SURGERY FOR CONGENITAL HEART DISEASE

SUBDIAPHRAGMATIC VENOUS HEMODYNAMICS IN THE FONTAN CIRCULATION

Tain-Yen Hsia, MD
Sachin Khambadkone, MD, MRCP
John E. Deanfield, FRCP
James F. N. Taylor, MD, FRCP
Francesco Migliavacca, PhD
Marc R. de Leval, MD, FRCS

Objective: We investigated the subdiaphragmatic venous physiology in patients subjected to the Fontan operation to understand some of the early and late problems of this circulation.

Methods: Flows were evaluated by Doppler ultrasonography in the subhepatic inferior vena cava, hepatic vein, and portal vein during respiratory monitoring and with a tilt table. Twenty control subjects (group A) and 56 patients who had the Fontan operation, 27 in functional class I (group B) and 29 in class III or IV (group C), were studied. Inspiratory/expiratory flow ratio was calculated to reflect respiratory effects, and upright/supine flow ratio was calculated to assess gravity effects. Inferior vena caval, hepatic venous, and wedged hepatic venous pressures were measured during catheterization in 21 control subjects and 25 Fontan patients. The difference between wedged and hepatic venous pressures represents the transhepatic venous pressure gradient.

Results: Fontan hepatic venous flow depended more on inspiration than control, but without difference between groups B and C (inspiratory/expiratory flow ratios: 1.7, 2.9, and 2.9, respectively; $P < .02$). Normal portal venous flow was higher in expiration; this effect was lost in group B and reversed in group C (inspiratory/expiratory flow ratios: 0.8, 1.0, and 1.3; $P < .0005$). Gravity reduced portal venous flow in groups A and B, but progression to functional class III or IV (group C) exacerbated this effect (upright/supine flow ratios: 0.8, 0.7, and 0.5; $P < .01$). Inferior vena caval, hepatic venous, and wedged hepatic venous pressures (in millimeters of mercury) in the Fontan groups were all elevated compared with the control group (inferior vena cava, 14.4 ± 4.4 vs 5.9 ± 2.3 ; hepatic vein, 14.7 ± 4.5 vs 5.9 ± 1.9 ; wedged hepatic vein, 14.7 ± 4.0 vs 8.3 ± 2.6 ; $P < .0001$). However, transhepatic venous pressure gradient in the Fontan group was lower than in the control group (0.5 ± 0.5 vs 2.4 ± 2.0 ; $P < .001$). Univariate analysis of inferior vena caval pressure and transhepatic venous pressure gradient showed significant inverse correlation ($r = 0.6$, $P < .002$).

Conclusions: In patients who are in functionally poorer condition after the Fontan operation, portal venous flow loses normal expiratory augmentation and adverse gravity influence is enhanced. These suboptimal flow dynamics, coupled with higher splanchnic venous pressures and lower transhepatic

From the Great Ormond Street Hospital for Children, NHS Trust, London, United Kingdom.

Supported by the National Science Foundation, USA.

Read at the Eightieth Annual Meeting of The American Association for Thoracic Surgery, Toronto, Ontario, Canada, April 30–May 3, 2000.

Dr Hsia is the recipient of the 1999 National Science Foundation

International Post-doctoral Research Fellowship Award, grant No. INT-9802808.

J Thorac Cardiovasc Surg 2001;121:436-47

Copyright © 2001 by The American Association for Thoracic Surgery

0022-5223/2001 \$35.00 + 0 12/6/112527

doi:10.1067/mtc.2001.112527

venous pressure gradients, suggest that hepatic sinusoids are congested, acting as “open tubes.” Transhepatic gradient loss is incrementally worse with higher caval pressures. These observations may be responsible for late gastrointestinal problems in patients who have had the Fontan operation. (J Thorac Cardiovasc Surg 2001;121:436-47)

Despite marked improvements in both survival and early functional outcome in patients undergoing the Fontan procedure, it has become clear that functional state may decline with the development of complications during long-term follow-up.¹ Of particular interest has been the prevalence of hepatic function abnormalities and the debilitating consequences of protein-losing enteropathy (PLE).¹⁻³ Although the causes for these late complications are thought to be related to venous congestion of the hepatic-portal axis, the splanchnic venous hemodynamics in patients who have had the Fontan operation have not been studied adequately.⁴

The absence of a ventricular power source and placement of the pulmonary vascular resistance in series with the systemic resistance result in significant tension being placed on the systemic venous return.⁵ In addition to this stress, the subdiaphragmatic venous circulation is further affected by gravity, interactions with the diaphragm, and the interposition of the hepatic resistance between the splanchnic inflow and outflow.

In an earlier work, we characterized the differential influence of respiration and gravity in the hepatic vein (HV), portal vein (PV), and subhepatic inferior vena cava (IVC) between normal subjects and healthy Fontan patients.⁶ The purpose of this study was to examine the flow and pressure dynamics between patients who are in functionally good condition and those in poor condition after the operation to determine and postulate some of the mechanisms behind late attrition in the Fontan circulation.

Methods

Flow dynamics. Fifty-six patients were studied 1 to 21 years (mean 10 ± 4 years) after their Fontan operation. Twenty-seven (48%) were in self-reported New York Heart Association (NYHA) functional class I; none had clinical signs of congestive heart failure, arrhythmia, major pulmonary arteriovenous malformations, PLE, or other known complications of the Fontan circulation. Of these patients, 18 (67%) had total cavopulmonary connections and the rest atriopulmonary connections.

Twenty-nine patients were in self-reported NYHA functional class III or IV with significantly reduced tolerance to routine activities associated with cyanosis, dyspnea, or arrhythmia. Of these, 19 (66%) patients had total cavopul-

monary connections and the rest atriopulmonary connections. Two patients, both with atriopulmonary connections, were known to have PLE with hypoalbuminemia and elevated fecal α_1 -antitrypsin levels.

Twenty age- and sex-matched normal volunteers were studied as controls. All subjects underwent HV, PV, and IVC Doppler ultrasonographic interrogation under simultaneous dynamic respiratory and electrocardiographic monitoring. A tilt table was used to allow measurements in the supine and upright positions (85° - 90° from horizontal plane).

Doppler ultrasound recordings. Measurements were made with an Acuson 128XP system (Acuson Corporation, Mountain View, Calif) using 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 upright position. At least 5 minutes were allowed before the upright examination for the subject to adjust to the postural change. A minimum of 3 full respiratory cycles was 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 Doppler beam. Because error produced by a non-zero angle is a cosine function, underestimation of the velocities was corrected with division by cosine of the angle.^{7,8}

Recordings were made in the left or middle HV (approximately 1 cm distal to the junction with the IVC) and the subhepatic IVC (1-2 cm distal to the junction with the 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.⁹ 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 to the identical location in the supine position as possible. Each Doppler flow signal was recorded on videotape and hard copy for off-line analysis.

Flow rate calculations. Mean flow rate (Q) was computed by the division of volume of blood (V) moving through the vessel by the time interval ($\Delta T = T_2 - T_1$) needed for this volume to cross.

$$Q = \frac{V}{\Delta T} \quad (1)$$

A rigorous treatment of the volume/flow relationship required the continuous computation of the product of mean instantaneous velocity ($v[t]$) and cross-sectional area ($A[t]$) or an integration

Fig 1. A pulsed wave Doppler ultrasound flow recording from the subhepatic inferior vena cava of a normal subject. Electrocardiogram is the *upper line*. The low-frequency tracing shows spontaneous respiration, with upward (*up arrows*) and downward (*down arrow*) deflections indicating the onset of inspiration and expiration, respectively. Flow below the zero reference line is antegrade toward the heart; above zero flow is retrograde. Note reversal of flow with atrial contractions (*oblique arrows*).

$$V = \int_{t_1}^{t_2} v(t) A(t) dt, \quad (2)$$

over ΔT . We assumed that changes in $A(t)$ within one 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 as

$$Q = \frac{A \int_{t_1}^{t_2} v(t) dt}{T\Delta}, \quad (3)$$

where A equaled $\pi(d/2)^2$, the cross-sectional diameter of the vein, and $\int_{t_1}^{t_2} v(t) dt$ the velocity-time integral (VTI) determined from the Doppler recording taken over time interval ΔT .

Respiratory effect. As demonstrated in Fig 1, with dynamic respiratory monitoring, the Doppler signal could be evaluated during inspiration, during expiration, or throughout a complete respiratory cycle.

When ΔT was the time interval for inspiration and antegrade VTI was evaluated during this period, Q represented the mean antegrade flow rate during the inspiratory phase of the respiratory cycle (Q_{in}). 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}/Q_{ex} in the supine position. Mean flow rate during inspiration is higher than during expiration when this ratio is more than 1, and vice versa.

Gravity effect. The effect of gravity on net flow rate was evaluated. Net flow rate (Q_{net}) was defined as the absolute total flow during a complete respiratory cycle obtained by subtracting retrograde VTI from antegrade VTI. The effect of gravity on Q_{net} was represented as the ratio of Q_{net} in the

upright position over that in the supine position. A ratio of less than 1 implies a reduced Q_{net} in the upright position.

Pressures. Twenty-five patients who underwent cardiac catheterization for various indications were studied 1 to 19 years (mean 6 ± 5 years) after the Fontan operation. Eight of these patients (32%) were in self-reported New York Heart Association functional class I or II and the rest in class III or IV. Also, 12 (48%) had IVC pressures (IVCP) more than or equal to 15 mm Hg. In terms of type of Fontan connection, 15 (60%) had total cavopulmonary connections and the rest atriopulmonary connections. Three patients had PLE. None had hepatic cirrhosis.

Catheterization data of 21 patients with normal right-sided cardiopulmonary anatomy were used as controls: 16 patients with a hemodynamically trivial patent ductus arteriosus underwent elective device closure; 2 underwent routine review after heart transplantation; 2 with mild aortic stenosis were assessed for balloon dilatation; and 1 had a coronary angiogram for Kawasaki disease. In all subjects, the IVC, HV, and wedged HV pressures were measured in the supine position and during respiratory apnea to minimize effects of positive-pressure ventilation.

Among the Fontan patients, 22 underwent both cardiac catheterization and flow measurements during the same hospital admission with Doppler measurements performed initially. Of these, 10 (45%) had IVCP more than or equal to 15 mm Hg ($IVCP \geq 15$). Data from these patients were compared with those with IVCP less than 15 mm Hg ($IVCP < 15$). Within the $IVCP < 15$ group, 4 patients (33%) were in functional class I or II, whereas there were 3 (30%) in the $IVCP \geq 15$ group.

During elective cardiac catheterization under general anesthesia, pressures in the subdiaphragmatic veins were measured. These were recorded through a saline filled, balloon-tipped catheter (Kimal, Uxbridge, England) connected to a pressure transducer that was zeroed against atmospheric pressure and level with the mid chest. Measurements were made in the IVC, in one of the HVs, and in the "wedged" position within the HV by inflating the balloon. The wedged HV pressure correlates closely with directly measured PV pressure.¹⁰ Mean pressure values were obtained during respiratory apnea. In patients with atriopulmonary connections, because pressure tracing in the IVC and HV mirrors that in the right atrium, mean pressures were calculated by averaging the "a" wave and "v" wave. Difference between the mean wedged HV and free HV pressures was the transhepatic venous pressure gradient (TVPG).

Room air oxygen saturation was obtained from all Fontan patients with a pulse oximeter (Datex-Ohmeda, Madison, Wis). The study protocols were approved by the hospital research ethics committee and informed consents were obtained for all subjects.

Statistical analysis. All data were expressed as mean $\pm$ standard deviation. For both flow and pressure data, differences among various groups were assessed by 1-way analysis of variance with Neuman-Keuls multiple comparison test to evaluate all intergroup significance.

Table I. Patient group characteristics

	Flow		Pressure	
	Class I	Class III/IV	Class I/II	Class III/IV
Age (y)	17 ± 6	13 ± 5	17 ± 6	14 ± 6
M/F ratio	20:7	22:7	4:4	11:6
Time since operation (y)	11 ± 4	8 ± 4	8 ± 6	7 ± 5
Diagnosis				
UVH, right	3	9	1	4
UVH, left	24	20	7	13
Type of connection				
TCPC/APC	18:9	19:10	6:2	10:7

M, Male; F, female; UVH, right, morphologically right univentricular heart; UVH, left, morphologically left univentricular heart; APC, atriopulmonary connection; TCPC, total cavopulmonary connection.

Table II. Results of flow rate calculations

	Respiratory effect (<i>Q_{in}/Q_{ex}</i>)	Gravity effect (<i>Q_{net}</i>): up/sup		Respiratory effect (<i>Q_{in}/Q_{ex}</i>)	Gravity effect (<i>Q_{net}</i>): up/sup
IVC					
Control	1.2 ± 0.3	1.0 ± 0.5	Control	1.2 ± 0.3	1.0 ± 0.5
Class I	1.6 ± 1.4	0.7 ± 0.3*	IVCP<15	1.5 ± 0.3	0.7 ± 0.2*
Class III/IV	1.5 ± 0.6	0.7 ± 0.2*	IVCP≥15	1.5 ± 0.6	0.8 ± 0.1*
<i>P</i> value	.4	<.02	<i>P</i> value	.2	<.05
HV					
Control	1.7 ± 0.5	0.8 ± 0.3	Control	1.7 ± 0.5	0.8 ± 0.3
Class I	2.9 ± 1.7*	0.6 ± 0.3*	IVCP<15	2.1 ± 0.7*	0.8 ± 0.3
Class III/IV	2.9 ± 1.9*	0.6 ± 0.4†	IVCP≥15	2.0 ± 0.3*	0.5 ± 0.3*‡
<i>P</i> value	<.02	.2	<i>P</i> value	<.04	<.05
PV					
Control	0.8 ± 0.3	0.8 ± 0.5	Control	0.8 ± 0.3	0.8 ± 0.5
Class I	1.0 ± 0.3*	0.7 ± 0.3	IVCP<15	1.0 ± 0.3*	0.6 ± 0.2
Class III/IV	1.3 ± 0.5*‡	0.5 ± 0.2*‡	IVCP≥15	1.4 ± 0.5*‡	0.6 ± 0.2
<i>P</i> value	<.0005	<.01	<i>P</i> value	<.0008	.4

P values by analysis of variance. Postanalysis by Neuman-Keuls test: **P* < .05 versus control, †*P* = .09 versus control, and ‡*P* < .05 versus class I or IVCP<15. *Q_{in}*, Inspiratory flow rate; *Q_{ex}*, expiratory flow rate; *Q_{net}*, net flow rate; sup, supine position; up, upright position; IVC, subhepatic inferior vena cava; HV, hepatic vein; PV, portal vein; IVCP<15, inferior vena caval pressure < 15 mm Hg; IVCP≥15, inferior vena caval pressure ≥ 15 mm Hg.

Results

Study group characteristics. Patient characteristics, including diagnosis at time of surgery, are listed in Table I. There were no differences in age, underlying diagnosis, and type of Fontan connection between functionally well and functionally poor groups. In the flow study, postoperative follow-up was longer in the patients in NYHA class I (*P* < .003) who also had higher room air oxygen saturation than those in class III/IV (92% ± 4% vs 87% ± 6%, respectively; *P* = .001). The control group had a mean age of 14 ± 5 years (*P* > .05 compared with both patient groups).

For the pressure study, patients in class I/II had the same length of follow-up as those in class III/IV, and oxygen saturation was higher in the class I/II than in the class III/IV group (93% ± 4% vs 88% ± 5%, respec-

tively; *P* < .05). Control subjects were younger (6 ± 5 years; *P* < .05) than either patient group. Between the IVCP<15 and IVCP≥15 groups, there were no differences in age (13 ± 6 vs 15 ± 6 years, respectively; *P* > .05) or time since Fontan operation (6 ± 5 vs 8 ± 5 years, respectively; *P* > .05).

Flow rate calculations. The results of the Doppler flow rate calculations are summarized in Table II. Because the proportions of patients with total cavopulmonary connections and atriopulmonary connections in class I and class III/IV are similar, and the objective is to evaluate differences between functional groups, data from various types of Fontan connections are presented together.

Respiratory effect. Forward flow was consistently higher during inspiration than expiration in the IVC,

Fig 2. Pulsed Doppler ultrasound recording with simultaneous respiratory monitoring from the portal vein in a control subject, a Fontan patient in functional class I, and a Fontan patient in functional class III. Owing to its tortuosity and anatomic variation, portal vein forward flow is recorded as a positive signal. Note the reduced velocities in control subjects but increased velocities in Fontan patients during inspiration.

but there was no difference in this inspiratory augmentation among the 3 groups.

HV flow in the Fontan groups was, however, more dependent on inspiration than in the control group; neither progression to class III/IV nor higher IVCP enhanced or reduced this effect.

Control PV flow was higher during expiration (Fig 2). This expiratory augmentation was absent in all Fontan patients. Whereas in Fontan patients in NYHA class I the inspiratory and expiratory flow rates were nearly the same ($Q_{in}/Q_{ex} = 1.0$), PV flow was the reverse of normal with higher flow during inspiration in those in class III/IV ($Q_{in}/Q_{ex} = 1.3$). Similarly, accentuation of portal flow during inspiration was significantly more pronounced in $IVCP \geq 15$ than $IVCP < 15$ patients.

Gravity effect. Although gravity did not have a significant influence on control IVC flow, it resulted in a similar 30% reduction in Fontan patients in both NYHA class I and class III/IV. There was no difference between the 2 IVCP groups.

Gravity reduced net flow in the control HV by 20%, but this reduction was more severe in both functional class groups, who lost an equivalent 40% of flow in the upright position. Comparing the 2 IVCP groups, however, whereas the lower-pressure group's flow reduction was the same (20%) as control, the decrement was significantly amplified (50%) in the higher-pressure group.

In the PV, gravity lowered flow equally between controls and Fontan patients in NYHA class I, but progression to class III/IV resulted in a significant further decline with an approximately 50% reduction

Fig 3. Pulsed Doppler ultrasound recordings with simultaneous respiratory monitoring from the portal vein in a Fontan patient in functional class III in the supine and upright positions. Scales of flow velocities are aligned to show the decreased flow velocities in the upright position. *m/s*, Meter per second. Again, note higher velocities are associated with inspiration.

Table III. Results of pressure measurements

	IVC	HV	Wegged HV	TVPG
Control	5.9 ± 2.3	5.9 ± 1.9	8.3 ± 2.6	2.4 ± 2.0
Class I/II	12.4 ± 2.7*	12.6 ± 2.5*	13.2 ± 2.4*	0.7 ± 0.3*
Class III/IV	16.1 ± 5.2*	16.3 ± 5.4*	16.0 ± 4.9*	0.4 ± 0.4*
<i>P</i> value	<.000001	<.0000001	<.000001	<.0004
Control	5.9 ± 2.3	5.9 ± 1.9	8.3 ± 2.6	2.4 ± 2.0
IVCP<15	11.4 ± 2.1*	11.6 ± 1.8*	12.2 ± 1.9*	0.6 ± 0.3*
IVCP≥15	18.6 ± 3.7*‡	18.8 ± 3.8*‡	19.0 ± 3.6*‡	0.2 ± 0.3*‡
<i>P</i> value	<.0000001	<.000001	<.0000001	<.0003

P values by analysis of variance. Postanalysis by Neuman-Keuls test: **P* < .05 versus control and ‡*P* < .05 versus IVCP<15. All pressures in millimeters of mercury. IVC, Subhepatic inferior vena cava; HV, hepatic vein; IVCP, inferior vena caval pressure; TVPG, transhepatic venous pressure gradient.

(Fig 3). No difference was observed between the 2 IVCP groups.

Pressure measurements. Results of the various pressure measurements are listed in Table III. Mean pressures in the IVC, HV, and wedged HV were significantly elevated in all Fontan groups compared with controls. Despite Fontan patients with class III/IV disease appearing to have higher systemic venous pressures than those with class I/II disease, the difference did not reach statistical significance (IVC, *P* = .075; HV, *P* = .07).

TVPG in all Fontan patients showed a significant reduction compared with controls. Fig 4 demonstrates the elevated wedged HV and free HV pressures in a Fontan patient but decreased TVPG compared with a control subject. The gradient in patients with class III/IV function appeared to be the smallest, with difference from patients with class I/II disease approaching

statistical significance (*P* = .1). However, TVPG in IVCP≥15 patients was significantly less than in the IVCP<15 group. When each patient's IVCP was plotted against the corresponding pressure gradient, univariate analysis revealed a significant inverse correlation between IVCP and TVPG (*r* = .6, *P* = .002) (Fig 5).

Discussion

Introduction of the Fontan operation 30 years ago revolutionized the treatment of complex congenital heart defects in which biventricular repair was not possible.⁵ Despite the multitude of modifications in the surgical procedure since, major changes in the systemic venous return have been a persistent consequence. Many late attrition problems associated with the Fontan circulation, such as hepatic dysfunction and PLE, are believed to be the result of these unique physiologic alterations.^{11,12} Despite this, few studies have analyzed the

Fig 4. Analog recordings of the wedged (*WHV*) and free hepatic venous (*HV*) pressures in a control subject and a Fontan patient in functional class III. Note the normal transhepatic venous pressure gradient is nearly abolished in the Fontan patient. Also, the *HV* pressures are less pulsatile than normal in this patient who had a total cavopulmonary connection.

effects of the Fontan circulatory physiology and its subsequent deterioration on the subdiaphragmatic venous territory. This region is composed of 2 dynamically distinct circulations: the splanchnic, which drains the gastrointestinal tract through added resistance of the liver, and the systemic, which channels blood from the lower extremities and kidneys. In our previous study,⁶ we described a transformation of respiratory and hydrostatic influences on IVC, HV, and PV flow in the Fontan patients. In this article, our investigation revealed further profound but variable differences in both the flow and pressure dynamics in these venous territories between patients in functionally good condition and those in functionally poor condition.

Because the perceived functionality in the Fontan population correlates poorly with objective measures of cardiovascular performance,¹³ we also examined the flow and pressure differences between Fontan patients with low and high systemic venous pressures. Mean right atrial pressure below 15 mm Hg is thought to be a "good" value in the Fontan circulation.¹¹ Chronic systemic venous hypertension is speculated to contribute to Fontan attrition, and increased pressure levels are associated with decreased functional performance and survival, as well as other complications.^{2,14} Of note, in

our study population, there were patients with reportedly good functional status but high caval pressures and vice versa. In addition, the length of postoperative follow-up was not different between the 2 pressure groups; thus, chronicity in a Fontan state does not seem to predict higher systemic venous pressure.

Instead of using maximal velocities or pulsatility ratios as indicators for flow dynamics in the subdiaphragmatic venous circulation,^{15,16} we calculated volumetric flow rate from Doppler recordings as a measure of flow. Because the flow profiles in these veins are not symmetrically parabolic, instantaneous maximal velocities cannot account for the continuous changes of flow throughout a cardiac or respiratory cycle. Similarly, degree of pulsatility does not yield dynamics pressure and flow information. In this study, volumetric flow rate is obtained by evaluating velocities continuously with respect to time and assuming a constant cross-sectional area in all 3 veins throughout a respiratory cycle. Both the main HV and the IVC just distal to it are transhepatic in location and have been shown to remain in rigid configuration during all phases of respiration.¹⁷ Furthermore, M-mode images of the PV diameter averaged over several cardiac cycles have produced agreement of ± 0.5 mm with the instant-

neous diameter measured from B-mode imaging.⁸ Separate vein dimension measurements were obtained in supine and upright positions because there is no evidence for invariability with orthostasis.

Flow dynamics

Respiration. Respiratory modulation of venous return, or so-called cardiopulmonary interaction, has been known to occur when inspiratory negative intrathoracic pressure provides additional energy for forward flow. Comparison of this inspiratory augmentation of total venous return between normal subjects and Fontan patients has not been performed.^{18,19} We have previously demonstrated in functionally well Fontan patients that cardiopulmonary interaction is amplified in the splanchnic circulation with minimal caval contribution. Our data here confirm this, showing that HV flow is mostly driven during inspiration. Thus, Fontan patients are likely to be more susceptible to disturbances to the respiratory mechanics such as diaphragm paralysis or significant pleural effusion, which need to be dealt with early. Interestingly, poor functional state or higher pressures required neither higher nor diminished respiratory drive for forward flow in the IVC or HV.

Blood flow in the normal PV is almost continuous except for a decrease during inspiration when the descending diaphragm transiently compresses the compliant and easily collapsible portal venules and hepatic sinusoids.²⁰ This is the site of resistance in the PV-HV axis.²¹ In addition to maintaining a TVPG, this compliant resistance provides a passive mechanism for portal pressure autoregulation and for control of splanchnic capacitance response to changes in either central venous pressures or blood volume shifts.^{22,23} The absence of this inspiratory reduction in Fontan patients suggests a decreased hepatic compressibility and reserve, where congested sinusoids act as fluid-filled columns that are always patent, allowing forward portal flow to occur during the same phase of respiration as its outflow, the HV. Sinusoidal dilatation and distention are widely known characteristics of hepatic congestion in patients with severe right-sided heart failure.²⁴ When systemic venous hypertension becomes worse, as in the $IVCP \geq 15$ group, more sinusoids become dilated, resulting in even higher PV flow during inspiration. Similarly, compared with class I, enhanced PV flow during inspiration in class III/IV may reflect a higher degree of sinusoidal congestion in the patients in functionally poorer condition.

Gravity. Hydrostatic forces are known to constantly affect the intravascular pressures within the abdominal venous system.²² Despite this, hydraulic changes caused by gravity are minimized in the systemic venous

Fig 5. Transhepatic venous pressure gradient (TVPG) and inferior vena cava (IVC) pressure in 25 Fontan patients. There was a significant inverse correlation between TVPG and IVC pressure.

circulation in human beings because of ventricular compensation,²² as is illustrated by our control IVC data. In the Fontan patients, however, presumably because of the absence of a ventricular input, gravity had a more significant influence on IVC flow.

Unlike the systemic blood flow, splanchnic venous blood flow has been found to decrease significantly in human beings during orthostasis.^{22,25} This is also confirmed by our results, which showed that 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 this is a vulnerable venous territory to hemodynamic stress. Indeed, the splanchnic/hepatic circulation, with its low mean transmural pressure and high capacitance, is subject to greater modification by external physical forces than almost any other regional circulation in the mammalian body.²⁶

Compared with the normal physiology, the effects of gravity on splanchnic circulation in Fontan patients are variable: (1) HV flow reduction is amplified in all Fontan groups except those with low caval pressures and (2) PV flow decrement is more severe in all Fontan patients except those in good functional condition. In other words, in the face of hydrostatic influences, higher systemic venous pressures result in poorer splanchnic outflow, whereas poorer functional status correlates with worse portal drainage. During orthostasis, normal splanchnic circulation autoregulates against increased outflow resistance by sustained vasoconstriction.²² Our data suggest that this mechanism is likely maintained in the HV when systemic venous pressure is low, and it is preserved in the PV when patients are functionally

well. However, in a failing Fontan circulation or one with high caval pressure, autoregulatory compensation appears to be overwhelmed, resulting in further decreased splanchnic flow and increased venous pooling. This poorer splanchnic flow dynamic may explain why so many of the late attritional complications are gastrointestinal in origin, such as ascites and PLE, both of which have been linked with splanchnic venous congestion.^{27,28}

Pressure dynamics. To date, no study has evaluated the occurrence or extent of portal hypertension in Fontan patients. Normally, portal pressure ranges from 7 to 12 mm Hg and the pressure gradient between the PVs and HVs (TVPG) ranges from 1 to 4 mm Hg.¹⁰ Our control data agree closely with these values. Pressures above these limits classically define the presence of portal hypertension and severity of cirrhosis.

Fontan patients evaluated in this study have central venous, hepatic venous, and portal hypertension. Elevation of the central venous pressures in the Fontan circulation is a recognized inevitable consequence, and transmission of the caval and hepatic venous pressure to the portal vein is also well described.²⁶ Surprisingly, the normal gradient between venous inflow and outflow through the liver is abolished in Fontan patients in whom portal pressure mirrors the hepatic and caval pressures. So far as we know, diminished transhepatic gradient has not previously been linked with portal hypertension in human beings. Normally, the intrahepatic vascular resistance at the sinusoidal level initially buffers the portal pressures from small changes in caval pressures, allowing only partial transmission of the elevated pressure.²³ However, as caval pressures continue to increase above the hepatic transmural pressure, the sinusoids are dilated and recruited to become an open tube system to allow synchronization of PV with HV flow, as well as pressure equalization.^{26,29,30} In dogs, serial elevations of the IVC pressure resulted in progressive increases in portal pressure, decreases in hepatic blood flow, and elimination of TVPG.³¹ Furthermore, in patients with congestive heart failure and high right atrial pressures, TVPG is also reduced.³² Nearly equal venous inflow and outflow pressures increase portal blood transit time through the liver, which together with enlarged hepatic blood volume due to higher outflow resistance results in congestion of the entire splanchnic macrocirculation and microcirculation.^{32,33} Because the PV and HV are in direct pressure and flow communication, it can be further speculated that in an atriopulmonary Fontan circulation, the observed HV regurgitation produced by atrial systole will place further stresses on the liver and gastrointestinal organs.^{16,34}

Although our data suggest that patients in functionally poorer condition have higher venous pressures and an even lower TVPG, progressively higher caval pressures significantly correlated with serially lower pressure gradients (Fig 5). Therefore, elevations of the systemic venous pressure lead to more hepatic congestion and portal hypertension, but deterioration of the Fontan circulation may not always predict transhepatic pressure equilibration.

Hepatic dysfunction and PLE. Hepatic sinusoidal congestion/dilatation and subsequent cellular damage resulting from pressure effects^{35,36} have long been recognized as consequences of HV outflow obstruction, such as Budd-Chiari syndrome or chronic elevation of systemic venous pressures in congestive heart failure. Although acute congestion of the liver may lead to enzymatic dysfunction, chronic unrelieved sinusoidal congestion can produce diffuse irreversible parenchymal necrosis and fibrosis, or the so-called "cardiac cirrhosis."^{22,27,37} This may explain the reported high incidence of hepatic dysfunction during late follow-up,^{3,12} significant correlation between raised systemic venous pressure with high aspartate transaminase levels,³⁸ and observations, within our institution and others,³⁹ of liver cirrhosis in the Fontan patient whose condition is deteriorating.

In addition to hepatic congestion, elevation of HV outflow pressure disturbs the balance of Starling forces governing passage of fluid across capillary walls and increases the trans-sinusoidal filtration of protein-rich hepatic fluids into the interstitium.^{27,30} Because the hepatic sinusoids are highly permeable to proteins,^{26,33} even slight elevation in hepatic vascular pressure will lead to excessively high lymphatic filtration through the thoracic duct.^{29,40} When impedance to systemic lymphatic outflow increases, as in the Fontan circulation or congestive heart failure, lymphatic flow can reverse, finding a least-resistance path into the peritoneal cavity forming ascites,^{26,30,41} or spill protein-rich lymph into the gut lumen.²⁷ PLE has been associated with other conditions in which splanchnic blood flow is impeded, such as other congenital heart diseases with high venous pressures and Budd-Chiari syndrome.^{38,42-45} This hypothesis of PLE pathogenesis is further supported by direct correlation between increasing systemic venous pressures and fecal α_1 -antitrypsin levels in late survivors of the Fontan operation.³⁸ Normal plasma protein levels can initially be maintained by compensatory increase in hepatic protein synthesis and decrease in catabolism,²⁷ explaining why some Fontan patients with elevated fecal α_1 -antitrypsin have no clinical signs of PLE.³⁸ With further hepatic dysfunction resulting from

fibrotic changes and failure of the compensatory mechanisms to keep pace with the enteric protein loss, hypoproteinemia and its sequelae will result.²⁷

Limitations

In our previous study, we have characterized the differential physiology in patients with different types of Fontan connections. Because our focus here is on changes in flow and pressure dynamics between opposing functional status, variations between Fontan connections were not examined.

Although Doppler ultrasound allows measurements of hepatic and portal volume flows with satisfactory reliability and reproducibility,^{8,46} this method is known to be prone to error whenever the angle of insonation between the ultrasound beam and blood flow axis is not zero.⁷ In our subjects, despite efforts to align the beam with the vessels, all had non-zero angles of incidence and correction protocols were used. Yet, instead of comparing absolute values of flow rates, we calculated ratios of flow rates to evaluate the various effects using each subject as his or her own control. In this manner, the cosine terms cancel each other and the error is neutralized.

Conclusions

Usually subtle respiratory and gravitational influences on subdiaphragmatic venous flow dynamics are profound and varied in patients who have had the Fontan operation. Unlike the normal, PV flow is augmented during the same phase of respiration as HV flow. Although progression to a worse functional state or elevation of the systemic venous pressure did not result in higher dependence on inspiration or worse hydrostatic effects in the IVC, splanchnic flow performs more poorly in the face of gravity. As a result of elevated central venous pressure, Fontan patients have portal hypertension but a reduced transhepatic gradient. The elimination of the pressure gradient is progressively worse with higher caval pressures. These peculiar flow and pressure arrangements result in congestion of the entire PV-HV axis, including the sinusoids of the liver, which may adversely affect the long-term function of the liver and gastrointestinal tract. Pharmacologic, interventional, and surgical modalities that optimize systemic venous pressure to allow adequate pulmonary blood flow without compromising splanchnic venous return may prevent or reverse some of the late Fontan attrition complications such as PLE.

We thank the consultants and staff of the Cardiothoracic Unit at Great Ormond Street Hospital for Children for their support and cooperation.

Received for publication May 4, 2000; revisions requested Aug 9, 2000; revisions received Sept 20, 2000; accepted for publication Oct 24, 2000.

Address for reprints: Marc R. de Leval, MD, FRCS, Cardiothoracic Unit, Great Ormond Street Hospital for Children, NHS Trust, Great Ormond St, London WC1N 3JH, United Kingdom (E-mail: hsia@welchlink.welch.jhu.edu).

REFERENCES

1. Gentles TL, Gauvreau K, Mayer JE Jr, Fishberger SB, Burnett J, Colan SD, et al. Functional outcome after the Fontan operation: factors influencing late morbidity. *J Thorac Cardiovasc Surg* 1997;114:392-403; discussion 404-5.
2. Driscoll DJ, Offord KP, Feldt RH, Puga FJ, Danielson GK. Five-to fifteen-year follow-up after Fontan operation. *Circulation* 1992;85:469-96.
3. Girod DA, Fontan F, Deville C, Ottenkamp J, Choussat A. Long-term results after the Fontan operation for tricuspid atresia. *Circulation* 1987;75:605-10.
4. Hsia TY, Khambadkone S, Redington AN, de Leval MR. Instantaneous pressure-flow velocity relations of systemic venous return in patients with univentricular circulation [letter]. *Heart* 2000;83:583.
5. de Leval MR. The Fontan circulation: What have we learned? What to expect. *Pediatr Cardiol* 1998;19:316-20.
6. Hsia TY, Khambadkone S, Migliavacca F, Deanfield JE, de Leval M. Effects of respiration and gravity on infra-diaphragmatic venous flow in normal and Fontan patients [abstract]. *Circulation* 1999;100(18 Suppl I):I-671.
7. Huntsman LL, Stewart DK, Barnes SR, Franklin SB, Colocousis JS, Hessel EA. Noninvasive Doppler determination of cardiac output in man: clinical validation. *Circulation* 1983;67:593-602.
8. Carlisle KM, Halliwell M, Read AE, Wells PNT. Estimation of total hepatic blood flow by duplex ultrasound. *Gut* 1992;33:92-7.
9. Abu-Yousef MM. Normal and respiratory variations of the hepatic and portal venous duplex Doppler waveforms with simultaneous electrocardiographic correlation. *J Ultrasound Med* 1991;11:263-8.
10. Armonis A, Patch D, Burroughs A. Hepatic venous pressure measurement: An old test as a new prognostic marker in cirrhosis? *Hepatology* 1997;25:245-8.
11. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. *J Cardiovasc Surg* 1998;115:1063-73.
12. van Nieuwenhuizen RC, Peters M, Lubbers J, Trip MD, Tijssen JGP, Mulder BJM. Abnormalities in liver function and coagulation profile following the Fontan procedure. *Heart* 1999;82:40-6.
13. Cyran S. Commentary: Functionality after the Fontan procedure—perceived reality and the pondering prince. *J Thorac Cardiovasc Surg* 1997;114:404-5.
14. Geggel R. Update on the modified Fontan procedure. *Curr Opin Cardiol* 1997;12:51-62.
15. Kaulitz R, Bergman P, Luhman I, Paul T, Hausford G. Instantaneous pressure-flow velocity relations of systemic venous return in patients with univentricular circulation. *Heart* 1999;82:294-9.
16. Arisawa J, Morimoto S, Ikezoe J, Naitoh H, Yamagami H, Kozuka T, et al. Pulsed Doppler echocardiographic assessment of portal venous flow patterns in patients after the Fontan operation. *Br Heart J* 1993;69:41-6.

17. Moreno AH, Katz AI, Gold LD. Integrated approach to the study of the venous system with steps toward a detailed model of the dynamics of venous return to the right heart. *IEEE Trans Biomed Eng* 1969;16:308-23.
18. Redington AN, Penny D, Shinebourne EA. Pulmonary blood flow after total cavopulmonary shunt. *Br Heart J* 1991;65:213-317.
19. Rabinovici N, Navot N. The relationship between respiration, pressure and flow distribution in the vena cava and portal and hepatic veins. *Surg Gynecol Obstet* 1980;151:753-63.
20. Moreno A, Burchell AR. Respiratory regulation of splanchnic and systemic venous return in normal subjects and in patients with hepatic cirrhosis. *Surg Gynecol Obstet* 1982;154:257-67.
21. Wheatley AM, Zhang X. Intrahepatic modulation of portal pressure and its role in portal hypertension. *Digestion* 1998;59:424-8.
22. Bradley SE. The hepatic circulation. In: Dow P, editor. *Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts*. Vol 2. Washington DC: American Physiological Society; 1963. p. 1387-438.
23. Greenway CV, Lautt WW. Distensibility of hepatic venous resistance sites and consequences on portal pressure. *Am J Physiol* 1988;254:H452-8.
24. Morl M. On the diagnosis of the Budd-Chiari syndrome and cardiac cirrhosis. *Endoscopy* 1981;13:169-72.
25. Culbertson JW, Wilkins RW, Ingelfinger FJ, Bradley SE. The effect of the upright posture upon hepatic blood flow in normotensive and hypertensive subjects. *J Clin Invest* 1951;30:305-11.
26. Brauer RW, Holloway RJ, Leong GF. Changes in liver function and structure due to experimental passive congestion under controlled hepatic vein pressures. *Am J Physiol* 1959;197:681-92.
27. Granger DN, Barrowman JA. Gastrointestinal and liver edema. In: Staub NC, Taylor AE, editors. *Edema*. New York: Raven Press; 1984:615-56.
28. Dunbar BS, Elk JD, Drake RE, Laine GA. Intestinal lymphatic flow during portal venous hypertension. *Am J Physiol* 1989;257:G94-8.
29. Elk JR, Drake RE, Williams JP, Gabel JC, Laine GA. Lymphatic function in the liver after hepatic venous pressure elevation. *Am J Physiol* 1988;254:G748-52.
30. Laine GA, Hall JT, Laine SH, Granger HJ. Transsinusoidal fluid dynamics in canine liver during venous hypertension. *Circ Res* 1979;45:317-23.
31. Higashiyama H, Yamaguchi M, Kumada K, Sasaki H, Yamaguchi T, Ozawa K. Functional deterioration of the liver by elevated inferior vena cava pressure: a proposed upper safety limit of pressure for maintaining liver viability in dogs. *Intensive Care Med* 1994;20:124-9.
32. Rapaport E, Weisbart MH, Levine M. The splanchnic blood volume in congestive heart failure. *Circulation* 1958;18:581-7.
33. Donald DE. Splanchnic circulation. In: Geiger SR, editor. *Handbook of physiology: a critical, comprehensive presentation of physiological knowledge and concepts*. Vol 3. Bethesda: American Physiologic Society; 1983. p. 219-40.
34. Hsia TY, Khambadkone S, Redington AN, Miglivaacca F, Deanfield JE, de Leval M. Effects of respiration and gravity on infra-diaphragmatic venous flow in normal and Fontan patients. *Circulation* 2000;102 (Suppl):III-148-53.
35. Lautt W. Effects of acute, passive hepatic congestion on blood flow and oxygen uptake in the intact liver of the cat. *Circ Res* 1977;41:787-90.
36. Safran AP, Schaffner F. Chronic passive congestion of the liver in man. *Am J Pathol* 1966;50:447-63.
37. Zimmerman HM, Hillsman JA. Chronic passive congestion of the liver. *Arch Pathol* 1930;9:1154-63.
38. Thorne SA, Hooper J, Kemp M, Somerville J. Gastro-intestinal protein loss in late survivors of Fontan surgery and other congenital heart disease. *Eur Heart J* 1998;19:514-20.
39. Lemmer JH, Coran AG, Behrendt DM, Heidelberger KP, Stern AM. Liver fibrosis (cardiac cirrhosis) five years after modified Fontan operation for tricuspid atresia. *J Thorac Cardiovasc Surg* 1983;86:757-60.
40. Starling E. The Arris and Gale lectures on the physiological factors in the causation of dropsy. *Lancet* 1896;1:1267-70.
41. Laine GA, Allen SJ, Katz J, Gabel JC, Drake RE. Outflow pressure reduces lymph flow rate from various tissues. *Microvasc Res* 1987;33:135-42.
42. Chan FK, Sung JJ, Ma KM, Leung YL, Yeung VT. Protein losing enteropathy in congestive heart failure: diagnosis by means of a simple method. *Hepatogastroenterology* 1999;46:1816-8.
43. Sekine S, Abe T, Seki K, Goto Y, Shibata Y, Yamagishi I. Hypoproteinemia caused by tricuspid regurgitation: report of a case. *Surg Today* 1998;28:1287-9.
44. Tsuchiya M, Oshio C, Asakura H, Ishii H, Aoki I, Miyairi M. Budd-Chiari syndrome associated with protein-losing enteropathy. *Gastroenterology* 1978;75:114-7.
45. Muller C, Globits S, Glogar D, Klepetko W, Knoflach P. Constrictive pericarditis without typical haemodynamic changes as a cause of oedema formation due to protein-losing enteropathy. *Eur Heart J* 1991;12:1140-3.
46. Moriyasu F, Ban N, Nishida O, Nakamura T, Miyake T, Uchino H, et al. Clinical application of an ultrasonic duplex system in the quantitative measurement of portal blood flow. *J Clin Ultrasound* 1986;14:579-88.

Discussion

Dr Hikaru Matsuda (*Osaka, Japan*). We have been conducting a similar study for patients who have had the Fontan operation in terms of PV or HV Doppler flow characteristics. We have found that the patients with higher central venous pressure have less PV flow.

I have 2 questions. First, what is the difference between the failing Fontan and the nonfailing Fontan states in terms of hemodynamics? Probably the patients with a failing Fontan circulation have higher venous pressure, and these are very reasonable results. Second, have you looked at the differences regarding the types of cavopulmonary connection—the patients with atriopulmonary connection and total cavopulmonary connection? Our results indicate that pulsatile flow may worsen this effect for the hepatic circulation.

Dr Hsia. We have defined good and failing Fontan states by New York Heart Association functional class. In addition, of the Fontan patients studied, 22 underwent both cardiac catheterization and Doppler measurements. These patients' flow dynamics were further divided into 2 groups: those with IVCPs less than 15 mm Hg and those with IVCPs more than or equal to 15 mm Hg, because pressures below 15 mm Hg had been described to be "good" values in a Fontan circulation.¹ On the basis of this criterion, while good functional state did not always indicate "good" hemodynamics and vice

versa, flow dynamics data between those with low and high IVCs revealed similar differences to those demonstrated by functional state classification, that the splanchnic circulation is more affected in patients with higher IVCs.

Concerning your second question, flow dynamics variation between different modifications of the Fontan operation had been critically examined in an abstract presented earlier at the American Heart Association meeting and is being published in *Circulation*. In brief, we found that the subdiaphragmatic venous flow dynamics in Fontan patients after total cavopulmonary connection were superior to those with atriopul-

monary connection. Therefore, having addressed this issue satisfactorily, we were able to focus this paper specifically on the flow dynamics consequences of the deteriorating Fontan circulation.

REFERENCE

1. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study. *J Cardiovasc Surg* 1998;115:1063-73.

ON THE MOVE?

Send us your new address at least six weeks ahead

Don't miss a single issue of the journal! To ensure prompt service when you change your address, please photocopy and complete the form below.

Please send your change of address notification at least six weeks before your move to ensure continued service. We regret we cannot guarantee replacement of issues missed due to late notification.

JOURNAL TITLE:

Fill in the title of the journal here. _____

OLD ADDRESS:

Affix the address label from a recent issue of the journal here.

NEW ADDRESS:

Clearly print your new address here.

Name _____

Address _____

City/State/ZIP _____

COPY AND MAIL THIS FORM TO:

Mosby
Subscription Customer Service
6277 Sea Harbor Dr
Orlando, FL 32887

OR FAX TO:

407-363-9661

OR PHONE:

800-654-2452
Outside the U.S., call
407-345-4000