Ventricular Afterload and Ventricular Work in Fontan Circulation

Comparison With Normal Two-Ventricle Circulation and Single-Ventricle Circulation With Blalock-Taussig Shunts

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Background—Recent studies have indicated that there are inherent limitations associated with Fontan physiology. However, there have been no quantitative analyses of the effects of right heart bypass on ventricular afterload, hydraulic power, and resultant overall hemodynamics.

Methods and Results—During routine cardiac catheterization, aortic impedance and ventricular hydraulic power were determined, both at rest and under increased ventricular work induced by dobutamine, in 17 patients with Fontan circulation, 15 patients with a single ventricle whose pulmonary circulation was maintained only by Blalock-Taussig shunts, and 13 patients who had normal 2-ventricle circulation. Both vascular resistance (nonpulsatile load on the ventricle) and pulsatile components of ventricular afterload (represented by low-frequency impedance) were significantly higher in the Fontan group than in the other groups (P<0.01), and this was associated with decreased cardiac output in the Fontan patients. In addition, hydraulic power cost per unit forward flow was 40% lower in the 2-ventricle circulation than in the single-ventricle circulation, suggesting lower ventricular efficiency in single-ventricle circulation attributable to the lack of a pulmonary ventricle. Furthermore, in the Fontan group, β-adrenergic reserve was markedly decreased because of a limited preload reserve.

Conclusions—Fontan physiology is associated with disadvantageous ventricular power and afterload profiles and has limited ventricular reserve capacity. Thus, to improve the long-term prognosis of patients after Fontan surgery, future research should be conducted into medical interventions that can overcome these limitations inherent in Fontan circulation. (Circulation. 2002;105:2885-2892.)

Key Words: Fourier analysis ■ Fontan procedure ■ heart defects, congenital ■ hemodynamics ■ patients

Although the Fontan operation has contributed greatly to the improvement of mortality rate in patients with a single ventricle,1,2 recent studies have emphasized a continuing risk of late failure and poor functional outcome in some long-term survivors.3-4 Decreased exercise tolerance and abnormal hemodynamic response to stress also have been clearly recognized in patients after this procedure.5-7 These results strongly suggest fundamental limitations inherent in Fontan physiology. Although it seems somewhat intuitive that the absence of a pulmonary ventricle in the Fontan circuit is disadvantageous and may be related to the reported adverse outcomes of this procedure, quantitative analyses of the effects of right heart bypass on ventricular afterload, hydraulic power, and resultant overall hemodynamics have been lacking.

Because ventricles eject pulsatile flow into a distensible arterial system, a complete description of ventricular afterload and hydraulic power driven by the ejecting ventricle must include both pulsatile- and steady-flow behaviors.8 Analysis of the arterial impedance spectrum is the best means of obtaining this information.8 Therefore, with the use of such analysis, the present study was conducted to test the hypothesis that the right heart bypass of the Fontan circuit is associated with an increase in both pulsatile and nonpulsatile load on the ventricle and leads to high hydraulic power cost in generation of cardiac output, resulting in limited rest and reserve capacity of ventricular performance. To better test this, we compared ventricular afterload and hydraulic power, both at rest and under increased contractility induced by β-adrenergic stimulation, among 3 circulatory states: single-ventricle circulation under the Fontan circuit, single-ventricle circulation with systemic-to-pulmonary shunts, and normal 2-ventricle circulation.
Methods

Patients
This study involved a total of 45 subjects: 17 patients with Fontan circulation (Fontan group, 4.5±3.8 years old), 15 patients whose pulmonary circulation was maintained only by systemic-to-pulmonary shunts (Blalock-Taussig shunts) under functional or anatomic single ventricle without antegrade flow across the pulmonary valve (BT group, 2.8±3.2 years old), and 13 patients who were considered to have normal 2-ventricle circulation (control group, 3.8±3.2 years old). Anatomic diagnoses for the Fontan and BT groups are summarized in Table 1. Total cavopulmonary connection surgery with an intra-atrial lateral tunnel had been performed for all Fontan group patients. None of the Fontan patients had baffle leaks or a shunt through a surgically created fenestration. There were no patients with hypoplastic left heart syndrome or heterotaxy syndrome in the Fontan or BT group. All Fontan and BT group patients were examined for aortopulmonary collaterals using angiograms. No significant collaterals were observed in any of the Fontan patients. Two patients in the BT group had significant collaterals, but data from these patients were included because such collaterals act as systemic-to-pulmonary shunts, rather like a BT shunt. Cardiac catheterization was performed at least 3 months after surgery in the Fontan and BT groups. All control patients had small or closed ventricular septal defect (VSD); calculated pulmonary to systemic flow ratio was 1. All VSD patients had a subpulmonic VSD, and cardiac catheterization was performed to examine aortic regurgitation and the deformity of aortic valves. There was no significant regurgitation in any of the patients studied. The parents of all patients provided written informed consent, and each institution’s committee on clinical investigation approved the procedures.

Procedures
During routine cardiac catheterization, aortic pressure and flow were measured simultaneously with a high-fidelity pressure transducer and a catheter-mounted flow velocity probe (Miller Instruments, Inc.). The catheter was advanced retrograde across the aortic valve to help stabilize it and to keep the sensor in the center of the stream. Maximum ascending aortic root cross-sectional area obtained from 2-dimensional echocardiograms was used to convert flow velocity to volume flow. Study results confirming the validity of this method for measuring instantaneous aortic volume flow have been reported previously.6,10 We also confirmed that there was good agreement between thermodilution cardiac output and cardiac output measured by a flow velocity probe and echocardiograms in the first 5 patients of the control group (r=0.93). In the normal controls, main pulmonary artery pressure and flow were also simultaneously measured to derive pulmonary impedance data and thereby evaluate both right ventricular and systemic ventricular work. Because pulmonary trunk diameter was relatively highly variable and because pulmonary flow profile may not be flat,31 we assumed that main pulmonary artery volume flow was equal to mean aortic volume flow. Ventricular cavity area was calculated from transthoracic 2-dimensional images obtained using an automated border detection echocardiographic system (Sonos 2500, Hewlett-Packard).12-13 We have reported previously that this method can be used to accurately calculate ventricular cavity area for various kinds of congenital heart disease, including single ventricles.13 In the patients described in the present study, there was a strong correlation between stroke volume measured by an aortic flow probe and stroke area measured by echo- graphic automated border detection (r=0.91, P<0.01), a finding that additionally confirms the validity of area measurements using automated border detection.

All measurements were taken both at rest and under increased ventricular work induced by intravenous administration of dobutamine (5 μg/kg per min). During cardiac catheterization and hemodynamic studies, all patients showed stable sinus rhythm.

Data Analysis
Two to 5 consecutive steady-state beats during expiration were signal averaged and used for impedance analyses. Mean ascending aortic volume flow was normalized to body surface area and was designated as cardiac index from a systemic ventricle (CI). We defined total cardiac index (CI) as the entire blood flow (both pulmonary and systemic) provided by the heart. For the Fontan and BT groups, CI, and CI, are equal. Ventricular contractility was assessed in terms of maximum rate of ventricular pressure rise (dP/dtmax), preload-adjusted maximal ventricular power (PWRmax). The preload-adjusted PWRmax, which has been reported to be a relatively load-independent index of contractility,14 was calculated as the maximum value of the instantaneous product of aortic pressure and flow divided by EDAI15, where EDAI is end-diastolic area normalized to body surface area. Ventricular diastolic stiffness was calculated as the difference between end-diastolic pressure (EDP) and minimum diastolic pressure divided by the difference in area between these 2 pressures. Impedance moduli were computed from Fourier components of pressure and flow data.15

Total vascular resistance (Rt) was defined as the nonpulsatile load on the systemic ventricle and was calculated as follows: For the BT and control groups, mean right atrial pressure (mRAP) was subtracted from mean ascending aortic pressure (mAoP), and the difference was divided by CI, For the Fontan group, mean pulmonary wedge pressure (mPWP) was subtracted from mAoP, and the difference was divided by CI. For the BT group, pulmonary blood flow index (QpI) was calculated as CI/(1+Qs/Qp), where Qs/Qp is systemic to pulmonary flow ratio, which was calculated with the Fick equation using measured oxygen saturation. Pulmonary vein saturation was assumed to be 98%.

Pulmonary vascular resistance index (Rpi) was calculated by subtracting mPWP from mean pulmonary artery pressure and dividing the difference by QpI. Characteristic impedance (Zc) was calculated by averaging all impedance moduli between 2 and 10 Hz. Arterial compliance was calculated using the method reported by Liu et al.16

Data on wave reflections were obtained by resolving the measured pressure and flow waveforms into their forward and reflected components, as previously described.3 Reflection factor was calculated as the ratio between peak amplitude of forward and backward pressure.17

Hydraulic power data were derived as follows:31 Mean power (Wm) is the product of mean flow and mAoP. Oscillatory power (Wo) is the sum of power harmonics (Wm) is the product of mean flow and mAOP. Oscillatory power (Wo) is the sum of power harmonics Wi [computed as Wi=(Qi)2 Zi cos(iθi), where Qi and Zi are the flow and impedance moduli and iθi is the impedance phase]. Total power (Wt) is the sum of the mean and oscillatory components, as follows: Wt=Wm+Wo.

However, total power alone does not express the efficiency of power output, because low flow results in low power expenditure. Therefore, we calculated the quantity Wt/CIs as the hydraulic power cost per unit forward flow. This ratio is an index of the efficiency of ventricular ejection, reflecting ventricular-vascular coupling states.19

The hydraulic power cost per unit forward flow for the heart as a whole in 2-ventricle circulation was calculated as the sum of Wt for systemic and pulmonary circulation divided by CI, (total Wt/CI).

Table 1. Anatomic Diagnoses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients in Fontan Group, n</th>
<th>Patients in BT Group, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tricuspid atresia</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary atresia with intact ventricular septum</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Single ventricle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant left</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Dominant right</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Functional single ventricle</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Patients with a functional single ventricle are those with 2 ventricles and double-outlet right ventricle with uncommitted or multiple ventricular septal defect complicated by a straddling atrioventricular valve.
Hemodynamics, Impedance, and Hydraulic Power at Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fontan Group</th>
<th>BT Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>101.0±13.0</td>
<td>111.8±13.8</td>
<td>107.2±15.9</td>
</tr>
<tr>
<td>CI, L/min per m²</td>
<td>3.5±0.9†</td>
<td>8.4±1.4*</td>
<td>5.6±1.4</td>
</tr>
<tr>
<td>Qp/Qs, dpm</td>
<td>1.0</td>
<td>1.26±0.59</td>
<td>1.0</td>
</tr>
<tr>
<td>AOP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>95.5±20.2</td>
<td>95.2±10.3</td>
<td>95.1±15.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>59.0±14.6</td>
<td>54.7±9.9</td>
<td>64.6±11.3</td>
</tr>
<tr>
<td>Mean</td>
<td>76.2±16.7</td>
<td>74.8±8.8</td>
<td>80.8±13.8</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>11.8±2.7</td>
<td>12.9±4.8</td>
<td>13.8±4.2</td>
</tr>
<tr>
<td>Rpl, dyne · s · cm⁻³ per m²</td>
<td>151±44</td>
<td>129±19</td>
<td>138±38</td>
</tr>
<tr>
<td>dp/dtmax, mm Hg/s</td>
<td>1196±342</td>
<td>1349±419</td>
<td>1369±562</td>
</tr>
<tr>
<td>PWmax/EDAI, mW/cm²</td>
<td>141±79</td>
<td>159±80</td>
<td>160±65</td>
</tr>
<tr>
<td>EDAI, cm²/m²</td>
<td>9.8±3.4†</td>
<td>12.6±4.5*</td>
<td>8.9±3.9</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>7.7±2.9†</td>
<td>11.5±3.1*</td>
<td>7.9±3.5</td>
</tr>
<tr>
<td>Stiffness, mm Hg/cm² per m²</td>
<td>1.03±0.56</td>
<td>0.84±0.22</td>
<td>1.02±0.54</td>
</tr>
</tbody>
</table>

Statistical Analysis

All values were expressed as mean±SD, and group comparisons were made using ANOVA followed by Bonferroni correction. Comparisons before and after dobutamine infusion were made using paired t test. *P<0.05 was considered statistically significant.

Results

Hemodynamics, Impedance, and Hydraulic Power at Baseline

Data of hemodynamics, impedance, and hydraulic power at baseline for each group are summarized in Table 2. There was no significant difference in heart rate (HR) among the groups. Consistent with previous reports, CI, of the Fontan group was significantly lower than that of the controls (P<0.01). In contrast, CI, of the BT group was significantly higher than that of the Fontan or control groups. There was no difference in aortic or pulmonary pressure among the 3 groups. Rpl values were similar among the groups. Ventricular contractility and diastolic stiffness were also similar among the 3 groups. Both EDAI and EDP were significantly higher in the BT group than in the Fontan and control groups.

Rt value in the Fontan group was significantly higher than that of the control group (P<0.005), and Rt of the BT group was markedly lower than that of the Fontan and control groups (P<0.005). In Fontan patients, in addition to an increase in Rt (a nonpulsatile measure of ventricular afterload), pulsatile load represented by the first harmonic impedance (Z1) was significantly elevated compared with that of the BT and control groups. This adversely affected ventricular ejection in Fontan patients, as indicated by negative correlation between Z1 and CI, (Figure 1A, CI=−0.02×Z1+9.28, r=−0.73, P<0.001). Zc and arterial compliance were similar among the 3 groups. The wave reflection factor was higher in the Fontan group than in the BT and control groups, suggesting increased wave reflection in the Fontan circulation. Figure 2 shows forward, backward, and measured pressure waveforms in representative patients from each group. A marked reflected wave (dashed line) is observed in the Fontan patient, whereas there is minimal reflection in the control patient. BT shunt patients often showed decreased backward pressure during systole, as shown in Figure 2, probably attributable to continuous shunt flow.
Hydraulic power data showed that both the Wm and Wt produced by a single ventricle in the Fontan circulation were significantly lower than those of the other groups (P<0.001). In contrast, Wm and Wt under single-ventricle circulation in patients with BT shunts were significantly greater than those of the left ventricle (LV) in normal 2-ventricle circulation. It is noteworthy that there was no significant difference in Wt/CIs, for the systemic ventricle among the 3 groups, despite marked differences in Wt values. This indicates that the venticle of a univentricular heart and the LV of a biventricular heart eject forward flow for the systemic circulation with the same hydraulic power cost. However, when the right ventricle (RV) was taken into account, hydraulic power cost for the heart as a whole in the control group (biventricular circulation) was ~40% lower than that of the LV only (7.2±1.3 versus 11.4±3.2) and that of the single ventricle in the Fontan (7.2±1.3 versus 12.6±2.4) and BT groups (7.2±1.3 versus 12.0±1.2). This suggests that lack of a RV results in higher energy requirements per unit forward flow. The relationship between Wt and CI, is more clearly shown by Figure 3A. This relationship fell on the same regression line (CI=0.005 Wt−0.14, r=0.99, P<0.001) for the single ventricle in the Fontan (●) and BT (▲) groups and the LV in the control group (■), whereas the relationship between total Wt and CI, for biventricular circulation was located at the upper-left side of the regression line (▲).

Changes After β-Adrenergic Stimulation With Dobutamine

Table 3 shows data obtained after dobutamine infusion. Dobutamine significantly increased HR, AOP, and contractility in each group. The amount of changes in those variables was similar among the groups (P=NS), although AOP of the control group tended to increase more than that of the Fontan group. CI, of all groups was also significantly increased by dobutamine, but more so in the BT and control groups than in the Fontan group (P<0.05). Thus, CI, in the Fontan group was significantly lower than in the other 2 groups (P<0.005) under β-adrenergic stimulation as well as at baseline. EDAI and EDP significantly decreased after dobutamine infusion in the Fontan group (P<0.05), whereas no change was observed in the other groups (P for changes <0.05).

There were no significant changes in Rt or Z1 after dobutamine infusion in the 3 groups. Thus, Rt and Z1 of the Fontan group were significantly higher than those of the other 2 groups (P<0.01). High Z1 after dobutamine was again associated with low CI, (Figure 1B, CI=−0.02×Z1+10.3, r=0.57, P<0.001).

In each group, Wt and Wm values were significantly increased by dobutamine, but changes were markedly smaller in the Fontan group than in the BT and control groups (P for changes, <0.01). Wt/CIs for systemic ventricle after dobutamine infusion was similar among the groups but was significantly higher than the value for the whole heart of the control group, again suggesting that lack of an RV results in higher hydraulic power cost per unit of forward flow. Thus, the relationships between mean values of Wt and CI, after dobutamine infusion (Figure 3B) were similar to those observed at baseline.

Because β-adrenergic responsiveness is known to be an important determinant of exercise capacity,21,22 to additionally elucidate factors responsible for the limited increase in CI, in response to dobutamine in patients with Fontan circulation, we performed multivariate analysis of changes in HR, afterload (Zc, Z1, Rt, C), preload (EDAI), and contractility (PWRmax/EDAI0.5), as well as group effect, as independent variables. We found that only the changes in EDAI had a significant correlation with the change in CI, indicating that limited preload reserve was attributable to diminished response of CI, to β-adrenergic stimulation under Fontan circulation.

Discussion

Ventricular Afterload in Fontan Circulation

Elevated systemic vascular resistance in Fontan physiology has commonly been observed.20,23 However, this value is only
an average, nonpulsatile property of the vascular load, and it does not indicate the role of pulsatile components of afterload in Fontan circulation. The present study demonstrated for the first time that the pulsatile component of ventricular afterload, represented by low-frequency impedance, is markedly elevated in Fontan circulation both at rest and under β-adrenergic stimulation and showed that it is closely related to decreased CI, in this circulation. It has been reported that low-frequency impedance is an important determinant of cardiac output. In patients with congestive heart failure, a

Figure 2. Forward (dotted lines), backward (dashed lines), and measured (solid lines) pressure waveforms in representative patients from each group.

Figure 3. Relationships between ventricular hydraulic power and cardiac index before (A) and after (B) dobutamine infusion.

- FONTAN
- BT
- Control (LV)
- Control (LV and RV)
This article was retracted in June 2012.

TABLE 3. Hemodynamics, Impedance, and Hydraulic Power After Dobutamine Infusion

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Fontan Group</th>
<th>BT Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>130.6±22.2†</td>
<td>135.1±17.2†</td>
<td>122.7±19.7†</td>
</tr>
<tr>
<td>Clv, L/min per m²</td>
<td>3.9±1.0†‡</td>
<td>10.1±2.3†‡</td>
<td>7.7±1.5†</td>
</tr>
<tr>
<td>Qp/Qs</td>
<td>1.0</td>
<td>1.32±0.56</td>
<td>1.0</td>
</tr>
<tr>
<td>AOP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>112.0±21.0†</td>
<td>115.7±29.1†</td>
<td>125.4±24.7†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>68.5±13.1</td>
<td>60.4±15.6*</td>
<td>78.2±17.3†</td>
</tr>
<tr>
<td>Mean</td>
<td>88.0±15.2†</td>
<td>86.7±21.8†</td>
<td>101.0±17.2†</td>
</tr>
<tr>
<td>Mean PAP, mm Hg</td>
<td>14.2±4.7†</td>
<td>14.9±4.8</td>
<td>16.8±5.3‡</td>
</tr>
<tr>
<td>PVRi, dyne · s · cm⁻⁵ per m²</td>
<td>165±49</td>
<td>131±39</td>
<td>124±30</td>
</tr>
<tr>
<td>dp/dtmax, mm Hg/s</td>
<td>2027±653†</td>
<td>2319±188†</td>
<td>2558±443‡</td>
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<tr>
<td>PWRmax/EDAI, mW/cm³</td>
<td>186±92‡</td>
<td>201±80‡</td>
<td>227±103‡</td>
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<tr>
<td>EDAI, cm²/m²</td>
<td>8.4±2.5‡</td>
<td>12.3±4.6*</td>
<td>8.1±2.6</td>
</tr>
<tr>
<td>EDP, mm Hg</td>
<td>5.8±2.9‡</td>
<td>9.3±4.1*</td>
<td>7.4±2.4</td>
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<tr>
<td>Stiffness, mm Hg/cm² per m²</td>
<td>0.92±0.58</td>
<td>0.83±0.49</td>
<td>0.84±0.38</td>
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<tr>
<td>Impedance data</td>
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<tr>
<td>Rt, dyne · s · cm⁻⁵ per m²</td>
<td>2145±400‡</td>
<td>712±214*</td>
<td>1046±259</td>
</tr>
<tr>
<td>Zl, dyne · s · cm⁻³ per m²</td>
<td>240±119†</td>
<td>112±54</td>
<td>127±53</td>
</tr>
<tr>
<td>Zc, dyne · s · cm⁻³ per m²</td>
<td>182±71‡</td>
<td>110±44‡</td>
<td>98±34</td>
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<td>Compliance, mL/mm Hg per m²</td>
<td>0.94±0.39‡</td>
<td>1.03±0.17</td>
<td>1.03±0.37</td>
</tr>
<tr>
<td>Reflection factor</td>
<td>0.20±0.08*</td>
<td>0.14±0.04</td>
<td>0.13±0.06</td>
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<td>Hydraulic power</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wm, mW/m²</td>
<td>715±249†‡</td>
<td>1965±805‡</td>
<td>1718±422‡</td>
</tr>
<tr>
<td>Wo, mW/m²</td>
<td>95.2±17.4‡</td>
<td>149.0±94.3†</td>
<td>113.3±64.0‡</td>
</tr>
<tr>
<td>Wt, mW/m²</td>
<td>828±251†‡</td>
<td>2398±799‡</td>
<td>1924±436‡</td>
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<tr>
<td>Wt/Cf, systemic</td>
<td>13.3±2.4</td>
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<td>13.7±2.8</td>
</tr>
<tr>
<td>Wt/Cf, total</td>
<td>13.3±2.4*</td>
<td>13.2±3.9*</td>
<td>8.9±3.9</td>
</tr>
</tbody>
</table>

Abbreviations are as in Table 1.
*P<0.05 vs control.
†P<0.05 vs BT group.
‡P<0.05 vs baseline.

decrease in low-frequency impedance can cause an increase in cardiac output, even without changes in resistance.24 Thus, elevation of Z1 seems to be an important characteristic of Fontan hemodynamics. Both wave reflections and arterial compliance affect low-frequency impedance.24,25 In the present study, there was no significant difference in arterial compliance among the 3 groups at rest or after dobutamine infusion, whereas the wave reflection index was significantly elevated in the Fontan group. Thus, increased Z1 in Fontan circulation could result from increased wave reflections. Because low-frequency impedance was not elevated in univentricular hearts in which pulmonary circulation was connected in parallel to the systemic circulation (BT group), characteristics specific to the Fontan circuit (in which pulmonary and systemic circulations are serially connected) seem to be responsible for this afterload profile.

Ventricular Hydraulic Power in Fontan Circulation

In addition to increased afterload, right heart bypass is associated with higher power expenditure per unit cardiac output (Figure 3). When RV power was not taken into account, the hydraulic power cost of the LV in normal 2-ventricle circulation was markedly higher and was equal to that of the single ventricle in Fontan circulation and that of the single ventricle with a BT shunt. This implies that if the Fontan procedure was performed in healthy subjects, the LV power for pulmonary circulation in right heart bypass circulation (Fontan Group) could result from increased wave reflections. However, there is not yet any clinical evidence to support this. The present study provides the first evidence of the importance of preserving hydraulic power for pulmonary circulation in right heart bypass circulation (Fontan physiology). Because our data show that Fontan circula-
tion produces low hydraulic power with high energy cost, even modest preservation of hydraulic power would be beneficial in this circulation.

It is interesting that there was no significant difference in systemic ventricle hydraulic power cost per unit CI, among the 3 groups, despite the marked difference in ventricular afterload. This suggests that CI, in Fontan patients decreases in proportion to the increase in the afterload.\textsuperscript{19,25} If true, this would be of clinical importance, because the single ventricle in the Fontan circulation could produce CI, if the ventricular afterload were appropriately reduced. The fact that a single ventricle with BT shunts, a palliative procedure often performed before Fontan surgery, can produce high CI, under decreased afterload directly supports this hypothesis. Therefore, if the ventricular afterload in Fontan physiology could be reduced, the relationships between CI, and Wt shown in Figure 3 for the Fontan group (\textbullet) would shift upward and rightward along the regression line. Several previous studies examined short-term hemodynamic effects of afterload-reducing therapy on Fontan hemodynamics and demonstrated a significant increase in cardiac output associated with a decrease in systemic vascular resistance.\textsuperscript{28,29} A finding that supports our belief that afterload-reducing agents are useful for the treatment of Fontan patients. In contrast, there have been only a few studies of the long-term effects of vasodilator therapies in patients after Fontan surgery, and results of these studies are not consistent.\textsuperscript{30,31} There is a need for clinical trials examining the effects of long-term use of afterload-reducing agents on Fontan hemodynamics and resultant functional outcome, including effects of dose, duration of administration, and type of agent.

**Response to \(\beta\)-Adrenergic Stimulation**

To the best of our knowledge, the present study is the first to examine hemodynamic responses to \(\beta\)-adrenergic stimulation in patients with Fontan circulation. We found that ventricular contractile response to dobutamine in Fontan patients was comparable with that of LVs in controls and that of single ventricles with BT shunts but that the increase in CI, induced by dobutamine was significantly smaller in the Fontan group than in the other 2 groups. Diminished \(\beta\)-adrenergic reserve is commonly observed in cases of congestive heart failure\textsuperscript{32,33} and is closely related to the decreased exercise capacity seen in patients with heart failure.\textsuperscript{21,22} Thus, our results may at least in part explain the decreased exercise tolerance observed in patients after the Fontan procedure. However, limited \(\beta\)-adrenergic reserve in patients with congestive heart failure generally is associated with attenuated inotropic response.\textsuperscript{32–34} In contrast, in the patients with Fontan circulation in the present study, limited \(\beta\)-adrenergic reserve was attributable to a limited preload reserve rather than a decreased inotropic response. This is consistent with a report by Gewillig et al.,\textsuperscript{7} who showed that decreased exercise tolerance in patients with Fontan circulation is associated with limited preload reserve but not with cardiac function. Their data and ours strongly suggest that abnormal exercise capacity in patients after the Fontan procedure is attributable to characteristics specific to Fontan physiology.

Recent studies have suggested that fenestration can have beneficial effects on the outcome of Fontan surgery,\textsuperscript{2,3} attributable to augmentation of ventricular preload by the right-to-left shunt through the fenestration.\textsuperscript{35} The present results obtained for dobutamine response also suggest that fenestration would help increase preload and thereby increase cardiac output, particularly when there is a need for increased cardiac output, such as during exercise.

In summary, Fontan circulation is associated with increases in both pulsatile and nonpulsatile components of ventricular afterload, resulting in decreased CI, at rest and under \(\beta\)-adrenergic stimulation. Right heart bypass inevitably causes higher ventricular power expenditure per unit of cardiac output compared with biventricular circulation. In addition, \(\beta\)-adrenergic reserve in Fontan circulation is decreased markedly, which is primarily attributable to the limited preload reserve associated with this circulation. Thus, to improve the long-term prognosis of patients after Fontan surgery, research should be conducted into medical interventions to overcome the limitations inherent in Fontan physiology.

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The four articles listed below have been retracted due to ethical violations. The corresponding author’s institution, Saitama Medical University, reported to the editors of Circulation, that Dr. Hideaki Senzaki did not receive approval for these studies from the institutional internal ethics committee. Furthermore, in each of the articles referenced below, it was determined that Dr. Senzaki misinformed the editors and readers of Circulation by stating that the studies had received the necessary approval from his institutional review board.


