Dynamics of oxygen uptake during exercise in adults with cyanotic congenital heart disease

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ABSTRACT The dynamic increase in oxygen uptake (VO₂) at the start of exercise reflects the circulatory adjustments to metabolic changes induced by the exercise. Because VO₂ measured at the lungs is the product of pulmonary blood flow and arteriovenous oxygen difference, pathologic conditions affecting the capacity of these factors to change would be expected to alter VO₂ kinetics. To determine whether measurement of VO₂ kinetics can detect conditions in which the pulmonary blood flow response to exercise is abnormal, VO₂ was measured, breath-by-breath, during the transition from rest to exercise in 13 adults with cyanotic congenital heart disease (central venoarterial shunting) and in nine normal subjects. The increase in VO₂ above baseline during the first 20 sec of exercise (phase I), reflecting the immediate increase in pulmonary blood flow, was diminished in the patients compared with that in normal subjects (14.8 ± 10.9 vs. 49.8 ± 19.2 ml of oxygen) (p < .001). The patients' phase I responses correlated with their reported physical activity tolerance (p < .01). In addition, the second phase of the VO₂ response kinetics was prolonged in patients compared with normal subjects (half-time = 63 ± 13 vs 15 ± 13 sec) (p < .001). We conclude that striking disturbances in VO₂ kinetics occur in patients with cyanotic congenital heart disease and that these measurements provide a useful noninvasive means of evaluating the degree to which the increase in pulmonary blood flow is constrained in response to exercise.

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OXYGEN UPTAKE at the lungs (VO₂) is the product of pulmonary blood flow and the difference in oxygen content between pulmonary vein and artery (Fick principle). Similarly, the dynamics of the increase in VO₂ at the start of exercise reflect the adjustments in pulmonary blood flow and arteriovenous oxygen difference [c(a–v)O₂] occurring in response to changing metabolic needs. The pattern and time course of the VO₂ response to exercise are well described in normal individuals. Figure 1 illustrates the changes observed in VO₂ when a normal individual proceeds from rest to constant-work rate exercise. As exercise begins, VO₂ increases abruptly, before venous blood from the exercising muscles has reached the central circulation. In these early seconds of exercise (phase I), the increase in VO₂ is determined almost exclusively by increased pulmonary blood flow rather than by changes in c(a–v)O₂. Accordingly, this initial response has been referred to as cardiodynamic gas exchange. After 15 to 20 sec of exercise, if the increment in VO₂ required by the work rate has not been achieved, VO₂ increases exponentially (phase II) to the exercise steady-state level. During this time, VO₂ reflects the changing cellular metabolism, and VO₂ kinetics are determined by the rate of increase in c(a–v)O₂ as well as any further increase in pulmonary blood flow. Oxygen content of the venous return during this phase is decreased to a greater extent than carbon dioxide content is increased because of the relatively greater tissue solubility of carbon dioxide. Thus a fall in the respiratory gas exchange ratio (R or PCO₂/PO₂) provides a marker for the beginning of phase II.

Because VO₂ kinetics are a function of blood flow and oxygen content in the pulmonary vasculature, the normal pattern described above may be altered when
the capacity to increase pulmonary blood flow or \( c(a - v)O_2 \) is constrained by disease. The capacity for increasing pulmonary blood flow is necessarily limited in patients with cyanotic congenital heart disease in whom pulmonary vascular resistance is increased. In this setting, the increase in venous return accompanying exercise may result in increased flow through the right-to-left shunt with little or no increase in flow through the pulmonary circulation.\(^{12, 13}\) The resulting increase in right-to-left shunt fraction causes a decrease in arterial oxygen content, and thereafter in central venous oxygen content, leaving less reserve for further widening of the pulmonary \( c(a - v)O_2 \).

Because the coexistence of an intracardiac right-to-left shunt and increased pulmonary vascular resistance may have profound effects on the determinants of alveolar \( V_O_2 \), we hypothesized that such patients would have abnormal \( V_O_2 \) kinetics in response to exercise. The reduced capacity to increase pulmonary blood flow at the start of exercise should be reflected in a reduction of the phase I \( V_O_2 \) response. Subsequently the combination of subnormal pulmonary blood flow and \( c(a - v)O_2 \) should be reflected in a slowing of the phase II \( V_O_2 \) response. To test these hypotheses, \( V_O_2 \) was measured breath-by-breath through the transition from rest to exercise in 13 adult patients with cyanotic congenital heart disease and in a control group of nine normal subjects who performed the same exercise protocol.

**Methods**

**Subjects.** Thirteen patients were selected from the UCLA Adult Congenital Heart Disease Program and the Harbor-UCLA Medical Center (table 1). Selection was based on the presence of cyanosis and the absence of contraindications to exercise testing. Eight patients were women and five were men, aged 24 to 46 years (mean age 34 years). Eleven patients had documented pulmonary vascular resistances at or above systemic level. The pulmonary vascular disease in patients 3 and 4 was a sequel to shunt operations for tetralogy of Fallot; the high pulmonary resistance in patient 2 resulted from large unobstructed aortopulmonary collaterals in the presence of tetralogy of Fallot and pulmonary atresia. Patient 13 had elevated, but subsystemic, pulmonary arterial pressures. Patient 12 had congenitally corrected transposition of the great arteries, moderate pulmonic stenosis (normal pulmonary arterial pressure), and a nonrestrictive ventricular septal defect. Ten of the 13 patients required therapeutic phlebotomy for symptomatic erythrocytosis. Nine normal volunteers of similar ages were recruited from hospital and laboratory personnel as control subjects. Their levels of fitness varied, but none was involved in an active training program. The project was approved by the institutional human subjects review committee and each subject gave written, informed consent before entering the study.

**Measurements.** To estimate the relative functional capabilities of the patients, each completed a questionnaire designed to ascertain the ability to perform a number of specific, common, daily activities.

All subjects performed exercise on an upright electromagnetically braked cycle ergometer. During the tests, the subjects breathed through a mouthpiece connected to a turbine volume transducer (Alpha Technologies). The volume transducer has a linear response of \( \pm 2\% \) throughout a range of flow rates of 6 to 200 liters/min. Before each study, the system was calibrated with known volumes of room air. Respiratory \( P_O_2 \), \( P_CO_2 \), and \( P_CO_2 \) were determined by mass spectrometry from a sample drawn continuously from the mouthpiece at 1 ml/sec. Known gas mixtures were used for calibration of the mass spectrometer. Delay times for the sample to reach the mass spectrometer were determined with each calibration. Heart rate was monitored beat-by-beat from the RR interval of the electrocardiographic signal.

Electrical signals from each transducer underwent analog-to-digital conversion for on-line, breath-by-breath computation of expired ventilation (\( V_E \)), respiratory exchange ratio (R), end-tidal \( P_O_2 \) and \( P_CO_2 \), and alveolar oxygen uptake (\( V_O_2 \)) and carbon dioxide output (\( V_CO_2 \)) (corrected for changes in lung gas stores) as previously described.\(^{14}\) Data from each test were displayed on-line and were simultaneously stored on digital tape for later analysis. Arterial oxygen saturation was monitored by ear oximetry (Biox II). In four patients, catheters were placed percutaneously into a brachial or radial artery for sampling of arterial blood for \( P_H, P_CO_2 \), and \( P_CO_2 \) determinations.

**Protocol.** The subjects were familiarized with the ergometer and mouthpiece before testing, and data collection was not begun until the subject appeared comfortable and ventilatory and gas exchange variables indicated a steady state. Each subject performed square-wave exercise tests consisting of 2 min of rest followed by 1 to 6 min of exercise. To obviate the need to overcome the inertia of accelerating the flywheel at the start of exercise, an electric motor was used to drive the flywheel at 60 rpm during the rest periods. The motor was then turned off as the subject began pedaling. The start of exercise was signaled by the change of a light from red to green within the subject’s view. To avoid startle responses, no verbal command was given.

For each patient an attempt was made to select a work rate that was low enough to achieve a steady state of \( V_O_2 \) within 3 to 4 min of exercise and that could be comfortably performed repeatedly in each testing session. Accordingly, the work rates employed ranged from \( "0" \) W (unloading cycling) to 20 W. Each patient completed six repetitions of the exercise test. Whenever possible, two 6 min tests and four 3 min tests were performed. Adequate time was allowed between repetitions for

\[ \text{FIGURE 1. Idealized representation (from data shown in ref. 6) of the } \]
\[ \text{normal pattern of oxygen uptake in response to constant–work rate exercise begun from rest. The phase III } V_O_2 \text{ level and the proportion of the increase in } V_O_2 \text{ occurring in phase II are dependent on the work rate, while work rate has a much smaller effect on the phase I increase (as drawn).} \]

\[ V_O_2 \text{ (liters/min)} \]

\[ \text{TIME (seconds)} \]
# PATHOPHYSIOLOGY AND NATURAL HISTORY—CONGENITAL HEART DISEASE

## TABLE 1

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<th>Subject</th>
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<th>Exercise $\dot{V}O_2$ (ml/min/kg)</th>
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[Hb] = hemoglobin; VSD = ventricular septal defect; PVD = pulmonary vascular disease; PA = pulmonary atresia; TOF = tetralogy of Fallot; BT = Blalock-Taussig anastomosis; PT = Pott’s anastomosis; ASD = atrial septal defect; CCTGA = congenitally corrected transposition of the great arteries; PS = pulmonic stenosis; DORV = double-outlet right ventricle; A-V = atrioventricular; S/P = status post.

\( ^* \text{a} \) = 7 patients (Nos. 3 to 9) achieving a steady state in exercise studies of 0 W work rate.

gas exchange, heart rate, and oxygen saturation to return to their resting baseline levels. The normal subjects also performed six repetitions from rest to exercise according to unloaded cycling and 20 W work rate exercise protocols.

**Analyses.** The breath-by-breath data from each of the six repetitions were converted to second-by-second data. To dampen noise and enhance resolution of reproducible events, the data from the six repetitions were temporally aligned to a mark at the start of exercise and superimposed to yield a single second-by-second averaged record for each subject. This averaged response was then used for data analysis.

The resting baseline value for any of the measured or calculated variables was taken as the averaged value over the 2 min before exercise. The exercise steady-state value was defined as the average value during the fifth and sixth minutes of exercise.

Based on results of previous studies showing that phase I of the gas exchange response lasts 15 to 20 sec in normal subjects,\(^2\) 3, 5, 7 phase I was defined as the first 20 sec of exercise, and the phase I component of the $\dot{V}O_2$ response was characterized as the cumulative increase in $\dot{V}O_2$ above its resting value during this period. The time course of the phase II response of $\dot{V}O_2$ was characterized as the time required to achieve half of the increment between the phase I value and exercise steady-state value, i.e., the half-time. The phase I and phase II responses of the patients were compared with those of the control subjects by the independent t test.

The activity questionnaire completed by each patient was graded by a numerical point system. Based on previously reported determinations of the metabolic cost (metabolic equivalents or "mets") of 21 different common daily activities,\(^15\) 16 the activities were divided into four groups of increasing metabolic cost. No points were assigned for activities that patients were reportedly unable to perform or for those they did not know whether they could perform. For each activity that the patient reported being able to perform to completion without stopping, points were assigned according to the following scoring system: 2 points were assigned for the one activity estimated to require 2 or 3 mets; 4 points were assigned for each of the nine activities estimated to require 3 to 5 mets; 6 points were assigned for each of the six activities requiring 5 to 7 mets; and 8 points were assigned for each of the five activities requiring 7 to 10 mets. The sum of points for each subject became his or her numerical activity score. The rank order of this score for the patient group was then correlated with the rank order of their
phase I $\dot{V}O_2$ response using Spearman’s rank correlation test. Data are presented as mean values ± 1 SD and statistical significance was defined at the level of $p < .05$.

**Results**

Nine of the patients performed transitions from rest to unloaded cycling, two from rest to a work rate of 10 W, one from rest to 15 W, and one from rest to 20 W. Of the normal subjects, all nine performed transitions from rest to unloaded cycling and six also performed transitions from rest to 20 W on separate testing days. Because different work rates result in different exercise steady states and might affect the time course of the responses, the data from the nine patients and nine normal subjects performing unloaded cycling form the basis of the following results, with reference to the other subjects and studies where appropriate.

$\dot{V}O_2$ response. Although both resting and unloaded cycling steady-state $\dot{V}O_2$ values were lower in the patients than in the normal subjects (282 ± 38 ml/min and 506 ± 35 ml/min for patients, and 330 ± 36 ml/min and 582 ± 86 ml/min for normal subjects; $p < .05$), there was no significant difference in these values when they were corrected for body weight (table 1). $\dot{V}O_2$ response dynamics to unloaded cycling for nine patients compared with nine normal subjects are shown in figure 2. That portion of the response occurring during phase I was significantly lower in the patients than in the normal subjects. Phase I data from all 22 individual subjects, including that from higher work rate exercise, show this to be a very consistent finding (figure 3). In fact, in three of the patients there was no discernible increase in $\dot{V}O_2$ until after 20 sec. The only phase I response that fell within the normal range was in patient 12, who was unique in the group in having normal pulmonary arterial pressure (table 1).

The half-times of phase II of the $\dot{V}O_2$ response could not be analyzed in two of the nine patients performing unloaded cycling because they did not achieve a steady state. In the remaining seven patients, the half-times were significantly longer than those in normal subjects (63 ± 13 vs 15 ± 13 sec) (figure 4). In three of the normal subjects the entire increment in $\dot{V}O_2$ required for unloaded cycling occurred during the first 20 sec of exercise (phase I), so there was essentially no phase II. In these subjects, the half-times were designated as 0 sec for purposes of data analysis.
Arterial blood oxygenation. Arterial oxygen saturation decreased in all patients during exercise. In most patients, the falling saturation was apparent by ear oximetry within 20 sec of the beginning of exercise. Arterial PO₂ values determined through the exercise transition in four patients confirmed this finding (figure 5).

Heart rate and oxygen pulse. The averaged heart rate data for seven normal subjects at rest and unloaded cycling and for 10 patients at all work rates are shown in figure 6. (The two patients who exercised for less than the full 6 min are not included in the figure, nor are two normal subjects and one additional patient whose electrocardiographic RR intervals could not be accurately analyzed by computer). In the patients, both resting and end-exercise heart rates were higher than those in the normal subjects (83 ± 10 and 109 ± 14 beats/min for patients vs 75 ± 7 and 85 ± 9 beats/min for normal subjects), although only the difference in exercise values was statistically significant (p < .01). The pattern of rise also differed in the two groups. Both had an increase in heart rate by about 15 beats/min during phase I. In the normal group, heart rate then decreased on average to a slightly lower plateau value. In the patient group, however, heart rate continued to increase and in most patients did not reach a steady state in the 6 min exercise period.

Oxygen pulse (ml of oxygen uptake per heart beat), obtained by dividing VO₂ by heart rate, is the product of stroke volume and (a – v)O₂. Because (a – v)O₂ is essentially constant during the first 20 sec of exercise, the phase I increase in oxygen pulse is an index of the corresponding increase in stroke volume. All of the normal subjects had an increase in oxygen pulse during phase I, and this increase was significantly greater in the normal subjects than in the patients (0.4 ± 0.5 ml oxygen/beat for patients vs 1.6 ± 0.7 ml oxygen/beat for normal subjects; p < .001) (figure 6). Four of the 11 patients in whom it could be evaluated had no measurable increase in oxygen pulse during phase I. The two remaining patients in whom oxygen pulse could not be evaluated were among the three who had no increase in VO₂ during phase I and therefore could not have had an increase in oxygen pulse. Thus six of the 13 patients had no significant phase I increase in oxygen pulse.

Activity assessment. Activity scores based on the activity questionnaire ranged from 4 to 76 out of a possible 114 for the 13 patients. The rank order of the patients with respect to this score was highly correlated with the magnitude of their VO₂ response during phase I (p < .01) (figure 7).

Discussion

The obligate relationship between cardiac output and VO₂ during exercise was recognized as early as 1913. Since then a number of experimental approaches have been used to demonstrate the effect of changing the cardiac output response to exercise on the
measured VO₂ response during phase I. Karlsson and Linnarson⁷ and Weill-Ravel et al.¹⁸ demonstrated that the phase I VO₂ response was attenuated if exercise was performed in the supine rather than upright position. The latter authors attributed this observation to the fact that venous return, cardiac output, and stroke volume are already elevated at rest in the supine position¹⁹ and thus increased very little at the start of exercise.¹⁸ Similar observations have been made when exercise was initiated from a baseline of unloaded cycling rather than from rest.¹ The use of pulsed Doppler²⁰ or impedance plethysmography¹¹ for the measurement of cardiac output during the exercise transition supports the concept of parallel changes in VO₂ and cardiac output in the early seconds of exercise.

The reports referred to above concern subjects with hearts in which right and left ventricular outputs were essentially equal. As noted previously, however, it is the changes occurring in the pulmonary circulation that determine VO₂ kinetics, a distinction that becomes important when the two circulations are congenitally dissociated, as in our patients. The small or absent VO₂ response during phase I in our cyanotic patients with pulmonary vascular disease is believed to reflect their known limited ability to increase pulmonary blood flow. Consistent with this conclusion is the larger phase I VO₂ response in patient 12, the only one who did not have pulmonary vascular disease (moderate pulmonary stenosis, nonrestrictive ventricular septal defect; table 1) and was therefore better able to increase pulmonary blood flow. Three patients in this study demonstrated no increase in VO₂ until 20 to 30 sec after the onset of exercise, implying that their pulmonary blood flows were fixed. The heart rate and oxygen pulse data indicate that in an additional three patients, the small increase in VO₂ during phase I was accomplished by an increase in heart rate alone without an increase in stroke volume.

Factors contributing to the kinetics of phase II are more complex. The very slow rise of VO₂ to the exercise steady state in the patient group is logically related both to the limited increase in pulmonary blood flow.

**FIGURE 6.** Heart rate and oxygen pulse responses to exercise in 10 patients (left) and seven normal subjects (right). Data are for all work rates in the patient group and for unloaded cycling studies in the normal subject group. The beginning of exercise is indicated by the solid vertical line, and the end of phase I by the interrupted line.

**FIGURE 7.** Rank order of phase I VO₂ as a function of rank order of activity score for 13 patients (p < .01). The line of identity is shown.
and the pattern of change in central venous oxygen content. The latter is dependent on systemic blood flow, rate of tissue extraction of oxygen, and the degree of arterial hypoxemia. The amount of oxygen extraction possible from the systemic capillary blood may in turn be affected by hemoglobin concentration since it determines oxygen carrying capacity, hematocrit level and red cell deformability since they affect blood viscosity and resistance to flow, and peripheral circulatory factors such as muscle capillary density, mitochondrial density, and oxidative enzyme levels since they affect oxygen extraction.

If both pulmonary arterial and pulmonary venous oxygen contents are changing simultaneously, the analysis becomes even more complex. The sigmoid shape of the oxyhemoglobin dissociation curve ensures that pulmonary venous blood is nearly fully saturated with oxygen and remains so during exercise even if there are minor fluctuations in alveolar Po2. However, a significant decrease in pulmonary venous oxygen saturation could occur in the exercise transition if there were either a considerable decrease in ventilation-perfusion matching or the development of diffusion limitation to oxygenation at the start of exercise. Because the patients reported here had relatively fixed pulmonary blood flows and did not have primary parenchymal lung disease, it is unlikely that during low level exercise they had either a significant increase in perfusion to poorly ventilated lung regions or a great enough increase in the rate of pulmonary blood flow to result in a change in oxygen equilibrium across the pulmonary capillary-alveolar membrane.

If pulmonary blood flow cannot increase in response to exercise, VO2 cannot increase until phase II when mixed venous oxygen content decreases and c(a-v)O2 across the pulmonary circulation widens. If it is assumed that most of the increase in right ventricular stroke volume induced by exercise occurs in phase I, the pattern of c(a-v)O2 change is approximated by the oxygen pulse measurement during phase II (figure 6). In the patient group, oxygen pulse increased during phase II, implying that despite the decreasing systemic arterial oxygen content (figure 5), c(a-v)O2 increased during phase II. This, together with the finding that heart rate increased in most patients throughout the exercise period, indicates that oxygen delivery did not increase adequately to meet the small increase in metabolic requirements imposed by unloaded cycling. This is in contrast to the normal subjects in whom heart rate often overshot the exercise steady-state level during phase I and then decreased slightly in phase II, suggesting that the blood flow increase during phase I was more than adequate to meet the oxygen requirement of the exercise.

The phase II half-times determined for the normal subjects were unusually rapid, in part because of the low work rates, which required little or, in some cases, no further increase in VO2 after the normal phase I increase. Many investigators have reported normal values for VO2 kinetics during exercise in human subjects, although to our knowledge none has analyzed kinetics at these very low work rates. Some investigators20,21 have reported VO2 half-times of 30 sec, regardless of the work rate performed. Others report that kinetics are somewhat prolonged by increasing work rates,22 by increasing work intensity,23 or at a given work rate by the untrained state.22,24 The VO2 half-times in these and other reports1,3,4,25 vary within a fairly narrow range, however, with mean values of 25 to 40 sec for a variety of testing protocols. In "untrained" individuals, exercising at 70% of maximal VO2, for example, Hagberg et al.22 reported an average VO2 half-time of 31 sec. Even this value is much lower than the half-times measured in the patients in this report.

Patients with cyanotic congenital heart disease have decreased exercise tolerance and low maximal VO2.26-29 Exercise capacity is presumably reduced because respiratory gas exchange is limited by the degree of pulmonary blood flow. Indeed, exercise performance in such patients has been correlated with pulmonary blood flow,29,30 and surgical procedures that increase pulmonary blood flow result in increased exercise capacity.31

We have shown that in addition to the previously described reduction in maximal gas exchange, certain patients with cyanotic congenital heart disease manifest marked abnormalities in their dynamic VO2 responses to submaximal exercise. Although in normal subjects, VO2 at the lungs closely reflects oxygen consumption in the tissues, intracardiac right-to-left shunting permits transient dissociation of these two processes because blood flow and c(a-v)O2 may be significantly different in the two circulations. This is important physiologically because the failure of VO2 to increase appropriately in response to increasing tissue oxygen requirements may compromise the ability to maintain an effective oxygen tension gradient between capillary and muscle mitochondria. In the chronically hypoxemic patient, this gradient may be near the critical level even at rest and may further decrease at the onset of exercise if the rate of increase of oxygen uptake at the lungs significantly lags behind the rate of increase of muscular oxygen consumption.
The phase I increase in VO$_2$ in response to exercise in the 13 patients with central venoarterial shunting strongly correlated with the patients’ reported functional status (figure 7). These findings are consistent with the known, requisite relationship between the VO$_2$ response and changing pulmonary blood flow and with the previously observed relationship between exercise capacity and resting pulmonary blood flow in similar patient populations. The capability of making objective quantitative measurements as described here may facilitate the serial evaluation of such patients in the course of their disease or in response to specific hematologic interventions such as phlebotomy. Thus the noninvasive measurement of VO$_2$ kinetics in response to a submaximal work rate yields data that reflect the fundamental pathophysiology in these patients with cyanotic congenital heart disease and is a potentially useful tool in clinical assessment and management.

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