Effects of Respiration and Gravity on Infradiaphragmatic Venous Flow in Normal and Fontan Patients

Tain-Yen Hsia, MD; Sachin Khambadkone, MD, MRCP; Andrew N. Redington, FRCP; Francesco Migliavacca, PhD; John E. Deanfield, FRCP; Marc R. de Leval, MD, FRCS

Background—In the Fontan circulation, pulmonary and systemic vascular resistances are in series. The implications of this unique arrangement on infradiaphragmatic venous physiology are poorly understood.

Methods and Results—We studied the effects of respiration and gravity on infradiaphragmatic venous flows in 20 normal healthy volunteers (control) and 48 Fontan patients (atriopulmonary connection [APC] n=15, total cavopulmonary connection [TCPC] n=30). Hepatic venous (HV), subhepatic inferior vena cava (IVC), and portal venous (PV) flow rates were measured with Doppler ultrasonography during inspiration and expiration in both the supine and upright positions. The inspiratory-to-expiratory flow rate ratio was calculated to reflect the effect of respiration, and the supine-to-upright flow rate ratio was calculated to assess the effect of gravity. HV flow depended heavily on inspiration in TCPC compared with both control and APC subjects (inspiratory-to-expiratory flow rate ratio 3.4, 1.7, and 1.6, respectively; P<0.0001). Normal PV flow was higher in expiration, but this effect was lost in TCPC and APC patients (inspiratory-to-expiratory flow rate ratio 0.8, 1.0, and 1.1, respectively; P=0.01). The respiratory influence on IVC flow was the same in all groups. Gravity decreased HV flow more in APC than in TCPC patients (supine-to-upright flow rate ratio 3.2 versus 2.1, respectively; P<0.04) but reduced PV flow equally in all groups.

Conclusions—Gravity and respiration have important influences on infradiaphragmatic venous return in Fontan patients. Although gravity exerts a significant detrimental effect on lower body venous return, which is more marked in APC than in TCPC patients, the beneficial effects of respiration in TCPC patients are mediated primarily by an increase in HV flow. These effects may have important short- and long-term implications for the hemodynamics of the Fontan circulation. (Circulation. 2000;102[suppl III]:III-148-III-153.)

Key Words: Fontan procedure ■ veins ■ hemodynamics ■ respiration ■ physiology

Introduction of the Fontan operation 30 years ago revolutionized the treatment of complex congenital heart defects where biventricular repair is not possible. During the ensuing years, attempts to improve hemodynamic performance and to decrease late problems of atrial arrhythmias and thromboembolic complications have led to several modifications in the surgical procedures. Despite these changes, the fundamental physiology of the Fontan circulation remains the same: namely, the venous return is dissociated from a ventricular power source, and the systemic vascular resistance is placed in series with the pulmonary vascular resistance.

Major changes in the systemic venous physiology have been described as a consequence of this unique circulatory arrangement. Studies of patients after either total cavopulmonary connection (TCPC) or atrioventricular connection (APC) have shown that the negative intrathoracic pressure generated by inspiration assists antegrade flow in the superior vena cava and the pulmonary artery.

Few studies have examined the infradiaphragmatic venous circulation. Compared with the superior vena caval territory, the infradiaphragmatic venous return is influenced by gravity, interactions with the diaphragm, and interposition of the liver between the portal and hepatic veins. The aim of the present study was to compare the roles of respiration and gravity on flow in the hepatic vein (HV), portal vein (PV), and subhepatic inferior vena cava (IVC) in normal healthy subjects and functionally well patients after APC or TCPC.

Methods

Study Groups

Forty-eight patients were studied 1 to 20 years (mean 10±4 years) after their Fontan operation. Thirty-three patients underwent the TCPC procedure (27 lateral tunnel and 6 extracardiac conduit), and 15 patients underwent the APC procedure. All patients were in self-reported New York Heart Association functional class I or II and were in sinus rhythm. None had clinical signs of congestive heart failure, major pulmonary arteriovenous malformations, protein-losing enteropathy, or other known complications of the Fontan circulation. Twenty age- and sex-matched normal volunteers were studied as control subjects.

All subjects underwent HV, PV, and IVC Doppler ultrasonographic interrogation under simultaneous dynamic respiratory and...
ECG monitoring. A tilt table was used to allow measurements in the supine and upright (85° to 90° from the horizontal plane) positions. The study protocol was approved by the hospital Research Ethics Committee, and informed consent was obtained for all subjects.

Doppler Ultrasonographic Recordings

Measurements were made with an Acuson 128XP system with a 2.5-MHz transducer. Pulsed-wave Doppler recordings in the HV, IVC, and PV were made with each subject breathing quietly in the supine and then the upright position. At least 5 minutes was allowed before the upright examination for the subject to adjust to the postural change. A minimum of 3 full respiratory cycles were recorded for each patient in both the supine and upright positions.

For each vessel, the site of sampling was guided by color flow mapping to position the sample volume at the center of the color signal and to create the smallest angle of insonation between the direction of blood flow and the Doppler beam. In most cases, antegrade venous flow has a negative Doppler signal, but because of the tortuosity or anatomic variations, some PV forward flow was recorded as a positive signal (Figure 1).

Recordings were made in the left or middle HV (~1 cm distal to junction with IVC) and the subhepatic IVC (1 to 2 cm distal to junction with HV). The portal flow signal was obtained in the main portal trunk before its division into the right and left branches according to previously published protocols. The instantaneous diameters of each vessel (d) in both the supine and upright positions were measured from the B-mode images at the same location as the Doppler interrogation; signals in the upright position were obtained as close as possible to the identical location in the supine position. Each Doppler flow signal was recorded on videotape and hard copy for off-line analysis.

Flow rate (Q) was computed as the division of volume of blood (V) moving through the vessel by the time (T) needed for this volume to cross.

\[ Q = \frac{V}{T} \]  

A rigorous treatment of the volume-flow relationship required the continuous computation of the product of velocity (v) and cross-sectional area (A), or an integration,

\[ V = \int_0^T v(t) A(t) dt \]

over time T. We assumed that changes in A(t) within 1 respiratory cycle were small in the moderately sized HV, IVC, and PV, all of which were transhepatic in location. Equation 1 could then be replaced with

\[ A \int_0^T v(t) dt \]

where A equals

\[ \pi(d/2)^2 \]  

and

\[ \int_0^T v(t) dt \]

the velocity-time integral (VTI) determined from the Doppler recording taken during time interval T.

Respiratory Effect

As demonstrated in Figure 2, with dynamic respiratory monitoring, the Doppler signal could be evaluated during inspiration, during expiration, or throughout a complete respiratory cycle. When T was the time for inspiration and antegrade VTI was evaluated during this period, Q represented the antegrade flow rate during the inspiratory phase of the respiratory cycle (Q_{inspiration}). In a similar
fashion, flow rates during expiration ($Q_{ex}$) were obtained. The effect of respiration on flow was expressed as a ratio of $Q_{in}$ to $Q_{ex}$ in the supine position. Flow rate during inspiration is higher than that during expiration when this ratio is $>1$, and vice versa.

**Percentage of Respiration-Dependent Flow in IVC and HV**

The difference between $Q_{in}$ and $Q_{ex}$ was taken to reflect flow derived solely from inspiration. Thus, the fraction of flow that depended on respiration was calculated from the $Q_{in}/Q_{ex}$ ratio. Expressed as a percentage, respiratory-dependent flow in the subhepatic IVC or HV is expressed as

$$\text{HV or IVC (\%) } = \frac{Q_{in} - Q_{ex}}{Q_{in} + Q_{ex}} \cdot 100 = \frac{(Q_{in}/Q_{ex}) - 1}{(Q_{in}/Q_{ex}) + 1} \cdot 100$$

Magnetic resonance mapping had shown that nearly 65% of the total venous return is from inferior territory. With splanchic circulation making up 25% of the cardiac output, the total inferior venous return is therefore contributed by HV and =62% is contributed by subhepatic IVC. With the amount of respiratory-dependent flow in HV and IVC known (from equation 4), the fraction of the total inferior venous return that results from inspiratory effort can be estimated as

$$\% = (\%_{\text{HV}})(0.38) + (\%_{\text{IVC}})(0.62)$$

where HV and IVC (%) represent percentages of respiratory-dependent flow in HV and IVC, respectively.

**Retrograde Flow Rate**

$Q_{re}$ was obtained through an evaluation of the VTI of the retrograde Doppler signal throughout a respiratory cycle. Antegrade flow rate ($Q_{an}$) corresponding to the same time interval was also calculated. The ratio of $Q_{re}$ to $Q_{an}$ represents the magnitude of retrograde flow with respect to antegrade flow.

**Gravity Effect**

The effects of gravity were evaluated for 2 quantities: net and retrograde flow rates. Net flow rate ($Q_{an}$) was defined as the absolute total flow during a complete respiratory cycle obtained by subtracting retrograde VTI from the antegrade VTI. The effect of gravity on $Q_{an}$ was represented as the ratio of $Q_{an}$ in the supine position to that in the upright position. A ratio of $>1$ implies a reduced $Q_{an}$ in the upright position.

The ratio of retrograde flows ($Q_{re}/Q_{an}$) in the supine over that in the upright position was also calculated to evaluate whether gravity increased flow reversal. A ratio of $<1$ indicated that there is an increased retrograde flow in the upright position.

Differences among control, TCPC, and APC were assessed by 1-way ANOVA with Newman-Keuls multiple comparison test. Intragroup paired $t$ tests were also performed to evaluate the various ratios within each study group. For example, if no difference existed between $Q_{re}$ and $Q_{an}$ in the control group, then the respiratory ratio ($Q_{re}/Q_{an}$) was an insignificant value. A probability value of $<0.05$ was considered statistically significant.

**Results**

**Study Group Characteristics**

TCPC and APC patient characteristics, including diagnosis at the time of surgery, are listed in Table 1. There were no differences in the underlying diagnosis or age at surgery between APC and TCPC groups ($P=NS$). However, APC patients were older ($P=0.0006$) and had a longer follow-up ($P=0.002$).

The control group had a mean age of $14\pm5$ years and a male-to-female ratio of $15:5$ ($P=NS$ compared with both patient groups).

**Flow Rate Calculations**

The results of the various Doppler flow rate calculations are summarized in Table 2. There were no quantitative differences between the lateral tunnel and extracardiac TCPC subgroups, so their data are presented together.

**IVC Flow**

Figure 3 shows the IVC flow profiles were in phase with the cardiac cycle in control and APC subjects, with antegrade flow following QRS complex and retrograde flow after atrial systole. TCPC flow was less overly dependent on the cardiac cycle but varied with respiration.

Forward flow was consistently higher in inspiration than expiration, but there was no difference in the magnitude of this inspiratory augmentation among the 3 groups. Retrograde flow was nearly the same between control and APC groups, whereas TCPC patients displayed minimal flow reversal during atrial systole. Gravity had no significant influence on either the net flow or retrograde flow in control subjects, but it decreased the former and increased the latter in both APC and TCPC patients.

**HV Flow**

Hepatic venous Doppler profiles among the 3 groups are shown in Figure 4. Although there was consistent retrograde atrial systolic flow in control and APC subjects, this was absent in TCPC patients, whose flow reversal occurred only during early expiration.

Control and APC subjects showed an inspiratory augmentation of flow, but forward flow in TCPC patients was “dominated” by the inspiratory phase. In a comparison of the respiratory effect, $Q_{re}/Q_{an}$ within the TCPC group, HV flow was significantly more inspiratory dependent than subhepatic IVC flow ($Q_{re}/Q_{an}$ $3.4\pm1.5$ versus $1.5\pm1.3$, respectively; $P<0.0001$). Gravity reduced net flow in the control group, but this adverse influence was more pronounced in the Fontan groups, with the APC patients having the largest flow reduction. Gravity minimally affected control retrograde flow, but it increased flow reversal in both TCPC and APC groups.

**Respiratory-Dependent Flow in IVC and HV**

The application of Table 2 results in equations 6 and 7, and Table 3 shows the percentages of respiratory-dependent antegrade flow in IVC and HV among the 3 groups. Although
there was no difference in the respiratory contribution to subhepatic IVC flow, 55% of HV flow and 30% of total inferior venous return in TCPC patients were dependent on inspiration.

**PV Flow**

PV forward flow in control subjects was independent of the cardiac cycle and declined near peak inspiration (Figure 1). In contrast, PV flow in TCPC and APC patients showed greater pulsatility and increased near peak inspiration.

Higher flow rates were recorded during expiration in the control group. This expiratory augmentation was absent in APC and TCPC patients, where no significant difference existed between inspiratory and expiratory flow rates. A similar degree of flow reversal was observed in all 3 groups. Gravity reduced net flow rates equally among the 3 groups. There was no difference in the respiratory contribution to subhepatic IVC flow, 55% of HV flow and 30% of total inferior venous return in TCPC patients were dependent on inspiration.

Table 2: Results of Flow Rate Calculations

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>IVC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1.24±0.29</td>
<td>0.25±0.19</td>
<td>1.16±0.40</td>
<td>2.07±1.75</td>
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<td>APC</td>
<td>1.45±0.28</td>
<td>0.22±0.11</td>
<td>1.91±1.05</td>
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<td>TCPC</td>
<td>1.32±1.31</td>
<td>0.06±0.11†‡</td>
<td>1.71±0.67†</td>
<td>0.88±0.34*</td>
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<tr>
<td>P</td>
<td>0.18</td>
<td>&lt;0.000002</td>
<td>&lt;0.01</td>
<td>&lt;0.0005</td>
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<tr>
<td>HV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>1.66±0.48</td>
<td>0.43±0.15</td>
<td>1.67±0.72</td>
<td>1.17±0.63</td>
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<tr>
<td>APC</td>
<td>1.55±0.43</td>
<td>0.52±0.18</td>
<td>3.19±2.76†</td>
<td>0.75±0.14†</td>
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<td>TCPC</td>
<td>3.40±1.53†‡</td>
<td>0.27±0.17†‡</td>
<td>2.08±1.26§</td>
<td>0.65±0.43*</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.0000001</td>
<td>&lt;0.000001</td>
<td>0.03</td>
<td>&lt;0.001</td>
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<tr>
<td>PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>0.78±0.25</td>
<td>0.12±0.10</td>
<td>1.85±1.22</td>
<td>1.07±0.73</td>
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<tr>
<td>APC</td>
<td>1.12±0.33†</td>
<td>0.07±0.08</td>
<td>1.76±0.99</td>
<td>0.68±0.41</td>
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<tr>
<td>TCPC</td>
<td>0.96±0.33†</td>
<td>0.10±0.15</td>
<td>2.22±1.49</td>
<td>0.62±0.40†</td>
</tr>
<tr>
<td>P</td>
<td>0.01</td>
<td>0.5</td>
<td>0.5</td>
<td>0.03</td>
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</table>

When ANOVA P<0.05, after analysis by Newman-Keuls test: *P<0.001 vs control, †P<0.05 vs control, ‡P<0.001 vs APC, §P<0.05 vs APC. Intragroup P values are <0.05 except when denoted (†).

**Discussion**

By freeing patients with univentricular physiology of chronic cyanosis and ventricular volume loading, modifications of the Fontan operation have markedly improved early functional outcome. However, there is a continuing late hazard and increasing frequency of complications during long-term follow-up.11 If late problems are the additive result of the chronic Fontan state, an understanding of the fundamental differences between the normal and Fontan physiology clearly becomes important. Despite the known major impact of the Fontan circulation on venous return, few studies have analyzed its hemodynamic consequences on the infradiaphragmatic venous territory. This region is composed of 2 dynamically distinct circulations: the splanchnic circulation drains the gastrointestinal tract through additional resistance of the liver, and the systemic circulation channels blood from the lower extremities and kidneys. The present data demonstrate a profound but variable effect of both respiration and gravity on these venous territories in Fontan patients.

Unlike previous Fontan studies in which maximal velocities or pulsatility ratios were used to assess infradiaphragmatic venous flow dynamics, we calculated volumetric flow rates from Doppler recordings. Because flow profiles are not symmetrically parabolic, instantaneous maximal velocities cannot reliably reflect the continuous changes of flow throughout a cardiac or respiratory cycle. Similarly, a pulsatility ratio does not adequately describe flow or hemodynamics.

In the present study, flow rates were obtained by recording velocities continuously with respect to time and assuming a constant cross-sectional area in all 3 veins. This assumption is valid because the main HV and the IVC, just distal to it, are transeptal in location and have been shown to remain in rigid configuration during all phases of respiration.12 Furthermore, the PV diameter has been documented to change by <±0.5 mm during the cardiorespiratory cycle.

**Flow Profiles**

HV and IVC flow profiles have been extensively examined in normal subjects. There is predominantly biphasic forward flow and a smaller reversed atrial systolic flow.14 Similarly, antegrade and retrograde HV and IVC flow profiles remain overtly cardia dependent in APC subjects, respectively, reflecting the capacitance and contractile function of the right atrium. This pattern is absent in TCPC subjects, where atrial work is excluded from the venous circulation. HV and IVC retrograde flows are reduced in TCPC subjects compared with control or APC subjects, and although speculative, by reducing hepatic venous regurgitation in a circulation devoid of ventricular energy, the TCPC may render a protective effect to the liver and the gastrointestinal tract.7

Normal PV flow profile is less well understood.8 Because of the interposed liver, portal venous flow is not in phase with...
the cardiac cycle and is more influenced by respiration (Figure 1). Like Arisawa et al., we found increased pulsatility in both APC and TCPC groups.

**Effect of Respiration**

Venous return is known to be influenced by the so-called cardiopulmonary interaction, where spontaneous breathing provides additional energy for forward flow. This has been shown separately in normal subjects and in Fontan patients. Our data confirm these observations. In correlation with the Doppler finding by Penny and Redington of a 24% increase in pulmonary blood flow during inspiration, 20% of our APC inferior venous return was respiratory dependent. Furthermore, the 30% respiratory dependency in the TCPC group agreed exactly with the magnetic resonance measurements of Fogel et al. in the lateral tunnel.

Interestingly, 15% of the total inferior venous return was dependent on respiration in the control subjects. Because none of the earlier studies had a comparison with a control group and used the same methodology, the particular importance of this cardiopulmonary interaction in a Fontan circulation has not been resolved. There have been no attempts to individually analyze the flow dynamics of the splanchnic and systemic contributions in the inferior venous return. Our data demonstrate that a greater proportion of inferior venous return in TCPC depends on respiratory-derived driving force. This is because the majority of HV flow, which makes up nearly 40% of inferior venous return, occurs during inspiration in TCPC. Normal cardiopulmonary interaction is therefore amplified in the splanchnic circulation with minimal additional caval contribution. One can consequently speculate that any disturbance to the ventilatory mechanics, such as paralyzed diaphragm or obstructive pulmonary diseases, may have a more detrimental effect on the TCPC hemodynamics and in particular in the splanchnic circulation.

In the control group, PV flow decreased during inspiration. Moreno et al. suggested that diaphragmatic descent on the liver transiently compresses the compliant sinusoids and portal venules, which are poorly distensible and easily collapsible. The absence of this inspiratory reduction in both Fontan groups may reflect either decreased hepatic compressibility or increased sinusoidal pressure and congestion, maintaining patency throughout the respiratory cycle. This may also explain the increased pulsatility seen in our APC patients, allowing the cardiac influences to be directly transmitted to the PV (Figure 1).

<table>
<thead>
<tr>
<th>TABLE 3. Percentages of Respiratory-Dependent Flow</th>
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<tbody>
<tr>
<td>IVC, %</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Control</td>
</tr>
<tr>
<td>APC</td>
</tr>
<tr>
<td>TCPC</td>
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Effect of Gravity
To date, no study has examined the effect of gravity on the Fontan circulation. Hydrostatic forces are constantly affecting the intravascular pressures within the abdominal venous system.10 Despite this, hydraulic changes due to gravity are minimized on the systemic venous circulation in humans because of ventricular compensation,10 as was illustrated with the control group data. In the Fontan patients, however, presumably because of the absence of a ventricular input, gravity had a more significant influence on venous return. There was a significant adverse effect on IVC flow, with reduced antegrade and enhanced retrograde flows in both Fontan groups, particularly in patients after APC.

Unlike the systemic flow, splanchnic venous blood flow has been found to decrease significantly in humans during orthostasis.10,19 This was also confirmed by our results where gravity significantly reduced net HV and PV flow rates in normal subjects. Because the splanchnic circulation is intrinsically susceptible to the adverse effect of hydrostatic forces, one might suggest that it is a rather vulnerable territory of the venous system to hemodynamic stressors. Gravity reduced HV flow more severely in Fontan patients, with the APC group having the poorest performance. Although in the present study the adverse effect of gravity on the portal system was not worse in the functionally well Fontan patients, this might not be the case in the functionally poor patients or in those with protein-losing enteropathy and clearly is an area that deserves further study.

Study Limitations
The APC patients were older and had longer follow-up periods than the TCPC patients. It is therefore possible that some of the differences reported here are the result of a longer duration in Fontan-type circulation.

Although the effect of gravity was investigated by studying our subjects in the upright position with the tilt table, we did not examine the influence of chronic exposure to hydrostatic forces. Standing upright for a prolonged period may cause additional effects on inferior venous return; however, this was beyond the scope of the present study.

The use of Doppler ultrasonography to evaluate flow rate has been known to be prone to error whenever the angle of insonation between the ultrasound beam and blood flow axis is not 0°.20 This error is a cosine function; therefore, a non-0° angle will always underestimate the actual flow rate. In our subjects, despite all efforts to align the beam with the vessels, all had non-0° angles of incidence, and angle correction protocols were used. Instead of comparing absolute values of flow rates, we calculated the ratios of flow rates to evaluate the various effects, with each subject used as his or her own control. In this manner, the cosine terms cancel each other and the error is neutralized.

Conclusions
Respiration and gravity normally affect infradiaphragmatic venous flow dynamics. In patients with a well functioning Fontan circulation, these subtle influences can be profound and varied. Although HV flow, and thus inferior venous return, is markedly dependent on respiration in TCPC, APC has a poorer performance in the face of gravity and is associated with more hepatic venous regurgitation. Further studies are required to fully describe the potential impact of these unique venous hemodynamics on the ability of patients to respond to acute changes in respiratory mechanics and to assess the long-term effects of abnormal splanchnic venous return on hepatic and gastrointestinal function.

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References
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