Assessment of Symptoms and Exercise Capacity in Cyanotic Patients With Congenital Heart Disease*

Sven Gläser, MD; Christian F. Opitz, MD; Ulrike Bauer, MD; Roland Wensel, MD; Ralf Ewert, MD; Peter E. Lange, MD; and Franz Xaver Kleber, MD

Objectives: Patients with cyanotic congenital heart disease are generally thought to be limited by hypoxemia. To correlate exercise tolerance to the severity of the cardiac abnormality and to further characterize dyspnea in affected patients, we examined 25 adults with uncorrected cyanotic congenital heart disease.

Design and setting: Cohort study at a university hospital.

Methods: Symptom-limited cardiopulmonary exercise testing (CPX) was performed on a treadmill. Expiratory gas was analyzed breath by breath for evaluation of maximal exercise performance, ventilation, and ventilatory efficiency in combination with blood gas analysis during rest and exercise. Symptoms were assessed by the ability index and New York Heart Association class, and the results were compared to 101 healthy volunteers.

Results: PaO₂ decreased by 26 ± 8% (mean ± SD) with exercise (from 49 ± 12 to 36 ± 10 mm Hg), while PaCO₂ was only slightly decreased compared to control subjects. Peak oxygen uptake (VO₂) was significantly reduced when compared to control subjects: 16.7 ± 6.6 mL/kg/min vs 36.1 ± 7.7 mL/kg/min. Ventilatory efficiency was markedly impaired at rest (minute ventilation [Ve]/carbon dioxide output [VCO₂] ratio of 70 ± 18; control subjects, 53 ± 11; p < 0.005) and during exercise (Ve vs VCO₂ slope, 58 ± 31; control subjects, 26 ± 4; p < 0.005). At rest, ventilatory efficiency was correlated to resting pH and PaO₂, while during exercise it was linked to PaO₂. Ventilatory efficiency during exercise had the strongest correlation with observed symptoms, while hypoxemia and peak VO₂ were not significantly associated with symptomatic state.

Conclusion: CPX in patients with cyanotic congenital heart disease provides helpful parameters that better define the symptomatic state of these patients. The summation of disease-related factors is best reflected by ventilatory efficiency. This parameter offers additional and independent information when compared to peak VO₂ and the extent of cyanosis alone.

(CHEST 2004; 125:368–376)

Key words: cyanosis; exercise testing; heart disease, congenital; pulmonary ventilation

Abbreviations: AT = anaerobic threshold; CPX = cardiopulmonary exercise testing; MVV = maximal voluntary ventilation; NYHA = New York Heart Association; PETCO₂ = end-tidal carbon dioxide partial pressure; PETO₂ = end-tidal oxygen partial pressure; VCO₂ = carbon dioxide output; Ve = minute ventilation; VO₂ = oxygen uptake; VO₂AT = oxygen uptake at anaerobic threshold

Approximately 1.0% of all children are affected by congenital heart defects. In 1994, it was estimated that > 500,000 patients with significant functional cardiac malformations reach adulthood in the United States. Supplemerting echocardiography and cardiac catheterization data with cardiopulmonary exercise testing (CPX) offers an objective method to further characterize the limitations of the cardiovascular system in these patients.

Shunting of systemic venous blood into the arterial circulation through a central cardiac shunt alters ventilation due to an additional carbon dioxide load and hypoxemia, leading to impaired oxygen uptake (VO₂) at anaerobic threshold (AT) [VO₂AT] and under maximal exercise. Ventilatory efficiency—defined as the ratio of minute ventilation (Ve) vs carbon dioxide output (VCO₂) [at rest, Ve/VCO₂ ratio; under exercise, Ve vs VCO₂ slope]—has recently
been used to quantify ventilation/perfusion mismatch,3–6 and to describe the pathophysiology of dyspnea in patients affected by chronic heart failure.4 The impairment of ventilatory efficiency has been proven to significantly contribute to hyperpnea and dyspnea.5,7 Elevated values for the VE/\(\dot{VCO}_2\) ratio under exercise have been described in cyanotic patients with congenital heart defects.5,9 However, at present no studies have correlated these abnormalities in ventilatory efficiency with symptomatology and functional capacity in this patient population. This study attempts to further characterize functional limitation in adults affected by congenital cyanotic heart disease.

**Materials and Methods**

**Patients**

Twenty-five consecutive cyanotic patients with uncorrected congenital heart disease (12 women and 13 men) aged 18 to 59 years (mean age, 31 years; mean weight, 59 ± 12 kg; mean height, 171 ± 10 cm) underwent CPX. The study group consisted of patients treated in the outpatient clinic for congenital heart disease at the University Hospital Charité.

Two patients (patient 12/13 and patient 23/24) underwent evaluation twice with an interval of at least 6 months. Both patients were surgically palliated (with significant changes in clinical presentation, extent of cyanosis, and shunt volume) between both evaluations. The remaining patients did not undergo surgical corrections. Individual diagnoses are presented in Table 1.

**Control Group**

The control group consisted of 101 healthy volunteers aged 16 to 75 years (mean age, 37 years). Forty-five of them were women (mean weight, 60 ± 8 kg; mean height, 165 ± 6 cm), and 56 were men (mean weight, 78 ± 12 kg; mean height, 179 ± 9 cm). All persons were free of any cardiovascular, pulmonary, or other systemic disease, had physiologic resting and exercise ECGs, physical examinations, pulmonary function tests, and had no medications. The results have been published in part elsewhere.10

**Subjective Limitations**

The functional class of all patients was determined according to the New York Heart Association (NYHA) class11 and ability index.12

**CPX**

In every subject, symptom-limited CPX was performed according to the modified Naughton protocol10 on a treadmill (Woodway, Boston, MA). A Medical Graphics CPX system was used (Medical Graphics Corporation; St. Paul, MN). Details of the test protocol have been reported10 previously.

Before starting exercise, FEV\(_1\) was measured and multiplied by the factor 41 to estimate maximal voluntary ventilation (MVV)10 in all subjects. The ratio of maximal ventilation during exercise and MVV provided information about the breathing reserve (maximal VE/MVV).

CPX was preceded by a resting period of at least 5 min (after reaching a steady state for gas exchange represented by a plateau for \(V_{O_2}\), \(V_{CO_2}\), end-tidal oxygen partial pressure \([P_{ETO_2}]\), end-tidal carbon dioxide partial pressure \([P_{ETCO_2}]\), resting VE, BP, and heart rate). During the resting period, gas exchange, VE, and \(V_{E}/V_{CO_2}\) ratio were calculated as the mean value during the last minute prior to starting exercise.

During the exercise period, \(V_{O_2}\)AT (primarily according to the V-slope method14 and, if necessary, with further inspection of the \(V_{O_2}, V_{CO_2}, V_{E}/V_{CO_2}\), and \(P_{ETCO_2}\) kinetics) and VE vs \(V_{CO_2}\) slope were determined, and at maximal exertion (peak \(V_{O_2}\)), \(P_{ETCO_2}\) and \(P_{CO_2}\) were assessed. The terminal nonlinear part of the VE vs \(V_{CO_2}\) relationship was excluded from the analysis of the VE vs \(V_{CO_2}\) slope. Great effort was taken not to stop exercise prema-

**Table 1—Characteristics of Cyanotic Patients**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age, yr</th>
<th>Cardiac Malformation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–4</td>
<td>24–57</td>
<td>Eisenmenger syndrome (VSD)</td>
</tr>
<tr>
<td>5</td>
<td>49</td>
<td>Eisenmenger syndrome (ASD and partial anomalous pulmonary venous drainage)</td>
</tr>
<tr>
<td>6–9</td>
<td>23–57</td>
<td>Ebstein anomaly with ASD</td>
</tr>
<tr>
<td>10, 11</td>
<td>20–25</td>
<td>Pulmonary atresia with Fallot tetralogy</td>
</tr>
<tr>
<td>12, 13</td>
<td>21</td>
<td>Pulmonary atresia with double-outlet right ventricle</td>
</tr>
<tr>
<td>14, 15</td>
<td>22–30</td>
<td>Pulmonary atresia with Fallot tetralogy</td>
</tr>
<tr>
<td>16–19</td>
<td>18–39</td>
<td>Fallot tetralogy</td>
</tr>
<tr>
<td>20</td>
<td>42</td>
<td>Taussig-Bing syndrome</td>
</tr>
<tr>
<td>21–23</td>
<td>19–23</td>
<td>Tricuspid valve atresia</td>
</tr>
<tr>
<td>24</td>
<td>23</td>
<td>Tricuspid valve atresia with double-inlet left ventricle</td>
</tr>
<tr>
<td>25</td>
<td>18</td>
<td>Complete atrioventricular canal and pulmonary stenosis</td>
</tr>
<tr>
<td>26</td>
<td>24</td>
<td>Double-outlet right ventricle and atresia of the left pulmonary artery</td>
</tr>
<tr>
<td>27, 29</td>
<td></td>
<td>Congenitally corrected transposition of the great vessels, ASD, VSD, pulmonary stenosis</td>
</tr>
</tbody>
</table>

*VSD = ventricular septal defect; ASD = atrial-septal defect.

---

www.chestjournal.org
turely. Blood was sampled in a capillary tube from a cut earlobe during rest and maximal exertion in 23 patients.

Statistical Analysis

Unless stated otherwise, all data are presented as mean ± SD. Differences between groups were assessed using Kruskal-Wallis test and Mann-Whitney test; p < 0.05 was considered statistically significant.

RESULTS

Symptomatology and Exercise Gas Exchange

Eighteen patients were assigned to NYHA class II, 8 patients to NYHA class III, and 1 patient to NYHA class IV. Ability classification was II in 6 patients, III in 17 patients, and IV in 4 patients. Seven patients were unable to work professionally; the remaining 20 patients were able to do so with limitations (avoiding physical labor).

The changes in ventilatory parameters and differences in exercise capacity as compared to normal values are given in Table 2. The maximal aerobic capacity was markedly impaired in patients (Table 2). Patients reached a significantly lower maximal heart rate (145 ± 21 beats/min vs 177 ± 23 beats/min, p < 0.05) and maximal exercise time: 9 min, 53 s (± 0 min, 50 s) vs 26 min, 18 s (± 6 min, 40 s) [p < 0.05]. VE/VCO₂ ratio and VE vs VCO₂ slope were markedly impaired.

The extent of cyanosis, measured by the PaO₂, did not significantly correlate with all parameters of symptomatic state assessed in this study. PaO₂ at rest and under exercise were different for patients in NYHA class II vs III, and oxygen saturation showed a similar trend. However, the ability index was not related to PaO₂ at rest as shown in Figure 1. Inspection of the exercise-related decline in PaO₂ also failed to show an association with the ability index.

As shown in Figure 2, despite large SDs there were marked and significant differences in the VE/VCO₂ ratio and the VE vs VCO₂ slope in patients with various NYHA and ability classes, while peak VO₂ did correlate to the symptomatic state to some extent.

Acid-Base Balance and Ventilation

The results of blood gas analysis are shown in Table 3. At rest, reduced PaO₂ and increased VE (Table 2) were associated with slightly lowered PaCO₂ and HCO₃⁻ in cyanotic patients. During exercise, cyanosis worsened with a mean decrease in PaO₂ of 25.8 ± 8% to 35.6 ± 9.8 mm Hg at end of exercise. In contrast, HCO₃⁻ was held within the normal range and PaCO₂ showed a nonsignificant increase with exercise.

Although mean pH at rest remained within the normal range, this parameter was closely correlated to VE/VCO₂ ratio (R² = 0.56, p < 0.05), as well as to resting VE (R² = 0.37, p < 0.05). However, this correlation was not apparent during exercise.

The resting PaO₂ was correlated to the resting VE (Fig 3) and to VE/VCO₂ ratio (R² = 0.26). A correlation between PaO₂ and ventilatory efficiency (VE vs VCO₂ slope) was also found during exercise (R² = 0.52).

Figure 4 shows the correlation of end-tidal partial pressures and VE vs VCO₂ slope. In eight patients, VO₂AT could not be determined by the V-slope method even after further inspection of VO₂, VCO₂, VE/VO₂, and PETO₂ kinetics. The exhaustion of breathing reserve at peak exercise, estimated by maximal VE/MVV ratio, was significantly lower in patients than in control subjects (0.43 ± 0.13 vs 0.58 ± 0.13, p < 0.05).

DISCUSSION

Symptomatology and Exercise Gas Exchange

Patients with cyanotic congenital heart disease are generally thought to be limited by hypoxemia. Dyspnea, limited exercise capacity, lifestyle, and employment status are relevant factors for comprehensively evaluating the health of these patients. Consequently

Table 2—Results of CPX

<table>
<thead>
<tr>
<th>Variables</th>
<th>VO₂ mL O₂/kg/min</th>
<th>VE L/min</th>
<th>VE/VCO₂ Ratio</th>
<th>VE vs VCO₂ Slope</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AT</td>
<td>Peak</td>
<td>Rest</td>
<td>Rest</td>
</tr>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>12.8</td>
<td>16.7</td>
<td>16.0</td>
<td>69.6</td>
</tr>
<tr>
<td>± SD</td>
<td>4.9</td>
<td>6.6</td>
<td>3.9</td>
<td>17.9</td>
</tr>
<tr>
<td>Control subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>20.7</td>
<td>36.1</td>
<td>12.8</td>
<td>52.5</td>
</tr>
<tr>
<td>± SD</td>
<td>5.1</td>
<td>7.7</td>
<td>3.1</td>
<td>11.2</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt; 0.005</td>
<td>&lt; 0.005</td>
<td>&lt; 0.005</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Clinical Investigations
the ability index represents a supplemental tool in judging symptomatology.\textsuperscript{12} In this study, all patients stated an impaired quality of life. However, despite the severity of the cardiac malformations and the extent of cyanosis, 60\% of the patients showed only moderate impairment of daily fitness.

\textbf{\textit{V}˙\textit{O}_2 and Symptomatology of Patients}

Reductions of maximal \textit{V}˙\textit{O}_2 and exercise tolerance in comparable patients have been described by others.\textsuperscript{15–18} Maximal \textit{V}˙\textit{O}_2, originally defined as the \textit{V}˙\textit{O}_2 at which exercise of increasing intensity fails to increase \textit{V}˙\textit{O}_2 by at least 150 mL/min despite increasing work rates,\textsuperscript{7} was rarely seen in our patients.

The possible reasons for a missing plateau of the \textit{V}˙\textit{O}_2-work rate relationship are numerous.\textsuperscript{19} Muscular deconditioning, a failing increase of pulmonary blood flow during exercise, a rising systemic shunt volume, and increasing hypoxemia contribute to a limited respiratory gas exchange, maximal \textit{V}˙\textit{O}_2, and exercise capacity.\textsuperscript{20,21} Considering these limitations, determination of the highest \textit{V}˙\textit{O}_2 attainable for the given form of exercise—defined as peak \textit{V}˙\textit{O}_2—appears as the appropriate measure.\textsuperscript{19} In our patients, this parameter indicated a severely impaired functional capacity with a reduction in peak \textit{V}˙\textit{O}_2 of > 50\% when compared to control subjects. This limitation in exercise capacity cannot be explained by impaired ventilatory capacity since the breathing reserve, calculated at peak exercise, was even larger in patients than in control subjects.\textsuperscript{19}

\textbf{Determination of AT by Gas Exchange Kinetics in Cyanosis}

A markedly lowered \textit{V}˙\textit{O}_2AT confirmed a cardiac and muscular limitation and reduced exercise capacity. However, the \textit{V}˙\textit{O}_2AT could not accurately be determined by the V-slope method despite additional inspection of gas exchange kinetics in almost one third of the patients.

The V-slope method is based on ventilatory adaptations to acid-base changes during the transition from aerobic to anaerobic metabolism.\textsuperscript{14,19,22} This requires a strictly carbon dioxide-controlled ventilatory drive. Considering the possible role of a hypoxic contribution to ventilatory control in severe sustained cyanosis, a reliable determination of the AT by the V-slope method appears questionable. In addition, the alveolar hyperventilation necessary to maintain a stable \textit{PaCO}_2 makes a determination of the AT based on gas exchange kinetics more difficult.
Based on the data we obtained, it remains difficult to differentiate whether these eight patients actually did not recruit anaerobic metabolism during exercise or the determination of AT was obscured by alterations in ventilatory pattern and control. Thus, $V\dot{O}_2$AT values should be carefully interpreted in patients with cyanotic heart disease.

**Ventilatory Efficiency and Symptomatology of Patients**

An increased $V_E$ had been reported for different causes of hypoxemia, eg, for persons living at high altitude, and patients affected by cyanotic congenital heart disease. As previously described, the increase in ventilation correlates with the magnitude of the right-to-left shunt and therefore the severity of cyanosis. To our knowledge, no data were available describing the correlation between parameters of ventilatory efficiency and symptomatic state in this patient group. Our data show significantly elevated ventilatory requirements secondary to a marked reduction in ventilatory efficiency. The impaired ventilatory efficiency strongly correlates with the extent of cyanosis as determined by $P_{aO_2}$ values.

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/22005/)

**Figure 2.** Mean CPX results for groups in different NYHA and ability classes compared to control subjects. Peak $V_O_2$ is shown as milliliters of oxygen per kilogram per minute. *p < 0.05, compared to lower class; **p < 0.005, compared to lower class.

| Table 3—Results of Blood Gas Analyses at Rest and Under Maximal Exercise* |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Variables | $P_{aO_2}$, mm Hg | $P_{aCO_2}$, mm Hg | pH | $HCO_3^-$, mmol/L |
|          | Rest | Exercise | Rest | Exercise | Rest | Exercise | Rest | Exercise |
| Patients |     |          |      |          |      |          |      |          |
| Mean    | 48.8 | 35.6     | 32.9 | 38.0     | 7.44 | 7.40      | 23.3 | 22.2     |
| ± SD    | 12.4 | 9.7      | 1.9  | 5.3      | 0.03 | 0.05      | 1.4  | 1.7      |
| Control subjects |     |          |      |          |      |          |      |          |
| Mean    | 90.8 | 87.5     | 35.8 | 36.7     | 7.43 | 7.37      | 24.2 | 21.4     |
| ± SD    | 8.6  | 9.3      | 3.2  | 4.6      | 0.02 | 0.04      | 2.0  | 2.9      |
| p Value | < 0.005 | < 0.005 | < 0.005 | NS | NS | < 0.05 | < 0.05 | NS |

*NS = not significant.
at rest and under exercise. In contrast, no correlation between PaO₂ and ventilatory efficiency exists in healthy volunteers.

Factors that contribute to the impairment of ventilatory efficiency are elevated ventilation of physiologic or anatomic dead space or alveolar hyperventilation. Similarly, a decrease in PETCO₂ and an increase in PETO₂ can result from the elevated ventilation of physiologic dead space, as well as from alveolar hyperventilation. An increased ventilation of anatomic dead space should not influence PETO₂ significantly.

The dependence of ventilatory efficiency on physiologic dead space has been described in patients with chronic heart failure and pulmonary hypertension. Changes were considered to be due to pulmonary vasoconstriction with alveolar hypoperfusion and ventilation/perfusion mismatching. Our study included patients with primary pulmonary hyperperfusion due to left-to-right shunt and consecutive pulmonary hypertension (e.g., patients with Eisenmenger syndrome), or patients affected by pulmonary hypoperfusion (e.g., patients with pulmonary stenosis due to Fallot tetralogy). In both conditions, alveolar hypoperfusion leads to an increase in physiologic dead space and, therefore, impaired ventilatory efficiency. For these reasons, altered ventilation of physiologic dead space appears to be more important for the observed changes in ventilatory efficiency than possible variations in anatomic dead space ventilation.

Despite this possible role of increased dead space ventilation, the major impact on ventilatory efficiency in cyanotic patients is most likely due to alveolar hyperventilation. Considering the correlation of end-tidal partial pressures for oxygen and carbon dioxide with ventilatory efficiency under exercise among patients and control subjects (Fig 4), alveolar hyperventilation with resulting alveolar hypocapnia can be expected as the most important mechanism influencing ventilatory efficiency in our patients.

The shunting of oxygen-poor and carbon dioxide-rich blood necessitates an adequate hyperventilation of the pulmonary venous blood. Alveolar hyperventilation, as reflected in decreased PETCO₂ and increased PETO₂, provides a normalization of the PaCO₂ in the systemic circulation, which obviously is the major control mechanism in these patients and is not overcome by hypoxic ventilatory drive.

In our study, the extent of hypoxemia did not reflect the symptomatic state completely, while peak VO₂ did correlate with it to some extent. Overall, the summation of disease-related factors mentioned above seems to play a major role in determining the range of symptoms in these patients. Despite the
complexity of these alterations, ventilatory efficiency at rest and during exercise can reliably be used to quantify functional impairment in these patients.

Acid-Base Balance and Ventilation

Other investigators\textsuperscript{32–34} have described resting hypocapnia in comparable patients. The small, albeit significant, decrease in resting \( \text{HCO}_3^- \) suggests a mild respiratory-compensated metabolic acidosis. Despite a pH within the normal range, a significant correlation between resting \( \text{pH} \) and resting \( \dot{V}e \), respectively, resting ventilatory efficiency, was present.

pH-sensitive brainstem chemoreceptors control respiration even within the normal pH range\textsuperscript{35–37} in several species.\textsuperscript{38–41} The correlation between pH and ventilation in our patients confirms that acid-base homeostasis contributes to resting ventilation.

Due to the shunting of oxygen-poor and carbon dioxide-rich blood into the systemic circulation, a compensatory hyperventilation resulting in an appropriate alveolar and pulmonary venous hypocapnia\textsuperscript{42} did occur. Since shunt volume does increase with progressive exercise in Eisenmenger syndrome,\textsuperscript{43} alveolar hyperventilation increases proportionally to shunt volume in order to maintain a normal \( \text{PaCO}_2 \), whereas \( \text{PaO}_2 \) cannot be improved by hyperventilation in central cardiac right-to-left shunt. Considering the stable \( \text{PaCO}_2 \) at maximal exercise performance, an increasing hypoxic contribution to ventilatory control appears unlikely.

Study Limitations

It should be emphasized that the interpretation of our findings is based on noninvasive measurements. Therefore, some of the conclusions are based on assumptions with respect to exercise physiology in these complex lesions.

Clinically, it is a clear advantage of CPX being a well-tolerated and noninvasive but accurate tool for the evaluation of functional capacity. In the presence of such complex pathophysiologic states as cyanotic congenital heart disease, it certainly would be helpful to supplement these measurements with simultaneously obtained invasive hemodynamic and metabolic data. However, we think that such an invasive approach is hard to justify in this patient population.

Conclusion

In cyanotic patients with congenital heart disease, CPX with gas exchange analysis provides additional

![Figure 4. Correlation of exercise PETCO\textsubscript{2} (closed circles indicate control subjects; open circles indicate cyanotic patients) and exercise PETCO\textsubscript{2} (closed triangles indicate control subjects; open triangles indicate cyanotic patients) to VE vs VCO\textsubscript{2} slope.]
and independent information, permitting more accurate and objective evaluation of their symptomatic state. In our patients, cyanosis and VE alone did not accurately reflect the symptomatic state. Peak VO₂ did partially correlate with it, but was not able to describe the entire spectrum of symptoms as judged by the ability index and NYHA class.

Overall, the summation of disease-related factors is important for the determination of symptomatology in these patients. These complex alterations were reliably integrated by the ventilatory efficiency at rest and under exercise. Due to the fact that the AT could not be determined by the analysis of gas exchange kinetics in a number of cases, this established, motivation-independent parameter should carefully be interpreted in the assessment of symptoms in this group of patients.

ACKNOWLEDGMENT: We thank Karlman Wasserman, MD, PhD, Harbor-UCLA Medical Center, Torrance, CA, for his remarks and discussion of the manuscript.

REFERENCES

5 Reindl I, Kleber FX. Exerzional hyperpnea in patients with chronic heart failure is a reversible cause of exercise intolerance. Basic Res Cardiol 1986; 91(Suppl 1):37–43
7 Taylor HL, Buskirk A, Henschel E. Maximal oxygen intake as an objective measure or cardiorespiratory performance. J Appl Physiol 1955; 8:73–80
15 Casey FA, Craig BG, Mulholland HC. Quality of life in surgically palliated complex congenital heart disease. Arch Dis Child 1994; 70:382–386
21 Crawford DW, Simpson E, McElroy BM. Cardiopulmonary function in Fallot’s tetralogy after palliative shunting operations. Am Heart J 1967; 74:463–472
22 Wasserman K. Lactate and related acid base and blood gas changes during constant work and graded exercise. Can Med Assoc J 1976; 96:775–779
27 Olson EB. Physiological dead space increases during initial hours of chronic hypoxemia with or without hypocapnia. J Appl Physiol 1994; 77:1526–1531
35 Andrews RJ, Bringas JB, Alonzo G. Cerebrospinal fluid pH and pCO₂ rapidly follow arterial blood pH and pCO₂ with

Forthcoming Articles in CHEST

Field Exercise vs Laboratory Eucapnic Voluntary Hyperventilation To Identify Airway Hyperresponsiveness in Elite Cold Weather Athletes
Rundell and colleagues

White Coat Hypertension in Patients With Obstructive Sleep Apnea-Hypopnea Syndrome
Garcia-Rio and coauthors
Editorial comment by Ventura and Mehra

Clinical Utility of D-dimer in Patients With Suspected Pulmonary Embolism and Nondiagnostic Lung Scans or Negative CT Findings
Rathbun and coworkers
Editorial comment by Arnaud Perrier

Identical Twins With Primary Pulmonary Hypertension: Beraprost vs Epoprostenol
Berman Rosenzweig and coauthors