Prediction of the impact of venoarterial extracorporeal membrane oxygenation on hemodynamics

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The purpose of this study was to predict hemodynamics in venoarterial extracorporeal membrane oxygenation (ECMO) via percutaneous catheters has been widely used for the management of cardiogenic shock with respiratory failure (19). Although ECMO is a powerful life-saving treatment in these patients, ECMO may unexpectedly lead to hemodynamic disorders, including life-threatening pulmonary edema (15). ECMO was reported to induce excessive left ventricular (LV) and left atrial distension in 13–68% of supported patients, resulting in high mortality in these patients (6, 7, 14). Once ECMO support is initiated, there are major clinical concerns on how to withdraw ECMO. Inappropriate weaning from ECMO causes hemodynamic deterioration, whereas prolonged ECMO support results in numerous complications (5, 15). Despite these issues, there is no established framework for weaning from ECMO (2). Therefore, the development of a framework to predict and to avoid hemodynamic disorders should have great impact on safe management of ECMO in clinical settings.

The physiological principle of ECMO is straightforward: ECMO decreases the preload of the heart by withdrawing blood from the right atrium and increases cardiac output (CO) by returning blood to the aorta (Fig. 1A) (8). However, the lack of understanding concerning the effects of ECMO in quantitative terms makes it difficult to predict its hemodynamic impact. Accordingly, it is essential to know quantitatively how ECMO affects hemodynamics to accomplish safe initiation, stable maintenance, and secure discontinuation.

The Guyton’s classic concept of circulatory equilibrium, which consists of the CO curve and the venous return (VR) curve, is a powerful framework in understanding circulatory physiology (10). Sunagawa et al. (28) proposed the extended Guyton’s model that represents the cardiac pumping ability by the integrated CO curve, and the VR function by the VR surface (Fig. 1B). Uemura et al. (29, 30) validated the concept of the extended Guyton’s model in dogs. As the integrated CO curve has the unique advantage of covering both right and left heart functions, the different effects of ECMO on right and left heart can be studied. Furthermore, the different impact of ECMO on VR of right and left heart can be quantified, because the VR surface has unique slopes with respect to both right atrial pressure (PRA) and left atrial pressure (PLA). Therefore, we developed a framework to incorporate ECMO in the extended Guyton’s framework and predicted the impact of ECMO on circulatory equilibrium and hemodynamics.

The purpose of this study was to predict hemodynamics in response to weaning from ECMO in an animal model of LV dysfunction. We demonstrated that the proposed framework is capable of predicting hemodynamics under ECMO support and thus contributes to ensure safe management of ECMO in patients under critical hemodynamic conditions.

MATERIALS AND METHODS

Theoretical Consideration

Impact on the integrated CO curve. The integrated CO curve is derived from the right and left CO curves. In the right heart, the downstream pressure (Pd, i.e., PLA), is significantly related to pulmonary arterial pressure. Therefore it must be incorporated in the framework. Using logarithmic approximation, the CO curve of the right heart (CO_R) becomes:
CO_\text{R} = S_\text{R} \left[ \ln(P_{\text{RA}}) + H_\text{R} \right] - \left(1 - \text{EF}_\text{R}\right)P_{\text{LA}}/R_\text{P} \tag{1}

where S_\text{R} and H_\text{R} are empirical parameters of the right heart, EF_\text{R} is right ventricular (RV) effective ejection fraction (EF), and R_\text{P} is pulmonary vascular resistance. EF_\text{R} and R_\text{P} are known constant from previous studies (EF_\text{R} = 0.5 and R_\text{P} = 0.12 \text{mmHg} \cdot \text{ml}^{-1} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}) \cite{12, 20, 24}. Details of the derivation of Eq. 1 are provided in APPENDIX A.

In contrast, because the P_\text{LA}, i.e., P_{\text{RA}} is negligibly smaller compared with arterial pressure, the CO curve of the left heart (CO_\text{L}) is a simple logarithmic function as follows:

\begin{equation}
CO_\text{L} = S_\text{L} \left[ \ln(P_{\text{LA}}) + H_\text{L} \right] \tag{2}
\end{equation}

where S_\text{L} and H_\text{L} are empirical parameters of the left heart.

Since CO generated by ECMO (CO_{\text{ECM}}) increases arterial pressure, it increases afterload of the left heart. In contrast, systemic vascular resistance remains constant in the absence of baroreflex \cite{9}. Therefore, the increased afterload inevitably decreases CO_\text{L} without changing S_\text{L} or H_\text{L} for any given preload; that is, ECMO shifts the CO_\text{L} downward (Fig. 1C). Considering the afterload, we can obtain CO from the left heart under ECMO (CO_{\text{ONTV,L}}) as follows (see APPENDIX B):

\begin{equation}
CO_{\text{ONTV,L}} = S_\text{L} \left[ \ln(P_{\text{LA}}) + H_\text{L} \right] - \left(1 - \text{EF}_\text{L}\right) \times CO_{\text{ECM}} \tag{3}
\end{equation}

where EF_L represents LV EF. Equation 3 indicates that ECMO shifts CO_{\text{ONTV,L}} downward in proportion to CO_{\text{ECM}}.

As ECMO does not directly affect the afterload on the right heart, CO from the right heart under ECMO (CO_{\text{ONTV,R}}) is the same as Eq. 1, as follows:

\begin{equation}
CO_{\text{ONTV,R}} = S_\text{R} \left[ \ln(P_{\text{RA}}) + H_\text{R} \right] - \left(1 - \text{EF}_\text{R}\right)P_{\text{LA}}/R_\text{P} \tag{4}
\end{equation}

Simultaneous solution of Eqs. 3 and 4 yields the integrated CO curve under ECMO.

**Impact on the VR surface.** CO for a given stressed volume is calculated as a function of P_{\text{RA}} and P_{\text{LA}} as follows (see APPENDIX C):

\begin{equation}
CO = V/W - \left(G_\text{P}_{\text{LA}} + G_\text{P}_{\text{RA}}\right) - W/CO_{\text{ECM}} \tag{5}
\end{equation}

where V is the sum of the stressed blood volumes in systemic and pulmonary circulation, and W is the standard parameter characterizing the VR surface reported previously \cite{30}. G_P is conductances of systemic and pulmonary VR, respectively, and represent the slopes of the VR surface with respect to P_{\text{LA}} and P_{\text{RA}}, respectively. As ECMO drains and decreases the stressed volume of pulmonary circulation, ECMO shifts the VR surface downward along the CO axis (Fig. 1C).

Considering the impact of ECMO, CO under ECMO (CO_{\text{ONTV}}) is obtained as follows (see APPENDIX D):

\begin{equation}
CO_{\text{ONTV}} = V/W - \left(G_\text{P}_{\text{LA}} + G_\text{P}_{\text{RA}}\right) - W/CO_{\text{ECM}} \tag{6}
\end{equation}

where W, G_P, and G_S are conductances of systemic and pulmonary VR, respectively, and represent the slopes of the VR surface with respect to P_{\text{LA}} and P_{\text{RA}}, respectively. Equation 6 shows that ECMO shifts the VR surface downward.

Finally, a new circulatory equilibrium point is given by the intersection of the ECMO-shifted integrated CO curve and the ECMO-shifted VR surface, by simultaneous solving the newly derived equations of the integrated CO curve (Eqs. 3 and 4) and the VR surface (Eq. 6) (Fig. 1C).

**Animal Preparation**

We used 21 adult mongrel dogs of either sex, weighing 17.7 ± 0.9 kg (mean ± SD). Experiments and animal care were approved by the Committee on Ethics of Animal Experiment, Kyushu University Graduate School of Medical Sciences, and performed in strict accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health. We induced anesthesia with intravenous propofol (2 mg/kg) and pancuronium bromide (0.08 mg/kg), performed endotracheal intubation, and maintained an appropriate anesthesia level during the experiment by continuous infusion of propofol (0.85 mg·kg^{-1}·min^{-1}) and remifentanil hydrochloride (1.0–1.5 μg·kg^{-1}·min^{-1}). We placed a catheter...
(6-Fr) in the left femoral vein for administration of drugs and fluids. To stabilize autonomic tone independent of blood pressure, we isolated the carotid sinuses bilaterally and kept the intrasinus pressure constant at 120 mmHg (24). We cut the cervical vago-sympathetic trunks. We measured systemic arterial pressure by a catheter-tipped micromanometer (model PC-751; Millar Instruments, Houston, TX) placed in the ascending aorta via the left carotid artery. After a median sternotomy, we made a small pericardial incision at the level of the aortic root and placed an ultrasonic flow probe (model 20AS94; Transonic, Ithaca, NY) around the ascending aorta through the incision to measure CO. We placed fluid-filled catheters in right and left atria to measure PRA and PLA, respectively, and connected them 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 (11). We inserted a polyethylene tube each into right jugular vein and right femoral artery for withdrawing and reinfusing blood by ECMO, respectively. We connected a centrifugal pump (CBBPX-80; Medtronic, Minneapolis, MN) and an artificial lung (CX-RX15W; Terumo, Tokyo, Japan) in series and mounted an in-line ultrasonic flowmeter (model XL; Transonics, Ithaca, NY) in the circuit to measure COECM continuously.

To create a LV failure model, we ligated the left antero-descending coronary artery with a suture to induce myocardial infarction (MI), with an additional ligation as needed to elevate PLA up to 10 mmHg (11).

Experimental Protocol

Protocol 1: Determination of the CO curve. Eight normal and seven MI dogs were used. In each dog, we withdrew blood from the left femoral vein in a stepwise manner, 50 ml every minute for a total of 200 ml, and recorded CO, PRA, and PLA simultaneously (Fig. 2).

![Graph showing changes in arterial pressure (AP), CO, PRA, and PLA](image)

We then approximated the CO curve to Eqs. 1 and 2 to determine the parameters (SR, HR, SL, HL) using the least squares errors method. After the measurements, we returned the withdrawn blood to the animal via the femoral vein.

Protocol 2: Prediction of the circulatory equilibrium. We used the same animals tested in protocol 1. We started ECMO and increased COECM to 2.0 l/min. After stabilization, we decreased COECM stepwise to zero (0.5 l/min every minute) (Fig. 3A). We calculated EF, and V from Eqs. 3 and 6, respectively, using the data (COECM, PRA, and PLA) measured under COECM of 2.0 l/min and the parameters (SR, Hs, Sl, HL) obtained from protocol 1. Finally, we estimated the equilibrium points (COECM, PRA, and PLA) from Eqs. 3, 4, and 6 by the least squares errors method for COECM of 1.5, 1.0, 0.5, and 0 l/min and compared them with those measured.

Protocol 3: Estimation of CO curve and prediction of circulatory equilibrium under ECMO. In the clinical settings, the predetermined integrated CO curve is not available. Therefore, in this protocol, we estimated the CO curve from hemodynamic variables under ECMO. Six MI dogs were used. After hemodynamics was stabilized at maximum ECMO support (COECM at 2.0 l/min), we decreased COECM stepwise and recorded CO, PRA, and PLA under three ECMO flow rates of 2.0, 1.75, and 1.5 l/min. We then estimated the equilibrium points (COECM, PRA, and PLA) at COECM of 1.0, 1.5, and 0 l/min and compared them with those measured.

Data Acquisition

We digitized all analog signals at 200 Hz with a 16-bit analog-to-digital converter (PowerLab 16/35, AD Instruments, Dunedin,
New Zealand) and stored the data on a hard disk for subsequent analysis. We averaged all of the recorded data over 10 s. In addition, we normalized all data, except pressure data, to individual body weight.

**Statistical Analysis**

We expressed group data as means ± SD. We used analysis of excess variance to compare the entire relationship of the CO curves between normal and MI groups and used unpaired t-tests to compare individual parameters of the CO curves between the two groups. We used Student’s paired t-tests to compare hemodynamics before and after MI. We defined the level of statistical significance as P < 0.05. To test the goodness of fit of the CO curves and the identifiability of each parameter, we calculated the coefficient of determination (r^2) and asymptotic standard errors, respectively. Furthermore, we calculated r^2, standard error of estimate, bias, and limits of agreement (LOA) to test the goodness of fit and to assess the agreement in prediction of circulatory equilibrium. We performed statistical analyses using JMP 11 (SAS Institute, Cary, NC).

**RESULTS**

**Protocol 1: Baseline Characteristics of Normal and MI Dogs**

Figure 4 shows the measured PRA-CO and PLA-CO relations in representative normal and MI dogs. CO increases with increase in PRA or PLA, according to the Frank-Starling mechanism. These relations fitted reasonably well with a two-parameter logarithmic function, in both normal (n = 8) and MI (n = 7) groups, as shown in Table 1. In both groups, correlation coefficients of the entire CO curves were high, and asymptotic standard errors of all parameters were low. SR and SL in the normal group were 159.0 ± 29.9 and 93.1 ± 39.4 ml·min⁻¹·kg⁻¹, respectively. According to analyses of excess variance, invariance between two groups was rejected for SL only; in other words, SL was significantly different between normal and MI groups, whereas HL, SR, and HR were not. In
the comparison of individual parameters by unpaired t-test, \( S_L \) (56.9 ± 21.2 ml·min\(^{-1}·kg\(^{-1}\)) was significantly \( P < 0.05 \) smaller in the MI group than in the normal group, while \( S_R \), \( H_R \), and \( H_L \) were not significantly different between the normal and MI groups. Thus analysis of excess variance and unpaired t-test yielded the same conclusion.

Table 2 shows the baseline characteristics in normal and MI groups. The circulatory equilibrium points were similar between normal and before MI groups. MI increased PLA and V. These results indicate that LV dysfunction was well established in the MI group. As \( EFL \) and \( V \) were calculated when COECM was 2 l/min, the before MI group did not undergo ECMO, and, therefore, these data were not available.

**Protocol 2: Prediction of Circulatory Equilibrium Under venoarterial ECMO Using Predetermined CO Curve**

Illustrated in Fig. 5 are the relationships between the predicted equilibrium points and those measured as scatter plots (top) and Bland-Altman plots (bottom). In the scatter plots, the predicted total systemic flow, i.e., native left heart flow plus ECMO flow (left), was reasonably accurate over a wide range, from 70 to 190 ml·min\(^{-1}·kg\(^{-1}\). In addition, \( P_{RA} \) (middle) was well predicted over the physiological range from 2 to 6 mmHg in both groups. Accurate prediction of \( P_{LA} \) was obtained over a higher range of 9 to 15 mmHg in MI and over a lower range of 4 to 9 mmHg in normal animals (right). In Bland-Altman plots, most data points for total systemic flow, \( P_{RA} \), and \( P_{LA} \) were within the LOA, and there was only slight proportional bias without significant fixed bias.

**Protocol 3: Prediction of Circulatory Equilibrium Without Prior Knowledge of CO Curve**

Despite the absence of predetermined CO curves, total systemic flow, \( P_{RA} \), and \( P_{LA} \) predicted using CO curves estimated under ECMO matched reasonably well with the measured values over wide ranges (Fig. 6, top). The accuracy and the range of prediction were similar to those in protocol 2. In Bland-Altman plots (Fig. 6, bottom), although most data points were within LOA, both fixed bias and proportional bias were somewhat larger than those in protocol 2. In addition, the mean values of \( S_L \), \( H_L \), and \( EFL \) were 52.1, 0.59, and 0.75 ml·min\(^{-1}·kg\(^{-1}\), respectively. The mean ± asymptotic SEs of \( S_R \) and \( H_R \) were 159.9 ± 34.3 and −0.37 ± 0.15 ml·min\(^{-1}·kg\(^{-1}\), respectively.

**DISCUSSION**

Using the extended Guyton’s framework, we predicted the hemodynamic outcomes reasonably well under ECMO. The framework is critical in predicting hemodynamics and providing quantitative data beyond the qualitative knowledge available so far. Accurate prediction of hemodynamics allows appropriate circulatory management in patients undergoing ECMO.

The results of protocol 2 (prediction of the circulatory equilibrium) show reasonably good prediction of the circula-
hemodynamic changes induced by ECMO in normally functioning hearts and post-MI hearts. As ECMO affects the right and left heart differently, the impact of ECMO can never be elucidated without the concept of decoupling the pulmonary circulation from the systemic circulation. Furthermore, the significant match obtained in protocol 3 (estimation of CO curve and prediction of circulatory equilibrium under ECMO) demonstrates accurate estimation of the integrated CO curve under ECMO and also validates the quantitative analysis of the impact of ECMO. The similarity in the mean values of $S_R$, $H_R$, $S_L$, and $H_L$ between the MI dogs in protocol 1 and those in protocol 3 ($S_R$: 159.9 vs. 161.2 ml·min$^{-1}$·kg$^{-1}$; $H_R$: $-0.37$ vs. $-0.40$ ml·min$^{-1}$·kg$^{-1}$; $S_L$: 52.1 vs. 56.9 ml·min$^{-1}$·kg$^{-1}$; $H_L$: $0.59$ vs. $-0.60$ ml·min$^{-1}$·kg$^{-1}$) supports reasonably accurate estimation of parameters in protocol 3, despite the fact that parameters were estimated from narrower ranges in protocol 3 than in protocol 1.

There is no established guideline on weaning from ECMO, except one report for acute fulminant myocarditis (2). Although several weaning protocols by reducing COECM have been reported, the COECM reduction rate, observation duration, and monitoring parameters vary among protocols (5, 18). Cavarocchi et al. (3) suggested continuous hemodynamic monitoring by transesophageal echocardiography, but their protocol is complicated, time-consuming, and cumbersome in clinical settings. A few reports examined the predictive factors for successful withdrawal (1, 21). However, these reports provided no quantitative prediction of the hemodynamic values after termination of ECMO. In this study, we predicted circulatory equilibrium without discontinuing ECMO, and that is a great advantage in clinical settings. Discontinuation of ECMO in a hemodynamically unstable patient could trigger irreversible hypoxia and circulatory collapse and damage the artificial lung and circuit. Therefore, such discontinuation, even for a short duration, is unfavorable, and it is essential to predict the circulatory equilibrium in advance before terminating ECMO. Using our method, we are able to predict hemodynamics upon the termination of ECMO and identify patients who can tolerate weaning from ECMO. It is feasible to estimate circulatory equilibrium in clinical settings by the procedures in protocol 3, because the necessary hemodynamic measurements, $P_{RA}$, $P_{LA}$ (as pulmonary capillary wedge pressure), and $CO_{NTV}$, can be measured using a Swan-Ganz catheter. Although we have to reestimate patients’ system parameters during ECMO support, the procedures of protocol 3 can be completed in a short duration with little impact on hemodynamics.

In clinical settings, we often need to predict the impact of ECMO initiation on hemodynamics. This is particularly important because inappropriate initiation of ECMO may result in

![Graph showing relations between predicted and measured hemodynamic parameters](image-url)
hemodynamic disasters. To investigate the factors contributing to circulatory collapse under ECMO, we numerically simulated hemodynamics under various levels of ECMO support using Eqs. 3, 4, and 6. As shown in Fig. 7, ECMO changes $P_{LA}$. However, changes in $P_{LA}$ depend on cardiac function. ECMO decreases $P_{LA}$ when LV function is preserved, but increases $P_{LA}$ when LV function is poor (LV dysfunction). Moreover, the impact of ECMO interacts with RV function. In normal RV function (EF$_R$: 0.5), ECMO increases $P_{LA}$ only when EF$_L$ falls below 0.4. In RV dysfunction (EF$_R$: 0.3), however, ECMO increases $P_{LA}$, even when EF$_L$ is as high as 0.9. In other words, ECMO monotonically increases $P_{LA}$ in most patients who require ECMO support. The results of numerical simulation indicate that quantitative prediction of hemodynamics is a prerequisite for effective and safe management of patients under ECMO support, particularly in those with biventricular dysfunction. This result is consistent with previous reports that ECMO caused pulmonary edema in patients with severe LV dysfunction, even in the absence of valvular diseases (7, 14, 26). Furthermore, whether $P_{LA}$ is predicted to increase or decrease upon initiating ECMO may affect clinical judgments. For instance, we should initiate ECMO in a patient whose $P_{LA}$ is expected to decrease, but we may consider a LV assist device in another patient whose $P_{LA}$ is expected to increase upon initiating ECMO (13).

In this study, we expressed the integrated CO curve as a two-parameter logarithmic function instead of the three-parameter logarithmic function used in previous studies (29, 30). Despite fewer variables, the CO curves fitted as accurately (Table 1) as those expressed by three parameters. Moreover, the fact that cardiac function can be assessed by repeated changes of CO$_{ECM}$ is useful, because previous noninvasive methods of assessing cardiac function did not provide hemodynamics under extracorporeal support (4, 17). Regarding the cardiac function, lower $S_B$ in MI than in normal dogs (Table 1) signifies that contractile dysfunction in MI mainly causes deterioration of left heart function. In addition, significantly elevated $P_{LA}$ and declined CO after MI compared with before MI verified the severity of LV dysfunction (Table 2).

**Limitations**

First, we conducted all of the experiments of this study in anesthetized and open-chest dogs, and did not take into account the effects of anesthesia and surgical trauma on the cardiovascular system (31). Moreover, all of the parameters used in this analytic series are based on canine experiments and may be different from those in humans. Furthermore, we maintained arterial $P_{O_2}$ and arterial $P_{CO_2}$ within physiological ranges throughout the protocols by regulating oxygen concentration in the artificial lung. However, acute improvement of oxygenation when ECMO is initiated may result in dramatic change in cardiovascular properties in collapsed patients. Second, we isolated the carotid sinuses and cut the cervical vagosympathetic trunks bilaterally, because the baroreflex alters cardiovascular properties such as cardiac contractility, heart rate, stressed blood volume, and vascular resistance (9, 23). In other words, we predicted hemodynamics under unphysiologically stabilized conditions, eliminating the effects of baroreflex on the integrated CO curve and the VR surface. This well-
controlled experimental condition was essential to validate the proposed framework. However, in clinical settings, pathophysiological factors, such as baroreflex, arrhythmias, and concomitant medications, complicate the picture. Therefore, further study is required to validate the framework in the presence of the above confounders. Third, theoretically speaking, we could simulate hemodynamics under the closed-loop baroreflex condition by incorporating how the baroreflex changes the system parameters. However, this requires complex experiments to identify open-loop transfer functions of baroreflex in each parameter (23). Therefore, the estimation of impact of ECMO under the closed-loop condition remains challenging. Fourth, we used fixed parameters of EFR and VR surface ($W$, $W_S$, $G_P$, and $G_S$) because they have been shown to have small variations among individuals (9, 12, 22, 30). Whether individualized parameters improve the precision of the estimation remains to be seen. Especially, RV function would likely vary in heart failure patients, and, therefore, we should measure individual EFR to predict $P_{LA}$. However, we did not conduct this prediction study in a RV dysfunction model, and whether clinical estimation of RV function provides enough information to estimate EFR remains to be investigated. Finally, the conceptual and mathematical complexity of the proposed framework may limit its clinical application. Further simplification of the framework would help ease its applications under clinical settings.

In conclusion, using normal and MI canine models, we predicted the circulatory equilibrium under ECMO reasonably well using the extended Guyton’s concept, utilizing not only the measured CO curves, but also the estimated CO curves mimicking clinical settings. A hemodynamic simulation incorporating this model shows that $P_{LA}$ increases in proportion to $CO_{ECM}$ in severe LV dysfunction, especially in the presence of right heart failure. The proposed concept may facilitate appropriate circulatory management in critically ill patients undergoing ECMO.

APPENDIX A

According to the ventricular arterial coupling using the elastance concept, the intersection between the end-systolic pressure-volume relationship and the effective arterial elastance line determines stroke volume (SV) for a given preload as shown in Fig. 8. In the presence of down...

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Fig. 7. Simulated relations among $P_{LA}$, $CO_{ECM}$, and effective left ventricular ejection fraction ($EF_L$) under conditions of normal right ventricular function [effective right ventricular ejection fraction ($EF_R$) = 0.5; top] and right ventricular dysfunction ($EF_R$ = 0.3; bottom). Left: venoarterial ECMO increases or decreases $P_{LA}$ from 15 mmHg, depending on $EF_L$. Right: ECMO increases $P_{LA}$ when $EF_L < 0.4$ at $EF_R = 0.5$, while $P_{LA}$ increases $P_{LA}$ even when $EF_L = 0.9$ at $EF_R = 0.3$.

Fig. 8. The impact of downstream pressure ($P_d$) on ventricular arterial coupling. In the presence of $P_d$, the effective arterial elastance ($E_a$) line shifts upward (dashed to solid line), and the intersection between the end-systolic elastance ($E_{es}$) and $E_a$ lines shifts from the open circle to solid circle.
of $P_d$ the $P_d$ shifts the effective arterial elastance ($E_a$) line upward, and the intersection between the end-systolic pressure-volume relationship and the $E_a$ line shifts upward from the open circle to the solid circle. Since $P_d$ is given by:

$$P_d = \Delta SV \times E_{as} + \Delta SV \times E_a \quad (A1)$$

where $\Delta SV$ is the reduction in SV, and $E_{as}$ is end-systolic elastance. Rearranging Eq. A1 yields

$$\Delta SV = \frac{P_d}{(E_{as} + E_a)} \quad (A2)$$

The decrease in CO ($\Delta CO$) is obtained by dividing $\Delta SV$ by cardiac cycle ($T$) as

$$\Delta CO = \frac{P_d}{T(E_{as} + E_a)} \quad (A3)$$

According to a previous study (27),

$$E_{as} \left/ \left( E_{as} + E_a \right) \right. = E_{Fe} \quad \text{and} \quad R = \frac{R}{T}$$

where $E_{Fe}$ is defined as the ratio of SV to effective preload, and R is resistance. The effective preload is obtained by subtracting the unstressed volume from the end-diastolic volume.

Substituting these in Eq. A3 yields

$$\Delta CO = \frac{(1 - E_{Fe})P_d}{R} \quad (A4)$$

That is, the CO curve of right heart is:

$$CO_R = S_R \left[ \ln (P_{RA}) + H_R \right] - \left( 1 - E_{Fe} \right) P_{LA}/R_p \quad (A5)$$

**APPENDIX B**

We can obtain the impact of ECMO on CO in the same manner as in **APPENDIX A**. The $P_d$ produced by COECM is

$$P_d = R \times COECM \quad (B1)$$

Substituting Eq. B1 in Eq. A4 yields

$$\Delta CO = \left( 1 - E_{Fe} \right) \times COECM \quad (B2)$$

Finally, we can obtain $CO_{NTV,LA}$ as

$$CO_{NTV,LA} = S_L \left[ \ln (P_{LA}) + H_L \right] \left( 1 - E_{Fe} \right) \times COECM \quad (B3)$$

**APPENDIX C**

According to the theoretical analysis using a distributed vascular model, CO for a given stressed volume is expressed as a function of $P_{RA}$ and $P_{LA}$ by means of a simple linearized model of a flat surface. Dividing the total circulating volume ($V$) into stressed blood volume in the pulmonary circulation ($V_p$) and that in the systemic circulation ($V_s$), $V_p$ and $V_s$ become (29, 30)

$$V_p = C_p \times R_{VP} \times CO + C_p \times P_{LA} \quad (C1)$$

$$V_s = C_s \times R_{VS} \times CO + C_s \times P_{RA} \quad (C2)$$

where $C_p$ and $C_s$ are compliances of pulmonary and systemic circulation, respectively, and $R_{VP}$ and $R_{VS}$ are weighted parameters of pulmonary and systemic circulation, respectively, against the VR.

Using $V = V_p + V_s$ and substituting Eqs. C1 and C2 yields

$$CO = \left[ V - (C_pP_{LA} + C_sP_{RA}) \right] / (W_p + W_s) \quad (C3)$$

$$= V/W - (G_pP_{LA} + G_sP_{RA}) \quad (C3)$$

where $W_p = (C_pR_{VP})$, $W_s = (C_sR_{VS})$, and $W = (W_p + W_s)$ denote the parameters that define the maximum VR for a given stressed volume ($V$), and $G_p = (C_p/W)$ and $G_s = (C_s/W)$ are conductances of pulmonary and systemic VR, respectively, and are the slopes of VR with respect to $P_{LA}$ and $P_{RA}$, respectively.

**APPENDIX D**

ECMO drains and decreases the stressed volume from pulmonary circulation, thereby upsetting the balance of the pulmonary ($V_{P,ECM}$) and systemic VR ($V_{S,ECM}$) (Fig. 1A). We can calculate the quantitative impact of ECMO using these unbalanced VRs in the same manner as Eqs. C1 and C2

$$V_{P,ECM} = C_p \times R_{VP} \times CO_{NTV} + C_p \times P_{LA} \quad (D1)$$

$$V_{S,ECM} = C_s \times R_{VS} \times (CO_{NTV} + COECM) + C_s \times P_{RA} \quad (D2)$$

As the total circulating volume remains unchanged regardless of ECMO, the sum of $V_{P,ECM}$ and $V_{S,ECM}$ equals to the sum of the stressed blood volume without ECMO.

$$V_{P,ECM} + V_{S,ECM} = V_p + V_s \quad (D3)$$

$CO_{NTV}$ is obtained by substituting Eqs. D1 and D2 into Eq. D3, and rearranging as in Eq. 5:

$$CO_{NTV} = \left[ V - \left( (C_pP_{LA} + C_sP_{RA}) - W_pCOECM \right) / (W_p + W_s) \right]$$

$$= V/W - (G_pP_{LA} + G_sP_{RA}) - W_s/W \times COECM \quad (D4)$$

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: K. Sakamoto, K. Saku, T. Kakino, and A.T. performed experiments; K. Sakamoto and K. Saku analyzed data; K. Sakamoto and T.S. interpreted results of experiments; K. Sakamoto prepared figures; K. Sakamoto drafted manuscript; K. Sakamoto and T. Kishi edited and revised manuscript; T.I. and K. Sunagawa approved final version of manuscript; K. Sunagawa conception and design of research.

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