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Cardiorespiratory Response to Exercise After Modified Fontan Operation: Determinants of Performance

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Objectives. **This study sought to measure the cardiorespiratory responses to exercise and to identify the perioperative determinants of exercise performance in children, adolescents and young adults who underwent the modified Fontan operation.**

Background. **Several studies of the cardiorespiratory responses to exercise after the Fontan operation have demonstrated subnormal maximal oxygen uptake and exercise heart rate, but the perioperative variables that ultimately affect exercise responses have not been assessed systematically.**

Methods. **The study included 59 of the 548 patients who underwent a modified Fontan operation between January 1, 1984 and December 31, 1993 at the Mayo Clinic. Spirometry was performed at rest in all patients before exercise testing. The patients then exercised using a previously calibrated cycle ergometer and a 3-min incremental cycle exercise protocol. Multiple linear regression analysis was used to determine a subset of variables associated with oxygen uptake at peak exercise ($\dot{V}O_2$max), blood oxygen saturation (O_2sat) and heart rate at peak exercise (HRmax).**

Results. **$\dot{V}O_2$max ranged from 29% to 95% of normal value; O_2sat at peak exercise ranged from 77% to 96%; and HRmax ranged from 39.7% to 97.4% of normal value. Multivariate analysis showed that log $\dot{V}O_2$max/kg$^{2/3}$ was associated with age at exercise, male gender, body surface area, preoperative confluent pulmonary arteries and rest $\dot{V}O_2$max/kg$^{2/3}$. Preoperative left pulmonary artery stenosis, the presence of a classic Glenn anastomosis at exercise and rest O_2sat were associated with O_2sat at peak exercise. Age, body surface area at exercise, heart rate at rest and diastolic blood pressure were associated with HRmax at exercise.**

Conclusions. **Subnormal $\dot{V}O_2$max and HRmax values were demonstrated at peak exercise. Several perioperative variables were associated with $\dot{V}O_2$max and O_2sat at peak exercise. The presence of a classic Glenn anastomosis was associated with decreased O_2sat at peak exercise, suggesting intrapulmonary shunting with the classic Glenn anastomosis.**

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In 1971 Fontan et al. (1) described an operation for separation of the systemic and pulmonary venous return in patients with tricuspid atresia. Since their original description, several modifications of the operation have been described that allow the application of this surgical concept to various complex heart lesions with one functioning ventricle (2–4). All studies (5–9) of the cardiorespiratory responses to exercise after the Fontan operation demonstrated subnormal oxygen uptake at peak exercise ($\dot{V}O_2$max) and heart rate at peak exercise (HRmax). In some studies (5), cardiac output and stroke volume response to exercise were abnormally decreased. Although the Fontan operation theoretically eliminates right to left intracardiac shunts, several investigators (5) have shown that blood oxygen saturation (O_2sat) at rest is lower than normal, and it declines even further with exercise.

However, there has not been a systematic study of which perioperative variables affect cardiorespiratory responses to exercise. In addition, previous investigators (5–9) have studied a relatively small number of patients after the Fontan operation. The purpose of the present study was to determine the cardiorespiratory responses to exercise and to identify perioperative determinants of exercise performance in children, adolescents and young adults who have had the modified Fontan operation.

Methods

Patients. Between January 1, 1984 and December 31, 1993, 548 patients underwent a modified Fontan operation at the Mayo Clinic, 62 of whom had at least one postoperative exercise study. Only patients with rest O_2sat ≥85% were included in the study. Three of the 62 patients who underwent postoperative exercise testing had significant systemic arterial blood oxygen desaturation at rest (74%, 79%, 82%) and were excluded from the study. The remaining 59 patients constitute

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Abbreviations and Acronyms

AV	= atrioventricular
BSA	= body surface area
Classic Glenn	= anastomosis of superior vena cava and right pulmonary artery with interruption of pulmonary artery confluence
HRmax	= heart rate at peak exercise
O_2sat	= oxygen saturation of the blood
$\dot{V}E/\dot{V}O_2$	= ventilatory equivalent for oxygen
$\dot{V}O_2$	= oxygen uptake
$\dot{V}O_2$max	= oxygen uptake at peak exercise

the study group (37 male, 22 female; age at time of exercise: median 12 years, range 5 to 41; age at modified Fontan operation: mean [±SD] 11.8 ± 8.6 years, range 2 to 39). Exercise testing was performed 2 months to 13.4 years (mean 2.9 ± 2.9) after the modified Fontan operation.

A detailed data base for patients who have had the Fontan operation at the Mayo Clinic has been maintained and repeatedly updated (10–13). This data base includes all the perioperative variables of interest for the current study; 279 items that described 48 variables (Tables 1 and 2) were analyzed.

Exercise study. Spirometry was performed in all patients at rest before exercise testing. Exercise was performed with a previously calibrated cycle ergometer (Siemans-Elema, 300B), using the 3-min incremental cycle exercise protocol described by James et al. (14). The work load was based on patient gender, height and body surface area (BSA). The patients were encouraged to exercise to the point of exhaustion, and only the results that the examiner considered to represent a maximal cardiopulmonary effort were included in the analysis. During the exercise test, heart rate, respiratory rate, blood pressure, oxygen uptake, carbon dioxide production, minute ventilation, tidal volume and O_2sat were recorded. Heart rate and rhythm were monitored continuously throughout exercise. A 12-lead electrocardiogram was obtained with the patient at rest, at each work load and at 1-min intervals for 5 min after exercise testing. Blood pressure was measured at each work load with a mercury manometer connected to a programmable air compression cuff system (Narco Biosystem, PE300). All measurements of blood pressure were in the left arm unless a Blalock-Taussig anastomosis previously had been performed on the left side. The O_2sat was measured continuously by ear or finger oximeter. Oxygen uptake and carbon dioxide production were measured using breath by breath analysis. Gases were analyzed using a previously calibrated mass spectrometer. Effective pulmonary blood flow (hereafter referral to as cardiac output*) was measured at rest and at each work load using the acetylene–helium rebreathing technique (15).

Data analysis. Continuous variables were summarized as range (minimum, maximum) and mean value ± SD. The percent of predicted $\dot{V}O_2$max, heart rate and systolic and diastolic blood pressures was calculated for each patient were also summarized as range (minimum, maximum) and mean value ± SD. The major statistical method for analysis was multiple linear regression. The dependent variables of interest were peak exercise $\dot{V}O_2$max (adjusted for size), O_2sat and heart rate. A scaling factor of $kg^{2/3}$ was used for $\dot{V}O_2$max: $\dot{V}O_2max/kg^{2/3}$ (16). In addition, $\dot{V}O_2max/kg^{2/3}$ was analyzed as the natural log (i.e., log $\dot{V}O_2max/kg^{2/3}$) to account for the nonconstant variance present in this variable. Independent variables evaluated for their association with the dependent variables were the clinical, physiologic and surgical indexes in Table 1 and the rest value of the exercise variables, including heart

* In the presence of a right to left shunt, "cardiac output" will be underestimated using acetylene–helium rebreathing technique.

Table 1. Independent Predictive Variables Used for Univariate and Multivariate Analysis

Preoperative Variables	Perioperative Variables	Postoperative Variables
Age at operation	Arrhythmia	Any postop complications
Gender	Previous palliative operation*	Cardiac reoperation
Atrial and visceral situs	Fontan connection (type)	Duration of chest tube drainage
Caval return	Classic Glenn	Length of hospital stay
Ventricular morphology	AV valve patch or repair	Residual intracardiac shunt
AV connection	AV valve replacement	Postop arrhythmia
Anomalies of pulmonary venous return	Left PA or right PA reconstruction	Time between operation and exercise study
Confluence of PAs†	Pulmonary vein baffle	
AV valve abnormality	Bypass time	
Type of single ventricle	Aortic cross-clamp time	
Mean PA pressure	Mean postbypass RA pressure	
Pulmonary arteriolar resistance	Mean postbypass LA pressure	
Qp/Qs	Type of closure of pulmonary valve	
Ventricular end-diastolic pressure	Postop coronary sinus drainage	
LV ejection fraction		

*Bidirectional Glenn, Blalock-Taussig shunt, Blalock-Hanlon septectomy, central shunt. †Confluence or nonconfluence of pulmonary artery (PA) refers to native state of pulmonary artery. AV = atrioventricular; LA = left atrial; LV = left ventricular; postop = postoperative; Qp/Qs = ratio of pulmonary to systemic circulation; RA = right atrial.

Table 2. Exercise Data During Rest and at Peak Exercise

Variable	Rest (mean ± SD)*	Peak Exercise (mean ± SD)*
Heart rate (beats/min)	90.39 ± 17.56	148.34 ± 24.33
Systolic BP (mm Hg)	110.35 ± 15.41	136.3 ± 26.17
Diastolic BP (mm Hg)	71.46 ± 10.43	74.2 ± 10.3
O_2 saturation (%)	92.49 ± 2.89	89.51 ± 4.17
$\dot{V}O_2$ (liters/min)	0.24 ± 0.06	1.01 ± 0.44
$\dot{V}O_2$ (liters/min per $kg^{2/3}$)	0.03 ± 0.01	0.09 ± 0.02
Cardiac index (liters/min per m^2)	2.61 ± 0.79	4.58 ± 1.26
Stroke volume index (ml/m^2)	29.8 ± 10.2	34.1 ± 9.7
Tidal volume (liters)	0.49 ± 0.22	33.47 ± 5.49
Tidal volume/FVC (%)	22.47 ± 6.59	43.14 ± 9.62
Respiratory exchange ratio	—	1.05 ± 0.13
Minute ventilation (liters/min)	11.74 ± 11.36	38.44 ± 17.53
$\dot{V}E/\dot{V}O_2$	37.58 ± 9.20	37.06 ± 6.77

*Compared with expected value (14). BP = blood pressure; FVC = force vital capacity; $\dot{V}E/\dot{V}O_2$ = ventilatory equivalent for oxygen; $\dot{V}O_2$ = oxygen uptake.

rate, systolic and diastolic blood pressure, O_2sat and oxygen uptake ($\dot{V}O_2$) in Table 2. Independent variables with a p value <0.15 from univariate analysis were considered candidate predictors in the multivariate model along with age, gender and BSA. A stepwise forward variable selection process was then used to reduce the number of predictors by allowing independent variables to enter the model if the corresponding p value was >0.15. Variables remained in the model if their corresponding p value was <0.05.

Results

Dependent variables. *Maximal oxygen uptake.* The $\dot{V}O_2$max ranged from 0.30 to 2.20 liters/min (mean 1.01 ± 0.44), which represents a range of percent of predicted normal value (14) for $\dot{V}O_2$max of 29% to 95% (mean 60.5 ± 16.9%). When scaled for body size, $\dot{V}O_2$max ranged from 40 to 140 ml/min per $kg^{2/3}$ (mean 90 ± 22).

Significant variables associated with $\dot{V}O_2max/kg^{2/3}$ in a multivariate model are shown in Table 3. Patients with a larger BSA, male gender and preoperative pulmonary artery confluence had a higher $\dot{V}O_2max/kg^{2/3}$. Older patient age was associated with a lower $\dot{V}O_2max/kg^{2/3}$. A higher rest $\dot{V}O_2/kg^{2/3}$ was associated with a higher $\dot{V}O_2max/kg^{2/3}$.

Oxygen saturation at peak exercise. The O_2sat at peak exercise ranged from 77% to 96% (mean 89.5 ± 4.2%). Mean O_2sat in 13 patients with a classic Glenn shunt was 87.5 ± 5.1%, 90.6 ± 1.8% and in 7 with a bidirectional cavopulmonary connection. Significant variables associated with O_2sat at peak exercise are shown in Table 4. Patients with preoperative left pulmonary artery stenosis and a classic Glenn preoperatively or at the time of modified Fontan procedure had lower O_2sat at peak exercise. Higher O_2sat at rest was also associated with higher O_2sat at peak exercise.

Heart rate at peak exercise. Exercise heart rate ranged from 79 to 188 beats/min (mean 148.3 ± 24.3), and HRmax as a percent of predicted normal value (14) ranged from 39.7% to 97.4% (mean 76.6 ± 12.7%). Significant variables for predicting HRmax are shown in Table 5. Older patients had a lower HRmax. Higher heart rate at rest, larger BSA and higher diastolic blood pressure at rest were associated with a higher HRmax.

Independent variables of interest. *Blood pressure.* Systolic and diastolic blood pressures at rest ranged from 84 to 154 mm Hg (mean 110.4 ± 15.4) and 50 to 100 mm Hg (mean 71.5 ± 10.4), respectively, which are 70.8% to 142.6% and 75.4% to 146.8% of predicted values (14). At peak exercise, systolic blood pressure ranged from 96 to 220 mm Hg (mean 136 ± 26.2), which is 65% to 126.2% of predicted values. Diastolic blood pressure at peak exercise ranged from 54 to 98 mm Hg (mean 74.2 ± 10.3), which is 83.2% to 108.4% of predicted values.

Table 3. Univariate and Multivariate Analysis of Predictive Variables for log $\dot{V}O_2max/kg^{2/3}$

Variable	Estimated	SE	p Value Multivariate	p Value Univariate
Intercept	−1.329	0.467	0.0063	—
Age at exercise	−0.016	0.005	0.0034	0.956
Female gender	−0.160	0.061	0.0108	0.0001
BSA	0.585	0.120	0.0001	0.0417
PA confluent	−0.293	0.088	0.0016	0.0065
log $\dot{V}O_2/kg^{2/3}$ at rest	0.290	0.140	0.0445	0.092

BSA = body surface area; other abbreviations as in Tables 1 and 2.

Table 4. Univariate and Multivariate Analysis of Predictive Variables for Peak Exercise Oxygen Saturation

Variable	Estimated	SE	p Value Multivariate	p Value Univariate
Intercept	1.060	12.300	0.9316	—
Left PA stenosis	−3.230	1.045	0.0033	0.0096
Classic Glenn	−2.690	0.936	0.0060	0.0821
O_2sat at rest	0.968	0.133	0.0001	0.0001

Classic Glenn = connection between superior vena cava to right pulmonary artery; PA = pulmonary artery; O_2sat = oxygen saturation.

Table 5. Univariate and Multivariate Analysis of Predictive Variables for Maximal Heart Rate

Variable	Estimated	SE	p Value Multivariate	p Value Univariate
Intercept	−6.950	27.600	0.8016	—
Age at exercise	−1.350	0.585	0.0248	0.3458
BSA	34.020	13.160	0.0128	0.1278
Heart rate at rest	0.674	0.173	0.0003	0.0049
Diastolic BP at rest	0.989	0.295	0.0016	0.0010

Abbreviations as in Tables 2 and 3.

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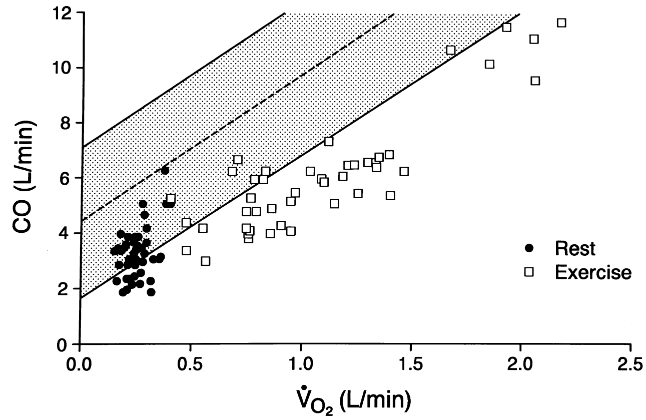


Figure 1. Relation between cardiac output (CO) and $\dot{V}O_2$. **Shaded area** = normal range.

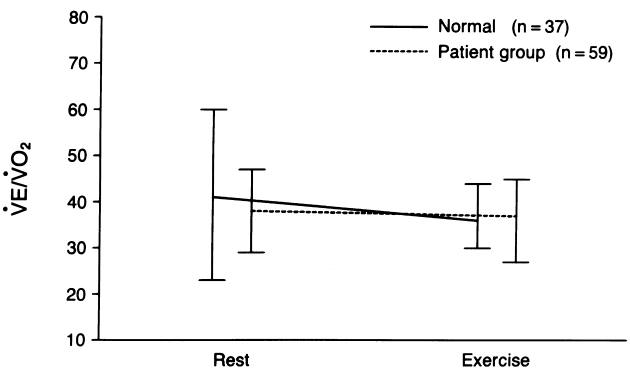


Figure 3. Comparison of $\dot{V}E/\dot{V}O_2$ between patients and normal subjects.

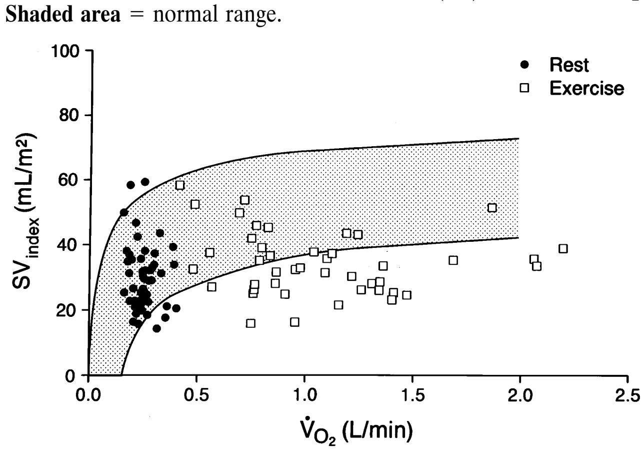
Cardiac output (effective pulmonary blood flow) and stroke. Volume. Cardiac index increased from 2.61 ± 0.79 liters/min per m^2 at rest to 4.58 ± 1.26 liters/min per m^2 at peak exercise. When the patients were compared with normal subjects (7), the cardiac output response to exercise was subnormal (Fig. 1). Mean cardiac factor (slope of cardiac output versus $\dot{V}O_2$) was 4.64 ± 2.39 (n = 42), which is subnormal (17,18).

Mean stroke volume index increased from 29.8 ± 10.2 ml/min per m^2 at rest to 34.1 ± 9.7 ml/min per m^2 at peak exercise. The stroke volume response to exercise was subnormal (Fig. 2).

Ventilatory indexes. None of the measurements of ventilatory function at rest predicted $\dot{V}O_2$max, peak exercise O_2sat or HRmax. Rest respiratory frequency, tidal volume and minute ventilation were normal. At peak exercise, the mean respiratory exchange ratio was 1.05 ± 0.13.

Mean ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) was 37.58 ± 9.2 at rest and 37.06 ± 6.77 at peak exercise, which is similar to normal values (Fig. 3) (7). The mean ratio of minute ventilation to maximal voluntary ventilation was 15 ± 7% at rest and increased to 53 ± 21% at peak exercise.

Figure 2. Relation between stroke volume (SV) index and $\dot{V}O_2$. **Shaded area** = normal range.



Cardiac rhythm. Forty-nine (83%) of 59 patients had normal sinus rhythm before and after exercise. Four patients had junctional rhythm; one had first-degree atrioventricular (AV) block; three had either second- or third-degree AV block; and two had atrial flutter or fibrillation at rest. During exercise, frequent premature ventricular contractions developed in 10 patients; 8 had nonspecific ST-T wave changes; 1 had ventricular tachycardia; and 1 had atrial fibrillation. All the abnormal cardiac rhythms returned to baseline rhythm after exercise. None of the cardiac arrhythmias predicted $\dot{V}O_2$max, O_2sat at peak exercise or HRmax.

Type of modified Fontan operation. Patients were classified according to four types of modified Fontan operation: 1) atriopulmonary connection (n = 37); 2) total cavopulmonary connection (n = 11); 3) intraatrial conduit (n = 8); and 4) heterotaxia syndromes (a variety of connections, n = 3). Univariate analysis revealed no association between type of Fontan modification and $\dot{V}O_2$max ($p = 0.1498$), O_2sat ($p = 0.8510$) or HRmax ($p = 0.8622$).

Discussion

There have been several studies of exercise physiology after the Fontan operation (6–9,11). In general, these studies have documented subnormal $\dot{V}O_2$max and HRmax. Some studies have revealed slightly subnormal O_2sat at rest and at peak exercise. Because of the relatively small number of patients in many of these previous studies, it was impossible to assess the determinants of these subnormal responses in a meaningful way. The current study assessed the cardiorespiratory responses to exercise in a relatively large cohort of 59 patients after the Fontan operation and used multivariate analysis to identify the determinants of exercise tolerance.

In this study we excluded patients with central hypoxia (O_2sat <85%) because these patients have incomplete separation of systemic and pulmonary venous return or marked intrapulmonary shunting and would be more representative of the physiology after a "fenestrated Fontan" than after a completed Fontan operation.

All studies such as this have an inherent selection bias because only a relatively small group (59 patients) of the total number of patients (548 patients) was studied. In this study, patients were selected for exercise testing if they returned to the Mayo Clinic for postoperative evaluation, and there were no contraindications to exercise. It is unclear whether this selection biased the data in a negative, positive or neutral fashion.

Maximal oxygen uptake. In 1986, Driscoll et al. (5) demonstrated a lower $\dot{V}O_2$max (percent of predicted) for patients undergoing operation at an older age than those at a relatively younger age. However, the data were collected from different patients who exercised at different ages. Subsequently, Nir et al. (9) reported the results of serial postoperative exercise studies in 25 patients who had undergone the Fontan operation. In that study, $\dot{V}O_2$max, total work performed and total exercise time were similar for the same patient, with an average of 3.5 years between the first and the last postoperative exercise test.

In the current study of 59 patients, older patients had a lower $\dot{V}O_2$max than younger patients, and female patients had a lower $\dot{V}O_2$max than male patients. The $\dot{V}O_2$max was lower if patients had had nonconfluent pulmonary arteries preoperatively. One can only speculate why this association might exist. Perhaps patients with nonconfluent pulmonary arteries are more likely to have different degrees of pulmonary artery stenosis after the Fontan operation, which could limit pulmonary blood flow, cardiac output and $\dot{V}O_2$max.

Blood oxygen saturation. The small but abnormal reduction from normal of systemic arterial O_2sat at rest and at peak exercise after the Fontan operation has been a source of interest for several years. Recently, Nir et al. (9) demonstrated that O_2sat at peak exercise declines with longer duration between Fontan operation and measurement of O_2sat at peak exercise. This observation suggested that intrapulmonary shunting increases with increasing time after operation. In the absence of a demonstrable intracardiac shunt, it has been suggested (9) that drainage of the coronary sinus to the pulmonary venous atrium may explain some of the desaturation. However, in the current study, drainage of the coronary sinus to the pulmonary venous atrium was not a significant predictor of abnormally decreased O_2sat at peak exercise.

Investigators (19) have also speculated that the presence of a classic Glenn anastomosis (known to be associated with the formation of pulmonary arteriovenous fistulas) may play a role in the mild hypoxemia noted after the Fontan operation. However, until the current study, this relation remained unproved. The current study found a strong relation between the presence of a classic Glenn anastomosis and subnormal O_2sat at peak exercise ($p = 0.006$). However, we did not find the same relation in a group of patients who had a bidirectional cavopulmonary connection. Preoperative left pulmonary artery stenosis was associated with lower O_2sat at peak exercise postoperatively. This factor may cosegregate with the presence of a Glenn anastomosis.

Heart rate. Our patients had a slightly lower HRmax than that in normal subjects. Blunted heart rate response to exercise has been (20–23) reported for several congenital cardiac defects both preoperatively and postoperatively. Decreased HRmax in congenital heart disease before operation could result from abnormal autonomic control of heart rate, sinus node dysfunction or various other factors. Postoperatively, decreased HRmax could be accentuated by damage to the sinus node or the sinus node artery during the surgical procedures. The cause of the blunted response to exercise in these patients is no doubt multifactorial. It is intriguing that perfusion of the carotid body with hypoxic blood is known to cause bradycardia (24). Also, relative bradycardia in subjects after acclimatization to high altitude has been described (25).

Cardiac output and ventricular morphology. Decreased cardiac output during exercise after the Fontan operation has been described by several investigators (5–9). The current study confirms this finding. One might speculate that patients with a single ventricle of the left ventricular type might have better cardiac output and higher $\dot{V}O_2$max than patients with a right ventricular or indeterminate form of single ventricle. Ventricular morphology did not affect $\dot{V}O_2$max. There was also no effect of ventricular morphology on O_2sat at peak exercise or HRmax. Previously, Rosenthal et al. (26) found a higher cardiac output at rest in patients who had had a total cavopulmonary connection (4.8 liters/min per m^2) than in those who had had an atriopulmonary connection (3.7 liters/min per m^2).

Ventilatory responses. Previous investigators (7,20) described abnormal ventilation at rest and during exercise in patients with a functional single ventricle and other forms of cyanotic congenital heart disease. Essentially, these patients have an abnormally increased respiratory rate, minute ventilation and increased $\dot{V}E/\dot{V}O_2$ (ratio of minute ventilation to oxygen consumption) at rest and during exercise. This abnormal ventilation results from hypoxemia and results in increased dead space. After elimination of the hypoxemia, these ventilatory patterns return to normal.

Conclusions. Cardiorespiratory exercise responses after the modified Fontan operation are complex and are influenced by numerous perioperative variables. Subnormal $\dot{V}O_2$max and HRmax after peak exercise were demonstrated. Several perioperative variables were associated with decreased $\dot{V}O_2$max and O_2sat at peak exercise. The presence of a classic Glenn anastomosis was associated with decreased O_2sat at peak exercise, suggesting intrapulmonary shunting with the classic Glenn anastomosis.

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