

Abnormal Ventilatory Response to Exercise in Adults With Congenital Heart Disease Relates to Cyanosis and Predicts Survival

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Background—Limited data exist with which to stratify risk in adult congenital heart disease (ACHD). An increased ventilatory response to exercise, expressed as ventilation per unit of carbon dioxide production (\dot{V}_E/\dot{V}_{CO_2} slope), is an established predictor of impaired survival in acquired heart disease. We sought to establish the distribution, relation to cyanosis, and prognostic value of the \dot{V}_E/\dot{V}_{CO_2} slope across a wide spectrum of ACHD patients.

Methods and Results—Five hundred sixty ACHD patients of varying diagnoses and 50 healthy controls underwent cardiopulmonary exercise testing at a single laboratory between 2001 and 2004. Patient age was 33.2 ± 12.9 years (mean \pm SD). Peak oxygen consumption was 23.5 ± 9.0 mL \cdot kg⁻¹ \cdot min⁻¹. \dot{V}_E/\dot{V}_{CO_2} slope for all patients was 36.3 ± 15.3 . The slope was raised in all ACHD groups compared with controls and was 73% higher in cyanotic patients. Cyanosis, with or without pulmonary arterial hypertension, was the strongest predictor of abnormal \dot{V}_E/\dot{V}_{CO_2} slope. The \dot{V}_E/\dot{V}_{CO_2} slope was the most powerful univariate predictor of mortality in the noncyanotic group and the only independent predictor of mortality among exercise parameters on multivariate analysis. In cyanotic patients, no parameter was predictive of death.

Conclusions—Ventilatory response to exercise is abnormal across the spectrum of ACHD. Cyanosis is a powerful stimulus for such exaggerated ventilatory patterns irrespective of the presence of pulmonary arterial hypertension. Increased \dot{V}_E/\dot{V}_{CO_2} slope is the strongest exercise predictor of death in noncyanotic ACHD patients. (*Circulation*. 2006;113:2796-2802.)

Key Words: congenital heart defects ■ exercise test ■ ventilation ■ prognosis

Despite major therapeutic advances in recent decades, adult patients with congenital heart disease (ACHD) have substantially higher mortality over the medium and long term than do healthy individuals with similar demographic characteristics.¹⁻⁵ The identification of ACHD patients at a heightened risk for such poor outcomes is of clinical relevance because it facilitates refinements in treatment that may ultimately improve individual patient outlook. Many of these patients are also limited in their everyday activities by debilitating symptoms such as exertional dyspnea.⁶⁻⁸ Exercise testing may be of value in evaluating the symptoms and prognosis of patients with ACHD. This idea is supported by observations that have been made in adult patients with ischemic or dilated cardiomyopathy. An enhanced ventilatory response to exercise, expressed as ventilation per unit of carbon dioxide production (\dot{V}_E/\dot{V}_{CO_2} slope), is an established

adverse prognostic marker in acquired cardiomyopathy. Indeed, in such individuals, the best prognostic value comes not from peak oxygen consumption, which is well entrenched as the primary measured variable in most centers, but rather from the \dot{V}_E/\dot{V}_{CO_2} slope (the ventilatory cost for clearing a unit of carbon dioxide).⁹⁻¹¹ Abnormal exercise ventilatory patterns have been reported in ACHD patients with cyanosis because of right-to-left shunting.¹²⁻¹⁵ If cyanosis has a direct adverse effect on ventilation patterns, it may affect any prognostic value derived from the ventilatory response to exercise.

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In a large contemporary cohort of cyanotic and noncyanotic ACHD patients with varying diagnoses, we sought to determine (1) the distribution of \dot{V}_E/\dot{V}_{CO_2} slope, (2) the

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relationship between cyanosis and \dot{V}_E/\dot{V}_{CO_2} slope, and (3) the association of \dot{V}_E/\dot{V}_{CO_2} slope and survival.

Methods

All cardiopulmonary exercise tests performed on ACHD patients at our center between 2001 and 2004 were analyzed retrospectively. In our center, cardiopulmonary exercise testing is performed either as part of clinical follow-up protocols or for the assessment of symptoms. The study population comprised 560 ACHD patients with various diagnoses. Cardiopulmonary exercise data were also gathered retrospectively from 50 healthy controls.

Diagnoses were made by echocardiography, cardiovascular magnetic resonance, and invasive imaging modalities. Cyanosis was defined as resting oxygen saturations <90% on room air. Survival status and time to death was assessed through the health service computer system, which is linked to a national database of patient survival held by the Office of National Statistics. Approval by the local ethics committee was obtained.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Exercise Testing

Cardiopulmonary exercise testing was performed with a treadmill and a modified Bruce protocol. This includes a stage 0 in which patients walk at a velocity of 1 mph at a 5% gradient. Ventilation, oxygen consumption, and carbon dioxide production were measured continuously with a respiratory mass spectrometer (Amis 2000, Innovision, Odense, Denmark). All patients were encouraged to exercise to exhaustion. Data were analyzed offline. Peak $\dot{V}O_2$ was defined as the mean of the highest 2 consecutive values of 15-second averages of $\dot{V}O_2$. The \dot{V}_E/\dot{V}_{CO_2} slope was obtained by linear regression analysis of the data acquired throughout the entire period of exercise.¹⁶

Statistical Analysis

Statistical calculations were performed with the Statview 5.0 (SAS Institute, Cary, NC) and S-Plus 6.0 (Insightful Corp, Seattle, Wash) packages. Numerical values are presented as mean \pm SD. Comparisons between groups were performed with ANOVA, unpaired

Student *t* test, or χ^2 test as appropriate. A nonparametric test (Wilcoxon rank sum) was used for the comparison of groups with sample size <21. Spearman rank correlation was used to estimate the correlation between resting oxygen saturations and \dot{V}_E/\dot{V}_{CO_2} slope. The relationship between cyanosis and \dot{V}_E/\dot{V}_{CO_2} slope was studied with univariate and multivariate stepwise forward linear regression. Prognostic association between \dot{V}_E/\dot{V}_{CO_2} slope and survival was assessed with univariate and multivariate Cox proportional risks analyses (stepwise forward). The hazard ratio (HR) with 2-sided 95% confidence intervals (CIs) and probability values by the likelihood ratio test are given. Subsequently, a Kaplan-Meier survival chart was generated for quartiles of \dot{V}_E/\dot{V}_{CO_2} slope. A 2-tailed probability value of 0.05 was used as the criterion for statistical significance.

Results

Population Characteristics

The population included all major ACHD diagnoses (Table 1). Mean age was 33.2 ± 12.9 years, and 53.2% of patients were male. Forty-five patients had complex lesions without pulmonary hypertension (double outlet or double inlet ventricle or complex pulmonary atresia). Nine patients with idiopathic pulmonary arterial hypertension followed in our center were also included. The majority of patients were in functional class I (47.6%). The mean age of the control group was 35.6 ± 10.3 years ($P=0.19$ compared with patients), and 60% were male.

Cyanosis was present in 14.6% of patients (male 42.7%, age 34.5 ± 12.7 years; Table 2). Cyanosis was most common in the group with Eisenmenger syndrome (80.1%), followed by patients with complex anatomy (61.7%).

During a median follow-up of 20.4 months, 25 patients died (7 in the Fontan group, 4 in the "complex diagnoses" group, 4 in the repaired tetralogy of Fallot group, 3 in the congenitally corrected transposition group, 3 in the valve disease group, and 1 in each of the Ebstein, Eisenmenger,

TABLE 1. Baseline Characteristics of ACHD Patients and Healthy Control Subjects

	n	Age, y	Male, %	NYHA 1, %	NYHA 2, %	NYHA 3, %
Normal controls	50	35.6 ± 10.3	60.0
ASD	28	44.0 ± 19.6	50.0	41.7	41.7	16.7
AVSD	8	43.2 ± 16.6	50.0	42.9	57.1	0.0
ccTGA	33	37.6 ± 13.4	48.5	40.7	44.4	14.8
Coarctation of the aorta	17	29.2 ± 8.6	52.9	62.5	31.3	6.3
Complex anatomy	45	32.7 ± 10.8	51.1	23.1	53.8	23.1
Ebstein's anomaly	20	36.7 ± 10.0	45.0	41.2	47.1	11.8
Eisenmenger syndrome	26	40.7 ± 15.5	26.9	16.0	48.0	36.0
Tetralogy of Fallot (repaired)	183	32.4 ± 12.0	57.0	61.6	30.5	7.9
Fontan-type operation	56	26.1 ± 7.5	50.0	32.0	54.0	14.0
Mustard operation	38	28.9 ± 7.1	60.5	60.0	34.3	5.7
PAH	9	31.9 ± 6.6	22.2	0.0	55.6	44.4
Rastelli-type operation	6	28.5 ± 11.4	66.7	66.7	16.7	16.7
Valvular disease	52	33.9 ± 12.8	63.5	54.3	32.6	13.0
VSD	22	34.7 ± 16.0	42.9	50.0	22.2	27.8
Other	17	32.3 ± 16.8	76.5	33.3	41.7	25.0
Total	610	33.4 ± 12.7	55.0	47.6	38.2	14.2

ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected (L-) transposition of great arteries; NYHA, New York Heart Association functional class; PAH, pulmonary arterial disease; and VSD, ventricular septal defect.

TABLE 2. Comparison of Demographic, Clinical, and Exercise Data Between Cyanotic and Noncyanotic ACHD Patients

	Cyanotic (n=82)	Noncyanotic (n=478)	P
Age, y	34.5±12.7	33.0±12.9	NS
Gender, % male	42.7	55.0	0.038
Body mass index, kg/m ²	21.9±4.1	24.3±6.6	0.019
NYHA, % in class I/II/III	11.0/58.9/30.1	53.9/34.8/11.2	<0.0001
Oxygen saturation (resting), %	87.6±5.5	97.2±2.8	<0.0001
\dot{V}_E/\dot{V}_{CO_2} slope	56.9±23.2	32.8±9.9	<0.0001
Peak \dot{V}_{O_2} , mL · kg ⁻¹ · min ⁻¹	15.9±6.3	24.7±8.8	<0.0001
RER at peak exercise	1.01±0.12	1.06±0.11	<0.0001

NYHA indicates New York Heart Association; RER, respiratory exchange ratio.

Mustard, and “other diagnoses” groups). Nine of these patients (36%) were cyanotic.

\dot{V}_E/\dot{V}_{CO_2} Slope Across the Spectrum of ACHD

Mean \dot{V}_E/\dot{V}_{CO_2} slope among all patients was 36.3 ± 15.3 , which was significantly higher than in the normal control subjects (25.6 ± 3.1 , $P < 0.0001$). Furthermore, mean \dot{V}_E/\dot{V}_{CO_2} slope was higher in all ACHD subgroups than in controls ($P < 0.05$ for all). The highest values were seen in the Eisenmenger population (71.2 ± 24.6), followed by patients with idiopathic pulmonary arterial hypertension (51.6 ± 15.0). The lowest \dot{V}_E/\dot{V}_{CO_2} slope was seen in patients with aortic coarctation (29.4 ± 5.6), followed by those with tetralogy of Fallot (30.9 ± 8.3 ; Figure 1). The \dot{V}_E/\dot{V}_{CO_2} slope increased with worsening functional class (class I 31.1 ± 11.3 , class II 39.5 ± 16.8 , and class III 45.0 ± 17.3 ; $P < 0.0001$, ANOVA). In 343 patients, semiquantitative echocardiographic assessment of systemic ventricular function (on a 6-point scale) within 1 year from the exercise test was available. There was no significant correlation between the \dot{V}_E/\dot{V}_{CO_2} slope and resting systemic ventricular function ($r = 0.09$, $P = 0.09$).

Effect of Cyanosis on \dot{V}_E/\dot{V}_{CO_2} Slope

\dot{V}_E/\dot{V}_{CO_2} slope was 73% higher in patients with cyanosis than in those without (56.9 ± 23.2 versus 32.8 ± 9.9 , $P < 0.0001$). A significant inverse correlation was present between resting oxygen saturations and the \dot{V}_E/\dot{V}_{CO_2} slope in the cyanotic group (Spearman $\rho = -0.45$, $P < 0.0001$).

Patients with cyanosis had a lower peak \dot{V}_{O_2} than those without (15.9 ± 6.3 versus 24.7 ± 8.8 mL · kg⁻¹ · min⁻¹, $P < 0.0001$), and lower peak \dot{V}_{O_2} correlated with higher \dot{V}_E/\dot{V}_{CO_2} slopes ($r = -0.52$, $P < 0.0001$). To test the hypothesis that this relation with peak \dot{V}_{O_2} was not the only mechanism by which cyanosis affected \dot{V}_E/\dot{V}_{CO_2} slope, we performed multivariate analysis. Cyanosis was a strong determinant of \dot{V}_E/\dot{V}_{CO_2} slope (increment in \dot{V}_E/\dot{V}_{CO_2} slope associated with cyanosis = 18.9, $P < 0.0001$), independent of the effect of peak \dot{V}_{O_2} (decrement in \dot{V}_E/\dot{V}_{CO_2} slope per mL · kg⁻¹ · min⁻¹ of peak $\dot{V}_{O_2} = 0.62$, $P < 0.0001$).

To determine whether pulmonary arterial hypertension per se was a stronger predictor of \dot{V}_E/\dot{V}_{CO_2} slope than cyanosis, we examined a subpopulation of patients with advanced

\dot{V}_E/\dot{V}_{CO_2}

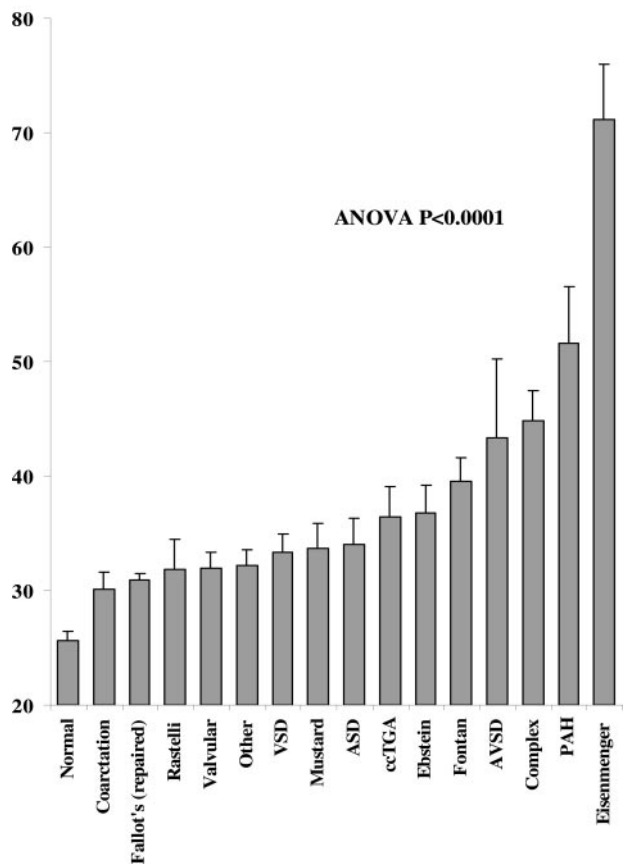


Figure 1. Distribution of the \dot{V}_E/\dot{V}_{CO_2} slope across the different ACHD diagnostic groups and in normal controls (mean and SE). ASD indicates atrial septal defect; AVSD, atrioventricular septal defect; ccTGA, congenitally corrected (L-) transposition of great arteries; PAH, pulmonary arterial disease; and VSD, ventricular septal defect.

pulmonary arterial hypertension, comprised of patients with Eisenmenger syndrome and idiopathic pulmonary arterial hypertension. We found that cyanotic patients had a substantially higher \dot{V}_E/\dot{V}_{CO_2} slope than noncyanotic patients (74.7 ± 24.4 versus 49.7 ± 11.5 , $P = 0.0021$), which suggests that cyanosis has an additive effect on the elevation of the \dot{V}_E/\dot{V}_{CO_2} slope to pulmonary arterial hypertension.

Of the 56 Fontan patients in the present study, 21 were cyanotic at rest. Mean \dot{V}_E/\dot{V}_{CO_2} slope was 39.5 ± 15.4 and was significantly higher in those with cyanosis (47.5 ± 19.7 versus 34.7 ± 9.5 , $P < 0.01$), which suggests that cyanosis is associated with raised \dot{V}_E/\dot{V}_{CO_2} slope even in populations of patients who do not have pulmonary hypertension.

\dot{V}_E/\dot{V}_{CO_2} Slope as a Predictor of Death in ACHD

The \dot{V}_E/\dot{V}_{CO_2} slope was the most powerful predictor of mortality available from the exercise testing data in the noncyanotic population. On univariate Cox analysis, \dot{V}_E/\dot{V}_{CO_2} slope (HR 1.076 per unit, 95% CI 1.038 to 1.115), peak \dot{V}_{O_2} (HR 0.900 per mL · kg⁻¹ · min⁻¹, 95% CI 0.837 to 0.969), and peak heart rate (HR 0.982 per unit, 95% CI 0.966 to 0.998) were predictive of mortality ($P < 0.05$ for all), whereas age, resting heart rate, and resting and peak blood pressure were

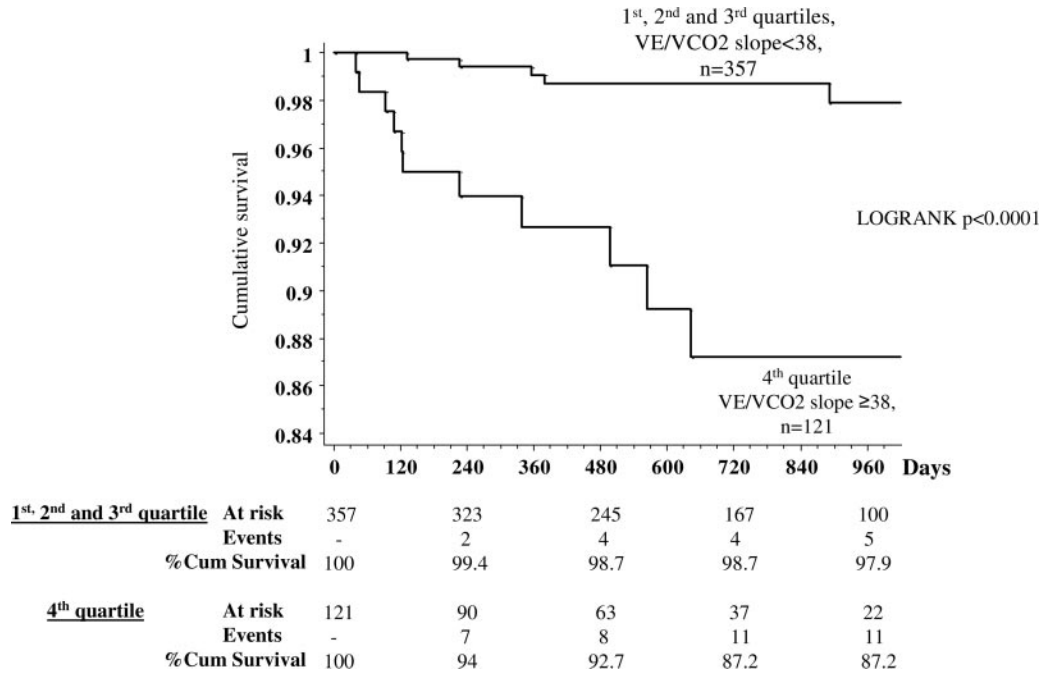


Figure 2. Kaplan-Meier survival chart of first, second, and third quartiles of \dot{V}_E/\dot{V}_{CO_2} slope in the noncyanotic population versus the fourth quartile (\dot{V}_E/\dot{V}_{CO_2} slope ≥ 38). %Cum indicates percent cumulative.

not. On stepwise forward multivariate analysis that included all univariate predictors, the only independent predictor of mortality was \dot{V}_E/\dot{V}_{CO_2} slope (HR 1.076 per unit, 95% CI 1.038 to 1.115). After we stratified noncyanotic patients into \dot{V}_E/\dot{V}_{CO_2} slope quartiles, those in the highest quartile (\dot{V}_E/\dot{V}_{CO_2} slope of ≥ 38) had a substantially higher mortality than the other 3 quartiles (13% mortality at 2 years versus 1% in the other groups), as shown in Figure 2. None of the exercise variables predicted mortality in the cyanotic population.

Discussion

This study shows that abnormal ventilatory response to exercise is present across the diagnostic spectrum of congenital heart disease, as assessed by an elevated \dot{V}_E/\dot{V}_{CO_2} slope. Cyanosis is a powerful stimulus for an abnormal ventilatory pattern, independent of pulmonary arterial hypertension. Elevated \dot{V}_E/\dot{V}_{CO_2} slope is a strong predictor of death in noncyanotic patients, stronger than peak \dot{V}_{O_2} .

Ventilatory Response to Exercise in ACHD

We found that an excessive ventilatory response to exercise is not restricted to complex lesions or severely symptomatic patients. Asymptomatic (New York Heart Association functional class I) patients and patients with simple lesions, such as atrial septal defects or aortic coarctation, demonstrated higher \dot{V}_E/\dot{V}_{CO_2} slopes than normal subjects. It may be that New York Heart Association classification underestimates the degree of symptomatic and functional impairment in ACHD patients. "Ordinary physical activity" is difficult to define in patients who have always been limited in their physical capacity.⁶

Cyanosis and Ventilatory Pattern

The presence of cyanosis was the most powerful predictor of abnormal ventilatory pattern in the present study population.

The mechanisms by which cyanosis affects ventilation are not well understood.^{12,14,15,17,18} Shunting of deoxygenated venous blood rich in hydrogen ions and carbon dioxide to the systemic circulation may be a strong stimulus for ventilation.¹³ Alveolar hyperventilation, reflected by a decrease in alveolar carbon dioxide and an increase in alveolar oxygen tensions, tends to compensate for the carbon dioxide that bypasses the lungs.¹⁴ Moreover, right-to-left shunting causes pulmonary hypoperfusion and thus an increase in physiological dead-space ventilation that could be an additional stimulant for ventilation.¹⁹ Ventilation/perfusion (\dot{V}/\dot{Q}) mismatch can result in a significant gas exchange inefficiency that can powerfully influence the ventilatory response during exercise. Indeed, compelling data implicate \dot{V}/\dot{Q} mismatch as an important source for the \dot{V}_E/\dot{V}_{CO_2} slope elevation both in acquired heart failure and in patients with residual pulmonary artery stenoses after repair of tetralogy of Fallot and patients with a Fontan procedure.^{19–23}

It is also theoretically possible that cyanosis might cause a chronic derangement of the peripheral and central chemoreceptors, which would make them excessively sensitive to minimal stimuli.^{24–27} However, cyanosis has been reported to be associated with depressed chemoreflex sensitivity (at least in terms of hypoxic response), which makes this explanation less plausible.¹⁸

In principle, impairment of gas transport across the alveolar-capillary membrane could also contribute to the observed elevation of the \dot{V}_E/\dot{V}_{CO_2} slope. However, the much greater ability of carbon dioxide than oxygen to diffuse through the alveolar capillary membrane means that significant diffusion limitation of carbon dioxide transport can only occur long after oxygen transport is catastrophically impaired beyond compatibility with survival. Even though the mechanism or mechanisms remain uncertain, the present study

confirms that cyanotic patients ventilate excessively during exercise, and this phenomenon is related to their reduced exercise tolerance.

Patients with cyanosis had a significantly lower respiratory exchange ratio at peak exercise (Table 2), a phenomenon that has been reported previously.⁶ The very abnormal pattern of connection between heart, lungs, and periphery in the cyanotic patients results in significantly abnormal kinetics of \dot{V}_{CO_2} and \dot{V}_O with exercise. This means that the usual benchmarks for interpretation of respiratory exchange ratio (as used in subjects with acquired heart disease) may not have the same meaning in patients with congenital heart disease.¹²

Ventilatory Pattern and Survival

The present study shows that the \dot{V}_E/\dot{V}_{CO_2} slope is a strong predictor of mortality in ACHD patients without cyanosis. To understand the meaning of this, we could begin by looking at acquired heart failure, in which enhanced \dot{V}_E/\dot{V}_{CO_2} slope is well recognized to predict adverse clinical outcome.^{9,28–30} There are several potential mechanisms to explain this association. For example, an enhanced \dot{V}_E/\dot{V}_{CO_2} slope is associated with depressed peak cardiac output and high pulmonary vascular resistance.^{9,11,27,31–33} It may also indicate an enhanced ventilatory reflex sensitivity, which, in turn, may carry prognostic information similar to that of impaired baroreflex sensitivity and depressed heart rate variability, although this is purely speculative.^{9,34–41}

The present study data demonstrated an association between \dot{V}_E/\dot{V}_{CO_2} slope and mortality in noncyanotic but not in cyanotic subjects. We speculate that in noncyanotic patients, there may be an underlying, prognostically ominous pathophysiological abnormality (eg, autonomic imbalance) analogous to that seen in acquired heart failure that drives enhancement of the \dot{V}_E/\dot{V}_{CO_2} slope.⁹ In contrast, right-to-left shunting in cyanotic patients leads to a large rise of the \dot{V}_E/\dot{V}_{CO_2} slope, which differs qualitatively from the pathophysiological processes seen in both acquired heart failure and noncyanotic ACHD patients and eclipses the prognostically important drivers of elevated \dot{V}_E/\dot{V}_{CO_2} slope. The relatively small number of events in the cyanotic group could limit the power of the survival analysis in this subgroup. Nevertheless, cyanotic patients had a much higher \dot{V}_E/\dot{V}_{CO_2} slope than noncyanotic subjects (56.9 ± 23.2 versus 32.8 ± 9.9) and yet no evidence of a correspondingly high mortality. Within the noncyanotic group, a difference in \dot{V}_E/\dot{V}_{CO_2} slope of that magnitude would be expected to be associated with a 6.2-fold increase in mortality. In reality, the actual hazard ratio for mortality in cyanotic compared with noncyanotic patients was 3.5 (95% confidence interval, 1.5 to 7.9).

Methods for Measuring \dot{V}_E/\dot{V}_{CO_2} Slope

The relationship between ventilation and carbon dioxide production is linear below the level of respiratory compensation. Above that level, however, ventilation increases out of proportion to carbon dioxide production, ie, the relationship deviates from linearity. Consequently, if all the data during exercise were included in the regression analysis, the steepness of the slope would be greater the further the patient progresses beyond the respiratory compensation point. If the

patient exerts a more strenuous effort, more data will be collected above the respiratory compensation point, and the slope of the regression line will be steeper than the slope of the (linear) relationship below the respiratory compensation point.

There is therefore a choice in how to measure the slope of the \dot{V}_E/\dot{V}_{CO_2} relationship. One option is to measure it over the entire exercise duration. This has the advantage of methodological simplicity and eliminates observer variability. However, the measurement thus obtained contains information from both parts of the curve and therefore could be considered to be conceptually less appealing as a scientific measure. An alternative option is to identify the respiratory compensation point and measure the slope using only the data before this point. This is conceptually appealing, but in practice, it can be difficult in some patients to identify this point unambiguously.

Guidance as to which \dot{V}_E/\dot{V}_{CO_2} slope measurement is clinically preferable can be sought from studies that compared the prognostic value of each, head-to-head. One such study, by Tabet et al,²⁸ found that the prognostic value of \dot{V}_E/\dot{V}_{CO_2} slope with the complete curve was greater than that of the \dot{V}_E/\dot{V}_{CO_2} slope from the data curtailed at the respiratory compensation point. Another study addressing this issue, by Arena et al,²⁹ also found no advantage in mortality prediction from curtailing data duration, although the authors did not curtail to the respiratory compensation point but rather to fixed and random fractions of the overall data duration. In summary, these comparative clinical data^{28,29} in patients with acquired heart failure would appear to support the use of whole-exercise measurement of \dot{V}_E/\dot{V}_{CO_2} slope in mortality prediction. The present study followed this whole-exercise convention, as have several others.^{9,10,19,25} However, the alternative convention of using only the data before the respiratory compensation point is also widely recommended and has been used successfully in many studies.^{30,42} It is important to be aware of the distinction between the 2 slopes being measured when one compares absolute values from different studies, because the whole-exercise slopes will have a systematic trend toward higher values.

We performed a post hoc analysis of the present study data to address this issue. We found the anticipated strong correlation between the 2 slopes ($r=0.93$, $P<0.0001$; Figure 3). Not surprisingly, the whole-exercise slope values were slightly higher (on average by 4.3). However, results of survival analysis with either convention for \dot{V}_E/\dot{V}_{CO_2} slope calculation were comparable; regardless of the convention chosen, the \dot{V}_E/\dot{V}_{CO_2} slope was a strong predictor of death in the noncyanotic ACHD population.

Clinical Implications

In acquired heart failure, cardiopulmonary exercise testing is a well-established investigation for grading severity and prognosis and is used routinely to assist physicians in making patient management decisions.^{9,26,27} In the present study of a large number of patients with varying ACHD diagnoses, we found that noncyanotic subjects in the highest \dot{V}_E/\dot{V}_{CO_2} slope quartile (≥ 38) had a substantially higher mortality (13% at 2 years) than other noncyanotic individuals (Figure 2). Even after pooling noncyanotic and cyanotic ACHD patients to-

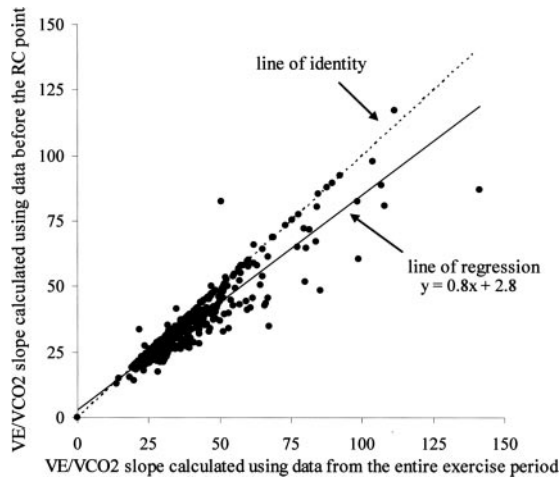


Figure 3. Relation of the \dot{V}_E/\dot{V}_{CO_2} slopes calculated from the entire exercise period and from data up to the respiratory compensation (RC) point.

gether, mortality was still substantially higher in those in the top quartile of \dot{V}_E/\dot{V}_{CO_2} slope (15% versus 1% at 2 years).

Cardiopulmonary exercise testing that includes calculation of a \dot{V}_E/\dot{V}_{CO_2} slope appears to be a feasible and practical way of assessing individual risk for patients with ACHD. In a manner analogous to its use in acquired heart failure, it may develop into a powerful tool to inform decisions regarding the need for interventions, including reoperation and cardiac transplantation.

In the past, regular physical activity has not been actively encouraged and has often been advised against in patients with ACHD. As a result, many patients led a sedentary lifestyle. Lower exercise capacity in otherwise healthy subjects is known to predict poor outcomes.⁴³ The beneficial effect of exercise training on exercise capacity in acquired heart failure is now widely accepted and has also been shown to reduce the \dot{V}_E/\dot{V}_{CO_2} slope.^{44,45} Studies of systematic training in ACHD have shown that exercise training in specific cohorts of ACHD patients is safe and might be beneficial.⁴⁶ Regular low-grade physical exercise should be discussed and encouraged in contemporary ACHD practice, even though there are still limited data on its beneficial effects. We speculate that regular physical activity and a nonsedentary lifestyle extended to all ACHD cohorts, irrespective of their functional class, may have a beneficial effect on overall prognosis and needs to be examined in future studies.

Study Limitations

Cardiopulmonary exercise testing was not performed on every patient with ACHD in our institution, and there may be some bias toward more symptomatic subjects and specific diagnostic subgroups. However, half of the study patients were asymptomatic, and we believe our cohort to be representative of contemporary tertiary ACHD practice. Moreover, it is possible that the retrospective identification of normal control subjects and the small size of some diagnostic subgroups might have added some degree of bias in the analysis. Larger studies with a longer period of follow-up that include patients who are currently not attending tertiary centers are likely to provide additional information on the

prognostic value of cardiopulmonary exercise testing in individual ACHD lesions and its potential role in assessing disease progression and response to therapeutic intervention. Furthermore, invasive studies that include arterial blood sampling and assessment of chemoreflex sensitivity may shed additional light on the mechanisms of hypoxia and its complex interplay with cardiopulmonary exercise performance and \dot{V}_E/\dot{V}_{CO_2} slope in this expanding patient group.

Conclusions

The ventilatory response to exercise is excessive across the diagnostic spectrum of ACHD. Cyanosis is a powerful stimulus for this abnormal ventilatory response, irrespective of pulmonary arterial hypertension. Higher \dot{V}_E/\dot{V}_{CO_2} slopes identify noncyanotic patients at greater risk of death over midterm follow-up. A \dot{V}_E/\dot{V}_{CO_2} slope ≥ 38 identifies noncyanotic patients with a 10-fold increased risk of mortality, who therefore deserve special attention.

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Disclosures

None.

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CLINICAL PERSPECTIVE

The expansion of the population of patients with congenital heart disease who survive to adulthood is a testament to the successful development of management strategies but means that there is a growing need to stratify risk so that care can be targeted at the part of this population at greatest risk. In this study from a single large center specializing in adults with congenital heart disease, ventilatory inefficiency during exercise (as measured by the \dot{V}_E/\dot{V}_{CO_2} slope) was found to be a strong predictor of survival. The strongest stimulus to this exercise hyperventilation was found to be cyanosis (irrespective of the presence of pulmonary arterial hypertension). Above a \dot{V}_E/\dot{V}_{CO_2} slope of 38 in noncyanotic patients, there was a 10-fold increased risk of death; these patients may merit special attention.