return surface. Modeling the CO curve on the basis of those parameters is clearly required in future studies.

Analysis of the Circulatory Equilibrium

The venous return surface, combined with the integrated CO curve in the three-dimensional diagram, enables us to make intuitive and in-depth analyses of the contribution of the individual system components to hemodynamics. Figure 9 illustrates the effect of left heart failure on circulatory equilibrium. Integrated CO curves, which were experimentally obtained from a dog under normal and left heart failure conditions, are superimposed on the standard venous return surface in Fig. 9A. Under the normal condition, the integrated CO curve intersects at a CO of 115 ml·min⁻¹·kg⁻¹, with a P_RA of 2.5 mmHg and a P_LA of 4.1 mmHg. In contrast, left heart failure lessens the slope of the CO curve and diverts it toward the axis of P_LA. At the intersection of the standard surface and the CO curve under left heart failure, although the CO decreased (85 ml·min⁻¹·kg⁻¹), the increase in P_LA (9.3 mmHg) was modest. When the stressed blood volume is increased to simulate the baroreflex response (+8 ml/kg), the surface shifts upward (Fig. 9B). The intersection reached a new equilibrium point, where P_LA increased drastically (15.9 mmHg) with a slight increase in P_RA and a partial recovery of CO. Although this analysis is hypothetical, the graphical analysis represents the typical hemodynamics of left heart failure (2, 4, 10, 23, 35). Notwithstanding its simplicity, the framework for the venous return surface provides a very powerful tool for analysis of complicated hemodynamics in the clinical setting.

Comparison with Previous Studies of Cardiovascular Modeling

Many studies have modeled hemodynamics of the cardiovascular system (3–5, 20, 31, 33). The parallel circuit model of Caldini et al. (5) seems to be more appropriate than our serial model for an anatomically oriented analysis of hemodynamics within a single circulation, i.e., the analysis of blood redistribution between the splanchnic and nonsplanchnic circuits. Levy (20) simplified blood distribution between the arterial and venous compartments with a lumped serial model. Although these models could analyze hemodynamics within a single circulation, they were not intended to deal with blood redistribution between the systemic and the pulmonary circulation. In contrast, the two-compartment model of Guyton et al. (15) and the multiple-circuit model proposed by Sylvester et al. (31) can address this issue. These studies, however, went no further than a theoretical analysis and remain insufficient for clinical application. The two-compartment model of Guyton et al. is complicated. It fails to express venous return curves parametrically; consequently, neither the stressed blood volume nor the curve shifts in response to changes in stressed blood volume can be estimated (15). Sylvester et al. (31) integrated systemic and pulmonary venous return curves into a single curve and expressed it parametrically. However, extensive experimental validations of the model are needed. In addition, because the pressure axis of their integrated venous return curve was the weighted average of P_RA and P_LA, we were unable to uniquely determine their individual values from the equilibrium point in their diagram.

There have been serious debates among cardiovascular physiologists regarding cause-effect relations between CO/venous return and atrial pressure, i.e., which variable determines the others? Brengelmann (3), Levy (20), and Tyberg (33) argued that as CO increases, the venous reservoir is depleted (i.e., blood is translocated from the veins to the arteries), and, therefore, venous pressure (i.e., atrial pressure) decreases. In the heart, atrial pressure determines CO according to the Frank-Starling mechanism. In contrast, in response to the work of Levy, Guyton (14) commented that he considered CO and atrial pressures to be the effects, or dependent variables. Blood volume and the mechanical properties of the heart and vasculature, such as heart rate, ventricular contractility,
and vascular resistance, are the cause. The CO curve or venous return curve discloses those properties through the relation between the flow and atrial pressures. As we demonstrated in Eq. 1, under a given stressed volume, venous return/CO and atrial pressure have a linear relation. In other words, once venous return is determined, atrial pressure is automatically determined and vice versa. Therefore, our framework is consistent with Guyton’s comment on the work of Levy. As far as the prediction of hemodynamics is concerned, however, the difference between their interpretations and ours does not impact the result of this study, because we are able to obtain the same equilibrium point with either interpretation (14, 20).

Application of This Framework

Accurate predictions of CO and filling pressures after therapeutic interventions are vital in the management of heart failure, as suggested by the classification of Forrester (10) and other previous studies (11, 21). Although the Swan-Ganz catheter allows us to estimate CO and filling pressures, such devices do not allow us to estimate the venous return curve or mean circulatory filling pressure (6). In contrast, because the parameter values of the venous return surface were invariable among animals, it is conceivable that the same standard values obtained from this investigation might be used for patients. If this is the case, for given values of CO, P LA, and P RA, all of which can be easily obtained by Swan-Ganz catheters, we can uniquely define the venous return surface and estimate stressed blood volume of patients without the need to perform total heart bypass (6). The clinical usefulness of knowing the venous return surface would be markedly increased if the integrated CO curve could be estimated. This would enable accurate prediction of the CO, P RA, and P LA in response to various therapeutic interventions, which induce changes in loading condition, or changes in the pumping ability of the heart, i.e., changes in CO curves. These should help optimize hemodynamic management and improve patient prognosis (10, 21).

Limitations

In this investigation, we isolated baroreceptors and fixed the autonomic tone. 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 (9, 24, 27). How changes in autonomic tone under the closed-loop condition affect the CO curve and venous return surface remains to be investigated.

We assumed that there is no fluid shift between the intravascular and extravascular space and that the volume perturbations exclusively changed the stressed blood volume. We assumed that the changes of cardiac volume and volume shifts between the heart and vasculatures are rather small. However, this may not be the case if the ventricles are extremely compliant, as in those with extensive remodeling (32). In such cases, the volume shifts between the heart and the vasculatures become significant. Further studies are required to clarify these relations to facilitate the future clinical application of this framework.

All the experiments of this study were conducted in anesthetized, open-chest dogs. Anesthesia and surgical trauma affect the cardiovascular system significantly (34). Whether this equilibrium framework can be applied to conscious, closed-chest animals (including humans) remains to be seen. We used two pumps for total heart bypass. However, it is well known that the CO of the two sides of the heart is not identical because of the anatomic shunt between the systemic and pulmonary circulations, e.g., the bronchial artery. However, the difference between the flow rates was <3% of CO. Therefore, it is unlikely that such a minor difference in CO would influence the conclusion of this study.

Conclusion

We were able to characterize the venous return properties of the systemic and pulmonary circulations in a simple manner using the flat venous return surface. Equating the standard venous return surface with the measured integrated CO curves, under a variety of stressed blood volumes and cardiac functions, enabled us to accurately predict hemodynamics.

APPENDIX

Concept of Integrated Venous Return

Using a distributed model, Sagawa and Sunagawa and their co-workers (24, 30) modeled the vascular system. Suppose that compliance and resistance are distributed in the systemic circulation (Fig. 10). When the compliance distribution [C(x)] and pressure distribution [P(x)] are expressed as a function of distance (x) from the venous port, then stressed blood volume (V S ) in the systemic circulation can be described as

\[ V_S = \int_0^L P(x)C(x)dx \quad (A1) \]

where \( L \) represents the distance between the arterial and venous ports. If we denote the cumulative resistance over a distance \( x \) from the venous port by \( R(x) \), the serial pressure distribution can be expressed as

\[ P(x) = R(x)COV + P_{RA} \quad (A2) \]

Substituting Eq. A2 into Eq. A1 yields

\[ V_S = COV \int_0^L C(x)R(x)dx + P_{RA} \int_0^L C(x)dx \quad (A3) \]

Fig. 10. Vascular system modeled by a distributed system. C(x), P(x), and R(x), compliance, pressure, and cumulative resistance over a distance \( x \) from the venous port; \( L \), distance between arterial and venous ports.
When $C_vD_{CS}(x)$ is substituted for $C(x)$, where $C_v$ is the total systemic vascular compliance and $D_{CS}(x)$ is the normalized distribution of compliance as a function of $x$ (thus $\int_0^1D_{CS}(x)dx = 1$), Eq. A3 can be rewritten as

$$V_S = CO_vC_S\int_0^1D_{CS}(x)R(x)dx + P_{xa}C_S\int_0^1D_{CS}(x)dx \quad (A4)$$

The first integral term, which sums cumulative resistance weighted by systemic compliance distribution, is equivalent to the resistance for systemic venous return, $R_{VS}$, of Guyton et al. (16, 17). Because the second integral is unity, Eq. A4 can be rewritten as

$$V_S = CO_vC_Sr_{VS} + P_{xa}C_S \quad (A5)$$

Stressed blood volume in the pulmonary circulation ($V_P$) can be related to $CO_v$ and $P_{LA}$ by the following equation

$$V_P = CO_vC_{P}r_{VP} + P_{LA}C_P \quad (A6)$$

where $C_P$ is the total pulmonary compliance and $R_{VP}$ is the resistance for pulmonary venous return.

For a given condition, the sum of the stressed blood volumes in the systemic circulation and pulmonary circulation, $V$ (i.e., $V_S + V_P$), remains constant, irrespective of its distribution. Thus adding Eqs. A5 and A6 and rearranging yields

$$CO_v = V/W - G_Pp_{ra} - G_Pp_{LA} \quad (A7)$$

where $W$, $G_S$, and $G_P$ are linear parameters and are expressed as

$$W = C_Sr_{VS} + C_Pr_{VP} \quad (A8)$$

$$G_S = C_P/W \quad (A9)$$

and

$$G_P = C_P/W \quad (A10)$$

For a given $V$, $CO_v$ can be related to $P_{RA}$ and $P_{LA}$ by a surface expressed by Eq. A7 (Fig. 1B). When $V$ is kept constant, $CO_v$ decreases with increases in $P_{RA}$ and/or $P_{LA}$.

From Eqs. A6–A10, once $C_S$, $r_{VS}$, $C_P$, and $r_{VP}$ are given, we can estimate $W$, $G_S$, and $G_P$. Lee and Goldman (19) reported $C_S$ as 1.9 ml·mmHg⁻¹·kg⁻¹ and $r_{VS}$ as 0.056 mmHg·ml⁻¹·min⁻¹·kg in eight dogs. Shoukas (26) reported $C_P$ as 0.31 ml·mmHg⁻¹·kg⁻¹ and $r_{VP}$ as 0.077 mmHg·ml⁻¹·min⁻¹·kg in nine dogs. Estimated $W$, $G_S$, and $G_P$ were 0.131 min, 14.56 ml·min⁻¹·mmHg⁻¹·kg⁻¹, and 2.39 ml·min⁻¹·mmHg⁻¹·kg⁻¹, respectively. These values are in good agreement with those obtained in our experiment.

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