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Effects of Chronic Hypoxemia on Chemosensitivity in Patients With Univentricular Heart

TUAN PENG CHUA, BSc, MD, MRCP, LAURENCE ISERIN, MD,
JANE SOMERVILLE, MD, FRCP, FACC, ANDREW J. S. COATS, DM, FRCP, FACC

London, England, United Kingdom

Objectives. **We sought to compare the arterial blood gas chemosensitivity in relation to exercise ventilatory response in patients with univentricular heart and cyanosis and in patients with univentricular heart and Fontan-type circulation without cyanosis.**

Background. **Patients with univentricular heart demonstrate excessive ventilation during exercise. Chronic hypoxemia may alter chemoreceptor function, affecting ventilation.**

Methods. **Cardiopulmonary exercise testing was performed in 10 patients with rest or stress-induced cyanosis (cyanotic group: mean age ± SE 30.5 ± 2.3 years; 5 men), 8 patients without cyanosis with Fontan-type circulation (Fontan group: mean age 29.4 ± 1.5 years; 4 men) and 10 healthy control subjects (normal group: mean age 30.7 ± 1.9 years; 5 men). Hypoxic and hypercapnic chemosensitivity were assessed by using transient inhalations of pure nitrogen and the rebreathing of 7% CO_2 in 93% O_2, respectively.**

Results. **Peak O_2 consumption was comparable in both patient groups (21.7 ± 2.5 [cyanotic group] vs. 21.0 ± 1.9 ml/kg per min [Fontan group]) but was lower than that in the normal group (34.7 ± 1.9 ml/kg per min). The ventilatory response to exercise, characterized by the regression slope relating minute ventilation to CO_2 output, was higher in the cyanotic group (43.4 ± 4.0) than in the Fontan group (31.4 ± 3.0, p = 0.02) and the normal group (23.1 ± 1.1). Hypoxic chemosensitivity was blunted in the cyanotic group compared with that in the Fontan and normal groups (0.148 vs. 0.448 [p = 0.02] vs. 0.311 liter/min per percent arterial O_2 saturation, respectively) and did not correlate with the ventilatory response to exercise (r = −0.36, p = 0.29). In contrast, hypercapnic chemosensitivity represented by the slope of the hypercapnic-ventilatory response line was similar in the cyanotic, Fontan and normal groups (1.71 vs. 1.76 vs. 1.70 liter/min per mm Hg, respectively), but the response line had shifted to the left in the cyanotic group (x intercept = 31.9 vs. 39.9 mm Hg [p = 0.026]), compared with 45.2 mm Hg in normal subjects. These findings suggest that in the cyanotic group, ventilation is greater for a given level of arterial CO_2 tension and thus may partly explain the increased exercise ventilatory response in this group.**

Conclusions. **Hypoxic chemosensitivity is blunted in patients with univentricular heart and cyanosis and does not determine the exercise ventilatory response. CO_2 elimination appears more important. The blunting of hypoxic chemosensitivity is reversible once chronic hypoxemia is relieved, as evident in the Fontan group.**

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Univentricular hearts by definition have both atrioventricular (AV) valves or a common AV valve open into a single ventricular chamber (1). Patients who have had a palliative operation such as a Blalock-Taussig shunt continue to have cyanosis and ventricular overload. Over the last 20 years, however, more definitive operations, undertaken during childhood or early adult life, have aimed to reduce ventricular overload and to correct hypoxemia. In the Fontan operation (2) or modifications of it (3), the systemic venous return is directed to the pulmonary artery, with a direct connection between the right atrium and the main pulmonary artery or a cavopulmonary connection that bypasses the right atrium. Consequently, both ventricular overload and cyanosis are reversed or reduced (4,5).

Patients with univentricular heart demonstrate excessive exercise ventilation, whose mechanisms are not fully understood (6). Chemoreceptor function is important in the control of ventilation, and a significant correlation has been demonstrated between chemosensitivity and the exercise ventilation in healthy subjects (7,8). However, chemoreceptor function may be altered by the chronic hypoxemia present in patients with univentricular heart. Indeed, chronic hypoxemia has been reported (9) to blunt the hypoxic chemosensitivity in patients with cyanotic heart disease.

The objective of this study was to investigate the effects of chronic hypoxemia on the chemosensitivity in patients with univentricular heart and cyanosis. Specifically, both the hy-

From the Department of Cardiac Medicine and Grown-up Congenital Heart (GUCH) Unit, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College School of Medicine, London, England, United Kingdom. Dr. Chua was the recipient of a Junior Research Fellowship from the British Heart Foundation, London. Dr. Iserin was supported by the Federation Francaise de Cardiologie, Paris, France; and Dr. Coats is the Viscount Royston Professor of Clinical Cardiology.

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Address for correspondence: Dr. Tuan Peng Chua, Department of Cardiac Medicine, National Heart and Lung Institute, Dovehouse Street, London SW3 6LY, England, United Kingdom.

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Abbreviations and Acronyms

ANOVA = one-way analysis of variance
AV = atrioventricular
Sa_{O_2} = arterial O_2 saturation

poxic and the hypercapnic chemosensitivity of these patients were determined. The relation between chemosensitivity and the exercise ventilatory response was studied. To assess whether the abolition of hypoxemia affected the chemosensitivity, we also studied a control group of patients with univentricular heart and Fontan-type circulation without cyanosis and compared the results. This study may aid the further understanding of the control of ventilation in patients with univentricular heart.

Methods

Ten patients with double-inlet univentricular heart and rest or stress-induced cyanosis were studied (cyanotic group: mean age ± SE 29.9 ± 2.5 years; 5 men). The clinical characteristics of these patients are given in Table 1. As a comparison, eight patients with Fontan-type circulation whose hypoxemia had been relieved (Fontan group: mean age 29.4 ± 1.5 years; 4 men) were also studied. Most of these patients had the Fontan-type operation performed during early adult life; their clinical characteristics are given in Table 2. There were no specific selection criteria and all adult patients with univentricular heart in our hospital were asked to participate. Most patients agreed and were studied in random order. In terms of ventricular function, the echocardiographic shortening fraction was comparable for both groups of patients (23.6 ± 0.7% in the cyanotic group vs. 24.3 ± 0.7% in the Fontan group). In addition, 10 healthy control subjects (normal group: mean age 30.7 ± 1.9 years [range 24 to 39]; 5 men) were studied.

Cardiopulmonary exercise testing was performed in all subjects. They were exercised to exhaustion according to the Bruce protocol (10), with the addition of a "stage 0" at 1.0 mph and a 5% gradient. Blood pressure was measured manually by mercury sphygmomanometer before and during exercise. Arterial oxygen saturation (Sa_{O_2}) was monitored during exercise by using a pulse oximeter (model N200E, Nellcor) with a probe placed on the right supraorbital artery. Respiratory gas exchange analysis was carried out by respiratory mass spectrometry (Amis 2000, Innovision, Odense, Denmark) every 10 s with use of the inert gas dilution technique (11). The ventilatory response to exercise was defined by the slope of the regression line relating the values of minute ventilation to those of CO_2 output obtained every 10 s during the exercise (12,13). Both minute ventilation and CO_2 output were measured in liters per minute and thus the slope has no dimensions.

Hypoxic and the hypercapnic chemosensitivity were determined by using transient hypoxia and the rebreathing of CO_2, respectively, in all subjects, as briefly described later. The study

Table 1. Clinical Characteristics of Patients With Univentricular Heart and Rest or Stress-Induced Cyanosis

Pt No.	Age (yr)/ Gender	Diagnosis	Operation	Rest Sa_{O_2} (%)	Hb (g/100 ml)	Arterial Blood Gases at Rest				Ability Index (ref 32)	Rx	Echo SF (%)	Vo_2max (ml/kg per min)
						pH	Po_2	Pco_2	HCO_3				
1	38/F	DILV, TGA, PHT	None	95	19.1	7.39	8.46	4.66	21.1	2	None	NA	20.7
2	30/M	DILV, TGA, Sub-PS	None	95	14.0	7.45	9.61	2.48	13.0	2	Fur, ACEI	25	38.9
3	32/F	DILV, TGA, PS	None	93	15.0	ND	ND	ND	ND	1	B, ACEI	17	21.7
4	43/F	DILV, TGA, PS	None	93	18.3	7.40	7.59	3.85	18.0	1	None	25	15.5
5	28/F	DILV, PA	Waterston	90	15.9	7.45	6.92	4.21	22.2	2	None	25	15.9
6	25/F	DILV, PA	Right and left B-T	82	15.8	ND	ND	ND	ND	3	B	30	18.0
7	23/M	DILV, TGA, PHT	None	95	14.7	7.39	9.35	4.99	22.6	2	Fur, ACEI, Amio	25	28.4
8	19/M	DIRV, PA	Right and left B-T	80	17.7	7.41	5.71	4.69	22.2	3	Fur, ACEI	10	10.3
9	31/M	DILV, DOLV, Sub-PS	Left B-T	91	15.8	7.41	8.42	3.23	15.4	2	Digoxin	27	20.9
10	36/M	DILV, TGA, PS	Left B-T	89	18.0	7.39	6.87	4.28	20.3	1	None	28	26.3

ACEI = angiotensin-converting enzyme inhibitor; Amio = amiodarone; B = bumetanide; B-T = Blalock-Taussig shunt; DILV = double-inlet left ventricle; DIRV = double-inlet right ventricle; DOLV = double-outlet left ventricle; Echo SF = echocardiographic shortening fraction; F = female; Fur = furosemide; Hb = hemoglobin; M = male; NA = not available; ND = not done; PA = pulmonary atresia; PHT = pulmonary hypertension; PS = pulmonary stenosis; Pt = patient; Rx = medication; Sa_{O_2} = arterial O_2 saturation; Sub-PS = subpulmonary stenosis; TGA = transposition of great arteries; VO_2max = maximal oxygen consumption.

Table 2. Clinical Characteristics of Patients With Univentricular Heart and Fontan-Type Circulation

Pt No.	Age (yr)/ Gender	Diagnosis	Operation	Age at Operation (yr)	Rest Sa_{O_2} (%)	Ability Index (ref 32)	Rx	Echo SF (%)	V_{O_2}max (ml/kg per min)
11	32/M	DILV, PS, TGA	Fontan	18	92	1	Fur	30	31.8
12	28/F	DILV, PS	TCPC	27	95	1	War	NA	19.1
13	29/M	DILV, PS	Fontan	23	97	2	ACEI, Digoxin, Amio, War	21	24.7
14	24/F	DIRV, DORV, PS	TCPC	23	90	2	Fur, Amio, War	25	20.4
15	24/F	DIRV, PA	TCPC	22	93	3	Digoxin, War	15	15.8
16	35/M	DILV, PS	Fontan	12	98	1	Sotalol, War	27	22.3
17	35/F	DIRV, PS	Fontan	25	97	2	Fur, Digoxin, War	25	14.8
18	28/M	DILV, PS	Fontan	21	96	1	Fur, ACEI, Amio, War	27	19.4

DORV = double-outlet right ventricle; TCPC = total caval-pulmonary connection; War = warfarin; other abbreviations as in Table 1.

was approved by the local ethics committee, and subjects gave informed written consent.

Transient hypoxic chemosensitivity test. The transient hypoxic method (14) for assessing hypoxic chemosensitivity was used for practical and safety reasons as subjects were not exposed to prolonged episodes of hypoxia and the depressant effects of prolonged hypoxia on central respiratory drive were avoided. The transient hypoxic chemosensitivity test was performed while subjects were seated and after a period of quiet breathing. Each subject wore a nose clip and breathed through a pneumatic respiratory valve (Innovision) that separated the expirate from the inspirate. The inspirate port was further connected to a T valve placed behind the subject and, depending on the position of the T valve, the subject breathed either room air or pure nitrogen from a 4-liter reservoir bag that was quietly refilled from a gas cylinder containing pure nitrogen. Minute ventilation was measured breath by breath using a heated pneumotachograph and continuous monitoring of O_2 and CO_2 was done at the mouth by mass spectrometry (Amis 2000, Innovision). The pneumotachometer and mass spectrometer were calibrated before each test. Sa_{O_2} was measured by using a pulse oximeter (model N-200E, Nellcor) set at fast mode with a response time of 2 to 3 s and a lightweight ear probe clipped gently on the subject's right ear lobe. After the subject breathed room air for several minutes, the T valve was turned during the expiratory phase of the previous breath so that pure nitrogen was inhaled for 2 to 10 breaths. This procedure was repeated 10 times so as to provide a wide range of Sa_{O_2} readings, with ~2-min intervals of air breathing between exposures to allow Sa_{O_2} and end-tidal CO_2 to return to the subject's baseline levels. The maximal minute ventilation after each period of nitrogen inhalation was obtained by averaging the two largest consecutive breaths. We found the two-breath period optimal in maintaining sensitivity and reproducibility of the transient hypoxic test as did Edelman et al. (14). The maximal ventilation was then plotted against the lowest Sa_{O_2} reached for every period of nitrogen inhalation. The transient hypoxic chemosensitivity was obtained as the slope of the best fit line relating ventilation to Sa_{O_2}, calculated by least-squares linear regression analysis and expressed in terms of liters per minute per percent arterial O_2.

CO_2 rebreathing technique. Central hypercapnic chemosensitivity was assessed using the rebreathing of 7% CO_2 in 93% O_2 (15). After a period of quiet breathing, subjects rebreathed through a 6-liter bag containing a gas mixture of 7% CO_2 in 93% O_2 for 4 min; the test was stopped sooner if they were too breathless to continue or if end-tidal CO_2 concentration exceeded 10%. The high O_2 concentration provided O_2 for metabolism and prevented the development of hypoxic stimulus to ventilation. Minute ventilation was measured breath by breath using a heated pneumotachograph and O_2 and CO_2 were continuously monitored at the mouth by mass spectrometry. The ventilatory response increased linearly with rising end-tidal CO_2 concentration, reflecting the change in arterial CO_2 tension due to endogenous CO_2 production. The central hypercapnic chemosensitivity was obtained as the regression slope relating minute ventilation to end-tidal CO_2 concentration and expressed as liters per minute per mm Hg.

Statistical analysis. The results are presented as mean value ± SE. To assess the significance of results, the Student *t* test or one-way analysis of variance (ANOVA) corrected by the Scheffe procedure for multiple comparisons was used when appropriate. The relation between variables was assessed by using linear regression analysis. A p value < 0.05 was considered significant.

Results

Cardiopulmonary exercise responses. The cardiopulmonary exercise responses of the two groups of patients with univentricular heart (cyanotic and Fontan groups) and those of the normal subjects are summarized in Table 3. Peak O_2 consumption was similar in the cyanotic and Fontan groups but was lower than that in the normal group. Exercise duration and the heart rate at peak exercise were also lower in the two patient groups than in the normal group. All patients remained in sinus rhythm during exercise. Systolic blood pressure both at rest and at peak exercise was comparable in the two patient

Table 3. Summary of Cardiopulmonary Exercise Responses in the Three Study Groups

	Patients With Univentricular Heart			
	Cyanotic Group (A)	Fontan Group (B)	Healthy Control Subjects (normal group: C)	$p < 0.05$
Maximal O_2 consumption (ml/kg per min)	21.7 ± 2.5	21.0 ± 1.9	34.7 ± 1.9	A vs. C; B vs. C
$\dot{V}_E - \dot{V}CO_2$ slope	43.40 ± 4.00	31.35 ± 2.70	23.28 ± 1.10	A vs. B; A vs. C
Exercise time (s)	548 ± 43	631 ± 55	919 ± 26	A vs. C; B vs. C
Respiratory exchange ratio	1.09 ± 0.06	1.16 ± 0.04	1.19 ± 0.04	None
Rest heart rate (beats/min)	92.2 ± 4.5	75.0 ± 6.7	74.4 ± 2.6	None
Peak heart rate (beats/min)	154.7 ± 4.8	133.4 ± 10.0	174.7 ± 2.4	A vs. C; B vs. C
Rest systolic blood pressure (mm Hg)	115.6 ± 3.5	111.9 ± 4.0	113.2 ± 5.6	None
Peak exercise systolic blood pressure (mm Hg)	147.7 ± 6.9	137.5 ± 4.5	147.1 ± 8.6	None
Rest Sao_2 (%)	90.6 ± 1.8	95.1 ± 1.1	99.9 ± 0.1	A vs. B; A vs. C; B vs. C
Peak exercise Sao_2 (%)	66.2 ± 3.8	90.5 ± 2.1	99.6 ± 0.2	A vs. B; A vs. C; B vs. C

Data are expressed as mean value ± SE. Sao_2 = arterial O_2 saturation; $\dot{V}_E - \dot{V}CO_2$ slope = slope of regression relating minute ventilation and CO_2 output.

groups and normal subjects. The ventilatory response to exercise, as characterized by the slope of the regression relating minute ventilation to CO_2 output during exercise, was higher in the cyanotic group than in the Fontan group and normal subjects. The ventilatory response to exercise was higher in the Fontan group than in normal subjects ($p = 0.18$ [NS]).

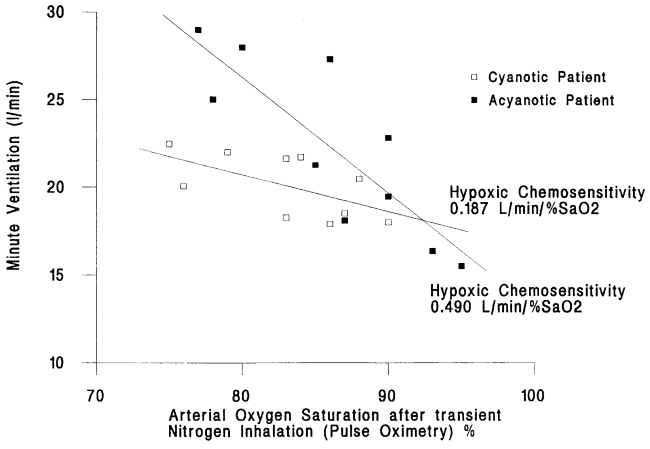
Also shown in Table 3, the mean Sao_2 at rest was 90.6 ± 1.8% for the cyanotic group compared with 95.1 ± 1.1% for the Fontan group and 99.9 ± 0.1% for healthy subjects. At peak exercise, these values decreased significantly to 66.2 ± 3.8% ($p < 0.0001$) in the cyanotic group but were only modestly reduced to 90.5 ± 2.1% ($p = 0.01$) in the Fontan group and to 99.6 ± 0.2% ($p = 0.10$) in normal subjects. In the cyanotic group, Sao_2 at rest correlated with maximal O_2 consumption ($r = 0.69$, $p = 0.03$) but Sao_2 at peak exercise did not correlate with maximal O_2 consumption ($r = 0.47$, $p = 0.2$). In fact, the level of arterial hypoxemia at which some of these patients continued to exercise was remarkable and was as low as 48%. The ventilatory response to exercise also did not correlate with peak exercise arterial O_2 desaturation ($r = -0.48$, $p = 0.2$).

Chemosensitivity. Hypoxic chemosensitivity was significantly lower in the cyanotic group than in the Fontan group (0.148 ± 0.039 vs. 0.448 ± 0.120 liter/min per $\%Sao_2$, [$p = 0.019$], compared with 0.311 ± 0.037 liter/min per $\%Sao_2$ in normal subjects). A graphic illustration of the difference in the hypoxic chemosensitivity in two representative patients is given in Figure 1. In the cyanotic group, hypoxic chemosensitivity correlated with Sao_2 at peak exercise ($r = 0.73$, $p = 0.02$) and was inversely related to the degree of decrease in Sao_2 during exercise ($r = -0.63$, $p = 0.05$) (Fig. 2). However, in this group there was no correlation between hypoxic chemosensitivity and Sao_2 at rest ($r = 0.36$, $p = 0.35$).

To see whether there was an association between hypoxic chemosensitivity and the ventilatory response to exercise in the two groups of patients, we examined the relation between hypoxic chemosensitivity and the slope relating minute ventilation to CO_2 output. There was no correlation between these variables in the cyanotic group ($r = -0.36$, $p = 0.29$), but an association was evident in the Fontan group, whose hypoxemia had been relieved ($r = 0.95$, $p = 0.05$), as shown in Figure 3 (this association remains strong even if the leverage point on the upper right corner of the graph for the Fontan group is omitted [$r = 0.68$, $p = 0.09$]).

Hypercapnic chemosensitivity, as judged by the slope of the ventilatory response line to hypercapnia, was similar in all three groups (1.71 ± 0.26 [cyanotic group] vs. 1.76 ± 0.24 [Fontan group] vs. 1.70 ± 0.18 [normal group] liter/min per

Figure 1. Diagram showing the blunted level of hypoxic chemosensitivity in a patient with univentricular heart and cyanosis (0.187 liter/min per $\%Sao_2$) compared with that in an acyanotic patient with Fontan-type circulation (0.490 liter/min per $\%Sao_2$), as represented by the reduced slope of the regression line relating ventilatory response and Sao_2. l, L = liters.



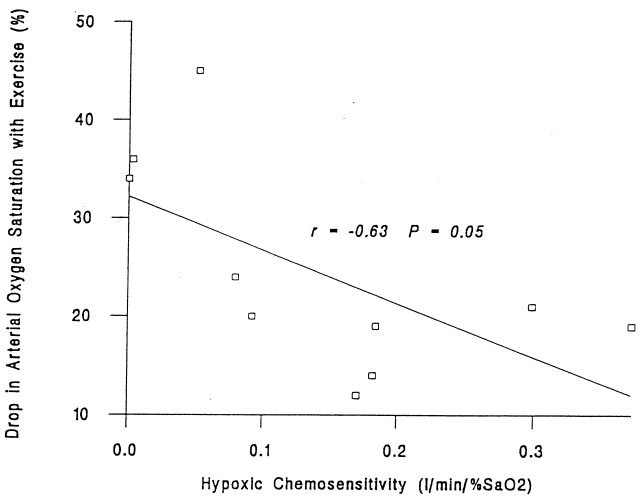


Figure 2. Relation between hypoxic chemosensitivity and the degree of decrease in Sao_2 during exercise in patients with univentricular heart and cyanosis. This relation suggests that in these patients, the blunting of hypoxic chemosensitivity is greater the greater the level of arterial O_2 desaturation with exercise. l = liters.

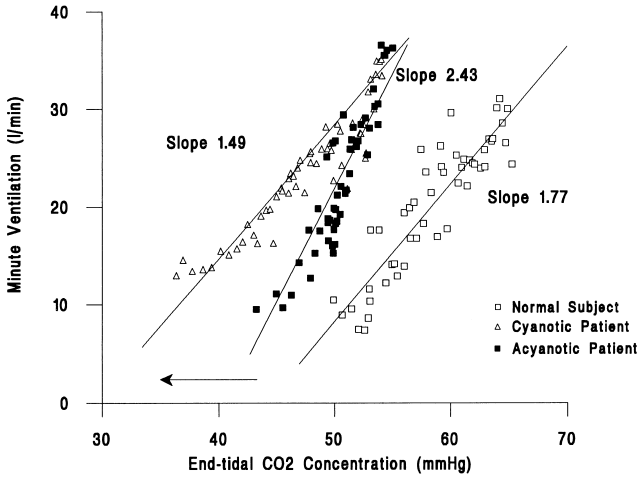
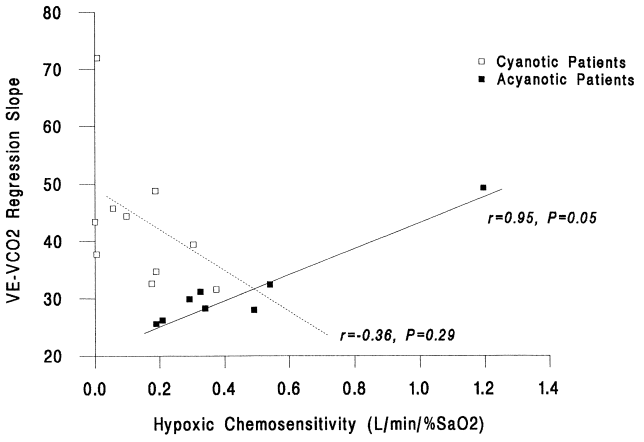


Figure 4. Diagram showing the shift of the hypercapnic-ventilatory response line to the left **(arrow)** in a patient with univentricular heart and cyanosis compared with findings in a patient without cyanosis with Fontan-type circulation and in a healthy subject. Despite the higher slope of the response line seen in the patient without cyanosis shown here, the mean slope in this group of patients did not differ significantly from that of the other two groups. l = liters.

mm Hg; $p > 0.5$ for all group comparisons). However, on further analysis, the response line was noted to have shifted to the left in the cyanotic group (x intercept = 31.9 ± 2.3 [cyanotic group] vs. 39.9 ± 1.2 [Fontan group] vs. 45.2 ± 1.6 [normal group] mm Hg; cyanotic vs. Fontan group, $p = 0.026$; cyanotic vs. normal group, $p = 0.0002$; Fontan vs. normal group, $p = 0.18$), suggesting that patients with cyanosis have greater ventilation for a given level of arterial CO_2. Representative hypercapnic-ventilatory response lines of three subjects are shown in Figure 4.

The relation between hypercapnic chemosensitivity and the ventilatory response to exercise in the two groups of patients was assessed and a significant correlation between the two variables was seen in the cyanotic group ($r = 0.83$, $p = 0.003$) but not in the Fontan group ($r = 0.61$, $p = 0.10$ [Fig. 5]).

Figure 3. Relation between hypoxic chemosensitivity and the ventilatory response to exercise as characterized by the slope of the regression line relating minute ventilation to CO_2 output (VE-VCO2 Regression Slope) in patients with univentricular heart and cyanosis and in patients with univentricular heart and Fontan-type circulation without cyanosis. There is no correlation between hypoxic chemosensitivity and the exercise ventilatory response in the cyanotic group, suggesting that hypoxic chemosensitivity is not important in determining exercise ventilation in these patients. In comparison, a strong association is evident in the acyanotic group (this association remains strong even if the leverage point on the **upper right corner** of the graph for the acyanotic group is omitted, $r = 0.68$, $p = 0.09$). L = liters.



Discussion

Cardiopulmonary exercise responses. We have demonstrated a reduced exercise tolerance and peak O_2 consumption in patients with a univentricular heart compared with those of normal subjects, a finding in agreement with other studies (6). The exercise duration and peak O_2 consumption were similar in the cyanotic and Fontan patient groups even though the Fontan-type circulation in the latter group reduced ventricular overload and relieved cyanosis. There are several possible explanations for this finding. Most patients in the Fontan group underwent the operation at an older age and, in keeping with previous findings of patients who have had such definitive surgery after 10 years of age (4,9,16), they may not have had subsequent improvement in their ventricular function. In one study (17), a decline in myocardial function was not prevented even though Fontan-type operations were carried out early to avoid an age-related decrease in myocardial function, perhaps suggesting that the natural history of these patients is one of gradual decline in heart function despite attempts to reverse this decline. The mean echocardiographic shortening fraction in our Fontan group was indeed not significantly better than that in the cyanotic group, whose patients had not been

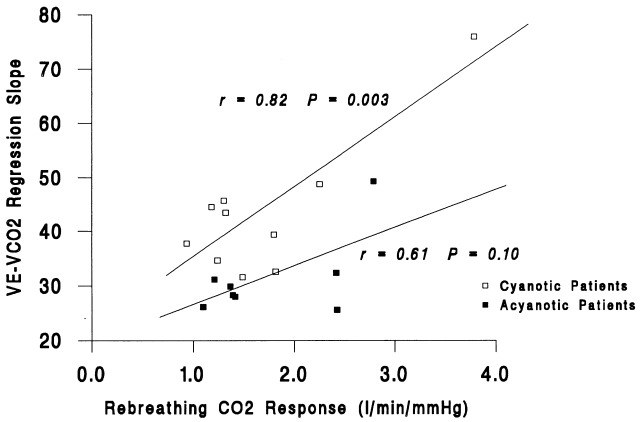


Figure 5. Relation between rebreathing hypercapnic chemosensitivity and the ventilatory response to exercise (VE-VCO2 Regression Slope) in the patients with univentricular heart with and without cyanosis. The significant correlation between hypercapnic chemosensitivity and the exercise ventilatory response in the patients with cyanosis suggests that CO_2 elimination is more important than hypoxic chemosensitivity in the control of exercise ventilation in these patients. l = liters.

surgically treated. That exercise capacity in the Fontan group was not better in our study may also be related to the number of patients (three of eight, Table 2) with right ventricular morphology. Such morphology, in contrast to left ventricular morphology, is associated with a poorer adaptation of ventricular function (18). We also cannot exclude the possibility that the Fontan procedure may have been performed in some patients because they were more limited and may not have been carried out in patients who were well, thus creating an unintended bias.

The heart rate response to exercise in both groups of patients with univentricular heart was comparable but lower than that of normal subjects. These findings may be due to the down-regulation of myocardial beta-receptors (19); the direct effect of arterial hypoxemia, especially in the patients with cyanosis (20); or the influence of negative chronotropic agents such as digoxin and amiodarone, which some patients were receiving for paroxysmal supraventricular arrhythmias. Blood pressure responses with exercise did not differ significantly in the patient groups and normal subjects, in keeping with previous data (6,16).

In the cyanotic group, exercise capacity was influenced by rest Sao_2 but not by the degree of desaturation during exercise. This observation may be explained by the fact that rest Sao_2 is related to the degree of pulmonary flow, which in turn is known to affect exercise capacity (9). Exercise capacity was not affected by the level of arterial O_2 desaturation at peak exercise. This finding may be due to metabolic adaptations such as increased erythropoiesis (despite venesection in some patients), chronic bicarbonate depletion (Table 1), which may have caused an increased exercise acidosis and shifted the hemoglobin O_2 dissociation curve further to the right (21,22), and possible peripheral changes in these patients including proliferation of muscle capillaries (23).

Blunting of hypoxic chemosensitivity. In our study, hypoxic chemosensitivity was blunted in the cyanotic group compared with that in the Fontan group and normal subjects. Indeed, the hypoxic chemosensitivity in the cyanotic group was inversely related to the degree of decrease in Sao_2 during exercise. There are several explanations to account for the blunting of hypoxic chemosensitivity. 1) The blunting may be due to sensory adaptation, characteristic of all sensory receptors, such that the response of chemoreceptors to a given stimulus decreases with time and intensity of the stimulus (24). 2) In patients with cyanosis, the shift of the hemoglobin-O_2 dissociation curve to the right due to chronic bicarbonate depletion and increased 2,3-diphosphoglycerate may also increase the O_2 content in blood at any given value of Sao_2 (21,25). In other words, at a given level of Sao_2, there is actually more chemoreceptor oxygenation because of the shift in hemoglobin-O_2 dissociation curve. 3) The proliferation of capillaries in the carotid bodies due to chronic hypoxemia may increase tissue oxygenation and contribute to the blunting (9). 4) Chronic hypoxemia may have caused the failure of functional maturation of carotid chemoreceptors. Animal studies have shown that chronic hypoxemia from birth impaired the normal maturational increase in hypoxic chemosensitivity occurring during the first few days postnatally (26–28). However, this last mechanism should also be operative in the patients with Fontan-type circulation.

The blunting of hypoxic chemosensitivity, however, appears to be reversible, as suggested by the return of the hypoxic chemosensitivity to normal values in our Fontan group. Although these patients demonstrated a small decrease in rest and exercise Sao_2, it did not appear to be large enough to cause any obvious blunting of chemoreception; rather, a trend to increased sensitivity was seen.

Chemosensitivity and the ventilatory response to exercise. No correlation between hypoxic chemosensitivity and the ventilatory response to exercise was seen in the patients with univentricular heart and cyanosis. This finding supports the notion that the increased ventilation in such patients is not directly due to a response to hypoxemia. By contrast, there was a correlation between hypoxic chemosensitivity and the ventilatory response to exercise in the Fontan group, suggesting that hypoxic chemosensitivity may in part mediate the increase in exercise ventilatory response in these patients once the blunting of hypoxic chemosensitivity is reversed.

Hypercapnic chemosensitivity, as judged by the slope of the ventilatory response line to hypercapnia, was similar in both groups of patients and in the normal subjects. However, the hypercapnic-ventilatory response line had shifted to the left in the cyanotic group, suggesting that they had greater ventilation for a given level of arterial CO_2 tension. This may explain the increased ventilatory response to exercise compared with that of the Fontan group and normal subjects. Indeed, the hypercapnic chemosensitivity correlated significantly with the ventilatory response to exercise, indicating that CO_2 elimination is

more important than chronic hypoxemia itself in the control of ventilation in these patients with cyanosis. As evident from the rest arterial blood gases shown in Table 1, there was chronic bicarbonate depletion and a tendency toward a metabolic acidosis compatible with that observed in other studies (29). The shift of the hypercapnic-ventilatory response line to the left may therefore be caused by the compensatory metabolic acidosis seen in these patients. Metabolic acidosis is known to cause such a shift (30). With the correction of chronic hypoxemia, as in patients with Fontan-type circulation, the hypercapnic-ventilatory response line was noted to shift to the right toward normal. This finding may account for the intermediate ventilatory response to exercise in the Fontan group.

Conclusions. We have shown that the exercise capacity of patients with a univentricular heart is lower than that of normal subjects regardless of surgical correction. The ventilatory response to exercise is increased in these patients, especially in those with cyanosis. Exercise hypoxemia does not appear to limit exercise in these patients but influences the level of blunting of hypoxic chemosensitivity. This may be due to sensory adaptation, whereas prevention of arterial O_2 desaturation allows a normal or even an augmented hypoxic chemosensitivity to be maintained. The elimination of CO_2 appears more important than chronic hypoxemia in the control of exercise ventilation in the patients with cyanosis. The shift of the hypercapnic-ventilatory response line to the left may account for the increased ventilation in these patients. However, the blunting of hypoxic chemosensitivity is reversible, as demonstrated by the return of hypoxic chemosensitivity to normal values in the Fontan group, in whom chronic hypoxemia had been relieved. In the latter patients, hypoxic chemosensitivity may subsequently assume a role in mediating the exercise ventilatory response. There is also a return of the hypercapnic-ventilatory response line toward normal. All these observations reflect important adaptations to chronic hypoxemia in patients with univentricular heart in relation to the control of exercise ventilation. However, these physiologic changes are not permanent and are potentially reversible after the abolition of hypoxemia with Fontan-type procedures.

Limitations of the study. The small number of patients with univentricular heart in this study is a potential limitation of our study. We also did not directly measure arterial blood gases during exercise in these patients because of possible complications in inserting indwelling arterial cannulas in patients with weak forearm pulses consequent to previous shunt operations and because most patients with Fontan-type circulation were receiving anticoagulant therapy. The accuracy of the pulse oximeter used in this study has been shown to be good and within ±3% of values obtained with direct arterial blood gas measurement (31). From respiratory gas monitoring during chemosensitivity assessment, there was also no significant difference in baseline end-tidal CO_2 fractional concentration in the two groups of patients ($4.47 \pm 0.04\%$ in the cyanotic group vs. $4.73 \pm 0.09\%$ in the Fontan group, $p = 0.36$) to suggest that the chemosensitivity was affected by differences in baseline arterial CO_2 tension.

There may be changes in chemosensitivity during exercise. However, the measurement of hypoxic chemosensitivity during exercise requires exposing these patients, who may already have severe hypoxia during exercise, to even more hypoxia with the transient inhalation of pure nitrogen, which may be dangerous. Similarly, measuring hypercapnic chemosensitivity during exercise by rebreathing of CO_2 is very uncomfortable and again may be dangerous, possibly causing headaches or fits. For this reason, we did not measure chemosensitivity during exercise. Nevertheless, chemosensitivity at rest is a valid measure of chemoreceptor function in relation to the control of ventilation, a view supported by the significant correlation demonstrated between chemosensitivity measured at rest and the exercise ventilatory response in normal subjects (7,8).

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