Changes in venous return parameters associated with univentricular Fontan circulations

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Macé, Loïc, Patrice Dervanian, Armand Bourriez, Guy M. Mazmanian, Virginie Lambert, Jean Losay, and Jean-Yves Neveux. Changes in venous return parameters associated with univentricular Fontan circulations. Am J Physiol Heart Circ Physiol 279: H2335–H2343, 2000.—To clarify the physiology of venous return (Qvr) in Fontan circulations, venous return conductance (Gvr) and mean circulatory filling pressure (Pmcf) were determined in pentobarbital sodium-anesthetized pigs. Relationships between Qvr and right (biventricular, n = 8) or left (Fontan, n = 8) filling pressures are described by straight lines with significant correlation coefficients. Estimated Pmcf values were correlated with observed Pmcf values in either circulations (P ≤ 0.02); Gvr was smaller in Fontan than in biventricular circulations (4.51 ± 0.36 vs. 7.83 ± 0.69 ml·min⁻¹·kg⁻¹·mmHg⁻¹, P = 0.002) and inversely correlated with pulmonary vascular resistances in Fontan circulations (P = 0.01). Estimated Pmcf (20.5 ± 1.4 vs. 11.1 ± 0.9 mmHg, P = 0.001) and observed Pmcf (21.8 ± 1.3 vs. 10.6 ± 0.8 mmHg, P < 0.001) were higher in Fontan versus biventricular circulations, respectively. Pulmonary artery pressure in Fontan circulations was correlated with either Pmcf (P ≤ 0.04). We conclude that in Fontan circulations 1) pulmonary vascular resistances induce a proportional decrease in Gvr, and 2) volume loading, while increasing Pmcf, maintains systemic blood flow at a biventricular level.

heart defect; congenital; single ventricle physiology; mean circulatory filling pressure; venous return conductance

UNIVENTRICULAR FONTAN circulation (7) has gained a wide acceptance as a functional corrective procedure for complex congenital heart defects with single ventricle physiology (3, 4). Basically, the concept is to place the pulmonary circulation in series with the systemic circulation rather than the parallel circulatory arrangement that is present before repair (8, 30). After this operation, the single ventricle is responsible for perfusion of both the systemic and pulmonary circulations, resulting in: 1) an unusual pathophysiology of a passive pulmonary pressure-flow relationship regulated by the pressure difference between the pulmonary arterial pressure (Ppa) and left atrial pressure (Pla) (8), and 2) additional resistance to venous return (RVR) due to the location of the pulmonary circulation at the end of the circulatory system (3). Of primary importance, the absence of right ventricular function means that the cardiac and vascular factors that determine venous return (Qvr) (14) may become of critical hemodynamic importance in maintaining systemic blood flow (SBF) (3), because Qvr is eight times more influenced by an increase in RVR than by a similar increase in systemic vascular resistances (SVR) (15). Moreover, it has been demonstrated that the essential function of the right ventricle is to maintain a low pressure in the highly compliant systemic venous system, and perfusion of both pulmonary and systemic circulations may be amply provided by the normal left ventricle (8). Although the consequences of Fontan circulations on cardiac function have long been researched (3, 8, 10, 30), the potential changes in the vascular factors determining Qvr have not yet been studied in such circumstances.

In light of Guyton’s theory on the circulatory system (13–17), factors that determine Qvr have been extensively studied (18, 23, 34–35) and discussed (1, 23, 38) in biventricular circulations. First, just as the cardiac output curve (Frank-Starling mechanism) reflects the ability of the heart to pump blood, the Qvr curve described by Guyton provides fundamental insight into the vascular factors that affect the tendency for blood to return to the heart. The relationship between Qvr and mean central venous filling pressure (Pmcf) defines a Qvr curve characterized by a straight line with a negative slope and a positive x-intercept named as the estimated mean circulatory filling pressure (Pmcf) (13, 16, 17). Thereby, Qvr = a – b·Pmcf, where b is the conductance for Qvr (Gvr) and 1/b represents the RVR between the point in the circulatory system where Pmcf exists and the right atrium where Pmcf is measured (5, 38). Located in small veins and venules (34), Pmcf is the pressure throughout the cardiovascular system at zero flow. Its value is estimated by extrapolating on the Qvr curve to Qvr = 0, where Pmcf = Pmcf = a/b, or observed during a transient circulatory arrest. Any changes in Qvr parameters (i.e., Pmcf and Gvr), which are indepen-

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dent of the characteristics of the heart (14, 23, 35), will markedly induce change in Qvr. Second, under steady-state conditions, Qvr must be equal to cardiac output because the heart can only pump what it receives. Therefore the Qvr curve coupled with the cardiac response curve defines the steady-state SBF and Pcv of the cardiovascular system at the intersection of the venous and cardiac function curves (13). At this obligatory equilibrium point, Guyton predicts that Qvr depends on the driving force or pressure gradient between Pmcf and Pcv, and Gvr. Therefore SBF = Qvr = (Pmcf - Pcv)Gvr (1, 13, 14, 17, 18, 38). All factors on the right-hand side of the equation are relatively independent of each other (14). Qvr parameters are mainly affected by blood volume, venous tone, and peripheral resistances. Conversely, Pcv is a common factor that affects both the ability of the heart to sustain cardiac output and the ability of blood to return to the heart when it is failing (14).

The purpose of the present study was to determine whether the location of pulmonary vascular resistance (PVR) at the end of the circulatory system may change the vascular factors determining Qvr and whether Guyton’s principles could accurately provide new insights into the cardiac and vascular factors that determine Qvr in univentricular Fontan circulations. First, we reasoned that Pla, and not right atrial pressure (Pra), is the downstream pressure for Qvr in univentricular Fontan circulations. Second, we hypothesized that maintenance of an adequate Qvr may be obtained owing to changes in Qvr parameters occurring in response to the additional RVR produced by the location of PVR at the end of the systemic venous system. Therefore, Gvr and estimated and observed Pmcf were determined in two groups of pentobarbital sodium-anesthetized open-chest pigs, either in biventricular or univentricular Fontan circulations, while preserving SBF in each case with volume-loading adjustments.

Qvr curves were obtained using a novel experimental model with an adjustable atrioventricular valve annuloplasty that allowed us to induce transient inverse relationships between Pmcf and Qvr in biventricular circulations and between Pla and Qvr in univentricular Fontan circulations.

METHODS

Animal preparation. Sixteen large white pigs weighing 31.4 ± 4 kg were medicated before the experiment with an intramuscular injection of ketamine hydrochloride (10 mg/kg) and atropine sulfate (0.2 mg/kg) and were anesthetized with pentobarbital sodium (30 mg/kg iv). Orotracheal intubation was aided by pancuronium bromide (0.2 mg/kg). Animals were ventilated using a Servo 900D volume-cycle respirator (Siemens, Solna, Sweden) with oxygen-enriched air and 0.5% halothane (20 breaths/min, tidal vol 10 ml/kg). Anesthesia was maintained using supplemental doses of pentobarbital sodium (3 mg·kg⁻¹·h⁻¹). Thereafter, blood gas tensions, arterial oxygen saturation, pH and hematocrit values were measured using a Dow-Corning blood gas system (Ciba Corning, Medfield, MA) and were kept within physiological values. Body temperature was maintained at 39°C using a thermocontrolled operating table. Baseline hemodynamic values were recorded before further manipulations. The animals used in this study were maintained in accordance with the Guide for the Care and Use of Laboratory Animals by the National Research Council (1996).

Study design. Experiments were randomly divided into two groups, and biventricular (n = 8) or univentricular Fontan (n = 8) experimental circulations were surgically constructed. In each case the postoperative SBF was approximately set to the baseline level, to determine Pcv, the downstream pressure for Qvr, which is Pra in biventricular circulations and Pla in univentricular circulations. To elaborate Guyton’s Qvr curves implies that we induce a transient increase in Pcv (the independent variable, contrary to the usual convention) and record the resulting changes in Qvr (the dependent variable) (13, 17). Thus Guyton’s Qvr curves were obtained using a novel experimental method with an adjustable tricuspid (biventricular) or mitral (Fontan) valve annuloplasty. Transient tightening of the annuloplasty resulted in an increase in Pcv and a decrease in ventricular end-diastolic pressure, and thus in ventricular output, paralleling changes in Qvr. The studied relationship was between Pmcf and pulmonary blood flow (biventricular) and between Pla and aortic blood flow (univentricular). Pulmonary

Fig. 1. Surgical preparation: experimental biventricular circulation (A) and Fontan circulation (B).
or aortic blood flows in steady-state conditions were assumed to be equal to SBF. Observed Pmcf was determined using electrically induced ventricular fibrillation. Qvr curves were considered to be adequately determined if: 1) a linear relationship was demonstrated in each experiment between Pcv and Qvr, using regression analysis, and 2) a correlation was established in biventricular and Fontan circulations between estimated (zero-flow intercept of the Qvr curve) and observed (fibrillation) Pmcf.

Surgical preparations. A midline sternotomy was performed, and the anterior pericardium was opened and suspended. Preparations were realized under cardiopulmonary bypass, snares were tightened around the caval cannulas and ventricular fibrillation was electrically induced.

In biventricular circulations, an adjustable tricuspid annuloplasty was performed through a right atriotomy. Both ends of a double-running 3-0 polypropylene suture (around the annulus of the anterior and posterior leaflets of the tricuspid valve) were brought outside the heart through the caval cannulas and ventricular fibrillation was electrically induced.

In Fontan circulations, an adjustable mitral annuloplasty was performed through a left atriotomy using a circumferential annular running suture. The heart was defibrillated after usual deairing procedures. Fontan circulations were realized according to previously described models (24, 27). Briefly, two polytetrafluoroethylene 16-mm-diameter conduits (FEP ringed Gore-Tex Vascular Graft, Gore and Associates, Elkton, MD), reinforced with polyethylene cannulas, were introduced in the inferior and superior venae cavae, and connected to a Y-shaped conduit of our design, which was introduced into the distal main pulmonary trunk. The proximal part of the divided pulmonary trunk was anastomosed to the left atrial appendage to divert the coronary sinus flow into the left atrium, avoiding a distension of the right ventricle (Fig. 1A).

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Experimental protocol. Experiments were performed after a 20-min stabilization period to further bypass interruption. Systemic blood flow was set to its initial baseline level using only volume-loading adjustments with fresh heparinized homologous blood. Volume loading was 1.6 ± 1.2 versus 50.1 ± 6.1 ml/kg in biventricular versus Fontan circulations, respectively (P < 0.001). At that time, steady-state control hemodynamics were recorded in open-chest animals.

Increasing degrees of atrioventricular valve stenosis were applied, using 7–10 hemodynamic measurements in each experiment at 2-min intervals (13, 17). Hemodynamic responses during these transient changes showed an initial increase in Pcv and a decrease in Qsv, during 3–4 s followed by a plateau aspect of hemodynamics until 10 s in either group. Data were recorded over this latter period of steady-state response during which ventilation was stopped (16). Thereafter, the snare was released allowing the system to go back to the control equilibrium state. A plot of pressure-flow points assessed the relationship between Pcv and Qsv to determine Gv (expressed as ml·min−1·kg−1·mmHg−1). Extrapolation of the slope to the zero-flow intercept was used to estimate Pmcf (17). RVR values were defined as 1/Gv·80 (expressed as 103 dyn·s·cm−5·kg).

Observed Pmcf was measured 7–10 s after an electrically induced ventricular fibrillation and recorded in the systemic venous system (right atrium, biventricular circulations; pulmonary artery, Fontan circulations) before the onset of baroreflex action (16, 34, 35).

Epicardial echocardiographic control during Pcv transient changes ruled out any atrioventricular valve insufficiency. Intraoperative pressure measurements revealed no gradient across the Fontan pathways. At the end of the experiments, the pigs were euthanized with a lethal dose of pentobarbital sodium. Postmortem examinations disclosed no thrombus formations in conduits nor disruption of an atrioventricular valve annuloplasty.

Table 1. Steady-state hemodynamics in biventricular and univentricular Fontan circulations

<table>
<thead>
<tr>
<th></th>
<th>Biventricular Group</th>
<th>Baseline</th>
<th>Biventricular</th>
<th>Fontan Group</th>
<th>Baseline</th>
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<tr>
<td>HR, beats/min</td>
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<tr>
<td>SBF, ml·min−1·kg−1</td>
<td>106 ± 4</td>
<td>114 ± 7</td>
<td>110 ± 7</td>
<td>112 ± 7</td>
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<tr>
<td>Pao, mmHg</td>
<td>64.5 ± 4</td>
<td>67.4 ± 2</td>
<td>62.7 ± 7</td>
<td>65.4 ± 3</td>
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<tr>
<td>Ppa, mmHg</td>
<td>52.3 ± 2.4</td>
<td>52.8 ± 3</td>
<td>50.7 ± 2.2</td>
<td>62.2 ± 1.4</td>
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<tr>
<td>Pla, mmHg</td>
<td>9.1 ± 0.7</td>
<td>9.8 ± 0.5</td>
<td>9 ± 0.5</td>
<td>20.6 ± 1.2</td>
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<td>P1a, mmHg</td>
<td>2.6 ± 0.7</td>
<td>3.1 ± 0.4</td>
<td>2.1 ± 0.5</td>
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<td>P1a, mmHg</td>
<td>1.7 ± 0.6</td>
<td>2.2 ± 0.3</td>
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Values are means ± SE of 16 pigs (biventricular, n = 8; Fontan, n = 8). HR, heart rate; SBF, systemic blood flow; Pao, mean aortic pressure; Ppa, mean pulmonary arterial pressure; Pla, mean left atrial pressure; SBF, systemic vascular resistances; PVR, pulmonary vascular resistances; TVR, total vascular resistances. *P = not significant, †P = 0.02, ‡P = 0.01, and §P = 0.09 different from corresponding baseline.
were displayed on-line and continuously recorded on a multichannel direct-writing ink recorder (Gould, Cleveland, OH).

SVR values were calculated as \((P_{ao} - P_{ra})/SBF\) for biventricular or \((P_{ao} - P_{pa})/SBF\) for Fontan. PVR values were calculated as \((P_{pa} - P_{la})/SBF\). Total vascular resistances (TVR) in Fontan circulations were calculated as \((P_{ao} - P_{la})/SBF\). Vascular resistances were expressed as \(10^3\) dyn·s·cm\(^{-5}\)·kg.

**Statistical analysis.** Group data are expressed as means ± SE. All data from individual pigs were stored and analyzed with a software package (Statview 5, Abacus Concepts, Berkeley, CA). Hemodynamic comparisons were performed using a Wilcoxon signed-rank test or a Mann-Whitney U test for non-normally distributed data, as appropriate. In each experiment, dependence of \(Q_{vr}\) on \(P_{cv}\) was analyzed by performing linear regression analysis. The eight slopes in each group were averaged to yield a single conductance for that curve. \(Q_{vr}\) parameters were skewed and thus summarized using the median, 25th, 75th, and 90th percentiles. The probability for a correlation between continuous variables was assessed using Spearman rank statistics. A value of \(P < 0.05\) was considered statistically significant.

**RESULTS**

**Surgery and steady-state hemodynamics.** Biventricular and univentricular circulations were not statistically different for 1) animal weight, 32.7 ± 1.5 versus 30.2 ± 1.4 kg (\(P = 0.27\); 2) extracorporeal circulation time, 33.8 ± 4.2 versus 38.3 ± 2.9 min (\(P = 0.46\); and 3) ventricular fibrillation time, 11.4 ± 1.1 versus 13.5 ± 0.7 min (\(P = 0.12\)). There was no significant difference in baseline hemodynamics between biventricular and univentricular groups (Table 1). Postoperative hemodynamics were not significantly different from baseline values in biventricular circulations (Table 1). Conversely, postoperative hemodynamics in Fontan circulations, for a SBF not different from the baseline value (\(P = 0.49\)), showed marked increases in \(P_{la}\), from 2.1 ± 0.5 to 7 ± 0.9 mmHg (\(P = 0.01\)), and in \(P_{pa}\), from 9 ± 1.1 to 20.6 ± 1.2 mmHg (\(P = 0.01\)). PVR increased by 138 ± 37% (\(P = 0.02\)), without significant changes in SVR (Table 1). TVR after construction of Fontan circulations were higher than SVR in biventricular circulation without reaching statistical significance (\(P = 0.09\)).

**Characteristics of \(Q_{vr}\) curves.** The relationships between \(Q_{vr}\) and \(P_{ra}\) or \(P_{la}\) described straight lines with significant correlation coefficients \((r)\) in each experiment and in either group (biventricular, \(r = 0.94 ± 0.01\); univentricular, \(r = 0.98 ± 0.01\)). Figure 2 shows a representative experiment in Fontan circulations. The number of transient-induced changes in \(P_{cv}\) was

![Fig. 2. Representative experiment in Fontan circulations. A: hemodynamics effects of tightening the mitral annuloplasty. An increase in left atrial pressure (\(P_{la}\)) and a decrease in aortic pressure (\(P_{ao}\)) were observed without significant change in pulmonary arterial pressure (\(P_{pa}\)), demonstrating the pivoting pressure of the Fontan circulatory system. B: observed mean circulatory filling pressure (\(P_{mcf}\)), measured 7–10 s after induction of electrical fibrillation, showing the onset of baroreflex action at a latter stage. C: linear regression analysis of transient changes in aortic blood flow/venous return. a.u., Arbitrary units.](http://ajpheart.physiology.org/)

\[slope = -5.14\]
\[X \cdot intercept = 17.3 \text{mmHg}\]
\[r = 0.98\]
Venous return in univentricular Fontan circulations was similar and strongly correlated with either estimated \( r = 0.94, \text{slope} = 1.14, P = 0.04 \) or observed \( P_{\text{mcf}} \) \( r = 0.97, \text{slope} = 1.06, P = 0.02 \).

The pressure gradient for \( Q_{\text{vr}} \) expressed as estimated \( P_{\text{mcf}} - P_{\text{la}} \), was significantly higher in Fontan than in biventricular circulations, 13.4 ± 1.1 versus 8.8 ± 0.9 mmHg \( P = 0.01 \). The Fontan transpulmonary gradient, 12.9 ± 1.4 mmHg, was correlated with the corresponding pressure gradient for \( Q_{\text{vr}} \) \( r = 0.89, P < 0.05 \); Fig. 5B).

**Discussion**

The essential function of the right ventricle has been clearly demonstrated using a hydraulic model of the circulatory system (8). However, potential differences in regulatory mechanisms of \( Q_{\text{vr}} \) between two closed-loop circulatory systems with SVR and PVR located in series, one with a subpulmonary ventricle and the other without, remain unknown. The new findings of this study demonstrate that the pathophysiology of Fontan circulations can be analyzed according to Guyton’s principles and also show marked changes in the vascular factors (i.e., \( G_{\text{vr}} \) and \( P_{\text{mcf}} \)) that determine \( Q_{\text{vr}} \). Thus this study found evidence that placing SVR and PVR in series decreases \( G_{\text{vr}} \). Moreover, the increase in pulmonary vascular input impedance induced a proportionally greater decrease in \( G_{\text{vr}} \). The greater the decrease in \( G_{\text{vr}} \), the more an increase in the pressure gradient for \( Q_{\text{vr}} \) is necessary to keep SBF at a biventricular level, because forces of flow resistances must be counteracted by a potential energy of pressure between \( P_{\text{mcf}} \) (similar to \( P_{\text{pa}} \)) and \( P_{\text{la}} \). Taken together, these data suggest that \( Q_{\text{vr}} \) may be an independent variable of the SBF in Fontan circulations.

**Components of the model.** To compare hemodynamics between biventricular and Fontan circulations, important conditions have been fulfilled: 1) protocols were similar in both groups; 2) postoperative SBF was set to its baseline value to avoid simultaneous changes in preload, afterload, and SBF (24); 3) anesthesia caused a desirable decrease in baroreflex sensitivity (12, 18, 35); 4) use of extracorporeal circulation and transient ventricular fibrillation time did not affect hemodynamics in the biventricular group, indicating that univentricular Fontan hemodynamics were per se related to the circulatory arrangement; and 5) steady-state hemodynamic changes in \( P_{\text{la}} \) and PVR between baseline and experimental Fontan circulations were similar to those reported previously for either a decreased (20, 27, 36) or preserved resulting SBF (24).

None of the previously reported methods to obtain \( Q_{\text{vr}} \) curves in either biventricular circulation [using right heart bypass (2, 12, 13, 16, 23, 32) or intermittent positive-pressure ventilation (5, 31, 38)] or univentricular circulation [using left heart bypass (22, 23)] could be adapted to our study. As the downstream pressure for \( Q_{\text{vr}} \) is \( P_{\text{ra}} \) in biventricular and \( P_{\text{la}} \) in univentricular circulations, we used an adjustable tricuspid or mitral annuloplasty to induce transient increases in \( P_{\text{cv}} \), with comparable methodologies in
biventricular and univentricular circulations. To determine observed Pmcf, we used an electrical fibrillation that is known to be the more reliable method (9, 13, 16, 17, 34, 35). Furthermore, our delay of 7–10 s before recording was sufficiently short to eliminate baroreceptor reflexes in response to the fall in Pao (Fig. 2B) (38).

Validation of our novel experimental approach was supported by three observations. First, relationships between Pcv and Qvr described curves that behave in a linear fashion similar to those using right or left heart bypass preparations (5, 31, 38). Second, high correlation coefficients were observed between estimated and observed Pmcf values (5, 31, 38). Third, biventricular Pmcf measurements are consistent with previously reported data in pig experiments (5, 29, 38).

Gvr in Fontan circulations. The present study demonstrates that in Fontan circulations, PVR were similar to RVR and induced the characteristic downward rotation of the Qvr curve due to the proportional decrease in Gvr (13). Moreover, PVR values are increased in Fontan circulations (3, 20, 24, 27, 36), reducing Gvr as much. This can be related to: 1) a lack of dilatation and recruitment of the pulmonary vessels, 2) an asymmetric pulmonary perfusion, and 3) the loss of pulsatility of the pulmonary blood flow (3). The apparent resistance of pulmonary circulation to perfusion using steady flow is greater than that observed when pulsatile flow is present, accounting at worst for a fourfold increase in PVR in the neonatal period (19) precluding the use of this therapeutic approach in infancy. Mandelbaum and Burns (25) showed a 127% increase in PVR during nonpulsatile pulmonary perfusion, which is comparable to the data of the present study. Milnor et al. (26) demonstrated that estimation of the hydraulic flow obeying the Ohm’s law (steady-state pressures and flows) underestimates the real energy required by SBF to go through the pulmonary vascular bed. Hydraulic power is converted into a pure pressure gradient, increasing the necessary energy for the pulmonary blood flow to go through the pulmonary vascular bed.

Driving force for Qvr in Fontan circulations. The pressure gradient for Qvr, similar to the transpulmonary gradient, is higher than in biventricular circulations to counteract the increase in RVR. Thus Guyton’s concept could be applied to Fontan circulations in which Qvr depends on the difference between upstream pressure or vis a tergo, PmcF, and downstream pressure or vis a fronte, Pia, for Qvr (1, 17, 35). Therefore, slight changes in PmcF or Pia may induce marked changes in Qvr, as previously emphasized by Furey et al. (8).

Table 2. Distribution of parameters describing venous return curves in biventricular and Fontan circulations

<table>
<thead>
<tr>
<th></th>
<th>Means ± SE</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
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<tr>
<td>Gvr, ml·min⁻¹·kg⁻¹·mmHg⁻¹</td>
<td></td>
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<tr>
<td>Biventricular</td>
<td>7.83 ± 0.69</td>
<td>6.3</td>
<td>7.5</td>
<td>9.6</td>
<td>10.2</td>
</tr>
<tr>
<td>Fontan</td>
<td>4.51 ± 0.36</td>
<td>3.7</td>
<td>4.3</td>
<td>5.5</td>
<td>5.9</td>
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<tr>
<td>Estimated Pmcf, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biventricular</td>
<td>11.1 ± 0.9</td>
<td>9.9</td>
<td>11.2</td>
<td>12.8</td>
<td>14.1</td>
</tr>
<tr>
<td>Fontan</td>
<td>20.5 ± 1.4†</td>
<td>18.2</td>
<td>20.3</td>
<td>23.2</td>
<td>26.1</td>
</tr>
<tr>
<td>Observed Pmcf, mmHg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biventricular</td>
<td>10.6 ± 0.8</td>
<td>8.8</td>
<td>11.3</td>
<td>12.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Fontan</td>
<td>21.8 ± 1.3‡</td>
<td>19.7</td>
<td>21.3</td>
<td>23.8</td>
<td>27.4</td>
</tr>
</tbody>
</table>

Venous return parameters of 16 pigs (biventricular, n = 8; Fontan, n = 8). Gvr, venous return conductance; PmcF, mean circulatory filling pressure. *P = 0.002, †P = 0.001, and ‡P < 0.001 different from corresponding biventricular circulations.

Fig. 5. Determinants of venous return in Fontan circulations: a good correlation between pulmonary vascular resistance (PVR) and resistance to venous return (RVR) (A); and a good correlation between the transpulmonary gradient and gradient for venous return expressed as estimated PmcF−Pia (B).
Another important finding of this study is that $P_{mcf}$ is similar to $P_{pa}$. Interestingly, a similar equalization between regional $P_{mcf}$ and portal pressure is seen in the splanchnic venous circulation when high venous distending pressures are present (6). However, the increase in $P_{mcf}$ resulted from volume loading that increased the stressed blood volume (34, 35). This led to a rightward parallel shift of the $Q_{vr}$ curve (13) keeping the SBF at its initial baseline value despite the decrease in $G_{vr}$. Moreover, our results demonstrated that $P_{mcf}$ and thus $P_{pat}$ was the “pivoting pressure” for $Q_{vr}$ in Fontan circulations (35, 38). During transient decrease in $Q_{vr}$, it was mathematically demonstrated that pressure downstream $P_{mcf}$ increases, pressure upstream $P_{mcf}$ decreases, and $P_{mcf}$ remains stable and thus was called the pivoting pressure of the circulatory system (34, 38). Due to the particular location of $P_{mcf}$ in Fontan circulations, this principle could be directly measured for the first time (Fig. 2, A and B). This observation is supported by the work of Sade and Dearing (36): “the value of $P_{pa}$ does not vary more than 1 mmHg from zero flow to full LV [left ventricular] bypass in experimental Fontan circulations”; as well as by Kresh and colleagues (21, 22), who demonstrate a linear pulmonary artery pressure-flow relationship by means of both computer and experimental simulations of univentricular left heart support.

$P_{mcf}$ is located at the level of small veins and venules within biventricular circulations (34, 38). In Fontan circulations, it was located further downstream at pulmonary artery level. However, increasing $P_{mcf}$ is certain to increase peripheral vessel dimensions (17) and thereby decrease the distance between the point where $P_{mcf}$ exists in biventricular circulations and the point where $P_{mcf}$ exists in Fontan circulations.

The second pressure that determines the pressure gradient for $Q_{vr}$ in Fontan circulations is $P_{la}$, which was obviously higher than $P_{ra}$ in biventricular circulations. First, the left or systemic ventricle is about one-half as compliant as the right ventricle. Second, our experimental biventricular and Fontan circulations were functioning under two different cardiac function curves. These results are in agreement with previously reported studies allowing the comparison of baseline biventricular hemodynamics versus Fontan hemodynamics (20, 24, 27, 36). This could be related to: 1) a right-to-left ventricular interaction loss, which constitutes an inherent drawback to any experimental univentricular model, implying that this observation cannot necessarily be applied to the clinical practice because it has been considered that the additional load of the PVR can be easily accommodated by the normal left ventricle (8); and 2) an heterometric autoregulation due to TVR increase (24) or more accurately to total impedance increase of the Fontan circulatory system (37), which might explain the difficulties of SBF adaptation of univentricular circulations. Anyway, it has been shown that decreasing $P_{la}$ by either using a left heart bypass or increasing left ventricular contractility, significantly increases SBF (8, 36). Moreover, the increase in $P_{ao}$ observed in Fontan circulations could not change $G_{vr}$ and might only decrease $P_{mcf}$ due to a change in vascular capacity (11). Furthermore, although our single ventricle model could be considered a failing heart and consequently could have intensified the heart sensitivity to an afterload increase, this could not have influenced either $G_{vr}$ as reported by Poulser et al. (32) in an experimental model of cardiac failure, or $P_{mcf}$ because the blood volume conveyed from the systemic vascular bed to the pulmonary circulation participates in the overall stressed volume in univentricular circulations.

**Limitations.** Use of an extracorporeal circulation could be associated with a change in venous tone. This limitation is somewhat offset because biventricular and univentricular Fontan circulations were subjected to identical study protocols, and no significant volume loading was necessary in biventricular circulations. Furthermore, experiments were performed in a sufficiently short period to avoid the occurrence of a significant stress relaxation, and volume loading, in univentricular circulations, was performed with blood, allowing a more durable vascular expansion (33). However, our preparation did not allow us to examine other factors that could influence $Q_{vr}$ in univentricular circulations, such as gravity, ventilation, passive elastic recoil of the veins, venous tone, reflex, and humoral mechanisms (34, 35).

There are several limitations in $P_{mcf}$ assessment. First, in biventricular circulations, $P_{mcf}$ is the pressure in systemic vessels, excluding pulmonary vessels (17) in which $P_{mcf}$ is 2–3 mmHg higher (35). In univentricular circulations, $P_{mcf}$ reflected the zero-flow pressure in both systemic and pulmonary vessels. Second, more accurate measurements of the observed $P_{mcf}$ for the Fontan circulation could have been obtained using a triple mechanical transfer of blood between the aorta, systemic veins, and left atrium, to avoid an imperfect blood-volume redistribution throughout the entire cardiovascular system (17, 29). However, it is likely that this effect was small and should not have influenced $P_{mcf}$ more than 1 mmHg (35). Third, $P_{mcf}$ measured at 7 s after cardiac arrest may not accurately estimate “total body venous tone,” because it may omit the splanchnic venous bed, but because we used blood volume addition (9) our $P_{mcf}$ measurements may not be influenced. However, to properly assess this issue would require a simultaneous measurement of the portal venous pressure.

The $Q_{vr}$ curve of the entire circulation is a composite of $Q_{vr}$ measurements from several compartments (i.e., superior and inferior venae cavae and splanchnic circulation) associated with different time constants and $Q_{vr}$ parameters. Caldini et al. (2) described fast and slow time-constant (splanchnic circulation) venous compartments. To determine their potential influences, superior and inferior venae cavae and portal vein pressure-flow relationships might be separately studied in future experiments (3, 6). However, it was recently reported that neither the fast nor the slow time-constant compartments represented a particular anatomical region or vascular bed (28).
Finally, our study did not allow us to determine the critical pressure for \( Q_{vr} (P_{la} \) under which the SBF could no longer improve, leading to the "plateau" aspect of Guyton's \( Q_{vr} \) curve). Nevertheless, it can be ascertained from the studies of Furey et al. (8), Kresh et al. (21, 22), and Sade and Dearing (36) that an increase in left ventricular efficiency leads to negative pressure at the left atrial level and consequently to a pulmonary venous collapse (instead of the collapse of the major veins in biventricular circulations), thus determining the critical pressure for \( Q_{vr} \).

**Modeling the Fontan operation.** The findings of this study provide a link between changes in \( Q_{vr} \)-determining factors and several clinical observations, suggesting a graphical analysis of Fontan circulations (18) and consequently offering a physiological approach instead of pragmatic decision making.

Between biventricular and Fontan circulations, there are changes in the three factors that determine \( Q_{vr} \). First, the decrease in \( G_{vr} \) may lead to a downward rotation of the \( Q_{vr} \) curve. Second, volume loading brings back SBF at a biventricular level at the expense of an increase in \( P_{mcf} \), which induces a rightward parallel shift of the \( Q_{vr} \) curve. Finally, \( P_{la} \), and not \( P_{ra} \), is the downstream pressure for \( Q_{vr} \) (Fig. 6A). However, these three factors may not be independent from each other, as in biventricular circulations, because volume loading, while increasing \( P_{pa} \) and \( P_{mcf} \), decreases PVR and thus RVR by the recruitment of pulmonary vessels (3, 36).

In high-risk patients, the presence of a diastolic or systolic myocardial dysfunction in Fontan circulations will have a dramatic consequence on \( Q_{vr} \) (Fig. 6B) (10). In each case, because \( P_{la} \) is the back pressure for \( Q_{vr} \), the driving force for \( Q_{vr} (P_{mcf} - P_{la}) \) will decrease, because \( P_{mcf} \) will not change unless the presence of a low cardiac output induces a reflex venoconstriction (34). An increase in PVR will also cause adverse consequences due to the simultaneous decrease in \( G_{vr} \) (Fig. 6C). However, interactions between cardiac and vascular factors may be more complex because cardiac contractility mainly influences end-systolic volume, whereas vascular factors primarily influence end-diastolic volume (34), which is of primary importance in Fontan circulations (10).

In summary, the present study allows for the first time the ascertaining of changes in \( Q_{vr} \) parameters associated with univentricular Fontan circulations, owing to a new experimental model for determining \( Q_{vr} \) curves. The pathophysiological mechanisms of \( Q_{vr} \) in univentricular Fontan circulations are therefore as follows: 1) placing SVR and PVR in series without a subpulmonary ventricle increases RVR, which is similar to PVR; the loss of pulsatility of the pulmonary blood flow induces a greater increase in PVR and thus a greater decrease in \( G_{vr} \); 2) because \( Q_{vr} = (P_{mcf} - P_{la})\cdot G_{vr} \), the greater the decrease in \( G_{vr} \), the more an increase in the driving force or pressure gradient for \( Q_{vr} \) is necessary to keep the SBF constant, because forces of pulmonary flow resistance must be counteracted by the pressure gradient between \( P_{mcf} \) and \( P_{la} \). Furthermore, Guyton's principles could provide a unique opportunity to study the regulatory mechanisms of \( Q_{vr} \) in various circulatory states resulting from the surgical construction of univentricular Fontan circulations, including partial versus complete Fontan circulations, and the effects of positive- or negative-pressure ventilation (3).
REFERENCES


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