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A computational study of the Fontan circulation with fenestration or hepatic vein exclusion

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Abstract

Fontan patients may undergo additional surgical modifications to mitigate complications like protein–losing enteropathy, liver cirrhosis, and other issues in their splanchnic circulation. Recent case reports show promise for several types of modifications, but the subtle effects of these surgeries on the circulation are not well understood. In this paper, we employ mathematical modeling of blood flow to systematically quantify the impact of these surgical changes on extracardiac Fontan hemodynamics. We investigate two modifications: (1) the fenestrated Fontan and (2) the Fontan with hepatic vein exclusion. Closed–loop hemodynamic models are used, which consist of one–dimensional networks for the major vessels and zero–dimensional models for the heart and organ beds. Numerical results suggest the hepatic vein exclusion has the greatest overall impact on the hemodynamics, followed by the largest sized fenestration. In particular, the hepatic vein exclusion drastically lowers portal venous pressure while the fenestration decreases pulmonary artery pressure. Both modifications increase flow to the intestines, a finding consistent with their utility in clinical practice for combating complications in the splanchnic circulation.

Keywords

Fontan circulation; Protein–losing enteropathy; Computational hemodynamics; Cardiovascular mechanics; One–dimensional blood flow; Hypoplastic left heart syndrome

1. Introduction

The Fontan circulation is a standard palliative solution for patients with single ventricle hearts and other cardiac abnormalities [1]. For patients with hypoplastic left heart syndrome (HLHS), this circulation is typically the third and final surgery they receive which transitions

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Conflicts of interest

None declared.

their cardiovascular system to function with a single right ventricle pump. It is characterized by the systemic organs and lungs in series with passive blood flow into the lungs via a surgical modification. A schematic of the Fontan physiology can be found in Fig. 1.

Fontan patients may experience challenging complications in their splanchnic circulation, like protein-losing enteropathy and liver cirrhosis [2–5]. Clinicians speculate these issues arise in part from an increase in systemic venous and portal venous pressures caused by the Fontan connection (see e.g. Refs. [6,7]), but there is still uncertainty in both the mechanisms through which these complications develop and the best path for treatment. Surgeons have had some success in managing complications by introducing a fenestration or hepatic vein exclusion into the Fontan physiology [8–13].

A fenestration is path near the Fontan connection which diverts a small portion of blood directly to the heart [8,9]. In the extracardiac Fontan, a path may be established by creating a small hole in both the continuation of the inferior vena cava and the atrium, and then surgically connecting them together. We remark that fenestrations may be given at the time of Fontan conversion, usually with the expectation that the small hole or conduit will eventually close [14]. Our modeling focuses on quantifying the effect of fenestrations created after the Fontan surgery in response to complications.

The hepatic vein exclusion establishes a circulation which diverts blood from the liver, through the hepatic veins, directly to the heart; this may be achieved by connecting the hepatic veins to the atrium [10,11]. The idea for this modification is the expectation that atrial pressure will be lower than the pressure in the pulmonary arteries and vena cavae. In turn, patients with elevated pressures around their intestines and liver may experience a decongestion of the splanchnic circulation after hepatic exclusion, along with the mitigation of intestinal and hepatic problems.

The purpose of this paper is to employ closed-loop, one-dimensional/zero-dimensional cardiovascular models to study the impact of the fenestration or the hepatic vein exclusion on extracardiac Fontan hemodynamics. We consider fenestration conduits of different sizes, and also vary the mesenteric vascular resistance to simulate complications in the splanchnic circulation [15].

2. Mathematical modeling for HLHS

Computational modeling has proven to be a powerful tool for describing the inherently complex hemodynamics in different post-surgical HLHS physiologies. Research in this area has considered each stage in the typical course of treatment for this patient population: the Norwood, the Glenn, and the Fontan surgeries. Popular modeling approaches include lumped parameter descriptions (zero-dimensional models) and also three-dimensional fluid dynamic models coupled to zero-dimensional models.

Systems of algebraic and ordinary differential equations, i.e. zero-dimensional or lumped-parameter models, provide simple mathematical descriptions for various physiologies. Early work by Barnea et al. employed a purely algebraic model of fluid flow to study oxygen transport in a single ventricle parallel circulation [16]. Migliavacca et al. developed a

pulsatile, closed-loop model of the Norwood circulation to explore the sensitivity of pulmonary and systemic flow to changes in different hemodynamic parameters, including heart rate and the geometry of the shunt which establishes the parallel circulation [17]. The works of Vallecilla et al. used zero-dimensional models of variations on the Glenn physiology to characterize oxygen transport and other hemodynamic variables; in particular, they modeled the effect of exercise and a high altitude environment on blood flow [18,19]. Other researchers studied complications of HLHS by modeling pre- and post- surgical conditions [20]. Lastly, several groups have considered mathematical descriptions of the Fontan physiology. A collection of papers by Watrous et al. and Chin et al. present a general software framework, complete with a graphical user interface, for computational hemodynamics using zero-dimensional models, and consider examples of normal and Fontan circulations [21,22]. Kung et al. and Van De Bruaene et al. created Fontan models to investigate the effect of exercise, and carefully refined their approach with clinical data [23,24]. Recent work by Di Molfetta et al. describes models for the Fontan circulation and other HLHS physiologies for studying the impact of ventricular assist devices on blood flow [25].

Other computational work devoted to HLHS relies on geometric multiscale models, i.e. zero-dimensional models coupled to the Navier-Stokes equations or reduced (one-dimensional) versions thereof. This approach enables the characterization of complex blood flow patterns in a region of interest while still accounting for peripheral hemodynamics using lumped-parameter models. For well-posedness and numerical considerations of these coupled models, see e.g. Refs. [26–28]. Some representative work on closed-loop geometric multiscale models include [29–34].

Most of the work using geometric multiscale modeling for HLHS focuses on the total cavopulmonary connection (TCPC). This pathway links the vena cava directly to the pulmonary arteries and allows passive flow of unoxygenated blood back to the lungs. In these studies, computational experiments characterize flow patterns in the TCPC and the corresponding impact on venous return. Geometric multiscale models of the TCPC typically use finite element approximations of the Navier-Stokes equations for the connection itself and surrounding vessels, and zero-dimensional models for outflow boundary conditions. Early papers by Dubini et al., de Leval et al., and Miglavacca et al. constructed such models to investigate the effect of TCPC geometry on flow to each lung and fluid energy loss [35–37]. Later work from Hsia et al. and de Zélicourt et al. exhibited similar computational experiments, but with models generated from patient data [38,39]. Recent research from Marsden and her collaborators considered, among many topics, the effect of exercise and novel surgical techniques on flow in the TCPC [40,41].

We remark that geometric multiscale models have been used to study other aspects of HLHS physiologies beyond the TCPC in the extracardiac Fontan. Relevant work by Albal et al. employs three-dimensional fenestration models to study the impact of fenestration geometry on flow [42]. The Norwood physiology has also been studied using geometric multiscale models; some representative research includes the work of Qian et al., Hsia et al., and Moghadam et al. [33,38,43]. Lastly, one-dimensional blood flow modeling for the Fontan physiology has appeared in the work of Corno et al. [44].

In this paper, we use one-dimensional/zero-dimensional geometric multiscale models to investigate cardiovascular changes established by the fenestration or hepatic vein exclusion. The systemic arteries, systemic veins, pulmonary arteries, pulmonary veins, and portal veins are described by networks of one-dimensional elastic tubes. The heart and organ beds are modeled by systems of algebraic and ordinary differential equations. This approach provides high anatomical detail for regions in the cardiovascular system comprised of the major vessels, yet is computationally more tractable than models derived from three dimensional fluid dynamics. In particular, this framework is important for our application since HLHS physiologies result from direct surgical modification of the major vessel network topologies.

Numerical experiments in this paper investigate the impact of these surgical modifications on pressure and flow waveforms and on relevant clinical variables. Our vessel network models include the splanchnic circulation, enabling us to carefully quantify the effect of surgical changes on this part of the cardiovascular system. While there has been extensive computational research devoted to HLHS, these surgical modifications have not been systemically compared with mathematical modeling. Further, one-dimensional/zero-dimensional models have not been widely used to study post-surgical physiologies of HLHS patients.

A summary of this paper is as follows. In Section 3, we discuss mathematical models for the major vessels, heart, and organ beds. We describe our experimental setup and the construction of the three Fontan models: the standard (unmodified) Fontan, the fenestrated Fontan, and the Fontan with hepatic vein exclusion. Section 4 briefly organizes the results from our numerical experiments, and a discussion of these results in the context of the clinical literature follows in Section 5. Conclusions are given in Section 6.

3. Models and methods

Our modeling approach, adapted from the work of Mynard and others, uses one-dimensional equations for blood flow in the major vessel networks and zero-dimensional equations for the heart and organ beds [29,45,46]. Subsections 3.1–3.4 closely follow the methods section in our recent paper [32].

3.1. One-dimensional blood flow for major vessels

A popular model for flow along the axial dimension x of an elastic vessel is the following nonlinear hyperbolic system for the variables A , vessel cross sectional area, and U , blood velocity averaged over a cross section:

$$\frac{\partial A}{\partial t} + \frac{\partial(AU)}{\partial x} = 0, \quad (1)$$

$$\frac{\partial U}{\partial t} + \frac{1}{2} \frac{\partial U^2}{\partial x} + \frac{1}{\rho} \frac{\partial p}{\partial x} = -2\pi\nu \frac{\alpha}{\alpha - 1} \frac{U}{A}, \quad (2)$$

$$p=p_0+\psi(A;A_0,\beta). \quad (3)$$

These equations are derived from asymptotic reduction of the Navier–Stokes equations, assuming the fluid is incompressible, flow is axially symmetric, and vessel length is much greater than the radius. The parameters are the fluid density ρ , the kinematic viscosity ν , and a nondimensional parameter $\alpha > 1$ determined by the a priori selection of an axial velocity profile.

Let $A_0 = \frac{1}{4}\pi D_0^2$. The equation of state for our model, relating pressure to area through (3), is:

$$\psi(A;A_0,\beta)=\beta(D_0)\left(A^{1/2}-A_0^{1/2}\right), \quad (4)$$

$$\beta(D_0)=\frac{16}{3}\frac{1}{D_0\pi^{1/2}}(k_1\exp(k_2D_0)+k_3), \quad (5)$$

for some parameters $k_1 > 0$, $k_2 < 0$, and $k_3 > 0$. These equations assume the vessel wall is a linear elastic membrane and that the parameter β obeys a heuristic scaling law depending on A_0 (see e.g. Refs. [47,48]).

Equations (1)–(3) may be transformed into another hyperbolic system for the variables W_1 and W_2 , called the Riemann invariants:

$$\frac{\partial W_1}{\partial t} + \lambda_1 \frac{\partial W_1}{\partial x} = -2\pi\nu \frac{\alpha}{\alpha-1} \frac{U}{A} - 4(U+c-c_0) \frac{dc_0}{dx}, \quad (6)$$

$$\frac{\partial W_2}{\partial t} + \lambda_2 \frac{\partial W_2}{\partial x} = -2\pi\nu \frac{\alpha}{\alpha-1} \frac{U}{A} + 4(U-c+c_0) \frac{dc_0}{dx}, \quad (7)$$

with $c=c(A) := \left(\frac{A}{\rho} \frac{d\psi}{dA}\right)^{1/2}$ and $c_0 = c(A_0)$. The following algebraic equations relate the physical variables A and U to λ_1 , λ_2 , and the Riemann invariants:

$$\lambda_1 = U + c(A), \quad W_1 = U + 4(c(A) - c(A_0)), \quad (8)$$

$$\lambda_2 = U - c(A), \quad W_2 = U - 4(c(A) - c(A_0)) \quad (9)$$

The form of (6)–(7) is amenable to a method of characteristics based approximation scheme. We employ the numerical method presented in Ref. [49] to approximate the Riemann invariants, and from Equations (8) and (9) recover the physical variables A and U .

3.2. Vessel junctions

Vessels are oriented with respect to their axial dimension, i.e. the axial variable x increases from vessel inlet to the outlet (see Fig. 2). For a given junction, vessels with outlets at the junction are termed incoming vessels, and those with inlets at the junction are termed outgoing vessels. Consider a junction containing N_{in} incoming vessels and N_{out} outgoing vessels, with corresponding one-dimensional variables A_k , U_k ($k = 1, \dots, N_{\text{in}}$) and $\tilde{A}_j$, $\tilde{U}_j$ ($j = 1, \dots, N_{\text{out}}$) respectively. The following set of Equations (10)–(14) determine boundary conditions for the one-dimensional vessels at the junction.

$$W_{1,k} = U_k + 4(c(A_k) - c(A_{0,k})), \quad \text{for } k = 1, \dots, N_{\text{in}}, \quad (10)$$

$$W_{2,j} = \tilde{U}_j - 4(c(\tilde{A}_j) - c(\tilde{A}_{0,j})), \quad \text{for } j = 1, \dots, N_{\text{out}}, \quad (11)$$

$$Q_{\text{add}} + \sum_{k=1}^{N_{\text{in}}} A_k U_k = \sum_{j=1}^{N_{\text{out}}} \tilde{A}_j \tilde{U}_j, \quad (12)$$

$$\frac{\rho}{2}(U_1)^2 + p(A_1) = \frac{\rho}{2}(U_k)^2 + p(A_k), \quad \text{for } k = 2, \dots, N_{\text{in}}, \quad (13)$$

$$\frac{\rho}{2}(U_1)^2 + p(A_1) = \frac{\rho}{2}(\tilde{U}_j)^2 + p(\tilde{A}_j), \quad \text{for } j = 1, \dots, N_{\text{out}}. \quad (14)$$

Equations (10)–(11) are derived from the hyperbolic system for one-dimensional blood flow and enforce the algebraic relationship between the physical variables and the Riemann invariants W_1 and W_2 . Equation (12) enforces mass conservation and also incorporates some additional flow Q_{add} ; this function may be specified to add blood volume to the model for calibration purposes. The last set of Equations (13)–(14) describe continuity of total pressure at the junction.

3.3. Organ bed models

We employ the standard electrical analogy for mathematically describing organ beds. They are given as circuits with resistor and capacitor elements, and are adapted from the closed loop networks in Ref. [45]. The models contain arterial and venous compliances, C_{art} and C_{ven} , and a resistance specified by R_{cap} . The circuits include additional resistances

determined by the characteristic impedances of the incoming and outgoing vessels, given by $\rho A_0^{-1} c(A_0)$ and identified as $R_{\text{art},k}$ ($k = 1, \dots, N_{\text{in}}$) and $R_{\text{ven},j}$ ($j = 1, \dots, N_{\text{out}}$) respectively.

$$p_{\text{art},k} - p_{\text{art}} = Q_{\text{art},k} R_{\text{art},k}, \quad k=1, \dots, N_{\text{in}}, \quad (15)$$

$$p_{\text{ven}} - p_{\text{ven},j} = Q_{\text{ven},j} R_{\text{ven},j}, \quad j=1, \dots, N_{\text{out}}, \quad (16)$$

$$p_{\text{art}} - p_{\text{ven}} = Q_{\text{cap}} R_{\text{cap}}, \quad (17)$$

$$C_{\text{art}} \frac{dp_{\text{art}}}{dt} = Q_{\text{art}} - Q_{\text{cap}}, \quad (18)$$

$$C_{\text{ven}} \frac{dp_{\text{ven}}}{dt} = Q_{\text{cap}} - Q_{\text{ven}}, \quad (19)$$

$$Q_{\text{art}} = \sum_{k=1}^{N_{\text{in}}} Q_{\text{art},k}, \quad (20)$$

$$Q_{\text{ven}} = \sum_{j=1}^{N_{\text{out}}} Q_{\text{ven},j}. \quad (21)$$

The organ bed model is governed by system (15)–(21). Equations (15)–(16) relate pressures in the arteriole and venule compartments to pressures within the incoming and outgoing vessels, via the characteristic impedances. Equations (17)–(19) describe pressure and flow between the arterial and venous sides of the bed, and (20,21) enforce conservation of mass.

In Ref. [50], the authors derived equations relating the organ bed parameters to the arteriole and venule pressures, respectively p_{art} and p_{ven} . First, we are given a reference resistance $R_{\text{cap,ref}}$ and reference compliances and volumes on the arterial and venous sides respectively $C_{\text{art,ref}}$, $C_{\text{ven,ref}}$, $V_{\text{art,ref}}$, $V_{\text{ven,ref}}$. Equations (22)–(23) define the effective arteriole and venule wall distenibilities

$$\Gamma_{\text{art}} = \frac{C_{\text{art,ref}}}{2V_{\text{art,ref}} - C_{\text{art,ref}}(p_{\text{art,ref}} - p_{\text{ext}})}, \quad (22)$$

$$\Gamma_{\text{ven}} = \frac{C_{\text{ven,ref}}}{2V_{\text{ven,ref}} - C_{\text{ven,ref}}(p_{\text{ven,ref}} - p_{\text{ext}})}, \quad (23)$$

and appear in the state equations, (24,25) relating pressure to volume:

$$V_{\text{art}} = V_{\text{art,ref}} \frac{(1 + \Gamma_{\text{art}}(p_{\text{art}} - p_{\text{ext}}))^2}{(1 + \Gamma_{\text{art}}(p_{\text{art,ref}} - p_{\text{ext}}))^2}, \quad (24)$$

$$V_{\text{ven}} = V_{\text{ven,ref}} \frac{(1 + \Gamma_{\text{ven}}(p_{\text{ven}} - p_{\text{ext}}))^2}{(1 + \Gamma_{\text{ven}}(p_{\text{ven,ref}} - p_{\text{ext}}))^2}. \quad (25)$$

By definition, the compliances are computed as follows

$$C_{\text{art}} = \frac{dV_{\text{art}}}{dp_{\text{art}}} = 2\Gamma_{\text{art}} V_{\text{art,ref}} \frac{(1 + \Gamma_{\text{art}}(p_{\text{art}} - p_{\text{ext}}))}{(1 + \Gamma_{\text{art}}(p_{\text{art,ref}} - p_{\text{ext}}))^2}, \quad (26)$$

$$C_{\text{ven}} = \frac{dV_{\text{ven}}}{dp_{\text{ven}}} = 2\Gamma_{\text{ven}} V_{\text{ven,ref}} \frac{(1 + \Gamma_{\text{ven}}(p_{\text{ven}} - p_{\text{ext}}))}{(1 + \Gamma_{\text{ven}}(p_{\text{ven,ref}} - p_{\text{ext}}))^2}. \quad (27)$$

The relationship between the resistance and volumes is given:

$$R_{\text{cap}} = R_{\text{cap,ref}} \left(\left(\frac{V_{\text{art,ref}}}{V_{\text{art}}} \right)^2 + \left(\frac{V_{\text{ven,ref}}}{V_{\text{ven}}} \right)^2 \right). \quad (28)$$

Fig. 4 depicts the liver model, including the hepatic artery and hepatic portal vein. Inclusion of the liver and splanchnic circulation is important for our application, since Fontan patients experience complications in this area. The governing equations are similar to (15)–(21) and are omitted for brevity.

3.4. Heart model for a closed loop vessel network

A schematic of the heart model is given in Fig. 5. It describes flow through the atrium, ventricle, interior valve (between the chambers), and exterior valve (at the interface of the

ventricle with the outgoing vessel). The variables for the interior and exterior valves are labeled with “int” and “ext” respectively. The governing equations are given in (29)–(37).

$$p_a = E_a(t) \frac{(V_a - V_a^0)}{V_a^0} + K_a p_a \frac{dV_a}{dt}, \quad (29)$$

$$p_v = E_v(t) \frac{(V_v - V_v^0)}{V_v^0} + K_v p_v \frac{dV_v}{dt}, \quad (30)$$

$$L_{\text{int}} \frac{dQ_{\text{int}}}{dt} + (B_{\text{int}} |Q_{\text{int}}| + R_{\text{int}}) Q_{\text{int}} = H(p_a, p_v; \zeta_{\text{int}}) (p_a - p_v), \quad (31)$$

$$L_{\text{ext}} \frac{dQ_{\text{ext}}}{dt} + (B_{\text{ext}} |Q_{\text{ext}}| + R_{\text{ext}}) Q_{\text{ext}} = H(p_v, p(A_{\text{out}}); \zeta_{\text{ext}}) \times (p_v - p(A_{\text{out}})), \quad (32)$$

$$\frac{dV_a}{dt} = -Q_a, \quad (33)$$

$$\frac{dV_v}{dt} = -Q_v, \quad (34)$$

$$Q_a = Q_{\text{int}} - \sum_{k=1}^{N_{\text{in}}} Q_{\text{in},k}, \quad (35)$$

$$Q_v = Q_{\text{ext}} - Q_{\text{int}}, \quad (36)$$

$$Q_{\text{out}} = Q_{\text{ext}}. \quad (37)$$

Equations (29) and (30) relate the pressures and volumes of each chamber through a time periodic elastance function $E(t)$ and a viscoelastic parameter K , with subscripts “a” and “v” corresponding to the atrium and ventricle respectively. The parameter V^0 is the residual volume of the chamber.

The elastance function $E(t)$ is specified as part of the model and takes a form adapted from Ref. [45]. For example, it depends on minimum and maximum elastance parameters $E_{\min}$ and $E_{\max}$ as well as others which govern the shape and time of contraction; see Equations (38)–(44).

$$E(t) = \frac{(E_{\max} - E_{\min})}{k} \left(\frac{g_1(t)}{1+g_1(t)} \frac{1}{1+g_2(t)} \right) + E_{\min}, \quad (38)$$

where

$$g_i(t) = \left(\frac{t - t_{\text{onset}}}{\tau_i} \right)^{m_i}, \quad i=1, 2, \quad \text{and} \quad (39)$$

$$k = \max_{t \in [0, T_{\text{heart}}]} \left(\frac{g_1}{1+g_1} \frac{1}{1+g_2} \right),$$

and where

$$T_{\text{heart}} = \text{heart period}, \quad (40)$$

$$m_1, \tau_1 = \text{parameters governing shape of contraction}, \quad (41)$$

$$m_2, \tau_2 = \text{parameters governing shape of relaxation}, \quad (42)$$

$$t_{\text{onset}} = \text{time at which contraction begins}, \quad (43)$$

$$E_{\min}, E_{\max} = \text{minimum and maximum elastances}. \quad (44)$$

Equations (31)–(32) describe flow through the interior and exterior valves, as driven by the pressure gradient. The parameters include scalings R and B for the linear and nonlinear resistances respectively, and the valve inductance L . The function in the source term is a smoothed version of the heaviside function, depending on parameters ζ_{int} and ζ_{ext} , which help in calibrating the shape of arterial waveforms. It takes the form:

$$H(p_1, p_2; \zeta) := (1 + e^{-\zeta(p_1 - p_2)})^{-1}. \quad (45)$$

Lastly, Equations (33)–(37) enforce conservation of mass.

3.5. Model construction and numerical parameters

Our one-dimensional/zero-dimensional Fontan models are adapted from the normal circulation model presented in Ref. [45]. Diagrams for these vessel networks, with node and vessel labeling, can be found in Figs. 6–8. Networks are connected together with organ bed and heart models from the previous sections, thereby creating a closed-loop. The vessel network topology in these figures corresponds to the standard (extracardiac) Fontan physiology; models for the fenestrated Fontan and Fontan with hepatic vein exclusion are small modifications of the network for the standard Fontan, to be described below. We remark that most parameters in our models are held at their reference values. This study does not consider situations where patient-to-patient variability may be significant, which would require approaches related to efficient exploration of parameter distributions and development of patient-specific models [51]. Furthermore, variability may be augmented by the progression of the disease or the presence of other pathological conditions. Future work will address these challenges.

Different types of fenestrations have been clinically used for the extracardiac Fontan [9,13,52]. We consider a tube fenestration emanating from the extracardiac conduit (the synthetic conduit extending from the inferior vena cava to the pulmonary artery), as described in Ref. [53]. It is modeled by two short vessels placed on either side of a small resistance, governed by the equations for an organ bed from Section 3.3, but with the arterial and venous compliances set to zero. The resistance parameter accounts for the oblique orientation of the fenestration tube with respect to the inferior vena cava, and allows for a small pressure gradient between the inferior vena cava and the atrium. For a discussion of pressure losses at junctions depending on vessel bifurcation geometry, see e.g. Refs. [54,55]. The fenestration model is added to the standard Fontan vessel network to create the fenestrated Fontan model, and we consider fenestration conduit diameters of 6 mm, 8 mm, and 10 mm. These sizes are close to the range of diameters seen in clinical practice [53,56,57].

The hepatic vein exclusion is modeled by connecting the right and common hepatic veins in the standard Fontan model directly to the atrium. Refer to [10] for a diagram of this modification.

Schematics of these models, with the splanchnic circulation shown in more detail, are given in Figs. 9 and 10. Besides the different vessel network topologies, all parameters for the standard Fontan, fenestrated Fontan, and Fontan with hepatic vein exclusion are the same and can be found in the supplementary information. The parameter β for each vessel is set according to the scaling law with respect to A_0 , as discussed in Section 3.1.

The numerical method of characteristics is used to approximate solutions to system (6)–(7), with parameters $\alpha = 1.1$ and $\nu = 3.019 \times 10^{-2} \text{ cm}^2/\text{s}$ [49]. We take $h = 5 \times 10^{-2} \text{ cm}$, and $t = 8.57142 \times 10^{-5} \text{ s}$. The initial conditions for the vessels are $A = A_0$ and $U = 0$. The organ bed volumes are initially set to the reference volumes. Initial conditions for the heart and organ beds can be found in the supplementary information. In all simulations we add an additional 200 mL of blood into the model, over the first four cardiac cycles with period $T_{\text{heart}} = 6 / 7 \text{ s}$, in the vessel junction corresponding to node 56. This is done by setting Q_{add} in Equation (12) to:

$$Q_{\text{add}}(t) = \begin{cases} 50/T_{\text{heart}} & \text{if } t \leq 4T_{\text{heart}}, \\ 0 & \text{otherwise.} \end{cases}$$

The addition of blood volume allows for the calibration of mean pressures within the models.

3.6. Scaling the mesenteric resistance

It remains an open question as to how intestinal and hepatic problems, like protein-losing enteropathy and liver cirrhosis, develop in Fontan patients. Several theories exist which relate to vasoconstriction induced by low cardiac output. This compensatory process results in decreased flow to the mesenteric circulation [15,58]. Other work has uncovered unexpected features in the mesenteric waveform and increased mesenteric vascular resistance in Fontan patients [59,60]. We explore this hypothesis relating mesenteric vascular resistance to complications like protein-losing enteropathy by allowing the resistance in mesenteric circulation of our models to vary. In particular, we compare the hemodynamics in each of the three Fontan configurations as an index γ , referred to as the mesenteric resistance index, scales the arterial vessel stiffness and reference resistance in the intestinal organ bed. More precisely, the reference organ bed parameters for the intestine are scaled as follows:

$$R_{\text{ref,art}} \rightarrow \gamma R_{\text{ref,art}},$$

$$\Gamma_{\text{art}} \rightarrow \Gamma_{\text{art}}/\gamma.$$

The first equation describes narrowing of vessel cross sectional area, and the second equation corresponds to a stiffening of the vessel walls as a result of vasoconstriction-induced eutrophic remodeling [61–63]. Since the precise mechanisms leading to an increase in mesenteric resistance for Fontan patients are generally unknown, we choose to scale these parameters by the same positive power of γ .

4. Results

In all of our simulations, models are run for fifteen cardiac cycles, at which point we observe a periodic steady state. For relevant clinical variables, mean values of pressure and flow waveforms are computed by averaging over the last full cardiac cycle.

4.1. The standard Fontan circulation

We first explore hemodynamics in the standard Fontan circulation and the effect of increasing mesenteric vascular resistance. Waveforms in the ascending aorta for the full simulation of the standard Fontan are depicted in the left panel of Fig. 11. In the right panel of Fig. 11, we see a pie chart of the arterial blood flow distribution to different vascular beds, computed as:

$$\text{flow distribution to vascular bed} = 100 \times \frac{\text{mean flow into vascular bed}}{\text{mean aortic flow}}.$$

The left panel of Fig. 12 demonstrates the effect of increasing the mesenteric resistance index (from $\gamma = 1$ to $\gamma = 4$) on the flow waveform in the superior mesenteric artery (SMA) in the standard Fontan circulation. The mean flow decreases as γ increases, and in particular there is a substantial reduction of flow during diastole. At the highest resistance index there is even some backward, or regurgitant, flow. Small values of diastolic flow in Fontan patients with protein-losing enteropathy have been clinically observed, as in echo-doppler measurements of blood flow illustrated in the right panel of Fig. 12 [15,64].

In Table 1, We compare variables computed from our standard Fontan model, with $\gamma = 1$, to clinical data compiled in Ref. [65]. Since our vessel networks are adapted from the adult circulation model in Ref. [45], we normalize volumes by a body surface area of 1.5 m^2 corresponding to the mean from a collection of adult Fontan patients [23]. Variables are computed according to Table 2, cardiac index corresponds to cardiac output normalized by body surface area, and end-diastolic and systolic pressures are estimated from the right ventricular PV loop.

4.2. Fenestration and hepatic vein exclusion

Next, we analyze the effects of the fenestration and hepatic vein exclusion. Fig. 13 depicts clinical variables, some defined in Table 2 and others extracted from pressure and flow waveforms, for each Fontan configuration as the mesenteric resistance index varies.

Figs. 14 and 15 provide a more detailed look into the splanchnic circulation, depicting relative mean flow and pressure changes in the fenestration or hepatic exclusion, as compared to the standard Fontan.

In Figs. 16 and 17, we explore changes in Ea , Ees , and the contractility-afterload mismatch among the different Fontan configurations, as the mesenteric resistance index varies. These variables are defined in Table 2 following [58,66] and are easily computed with patient data, i.e. PV loops and arterial blood pressure measurements. We remark that this approach has been validated on an animal model [66].

Lastly, Fig. 18 provides insight into the effect of these surgical modifications on systemic arterial oxygen delivery and oxygen saturation. For an explanation these variables and their calculation, see the appendix.

5. Discussion

Ejection fraction and cardiac output are measures of cardiac performance; small values may indicate diminished heart strength, abnormalities in the peripheral vasculature, or other physiological problems. As expected, in the top two panels of Fig. 13, cardiac output and ejection fraction decrease when γ increases. Each surgical modification increases both variables, with the 10 mm fenestration and the hepatic exclusion having the largest impact. This trend in cardiac output is consistent with clinical data for fenestrated Fontans [12].

In the middle left panel, we notice the fenestration has almost no effect on the pressure in the portal venous circulation, whereas the hepatic exclusion drastically decreases the portal venous pressure to a normal level of ≈ 10 mmHg [10,67]. We also remark that pulmonary artery and portal venous pressures from our standard Fontan model with $\gamma = 1$ are consistent with clinical data for Fontan patients with pulmonary artery pressures greater than 15 mmHg [2]. This subset of patients have wedged hepatic venous pressures¹ around 20 mmHg, consistent with results in Fig. 13.

The middle right panel indicates the fenestration leads to a drop in the pulmonary artery pressure, while the hepatic exclusion leads to a small increase. These changes in pulmonary artery pressure for the fenestration align with results from a surgical report where measurements are taken pre and post operation [9]. Overall, the fenestration seems to relieve pulmonary arterial hypertension while the hepatic exclusion seems to mitigate portal venous hypertension.

In the bottom left panel of Fig. 13, we examine a clinical index used to assess flow distribution in the splanchnic circulation: the ratio of mean SMA flow to mean celiac artery flow. As mesenteric resistance increases, flow is diverted from the intestine to other parts of the splanchnic circulation via the celiac artery, thereby decreasing this ratio. This index was found to be smaller in Fontan patients with abnormal enteric protein loss (AEPL) as compared to patients without AEPL [60]. Its decrease in our model is consistent with an increase in γ , used to simulate the onset of splanchnic complications.

Finally, in the bottom right panel of Fig. 13, one notices an increase in the mean SMA flow for both the fenestration and hepatic vein exclusion, with the latter modification providing the largest increase.

Figs. 14 and 15 provide more detail regarding the hemodynamics in the splanchnic and pulmonary circulations. Each bar corresponds to the relative percent change in mean flow or mean pressure in a given vessel, as compared to the standard Fontan model. Fig. 14 depicts the impact of different fenestration sizes, with a larger fenestration leading to greater relative changes. Further, the fenestrated Fontan has lower pulmonary artery pressure but almost no

¹This measurement serves as an estimate of the pressure in the portal veins.

change in the portal venous pressure. The overall hemodynamic changes from the standard Fontan to the fenestrated Fontan are relatively mild, with no relative differences in flow or pressure exceeding about 30 %.

In contrast, as depicted in Fig. 15, the hepatic exclusion leads to larger relative changes in the splanchnic circulation, most strikingly in flow and pressure in the common hepatic vein and hepatic portal vein. This drop in pressure highlights the effectiveness of this modification in combating venous and portal venous congestion, thought to be factors potentially leading to complications in the Fontan physiology [2,68,69].

The decrease in portal venous pressure after the hepatic exclusion leads to a substantial increase in flow through the superior mesenteric artery to the intestines, and through the celiac artery to the liver and the rest of the splanchnic circulation. Physicians have suggested that protein-losing enteropathy and other splanchnic problems are correlated with low flow to this part of the circulation, so enhanced perfusion may mitigate complications from the Fontan physiology [15]. We remark that the fenestration also increases perfusion in this area, as seen in Fig. 14, despite a small increase in the portal venous pressure. In sum, the success of both fenestrations and hepatic exclusions in resolving protein-losing enteropathy may be due to their similar effect on blood flow to the intestines and liver [9,10].

Figs. 16 and 17 show trends in the arterial and end-systolic elastances and their ratio, the contractility-afterload mismatch. The arterial elastance provides a rough measurement of the “afterload” experienced by the ventricle, i.e. the effective resistance of the vessel trees and organ beds combined. The end-systolic elastance is an index for contractility, or strength of the ventricle. High values of E_{es} indicate a firm and muscular contraction, while low values suggest the ventricle is too compliant at the end of systole. We are particularly interested in this ratio since physicians observed a larger contractility-afterload mismatch in Fontan patients diagnosed with protein-losing enteropathy, compared to patients without this problem [58].

The left panel of Fig. 16 depicts an increase in E_a as γ increases. This observation aligns well with clinical data showing an increase in E_a in Fontan patients with protein-losing enteropathy [58], and is consistent with the increase in afterload due to an increase in mesenteric resistance. Further, we observe a decrease in E_a and an increase in E_{es} for the fenestration and hepatic exclusion, when compared to the values for the standard Fontan. This difference indicates both surgical modifications to the standard Fontan decrease afterload and increase contractility, as measured by these clinical indices. The decrease in E_a and increase in E_{es} for both the fenestration and hepatic exclusion may be partially explained by a fairly large increase in stroke volume and mean arterial pressure respectively, since both modifications increase blood flow into the heart. We remark that maximum ventricular pressure and end-systolic elastance also increase after these modifications, but apparently in a milder fashion.

The increase in E_{es} shown in Fig. 17 indicates the hepatic exclusion leads to the most efficient hemodynamic configuration considered, followed by the 10 mm fenestration. In

sum, both the fenestration and hepatic exclusion lead to more optimal cardiovascular physiologies as measured by the contractility–afterload mismatch.

Finally, Fig. 18 depicts the approximate systemic arterial oxygen saturation and oxygen availability, for each Fontan configuration. The fenestration and hepatic exclusion both increase cardiac output by allowing deoxygenated blood to flow directly into the heart. In turn, oxygen saturation decreases after these surgical modifications, consistent with clinical data for fenestrated Fontans [9,12]. The fenestration has the largest impact on saturation, with the 8 and 10 mm conduits leading to smaller saturations than seen in the hepatic exclusion.

The right panel of Fig. 18 reveals the fenestration and hepatic exclusion increase systemic arterial oxygen availability, with the hepatic exclusion having the greatest effect. Results from our model may be compared to clinical data of fenestrated Fontan patients who had their fenestration closed, or occluded [70], with measurements taken before and after occlusion. The majority of patients saw a drop in systematic arterial oxygen availability after occlusion. This finding is consistent with our results, where the standard Fontan model is taken to be a circulation with an occluded fenestration. Further, values for oxygen availability from Ref. [70] are close to our results when normalized by a body surface area of 1.5 m².

6. Conclusions

In this paper we described models for three variations of the Fontan physiology: (1) the standard, unmodified Fontan, (2) the fenestrated Fontan, and (3) the Fontan with hepatic vein exclusion. Three diameters for the fenestration conduit were considered. Models were constructed from closed loop networks of one–dimensional elastic vessels coupled to zero–dimensional models for the heart and organ beds. The resistance in the intestines was varied to simulate complications in the splanchnic circulation.

As the mesenteric resistance increased, our models produced superior mesenteric artery waveforms and ratios of SMA to CA flow aligning with clinical data from Fontan patients affected by protein–losing enteropathy. We found that both the modifications to the standard Fontan physiology increased cardiac output, with the hepatic vein exclusion having the largest effect. The hepatic vein exclusion led to the largest overall changes with respect to standard Fontan hemodynamics, with a notable drop in the mean pressure of the portal vessels; this pressure drop increased flow to the intestines. The fenestration also increased mesenteric flow, but did not decrease the pressure in the portal circulation; instead, our results show a drop in the pulmonary artery pressure. Both the fenestration and hepatic vein exclusion lead to favorable changes in the contractility–afterload mismatch and the systemic arterial oxygen availability, while leading to small decreases in systemic arterial oxygen saturation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

A. Oxygen transport

In this section we describe equations for oxygen flow. Schematics of the standard Fontan model and modified Fontan models are provided in Fig. 19.

Variables for oxygen transport are defined as follows. Oxygen content, in (mL O_2)/(mL blood), is defined to be C_a , C_{sv} , and C_{pv} for the systemic arteries, systemic veins, and pulmonary veins respectively. The variable Q is cardiac output in mL/s, taken as the mean aortic flow. For the modified Fontan models, variables $\tilde{Q}$ and Q_{pv} in mL/s denote mean fenestration/hepatic venous flow or mean pulmonary venous flow respectively. We assume the rate of oxygen uptake in the lungs and depletion in the systemic organs are equal and the same for all models, denoted R_{O_2} in (mL O_2)/s [16].

Following [16], we derive equations imposing conservation of oxygen for the standard and modified Fontan models. For the standard Fontan model, one has:

$$QC_a - R_{O_2} = QC_{sv}, \quad (46)$$

$$QC_{sv} + R_{O_2} = QC_{pv}. \quad (47)$$

Equations (46) and (47) are conservation of oxygen through the systemic organs and lungs respectively. For the modified Fontan model we have similar equations:

$$QC_a - R_{O_2} = QC_{sv}, \quad (48)$$

$$Q_{pv}C_{sv} + R_{O_2} = Q_{pv}C_{pv}, \quad (49)$$

$$\tilde{Q}C_{sv} + Q_{pv}C_{pv} = QC_a. \quad (50)$$

To compute systemic oxygen availability QC_a for the modified Fontan models, we make the following assumptions. First, we assume for the standard Fontan model that the blood in the pulmonary veins and systemic arteries have the maximum possible oxygen content equal to

$C_{pv} = C_a = 0.22 \text{ (mL } O_2\text{)/(mL blood)}$ [16]. According to the data in Ref. [70], we assume the oxygen saturation in the systemic veins is 60%, i.e. $C_{sv} = 0.6 \times C_a$. Given the cardiac output Q from the standard Fontan model with $\gamma = 1$, we compute the rate of depletion of oxygen from (46)–(47) as:

$$R_{O_2} = QC_{pv} - QC_{sv} = 0.4 \times QC_a.$$

We assume oxygen depletion R_{O_2} is the same for the modified Fontan models and use the value computed above. Equations (48) and (49) then give the systemic oxygen availability for the modified Fontan models, as a function of their cardiac output Q , pulmonary venous flow Q_{pv} , R_{O_2} , and $C_{pv} = 0.22 \text{ (mL } O_2\text{)/(mL blood)}$:

$$QC_a = R_{O_2} \left(1 - \frac{Q}{Q_{pv}} \right) + QC_{pv}.$$

The systemic arterial saturation can be computed as $100\% \times C_a / C_{pv}$.

Appendix B. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.compbimed.2017.08.024>.

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Fig. 1.
A schematic of the Fontan physiology.

Fig. 2.

A sketch of a single vessel junction with N_{in} incoming vessels and N_{out} outgoing vessels.

Fig. 3.

A sketch of the organ bed model. The parameters R_{cap} , C_{art} , and C_{ven} are the resistance, arterial compliance, and venous compliance respectively.

Fig. 4.

A sketch of the liver model, including the hepatic artery and hepatic portal vein. Parameters are analogous to those defined in the organ bed model given in Fig. 3.

Fig. 5.

A sketch of the heart model, including incoming vessels which drain blood into the atrium, and an outgoing vessel which carries blood ejected from the ventricle. The heart valves in the model are represented by two diodes. Flow through the interior valve is Q_{int} and flow through the exterior valve is Q_{ext} . The variables p , Q , and V are chamber pressure, flow, and volume respectively.

Fig. 6.

Topology of the systemic arteries for the standard Fontan physiology, adapted from Ref. [45]. The non-squared numbers label the vessels and the squared numbers label the nodes. Red squared numbers correspond the interior nodes, or vessel junctions, and black squared numbers correspond to an organ bed or the heart. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 7.

Topology of the systemic veins and pulmonary arteries for the extracardiac Fontan physiology, adapted from Ref. [45]. The non-squared numbers label the vessels and the squared numbers label the nodes. Red squared numbers correspond the interior nodes, or vessel junctions, and black squared numbers correspond to an organ bed or the heart. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 8.

Topology of the pulmonary and portal circulations for the standard Fontan physiology, adapted from Ref. [45]. The non-squared numbers label the vessels and the squared numbers label the nodes. Red squared numbers correspond the interior nodes, or vessel junctions, and black squared numbers correspond to an organ bed or the heart. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Fig. 9.

A schematic of the standard Fontan physiology without any surgical modifications. The splanchnic circulation is shown in more detail.

Fig. 10. Schematics of the Fontan with fenestration on the left and with the hepatic vein exclusion on the right. The modifications are shown in bold and all caps.

Fig. 11.

The figure on the left displays pressure and flow in the ascending aorta of the standard Fontan circulation reaching a periodic steady state. The pie chart on the right displays the arterial flow distribution to different vascular beds.

Fig. 12.

On the left are flow waveforms in the superior mesenteric artery of the standard Fontan circulation, with increasing values of the mesenteric resistance index γ . On the right are experimental measurements of SMA flow adapted from Ref. [15] with permission (© 2007, the Author Journal compilation © 2007 *Congenital Heart Disease*, Wiley Publishing, Inc.).

Fig. 13.

The figures above display several model outputs for the standard Fontan, fenestrated Fontan, and Fontan with hepatic vein exclusion.

Fig. 14.

The figures above display percent change of mean flow and mean pressure values for the fenestrated Fontan with $\gamma = 1$. The vessels are the ascending aorta (AA), abdominal aorta (AB), celiac artery (CA), hepatic artery (HA), superior mesenteric artery (SMA), common hepatic vein (HV), inferior vena cava (IVC), hepatic portal vein (HPV), pulmonary artery (PA), and pulmonary vein (PV).

Fig. 15.

The figures above display percent change of mean flow and mean pressure values for the Fontan with hepatic exclusion with $\gamma = 1$. The vessels are the ascending aorta (AA), abdominal aorta (AB), celiac artery (CA), hepatic artery (HA), superior mesenteric artery (SMA), common hepatic vein (HV), inferior vena cava (IVC), hepatic portal vein (HPV), pulmonary artery (PA), and pulmonary vein (PV).

Fig. 16.
Plots of the arterial elastance and end-systolic elastance for different configurations and values of the mesenteric resistance index γ .

Fig. 17.
Plots of the contractility–afterload mismatch for different configurations.

Fig. 18.
Plots of systemic arterial oxygen saturation on the left and oxygen availability on the right.

Fig. 19. Schematics of the standard Fontan on the left and the modified Fontan on the right (either the fenestration or hepatic vein exclusion).

Table 1

Clinical variables from our model compared to those extracted from clinical data, compiled in Ref. [65].

variable	our model	reported in Ref. [65]
cardiac index ($\text{L min}^{-1} \text{ m}^{-2}$)	2.5	2.9, 2.1
stroke volume index (mL m^{-2})	38.3	39, 40
RV end–diastolic/systolic volume index (mL m^{-2})	86.3/48	72/33, 76/36
RV end–systolic/diastolic pressure (mmHg)	112.9/5.8	–/6.6, –/8
vena cava mean pressure (mmHg)	15.4	10.6, 10
sys. artery systolic/diastolic/mean pressure (mmHg)	113.4/68.7/90	124/70/88
pul. artery mean pressure (mmHg)	15.3	9

Table 2

Some clinical variables considered in the comparison of the different Fontan configurations.

variable	abbrev.	computed as
end-diastolic volume (mL)	<i>EDV</i>	maximum ventricular volume
end-systolic volume (mL)	<i>ESV</i>	minimum ventricular volume
stroke volume (mL)	<i>SV</i>	end-diastolic volume – end-systolic volume
ejection fraction	<i>EF</i>	stroke volume ÷ end-diastolic volume
cardiac output (L min ⁻¹)	<i>CO</i>	mean aortic flow
arterial elastance (mmHg mL ⁻¹)	<i>Ea</i>	maximum ventricular pressure ÷ stroke volume
end-systolic elastance (mmHg mL ⁻¹)	<i>Ees</i>	mean arterial pressure ÷ end systolic volume
contractility–afterload mismatch	<i>Ea/Ees</i>	arterial elastance ÷ end systolic elastance