Prediction of haemodynamics after interatrial shunt for heart failure using the generalized circulatory equilibrium

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Abstract

Aims Interatrial shunting (IAS) reduces left atrial pressure in patients with heart failure. Several clinical trials reported that IAS improved the New York Heart Association score and exercise capacity. However, its effects on haemodynamics vary depending on shunt size, cardiovascular properties, and stressed blood volume. To maximize the benefit of IAS, quantitative prediction of haemodynamics under IAS in individual patients is essential. The generalized circulatory equilibrium framework determines circulatory equilibrium as the intersection of the cardiac output curve and the venous return surface. By incorporating IAS into the framework, we predict the impact of IAS on haemodynamics.

Methods and results In seven mongrel dogs, we ligated the left anterior descending artery and created impaired cardiac function with elevated left atrial pressure (baseline: 7.8 ± 1.0 vs. impaired: 11.9 ± 3.2 mmHg). We established extracorporeal left-to-right atrial shunting with a centrifugal pump. After recording pre-IAS haemodynamics, we changed IAS flow stepwise to various levels and measured haemodynamics under IAS. To predict the impact of IAS on haemodynamics, we modelled the fluid mechanics of IAS by Newton’s second law and incorporated IAS into the generalized circulatory equilibrium framework. Using pre-IAS haemodynamic data obtained from the dogs, we predicted the impact of IAS flow on haemodynamics under IAS condition using a set of equations. We compared the predicted haemodynamic data with those measured. The predicted pulmonary flow ($r^2 = 0.88$, root mean squared error (RMSE) 11.4 mL/min/kg, $P < 0.001$), systemic flow ($r^2 = 0.92$, RMSE 11.2 mL/min/kg, $P < 0.001$), right atrial pressure ($r^2 = 0.92$, RMSE 0.71 mmHg, $P < 0.001$), and left atrial pressure ($r^2 = 0.83$, RMSE 0.95 mmHg, $P < 0.001$) matched well with those measured under normal and impaired cardiac function. Using this framework, we further performed a simulation study to examine the haemodynamic benefit of IAS in heart failure with preserved ejection fraction. We simulated the IAS haemodynamics under volume loading and exercise conditions. Volume loading and exercise markedly increased left atrial pressure. IAS size-dependently attenuated the increase in left atrial pressure in both volume loading and exercise. These results indicate that IAS improves volume and exercise intolerance.

Conclusions The framework developed in this study quantitatively predicts the haemodynamic impact of IAS. Simulation study elucidates how IAS improve haemodynamics under volume loading and exercise conditions. Quantitative prediction of IAS haemodynamics would contribute to maximizing the benefit of IAS in patients with heart failure.

Keywords Interatrial shunting; Heart failure; Circulatory equilibrium; Haemodynamics

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Introduction

The number of patients with heart failure (HF) is increasing with aging of the population.1 Regardless of the underlying aetiology of HF, 70–90% of patients with acute decompensated HF present with pulmonary congestion resulting from elevated left atrial pressure (P_LA).2,3 Frequent occurrence of acute decompensated HF leads to progressive deterioration of cardiac function and quality of life, resulting in poor survival outcome.4 Therefore, we need new strategies to prevent the acute elevation of P_LA in patients with HF.

Interatrial shunting (IAS) by transvenous catheter technique has been developed recently.5–8 IAS translocates blood volume from the pulmonary circulation to the systemic circulation and prevents the acute increase in P_LA. The degree of volume translocation depends on the pressure gradient between P_LA and right atrial pressure (P_RA). The interatrial shunt device system (IASD®), which was developed by Corvia Medical, Inc., is composed of left and right atrial discs (19 mm outer diameter) with an 8 mm communication. In a Phase 2 trial (REDUCE LAP-HF I), Feldman et al.6 reported that IASD® improved the NYHA score, increased the distance of 6 min walk, and attenuated the increase in pulmonary capillary wedge pressure (PCWP) during exercise. In contrast, IAS had little effect on PCWP or systemic flow (QS) at rest in patients with HF and preserved ejection fraction (HFrEF). The V-Wave® device (V-Wave Ltd.) with a 5.1 mm inner diameter is designed to prevent right-to-left atrial flow. In a Phase 1 clinical trial, Del Trigo et al.7 reported that the V-Wave® system improved the NYHA score and the distance of 6 min walk in patients with HF and reduced ejection fraction (HFpEF). Because various conditions other than the IAS size, such as right and left cardiac function, vascular properties, and stressed blood volume, may also affect the haemodynamic impact of IAS, the benefit of IAS varies among patients with HF. Wessler et al.8 reported that IASD® suppressed PCWP during exercise to a greater extent in patients with high PCWP at rest than in those with low PCWP. However, we do not have an established method or a single marker that detects responder or non-responder to IAS or indicate the appropriate device size for individual patients with HF. Quantitative prediction of the impact of IAS on haemodynamics is crucial and may allow appropriate selection of patient and device.

Guyton9 proposed that the intersection of the cardiac output (CO) curve, and the venous return curve represents the circulatory equilibrium. Sunagawa et al.10 extended this framework to include the pulmonary circulation by introducing P_LA and representing the CO curves and venous return as a function of P_RA and P_LA. They derived the analytical representation of the CO curve using the framework of ventricular arterial coupling and the venous return surface using the resistance-compliance distributed circuit (generalized circulatory equilibrium). The generalized circulatory equilibrium enabled us to predict haemodynamics under extracorporeal membrane oxygenation and left ventricular assist device.11–14

Using the concept of generalized circulatory equilibrium, we developed a simple framework to predict the impact of IAS on haemodynamics aiming to optimize IAS therapy in individual patients with HF. We validated the framework using a dog model of IAS with graded changes of the left to the right atrial shunt flow.

Methods

Theoretical considerations

Because IAS does not directly change the cardiac function or vascular properties, we consider that IAS haemodynamics can be modelled by simply applying the equation: QIAS = Q_R − Q_S in generalized circulatory equilibrium, where QIAS is the shunt flow, Q_R is pulmonary flow, and Q_S is systemic flow.

We derived the integrated CO curves from the left and right CO curves. In the left heart, the CO curve is a simple logarithmic function of P_LA as follows:

\[ Q_S = S_L \left[ \ln(P_{LA} - F_L) + H_L \right] \]

where S_L, F_L, and H_L are empirical parameters of the left heart. The values of F_L and H_L used in this study are 2.03 and 0.8, respectively, based on a previous report.12 In the right heart, the downstream pressure of the pulmonary artery, that is, P_LA, is not negligibly small relative to the mean pulmonary arterial pressure. We previously reported that the downstream pressure could be incorporated into the CO curves by the following equation:13–14:

\[ Q_R = S_R \left[ \ln(P_{RA} - F_R) + H_R \right] - \frac{1 - RVEF_e P_{LA}}{R_P} \]

where S_R, F_R, and H_R are empirical parameters of the right heart, RVEF_e is effective RV ejection fraction, and R_P is pulmonary vascular resistance. In this study, we set F_R = 2.13, H_R = 1.9, and RVEF_e = 0.6 for normal RV function, and R_P = 0.1 mmHg/mL/min/kg for normal pulmonary circulation as reported previously.12,14,15

We previously reported that in a distributed resistance-compliance vascular model, the following equations represent the stressed blood volume of the systemic circulation and pulmonary circulation:11:

\[ V_S = W_S Q_S + C_S P_{RA} \]  
\[ V_P = W_P Q_P + C_P P_{LA} \]

where \( V_S, V_P, V_L \) are stressed blood volume of systemic circulation, pulmonary circulation, and the sum of the two, respectively. \( W_S, W_P, C_S, \) and \( C_P \) are vascular parameters, respectively. We set \( W_S = 0.106 \text{ min}, W_P = 0.024 \text{ min}, \)
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$C_S = 2.53 \, \text{mL/mmHg/kg}$, and $C_P = 0.45 \, \text{mL/mmHg/kg}$ from previous reports.\textsuperscript{11,13,15,16}

We used Newton’s second law to model the IAS fluid dynamics as follows:\textsuperscript{17}

$$Q_{IAS} = Q_P - Q_S$$ \hspace{1cm} (6)

$$Q_{IAS} = C_d S_{IAS} \sqrt{\frac{2(P_{LA} - P_{RA})}{\rho}}$$ \hspace{1cm} (7)

where $Q_{IAS}$, $C_d$, $S_{IAS}$, and $\rho$ are IAS flow, discharge coefficient, cross-sectional area of IAS, and density of blood, respectively. We set $C_d = 0.74$ (unitless) and $\rho = 1.05 \, \text{g/cm}^3$ as reported previously.\textsuperscript{17,18} Once we have determined $S_L$, $S_R$, and $V_I$, we can predict IAS haemodynamics by simultaneously solving these seven equations. Details of the calculation are given in the Supporting Information.

**Animal preparation**

We used seven adult mongrel dogs weighing 14.3–17.9 kg. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1985). The Committee on Ethics of Animal Experiments at Kyushu University Graduate School of Medical Sciences approved the experiments.

We induced anaesthesia with intravenous pentobarbital sodium (25 mg/kg) and pancuronium bromide (0.08 mg/kg), performed endotracheal intubation, and maintained an appropriate anaesthesia level during the experiment by continuous infusion of isoflurane (1–2%). We kept body temperature between 37°C and 38°C. We bilaterally denervated the carotid sinuses and vagotomised to abolish the neural reflexes including baroreflex. We inserted a 5Fr sheath into the right femoral artery to measure arterial pressure (AP). We inserted a high-fidelity micromanometer (Millar Instruments, Houston, TX) into LV through the free wall. We inserted a pair of draining cannula and fluid-filled catheters each into the left (LA) and right atria (RA). We connected the fluid-filled catheters to pressure transducers (model DX-360; Nihonkohden, Tokyo, Japan) to measure $P_{LA}$ and $P_{RA}$. We connected the two cannulas via a centrifugal pump (CBBPX-80; Medtronic, Minneapolis, MN) to mimic IAS and mounted an in-line ultrasonic flowmeter (model XLI; Transonics, Ithaca, NY) in the circuit to measure $Q_{IAS}$ continuously. We also placed an ultrasonic flowmeter (model PSB; Transonic, Ithaca, NY) around the ascending aorta to measure $Q_S$ (Supporting Information, Figure S2). We estimated $Q_P$ as the sum of $Q_S$ and $Q_{IAS}$ ($Q_P = Q_{IAS} + Q_S$).

**Experimental protocols**

Under normal conditions, we first clamped the shunt circuit ($Q_{IAS} = 0$) and recorded baseline $Q_S$, $Q_P$, $P_{LA}$, and $P_{RA}$ (Figure 1). Using the baseline haemodynamic data, we estimated $S_L$, $S_R$, and $V_I$ from equations 1–5. We changed $Q_{IAS}$ stepwise to vary the ratio of the pressure gradient between $P_{LA}$ and $P_{RA}$ to $Q_{IAS}$ at 90, 60, 30, and $10 \times 10^{-3} \, \text{mmHg/mL/min/kg}$. In each step, after waiting for 1 min, we recorded $Q_S$, $Q_{IAS}$, $P_{LA}$, and $P_{RA}$ for 10 s. Because we created an artificial shunt, we estimated effective $S_{IAS}$ from $Q_{IAS}$ and the pressure gradient between $P_{LA}$ and $P_{RA}$ using equation 7. We predicted $Q_S$, $Q_P$, $P_{LA}$, and $P_{RA}$ from $S_L$, $S_R$, $V_I$, and $S_{IAS}$ and compared the predicted values with those measured.

After the experiment in the normal heart condition, we ligated the left anterior descending artery to create impaired cardiac function. One hour after the left anterior descending artery ligation, we repeated the same protocol as described above.

**Computational simulation**

Flash pulmonary oedema is a cardinal feature of HFP EF and is caused by an acute increase of $P_{LA}$ after volume loading or exercise.\textsuperscript{19,20} HFP EF may be a good indication for IAS intervention because IAS prevents the acute increase in $P_{LA}$. To elucidate the haemodynamic benefits of IAS in HFP EF patients, we performed a computational simulation study of haemodynamics with IAS under volume loading and exercise conditions in HFP EF patients using the proposed framework.

We determined the haemodynamic parameters of HFP EF patients based on previous reports as follows. Maeder et al.\textsuperscript{21} and Kaye et al.\textsuperscript{22} simulated exercise haemodynamics with IAS using a multi-factor haemodynamic model. To determine the CO curve, we used the following equation that we reported previously.\textsuperscript{12,23}

$$CO = \frac{1}{k E_{es}} \left( \ln\left( \frac{P_a - F}{H} \right) + H \right)$$ \hspace{1cm} (8)

where $E_{es}$, HR, $P_a$, are end-systolic elastance of ventricles, heart rate, resistance, and atrial pressure of systemic or pulmonary circulation, respectively; $k$ is the stiffness component of the ventricle. $F$ and $H$ are constants of the CO curve. We used equations 3–5 to determine the venous return surface. First, we determined $E_{es}$, R, and HR based on the simulation report of Kaye et al.\textsuperscript{22} We set $F$ to 0 to simplify the equation. The remaining parameters, that is, $k$, $H$, $W$, and $C$, were determined to reproduce the haemodynamics according to previous reports.\textsuperscript{21,22}

To simulate the exercise condition based on the report of Kaye et al.\textsuperscript{22} we increased $E_{es}$, heart rate and stressed volume; decreased resistance; and assumed the exercise conditions in HFpEF patients using the proposed framework.
intensity to be 0.63 W/kg, which was the limiting exercise intensity. We changed these parameters (Esr, heart rate, stressed volume, and resistance) linearly from 0 to 1 W/kg work rate. Details of the simulation parameters are given in the Supporting Information.

Protocol for the simulation study

In the volume loading simulation, we set baseline Qs at 5.3 L/min by changing stressed blood volume for various shunt sizes ranging from 0 to 20 mm in diameter. We then loaded blood volume until 1000 mL. In the exercise simulation, we set the same baseline as the volume loading simulation and changed exercise-related parameters according to the work rate from 0 to 1 W/kg.

Data analysis

We digitized all data at 200 Hz using a 16-bit analogue to digital converter (Power Lab 16/35; ADInstruments, NSW, Australia) and stored in a dedicated laboratory computer system. We averaged digitized data over 10 s when time-series data reached a steady state.

Statistical analysis

We expressed data as mean ± SD and used paired t-test to compare haemodynamics before and after the left anterior descending artery ligation. Repeated measures ANOVA was used for comparison of haemodynamic data under various IAS conditions. Differences were considered significant at P < 0.05. We performed the statistical analysis using R.
Results

Creation of impaired cardiac function in dogs

Table 1 shows haemodynamics before (Normal) and after induced myocardial infarction (Impaired). We determined SL, SR, and VT using haemodynamic data under Normal and Impaired conditions. Myocardial infarction significantly increased PLA and PRA and decreased SL. In contrast, myocardial infarction did not change SR significantly. VT remained unchanged irrespective of the induction of myocardial infarction.

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Figure 2 shows the representative time series of IAS haemodynamics. Increases in Q _IAS_ decreased AP, P _LA_ and Q _S_ but increased P _RA_. At maximum Q _IAS_ [(P _LA_ − P _RA_)/Q _IAS_ = 10 × 10⁻³ mmHg/mL/min/kg], the pressure difference between P _LA_ and P _RA_ was <1 mmHg. Haemodynamic data during IAS are summarized in Supporting Information, Table S1. As described in the Methods section, we determined S _L_, S _R_, and V _T_ and predicted haemodynamics at various levels of IAS flow. Figure 3 demonstrates the relationship between predicted and measured Q _P_, Q _S_, P _RA_, and P _LA_. The narrower error distributions and 95% confidence intervals show reasonable accuracy of the proposed framework.

Computational Simulation Study

Illustrated in Figure 4 is the simulated IAS haemodynamics during acute volume loading in HfPEF. Volume loading markedly increased venous pressures (P _RA_ and P _LA_) (Figure 4C and D) but marginally increased CO (Q _P_ and Q _S_) (Figure 4A and B), illustrating volume intolerance in HfPEF patients. IAS size-dependently attenuated the increase in P _LA_ (Figure 4D), implying that IAS improves volume tolerance at the expense of increased P _RA_ (Figure 4C) and Q _P_ (Figure 4A). The P _LA_ suppressing effect diminished when the IAS size was 8 mm or larger (Figure 4E).

Figure 5 illustrates the simulated IAS haemodynamics during exercise in HfPEF. As in the case of volume loading, IAS attenuated the increase in P _LA_ (Figure 5D and E). Exercise-induced increases in E _es_ and heart rate and decrease in resistance could lower P _LA_. However, exercise-induced increase in stressed volume counteracts these P _LA_-lowering effects and increases P _LA_. These results imply that volume intolerance of HfPEF leads to an increase in P _LA_ during exercise.

Discussions

In this study, we proposed a framework to predict the haemodynamic impact of IAS. In a dog model of IAS, the framework predicted haemodynamics under various IAS flow rates reasonably well in both normal and impaired cardiac

### Table 1 - Haemodynamics under normal and impaired left ventricular function

|                      | Normal       | Impaired     |
|----------------------|--------------|--------------|
| AP (mmHg)            | 119.3 ± 25.8 | 126.2 ± 21.0 |
| HR (b.p.m.)          | 147.9 ± 23.7 | 141.6 ± 18.5 |
| P _LA_ (mmHg)        | 7.8 ± 1.0    | 11.9 ± 3.2   |
| P _RA_ (mmHg)        | 5.5 ± 1.0    | 6.4 ± 1.2    |
| CO (mL/min/kg)       | 100.6 ± 30.0 | 89.3 ± 35.9  |
| Predicted S _L_ (mL/min/kg) | 50.0 ± 17.7 | 37.0 ± 16.6  |
| Predicted S _R_ (mL/min/kg) | 80.0 ± 26.2 | 77.9 ± 32.1  |
| Predicted V _T_ (mL/kg) | 30.5 ± 2.5  | 33.0 ± 2.6   |

Data are expressed as mean ± SD. S _L_ and S _R_ are parameters of the logarithmic function for left and right hearts, respectively. AP, arterial pressure; CO, cardiac output; HR, heart rate; P _LA_, left atrial pressure; P _RA_, right atrial pressure; V _T_, total stressed blood volume. P < 0.05.
function. Computational simulation study indicated that IAS below 20 mm in diameter size-dependently attenuated the increase in PLA in both volume loading and exercise loading under the HFpEF conditions.

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In theory, IAS does not alter $S_p$, $S_L$, pumping ability of the heart, $V_T$, or total stressed blood volume. However, IAS translocates the stressed blood volume from the pulmonary to the systemic circulation, depending on the pressure gradient between the right and left atria as well as IAS size. Thus, we modelled IAS haemodynamics by the shunt flow from the systemic circulation to the pulmonary circulation ($Q_{IAS} = Q_P - Q_S$) in generalized circulatory equilibrium. As shown in Figure 3, the proposed framework can predict IAS haemodynamics under various shunt flow rates irrespective of cardiac function. It is well known that the generalized circulatory equilibrium accurately describes the overall integrated haemodynamics, which is defined by the pressure and flow of the right and left heart. Once we established the model using haemodynamic parameters in a given condition, we could predict haemodynamics under various conditions such as myocardial infarction, blood volume gain and/or loss, extra-corporeal membrane oxygenation, and left ventricular assist device. The results of this study also support the robustness of generalized circulatory equilibrium.

Except for severe HF, $Q_S$ hardly decreases because the oxygen demand of the whole body determines $Q_S$. Therefore, the presence of IAS may not reduce $Q_S$ or $P_{LA}$ at rest. In contrast, IAS attenuates the $P_{LA}$ elevation against the increase of venous return to the left atrium. Because the slope of the CO curve is much steeper in the right ventricle than the left ventricle, the increase in $P_{LA}$ by IAS may be small compared with the decrease in $P_{LA}$.
Real-world validation

In order to validate the clinical feasibility of our proposed framework, we applied the data from the REDUCE LAP-HF I trial\(^6\) to our framework and compared the predicted values with those measured. To apply the clinical data to the simulation, we had to incorporate some assumptions into the framework. PRA and PLA were substituted by central venous pressure (CVP) and PCWP, respectively. Cd for clinical IAS was calculated from post-IAS pressure gradient (PCWP - CVP), QIAS, and equation 7 in the theoretical considerations section. We also assumed patients’ height to be 170 cm and adjusted the body weight to match the mean BMI in the original data.\(^8\)

We predicted post-IAS haemodynamics using baseline haemodynamics [CO, PCWP, CVP, systemic vascular resistance (Rs), and Rp]. As shown in Table 2 (constant \(V_I\)), we succeeded to predict the trend of haemodynamic changes after IAS. The predicted arterial pressure (AP), Qs, and PLA are lower than those measured at 6 months after IAS. Because our proposed framework predicts acute haemodynamic change after IAS, altered \(V_I\) in the chronic phase may contribute greatly to those differences. Considering this possibility, we adjusted post-IAS \(V_I\) so that mean post-IAS AP equalled that at baseline (adjusted \(V\)) and obtained better prediction of haemodynamics.

Optimization of interatrial shunting for clinical application

We predicted post-IAS haemodynamics using pre-IAS CO, \(P_{LA}\), and \(P_{RA}\). Because these parameters are generally available in clinical settings, we can predict post-IAS haemodynamics in each patient. It is well known that responders and non-responders to IAS therapy exist because several cardiovascular properties determine the impact of IAS on haemodynamics. In addition, recent device development has allowed selection of several sizes of IAS. Because the IAS size also affects the degree of PCWP and systemic CO reduction, we need to choose the optimal device size according to cardiovascular properties, volume status, and body size in an individual patient with HF. The framework that we developed makes it possible to predict the haemodynamics after IAS and assess patient-specific haemodynamic risks such as post-IAS low CO, high pulmonary flow causing pulmonary congestion.
hypertension, and worsening of right HF, which contributes to the selection of patient and IAS size.

Kaya et al.\textsuperscript{22} reported exercise haemodynamics in the presence of IAS using a multi-element haemodynamic model. Because they adjusted model parameters from human mass haemodynamic data, they did not address haemodynamic simulation in individual patients. Our proposed framework that allows prediction of patient-specific post-IAS haemodynamics using pre-IAS haemodynamic data is potentially applicable for IAS management in the clinical setting.

The results of previous clinical trials\textsuperscript{5–8} indicate that HFpEF is a good indication for IAS because rapid pulmonary congestion is a cardinal manifestation of HFpEF. In our simulation of HFpEF conditions, although baseline haemodynamics is relatively normal, volume loading or exercise significantly increases PLA (Figures 4 and 5). IAS markedly attenuates the increase in PLA in a size-dependent manner.

![Figure 5: Exercise simulation studies](image)

**Table 2** Prediction of IAS haemodynamics from real-world data

|                | Baseline | Measured | Prediction from pre-IAS Constant VT | Adjusted VT |
|----------------|----------|----------|-------------------------------------|-------------|
| Qp/Qs          | —        | 1.27     | 1.27                                | 1.26        |
| Qp (L/min)     | 4.6      | 6.1      | 5.5                                 | 5.6         |
| Qs (L/min)     | 4.6      | 4.8      | 4.3                                 | 4.5         |
| AP (mmHg)      | 96       | 97       | 91 (96 = Baseline)                 |             |
| PLa (mmHg)     | 17.4     | 16.5     | 14.4                                | 16.0        |
| PrA (mmHg)     | 9.0      | 10.6     | 9.6                                 | 11.4        |

Data are expressed as mean ± SD. AP, atrial pressure; IAS, interatrial shunt; PrA, left atrial pressure; Prs, right atrial pressure; Qp, pulmonary flow; Qs, systemic flow; VT, total stressed blood volume.
The relationship between the exercise capacity and IAS diameter under various degrees of diastolic dysfunction in heart failure with preserved ejection fraction (HFrEF) in simulation study. We assumed left atrial pressure ($P_{LA}$) = 28 mmHg as the exercise capacity under IAS (A) and compared the exercise capacity among three levels of diastolic dysfunction in HFP EF condition (B). We altered diastolic function in HFP EF by changing $k$, which represents the ventricular stiffness and governs the curvilinearity of the cardiac output curve (mild = 1.23, moderate = 1.3, severe = 1.35). See text Area not defined Methods section for detail, regarding the definition of the intensity of exercise (0 to 1 W/kg). In mild HFP EF, $P_{LA}$ does not exceed 28 mmHg by exercise under 1 W/kg when IAS size is over 5 mm. IAS strikingly increases exercise capacity, especially in moderate HFP EF. In severe HFP EF, IAS increases exercise capacity slightly. The solid line represents mild HFP EF, broken line represents moderate HFP EF, and dotted line represents severe HFP EF.

Conclusions

In conclusion, we predicted the impact of IAS on haemodynamics reasonably well using the generalized circulatory equilibrium. Simulation study reveals how IAS attenuates the elevation of $P_{LA}$ during volume loading conditions and exercise. Computational prediction of haemodynamics before the creation of an IAS would contribute to maximizing the benefit of IAS.

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Conflict of interest

Nishikawa T., Uike K., Uemura K., Tohyama T., and Yoshida K. have nothing to declare. Saku K. and Kishi T. worked in a department endowed by Omron Healthcare Co. Saku K. received honoraria from Japan ABIOMED Inc. Sunagawa K. worked in a department endowed by Omron Healthcare Co.
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**Supporting information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1. Supporting Information**

Table S1. Haemodynamics under mimicked interatrial shunting
Table S2. Values of model parameters that vary during exercise.
Table S3. Values of model parameters that are constant during exercise.
Figure S1 Supporting Information

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