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Abnormal Dynamic Cardiorespiratory Responses to Exercise in Pediatric Patients After Fontan Procedure

WILLIAM BRAD TROUTMAN, MD,* THOMAS J. BARSTOW, PHD,† ALVARO J. GALINDO, MD, DAN M. COOPER, MD†

Westwood and Torrance, California

Objectives. **Novel protocols were used to focus on dynamic cardiorespiratory function during submaximal exercise and on the recovery from 1-min pulses of exercise in children who had undergone Fontan corrections for single-ventricle lesions.**

Background. **Particularly in children, maximal oxygen uptake ($\dot{V}O_2$max), which is commonly used to assess the functional capability of patients after the Fontan procedure, is highly effort dependent and not physiologic and leads to uncomfortable metabolic and cardiorespiratory stress. Alternative approaches include the measurement of dynamic responses during progressive exercise and recovery after short bursts of exercise. These strategies yield mechanistic insight into cardiorespiratory impairment and can be used to gauge limitations in daily life activity.**

Methods. **Sixteen patients (mean [±SD] age 12.2 ± 2.4 years; 9 boys) and 10 age-matched control subjects (mean age 12.2 ± 2.4 years; 6 boys) performed two separate cycle ergometer tests in which gas exchange was measured on a breath by breath basis: 1) Progressive exercise was used to determine the dynamic relation among $\dot{V}O_2$, carbon dioxide production ($\dot{V}CO_2$), ventilation ($\dot{V}E$), heart rate (HR) and work rate (WR). 2) A 1-min constant WR test was used to determine the recovery time for gas exchange and HR.**

Results. **Peak $\dot{V}O_2$ and anaerobic threshold were reduced in patients who underwent the Fontan procedure compared with control subjects by 57% and 52%, respectively ($p < 0.001$). Dynamic relations during progressive exercise—$\Delta\dot{V}O_2/\Delta$HR and $\Delta\dot{V}O_2/\Delta$WR—were decreased ($p < 0.001$) and $\Delta\dot{V}E/\Delta\dot{V}CO_2$ was increased ($p < 0.005$) in the Fontan group patients. Recovery times for HR and $\dot{V}O_2$ were prolonged in the Fontan group patients by 154% and 69%, respectively ($p < 0.01$).**

Conclusions. **The results demonstrate that submaximal gas exchange responses to progressive exercise and recovery times after brief high intensity exercise are abnormal in patients after the Fontan procedure. These observations complement the findings of reduced $\dot{V}O_2$max observed here and by others. We speculate that the mechanisms for these responses are related to 1) a pervasive reduction in stroke volume for both low and high intensity exercise, 2) an abnormal linkage of ventilation to tissue carbon dioxide production, and 3) increased dependence on anaerobic metabolism in skeletal muscles. The prolonged recovery of HR and $\dot{V}O_2$ provides a possible mechanism for reduced physical activity.**

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The Fontan procedure, in which the systemic and pulmonary circulations are separated, has become the surgical therapy of choice for selected patients with complex congenital heart defects or single-ventricle lesions (1). Although the Fontan procedure has resulted in improvements in cardiorespiratory function, the long-term outlook remains guarded, and additional surgical or medical interventions, or both, are often necessary. Cardiorespiratory function under rest conditions is of limited value in determining physiologic impairment; however, exercise testing in patients who have undergone the Fontan procedure has become an important tool for clinical decision making and evaluation of outcomes in these patients (2–5).

Most exercise protocols in children rely on the maximal oxygen uptake test ($\dot{V}O_2$max), in which the subject exercises to the limit of his or her tolerance. However, as has been recently reviewed (6), there may be theoretical and practical reasons for the use of alternative approaches to exercise testing in children. The natural patterns of activity in children are known to consist of brief bursts of exercise of varied intensity that last seconds to minutes (7). In contrast, a maximal progressive exercise test typically consists of continuous exercise that usually lasts ~10 min, and at least half of the time is spent in the high intensity exercise range (8). Achievement of a true $\dot{V}O_2$max (i.e., a plateau or reduction in $\dot{V}O_2$ while work rate [WR] is increasing), does not usually occur even in healthy, well motivated children in the laboratory setting (9). For patients with underlying cardiac disease, many clinicians and investigators are uncomfortable about the intense coaxing of subjects, which is a necessary component of maximal exercise tests.

From the Division of Pediatric Cardiology, Department of Pediatrics, School of Medicine, University of California Los Angeles, Westwood; and †Division of Respiratory and Critical Care, Department of Pediatrics, Harbor-UCLA Medical Center, Torrance, California. This work was supported by Grant HD 269239 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

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*Present address and address for correspondence: Dr. William B. Troutman, 81 MDOS/SGOC, 301 Fisher Street, Room 1A132, Keesler Air Force Base, Mississippi 39534-2519. E-mail: William_B_Maj.Troutman@KAFBVA.Mednet.AF.MIL.

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Abbreviations and Acronyms

AT = anaerobic threshold
ECG = electrocardiogram, electrocardiographic
HR = heart rate
P_{ETCO_2} = end-tidal carbon dioxide concentration
$\dot{V}_{CO_2}$ = carbon dioxide production
$\dot{V}_E$ = ventilation
$\dot{V}_{O_2}$ = oxygen uptake
$\dot{V}_{O_2}$max = maximal oxygen uptake
WR = work rate

We hypothesized that alternative strategies to exercise testing in children with Fontan corrections would be useful in the evaluation of functional cardiorespiratory status. Specifically, by focusing on dynamic submaximal and kinetic exercise responses and on protocols involving brief (1-min) periods of exercise, we reasoned that alternative tests have the potential to provide information about cardiorespiratory function that is relevant to real-life activities. Finally these newer approaches may help distinguish real cardiorespiratory impairment from the effects of deconditioning, a confounding variable often encountered when attempting to interpret exercise responses in patients with chronic diseases.

Methods

Patients. Sixteen children who had undergone the Fontan procedure and 10 healthy control subjects comprised the study group. The patients were recruited from pediatric cardiology clinics at UCLA Center for Health Sciences, Harbor-UCLA Medical Center and outside referring centers. Inclusion requirements were 1) the Fontan correction for single-ventricle lesions, 2) the ability to perform in-laboratory cycle ergometer exercise (i.e., roughly ≥6 years old), 3) >6 months since operation, and 4) sinus rhythm. Healthy age-matched control subjects were recruited from medical center personnel and their contacts. The control subjects were not receiving medications and were known to be free of cardiac and other chronic diseases. This project was approved by the appropriate institutional review boards, and informed consent was obtained from all participants and their parents or guardians.

Exercise protocols. Each subject performed a ramp-type progressive cycle ergometer exercise test (8,9). The ramp test is so named because the WR increases linearly. The subject continues to exercise until the limit of his or her tolerance has been reached. The ramp protocol has been used extensively in children and adults. Data from the ramp test were used to determine the maximal or (more appropriately) peak $\dot{V}_{O_2}$, lactate or anaerobic threshold (AT) and submaximal relations among gas exchange variables, WR and heart rate (HR).

In addition, each subject performed a 1-min constant WR cycle ergometer test. For the Fontan group patients, the WR for this test was calculated as 2 W/kg. We estimated that this WR would most likely represent an effort that was at least above the subject's AT on the basis of previous studies of 1-min tests in children (10), on preliminary studies in our laboratory and on previous studies of maximal exercise testing in post-Fontan procedure patients. In the control subjects, two 1-min tests were performed: the first at 2 W/kg and the second at 3.5 W/kg. The higher WR test was performed by the control subjects to ensure a comparison of similar absolute as well as relative WR input between patients and control subjects would be feasible.

In the control subjects, the 2-W/kg rate corresponded to a mean value of 63% of the peak power found in the progressive exercise tests, but in Fontan group subjects, the 2-W/kg rate corresponded to a mean value of 120% of peak power. The 3.5-W/kg test in the control subjects represented 110% of peak power; this was not statistically different from the relative intensity of the 2-W/kg test in the Fontan group subjects. However, the peak power achieved by the Fontan group subjects during progressive exercise testing was obtained without as vigorous a level of coaxing and cajoling, as was used for the control subjects. We do not know whether the peaks achieved were true maximal values in the Fontan subjects, although it is reasonable to speculate that they probably were not.

The 1-min tests were performed either on the same day as the ramp test or on a separate occasion. When the two tests were performed on the same day, we allowed sufficient time between the protocols to ensure that HR and $\dot{V}_{O_2}$ levels had returned to rest values. Each 1-min test was preceded by 3 min and followed by 8 min of unloaded cycling. Finally, each subject was asked which exercise test he or she preferred (i.e., 1-min or progressive maximal test).

Breath by breath measurement of gas exchange. The exercise was performed on an electromagnetically braked and calibrated cycle ergometer. Ventilation ($\dot{V}_E$) and gas exchange were measured on a breath by breath basis. The subjects breathed through a mouthpiece connected to a turbine flow meter and a low resistance valve for continuous measurements of inspired and expired volume. The apparatus dead space was 90 ml. Carbon dioxide and oxygen concentrations were measured with a mass spectrometer that continuously collected samples from the mouthpiece at a rate of 1 ml/s. Ventilation, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$ and end-tidal carbon dioxide concentrations (P_{ETCO_2}) were computed online on a breath by breath basis as previously described (11). HR was measured on a beat by beat basis with a standard lead I electrocardiogram (ECG). The Fontan group patients also had 12-lead ECG, pulse oximetry and blood pressure monitoring during all exercise studies.

Data analysis. *Progressive exercise protocols.* Peak HR and $\dot{V}_{O_2}$ were obtained from the ramp test with the use of 10-s averaged data. The noninvasive measurement of AT was made with the well described characteristic patterns of gas exchange associated with increased lactic acid production (8,9). The criteria include an abrupt increase in 1) respiratory exchange ratio ($\dot{V}_{CO_2}/\dot{V}_{O_2}$), 2) ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}_{O_2}$), and 3) P_{ETCO_2}. These abrupt increases can be used to

determine the AT only if $\dot{V}E/\dot{V}CO_2$ and $PETCO_2$ are simultaneously unchanging.

One-minute test. The recovery response data from the 1-min test were assumed to be single-exponential decay as previously described (12,13). The data were fitted to the equation

$$y = a \cdot e^{-t/\tau},$$

where y = $\dot{V}O_2$ or HR, a = end-exercise (i.e., peak) value for $\dot{V}O_2$ or HR, t = time, and τ = time to reach 63% of recovery values after the peak exercise value. We used nonlinear, curve-fitting algorithms provided in the BMDP software package (14).

Statistical analysis. Results are reported as mean value ± SD. Fontan data were compared with control data with use of the unpaired *t* test. In cases of multiple comparisons, we used analysis of variance. If the analysis of variance was significant, comparisons between Fontan and control subjects were accomplished with a modified *t* test (Dunnett's test). A p value <0.05 was considered significant.

Results

Patient profile. The control (six boys, four girls) and Fontan (nine boys, seven girls) group subjects were comparable in age (12 ± 3 vs. 12 ± 2 years, respectively; p = NS) and weight (49 ± 13 vs. 43 ± 17 kg, respectively; p = NS). Height was significantly greater in the control subjects (160 ± 20 cm) than in the Fontan group subjects (146 ± 14 cm, $p < 0.05$). The Fontan group patients had the following anatomic diagnoses: tricuspid atresia (10 patients), double-inlet left ventricle (5 patients) and double-outlet right ventricle (1 patient). The patients were 6 ± 3 years status post the Fontan procedures of modified lateral tunnel (seven patients), classic (five patients), Björk modifications (three patients) and external conduit (one patient). Fifteen Fontan group subjects and all 10 control subjects completed the protocol. One 8-year old Fontan group subject was able to complete only the 1-min test. Finally, 14 of 15 Fontan group subjects and 8 of the 10 control subjects preferred the 1-min test to the ramp test when asked by the investigators at the end of the protocol.

Peak values and AT. The peak HR in the Fontan group subjects (164 ± 16 beats/min) was 17% lower than that obtained by control subjects (197 ± 11 beats/min, $p < 0.001$). Peak work for the Fontan subjects was 78 ± 32 W compared with 162 ± 58 watts for the control subjects ($p < 0.001$). Peak $\dot{V}O_2$ and AT for the Fontan group subjects were 57% and 52% of those of the control subjects, respectively. Oxygen saturation by pulse oximetry decreased from a mean of 90.7 ± 3.8% at rest to 88.9 ± 4.2% at peak exercise ($p < 0.001$) in the Fontan group subjects.

Dynamic exercise responses. The dynamic relations of HR, WR and gas exchange variables during submaximal portions of progressive exercise have been characterized in children (9,15–17). We used standard linear regression techniques to determine the best-fit equation of the data from 30 s after start of exercise to 30 s before peak exercise. Slopes from the regression analyses in each subject were used to characterize 1) $\Delta\dot{V}O_2/\Delta HR$, 2) $\Delta\dot{V}O_2/\Delta WR$, and 3) $\Delta\dot{V}E/\Delta\dot{V}CO_2$. Data from a control subject and a Fontan group subject illustrating the relations of $\dot{V}O_2$ and HR during submaximal exercise are shown in Figure 1.

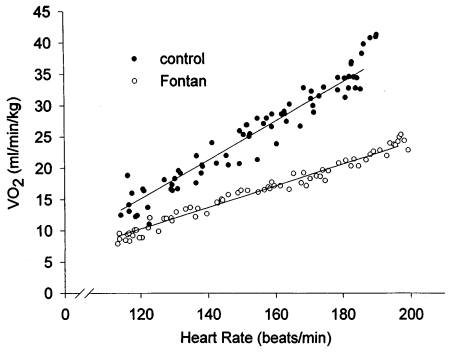
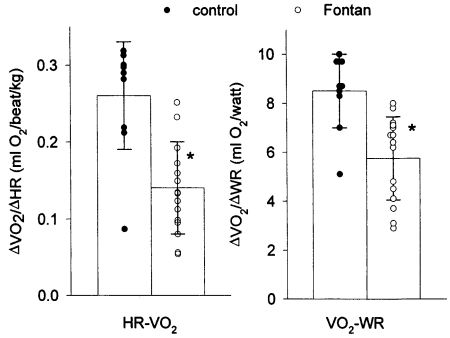


Figure 1. Relation between $\dot{V}O_2$ and HR during progressive exercise in individual 12-year old control and Fontan group subjects. In both cases, there was a characteristic largely linear relation between the two variables (**solid lines** indicate best-fit lines by linear regression). As demonstrated for these two groups, the slope of the relation ($\Delta\dot{V}O_2/\Delta HR$) was lower in the Fontan group patients.

The $\Delta\dot{V}O_2/\Delta HR$ relation was decreased by 54% in the Fontan subjects compared with that of control subjects (Fig. 1 and 2). Similarly, the oxygen cost of work ($\Delta\dot{V}O_2/\Delta WR$) was decreased by 32% compared with that of control subjects (Fig. 2). The dynamic ratio of $\dot{V}E$ to $\dot{V}CO_2$ ($\Delta\dot{V}E/\Delta\dot{V}CO_2$) was significantly increased in the Fontan group subjects (control 30 ± 4, Fontan 39 ± 7, $p < 0.005$). Finally, mean $PETCO_2$ during exercise was lower in the Fontan group subjects (control 40 ± 2 mm Hg, Fontan 32 ± 3 mm Hg, $p < 0.001$).

Recovery from 1-min test. A representative example of recovery data from an individual patient is provided in Figure 3. HR recovery was significantly delayed in the Fontan subjects compared with that of the control subjects. τHR in the Fontan group subjects was 159% longer than τHR observed during the 2-W/kg test in the control subjects and 65% longer than τHR

Figure 2. Relation between $\dot{V}O_2$ and HR and between $\dot{V}O_2$ and work rate (WR) during progressive exercise in control and Fontan group subjects. Abnormal slopes were found for both of these relations in the Fontan group subjects (*$p < 0.05$).



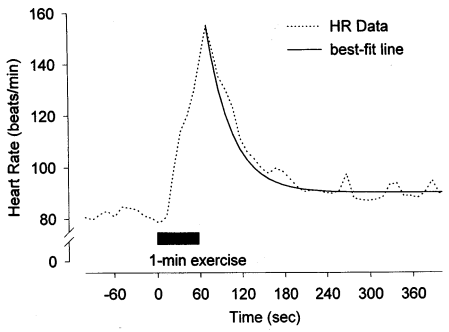


Figure 3. HR response before, during and after 1 min of exercise in a 14-year old Fontan group subject. The recovery kinetics were quantified using a single exponential, as shown.

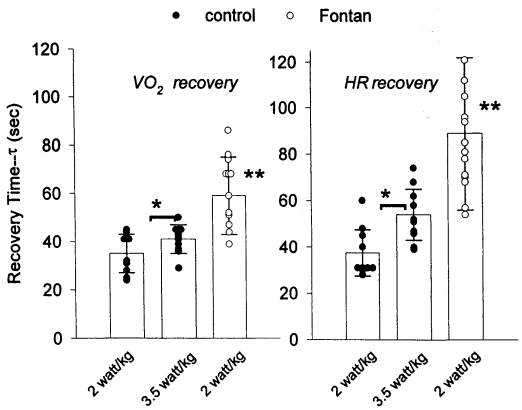
observed during the 3.5-W/kg test in the control subjects. In the control subjects, HR recovery was significantly longer for the 3.5-W/kg protocol than for the 2-W/kg protocol (Fig. 4).

$\dot{V}O_2$ recovery was also significantly prolonged in the Fontan group patients. In the Fontan group subjects, $\tau\dot{V}O_2$ was 69% longer than $\tau\dot{V}O_2$ observed during the 2-W/kg test in the control subjects and 44% longer than $\tau\dot{V}O_2$ observed during the 3.5-W/kg test in the control subjects. In the control subjects, $\dot{V}O_2$ recovery was significantly longer for the 3.5-W/kg protocol than for the 2-W/kg protocol (Fig. 4).

Discussion

Fontan group subjects demonstrated impaired responses to the dynamic, submaximal portion of progressive exercise tests. The ATs were low, and there were abnormal relations between 1) $\dot{V}O_2$ and WR, 2) $\dot{V}O_2$ and HR, and 3) $\dot{V}E$ and $\dot{V}CO_2$. In addition, recovery kinetics for both HR and $\dot{V}O_2$ in response to 1-min constant WR exercise were significantly prolonged. Collectively, these results suggest 1) a pervasive reduction in stroke volume in both low and high intensity exercise, 2) an abnormal linkage of $\dot{V}E$ to tissue carbon dioxide production, and 3) increased anaerobic metabolism in the performance of exercise. Moreover, the abnormally prolonged recovery of HR and $\dot{V}O_2$ from brief exercise in the Fontan group subjects provides an intriguing putative mechanism for reduced physical activity in these patients.

Figure 4. HR and $\dot{V}O_2$ recovery times for control and Fontan group subjects. In control subjects, recovery times were longer after the higher work rate protocols (*$p < 0.05$). In Fontan group subjects, recovery times were prolonged compared with the same absolute (2 W/kg) and relative (3.5 W/kg) protocols in control subjects (**$p < 0.001$).



Dynamic exercise response. Possible mechanisms responsible for the abnormal relation between $\dot{V}O_2$ and HR (i.e., the low slopes of $\Delta\dot{V}O_2/\Delta HR$ [Fig. 1 and 2]) can be derived from the Fick equation, in which

$$\dot{V}O_2 = SV \cdot HR \cdot (a - \bar{v})\, dO_2,$$

$$\dot{V}O_2/HR = SV \cdot (a - \bar{v})\, dO_2,$$

where SV = stroke volume, and $(a - \bar{v})\, dO_2$ = the difference between arterial and mixed venous oxygen content; $(a - \bar{v})\, dO_2$ was not measured during our study because all data were obtained noninvasively. However, the probable effect (if any) of reduced cardiac output relative to tissue demand is a widening of the $(a - \bar{v})\, dO_2$ value (18). We speculate that the reduced $\Delta\dot{V}O_2/\Delta HR$ in the Fontan group subjects is due in part to decreased stroke volume during exercise compared with that in healthy control subjects.

The relation between $\dot{V}O_2$ and WR was also abnormal in the Fontan group subjects (Fig. 2). $\Delta\dot{V}O_2/\Delta WR$ provides insight into the coupling of cellular energy metabolism (measured as the actual work performed on the ergometer) and whole body oxygen uptake (19). Our finding of lower slopes of the $\dot{V}O_2$ and WR relation (a low oxygen "cost" of exercise) might seem, at first glance, quite unexpected. Why would subjects with an impaired cardiovascular system be "more efficient" than normal subjects in utilizing oxygen to perform physical work?

A possible explanation for the lower oxygen cost in Fontan group subjects is greater utilization of existing nonaerobic pathways of energy metabolism during exercise. In this paradigm, the oxygen cost is low during exercise not because of a more efficient coupling between oxygen uptake and mechanical work but because part of the energy expenditure for muscular work is generated by an increased reliance on anaerobic metabolism. Consistent with this was our finding of a reduced AT in Fontan group subjects; the low AT indirectly indicates that lactic acid is reaching the circulation from the working muscles at lower WRs and metabolic rates than in control subjects. The most likely explanation for the low AT is a generally reduced cardiac output for the work performed. As a result, muscle oxygen delivery is relatively inadequate and anaerobic metabolism is required at lower WRs than that in control subjects.

Information about the ventilatory response was also obtained from the submaximal portion of the progressive exercise tests. The elevated slope of $\Delta\dot{V}E/\Delta\dot{V}CO_2$ suggests excessive ventilation in Fontan subjects compared with control subjects as shown by the modified alveolar gas equation

$$\dot{V}E = [863 \cdot PaCO_2^{-1} \cdot (1 - VD/VT)^{-1}] \cdot \dot{V}CO_2,$$

where $\dot{V}_E$ = minute ventilation, $\dot{V}_{CO_2}$ is carbon dioxide production, P_{aCO_2} is arterial carbon dioxide tension, and V_D/V_T = ratio of deadspace to tidal volume. The two most likely explanations for excessive ventilation are increased V_D/V_T and changes in chemoreceptor setpoint for P_{aCO_2}. Our data indirectly support the second mechanism because the finding of low P_{ETCO_2} during exercise in the Fontan subjects compared with control subjects suggests low alveolar and arterial partial pressures of carbon dioxide. The mechanism for this lower setpoint is not readily apparent but may be related to an altered pattern of pulmonary blood flow or an abnormal coupling of carbon dioxide production to $\dot{V}_E$ in patients who have undergone thoracotomies. Alternatively, a lowering of the carbon dioxide setpoint could result from hypoxic ventilatory drive reflected in the small but significant reduction in oxygen saturation observed in the present study and recently by Durongpisitkul et al. (5).

Kinetic exercise response. The transition from rest to exercise or from one level of exercise to another represents a profound metabolic challenge to the organism, and both aerobic and nonaerobic pathways of energy metabolism are suddenly activated (20). Blood flow must increase to the working muscle to facilitate oxygen uptake and carbon dioxide removal, and the heart and lungs must quickly adjust to meet these increased tissue demands.

Investigations into the underlying mechanisms of onset and recovery exercise kinetics (e.g., the concepts of oxygen deficit and debt [20]) constitute an important chapter of modern exercise physiology. An inability to normally deliver oxygen at the onset of exercise leads to slower oxygen uptake response to exercise and an increased oxygen deficit. The initial oxygen lack is compensated for by increased anaerobic metabolism and local lactate accumulation. Thus, the prolonged recovery found in the Fontan group patients suggests "payment" of an increased oxygen debt. Consistent with this finding is the observation that recovery kinetics were longer in the control subjects in the higher than with the lower WR protocols (Fig. 4). The higher WR protocol represented a "supramaximal" WR, one likely to be associated with increased lactate production and greater oxygen deficits and debts.

Prolonged onset and recovery kinetics to exercise are observed in other populations with abnormal cardiac outputs, such as adults with a variety of cardiac abnormalities (21–23). Moreover, Drakonakis and Halloran (24) measured oxygen uptake recovery from exercise in children with a variety of congenital heart lesions and found that children with cyanotic lesions showed markedly slowed recovery times after exercise.

Clinical implications. A factor that often confounds the comparison of exercise data between patients and control subjects is the potential influence of relative physical inactivity. As was noted by Bergman and Stamm (25) in the 1960s, the presence of even innocent murmurs in children led to reduced participation in school physical education programs. It is not an unreasonable assumption that patients who have undergone Fontan procedures probably do not participate in physical activity of the same duration and intensity as do otherwise healthy children. As a consequence, many of the abnormal responses to exercise could simply result from deconditioning rather than from real physiologic impairment.

Although it is impossible to completely distinguish deconditioning effects from physiologic impairment, our data suggest there is a real underlying abnormality in the Fontan group subjects. The HR and $\dot{V}_{O_2}$ recovery data were prolonged in the Fontan group subjects compared with the control subjects for both the 2- and 3.5-W/kg protocols. An increased relative work intensity, as seen in the control subjects, does lead to longer recovery kinetics (Fig. 4). Had we compared the two groups only at the 2-W/kg protocol (the same absolute intensity), then we would not have known whether the recoveries were prolonged at the same relative intensity, and we could not have ruled out a deconditioning effect. However, the recoveries in the Fontan subjects were prolonged even compared with the same relative intensity in the control subjects. This observation indicates that the mechanisms of abnormal cardiorespiratory response to exercise in the Fontan group subjects are not solely due to relative physical inactivity.

The clinical implications of prolonged recovery kinetics for both HR and $\dot{V}_{O_2}$ in these children are intriguing. Recent work from this and other laboratories has characterized the temporal nature of spontaneous physical activity in children as consisting of frequent bouts, ~80 to 90 per hour, with a mean duration of ~20 s and time for recovery of ~26 s (26). The prolonged HR and $\dot{V}_{O_2}$ in the Fontan group subjects could be expected to lead to a longer duration between exercise bouts and, consequently, an overall reduction in physical activity. Whether frequency and levels of spontaneous physical activity are in fact reduced after the Fontan procedure remains to be determined.

In summary, the results of this study revealed an abnormal response to exercise in both low and high intensity exercise ranges. The mechanism is most likely a decrease in stroke volume and an abnormal reliance on anaerobic metabolism even during low intensity exercise. The excessive ventilatory response to exercise is explained by a decrease in the carbon dioxide setpoint or an abnormal linkage between tissue carbon dioxide production, but the mechanism of this abnormality is not known.

These findings are consistent with the results of maximal exercise testing that, in our patients, were reduced to about the same degree as has been observed in other patients undergoing the Fontan procedure (5,27). However, the information gained from the dynamic analysis of progressive exercise and from the 1-min tests probably better reflects cardiorespiratory responses to natural occurring physical activity than do maximal tests.

From a methodologic perspective, the dynamic and kinetic data are less dependent on maximal voluntary effort than are data from traditional testing and do not require prolonged exercise in the high intensity range. The focus on recovery kinetics of breath by breath and HR data allow the design of exercise protocols in which a relatively brief input is easily accompanied by 5 or 10 min of observation during recovery, providing sufficient data for accurate curve-fitting and other

subsequent analyses. Finally, the brief exercise protocols were preferred to traditional maximal exercise protocols by both the control and Fontan group subjects. This is an important consideration because the use of exercise testing in children depends in large part on the willingness of the subject to cooperate in multiple protocols designed to determine the course of a disease or its therapy over time.

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