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Control of ventilation during exercise in patients with central venous-to-systemic arterial shunts

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SIETSEMA, KATHY E., DAN M. COOPER, JOSEPH K. PERLOFF, JOHN S. CHILD, MICHAEL H. ROSOVE, KARLMAN WASSERMAN, AND BRIAN J. WHIPP *Control of ventilation during exercise in patients with central venous-to-systemic arterial shunts.* *J. Appl. Physiol.* 64(1), 234-242, 1988.—The diversion of systemic venous blood into the arterial circulation in patients with intracardiac right-to-left shunts represents a pathophysiological condition in which there are alterations in some of the potential stimuli for the exercise hyperpnea. We therefore studied 18 adult patients with congenital (16) or noncongenital (2) right-to-left shunts and a group of normal control subjects during constant work rate and progressive work rate exercise to assess the effects of these alterations on the dynamics of exercise ventilation and gas exchange. Minute ventilation (\dot{V}_E) was significantly higher in the patients than in the controls, both at rest (10.7 ± 2.4 vs. 7.5 ± 1.2 l/min, respectively) and during constant-load exercise (24.9 ± 4.8 vs. 12.7 ± 2.6 l/min, respectively). When beginning constant work rate exercise from rest, the ventilatory response of the patients followed a pattern that was distinct from that of the normal subjects. At the onset of exercise, the patients' end-tidal PCO_2 decreased, end-tidal PO_2 increased, and gas exchange ratio increased, indicating that pulmonary blood was hyperventilated relative to the resting state. However, arterial blood gases, in six patients in which they were measured, revealed that despite the large \dot{V}_E response to exercise, arterial pH and PCO_2 were not significantly different from resting values when sampled during the first 2 min of moderate-intensity exercise. Arterial PCO_2 changed by an average of only 1.4 Torr after 4.5-6 min of exercise. Thus the exercise-induced alveolar and pulmonary capillary hypocapnia was of an appropriate degree to compensate for the shunting of CO_2 -rich venous blood into the systemic arterial circulation. Arterial acid-base balance consequently appeared to be regulated similarly to that of normal subjects. We hypothesize that the patients' large increases in \dot{V}_E in response to exercise reflect primarily the stimulus from arterial pH- and PCO_2 -regulating mechanisms.

pulmonary circulation; cyanotic congenital heart disease; exercise hyperpnea; alveolar ventilation; acid-base regulation

blood, with reduced PO_2 and increased PCO_2 and H^+ concentration, introduces additional and potentially potent ventilatory stimuli into the systemic circulation, any of which might contribute to hyperpnea and dyspnea.

In the resting state hypoxemia is invariably present with significant right-to-left shunts. Hypercapnia is uncommon, however; in fact, most investigators report chronic hypocapnia in patients with cyanotic congenital heart disease (8, 12, 14, 24, 27, 28). During exercise, O_2 consumption and CO_2 production rise, changing the composition of central venous blood. In patients with right-to-left shunts, arterial blood gas tensions may therefore change considerably during exercise, particularly if the magnitude of the right-to-left shunt also increases appreciably (8, 9). The increment in flux of humoral ventilatory stimuli into the arterial blood should therefore depend on both the metabolic rate and the augmentation of the right-to-left shunt. The actual ventilatory response to the exercise stress will depend on the contribution of chemoreceptor stimulation to ventilatory control during exercise. Thus patients with variable degrees of right-to-left shunt are unique models for the study of the role of chemoreception in the ventilatory response to exercise, especially with respect to the arterial pH and blood gas regulatory features of the control. To investigate the effect of right-to-left shunt on exercise hyperpnea, we studied ventilatory and gas exchange dynamics, breath by breath, in 18 patients with right-to-left shunts and in a control group of normal subjects during both submaximal constant work rate exercise and symptom-limited progressive work rate exercise. The results demonstrated that exercise ventilation was considerably higher in patients than in control subjects. In addition, patients followed a pattern in the non-steady state that was distinctly different from normal controls. The abnormal pattern and increased magnitude of the exercise hyperpnea of the patients resulted in their maintaining relative constancy of systemic arterial pH and PCO_2 through the transition from rest to moderate exercise.

METHODS

Subjects. Eighteen adult patients with intracardiac right-to-left shunts were studied. Characteristics of the patients and their major diagnoses are shown in Table 1. Sixteen had cyanotic congenital heart disease, and two

INCREASED LEVELS of ventilation and exertional dyspnea occur commonly in patients with cyanotic congenital heart disease (8, 12, 14, 24). These patients, although heterogeneous with respect to their cardiac lesions, have in common diversion of venous blood into the systemic arterial circulation (right-to-left shunt). The shunted

TABLE 1. *Physical characteristics and cardiac diagnoses of subjects*

Subj No.	Age, yr	Sex	Wt, kg	Exercise Work Rate,* W	Resting Sa _o ₂ † %	Diagnoses
<i>Patients</i>						
1	45	F	49	0	69	Ventricular septal defect, PVD
2	29	F	49	0	50	Tetralogy of Fallot, pulmonary atresia
3	41	M	62	0	85	Tetralogy of Fallot, S/P BT, PVD
4	30	M	50	0	68	Tetralogy of Fallot, S/P PT, PVD
5	24	F	59	0	92	Single ventricle, PVD
6	31	F	48	0	81	Atrial septal defect, PVD
7	46	F	57	0	88	Ventricular septal defect, PVD
8	26	M	67	0	80	Single ventricle, PVD
9	34	F	57	0	80	Common A-V canal, PVD
10	32	F	55	0	73	Single ventricle, PVD
11	32	F	60	10	76	Ventricular septal defect, PVD
12	29	F	74	15	93	Atrial septal defect, PVD
13	29	M	77	10	92	Atrial septal defect, PVD
14	30	M	57	20	94	Double outlet right ventricle, PVD
15	46	M	70	10	93	Ventricular septal defect, CCTGA, PS
16	28	F	57	15	77	Single ventricle, pulmonary atresia, S/P BT
17	42	M	77	20	94	Recurrent PE, PH, patent foramen ovale
18	63	F	62	0	94	Idiopathic PH, patent foramen ovale
Mean±SD	35±10		60±9		82±12	
<i>Normal subjects</i>						
1	30	F	49	0		
2	23	M	59	0		
3	29	M	66	0		
4	24	F	61	0		
5	26	F	61	0		
6	35	M	78	0		
7	36	M	76	0		
8	21	F	50	0		
9	31	M	62	0		
Mean±SD	28±5		62±10			

PVD, pulmonary vascular disease; PH, pulmonary hypertension; S/P BT, status-post Blalock-Taussig anastomosis; S/P PT, status-post Pott's anastomosis; CCTGA, congenitally corrected transposition of the great arteries; PE, pulmonary emboli; PS, pulmonic stenosis; A-V, atrioventricular. * Work rates for constant-load exercise tests; work rates designated as 0 W represent unloaded cycling (a true work rate of ~7 W). † Resting O₂ saturation (Sa_o₂) determined as mean value measured by ear oximeter during resting periods preceding onset of constant-load exercise.

had right-to-left shunts through patent foramina ovale, consequent to systemic level pulmonary hypertension acquired as adults (idiopathic in one and recurrent pulmonary emboli in the other). Thirteen of the patients with cyanotic congenital heart disease had pulmonary vascular resistances at or above systemic levels, and one had elevated but subsystemic pulmonary vascular resistance (*patient 14*). The two others had pulmonic stenosis or atresia (*patients 15* and *16*, respectively) with normal pulmonary arterial pressures distal to the stenosis.

Nine subjects of similar ages but without cardiac or pulmonary disease served as controls (Table 1).

The project was approved by the Institutional Human Subjects Committee, and all subjects gave written informed consent before participation.

Measurements. Exercise was performed on an upright electromagnetically braked cycle ergometer. During the tests, the subjects breathed through a mouthpiece connected to a turbine volume transducer (SensorMedics). Before each study, the system was calibrated using known volumes of room air. The volume transducer has a linear response varying less than ±2% over a flow range of 6–200 l/min. Respired PO₂, PCO₂, and PN₂ were deter-

mined by mass spectrometry (Perkin-Elmer) from a sample drawn continuously from the mouthpiece at 1 ml/s. Known gas mixtures were used for calibration. Delay times for the sample to reach the mass spectrometer relative to the flow signal were determined with each calibration as previously described (3, 5). Arterial O₂ saturation was monitored by ear oximetry (Biox II).

Electrical signals from each transducer underwent analog-to-digital conversion for on-line, breath-by-breath computation of expired (\dot{V}_E) and inspired (\dot{V}_I) ventilation, respiratory exchange ratio (R), end-tidal PO₂ and PCO₂, and alveolar (i.e., corrected for changes in lung gas stores) O₂ uptake ($\dot{V}O_2$) and CO₂ output ($\dot{V}CO_2$) using a Hewlett-Packard model 1000 digital computer as previously reported (3, 5). Data from each test were displayed on-line on a strip-chart recorder and were simultaneously stored on digital tape for later analysis. Catheters were placed percutaneously into a brachial artery in six patients for blood sampling for determination of arterial pH, PCO₂, and PO₂.

Protocols. Both constant and progressive work rate exercise tests were done.

Each subject performed constant work rate exercise

tests from rest. To obviate the need to overcome inertia in accelerating the ergometer flywheel at the start of exercise, an electric motor was used to drive the flywheel at 60 rpm during the rest periods while the pedals remained motionless; the motor was automatically turned off in synchrony with the start of exercise. The signal to begin exercise consisted of a change from red to green of a light positioned in front of the subject. The subjects were familiarized with the testing equipment and procedures before beginning the studies, and data collection was not begun until the subject appeared comfortable and relaxed and until monitored variables indicated a steady state. The subjects were quietly reminded to watch for the start signal 30–60 s before each test, but no verbal command was given at the time of exercise onset.

For each patient, an attempt was made to select a work rate that was low enough to achieve a steady state of gas exchange by 3–4 min and that could be comfortably performed repeatedly in each testing session. Accordingly, the work rates employed ranged from unloaded cycling ("0" W, actually shown to be a work rate of ~7 W on calibration) to 20 W. Each subject 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 gas exchange, ventilation, heart rate, and O₂ saturation to return to their resting base-line levels. The normal subjects also performed six repetitions of 3–6 min of unloaded cycling exercise begun from rest.

Fifteen of the 18 patients and all control subjects performed progressive exercise tests consisting of a warm-up period of 2 or 3 min of unloaded cycling followed by increasing work rate either continuously (ramp) or at 1-min intervals (36). The rate of increase of work rate varied from 5 to 10 W/min by either method. The tests were symptom limited in that the patients were instructed to stop exercise at such a time as he or she experienced symptoms that would normally lead to termination of activities in daily routine. Thus no attempt was made to ensure that a true maximal exercise level was achieved.

Analysis. Breath-by-breath data from the six constant work rate tests for each subject were time-averaged on a second-by-second basis after alignment of the data to a mark at the start of exercise as previously described (4). The time-averaged constant work rate tests for each subject were used to determine ventilation and gas exchange dynamics. The dynamic responses were defined as having three phases: phase I consisted of the first 15–20 s (before humoral stimuli reflecting the increase in muscle metabolism reaches the central circulation), which is normally characterized by abrupt increases in $\dot{V}E$ and gas exchange; phase II consisted of the time of the subsequent rise of variables from the end of phase I to steady-state levels; and phase III represented the steady state. Resting values of the measured variables were taken as the average for the 2 min before exercise onset. Steady-state exercise responses were taken as the average for the 6th min of exercise. Phase I values were defined as the level at which gas exchange or $\dot{V}E$ plateaued after the initial increase (lasting for 15–20 s) after

exercise onset, as previously described (20, 21, 37). If a clear plateau was not apparent, the value attained by 20 s exercise was considered to represent the phase I response.

Data from the patient group were compared with those of the control group using the unpaired *t* test. The correlations between subject variables and measured responses were tested using linear regression. Changes in arterial blood gas values during exercise were analyzed using analysis of variance and Dunnett's multiple range test for repeated measures. Data are presented as means \pm SD, and significance was defined at the level of $P < 0.05$.

RESULTS

All 18 patients performed constant work rate exercise tests. For 11 of the patients the work rate employed was unloaded cycling; two of these patients, however, were unable to sustain pedaling long enough to attain a steady state for gas exchange. The unloaded cycling exercise resulted in an average increase in $\dot{V}O_2$ of 223 ± 37 ml/min for the nine patients and 252 ± 65 ml/min for the controls (i.e., approximately doubling resting metabolic rate). The other seven patients performed exercise at a work rate of 10, 15, or 20 W (Table 1). Because different work rates result in different steady-state levels of ventilation and gas exchange, the results pertaining to steady-state exercise will be presented as the average responses of the nine normal subjects and the nine patients who were able to complete 6 min of unloaded cycling exercise. The other patients will be included in discussion of phase I responses and progressive work rate exercise responses.

The dynamic changes in $\dot{V}O_2$ and heart rate during exercise in 13 of the subjects has been reported previously (25).

Steady-state $\dot{V}E$ responses. Resting and steady-state exercise $\dot{V}E$ levels were increased in the patients compared with the control subjects (Fig. 1) (rest: 10.7 ± 2.4 l/min for patients vs. 7.5 ± 1.2 for controls; exercise: 24.9 ± 4.8 l/min for patients vs. 12.7 ± 2.6 for controls). The increase in ventilation induced by unloaded cycling exercise was also greater in the patients (14.2 ± 3.3 vs. 5.2 ± 1.7 l/min).

Neither the resting arterial O₂ saturation nor the change in saturation during exercise (Fig. 2) was found to have a significant correlation with the change in $\dot{V}E$ during exercise (correlation coefficients: -0.31 and 0.16 , respectively).

Phase I $\dot{V}E$ responses. The greater ventilatory response of the patients was evident immediately at the onset of exercise (Fig. 1). The increase in $\dot{V}E$ during phase I was 6.63 ± 3.01 l/min above resting levels in the patients, which was significantly greater than the 3.29 ± 0.94 l/min increase of the normal subjects. When expressed as the percent increase in $\dot{V}E$ above resting levels, the difference between the phase I ventilatory responses in patients and normal subjects is less marked ($63 \pm 32\%$ for patients and $45 \pm 15\%$ for normal subjects) and does not reach statistical significance due to the wide range of responses in the patient group.

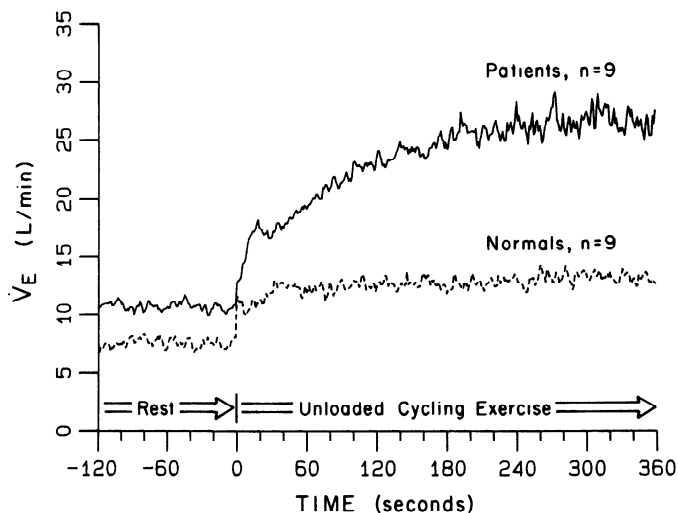


FIG. 1. Ventilatory response to exercise in patients with right to-left shunts and in normal subjects. Data are averaged responses of 9 patients (—) achieving a steady state of unloaded cycling exercise and 9 normal subjects (---) performing the same protocol. Exercise began at time 0. \dot{V}_E , minute ventilation.

In the normal group, the percentage increase in \dot{V}_E during phase I was, on average, of similar magnitude as the corresponding increase in $\dot{V}O_2$ (Fig. 3). In the patients, however, the \dot{V}_E responses in phase I were consistently greater than the $\dot{V}O_2$ responses, which were significantly less than normal (25).

\dot{V}_E and gas exchange. When steady-state \dot{V}_E is plotted as a function of $\dot{V}CO_2$ during rest and exercise, it is apparent that the ventilatory cost of clearing a given amount of CO_2 is increased in the patient group (Fig. 4).

There was a characteristic pattern of \dot{V}_E and gas exchange response to constant work rate exercise in the patients with right-to-left shunts. This pattern is illustrated in Fig. 5, which shows data from one representative patient and an age- and sex-matched control subject. \dot{V}_E increased abruptly at exercise onset in the patient, accompanied by a decrease in end-tidal PCO_2 (PET_{CO_2}) of 2.5 Torr and an increase in end-tidal PO_2 (PET_{O_2}) of 5 Torr, indicating that pulmonary capillary blood was acutely hyperventilated relative to the resting state. This is not a phenomenon typically observed in normal subjects who initially have no change and then an increase in PET_{CO_2} and decrease in PET_{O_2} by the end of phase I. These levels are then maintained during phases II and III of moderate exercise (Fig. 5). The end-tidal gas tensions thus changed in the opposite directions in the patient compared with the control and remained relatively constant throughout the remainder of exercise. The response pattern to constant work rate exercise was typical of all of the patients, regardless of the presence or absence of pulmonary hypertension or whether the shunt was congenital or acquired.

The large and abrupt ventilatory responses of the patients resulted in $\dot{V}CO_2$ increasing more than $\dot{V}O_2$ at exercise onset. This disparity persisted throughout the non-steady state with the result that R , having increased above 1 initially, decreased gradually to the exercise steady-state level as $\dot{V}O_2$ and $\dot{V}CO_2$ reached their steady-state levels (Fig. 5). This is in contrast to the response

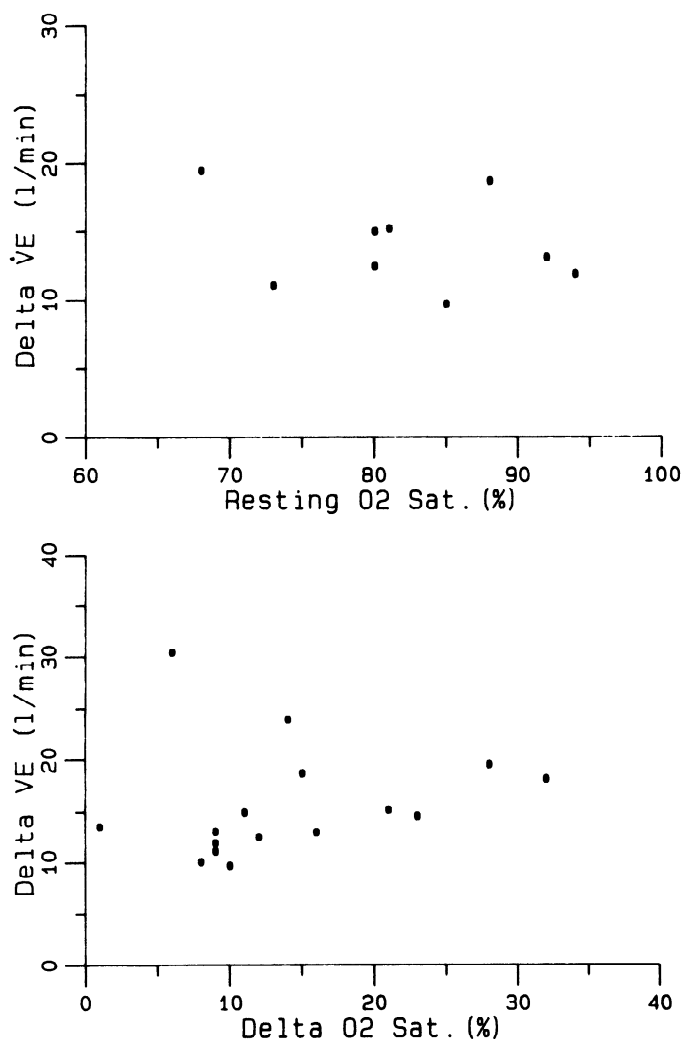


FIG. 2. Increase in \dot{V}_E during exercise as a function of degree of arterial desaturation. Top: increment in minute ventilation (\dot{V}_E) during unloaded cycling as a function of resting O_2 saturation ($n = 9$, i.e., those patients achieving a steady state of unloaded cycling exercise). Bottom: \dot{V}_E response to exercise as a function of accompanying decrease in arterial O_2 saturation ($n = 16$, i.e., those patients achieving a steady state for gas exchange during exercise of any work rate).

in normal subjects in whom R remains stable during phase I and then decreases transiently during phase II consequent to $\dot{V}O_2$ kinetics leading those of $\dot{V}CO_2$ (6, 21, 37). Although the \dot{V}_E increase is greater in the patient in phase I, $\dot{V}CO_2$ and $\dot{V}O_2$ responses are smaller in the patient compared with the control during this phase.

In contrast to the findings during constant work rate exercise, during increasing work rate exercise, PET_{CO_2} decreased progressively and PET_{O_2} and $\dot{V}_E/\dot{V}CO_2$ progressively increased (Fig. 6).

Arterial blood oxygenation and acid base. Systemic arterial O_2 saturation, as determined by ear oximetry for the 15 patients in whom continuous records are available, is shown in Fig. 7. All patients had a decrease in arterial O_2 saturation during exercise, in most cases beginning immediately at the onset of pedaling.

Arterial blood PCO_2 and pH obtained in six of the patients during exercise are shown in Fig. 8. Despite diversion of the CO_2 -rich venous blood into the systemic arterial circulation during exercise and despite the un-

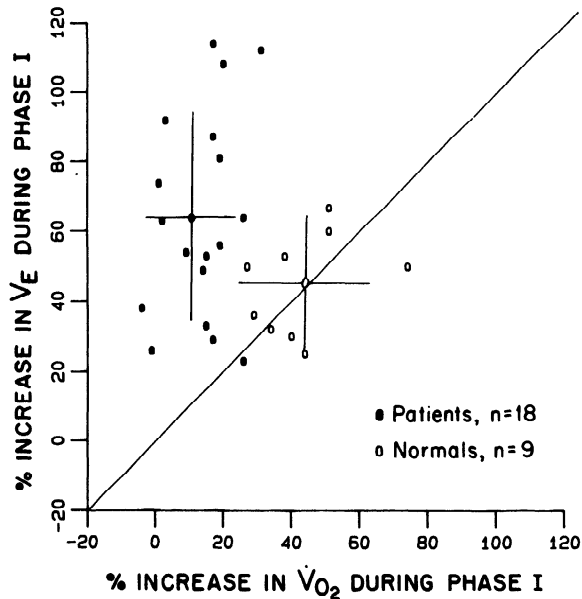


FIG. 3. Relative increase in minute ventilation (\dot{V}_E) and O_2 uptake ($\dot{V}O_2$) during phase I of exercise in patients and normal subjects. For patient group ($n = 18$) \dot{V}_E increased by $63 \pm 32\%$ and $\dot{V}O_2$ by $13 \pm 10\%$ in phase I. For normal subjects ($n = 9$) \dot{V}_E increased by $45 \pm 15\%$ and $\dot{V}O_2$ by $43 \pm 14\%$ in phase I. Mean values \pm SD and line of identity are drawn.

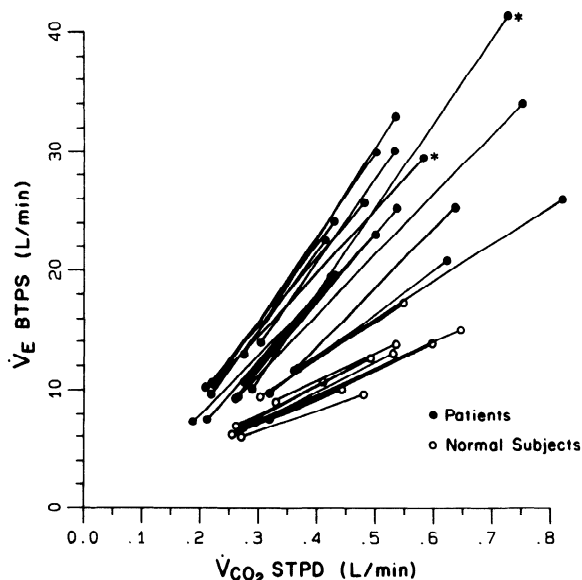


FIG. 4. Minute ventilation (\dot{V}_E) as a function of CO_2 output ($\dot{V}CO_2$) at rest and in steady state of exercise for 16 patients achieving an exercise steady state and 9 normal subjects. * Patients with normal pulmonary vascular pressures.

usually large \dot{V}_E response to exercise, arterial PCO_2 and pH remained relatively unchanged from rest immediately after the start of exercise. For five patients in whom blood gases were determined during constant work rate exercise, the arterial PCO_2 of the first sample collected after exercise onset (30–120 s into exercise) was within 1 Torr of the resting value (range -1 to $+1$, mean -0.4) (NS). For the last blood sample drawn (4.5–6 min into exercise) arterial PCO_2 was an average of 1.4 Torr above resting levels (range 0–3 Torr), which was statistically significant. Neither the first nor last sample of blood drawn during constant work rate exercise had a pH that

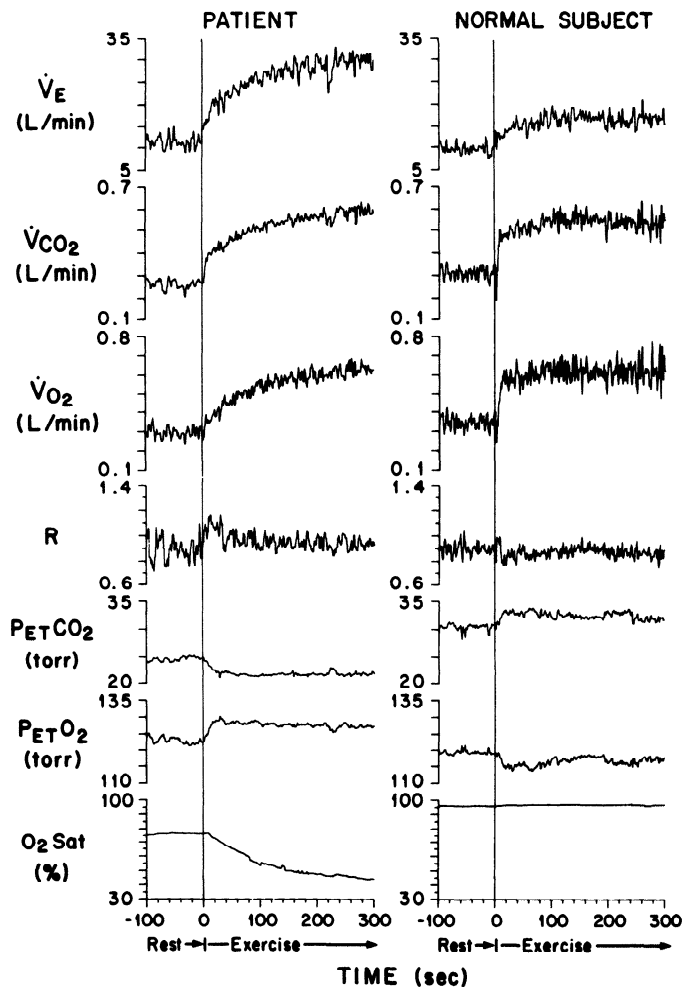


FIG. 5. Pattern of change of ventilation, gas exchange, end-tidal gas tensions, and O_2 saturation after transition from rest to exercise in 1 representative patient with congenital heart disease (left) and 1 normal subject (right). Two subjects have similar resting and steady-state exercise O_2 uptake ($\dot{V}O_2$) levels (using 15-W and 20-W work rates for patient and normal subject, respectively), and variables are shown scaled identically. Each data set is averaged response of 6 individual repetitions of study as described in text. Exercise began at time 0. \dot{V}_E , minute ventilation; $\dot{V}CO_2$, CO_2 output; $\dot{V}O_2$, O_2 uptake; R, respiratory exchange ratio; $PETCO_2$, end-tidal PCO_2 ; $PETO_2$, end-tidal O_2 ; O_2 Sat, O_2 saturation.

was significantly different from the resting values.

For the progressively increasing work rate tests, arterial PCO_2 rose by 3–7 Torr in the congenital heart disease patients at maximal exercise and decreased only in patient 17 (Fig. 8), who had a small, noncongenital right-to-left shunt.

DISCUSSION

After the onset of constant work rate exercise, initiated from rest, there is normally an abrupt increase in \dot{V}_E to a level that is maintained for ~ 15 – 20 s (phase I), followed by an exponential increase in \dot{V}_E (phase II) to the exercise steady-state level, provided that the work rate is sufficiently large to require a steady state (phase III) \dot{V}_E discernibly greater than that obtained in phase I (20, 21, 37). The phase I increase in \dot{V}_E and therefore $\dot{V}CO_2$ is normally proportional to that of $\dot{V}O_2$, with the result that R generally remains at resting levels (21, 35, 37). There-

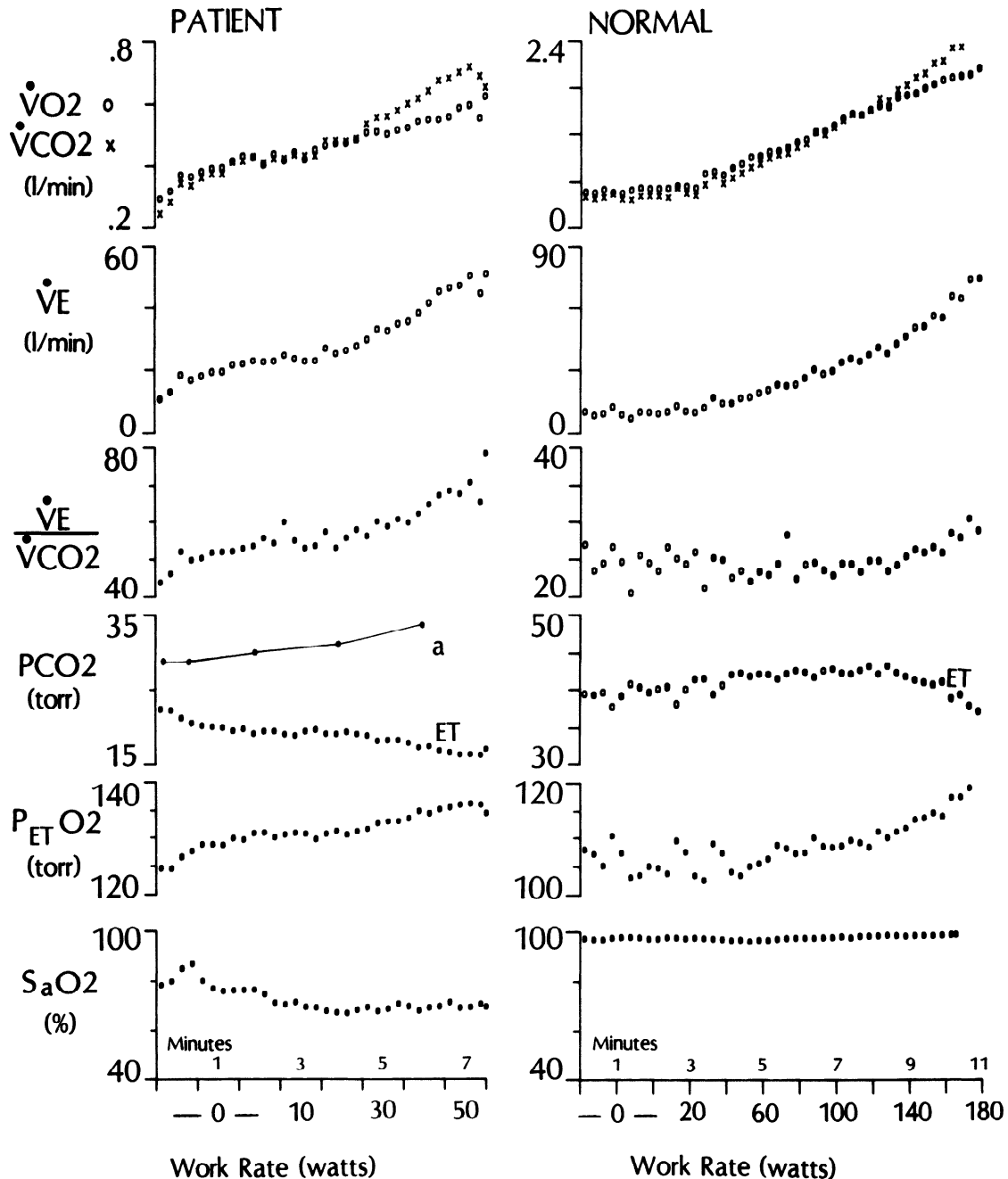


FIG. 6. Ventilation, gas exchange, end-tidal gas tensions, arterial PCO_2 , and arterial O_2 saturation (S_{aO_2}) for 1 patient (left) and 1 normal subject of similar size, age, and gender (right) during increasing work rate exercise. Work rate was increased by 10 W/min for patient and by 20 W/min for normal subject. See legend to Fig. 5 for definitions of abbreviations.

after, in phase II, the dynamics of the increase in $\dot{V}E$ track closely those of $\dot{V}CO_2$, both responses being slower than that of $\dot{V}O_2$ (6, 21, 37). Arterial pH and PCO_2 change little (1, 2, 13) throughout this non-steady state.

It has been suggested that the $\dot{V}E$ response in phase I is initiated by neuronal mechanisms originating in the cortex (11) or in response to movement (19) or metabolic changes (30) in the exercising limbs, or to central circulatory changes such as pulmonary vascular pressures or flows (17, 18, 22). The stability of arterial pH and PCO_2 in the steady state of moderate intensity exercise (15, 16, 31) has suggested to some investigators that after the initial response, $\dot{V}E$ is modulated by input from chemo-

receptors sensitive to PCO_2 or H^+ (7, 32).

We have demonstrated that patients with right-to-left shunts have larger-than-normal increases in $\dot{V}E$ in phase I. This results in acute alveolar hyperventilation (i.e., end-tidal gas tensions change abruptly and in the opposite direction from normal) (Fig. 5). There are several findings of note in the dynamic response to exercise in these patients. First, in phase I, $\dot{V}E$ increases more than $\dot{V}O_2$. If the phase I increase in $\dot{V}O_2$ is normally considered to be dependent to a great extent on an increase in pulmonary blood flow (23, 33, 35), then it is clear that in these patients the ventilatory response is dissociated from simultaneous changes in pulmonary blood flow. In

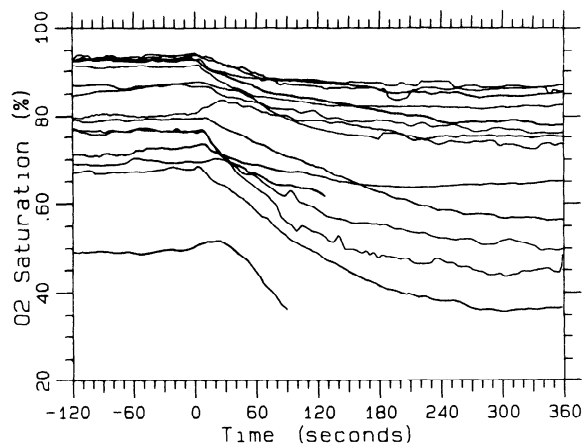


FIG. 7. Arterial O_2 saturation as determined by ear oximetry during constant work rate exercise ($n = 15$, i.e., all patients for whom continuous oximetry records were available). Exercise began at time 0.

addition, the pattern of response was similar in all patients, despite considerable heterogeneity with respect to their underlying cardiac lesions and the duration and degree of hypoxemia. Although only two of the patients had normal pulmonary vascular pressures (determined from prior cardiac catheterizations), their ventilatory responses were indistinguishable from the remainder of the group, indicating that pulmonary hypertension per se was not critical in determining this response. However, one could not rule out a ventilatory stimulus arising from pressure changes elsewhere in the right side of the circulation.

Despite the marked increase in \dot{V}_E and associated alveolar hyperventilation in the patient group, acute respiratory alkalemia was not observed. The ventilatory responses were therefore of appropriate magnitude to

accommodate both the increase in CO_2 flow to the lungs due to increased metabolic rate and the increase in CO_2 delivery into the arterial circulation via the right-to-left shunt. An increase in shunt fraction at the start of exercise is evidenced by the fall in O_2 saturation measured by ear oximeter in most patients during phase I of exercise (i.e., before central venous O_2 saturation would be expected to reflect the increase in muscle O_2 extraction).

Carotid body function has been reported to be abnormal in patient groups such as ours. Edelman et al. (10) and Sørensen and Severinghaus (26) have reported that patients with lifelong hypoxemia due to cyanotic congenital heart disease have blunted ventilatory responses to hypoxemia. Consistent with these observations, we found no correlation between the degree of hypoxemia or change in hypoxemia during exercise and the change in \dot{V}_E with exercise. In contrast to patients who have had carotid body resection and in whom ventilation in phase I was observed to increase normally (34), the right-to-left shunt patients have greater than normal \dot{V}_E responses in phase I. This could be interpreted as reflecting a higher "gain" for normal neurogenic ventilatory stimuli at exercise onset, the presence of abnormal stimuli related to increased cardiac or pulmonary arterial pressures, or the influence of arterial chemoreceptor function responding to the pH and/or PCO_2 changes caused by the shunted blood. The relative stability of arterial pH and PCO_2 in early exercise is consistent with the latter.

An increasing \dot{V}_E/\dot{V}_{CO_2} relationship during exercise has been reported by others (9, 12, 14, 29) in similar patient groups. Among the factors postulated to account for this is an abnormal increase in dead space-to-tidal volume ratio (V_D/V_T) during exercise. Gold et al. (14)

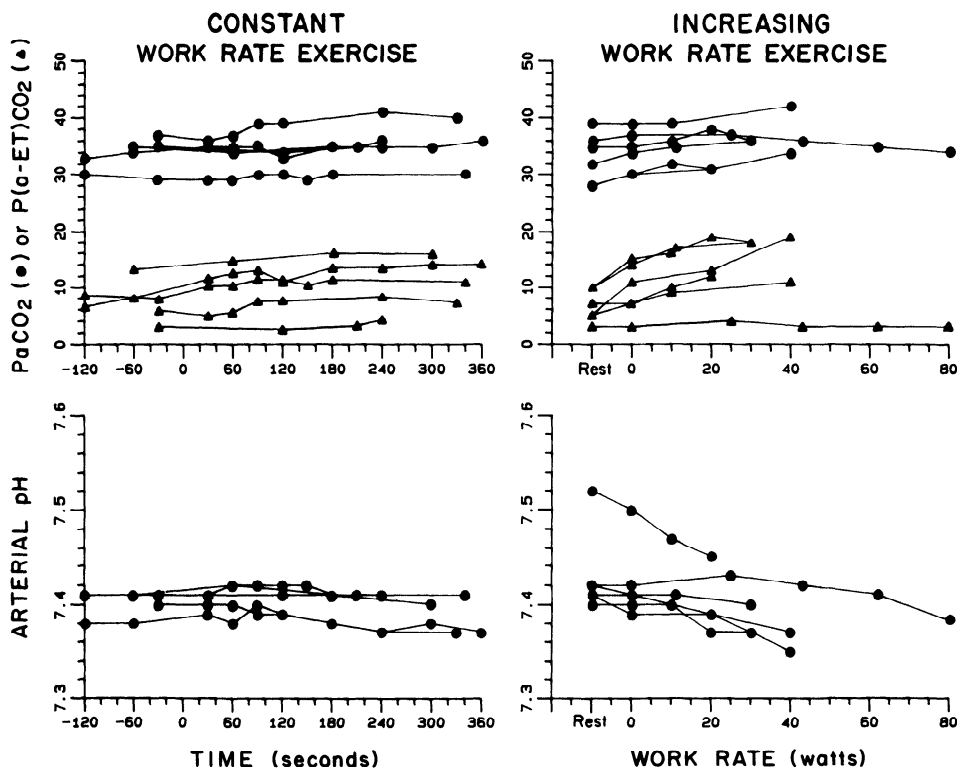


FIG. 8. Arterial PCO_2 (P_{aCO_2}), pH, difference between arterial and end-tidal PCO_2 and $[P(a-ET)CO_2]$ values for 5 patients during constant work rate exercise (left) and in 6 patients during increasing work rate exercise (right).

used arterial PCO_2 values to solve the modified Bohr equation for VD/VT in patients with shunt-operated tetralogy of Fallot and concluded that alveolar dead space did increase with exercise. In the presence of large right-to-left shunts, however, systemic arterial PCO_2 is not the same as ideal alveolar PCO_2 , and the disparity becomes even greater during exercise when mixed venous CO_2 content increases. In this setting, paradoxically, the calculated VD/VT actually reflects the magnitude of the shunt fraction.

Theodore et al. (29) reported a similarly elevated $\dot{V}E/\dot{V}CO_2$ response to exercise in a group of patients who were candidates for heart-lung transplantation, half of whom had right-to-left shunts due to cyanotic congenital heart disease. They attributed this to the presence of pulmonary hypertension presenting an additional drive to ventilation during exercise. The absence of acute respiratory alkalosis, either in our data or in their own (29), argues against the presence of additional exercise hyperpnea in excess of what is seen in normal subjects. In the present study the finding of comparable responses to exercise in patients with and without pulmonary hypertension suggests that it is the presence of the shunt itself rather than pulmonary hemodynamics that accounts for the marked hyperpnea.

The latter conclusion is consistent with the observations of Davies and Gazetopoulos (8), Eriksson and Bjarke (12), and Streider et al. (27), who noted that venous-to-arterial shunting of CO_2 increased the ventilatory requirements for a given metabolic rate in patients with cyanotic congenital heart disease. However, our study also examines the dynamics of the exercise response and makes the additional observations that the unusually large ventilatory response of these patients begins in the earliest phase after exercise onset and that with modest work rates the response is nearly isocapnic. In contrast, Davies and Gazetopoulos and Eriksson and Bjarke emphasized the development of respiratory acidosis in their patient groups during exercise. Davies and Gazetopoulos grouped their subjects according to resting O_2 saturation and observed that exercise-induced respiratory acidosis was most prominent in patients with the most severe cyanosis and therefore the largest right-to-left shunts. Hypercapnia was also evident in our patients during the progressive work rate exercise (Figs. 6 and 8) in which the CO_2 flow to the central circulation progressively increases. Our finding of little or no change in arterial PCO_2 during the constant work rate tests may therefore be dependent on the work rate selected. With a relatively modest increase in $\dot{V}CO_2$ in patients whose shunt fraction was not extremely large, arterial PCO_2 and pH may be regulated without difficulty. In contrast, at higher rates of CO_2 production and/or larger right-to-left shunts, the alveolar hyperventilation may not be sufficient to compensate for the CO_2 flow which bypasses the lungs. In these settings, as in our progressive exercise protocol, respiratory acidosis may result.

The ventilatory response to moderate-intensity exercise in patients with right-to-left shunts, although resulting in acute alveolar hyperventilation, is shown here to be effectively normal with respect to its influence on

systemic arterial pH homeostasis. Consequently, while not excluding the possibility that this acid-base regulation results from a fortuitous balance between ventilatory drives unrelated to pH homeostasis and the amount of CO_2 which bypasses the lungs, the consistency of the blood gas regulation throughout the transient in our subjects suggests that humoral factors such as PCO_2 , CO_2 flow, and/or H^+ may be involved in the control of ventilation in even the earliest phase of exercise.

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