Peripheral Vascular Adaptation and Orthostatic Tolerance in Fontan Physiology

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Background—The Fontan circulation is critically dependent on elevated venous pressures to sustain effective venous return. We hypothesized that chronically increased systemic venous pressures lead to adaptive changes in regional and peripheral vessels to maintain cardiac output, especially when patients are upright.

Methods and Results—Nine post–Fontan procedure patients (aged 13 to 24 years) and 6 age- and sex-matched controls were compared with techniques to measure circulatory responses (peripheral and compartmental blood flow, venous capacity, and microvascular filtration). Parameters studied included strain-gauge plethysmography measures of peripheral circulatory function, regional blood volume distribution by impedance plethysmography, and head-up tilt testing. Important differences between Fontan patients and controls were seen in several vascular compartments: (1) Calf capacitance was lower (median, 3.5 versus 5.5 mL/100 mL tissue; \(P=0.005\)), and resting venous pressure was higher (13.0 versus 10.5 mm Hg; \(P=0.004\)); (2) higher leg arterial resistance was observed (32.1 versus 22.2; \(P=0.03\)); (3) microvascular filtration pressures and threshold for edema were elevated; and (4) with head-up tilt testing, splanchnic flow was not reduced in Fontan patients versus controls (fractional change, +4% versus −32%; \(P=0.004\)), and splanchnic arterial resistance did not increase as expected (fractional change, +8% versus +79%; \(P=0.003\)).

Conclusions—Reduced venous compliance and increased filtration thresholds may act as adaptive mechanisms in maintaining venous return in Fontan circulation. Well-compensated Fontan subjects demonstrate superior orthostatic tolerance resulting from decreased compartmental fluid shifts in response to head-up tilt and higher vascular resistance. This results from increased venous stiffness and decreased splanchnic capacitance and may also be an adaptive mechanism to maintain venous return in these patients while standing. (Circulation. 2009;120:1775-1783.)

Key Words: Fontan procedure ■ orthostatic intolerance ■ splanchnic circulation ■ vascular capacitance

Univentricular heart is a common feature of many forms of complex cardiac disease, and the Fontan repair comprising total cavopulmonary connection offers a final common pathway to palliate these patients.\(^1\)–\(^3\) This is a highly abnormal circulation, in which the right ventricle is absent as an effective pump that allows pulsatile flow to be distributed to the pulmonary arteries.\(^5\)–\(^6\) Systemic venous return to the heart is highly dependent on peripheral venous properties and pulmonary artery pressure.\(^3\) Abnormalities in circulatory regulation after total cavopulmonary connection have been reported sporadically. However, integrative features of peripheral vascular function after long-term adaptation to the surgery have not been well characterized.\(^5\)–\(^12\)

Clinical Perspective on p 1783

We hypothesized that chronically increased systemic venous pressure leads to structural and functional changes in arteries and veins that alter venous capacitance, venous resistance, microvascular filtration, regional venous tone, peripheral and regional arterial regulation, and autonomic function corresponding to compartmental redistributions in blood volume. For example, venous compliance and function changes may produce increased microvascular filtration, resulting in edema and extravascular fluid collection often found in “failed-Fontan” patients.\(^13\)–\(^15\) Although this is most easily evident in dependent extremities, we hypothesized that vascular properties are also abnormal within the splanchnic vasculature with more important circulatory consequences because the splanchnic compartment is the single largest venous reservoir. This may be of special importance in the development of protein-losing enteropathy, a frequent and dire sequel to Fontan palliation.\(^16\) It is possible that subjects who are functioning well many years after the Fontan repair develop protective adaptations in the vascular system to maintain normal function in activities of daily living, especially in the upright state.

To investigate these hypotheses, we compared well-compensated patients with Fontan physiology with age- and sex-matched normal control subjects using noninvasive techniques. Peripheral venous capacity and microvascular filtra-
tion properties were studied with the use of venous occlusion strain-gauge plethysmography. Impedance plethysmography was used to measure regional circulatory responses at rest and during neurovascular stress including head-up tilt (HUT) and forced Valsalva maneuver and to measure limb, thoracic, and splanchnic blood flows.

**Methods**

**Subjects and Experimental Outline**
Nine subjects (4 female and 5 male) aged 13 to 24 years who had undergone Fontan surgery 8 to 19 years before testing and 6 age-matched healthy controls (3 male and 3 female) volunteered for the study (characteristics and hemodynamics of the subjects are described in Table 1). The control subjects were healthy, normotensive, and free from any systemic disorders. There were no smokers in either group. There were no competitive athletes in either group. Post-Fontan procedure patients who were medically unfit for testing lasting several hours, those with clinical evidence of cardiac failure, those on antiarrhythmia medications, and those with other serious systemic diseases, including patients with renal or hepatic disorders and failed-Fontan patients (patients with severe edema, anasarca, and malabsorption suggesting gut edema), were excluded. Our Fontan patients therefore comprised those with a “good” outcome only. Six of the Fontan subjects were taking low-dose aspirin, 3 of whom were additionally taking a very low dose (2.5 to 5 mg/d) of enalapril, 1 was taking Coumadin, and 2 were taking no medications. A thorough clinical examination, ECG, echocardiography, and baseline laboratory testing were obtained in all patients. Echocardiography revealed good single-ventricular function with no significant valvar dysfunction, and ECG (and periodic Holter monitoring) ruled out any arrhythmias in all subjects. All laboratory values were within the normal range. Written informed consent was obtained, and all protocols were approved by the institutional committee for protection of human subjects (institutional review board).

**Study Protocol**

All experiments were completed on a single visit, with the subject arriving in the morning ≥2 hours after a light breakfast. ECG was monitored continuously and recorded to assess heart rate and rhythm changes. Blood pressure was monitored with a finger plethysmograph (Finometer, TNO Biomedical Instrumentation, Amsterdam, Netherlands) placed on the right index finger and recalibrated every 5 minutes against oscillometric sphygmomanometer pressure. Leg blood pressure was measured intermittently by oscilometry on the calf contralateral to the strain gauge and was used to calculate the calf mean arterial pressure. A respiratory impedance plethysmograph (model 200 noninvasive monitoring system, Respiracor) monitored respiration. Respiratory, ECG, and Finometer pressure data were interfaced to a personal computer with the use of an analog-digital converter (DataQ Ind, Milwaukee, Wis), and custom-designed software was used to store data on a continuous basis. These data were multiplexed with a strain gauge and were effectively synchronized. The study was started after an initial 30-minute acclimatization period.

Strain-gauge measurements included peripheral blood flow by venous occlusion plethysmography, resting venous pressure, peripheral arterial resistance, and venous capacitance. Our facility and others have reported extensively on these methods before. The methods used are summarized in Figure 1.

Venous occlusion strain-gauge plethysmography to measure peripheral blood flow was used to measure forearm and calf blood flow (Figure 1, top panel and left bottom panel), compliance (volume-pressure relationship; Figures 2 and 3), and microvascular filtration (flow-pressure relationship; Figures 2 and 4) in the supine steady state in all subjects. Supine measurements were made after a 30-minute equilibration period with the use of occlusion cuffs placed ~10 cm above the knee and elbow. Strain gauges attached to a Whitney-type strain-gauge plethysmograph (Hokanson) were placed around the maximum diameter of the forearm and calf. Blood flows were estimated while subjects were in the supine position with the use of rapid cuff inflation to a pressure below diastolic pressure (eg, 40 mm Hg) but above the venous pressure to prevent venous egress. Systolic and diastolic blood pressures of the arm and leg were determined by oscillometry. Arterial inflow in milliliters per 100 milliliters of tissue per minute was estimated as the rate of change of the rapid increase in the limb cross-sectional area (Figure 1). Capacitance vessel (resting venous) pressure (Pv) was assessed in the steady state shortly after blood flow measurement, the occlusion cuff pressure was increased gradually until an increase in limb volume occurred, at which point Pv was measured.

Peripheral resistance was calculated in the forearm and calf with the use of the following formula: (mean arterial pressure−Pv)/blood flow.

Venous capacitance was measured by our previously documented techniques. Because >75% of the blood volume at any given point resides in the veins, they are the principal capacitance vessels. Venous capacitance is defined as the relative amount of blood volume that can be held in the peripheral veins at a given point in time. In brief (Figure 1), while subjects were in the supine position, the limb was gently raised above the heart level until no further decrease in volume was obtained. This was used to empty the limb and establish zero filling. After recovery with the limb once again flat, we used 10-mm Hg increases in pressure, starting at the first multiple of 10 larger than Pv, to a maximum of 60 mm Hg. Thus, if Pv were 5 mm Hg, the first occlusion pressure would be 10 mm Hg, whereas if Pv were 14 mm Hg, the first occlusion pressure would be 20 mm Hg. This produced progressive limb enlargement. Pressure was maintained for 4 minutes until a steady state was achieved as specified by Gamble et al. At lower congestion pressures, the limb size reaches a plateau representing venous filling alone. At higher pressures, a plateau is not reached. Instead, there are 2 components superimposed: a linear component representing microvascular filtration, which can be extracted from the total curve by least-squares

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**Table 1. Fontan Subject Characteristics and Surgical Data**

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex</th>
<th>Age, y</th>
<th>Diagnosis (Systemic Ventricle)</th>
<th>Type of Surgery</th>
<th>Years Since Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>18</td>
<td>Hypoplastic left heart syndrome (RV)</td>
<td>Lateral tunnel</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>13</td>
<td>Tricuspid atresia, pulmonary stenosis (LV)</td>
<td>Extracardiac Fontan</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>16</td>
<td>Tricuspid atresia, pulmonary atresia (LV)</td>
<td>Lateral tunnel</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>16</td>
<td>Hypoplastic left heart syndrome (RV)</td>
<td>Lateral tunnel</td>
<td>13</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>13</td>
<td>Ebstein, pulmonary atresia (LV)</td>
<td>Extracardiac Fontan</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>24</td>
<td>Hypoplastic left heart syndrome (RV)</td>
<td>Lateral tunnel</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>13</td>
<td>Double-inlet LV, pulmonary stenosis (LV)</td>
<td>Extracardiac Fontan</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>19</td>
<td>Tricuspid atresia, pulmonary stenosis (LV)</td>
<td>Lateral tunnel</td>
<td>16</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>17</td>
<td>Tricuspid atresia, pulmonary stenosis (LV)</td>
<td>Lateral tunnel</td>
<td>13</td>
</tr>
</tbody>
</table>

Pt indicates patient; RV, right ventricle; and LV, left ventricle.
methods, and a residual curve that reaches a plateau, which represents filling of capacitance vessels (Figure 1, right bottom panel). Once the volume response is partitioned, capacitance is calculated from the sum of residual portions, to which is added the estimate of supine venous volume obtained from raising the limb.

Curvilinear graphs of volume versus occlusion pressure were calculated and represent the volume-pressure or capacitance relation (Figure 2). Linear graphs of filtration rate as a function of occlusion pressure were also calculated. The slope of the slow increase in volume of the limb once rapid venous filling is complete provides an estimate of filtered flow. The linear relation between filtered flow and pressure at each pressure increment defines the microvascular filtration coefficient. The pressure intercept of the filtration curve is termed the isovolumetric pressure \( P_i \), which is defined as the minimum occlusion pressure required to produce a net increase in limb interstitial fluid.\(^{16,23}\) Above \( P_i \), intravascular fluid begins to extravasate because of microvascular filtration. Below \( P_i \), there is no net accumulation of filtrate.

Impedance Plethysmography to Measure Segmental Blood Flows

Impedance plethysmography can detect internal volume shifts, estimate cardiac output, measure regional fluid flows, and quantify relative body fluid volumes.\(^{24,25}\) Relations between impedance and fluid compartmentalization have been well established.\(^ {24}\) Tetrapolar impedance plethysmography was used to measure fluid volumes and blood flows in the thoracic (neck to xiphoid process), splanchnic (xiphoid process to iliac crest), pelvic (iliac crest to knee), and lower leg (knee to ankle) segments during test sequences. Measurements of baseline resistance (\( R_0 \)) and pulsatile resistance changes (\( \Delta R \)) were made. Disposable spot ECG electrodes were attached to the foot of the dominant leg at segmental limits on the same side of the body and on the dominant arm at the back of the hand. The impedance plethysmography introduced a high-frequency (50 kHz), low-amperage (0.1 mA root mean squared) constant current signal between the foot and hand electrodes that was not felt by the subject. Simultaneous \( R \) values were measured in each segment continuously. Records of \( R_0 \) were used to determine the fluid volume of each segment during each test sequence. The pulsatile \( \Delta R \) changes were used to obtain the total (mL/min) and relative (mL/100 mL of body tissue per minute) blood flow responses of each body segment to each test condition. These methods have been validated previously.\(^ {24,26} \) The measurements allow us to trace fluid shifts from thoracic to peripheral compartments during orthostatic stress.

Upright Circulatory Measurements

After supine measurements were obtained and the subjects were allowed to return to an equilibrium state, they were subjected to an
steady state. Pi was also measured. Arterial and venous properties
sure. Bottom, x axis intercept of the flow-pressure line (Pi) is the pressure at which microvascular filtration begins.

Figure 2. Compliance relationship and microvascular filtration relation derived from the Fontan subgroup. Top, x axis intercept of the volume-pressure curve (Pv) is the resting venous pressure. Bottom, x axis intercept of the flow-pressure line (Pi) is the pressure at which microvascular filtration begins.

upright tilt to 70 degrees for 10 minutes or until symptoms necessitated a return to the supine position. Limb blood flows were measured each minute by strain-gauge plethysmography, and impedance plethysmography fluid shifts, blood pressure, heart rate, and respirations were recorded continuously. Strain-gauge plethysmography was performed to measure limb arterial blood flow and capacitance volume-pressure relation, and the patient was returned to the supine position. In general, P, changes during tilt but reaches a steady state. P, was also measured. Arterial and venous properties during tilt were compared with supine data to define the relative contribution of active limb venoconstriction to the compliance relation and to determine changes in arterial and venous flow resistance, microvascular filtration, compartmental fluid shifts, and changes in cardiac output and blood volume with orthostatic stress.

Quantitative Valsalva Maneuver
The quantitative Valsalva maneuver was used to characterize sympathetic vasoconstrictive and parasympathetic cardiac responsiveness. The maneuver was performed with the patient in the supine position by blowing with an open glottis into a mouthpiece connected to the mercury column of a sphygmomanometer with an air leak. A 40- to 50-mm Hg pressure was maintained for 15 seconds. Blood pressure recovery in phase II and cardiopressor response in phase IV were used as indices of vasocostrictor and contractile integrity. Baroreceptor-mediated tachycardia in phase II and bradycardia in phase IV determine whether cardioagal reflexes are intact. Before the maneuver, blood pressure was averaged over 20 beats, and mean resting heart rate was calculated. The blood pressure response was quantified during straining and during the pressure overshoot. Because arterial tonometry was used to measure blood pressure, decreases of >20 mm Hg during early phase II combined with absent phase IV or late phase II were considered abnormal and indicative of blunted vasoconstrictive response.27

Statistical Analysis
Data were digitalized and stored in a computer and were analyzed offline with custom software. We used a nonparametric independent samples test (Wilcoxon/Mann-Whitney) for comparing hemodynamic data between Fontan and control subjects (Table 2), segmental arterial resistances (Figure 5), and segmental blood flows (Figure 6). Repeated-measures ANOVA was used for repeated measurements over time (change in volume with increase in pressure; Figure 3). Adjustment for multiple comparisons was done with the use of the Bonferroni correction. Filtration curves between 2 groups were compared by linear regression in Figure 4. Results were calculated with the use of SPSS (Statistical Package for the Social Sciences) software version 14.0 and graphed with the use of GraphPad Prism (California) software version 4. Results are reported as median and range; P<0.05 was considered significant. We measured normalized blood flow (blood flow divided by segmental volume) in units of mL/min per 100 mL of tissue and normalized arterial resistance (arterial resistance divided by segmental volume) in units of mm Hg/mL per minute per 100 mL of tissue.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Results are quantified in Table 2, with median and range shown. The 2 groups were similar in terms of age, height, weight, body surface area, heart rate, respiratory rates, and blood pressures.

Supine Hemodynamics
The Fontan subjects taking enalapril had blood pressures that were not statistically different from those of subjects not taking the medication. Fontan subjects had significantly lower end-tidal CO₂ throughout the testing period (P=0.001). Both groups had normal oxygen saturations, in the 97% to 100% range. There
was no significant difference between peripheral blood flows in both arms and legs between the 2 groups by strain-gauge plethysmography measurements. The peripheral resistance was significantly elevated in the leg in Fontan subjects compared with controls but was comparable in the arms in the 2 groups.

**Volume-Pressure Relation (Capacitance) and Peripheral Venous Properties by Strain-Gauge Plethysmography**

Figure 3 depicts arm and leg volume-pressure curves. With the use of Bonferroni correction, \( P_{\text{time}} \) and \( P_{\text{time}}/H11003 \) in the arm curves were <0.001 and 0.044 and in the leg were 0.002 and 0.050, respectively (both curves being statistically significant over time and between groups). The curves show that as we increase the limb occlusive cuff pressure, the limb volume initially increases steeply, followed by a more gradual increase. The volume change in both arms and legs in the Fontan group was less than that in the controls. The difference at each given pressure was statistically significant, suggesting reduced limb venous capacitance. The steeper slope of the capacitance relation in the control group suggests higher compliance compared with Fontan subjects, thus implying “stiffer” capacitance vessels in the Fontan circulation. Forearm \( P_c \) was similar for both groups (median, 8.9 versus 8.6 mm Hg) and did not reach statistical significance. Supine calf \( P_c \) was significantly (13 versus 10.5; \( P=0.004 \)) increased in the Fontan group, indicating increased supine ambient pressure in the leg veins. Figure 4 demonstrates the microvascular filtration relation (filtration rate versus \( P_v \)) in the arm and leg in Fontan versus control subjects. As \( P_v \) increased, the rate of filtration increased in both groups. There was no difference between the regression fits in the arms for Fontan and control subjects. Regression slopes were also not different in the legs, whereas the X intercept (\( P_i \)) was significantly greater in Fontan patients, suggesting a higher filtration threshold in the leg. Thus, for a given \( P_c \), filtration rate is significantly smaller in the lower extremities in the Fontan group. Net microvascular filtration begins at significantly higher leg venous pressures (higher \( P_i \)) in the Fontan group compared with controls, implying a higher threshold for edema formation.

**HUT Testing**

Impedance and segmental volume changes are shown in Figures 5 and 6. There were significant differences in the response to HUT in the 2 groups. In contrast to the normal increase in heart rate and diastolic pressure observed in control subjects, there was insignificant change in heart rate and blood pressures with HUT in the Fontan group. None of

### Table 2. Supine Hemodynamic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n=6)</th>
<th>Fontan (n=9)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>16.2 (13–24)</td>
<td>17.3 (13–24)</td>
<td>0.4</td>
</tr>
<tr>
<td>Height, cm</td>
<td>161.5 (151–169)</td>
<td>160.0 (145–175)</td>
<td>0.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>58.9 (47–64)</td>
<td>562 (49–98)</td>
<td>0.3</td>
</tr>
<tr>
<td>Body surface area, ( \text{cm}^2 )</td>
<td>1.6 (1.43–1.67)</td>
<td>1.6 (1.5–1.71)</td>
<td>0.5</td>
</tr>
<tr>
<td>Heart rate</td>
<td>74.5 (67–77)</td>
<td>63 (49–97)</td>
<td>0.6</td>
</tr>
<tr>
<td>Respiration</td>
<td>20 (17–25)</td>
<td>20 (14–24)</td>
<td>0.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118 (96–128)</td>
<td>124 (95–146)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>61 (52–70)</td>
<td>70 (50–83)</td>
<td>0.1</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>80 (66–89)</td>
<td>88 (68–104)</td>
<td>0.4</td>
</tr>
<tr>
<td>End-tidal CO(_2)</td>
<td>38 (35–45)</td>
<td>32 (26–34)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>13.2 (12.1–14.2)</td>
<td>13.4 (12.6–14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Arm ( P_c ), mm Hg</td>
<td>8.6 (6–11)</td>
<td>8.9 (5–14)</td>
<td>0.6</td>
</tr>
<tr>
<td>Arm arterial resistance, ( \text{mL/100 mL per minute} )</td>
<td>5.43 (3.5–17.5)</td>
<td>4.2 (1.9–11.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>Arm capacity, ( \text{mL/100 mL} )</td>
<td>3.7 (3–4.6)</td>
<td>2.5 (1.3–2.9)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Arm flux intercept</td>
<td>39.9 (23.3–48.7)</td>
<td>25.4 (11.9–43.5)</td>
<td>0.3</td>
</tr>
<tr>
<td>Leg ( P_c ), mm Hg</td>
<td>10.5 (8–12)</td>
<td>13 (12–18)</td>
<td>0.004*</td>
</tr>
<tr>
<td>Leg arterial resistance, ( \text{mL/100 mL per minute} )</td>
<td>22.2 (13.0–28.2)</td>
<td>32.0 (13.2–55)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Leg capacity, ( \text{mL/100 mL} )</td>
<td>5.5 (4.6–6.8)</td>
<td>3.5 (2.2–5)</td>
<td>0.005*</td>
</tr>
<tr>
<td>Leg flux intercept</td>
<td>15.1 (11.7–30)</td>
<td>27.4 (20–38.5)</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

Values are median (range). *\( P<0.05 \).
the subjects developed any symptoms of orthostatic intolerance (dizziness, nausea, heat, or headache) necessitating early return to the supine position. In the control group, 4 of 6 subjects mentioned lightheadedness and some nausea, although the changes in hemodynamics did not dictate early return to the supine position. At baseline, compartmental arterial resistances (trunk, splanchnic, and leg) were significantly higher in Fontan subjects than in control subjects. Control subjects demonstrated the expected decrease in splanchnic (−32%) and trunk blood flow (−35%) and increase in splanchnic (+79%) and trunk arterial resistance (+86%) with orthostasis. In contrast, Fontan subjects showed unchanged splanchnic blood flow and arterial resistances (+4% and +8%) with orthostasis, whereas trunk flow decreased (−19%) and resistance increased (+39%) to a lesser extent compared with control subjects. As shown in Figures 5 and 6, the segmental changes in both blood flows and arterial resistances in the Fontan group parallel those in the control group; however, the changes were minimal and insignificant with HUT, especially in the splanchnic compartment. Figure 5 shows the directional changes in segmental blood flows in the thoracic and splanchnic compartments and leg with HUT in control (left) and Fontan (right) subjects. The y axis shows the normalized segmental blood flows (mL/100 mL tissue per minute), and the x axis shows the change in value between supine and HUT in each individual subject. The thicker line in each panel depicts the median for each group. *The change in flow after HUT was significant in the control group (P < 0.05 in each compartment) but not in the Fontan group.

Figure 5. Fractional changes in segmental blood flows in the thoracic and splanchnic compartments and leg with HUT in control (left) and Fontan (right) subjects. The y axis shows the normalized segmental blood flows (mL/100 mL tissue per minute), and the x axis shows the change in value between supine and HUT in each individual subject. The thicker line in each panel depicts the median for each group. *The change in flow after HUT was significant in the control group (P < 0.05 in each compartment) but not in the Fontan group.

Valsalva Maneuver

In both the Fontan and control subjects, as expected, the Valsalva maneuver produced decreased trunk flow during the
early phase 2 (−8% and −15%), whereas splanchnic flow increased (1% versus 4%). The responses were again directionally similar but blunted in the Fontan group, although differences were not statistically significant in this small group of subjects.

**Discussion**

The “Fontan circulation” has long puzzled cardiologists and physiologists alike.2,3,6,11,28,29 Conceptually, at the level of the heart, systemic and pulmonary venous flows are separated, and a single ventricle provides the pumping function. However, the sustainability of this situation over a lifetime after surgery has been a source of intense speculation and research.2–15,16,28,29 The question of why some patients remain symptom free in the face of such abnormal circulatory physiology while others become edematous, develop protein-losing enteropathy, and succumb early to cardiac failure (failed Fontan) remains unclear but is of paramount importance for patient health.2–14,16

This is the first study to systematically study alterations in arterial blood flow and in the peripheral venous capacitance and microvascular filtration properties in subjects who have successfully adapted to the Fontan repair. Circulatory adjustments and alteration of venous properties, especially in the lower extremities, have been postulated to result from chronic exposure to the Fontan circulation, with the venous pressure sustaining forward flow to the pulmonary circuit.3–5,8,10,11 Our study reports several key physiological findings in the peripheral circulation, as follows.
1. Decreased vascular capacitance and compliance. Vascular capacitance and compliance are decreased in post-Fontan patients to sustain the increased venous pressure needed to propel venous return from the legs. This results in increased venous pressure at any given level of venous volume, thereby enhancing the gradient for venous return to the heart. This is of particular importance in a post-Fontan patient while standing, in which increased distensibility at the higher venous pressures necessary for sustaining Fontan blood flow would produce markedly increased venous pooling in the lower extremities, further compromising circulation. The level of lower limb venous pressure (Pv) has a critical impact on microvascular filtration. The elevated Pv, with lower capacitance is evidence of a stiffer lower extremity venous system in patients after creation of the Fontan circulation.3

2. Microvascular filtration. We have shown that the relationship of P, to microvascular filtration is linear, with the Fontan subjects showing onset of filtration at significantly higher pressures than the controls. These data indicate a higher filtration threshold in Fontan subjects. This may be an adaptive mechanism developed in response to chronic exposure to the Fontan circulation, preventing the onset of edema. We speculate that failure of such adaptation in some patients may be responsible for edema and anasarca formation in the failing Fontan circulation.

3. Peripheral arterial resistance. Lower-limb peripheral vascular resistance and splanchnic resistance were significantly elevated in Fontan subjects compared with control subjects, but the arm resistances were similar. This also suggests a chronic adaptive mechanism. The higher leg resistance after Fontan prevents leg pooling and enhances venous filling of the heart. Higher peripheral resistance increases elastic recoil of the capacitance vessels, thereby increasing venous return to the heart and maintaining preload.3,4,5,28,30 A normal person suddenly given Fontan physiology would be expected to pool all the blood in the lower body when upright, thereby losing postural tone and perhaps causing death. However, chronic exposure to increased lower body venous pressure results in functional adaptations of the vasculature that sustain venous return and prevent fluid extravasation.30

4. Reduced end-tidal CO2. The Fontan subjects had significantly lower end-tidal CO2 than the controls despite equal respiratory rate and respiratory volumes. Gisolf et al31 in an elegant study of end-tidal CO2 changes in human beings with postural change, demonstrated that cardiac output changes made an important contribution to alveolar CO2. Sznazki et al32 tested well-functioning Fontan patients with β-adrenergic stimulation and atrial pacing and demonstrated evidence of reduced cardiac output and β-adrenergic reserve, basically as a function of impaired preload and afterload properties of the circulation. Thus, chronic reduction in cardiac output may lead to alterations in gas exchange, reflected as reduced alveolar CO2 as was seen in our Fontan subjects. Furthermore, relatively lower blood flow in the legs with higher arterial resistance and lower capacitance may cause relatively lower capillary circulation and alter gas exchange especially in the legs, reducing the amount of CO2 returning to the lungs.

5. Better orthostatic tolerance. Our studies showed that asymptomatic, well-preserved Fontan patients had a significantly blunted response to HUT. The tilt does not translate blood as much out of the thoracic compartment. This is caused by reduced venous compliance (ie, increased stiffness) as well as increased arterial resistance in Fontan subjects compared with control subjects. These combine to reduce venous pooling in general, in particular to reduce splanchnic pooling, which enhances venous return to the heart. Similar decreases in Valsalva responses are noted, consistent with increased splanchnic venous stiffness and increased vasoconstriction.

Limitations of the Study

Only asymptomatic Fontan patients were studied in the present study. This is because the study protocol was a demanding one, and because all of the tests were performed on a single day, each subject had to be able to tolerate the lengthy testing. Therefore, we created a selection bias, and our findings can only be applied to well-adapted post-Fontan patients. Nevertheless, the results of investigating the peripheral vasculature of these preselected subjects may provide clues in regard to successful adaptations of asymptomatic Fontan patients. Further studies with the use of larger patient numbers and including symptomatic patients are needed. Treatment methods in edematous patients such as external compression to functionally decrease leg capacitance and increase leg peripheral resistance might be considered short-term therapy for such patients if our results are confirmed in symptomatic patients as well. Our results indicate overall stiffer segmental vascular compartments, suggesting a contracted blood volume. However, blood volume estimates were not performed as a part of the study protocol in our subjects and controls. The data suggest that the volume-pressure-capacitance relationship is altered in Fontan subjects, independent of the overall blood volume. The instruments used in our laboratory cannot be used in an inpatient setting, and further modifications would be necessary to study acutely sick or early postoperative patients. These complex methodologies do not lend themselves to routine outpatient testing and are at present utilized only for research purposes. Additionally, 3 of 9 of our patients were on very low doses of enalapril (which did not alter their diastolic blood pressures); however, other effects of angiotensin-converting enzyme inhibitors (on the bradykinin system) were not measured as a part of the protocol, and this is a potential limitation in this study.

In summary, our data indicate that there are significant adjustments to the peripheral venous circulation noted in subjects who were evaluated several years after the Fontan procedure, which help to prevent development of edema, maintain venous return, and sustain cardiac output. Furthermore, there is increased vascular resistance in other vascular compartments such as the splanchnic and thoracic compartments, with fewer fluid shifts in response to orthostasis and Valsalva maneuvers, leading to better orthostatic tolerance. One may infer a contracted blood volume, with poor tolerance to blood loss (or sudden vasodilatory stress as in sepsis), leading to sudden and severe hemodynamic deterioration, even in relatively asymptomatic Fontan subjects.

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Disclosures

None.

References


**CLINICAL PERSPECTIVE**

This study involves 9 well-compensated patients several years after the Fontan repair who were compared with 6 age-matched controls. Important differences between the Fontan and control subjects were seen in several vascular compartments. Calf capacitance was lower and resting venous pressure was higher in the Fontan group, suggesting a stiffer peripheral venous compartment, especially in the lower extremities. The reduced venous compliance and increased filtration thresholds possibly act as adaptive mechanisms in maintaining venous return in Fontan circulation. These well-compensated Fontan subjects also demonstrated superior orthostatic tolerance resulting from decreased compartmental fluid shifts in response to head-up tilt and higher vascular resistance. This results from increased venous stiffness and decreased splanchnic capacitance and may also be an adaptive mechanism to maintain venous return in these patients while standing. One may infer a contracted blood volume with poor tolerance to blood loss (or sudden vasodilatory stress as in sepsis), leading to sudden and severe hemodynamic deterioration, even in relatively asymptomatic Fontan subjects. We believe that this study contributes to an understanding of postoperative single-ventricle physiology, especially in regard to compartmental fluid shifts as well as changes in peripheral vascular properties in well-compensated patients exposed to the Fontan circulation over a long period of time. This study may form the baseline for further studies both in the immediate postoperative period and in decompensated patients to examine whether these protective mechanisms were somehow deranged, causing circulatory decompensation in failing Fontan patients.
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