Hemodynamic performance of the Fontan circulation compared with a normal biventricular circulation: a computational model study

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Liang F, Senzaki H, Kurishima C, Sughimoto K, Inuzuka R, Liu H. Hemodynamic performance of the Fontan circulation compared with a normal biventricular circulation: a computational model study. Am J Physiol Heart Circ Physiol 307: H1056–H1072, 2014. First published July 25, 2014; doi:10.1152/ajpheart.00245.2014.—The physiological limitations of the Fontan circulation have been extensively addressed in the literature. Many studies emphasized the importance of pulmonary vascular resistance in determining cardiac output (CO) but gave little attention to other cardiovascular properties that may play considerable roles as well. The present study was aimed to systematically investigate the effects of various cardiovascular properties on clinically relevant hemodynamic variables (e.g., CO and central venous pressure). To this aim, a computational modeling method was employed. The constructed models provided a useful tool for quantifying the hemodynamic effects of any cardiovascular property of interest by varying the corresponding model parameters in model-based simulations. Herein, the Fontan circulation was studied compared with a normal biventricular circulation so as to highlight the unique characteristics of the Fontan circulation. Based on a series of numerical experiments, it was found that 1) pulmonary vascular resistance, ventricular diastolic function, and systemic vascular compliance play a major role, while heart rate, ventricular contractility, and systemic vascular resistance play a secondary role in the regulation of CO in the Fontan circulation; 2) CO is nonlinearly related to any single cardiovascular property, with their relationship being simultaneously influenced by other cardiovascular properties; and 3) the stability of central venous pressure is significantly reduced in the Fontan circulation. The findings suggest that the hemodynamic performance of the Fontan circulation is codetermined by various cardiovascular properties and hence a full understanding of patient-specific cardiovascular conditions is necessary to optimize the treatment of Fontan patients.

Fontan circulation; computational model; cardiovascular properties; cardiac output; central venous pressure

The Fontan circulation is intrinsically abnormal due to the absence of a subpulmonary ventricle that provides energy to drive blood flow through the pulmonary circulation. The defect renders the Fontan circulation dependent critically on elevated central venous pressure to maintain cardiac output (CO). As a consequence, Fontan patients often have suboptimal hemodynamic conditions compared with normal biventricular subjects, such as higher venous pressure and lower CO (58, 59). More importantly, the single-ventricle defect significantly impairs the regulatory capacity of the circulatory system, resulting in profound cardiovascular limitations under stress, typically during exercise (27, 62, 76).

The unique single-ventricle physiology of the Fontan circulation has been extensively addressed in the literature (29, 33, 42, 49, 68). A prevalent viewpoint is that CO in a Fontan circulation is determined predominantly by pulmonary vascular resistance rather than by other cardiovascular properties (e.g., ventricular contractility and peripheral vascular resistance) that are generally known as important factors in the control of CO in a biventricular circulation (29, 42). The viewpoint can give a reasonable explanation as to why pulmonary vasodilators may increase resting CO and improve exercise tolerance in some Fontan patients (27, 78, 93). However, the predominant role of pulmonary vascular resistance might be challenged when the hemodynamic behaviors of the Fontan circulation are complicated by coexisting abnormalities in other cardiovascular properties. In fact, many patients with a Fontan circulation have been found to undergo chronic changes in peripheral vascular properties and progressive ventricular dysfunction after the operation (14, 24, 39, 61), i.e., few Fontan patients can sustain normal cardiovascular function in their long-term prognosis. In this sense, a thorough investigation on the ways in which different cardiovascular abnormalities affect hemodynamic characteristics of the Fontan circulation may provide useful knowledge to help doctors identify the factors that dominate the pathological hemodynamic conditions of a specific patient and accordingly implement the most efficacious therapy.

Computational modeling methods have been widely adopted to provide quantitative insights into hemodynamic phenomena associated with single-ventricular circulation (19, 32, 36, 40, 41, 51, 54, 55a, 63, 64, 83, 85, 87). However, the majority of existing studies focused on local hemodynamic phenomena, such as flow patterns, wall shear stress distribution in a cavo-pulmonary anastomosis, or associated energy loss (19, 32, 36, 83, 85, 87). In studies where systemic hemodynamics was addressed, cardiovascular properties were usually fixed (55a),
tuned to specific patients (40, 54, 63, 64), or adjusted to represent certain physiological conditions (41, 51). So far, little effort has been taken to comprehensively study the hemodynamic performance of the Fontan circulation in a wide range of cardiovascular conditions.

The present study was therefore carried out to systemically investigate the hemodynamic performance of the Fontan circulation under various cardiovascular conditions, with emphasis on addressing the responses of clinically relevant hemodynamic variables (such as CO and central venous pressure) to variations in cardiovascular properties, particularly those related to ventricular function and cardiac loading conditions. For this purpose, we constructed a computational model for the Fontan circulation. The model explicitly expressed cardiovascular properties (such as ventricular contractility, pulmonary vascular resistance, etc.) with lumped parameters, thus allowing the hemodynamic impacts of any cardiovascular property of interest to be studied separately and quantitatively. We first identified the model parameters that dominate the model-simulated results for hemodynamic variables of concern by performing model sensitivity analysis and subsequently quantified the hemodynamic effects of each model parameter by means of numerical experiments. Moreover, a parallel study was carried out for the biventricular circulation as a comparison to highlight the unique characteristics of the Fontan circulation.

METHODS

Model Development

A computational model was first constructed for a normal biventricular circulation with the lumped parameter modeling method. The resulting model consisted of a limited number of parameters but carried sufficient details to account for the key hemodynamic behaviors, such as cardiac dynamics and its interactions with preload and afterload. A Fontan circulation model was obtained later by incorporating a total cavopulmonary connection (TCPC), which bypasses the right atrium and ventricle, into the biventricular circulation model. As a consequence, the left ventricle is the unique normally functioning ventricle in the modeled Fontan circulation. An electric circuit analogy of the biventricular circulation model is shown in Fig. 1A and that of the Fontan circulation model is shown in Fig. 1B.

Fig. 1. Electric circuit analogies of the biventricular circulation model (A) and the Fontan circulation model (B). Notation of parameters: E, elastance; L, inertance; R, viscous resistance; C, compliance; B, Bernoulli’s resistance; S, viscoelasticity coefficient; Pit, intrathoracic pressure; Ppc, pericardium pressure. ra, right atrium; rv, right ventricle; tv, tricuspid valve; pv, pulmonary valve; pua, pulmonary artery; puc, pulmonary capillary; puv, pulmonary vein; la, left atrium; lv, left ventricle; mv, mitral valve; av, aortic valve; ao, aorta; art, systemic artery; cap, systemic capillary; ven, systemic vein; ivc, inferior vena cava; svc, superior vena cava; ten, atrial tunnel; _l, lower body; _u, upper body.

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Modeling of the pulmonary and systemic vascular systems. The pulmonary vascular system was represented by three serially arranged compartments that represent the arterial, capillary, and venous vascular portions, respectively. The systemic vascular system was divided into aorta, vena cava, and two parallel-arranged upper-body and lower-body subsystems (see Fig. 1). Each vascular portion was represented by a Windkessel model consisting of three parameters [namely, resistance (R), compliance (C), and inertance (L)] that account for the viscous resistance to blood flow, wall deformability, and blood inertia of the vascular portion, respectively. If we name the C elements as “P” nodes and the nodes between R and L elements as “Q” nodes along the pathway of blood flow (see Fig. 2), the governing equations for blood flow can be formulated by imposing mass or momentum conservation at the nodes.

At a P node, formulating mass conservation yields
\[ \frac{dP_j}{dr} = \frac{Q_j - Q_{j+1}}{C_j}, \]  
and at a Q node, momentum conservation reads
\[ \frac{dQ_j}{dr} = \frac{P_{j-1} - Q R_j - P_j}{L_j}, \]
where \( P_j \) and \( P_{j-1} \) denote the blood pressures at the \( C_j \) and \( C_{j-1} \) elements, respectively; \( t \) is time; \( Q_j \) and \( Q_{j+1} \) represent, respectively, the inflow to and outflow from the \( C_j \) element; and \( R_j \) and \( L_j \) are the resistance and inertance that link the \( C_j \) and \( C_{j-1} \) elements.

Modeling of the heart. Modeling of cardiac contraction/relaxation. The heart was modeled as a four-chamber organ according to its anatomical structure. The contracting/relaxing action of each cardiac chamber was represented by a time-varying elastance function derived from the well-known myocardial elastance theory (81). In previous studies (34, 74), blood pressure \( (P_v) \) in each cardiac chamber was defined as a function of elastance \((E)\) and chamber volume \((V)\). In the present study, we further took into account the viscoelastic property of cardiac walls to more reasonably describe cardiac hemodynamics
\[ P_v(t) = E(t)(V - V_0) + \frac{dV}{dt}, \]
where \( V_0 \) refers to the unstressed volume (here set to be zero) and \( S \) is the viscoelasticity coefficient of the cardiac walls, which is herein taken to be a function of \( P_v \) (84).

The elastance function \([E(t)]\) was used to account for the dynamic contraction-relaxation behavior together with the passive mechanical properties of the cardiac chamber, which was herein defined as the sum of a time-varying component and a constant in light of the models adopted in previous studies (34, 47)
\[ E(t) = E_a e(t) + E_p. \]
Here, the first term on the right-hand side describes the time-varying chamber elastance resulting from the active stimulation of myocardial fibers, with a peak value of \( E_a \) which represents the contractility of the myocardium, while the second term \( (E_p\) herein termed passive elastance) represents the baseline stiffness of the cardiac chamber in the absence of active stimulation, reflecting the passive mechanical properties of myocardial fibers. \( E_a \) and \( E_p \) are denoted, respectively, by \( E_{lea} \) and \( E_{lep} \) for the left ventricle, \( E_{rea} \) and \( E_{rpe} \) for the right atrium, \( E_{lea} \) and \( E_{lep} \) for the right ventricle, and \( E_{rea} \) and \( E_{rpe} \) for the left atrium. \( e(t) \) is a normalized time-varying function of the active elastance and was expressed by a piecewise function. The function takes different forms for the ventricles and atria.

For the left and right ventricles, we modified the elastance function used in Refs. 34, 47 to further account for the effect of the time constant of isovolumic relaxation on diastolic function,
\[ e_a(t) = \begin{cases} 0 & 0 \leq t \leq T_{vcp} \\ \frac{0.5 \left[ 1 - \cos \left( \frac{\pi}{2} T_{vcp} \right) \right] + \exp \left( - \frac{(T_{vcp} - T_0)}{\tau_{ur}} \right) \cos \left( \frac{\pi}{2} T_{vcp} \right)}{\exp \left( - \frac{(T_{vcp} - T_0)}{\tau_{ur}} \right)} & T_{vcp} < t \leq T_0 \end{cases} \]

and for the left and right atria, the function proposed in our previous studies (47) was adopted,
\[ e_a(t) = \begin{cases} 0.5 \left[ 1 + \cos \left( \frac{\pi}{2} (T_0 - t_{ar}) / T_{ar} \right) \right] & 0 \leq t \leq t_{ar} + T_{arp} - T_0 \\ 0 & T_{arp} - T_0 < t \leq t_{ar} \end{cases} \]
\[ + \begin{cases} 0.5 \left[ 1 - \cos \left( \frac{\pi (t - t_{uc})}{T_{uc}} \right) \right] & t_{uc} < t \leq t_{uc} + T_{ucp} \\ 0.5 \left[ 1 + \cos \left( \frac{\pi (t - t_{uc})}{T_{uc}} \right) \right] & t_{uc} + T_{ucp} < t \leq T_0 \end{cases} \]

Here, the subscript “\( V \)” denotes the ventricles and “\( A \)” the atria, \( T_0 \) is the duration of a cardiac cycle, \( T_{vcp} \) and \( T_{ucp} \) refer, respectively, to the durations of ventricular contraction and atrial contraction, \( T_{arp} \) is the duration of atrial relaxation, \( \tau_{ur} \) is the time constant of ventricular isovolumic relaxation, and \( t_{uc} \) and \( t_{ar} \) denote, respectively, the times when the atria begin to contract and relax.

It is worth noting that the mathematical expressions of cardiac elastance function present significant variations in the literature (77), although most of them have been constructed based on the elastance theory (81). In the present study, the ventricular elastance function has been formulated to clearly parameterize the different aspects of ventricular function so that the hemodynamic effects of ventricular function can be quantitatively studied by varying a limited number of model parameters (i.e., \( E_a, E_p, \) and \( \tau_{ar} \)) in the simulations.

Modeling of cardiac valves. The pressure gradient \( (\Delta P_v) \) across a cardiac valve was related to transvalve flow rate \( (Q_v) \) by (47, 84).

**Fig. 2.** A typical P node (A) and Q node (B) along flow pathway.
\[ \Delta P_{cv} = R_{cv}Q_{cv} + B_{cv}Q_{cv} \left| \frac{dQ_{cv}}{dt} \right| + L_{cv} \frac{dQ_{cv}}{dt} + R_{do}Q_{cv}, \]  

where \( R_{cv}, B_{cv}, \) and \( L_{cv} \) represent, respectively, the transvalve viscous resistance, Bernoulli’s resistance, and blood inertance when the valve is opened; and \( R_{do} \) is a nominal resistance used to control the opening and closing of the cardiac valve so that ventricle-to-atrium or artery-to-ventricle reverse flow does not occur. Here, \( R_{do} \) plays the role of a diode, with its value being dynamically switched between infinity and zero depending on time-dependent hemodynamic conditions. Taking the aortic valve as an example,

\[
R_{do} = \begin{cases} 
0 & P_{lv} - P_{ao} > 0 \\
\infty & P_{lv} - P_{ao} < 0 & \text{or } Q_{ao} \to 0 
\end{cases}
\]  

where \( P_{lv} \) and \( P_{ao} \) refer, respectively, to the blood pressures in the left ventricle and the aorta and \( Q_{ao} \) is the blood flow rate across the aortic valve. When the value of \( R_{do} \) is switched from \( \infty \) to 0, the valve is opened; otherwise, the valve is closed.

**Relationship Between Ventricular Systolic Duration and Heart Rate.** Heart rate (HR) is an important physiological factor involved in the regulation of CO. A change in HR alters not only the length of ventricular systolic duration but also the proportion of systolic duration to the entire cardiac cycle. Although many formulas have been used to account for the variation of systolic duration with HR (34, 60), so far, no formula has been confirmed to be valid over a wide range of HR. Fortunately, a large amount of in vivo data on the relationship between ECG QT interval and RR interval (60) has been reported in the literature (1, 8, 15, 20, 37, 69, 70). These data allowed us to construct a theoretical formula for the QT-RR relation by means of data fitting. Herein, a second-degree polynomial function was used to fit the in vivo data (see Fig. 3).

\[
QT = -0.33RR^2 + 0.69RR + 0.029.
\]  

Here, QT (with its unit being second) represents the ventricular electrical systole ranging from the beginning of the QRS complex to the end of the T wave on an ECG. QT is closely related to but not a strict measure of the systolic duration (\( T_{vcp} \)) defined in our ventricular model (Eq. 5). Herein, we assumed that \( T_{vcp} \) and QT are linearly related (\( T_{vcp} = \alpha QT \)). The constant \( \alpha (=0.714) \) was determined by fitting the modeled ventricular elastance curve (at HR = 80 beats/min) to measured data (74) (see Fig. 4). For other time parameters used in the atrial model (Eq. 6), since reports on their relations to HR are rare, we assumed them to be functions of \( T_{vcp} \): \( T_{ar} = 0.6T_{vcp}, T_{arp} = T_{ar} - 0.05, T_{acp} = T_{arp} - 0.5, T_{ac} = T_{acp} - 0.05, \) and \( t_{au} = t_{ar} + T_{ar} \).

**Relationship Between \( T_{au} \) and HR.** The time constant (\( \tau_{au} \)) of ventricular isovolumic relaxation varies with HR (7, 22, 48, 79). Their relationship was approximated by an exponential function derived from data fitting (see Fig. 5).

\[
\tau_{au} = 30.2e^{-HR/81.2} + 31.4.
\]  

Here, the unit of \( \tau_{au} \) is taken to be millisecond in line with the measured data but will be converted to second when used in Eq. 5.

**Numerical Methods**

The models of the biventricular circulation and Fontan circulation were each governed by an ordinary differential equation system (see **APPENDIX** for the details of the governing equations) coupled with algebraic equations that describe the nonlinear elements (i.e., cardiac elastances). The equation system was solved in an explicit time-
marching manner using a multivariable fourth-order Runge-Kutta method (45). The numerical time step was fixed at 0.0002 s, which was found to enable a stable convergence of all the simulations carried out in the present study. A computer code was written in FORTRAN language for each model and run on a personal computer installed with a Linux OS. The inputs to the codes consist of values of model parameters and initial values of model state variables. Since the assigned initial conditions may deviate from the converged state of the models, each simulation was repeated for several cardiac cycles until a periodic solution (the maximum percentage change in simulated blood pressures between the last 2 cardiac cycles is <0.01%) was obtained. Convergence of the models is guaranteed by the closed-loop nature of the models in which any perturbations introduced by the initial conditions will be swept out when a global hemodynamic balance over the cardiovascular system is achieved after repeated simulations. Our numerical experiments proved that the simulations converged rapidly (usually converged within 100 cardiac cycles) in spite of random changes in assigned initial conditions. However, it should be noted that the initial conditions can significantly affect the results of simulation. For instance, a variation in initial total blood volume (sum of the blood volumes assigned to the vascular “C” components and cardiac chambers) can induce considerable changes in simulated central venous pressure and CO. With these in mind, we have adjusted the initial conditions together with model parameters to allow simulated hemodynamic variables to fall within the ranges of measured data.

Parameter Assignment

Biventricular model. Model parameters were initially assigned based on population-averaged data reported in the literature so that the biventricular circulation model can capture the general hemodynamic characteristics of healthy young adult subjects. The height and weight of the simulated subject were set, respectively, to be 175 cm and 75 kg. Accordingly, the body surface area was calculated to be 1.92 m². The total vascular compliance (Ctot) and pulmonary vascular compliance (Cpul) were related to body weight, respectively, by Ctot = 2.1 × weight (90) and Cpul = 0.408 × weight (55). The distribution of vascular compliance along the pulmonary vascular system was set to be 0.08:0.65:0.27 for the artery, capillary, and venous beds (67) and that of resistance was set to be 0.46:0.34:0.20 (12). The parameters used in the cardiac model were derived from Refs. 45, 47, 84. Other model parameters were assigned based on the data reported in Refs. 25, 34, 47, 90 but were further refined to improve the agreement between model simulations and measured data. Herein, data fitting was targeted on the systemic hemodynamic data, such as CO, mean aortic pressure, mean pulmonary arterial pressure, and mean central venous pressure. Accordingly, the total systemic vascular resistance, the total pulmonary vascular resistance, and the total blood volume were adjusted via a parameter optimization algorithm (herein the Nelder-Mead method employed in our previous studies; Refs. 46, 82) where the values of the parameters and total blood volume are iteratively modified to minimize the root mean squared error between model simulations and measured data. The resulting parameter values (herein taken as the default parameter values) for the biventricular circulation model are summarized in Table 1. Hemodynamic variables simulated under resting conditions (HR = 75 beats/min) are compared with in vivo data in Table 2. It is observed that all the simulated results (column 3) fall within the ranges of in vivo data (column 2, population-based data acquired in adult subjects free from severe cardiovascular diseases; Refs. 4, 5, 10, 11, 13, 18, 23, 50, 52, 71, 73, 80, 94).

Fontan model. When a Fontan circulation model (herein named baseline Fontan model) was initially created by modifying the biventricular circulation model, the values of model parameters were maintained unchanged. The new parameters involved in the Fontan model are those used to describe the lateral atrial tunnel (or extracardiac conduit). These parameters are not derivable from the literature, although there exist a number of studies addressing energy loss or flow resistance associated with TCPC (32, 85). We herein estimated the parameters from the geometric data of atrial tunnel or extracardiac conduit measured in Fontan patients (2, 91). Based on the measured data, the diameter and length of the atrial tunnel in an adult Fontan patient were assumed to be 25 and 63.7 mm, respectively. Further assuming the intratunnel blood flow to be laminar and Newtonian, we calculated the flow resistance (Rten in Fig. 1B) of the tunnel to be 2.93E-6 mmHg·s·ml according to Poiseuille’s Law. Blood inertia (Lten in Fig. 1B) in the tunnel was obtained by integrating the flow momentum equation along the tunnel, which was 0.001 mmHg·s²·ml. Due to the lack of data on the mechanical properties of the tunnel wall, the compliance of the tunnel (Cten in Fig. 1B) could not be derived theoretically and was herein assumed to be 0.1 ml/mmHg. Hemody-

### Table 1. Default values of the parameters used in the biventricular circulation model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Heart</th>
<th>Cardiac valves</th>
<th>Pulmonary vascular system</th>
<th>Aorta</th>
<th>Vena cava</th>
<th>Systemic vascular system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eren = 0.13</td>
<td>Eren = 0.13</td>
<td>Eren = 0.48</td>
<td>Eren = 0.05</td>
<td>Ssa = Psa × 0.0005</td>
<td>Ssa = Psa × 0.0005</td>
<td>Ssa = Psa × 0.0005</td>
</tr>
<tr>
<td>Elen = 0.25</td>
<td>Elen = 0.25</td>
<td>Elen = 2.87</td>
<td>Elen = 0.056</td>
<td>Ssa = Psa × 0.0005</td>
<td>Ssa = Psa × 0.0005</td>
<td>Ssa = Psa × 0.0005</td>
</tr>
<tr>
<td>Lsv = 5E-4</td>
<td>Lsv = 1E-5</td>
<td>Rsv = 1E-3</td>
<td>Lsv = 5E-4</td>
<td>Rsv = 1.5E-5</td>
<td>Rsv = 1.5E-5</td>
<td>Rsv = 1.5E-5</td>
</tr>
<tr>
<td>Lrv = 5E-4</td>
<td>Lrv = 1E-5</td>
<td>Rrv = 1E-3</td>
<td>Lrv = 5E-4</td>
<td>Rrv = 1.5E-5</td>
<td>Rrv = 1.5E-5</td>
<td>Rrv = 1.5E-5</td>
</tr>
<tr>
<td>Lpv = 4E-4</td>
<td>Lpv = 0.035</td>
<td>Cpul = 2.45</td>
<td>Lpv = 2E-4</td>
<td>Rpul = 0.0259</td>
<td>Rpul = 0.0259</td>
<td>Rpul = 0.0259</td>
</tr>
<tr>
<td>Lv = 3E-4</td>
<td>Lv = 0.0152</td>
<td>Cpul = 8.26</td>
<td>Lpv = 2E-4</td>
<td>Cpul = 19.89</td>
<td></td>
<td></td>
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<td>Lao,1 = 0.015</td>
<td>Ra1,1 = 0.043</td>
<td>Lao,1 = 0.01</td>
<td>Ra1,1 = 0.1</td>
<td>Cao = 1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lao,1 = 1E-3</td>
<td>Rsv = 7.1E-3</td>
<td>Cao = 16.75</td>
<td>Lao,1 = 1E-3</td>
<td>Rsv = 1.7E-2</td>
<td>Cao = 2.28</td>
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</tr>
<tr>
<td>Lao,1 = 5E-3</td>
<td>Ra1,1 = 0.9</td>
<td>Cao,1 = 0.56</td>
<td>Lao,1 = 5E-4</td>
<td>Cao,1 = 0.21</td>
<td>Cao,1 = 0.26</td>
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</tr>
<tr>
<td>Lao,1 = 1E-3</td>
<td>Ra1,1 = 0.043</td>
<td>Cao,1 = 93.2</td>
<td>Lao,1 = 5E-4</td>
<td>Cao,1 = 0.5</td>
<td>Cao,1 = 0.036</td>
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<tr>
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<td>Cao,1 = 0.076</td>
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<td>Ra1,1 = 0.1</td>
<td>Cao,1 = 12.7</td>
<td>Lao,1 = 5E-4</td>
<td>Cao,1 = 0.5</td>
<td>Cao,1 = 0.036</td>
<td></td>
</tr>
</tbody>
</table>

Units of parameters are as follows: elastance (E), mmHg·s·ml; viscoelasticity coefficient (S), mmHg·s·ml⁻¹; resistance (R), mmHg·s·ml⁻¹; inertance (L), mmHg·s²·ml⁻¹; compliance (C), ml/mmHg; Bernoulli’s resistance (B), mmHg·s²·ml⁻². See text and Fig. 1 legend for additional definitions.

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Table 2. Comparisons between simulations and measurements

<table>
<thead>
<tr>
<th>Variable or Index</th>
<th>Measured Data (Biventricular)</th>
<th>Simulation (Biventricular)</th>
<th>Measured Data (Fontan)</th>
<th>Simulation (Baseline Fontan)</th>
<th>Simulation (Physio. Fontan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI, l/min (^{-1})</td>
<td>2.8–4.2 ((33, 4)), 3.2 ((80))</td>
<td>3.3</td>
<td>2.9 ((59)), 2.1 ((58))</td>
<td>1.8</td>
<td>2.3</td>
</tr>
<tr>
<td>SV, ml/m(^2)</td>
<td>30–65 ((39), 52.7 ((4))</td>
<td>44.2</td>
<td>39 ((59)), 40 ((58))</td>
<td>24.1</td>
<td>38.9</td>
</tr>
<tr>
<td>CCV, ml/m(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV (end-diast./syst.)</td>
<td>63/16 ((4), 58/18 ((71))</td>
<td>65.6/21.4</td>
<td>72/33 ((59), 76/36 ((58))</td>
<td>36.2/11.0</td>
<td>59.4/20.5</td>
</tr>
<tr>
<td>LA (maxi.)</td>
<td>22 ((4), 15–42 ((5))</td>
<td>22.0</td>
<td>–</td>
<td>–</td>
<td>11.4</td>
</tr>
<tr>
<td>RV (end-diast./syst.)</td>
<td>68/21 ((33))</td>
<td>69.9/25.7</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RA (maxi.)</td>
<td>21 ((33), 18–50 ((5))</td>
<td>22.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV (end-diast.)</td>
<td>90–140 ((4–12) ((73))</td>
<td>118.3/6.8</td>
<td>–/6.6 ((59)), –/8 ((58))</td>
<td>70.3/3.5</td>
<td>115.5/6.0</td>
</tr>
<tr>
<td>LA (mean)</td>
<td>7.9 ((11), 7.5 ((10))</td>
<td>7.2</td>
<td>–</td>
<td>3.6</td>
<td>5.8</td>
</tr>
<tr>
<td>RV (end-diast.)</td>
<td>17–31.5/0.5–7 ((23))</td>
<td>27.7/6.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>RA (mean)</td>
<td>4.9 ((11), 2–5 ((5))</td>
<td>4.2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>VC (mean)</td>
<td>4.7 ((33), 5.9 ((80))</td>
<td>10.6 ((50), 10 ((58))</td>
<td>8.4</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>SA (syst./diast./mean)</td>
<td>123/77/92 ((82))</td>
<td>118.5/76/93.9</td>
<td>124/70/88 ((90))</td>
<td>71.6/47/157.0</td>
<td>115.8/64, 58/6.8</td>
</tr>
<tr>
<td>PA (syst./mean)</td>
<td>230/15 ((88))</td>
<td>25.1/10.4/15.3</td>
<td>9 ((80)) (mean)</td>
<td>7.9 (mean)</td>
<td>11.5 (mean)</td>
</tr>
</tbody>
</table>

CI, cardiac index; SV, stroke volume; CCV, cardiac chamber volume; LV, left ventricle; LA, left atrium; RV, right ventricle; RA, right atrium; VC, vena cava; SA, systemic artery; PA, pulmonary artery. Reference numbers are in parentheses. Characteristics of biventricular subjects involved in in vivo measurements of hemodynamic variables: Ref. 4: mean value in normal young subjects (7 male, 7 female, mean age: 28.9 yr); Ref. 5: normal reference range determined from measurements in 11 normal male subjects (age: 29–80 yr); Ref. 10: mean value in 3 subjects free from cardiovascular disease (2 male, 1 female, mean age: 43 yr); Ref. 11: mean value in 18 normal subjects (11 male, 7 female, mean age: 21 yr); Ref. 13: mean value in 28 patients who were critically ill but without severe cardiovascular diseases; Ref. 18: mean value in 8 subjects with a normal cardiovascular-pulmonary system; Ref. 23: normal reference range determined from measurements in 79 normal male subjects (age: 29–80 yr); Ref. 50: mean value in 40 adult patients with moderate cardiovascular diseases; Ref. 52: mean value in 183 normal male subjects (age: 30–39 yr); Ref. 71: mean value in 63 normal male subjects (mean age: 56.7 yr); Ref. 73: normal reference range obtained in population-based in-vivo studies; Ref. 80: mean value in 5 normal adults; Ref. 92: mean value in 23 normal males (mean age: 38.4 yr); Ref. 94: mean value in 105 adults (51 men, 54 women, mean age: 39 yr) with sinus rhythm but free from other cardiovascular diseases. Characteristics of Fontan patients involved in in vivo measurements of hemodynamic variables: Ref. 39: mean value in 9 patients (5 male, 4 female, age: 13–24 yr) with “good” clinical outcome after undergoing Fontan operation 8 to 19 yr ago; Ref. 58: mean value in 11 clinically stable Fontan patients (mean age: 22 yr); Ref. 59: mean value in 27 patients who had no history of any clinical event that required hospitalization during the first 10 yr after Fontan operation.

A

B

Fig. 6. Comparison between simulated (A) and measured (B) pulmonary arterial flow waveform for the Fontan circulation and the biventricular circulation. Each flow waveform has been normalized by its mean value averaged over a cardiac cycle to facilitate comparison. The measured data were adopted from Hager et al. (31), where the flow waveforms have been obtained by superimposing the waveforms measured in different subjects. To facilitate comparison, each flow waveform has been normalized by the mean flow rate averaged over a cardiac cycle. The simulations are comparable to the measurements in terms of the primary differences in the contour of flow waveform between the biventricular circulation and the Fontan circulation. For instance, both our results and the in

colic simulation for the baseline Fontan model shows that the biventricular-to-Fontan circulation conversion induces a significant reduction in the cardiovascular index (by 45.5%) and a marked increase in venous pressure (by 78.7%; column 5). However, the baseline Fontan model is found not to reasonably reproduce the in vivo data measured in Fontan patients without severe clinical symptoms (39, 58, 59, column 4). Under real physiological conditions the cardiovascular properties of a Fontan circulation may differ from those of a normal biventricular circulation due to the onset of adaptive responses to impaired hemodynamic conditions after the Fontan operation. For instance, a Fontan circulation usually has increased peripheral vascular resistance and reduced venous compliance (39, 43). Therefore, we adjusted the model parameters (by increasing the peripheral vascular resistance by 22.6%, reducing the systemic venous compliance by 36% and reducing resting HR from 75 to 60 beats/min based on the data reported in Ref. 39) to build a physiological Fontan circulation model. Moreover, pulmonary vascular compliance was reestimated based on the in vivo data reported in (75): \( C_{pulc} = 0.289 \text{ ml/mmHg}, C_{pulc} = 2.347 \text{ ml/mmHg}, \) and \( C_{pulc} = 0.975 \text{ ml/mmHg}. \) As can be seen from column 6 in Table 2, after parameter adjustment, the simulated CO, stroke volume, central venous pressure and aortic pressure get closer to the in vivo data (column 4).

To further examine the ability of our models to capture the hemodynamic differences between the biventricular and Fontan circulation, we investigated the transient pulmonary arterial flow, which is expected to be significantly influenced by bypass of the right heart. Figure 6A shows the pulmonary arterial flow waveforms simulated using the biventricular model and the physiological Fontan model (under resting conditions). Figure 6B shows the in vivo data measured in control subjects (17 healthy subjects with a normal biventricular circulation) and Fontan patients (5 Fontan patients with TCPC) (31), where the illustrated flow waveforms have been obtained by superimposing the waveforms measured in different subjects. To facilitate comparison, each flow waveform has been normalized by the mean flow rate averaged over a cardiac cycle. The simulations are comparable to the measurements in terms of the primary differences in the contour of flow waveform between the biventricular circulation and the Fontan circulation. For instance, both our results and the in

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Here, $S_{i,j}$ is the percentage change in a hemodynamic variable ($P_j$) induced by a small change in a model parameter ($x_i$), reflecting the sensitivity of $P_j$ to $x_i$. $S_{i,j}$ has been nondimensionalized to enable a cross comparison between sensitivity indexes calculated for different $P_j$, $x_i$ pairs. $X = (x_1, x_2, ..., x_n)$ represents the parameter vector at a sampling point ($n$ indicates the number of model parameters).

Finally, $S_{i,j}$ obtained at all sampling points was statistically analyzed by calculating the mean ($\bar{S}_{i,j}$) and standard deviation ($\sigma_{i,j}$) according to the following equations

$$S_{i,j} = \frac{x_i \partial P_j(X)}{P_j(X) \partial x_i} \times 100. \quad (11)$$

$$\bar{S}_{i,j} = \frac{1}{M} \sum_{k=1}^{M} S_{i,j}^k, \quad (12)$$

$$\sigma_{i,j} = \sqrt{\frac{1}{M} \sum_{k=1}^{M} \left( S_{i,j}^k - \bar{S}_{i,j} \right)^2}, \quad (13)$$

where $M$ represents the total number of sampling points (herein = 3,000) and $\bar{S}_{i,j}$ is the sensitivity index calculated at the no. $k$ sampling point.

The results of sensitivity analysis performed on the baseline Fontan model are reported in form of means $\pm$ SD in Table 3. Here, the larger the mean value of the sensitivity index, the stronger the influence of the parameter on the corresponding hemodynamic variable is. A large SD indicates the existence of strong correlation of the studied parameter with the remaining parameters in determining the sensitivity index. It is noted that the pulmonary vascular system has been evaluated as a whole with respect to total pulmonary resistance ($R_{pul}$), compliance ($C_{pul}$), and inertance ($I_{pul}$) by varying the $R$, $C$, or $L$ of different pulmonary vascular portions simultaneously in our sensitivity analysis. A similar evaluation was performed for the systemic vascular system as well.

From Table 3, seven model parameters were found to dominate the model-simulated results of the hemodynamic variables of interest [i.e., mean central venous pressure ($mPv$), mean left atrial pressure ($mPla$), mean aortic pressure ($mPao$), and CO], which include the maximum active elastance ($E_{act}$) and baseline passive elastance ($E_{bas}$) of the left ventricle, the total pulmonary vascular resistance ($R_{pul}$), the total pulmonary vascular compliance ($C_{pul}$), the total systemic vascular compliance ($C_{sys}$), the total systemic vascular resistance ($R_{sys}$), and the time constant of ventricular isovolumic relaxation ($\tau_{syst}$). $E_{iva}$ is a measure of left ventricular systolic function and $E_{ivp}$ and $\tau_{syst}$ together characterize left ventricular diastolic function.

Computation Conditions

Table 4. Ranges of model parameter variation assigned to the biventricular circulation model and the Fontan circulation model

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>Default Value</th>
<th>Range of Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{iva}$, mmHg/ml</td>
<td>2.87</td>
<td>(0.5 – 2.3) * $E_{iva}$0</td>
</tr>
<tr>
<td>$E_{ivp}$, mmHg/ml</td>
<td>0.056</td>
<td>(0.70 – 7.0) * $E_{ivp}$0</td>
</tr>
<tr>
<td>$\tau_{syst}$, ms</td>
<td>Function of HR</td>
<td></td>
</tr>
<tr>
<td>$R_{pul}$, mmHg/s/ml</td>
<td>0.076</td>
<td>(0.2 – 5.0) * $R_{pul}$0</td>
</tr>
<tr>
<td>$R_{sys}$, mmHg/s/ml</td>
<td>0.84 (Biventricle),*</td>
<td>(0.50 – 1.6) + $R_{sys}$0</td>
</tr>
<tr>
<td>$C_{syst}$, ml/mmHg</td>
<td>126.9 (Biventricle),*</td>
<td>(40 – 60) + $C_{syst}$0</td>
</tr>
<tr>
<td>$C_{sys}$, Fontan*</td>
<td>81.2</td>
<td></td>
</tr>
</tbody>
</table>

HR, heart rate. See text for additional definitions. *$E_{iva}$0, $E_{ivp}$0, $R_{pul}$0, $R_{sys}$0, and $C_{syst}$0 represent the default parameter values (column 2) used in the models.
the simulations, the initial conditions assigned to each model were fixed to highlight the effects of variations in model parameters.

RESULTS

Effects of Cardiac Parameters (HR, $E_{lv}$, $E_{lvp}$, and $\tau_{aw}$)

Figure 7 shows the comparisons between the Fontan and biventricular circulations regarding the effects of cardiac parameters (HR, $E_{lv}$, $E_{lvp}$, and $\tau_{aw}$). Note that when $E_{lv}$ was varied in the biventricular circulation model, $E_{lvp}$ was varied to the same degree to reflect synchronous stimulation of the left and right ventricles. Similarly, variations in HR were applied to both ventricles in the biventricular circulation model.

In the case of biventricular circulation, increasing HR is accompanied by a progressive increase in CO until HR reaches a high value (~140 beats/min) beyond which the effect is
blunted. Increasing HR, however, induces much less increase in CO in the case of Fontan circulation. The effects of $E_{lvp}$ on CO are much greater in the biventricular circulation than in the Fontan circulation. $E_{lvp}$ significantly affects the CO of both circulations, with the effects being more evident in the Fontan circulation. The effects of $\tau_{an}$ on CO are moderate, although slightly enhanced effects are observed for the Fontan circulation.

In comparison with CO, mPv is only moderately affected by the cardiac parameters [as indicated by the small ranges (<3 mmHg) of changes under all the simulated conditions]. The largest change in mPv is induced by variations in $E_{lvp}$ in the Fontan circulation (see Fig. 7G). Noticeably, the responses of mPv to variations in cardiac parameters differ significantly between the Fontan and biventricular circulations, implying the potential roles of the right ventricle in regulating venous pressure.

**Effects of Total Systemic Vascular Compliance (C_{sys}) and Resistance (R_{sys})**

A great influence of $C_{sys}$ on CO is predicted for both the Fontan and biventricular circulations, with the Fontan circulation showing a steeper change in CO with $C_{sys}$ (see Fig. 8A). Variations in $C_{sys}$ are accompanied by considerable changes in mPv in the Fontan circulation but only induce slight changes in mPv in the biventricular circulation (see Fig. 8C). Compared with $C_{sys}$, $R_{sys}$ has less influence on CO and mPv in both circulations, although its influence seems to be more evident in the biventricular circulation (see Fig. 8, B and D).

**Effects of Total Pulmonary Vascular Resistance (R_{pul})**

The effects of $R_{pul}$ on CO are pronounced, especially in the Fontan circulation (see Fig. 9A). Similar to $C_{sys}$, variations in $R_{pul}$ induce significant changes in mPv only in the Fontan circulation (see Fig. 9B).

**Changes in CO and mPv Induced by ±50% Changes in Model Parameters**

Table 5 summarizes the simulated changes in CO and mPv induced, respectively, by a 50% reduction and a 50% increase (relative to its default value) in each parameter for the Fontan and biventricular circulations. The results show that both CO and mPv in the Fontan circulation are strongly affected by $C_{sys}$.
Table 5. Simulated changes in CO and mPv induced respectively by a 50% reduction and a 50% increase in each model parameter (relative to its default value) for the Fontan and biventricular circulations

<table>
<thead>
<tr>
<th>Parameters/Variation in Parameter</th>
<th>Fontan</th>
<th>Fontan</th>
<th>Biventricular</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>−1.66</td>
<td>0.12</td>
<td>−3.27</td>
</tr>
<tr>
<td>50% increase</td>
<td>0.22</td>
<td>0.028</td>
<td>0.78</td>
</tr>
<tr>
<td>E_{sys}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>−0.67</td>
<td>0.039</td>
<td>−1.34</td>
</tr>
<tr>
<td>50% increase</td>
<td>0.26</td>
<td>−0.0076</td>
<td>0.66</td>
</tr>
<tr>
<td>E_{lvp}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>0.74</td>
<td>−0.54</td>
<td>0.53</td>
</tr>
<tr>
<td>50% increase</td>
<td>−0.56</td>
<td>0.40</td>
<td>−0.44</td>
</tr>
<tr>
<td>τ_{au}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>0.13</td>
<td>−0.13</td>
<td>0.063</td>
</tr>
<tr>
<td>50% increase</td>
<td>−0.16</td>
<td>0.15</td>
<td>−0.093</td>
</tr>
<tr>
<td>R_{pul}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>0.93</td>
<td>−0.88</td>
<td>0.55</td>
</tr>
<tr>
<td>50% increase</td>
<td>−0.66</td>
<td>0.61</td>
<td>−0.42</td>
</tr>
<tr>
<td>R_{sys}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>0.37</td>
<td>0.31</td>
<td>0.35</td>
</tr>
<tr>
<td>50% increase</td>
<td>−0.32</td>
<td>−0.27</td>
<td>−0.31</td>
</tr>
<tr>
<td>C_{sys}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% reduction</td>
<td>2.84</td>
<td>8.94</td>
<td>2.38</td>
</tr>
<tr>
<td>50% increase</td>
<td>−1.25</td>
<td>−3.58</td>
<td>−1.40</td>
</tr>
</tbody>
</table>

Note that 1) when a parameter is varied, other parameters are held at their default values; and 2) the default values of C_{sys}, and R_{sys} are different between the Fontan and biventricular circulations (see Table 4 for details).

followed by R_{pul} and E_{lvp}. When the two circulations are compared, it is observed that changes in CO and mPv with C_{sys}, E_{lvp}, τ_{au}, and R_{pul} are more pronounced, whereas changes in CO and mPv, with HR and E_{lva} are less evident in the Fontan circulation than in the biventricular circulation.

**DISCUSSION**

The physiological limitations of the Fontan circulation are due not only to the lack of a subpulmonary ventricle but also to the prevalence of systemic cardiovascular abnormalities in Fontan patients (14, 61). In the past decades, our understanding has been greatly deepened in both clinical and hemodynamic aspects as a consequence of numerous studies dedicated to this area (9, 19, 26, 29, 32, 33, 36, 40, 41, 44, 51, 54, 55a, 63, 64, 83, 85, 87, 88), which has accordingly contributed to a remarkable increase in survival rate and improvement in short-term outcomes in patients undergoing the Fontan operation (17).

However, the treatment of long-term survivors is still often confused by the onset of progressive hemodynamic deterioration and associated complications that eventually lead to late failure (17, 53, 56, 61). Theoretically, maintaining optimal or at least suboptimal hemodynamic conditions would be beneficial to the patients. This requires a thorough understanding about how the systemic hemodynamic conditions can be improved by certain clinical interventions when abnormalities occur in some portions of the Fontan circulation. To provide some insights into the question, we have employed a computational method to systemically investigate the effects of various cardiovascular properties on clinically relevant hemodynamic variables (e.g., CO, central venous pressure). In particular, we investigated the Fontan circulation compared with a normal biventricular circulation to identify the specific mechanisms underlying the regulation of CO and venous pressure in the Fontan circulation.

**Responses of CO to Variations in Cardiovascular Properties**

When a normal biventricular circulation is converted into a Fontan circulation by bypassing the right ventricle, our results show that CO becomes less sensitive to HR and ventricular contractility. The results are consistent with existing clinical findings. For instance, increasing HR or enhancing ventricular contractility has been found to induce less improvement of CO in Fontan patients compared with normal biventricular subjects (6, 27, 28, 78). In addition to HR and ventricular contractility, the effects of ventricular diastolic function, which have been difficult to be addressed in clinical studies, were investigated as well in the present study. Our results demonstrate that CO is more severely affected by ventricular diastolic dysfunction (characterized by increased diastolic stiffness (higher E_{lvp}) or prolonged isovolumetric relaxation (larger τ_{au})) in the Fontan circulation. Compared with E_{lvp}, the effects of τ_{au} are moderate. It should be noted, however, that the effects of τ_{au} have been studied by fixing HR at 60 beats/min in the simulations. To study whether the effects of τ_{au} are dependent on HR, we re-ran simulations under different HR conditions (HR = 60, 80, and 100 beats/min). The results revealed that the effects of τ_{au} on CO become more pronounced at a higher HR, whereas the effects of E_{lvp} are less affected by HR (see Fig. 10).

The effects on CO of systemic/pulmonary vascular properties also differ between the two circulations. The Fontan circulation exhibits an enhanced CO response to variations in systemic vascular compliance (C_{sys}) and pulmonary vascular resistance (R_{pul}). Interestingly, the influence of systemic vas-

![Fig. 10. Responses of CO to variations in τ_{au} (A) and E_{lvp} (B) at different HRs (simulated using the Fontan model).](http://example.com/fig10.png)
cular resistance ($R_{sys}$) on CO is slightly impaired in the Fontan circulation. A potential cause of the phenomenon may be the increased baseline value of $R_{sys}$ in the Fontan circulation.

It should be stressed that the relationships between CO and model parameters are nonlinear, with the slope being steeper in the low HR, low $E_{lvp}$, low $E_{sys}$, long $\tau_{aur}$, small $C_{sys}$, and low $R_{pul}$ regions. The nonlinearity of the relationships implies that the effectiveness of changing a cardiovascular property to improve CO is dependent on the baseline status of the property. Moreover, the effects of a cardiovascular property on CO may be coaffected by other cardiovascular properties. To test the hypothesis, we carried out additional simulations to study the changes of CO with various combinations of $R_{pul}$ and $E_{lvp}$ using the Fontan circulation model. The results show that the steepness of the relationship between CO and any of the two parameters depends strongly on the value of the other parameter (see Fig. 11).

**Responses of Central Venous Pressure to Variations in Cardiovascular Properties**

The responses of central venous pressure to variations in cardiovascular properties differ significantly between the Fontan circulation and the biventricular circulation. For example, venous pressure is highly sensitive to $C_{sys}$ and $R_{pul}$ in the Fontan circulation but only slightly affected by them in the biventricular circulation (see Figs. 8C and 9B). Deterioration in left ventricular diastolic function induces an increase in venous pressure in the Fontan circulation but a decrease in venous pressure in the biventricular circulation (see Fig. 7G). These results indicate that the right ventricle plays an important role not only in providing sufficient preload for the left ventricle but also in stabilizing venous pressure under various venous return conditions or when abnormalities develop in the pulmonary circulation or the left ventricle. The absence of a functional right (subpulmonary) ventricle in the Fontan circulation not only reduces CO but also significantly increases the variability of venous pressure.

**Clinical Implications**

Reduced CO and increased central venous pressure are the major manifestations of hemodynamic abnormalities in Fontan patients and have been found associated closely with some systemic complications, such as exercise intolerance, hepatic dysfunction, and protein-losing enteropathy (17). In particular, the status of hemodynamic abnormalities has a tendency to deteriorate progressively over time after the Fontan operation (56). This highlights the importance of active hemodynamic management in the care of long-term survivors. Although some studies have reported the beneficial roles of some medications [e.g., administration of sildenafil (30), amrinone (78), or sodium nitroprusside (93)] in increasing resting CO or improving ventricular performance, to date, evidence supporting the long-term effectiveness of certain interventions in systemically improving hemodynamic conditions remains absent. The present theoretical study demonstrates that the mechanisms underlying the regulation of CO and central venous pressure differ significantly between the Fontan circulation and the biventricular circulation, which implies that some conventional medications for treating patients with biventricular physiology might not be applicable to Fontan patients. According to our results, medications (for instance, administration of catecholamines) aimed to enhance ventricular contractility cannot be expected to significantly increase CO in Fontan patients. Comparatively, treatments targeted on improving the diastolic function of the systemic ventricle and reducing the pulmonary vascular resistance may be more effective. In addition to the maintenance of CO, the control of central venous pressure is another crucial issue in the care of Fontan patients. Our results show that diastolic dysfunction [characterized by increased ventricular diastolic stiffness ($E_{lvp}$) and/or prolonged $\tau_{aur}$] and increased pulmonary vascular resistance both lead to a marked increase in central venous pressure in the Fontan circulation, as is profoundly different from the phenomena observed in the biventricular circulation. This further stresses the clinical significance of improving ventricular diastolic function and reducing pulmonary vascular resistance. This viewpoint is consistent with the findings of some clinical trials. For instance, reducing pulmonary vascular resistance has been found to significantly improve hemodynamic conditions (78, 93), and ventricular diastolic dysfunction has been found to be an independent predictor of increased risk of perioperative morbidities and longer hospital stay for Fontan patients (9, 26, 88). In view of the importance of venous pressure control, reducing $C_{sys}$ may not be a good choice for improving CO in Fontan patients since it increases CO at the expense of elevating central venous pressure. Moreover, the findings regarding the variability in the effects of $\tau_{aur}$ with HR might provide some, although possibly limited, insights into the clinical observation that Fontan patients are usually affected by $\tau_{aur}$-dominated diastolic dysfunction early after the Fontan operation when the patients are younger with a higher baseline HR but subsequently affected primarily by chamber stiffness-dominated diastolic dysfunction at mid-term follow-up when the baseline HR has decreased with age (68).
Another insight from our study is that CO and central venous pressure are codetermined by multiple cardiovascular factors. For instance, the effectiveness of reducing pulmonary vascular resistance to increase CO is significantly blunted in the presence of severe ventricular diastolic dysfunction and vice versa (see Fig. 11). In this sense, a full understanding of the cardiovascular function of a Fontan patient is a precondition for making effective patient-specific therapeutic plans.

Increased systemic vascular resistance ($R_{sys}$) has been frequently found in postoperative Fontan patients (39, 43). This has naturally motivated the use of angiotensin-converting enzyme inhibitors (ACEI) to reduce systemic vascular resistance with an expectation to improve CO; however, the clinical benefits of the medication remain to be proven (68). According to our results, $R_{sys}$ has a much greater effect on aortic blood pressure than on CO, e.g., a 30% reduction in $R_{sys}$ induces a $<5\%$ increase in CO while causing an $\sim20\%$ drop in aortic pressure (see Fig. 12). In view of the importance of arterial pressure maintenance, the role of reducing $R_{sys}$ in improving CO is likely to be limited in Fontan patients. This is supported by previous clinical findings that ACEI did not significantly increase CO or improve exercise capacity in postoperative Fontan patients (39, 44). Nevertheless, it has been speculated that reducing $R_{sys}$ using ACEI might be beneficial for patients with severe ventricular systolic dysfunction (68). To test the speculation, we simulated the changes of CO and aortic pressure with $R_{sys}$ under various ventricular systolic/diastolic conditions using the Fontan model. It is noted that in the simulations when $E_{lva}$ is varied $E_{lvp}$ is held at its default value and vice versa. Figure 13 shows that the increase in CO induced by a reduction in $R_{sys}$ is larger with a small $E_{lva}$ (impaired systolic function) than with a large $E_{lva}$ (enhanced systolic function). Accordingly, for a small $E_{lva}$, aortic pressure decreases to a lesser degree when $R_{sys}$ is reduced. Differently from systolic function, the status of diastolic function does not significantly affect the strength of CO response to variations in $R_{sys}$, although with diastolic dysfunction (large $E_{lvp}$) the steepness of aortic pressure-$R_{sys}$ relation is observed to be slightly reduced as well (see Fig. 14). These simulation results partly support the speculation regarding the potential role of ACEI in improving CO in patients with severe systolic dysfunction.

**Limitations**

In the present study, the Fontan circulation has been modeled by representing the major cardiovascular properties with lumped parameters. The resulting model allowed us to quantitatively study the hemodynamic effects of any cardiovascular properties of interest by varying the corresponding model parameters. Despite the advantages, the model is inherently a low-order approximation of the circulatory system, in which many details of anatomy and hemodynamic phenomena have been simplified or omitted. For example, the present model does not include a detailed description of the arterial system and hence cannot reasonably account for arterial wave propagation phenomenon and its interaction with left ventricular dynamics. Since the present study focuses on hemodynamic variables averaged over a cardiac cycle (such as CO, mean venous pressure, and mean aortic pressure), the simplification would introduce negligible errors. However, when ventricular-arterial coupling is the primary interest [for instance, when studying the energetics of the heart in the Fontan circulation...]

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**Fig. 12.** Effects of variations in $R_{sys}$ on CO and mean aortic pressure (simulated using the Fontan model).

**Fig. 13.** Surface plots of CO (A) and mean aortic pressure (B) as a function of $E_{lva}$ and $R_{sys}$ (simulated using the Fontan model).
arterial wave propagation should be carefully addressed by developing a more detailed model for the arterial system. When modeling the heart, we did not account for the details of cardiac wall motion, which has been found to influence intraventricular flow and early diastolic filling (66). According to previous studies (9, 26, 74), the peak active elastance \(E_{la}\), the baseline passive chamber elastance \(E_{lp}\), and the time constant of isovolumic relaxation \(\tau_{iv}\) are the most representative indexes of ventricular function and hence the omitted details of cardiac wall motion are secondary for the description of ventricular function, at least in the scope of the present study. Another limitation associated with the modeling of the heart is that although we have assumed the left ventricle to be the systemic ventricle of the Fontan circulation, there are a number of Fontan patients with the right ventricle serving as a systemic pumping chamber (17). Since a systemic right ventricle may differ significantly from the left ventricle in both anatomical and functional properties, our results on the hemodynamic effects of cardiac parameters might fail to reflect the characteristics of a Fontan circulation with a systemic right ventricle. Further studies will be necessary to address this issue.

Each model parameter has been varied separately with other parameters being held at their default values to provide insight into the mechanisms underlying hemodynamic regulation. In real physiological conditions, however, several parameters may deviate simultaneously from their reference values, and, moreover, hemodynamic perturbations induced by a parameter variation should be always accompanied by regulatory responses acting to restore arterial pressure or tissue/organ perfusion. Therefore, the results obtained from a single parameter-variation study would provide a trend rather than an accurate prediction of in vivo hemodynamic changes. It is stressed that our model can readily be applied to study the hemodynamic effects of multiple parameters. Moreover, the present study has focused on quantifying the general hemodynamic responses to variations in cardiovascular properties using a generalized model of the Fontan circulation. To predict the hemodynamic impacts of certain operations in a specific patient, the model should be tuned to the patient by optimizing model parameters based on patient-specific clinical data. This issue has been addressed elsewhere, such as in recent studies on surgical planning (40, 63) and those from our group (46, 82).

The influence of cardiac valvular diseases on CO has not been addressed in the present study. In fact, patients with single-ventricle physiology are among the patient cohorts most susceptible to cardiac valvular diseases. A recent clinical study revealed that ~30% of patients undergoing Fontan procedure were affected by moderate to severe atrioventricular valve regurgitation (AVVR) (3). AVVR significantly deteriorates the pumping performance of the ventricle, and its close association with increased morbidity and mortality has been demonstrated (57). Therefore, incorporating AVVR in the modeling of the Fontan circulation would be necessary to more extensively study the hemodynamic characteristics of the Fontan circulation. The issue will be addressed in our future studies.

**Conclusions**

The present study analyzed the hemodynamic performance of the Fontan circulation compared with the normal biventricular circulation under various cardiovascular conditions using computational models. Obtained results demonstrate the inherent differences between the two types of circulation in the regulation of CO and central venous pressure. The main findings of the study include the following: 1) while increasing HR or ventricular contractility contributes significantly to the increase of CO in the normal biventricular circulation, the contribution is significantly reduced in the Fontan circulation; 2) the sensitivity of CO to pulmonary vascular resistance, ventricular diastolic function, and systemic vascular compliance is enhanced in the Fontan circulation; 3) the amount of CO change induced by a variation in cardiovascular parameter is dependent on the status of the entire cardiovascular system owing to the nonlinear nature of the CO-parameter relationship and the interaction among different parameters; 4) reducing systemic vascular resistance insignificantly contributes to the improvement of CO in the Fontan circulation unless ventricular systolic function is severely impaired; and 5) the absence of a subpulmonary ventricle in the Fontan circulation significantly increases the variability of the central venous pressure. The
findings may serve as a useful theoretical reference for clinical doctors to identify the major cardiovascular factors underlying patient-specific hemodynamic characteristics so as to implement efficacious hemodynamic management.

**APPENDIX**

Governing equations of the biventricular model were formulated by imposing mass or momentum conservation along the flow pathways. To facilitate the identification of hemodynamic variables, the equations are presented for heart, pulmonary vascular system, aorta, vena cava, and systemic vascular system, respectively.

**Heart**

\[
\frac{dV_{ia}}{dt} = Q_{svc} + Q_{ivc} - Q_{tv}, \quad (A1)
\]

\[
\frac{dQ_{tv}}{dt} = \frac{P_{ia} - P_{rv} - R_{tv}Q_{tv} - R_{do,tv}Q_{tv} - B_{tv}Q_{tv}}{L_{tv}}, \quad (A2)
\]

\[
\frac{dV_{pv}}{dt} = Q_{pv} - Q_{pvtr}, \quad (A3)
\]

\[
\frac{dQ_{pvtr}}{dt} = \frac{P_{rv} - P_{pca} - R_{pv}Q_{pv} - R_{do,pv}Q_{pv} - B_{pv}Q_{pv}}{L_{pv}}, \quad (A4)
\]

\[
\frac{dV_{la}}{dt} = Q_{la} - Q_{inv}, \quad (A5)
\]

\[
\frac{dQ_{inv}}{dt} = \frac{P_{la} - P_{lv} - R_{lv}Q_{inv} - R_{do,lv}Q_{inv} - B_{inv}Q_{inv}}{L_{inv}}, \quad (A6)
\]

\[
\frac{dV_{lv}}{dt} = Q_{lv} - Q_{lvt}, \quad (A7)
\]

\[
\frac{dQ_{lvt}}{dt} = \frac{P_{lv} - P_{vc} - R_{lv}Q_{lvt} - R_{do,lv}Q_{lvt} - B_{lv}Q_{lvt}}{L_{lvt}}, \quad (A8)
\]

where \( V \) represents the volume of blood (or cardiac chamber volume) contained in each cardiac chamber and \( Q \) is the blood flow rate across each cardiac valve. The subscripts denote the names of cardiac chamber or cardiac valve to which the variables and parameters correspond. The blood pressure (\( P \)) in each cardiac chamber is a function of chamber volume and elastance

\[
P_{ia} = E_{ia}V_{ia} + S_{ia} + P_{pc} + P_{it}, \quad (A9)
\]

\[
P_{rv} = E_{rv}V_{rv} + S_{rv} + P_{pc} + P_{it}, \quad (A10)
\]

\[
P_{la} = E_{la}V_{la} + S_{la} + P_{pc} + P_{it}, \quad (A11)
\]

\[
P_{lv} = E_{lv}V_{lv} + S_{lv} + P_{pc} + P_{it}, \quad (A12)
\]

where \( S \) represents the viscoelastic coefficient of cardiac chamber and was herein taken as a function of blood pressure in cardiac chamber (see Table 1); \( E \) is the time-varying elastance of cardiac chamber, which differs among the four cardiac chambers (see Eqs. 4–6 for details on their definition); and \( P_{pc} \) and \( P_{it} \) denote, respectively, the pericardial and intrathoracic pressures, and although both of them may vary with beating of the heart and breath, we herein assumed them to be a constant (\( P_{pc} = 3.0 \text{ mmHg}, \ P_{it} = -3.5 \text{ mmHg} \)) to simplify our analysis. In future studies, \( P_{pc} \) can be readily defined as a time-varying variable to investigate the effect of breath on blood circulation.

**Pulmonary Vascular System**

\[
\frac{dV_{pua}}{dt} = Q_{pv} - Q_{pua}, \quad (A13)
\]

\[
\frac{dQ_{pua}}{dt} = P_{pca} - P_{pav} - R_{pua}Q_{pua}, \quad (A14)
\]

\[
\frac{dV_{pav}}{dt} = Q_{pav} - Q_{pua}, \quad (A15)
\]

\[
\frac{dQ_{pav}}{dt} = P_{pav} - P_{pua} - R_{pav}Q_{pav}, \quad (A16)
\]

\[
\frac{dQ_{pua}}{dt} = P_{pua} - P_{la} - R_{pv}Q_{pua}, \quad (A17)
\]

where \( V \) and \( Q \) denote the volume of blood contained in and blood flow rate through a vascular portion, respectively. \( P \) is the blood pressure at the “\( C \)” component of a vascular portion, and is expressed as a function of \( V \) and \( C \), for example, pulmonary arterial pressure \( P_{pua} = V_{pua}/C_{pua} + P_{it} \). Note that blood pressures in the aorta, the vena cava and the systemic vascular system are expressed in a similar way as \( P_{pua} \) but without the inclusion of \( P_{r} \) since the vasculatures are located outside of the thoracic chamber. The subscripts of the parameters and variables indicate the names of vascular portions. Please refer to Fig. 1 for the details on the locations of the vascular portions in the cardiovascular system.

**Aorta**

\[
\frac{dV_{ao}}{dt} = Q_{ao} - Q_{ao_l} - Q_{ao_u}, \quad (A19)
\]

\[
\frac{dQ_{ao_u}}{dt} = P_{ao} - P_{art_u} - R_{ao_u}Q_{ao_u}, \quad (A20)
\]

\[
\frac{dQ_{ao_l}}{dt} = P_{ao} - P_{art_l} - R_{ao_l}Q_{ao_l}, \quad (A21)
\]

**Vena Cava**

\[
\frac{dV_{svc}}{dt} = Q_{svc} - Q_{svc_u}, \quad (A22)
\]

\[
\frac{dQ_{svc}}{dt} = P_{svc} - P_{ra} - R_{svc}Q_{svc}, \quad (A23)
\]

\[
\frac{dV_{svc_u}}{dt} = Q_{svc_u} - Q_{svc}, \quad (A24)
\]

\[
\frac{dQ_{svc_u}}{dt} = P_{svc} - P_{ra} - R_{svc}Q_{svc_u}, \quad (A25)
\]

**Systemic Vascular System**

**Upper body.**

\[
\frac{dV_{art_u}}{dt} = Q_{art_u} - Q_{art_u_u}, \quad (A26)
\]

\[
\frac{dQ_{art_u_u}}{dt} = P_{art_u} - P_{cap_u} - R_{art_u_u}Q_{art_u_u}, \quad (A27)
\]

\[
\frac{dV_{cap_u}}{dt} = Q_{art_u} - Q_{cap_u}, \quad (A28)
\]
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\[ \frac{dQ_{cap,u}}{dt} = \frac{P_{cap,u} - P_{ven,u} - R_{cap}Q_{cap,u}}{L_{cap,u}}, \]  
(A29)

\[ \frac{dV_{ven,u}}{dt} = Q_{cap,u} - Q_{ven,u}, \]  
(A30)

\[ \frac{dQ_{ven,u}}{dt} = \frac{P_{ven,u} - P_{svc} - R_{ven}Q_{ven,u}}{L_{ven,u}}, \]  
(A31)

**Lower body.**

\[ \frac{dV_{art,l}}{dt} = Q_{cap,l} - Q_{art,l}, \]  
(32)

\[ \frac{dQ_{art,l}}{dt} = \frac{P_{art,l} - P_{cap,l} - R_{art}Q_{art,l}}{L_{art,l}}, \]  
(A33)

\[ \frac{dV_{cap,l}}{dt} = Q_{art,l} - Q_{cap,l}, \]  
(A34)

\[ \frac{dQ_{cap,l}}{dt} = \frac{P_{cap,l} - P_{ven,l} - R_{cap}Q_{cap,l}}{L_{cap,l}}, \]  
(A35)

\[ \frac{dV_{ven,l}}{dt} = Q_{cap,l} - Q_{ven,l}, \]  
(A36)

\[ \frac{dQ_{ven,l}}{dt} = \frac{P_{ven,l} - P_{svc} - R_{ven}Q_{ven,l}}{L_{ven,l}}, \]  
(A37)

When converting the biventricular model into a single-ventricular model with TCPC (see Fig. 1B), equations governing hemodynamics in the right heart (Eqs. A1–A4, A9, and A10) were removed because the right heart is bypassed. In the meantime, governing equations for blood flows in the vena cava (Eqs. A22–A25) and the pulmonary artery (Eq. A13) were changed to reflect the incorporation of TCPC.

\[ \frac{dQ_{svc}}{dt} = \frac{P_{svc} - P_{pua} - R_{svc}Q_{svc}}{L_{svc}}, \]  
(A38)

\[ \frac{dQ_{svc}}{dt} = \frac{P_{svc} - P_{ten} - R_{svc}Q_{svc}}{L_{svc}}, \]  
(A39)

\[ \frac{dV_{ten}}{dt} = Q_{svc} - Q_{ten}, \]  
(A40)

\[ \frac{dQ_{ten}}{dt} = \frac{P_{ten} - P_{pua} - R_{ten}Q_{ten}}{L_{ten}}, \]  
(A41)

\[ \frac{dV_{pua}}{dt} = Q_{svc} + Q_{ten} - Q_{pua}, \]  
(A42)

where \( Q_{ten} \) refers to the blood flow rate through the atrial tunnel that connects the inferior vena cava with the pulmonary artery, \( P_{ten} \) is the blood pressure in the tunnel, and \( R_{ten}, L_{ten}, \) and \( C_{ten} \) represent, respectively, the flow resistance, blood inerance, and wall compliance of the tunnel.

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**DISCLOSURES**

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

**AUTHOR CONTRIBUTIONS**

Author contributions: F.L. and H.S. proposed and designed research; F.L. and C.K. developed models and performed numerical simulations; F.L., K.S., R.I., and H.L. analyzed data; F.L. interpreted results of experiments; F.L. prepared figures; F.L. drafted manuscript; F.L., H.S., C.K., K.S., R.I., and H.L. edited and revised manuscript; F.L., H.S., C.K., K.S., and H.L. approved final version of manuscript.

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