

Exercise Responses in Patients With Congenital Heart Disease After Fontan Repair: Patterns and Determinants of Performance

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After a Fontan repair for congenital heart disease, 42 patients underwent graded supine bicycle exercise tests at levels relevant to normal daily activities. Results were compared with those of 28 age-matched normal control subjects. At rest, the cardiac index, stroke index and systolic blood pressure were comparable in both groups, but increases with exercise were smaller in the patients with a Fontan circulation. The heart rate at rest was higher in the Fontan group, but this difference disappeared as soon as exercise started.

To determine whether there are limitations intrinsic to the Fontan circulation at these levels of exercise, the 10 best performers were compared with 10 age-matched control subjects; no differences were found in cardiac index, stroke

index, heart rate or blood pressure at any exercise level. Analysis of the determinants of cardiac output showed that at the other end of the spectrum poor performance after a Fontan operation did not result from inadequate levels of heart rate, but from an inability to increase or maintain stroke volume.

Multivariate analysis demonstrated that impairment of ventricular contractility, only when severe, predicted limited performance. There was no evidence of increased afterload, particularly in the poor performers. Therefore, ventricular filling, which is determined primarily by the pulmonary vascular bed, appears to be a major determinant of functional result after a Fontan repair.

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Increasing numbers of patients with a wide variety of complex congenital heart anomalies are offered a Fontan operation as definitive repair (1-7). The fundamental difference from normal is the absence of an adequate subpulmonary ventricle, so that the elevated systemic venous pressure is the driving force for transpulmonary flow. Several reports (8-10) have shown that maximal exercise performance in patients after the Fontan repair, although improved when compared with conditions before repair, is reduced when compared with that in normal subjects. However, clinicians are frequently impressed by the ability of most patients with a Fontan circulation to lead a normal life including moderate athletic activities (11).

This study set out to investigate responses of the Fontan

circulation to exercise levels relevant to daily activities. We aimed to find out whether normal performance could be achieved at these levels and which factors were responsible when exercise tolerance was limited.

Methods

Study patients. We studied 47 (23 male, 24 female) of 78 survivors of 104 Fontan procedures (early mortality 25%) performed at our institution between April 1975 and March 1988 who were living in England. Very early in the experience the strict selection criteria of Choussat and Fontan et al. (12) were used, but during the course of the study several modifications and exceptions were introduced. Of those patients not included in the study, 12 were considered too young to perform the exercise test (<5.5 years) and 3 had died during follow-up. Sixteen other patients declined investigation for nonmedical reasons; all are known to be alive and well (13 patients in functional class I, 3 patients in class II). No medical selection criteria were applied for inclusion in the study, but five patients were subsequently excluded from data analyses (see Results).

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Table 1. Surgery Details of the 42 Patients Who Underwent a Fontan Operation

	Diagnosis			Total
	Tricuspid Atresia	Pulmonary Atresia/IVS	Complex	
Total	23	8	11	42
Previous palliative surgery				
Blalock-Taussig	13 (8)	8 (4)	6 (2)	27 (14)
Waterston	3		1	4
Central shunt	1			1
PA band	2		3 (2)	5 (2)
Brock		1		1
Glenn	1			1
No surgery	3		1	4
Fontan connection				
RA-RV valved conduit	7			7
RA-PA				
Conduit	5	3	4	12
Direct	10	4	3	17
TCPC	1	1	4	6
Preoperative hemodynamics				
Mean PA pressure (mm Hg)	14.0 ± 4.3	[7.0-25.0]		
Qp/Qs	1.7 ± 0.7	[0.8-6.2]		
Arterial saturation (%)	84.5 ± 5.5%	[73%-95%]		
LVEDP (mm Hg)	9.4 ± 3.1	[4.0-18.0]		
Left PA/aorta (mm Hg)	1.14 ± 0.28	[0.64-1.7]		
Right PA/aorta (mm Hg)	1.12 ± 0.35	[0.53-2.1]		

IVS = intact ventricular septum; LVEDP = left ventricular end-diastolic pressure; PA = pulmonary artery; Qp/Qs = pulmonary to systemic flow ratio. RA-PA = right atrium to pulmonary artery; RA-RV = right atrium to right ventricle; TCPC = total cavopulmonary connection. Numbers in parentheses indicate a second similar procedure.

Clinical characteristics. In the group of the remaining 42 patients reported in this study, a wide variety of anomalies, surgical connections and surgical approaches are represented (Table 1). Almost all patients (38 of 42, 90%) had undergone palliative surgery before the Fontan operation either by banding of the pulmonary trunk, shunt procedures, a Brock procedure or a Glenn shunt.

Since the Fontan operation, one patient had a DDD pacemaker inserted for postoperative atrioventricular dissociation and two patients in the study group required additional surgery (one patient for reclosure of a tricuspid valve patch and one for conduit obstruction).

The clinical characteristics are summarized in Table 2. The mean age was 12.4 ± 5.2 years: the age at the Fontan operation was 8.0 ± 3.6 years with an interval from Fontan operation to exercise study of 4.5 ± 3.5 years. Eleven patients (26%) were receiving cardiac medication; 38 patients were in New York Heart Association (NYHA) class I, 3 in class II and 1 in class III. Postoperative hemodynamic data were available in 22 patients. Only five patients had a gradient across the surgical connection >2 mm Hg (range 2 to 6, mean 3.5). Mean pulmonary artery pressure was 12.5 ± 3.2 mm Hg (range 7 to 19). A mild right to left shunt was demonstrated in seven patients (four with a residual atrial septal defect, two

Table 2. Clinical Characteristics of the 42 Patients

	Mean	Range
BSA at study (m ²)	1.15 ± 0.25	0.73-1.67
Age at study (yr)	12.5 ± 5.2	5.6-28.1
Age at Fontan (yr)	8.0 ± 2.6	2.6-18.3
Fontan to study (yr)	4.5 ± 3.5	0.2-13.0
Postoperative hemodynamics (n = 22)		
Mean PA pressure (mm Hg)	12.5 ± 3.1	7-19
Mean RA-PA gradient (mm Hg)	0.8 ± 0.2	0-6
Aortic saturation (%)	94.8 ± 3.3	86-99
LVEDP	6.4 ± 3.2	3-14
Rest echocardiographic data		
LV dimension (% of normal)*	121 ± 17	94-166
Fractional shortening (%)	33 ± 6	16-48
Cardiothoracic index	0.51 ± 0.06	0.41-0.65
Drugs		
Digitalis	4	
Diuretics	6	
Antiarrhythmic agents	2	
Vasodilators	3	
Antiplatelet agents	3	
No drugs	31	

*Ref 13. BSA = body surface area; LV = left ventricular; other abbreviations as in Table 1.

with an unroofed coronary sinus and one with bridging veins from the coronary sinus to the left atrium).

Control group. The results of exercise testing in the patients were compared with those in 28 age-matched normal volunteers (12 male, 16 female) (age 12.9 ± 6.0 years) recruited from relatives of patients or staff or from other wards where they were hospitalized for minor noncardiac procedures. None of the control subjects was involved in competitive sports.

Exercise protocol. The study design was certified by the Ethical Committee at The Hospital for Sick Children. Informed consent was obtained from the patient or the parent where appropriate. All our data were obtained using a standard protocol in the same, quiet, darkened room.

Echocardiographic examination was performed with an Advanced Technology Laboratory Ultramark 8 ultrasonograph. All patients were evaluated for subaortic or aortic stenosis and aortic or mitral regurgitation; ventricular size and contractility were assessed and compared with normal left ventricular values where appropriate (13). The largest systolic aortic diameter was measured at the attachments of the aortic valve leaflets from inner edge to inner edge in the parasternal long axis to derive aortic cross-sectional area (14). Care was taken to use minimal gain settings.

The subject was then positioned supine in a calibrated electronically braked bicycle ergometer (Elema Shönander) positioned 46 cm above the examination table. Heart rate was monitored and continuous wave Doppler recordings of ascending aortic blood flow were obtained with a small dedicated 2.25 MHz nonimaging transducer from the suprasternal notch. Transaortic flow was identified by its loud, high-pitched audio signal and bright, well defined display. Only good quality studies with crisp spectral envelopes of the highest velocities were accepted for analysis. In five patients with transposed great vessels, a left parasternal position yielded the best tracings with highest velocities. The spectral envelopes of five consecutive cardiac cycles with the highest peak velocity were recorded and analyzed independently by two investigators. Percutaneous oxygen saturation (Ohmeda, Biox 3700, pulse oximeter), mean heart rate and systolic and diastolic blood pressure were recorded. Care was taken not to measure the blood pressure in an arm where a previous shunt might influence results.

Each subject then underwent 25 min of graded submaximal exercise. The work program consisted of five consecutive stages of 5 min each at 0.25, 0.50, 0.75, 1.0 and 1.5 W/kg. All variables were recorded by one investigator after 3 min of work in each consecutive stage, and again 2 and 5 min after the exercise.

Calculations. The aorta was assumed to be circular and its cross-sectional area was calculated accordingly. The velocity integral was measured using the Ultramark 8 software package. The stroke index was calculated as the product of the velocity integral and aortic cross-sectional

area divided by the body surface area. The cardiac index was calculated as the product of heart rate and stroke index.

Clinical data. All medical records were evaluated to determine biographic information, morphologic diagnosis, previous surgery, pre-Fontan hemodynamics and surgical technique. Furthermore, post-Fontan hemodynamics were also available in 22 patients. The parents and patients were questioned about current clinical status and medication.

Statistical analysis. Data were stored in a SIR (version 2) data base on an Ahmdahl mainframe computer and analyzed using SAS statistical packages (SAS Institute Incorporated). All data are expressed as mean values \pm SD. The interobserver variability of Doppler signal acquisition and processing at rest was $3.5 \pm 1.9\%$; the intraobserver variability of five resting values was $3.1 \pm 2.0\%$.

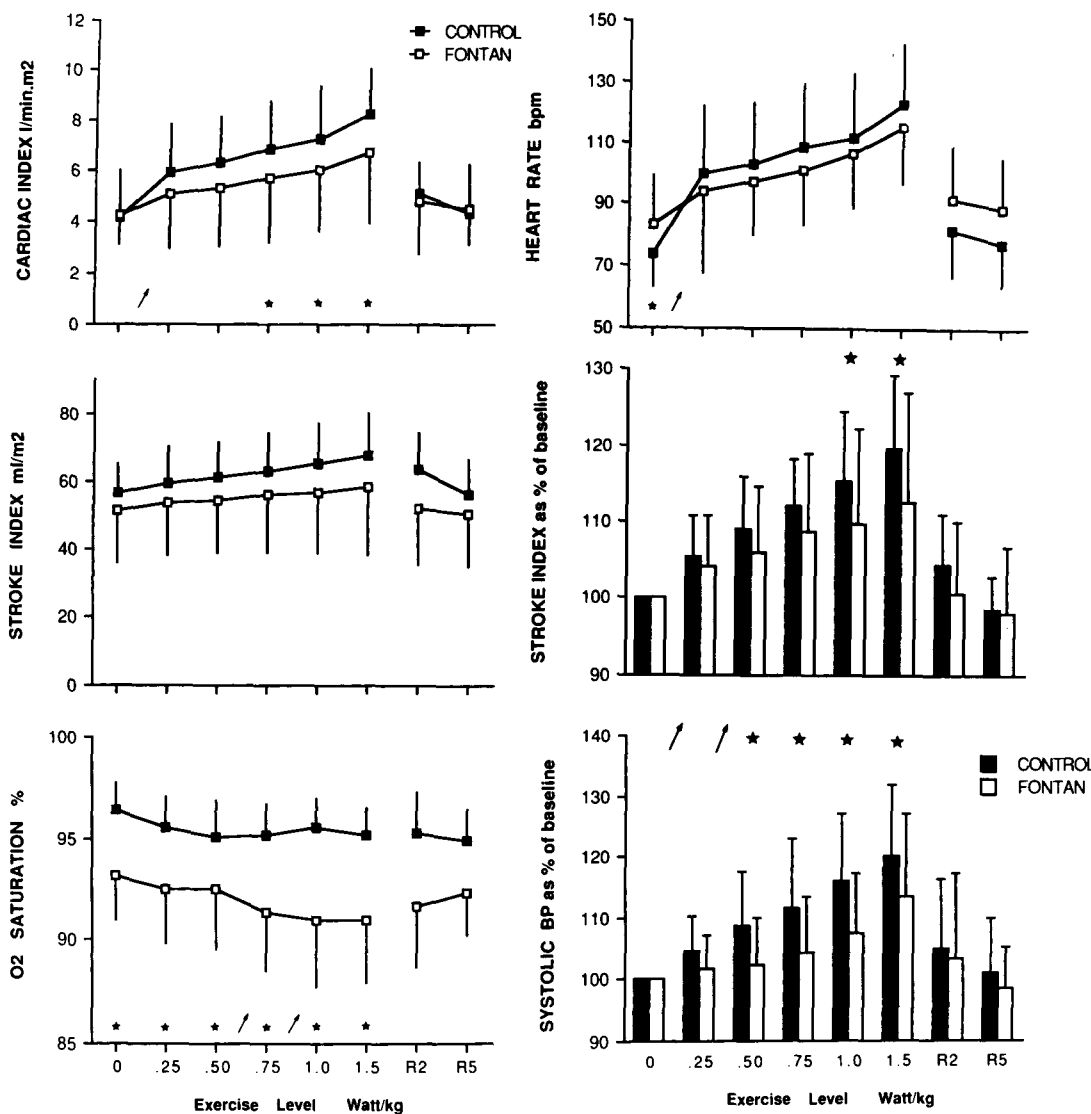
Data at rest and during exercise were analyzed by multivariate repeated measure analysis of variance; between-subjects effects (pooled data of patients versus control group [FG]) and within-subjects effects (level of activity [FL] and level by group interaction [FL*G]) are reported when of interest. Further, using the Repeated Profile statement of SAS, contrasts between adjacent levels were generated and interactions of the Fontan operation analyzed. A Student-Newman-Keuls multiple range test was performed on all main effect means; the level of significance was set at 0.05. Data from the recovery period were not included in the statistical analysis. *The heart rate for each exercise level* was also analyzed as a function of an age-predicted value derived from our controls.

In order to determine the best exercise performance obtained after a Fontan operation, we compared all variables of a subgroup of 10 patients who had the largest increase in cardiac output at the highest exercise level with a group of age-matched control subjects, eliminating patients with a valved right atrial-right ventricular connection who were analyzed separately. Similarly, the results of the 10 patients with the lowest increase in cardiac output were analyzed to try to determine patterns of heart rate and stroke volume associated with poor performance.

Univariate analysis was used to find factors that could predict limitation of increase in cardiac output and stroke volume at the highest exercise level for the whole group. Multiple regression techniques were employed to fit a model that predicted the change in cardiac output and stroke volume in patients using their morphologic, clinical, hemodynamic, surgical and rest echocardiographic variables.

Results

All of the 28 control subjects and all of the 47 study patients, except 1 patient who was developmentally delayed, finished the exercise protocol without complications. No subject was exhausted by the test and all reported that the effort required was similar to that involved in their normal



activities. At the highest work load of 1.5 W/kg, the normal control subjects had a heart rate of 124 ± 18 beats/min. The Doppler data of three patients with transposed great arteries were excluded: one because of poor quality tracings, two because of dynamic subaortic stenosis (at the highest exercise level Doppler velocities predicted a peak instantaneous gradient of 25 mm Hg and 39 mm Hg, respectively). All data from one patient were excluded because of atrial flutter.

Cardiac rhythm. All patients had sinus rhythm at rest and throughout the exercise study (except for one patient with chronic atrial flutter who was excluded from the study group). Frequent atrial ectopic beats were observed in two patients at rest, but disappeared as soon as exercise commenced. The one patient with a DDD pacemaker had sinus rhythm throughout the exercise study. No ventricular arrhythmia was observed in any patient.

Cardiac index (Fig. 1). The cardiac index at rest in the patients with a Fontan circulation was similar to that of the control subjects: $(4.3 \pm 1.6$ versus 4.2 ± 0.8 liters/min

Figure 1. Changes in cardiac index, heart rate, stroke index, oxygen saturation and blood pressure of the total Fontan group and age-matched control group. Mean values \pm SD. * $p < 0.05$ in multiple range test on main effect means. Arrows refer to the significance ($p < 0.05$) of contrasts between consecutive levels. R2 and R5 = values 2 and 5 min after exercise, respectively, which are not included in the statistical analysis. F values from repeated measures analysis of variance: cardiac index: FG = 3.4, $p = 0.06$; FL = 69, $p < 0.001$; FL*G = 5.1, $p < 0.001$. Heart rate: FG = 0.76, $p = 0.4$; FL = 94, $p < 0.001$; FL*G = 6.3, $p < 0.001$. Stroke index: FG = 2.6, $p = 0.1$; FL = 24, $p < 0.001$; FL*G = 1.6, $p = \text{NS}$. Arterial oxygen saturation: FG = 720, $p < 0.001$; FL = 7.9, $p < 0.001$; FL*G = 2.3, $p = 0.06$. Change in systolic blood pressure: FG = 9.6, $p < 0.01$; FL = 21, $p < 0.001$; FL*G = 2.8, $p < 0.03$. BP = blood pressure.

per m², $p = \text{NS}$). The response to exercise was divergent (FL*G = 5.1, $p < 0.001$) especially early in exercise ($F = 16$, $p < 0.001$). At the highest work load of 1.5 W/kg, the patients as a group had a lower cardiac index than that of the control group (6.7 ± 2.7 versus 8.2 ± 2.2 liters/min per m², $p <$

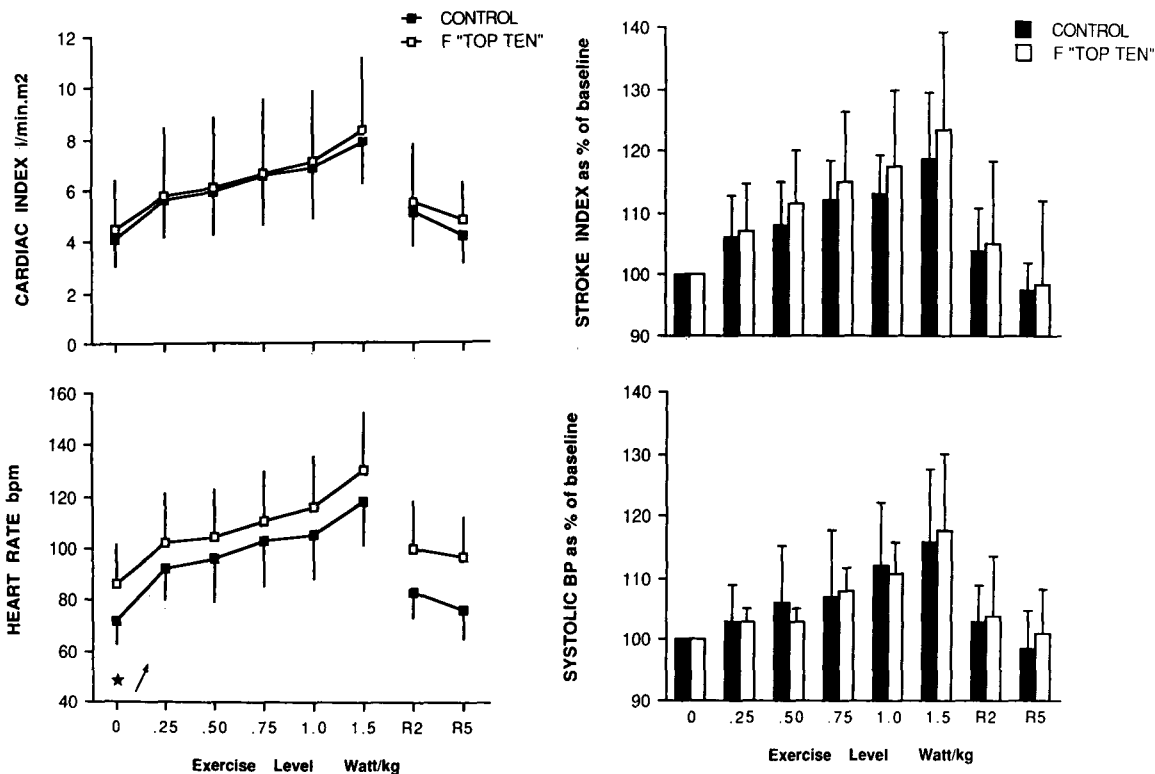


Figure 2. Hemodynamic responses of the "top ten" performers in the Fontan group compared with those of age-matched control subjects. Symbols as in Figure 1. F values: cardiac index: FG = 0.5, $p = \text{NS}$; FL = 56, $p < 0.001$; FL*G = 0.2, $p = \text{NS}$. Heart rate: FG = 1.4, $p = \text{NS}$; FL = 66, $p < 0.001$; FL*G = 0.9, $p = \text{NS}$. Change in stroke index: FG = 0.8, $p = \text{NS}$; FL = 15, $p < 0.001$; FL*G = 0.1, $p = \text{NS}$. Change in systolic blood pressure: FG = 1.1, $p = \text{NS}$; FL = 8.4, $p < 0.001$; FL*G = 1.7, $p = \text{NS}$.

0.05). The increments in cardiac index of 28 (68%) of the 41 patients were within the range of those achieved by our normal control subjects.

Stroke index. The stroke index was similar at rest in the patient and control groups (51.5 ± 18 versus 56.4 ± 10.3 ml/beat per m^2 , $p = \text{NS}$) and increased similarly with exercise in both groups (FL = 23, $p < 0.001$; FL*G = 1.6, $p = 0.18$). However, at the highest work load, patients with a Fontan circulation had a smaller increase in stroke index than did the control subjects ($p < 0.05$).

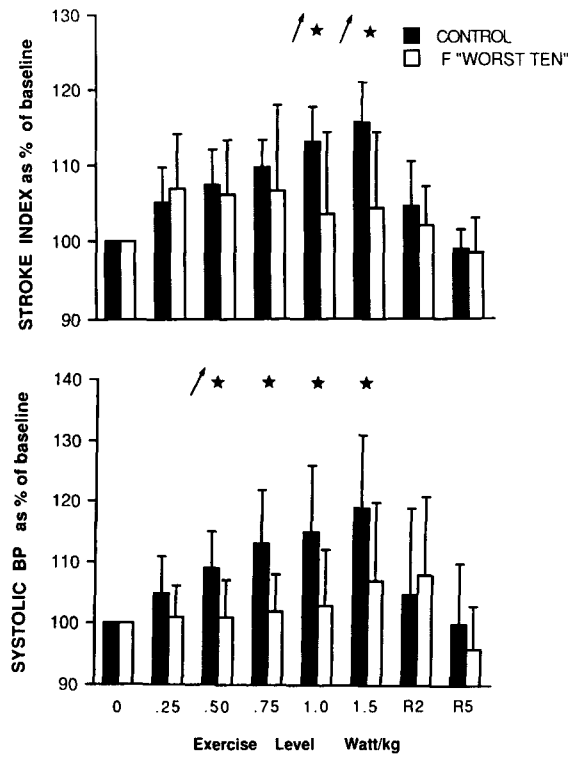
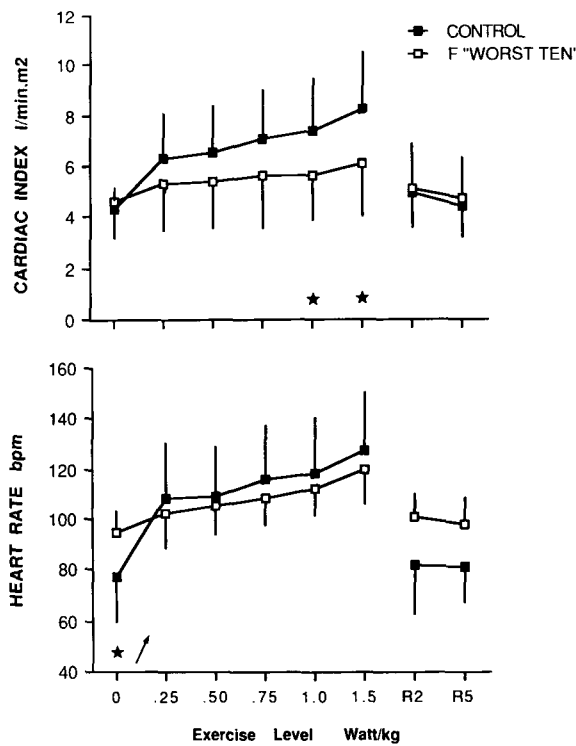
Heart rate. The rest heart rates in the Fontan and control groups were inversely related to age, the rate in the Fontan group being $12 \pm 14\%$ higher than that of the age-matched control group ($p < 0.01$). This difference disappeared once exercise began, and heart rates were comparable in both groups at all work levels.

Systolic blood pressure. The systolic blood pressure at rest was comparable in the two groups (109 ± 9 versus 109 ± 11 mm Hg, $p = \text{NS}$). With exercise, increases in systolic blood pressure were smaller in the Fontan group (FL = 22, $p < 0.001$; FG = 9.6, $p < 0.002$; FL*G = 2.9, $p < 0.03$).

Percutaneous oxygen saturation. At rest, the patient group had a lower oxygen saturation than that of the control group ($93.2 \pm 2.3\%$, range 88% to 98% versus $96.3 \pm 1.6\%$, range 94% to 99%; $p < 0.001$). This difference persisted throughout the exercise study, with a mild increase at the higher levels (FG = 720, $p < 0.001$; FL = 7.9, $p < 0.001$; FL*G = 2.3, $p < 0.05$).

"Top ten" patients in the Fontan group (Fig. 2). A subgroup of 10 patients with the highest increases of cardiac output after Fontan repair were compared with age-matched control subjects. The cardiac index, stroke index and blood pressure were the same at all levels of exercise without any interaction of group with activity level (for all three variables FL*G < 0.2, $p > 0.9$). The heart rate in the 10 patients in the Fontan group was higher at rest ($p < 0.05$) but comparable with normal values at all exercise levels. In this patient subgroup, there were no patients with a residual atrial septal defect or coronary sinus to left atrium connection. Nevertheless, the oxygen saturation at rest and during exercise remained mildly lower than in the control groups (FG = 21, $p < 0.001$; FL = 5.0, $p < 0.02$; FL*G = 1.5, $p = 0.25$). The more accentuated decrease of the oxygen saturation at the higher work loads, as seen for the whole Fontan group, was not present.

"Bottom 10" Fontan group (Fig. 3). Similarly, a subgroup of 10 patients with the lowest increase in cardiac output were compared with age-matched control subjects. Again, cardiac index, stroke index and systolic blood pressure were comparable at rest, but responses to exercise were quite divergent



(cardiac index: $FL^*G = 3.3$, $p < 0.03$; stroke index: $FL^*G = 8.0$, $p < 0.001$; systolic blood pressure: $FG = 1,929$, $p < 0.01$). The individual changes in stroke index showed different patterns: when starting exercise, 6 of the 10 patients showed an initial small increase and in 4 it remained unchanged. At the highest work load, 3 of the 10 patients had actually had decrease in stroke volume from baseline levels, in 4 it was unchanged and only the remaining 3 showed a mild increase.

Figure 4. Changes in cardiac index, stroke index, heart rate and systolic blood pressure (BP) in a patient after the Fontan operation and a 4 mm Hg gradient at rest across a right atrial-right ventricular valved connection. Baseline values: cardiac index 2.3 liters/min per m², stroke index 44 ml/m², heart rate 50 beats/min, systolic blood pressure 100 mm Hg.

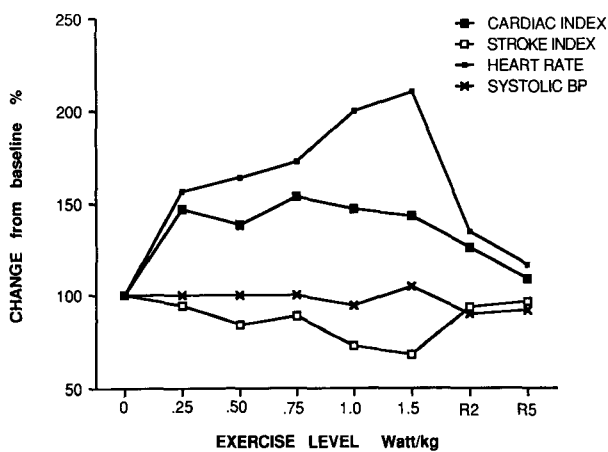


Figure 3. Hemodynamic responses of the "worst ten" performers in the Fontan group compared with age-matched controls. Symbols as in Figure 1. F values: cardiac index: $FG = 2.24$, $p = 0.1$; $FL = 15$, $p < 0.001$; $FL^*G = 3.3$, $p < 0.03$. Heart rate: $FG = 0.1$, $p = 0.8$; $FL = 18.7$, $p < 0.001$; $FL^*G = 3.7$, $p < 0.02$. Change in stroke index: $FG = 3.8$, $p = 0.06$; $FL = 11.9$, $p < 0.001$; $FL^*G = 7.2$, $p < 0.001$. Change in systolic blood pressure: $FG = 8.2$, $p < 0.01$; $FL = 5.6$, $p < 0.01$; $FL^*G = 1.9$, $p = 0.12$.

In the "top 10" Fontan group, the heart rate was higher at rest ($p < 0.01$) and comparable with that of normal subjects at all exercise levels.

Right atrial-right ventricular valved conduit connection. Results were different in the patients whose right ventricle was included in the Fontan circulation. At rest, the cardiac index was lower than in age-matched control subjects (3.0 ± 0.9 versus 4.1 ± 0.9 liters/min per m², $p < 0.05$), mainly because of a low stroke index at rest. Heart rates at rest in this subgroup were comparable with those of the control group. With exercise, none of these patients had an increase in stroke volume; two patients with a mild conduit gradient even showed a significant decrease in stroke volume at the highest exercise level, cardiac output being augmented only by an excessive increase in heart rate (Fig. 4).

Risk factor analysis of all 42 patients. Univariate analysis. Pearson correlation coefficients showed no significant relation of increase in cardiac output at the highest work load with age, age at Fontan operation, time since Fontan operation, diagnosis, surgical connection or approach, or pre- or

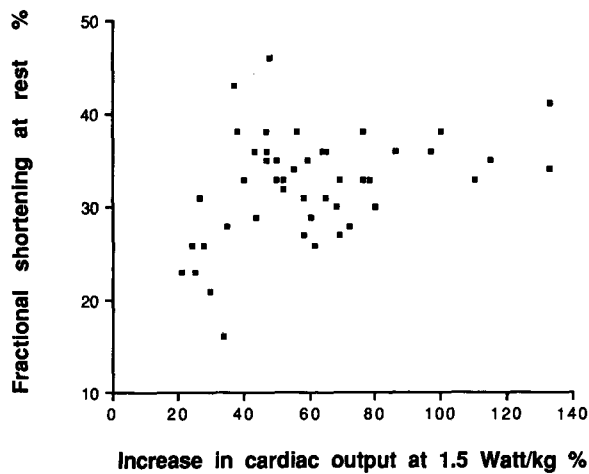


Figure 5. Lack of linear correlation between fractional shortening at rest and increase in cardiac index at the highest exercise level. All four patients with very low fractional shortening ($\leq 25\%$) performed poorly, but good contractility was not associated with good performance.

post-Fontan hemodynamics. There was no linear correlation between increase in cardiac output and fractional shortening when the latter was treated as a continuous variable (Fig. 5). However, poor ventricular function, defined as fractional shortening $< 25\%$, was associated with a poor increase in cardiac output ($p < 0.05$).

The presence of a right atrial-right ventricular valved connection was predictive of a poor increase ($p < 0.001$), and the diagnosis of pulmonary atresia with intact ventricular septum was predictive of a good increase in stroke volume at the highest work load ($p < 0.05$).

Multiple regression. Multiple regression techniques did not identify factors other than those found by univariate analysis that influenced increase in cardiac output at the highest exercise level. There was a significant model ($r^2 = 0.43$, $p < 0.001$) predicting lack of increase in stroke volume with the presence of a right atrial-right ventricular connection ($p < 0.001$), poor ventricular contractility (fractional shortening $< 25\%$) ($p < 0.03$) and a high preoperative mean pulmonary artery pressure (entered as a continuous variable) ($p < 0.03$). Thus, in patients without a right atrial-right ventricular connection and with reasonable ventricular contractility (fractional shortening $\geq 25\%$), elevated preoperative pulmonary artery pressure alone predicted limited exercise performance.

Discussion

Exercise performance in patients after the Fontan operation. This study has examined the exercise ability of patients after a Fontan operation over a range of exercise levels comparable to those that they might be expected to achieve during normal daily life. We tried to determine whether there

are limitations intrinsic to the Fontan circulation that might preclude normal cardiovascular responses to such levels of exercise. Invasive studies in normal subjects over a wide age range have shown that the mean pulmonary artery pressure rarely exceeds 25 mm Hg at moderate levels of exercise (15-18). Such pressures have been documented during exercise in patients with a Fontan circulation without a subpulmonary ventricle (10,11,19). Thus, provided that there is no gradient across the surgical connection, that the pulmonary vascular resistance is low and falls in the normal way with exercise and that diastolic and systolic ventricular function are both normal, one would predict that patients with a Fontan circulation would perform as well as normal subjects up to moderate levels of exercise. This was the case with our patients in the "top 10" group: there was no difference in cardiac index, stroke index, heart rate or blood pressure at any exercise level when we compared these performers with age-matched control subjects. We did not exercise patients to levels at which they themselves would anticipate failing to keep up with normal subjects; limited maximal exercise performance of a patient with a Fontan circulation has been demonstrated previously (8-10).

Although our patients with the best responses performed within normal limits, many of the other patients had suboptimal responses. Analysis of the determinants of cardiac output suggests that these poor responses were not due to inadequate levels of heart rate. A closer look at the 10 poorest performers showed that their heart rate at the highest exercise level was well within the range of the age-predicted values. However, the stroke volume, which was normal at rest, showed a variable pattern during exercise. In the "top 10" patient group stroke volume increased normally. In contrast, stroke volume in the "bottom 10" patient group, after an initial modest increase, decreased at the higher exercise levels, sometimes falling below baseline. An inadequate stroke volume must be related to either impaired ventricular contractility, excessive afterload or limited preload or a combination of these factors.

Role of ventricular contractility. In this study and in previous reports (8,20,21) exercise performance could not be related to assessment of ventricular contractility at rest when the latter was entered as a continuous variable. All of our patients with very low fractional shortening did perform poorly (Fig. 5), but so did a number of patients with better or even normal rest indexes of contractility. These findings imply that contractility by itself is not the limiting factor for exercise performance in these patients unless ventricular function is severely impaired.

Role of afterload. Excessive afterload during exercise, as assessed by the crude index of blood pressure in the absence of a fixed or dynamic ventricular outflow obstruction, was never found in patients after Fontan repair (19,20), especially not in our poor performers (Fig. 3); their systolic blood pressure was significantly lower at the higher exercise levels.

Therefore, afterload is unlikely to account for impaired stroke volume during exercise.

Role of preload. Thus, only preload is left by exclusion to affect significantly the stroke volume during exercise in the absence of severe ventricular dysfunction. Preload to the systemic ventricle in a Fontan circulation is determined by delivery from the pulmonary bed and by ventricular compliance, provided there is no atrioventricular valve obstruction. Invasive studies of graded supine exercise up to 100 W in normal adults have shown that the mean pulmonary artery pressure, very early in exercise, rises from 15 to 21 mm Hg, with further increases in cardiac output being matched by a corresponding decrease of pulmonary vascular resistance (15). Reanalyzing data of invasive studies using supine exercise in five patients after Fontan repair reported by Shachar et al. (19), we find a close correlation of increases in cardiac output with decreases in pulmonary vascular resistance ($r = 0.90$, $F = 12.7$, $p < 0.04$) and not with increases in transpulmonary gradient or ventricular function.

In our multivariate analysis, the preoperative mean pulmonary artery pressure, a crude index incorporating pulmonary vascular resistance and compliance, emerged as a significant predictor of a limited increase in stroke volume in patients with normal or mildly impaired ventricular function. Therefore, by deduction and multivariate analysis, there is evidence that in the absence of markedly impaired ventricular function, pulmonary venous return is an important limiting factor for exercise performance in the Fontan circulation. This emphasizes the importance of pulmonary vascular resistance and reactivity not only as a predictor of operative risk (12), but also of functional result in survivors after a Fontan procedure.

Limited compliance of the systemic ventricle is an additional possible explanation for inadequate stroke volume during exercise. We did not attempt to include noninvasive diastolic data in the multivariate model, because interpretation of these results in the absence of left atrial pressure or left ventricular filling pressure is difficult. It is encouraging to note that multiple regression techniques showed no decrease of performance with age or time since operation; some of our older patients performed very well up to 13 years after the Fontan operation.

A mild gradient at rest did not impede significant increases in cardiac output, thereby confirming results of Shachar et al. (19). However, these observations need to be interpreted with utmost care because severe outflow obstruction may be associated with only a mild gradient if the cardiac output at rest drops to low values.

Role of the subpulmonary ventricle. The value of incorporating the right ventricle into a Fontan circuit has been controversial (5,10,20-22). None of our seven patients with a right atrial-right ventricular connection increased their stroke volume throughout exercise. A fixed stroke volume might seem to be a major handicap, but most patients were

able to increase their cardiac output significantly by increasing their heart rate. The inability to increase stroke volume in this subgroup may be due to the relatively small, poorly compliant right ventricle in the circuit. The heart in three of the seven patients functioned as in a biventricular circulation because no forward flow in the pulmonary artery was observed in ventricular diastole and two of the three had mild holodiastolic pulmonary regurgitation. In this biventricular circulation, left ventricular stroke volume can only match the fixed right ventricular stroke volume. An advantage of a right atrial-right ventricular connection is that if a biventricular circulation can be obtained, the circuit is allowed to work at a lower systemic venous pressure than may be required for an atrial dependent circulation. However, a major drawback with a right atrial-right ventricular connection is the deterioration of conduits and the morbidity and mortality associated with reoperation (23,24).

Arterial oxygen saturation. The patients with a Fontan circulation exhibited mild oxygen desaturation at rest, even the subgroup in which no residual atrial septal defect had been found at postoperative cardiac catheterization (10,19). This is presumably because of defective oxygenation in the lungs from arteriovenous shunts or ventilation perfusion imbalances. Just like the normal subjects in our and other series (16), these patients had a very mild decrease (1% to 2%) of systemic oxygen saturation during exercise; however, this decrease was much more pronounced (>5%) in patients with a proved residual venous or atrial shunt. In those patients in whom a residual communication had previously been disproved, the saturation decreased by $\leq 4\%$.

Limitations of the study. Some technical aspects of the Doppler methods employed in this study warrant emphasis. It is crucial to determine the aortic cross-sectional area at the point where the Doppler velocity tracings are obtained to derive correct absolute values of stroke volume. Several studies (14,25-27) have reported different correlation coefficients at different sites of the aortic arch. Rest and exercise values from our control group are comparable with published data (17,18,28-30). However, the use of the aortic valve surface area may lead to overestimation of the effective cross-sectional area, especially in patients having a relatively big aortic valve due to a long-standing large systemic to pulmonary artery shunt. The distribution of rest stroke indexes in the patients was therefore mildly skewed to the higher values. Thus, our technique will overestimate mean stroke index and cardiac index in the Fontan group and underestimate differences from values in control subjects. We accounted for this problem by using the Repeated Profile statement of SAS and also by analyzing all data that incorporated the aortic area as a change from baseline, thereby removing the influence of this measurement.

Exercise Doppler studies assume that the cross-sectional area of the proximal aorta and the flow profile remain unchanged from one level of exercise to another. In our

study we compared changes in patients with a Fontan circulation with those of normal control subjects who performed at the same levels of exercise; it is unlikely that different changes large enough to alter our findings significantly would have occurred in either group.

An additional limitation is that "steady state" exercise may not be present by 3 min and that changes from 3 to 5 min might still be occurring. The use of a 3 min work load represents an attempt to balance the need for steady state hemodynamics with the patient's ability and willingness to finish the exercise protocol.

The findings of this study are inevitably influenced by patient selection. Although no medical entry criteria were applied, a profound selection had already occurred when patients were accepted for a Fontan repair and by survival from the operation. Both are unavoidable effects when studying long-term survivors and exclude the worst end of the spectrum of patients. Therefore, as medical selection criteria for definitive surgery improve, it becomes more difficult to discriminate risk factors in survivors.

Conclusions and clinical implications. Our study suggests that, at best, a Fontan type of circulation will allow normal hemodynamic responses of the patients to daily life activities. Impairment of ventricular contractility, only when it is severe, limits the functional result after a Fontan repair. In patients with normal or fair contractility, ventricular filling, which is determined by the impedance of the pulmonary vascular bed, appears to be the limiting factor for exercise performance.

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