The development of rapidly responding oxygen and carbon dioxide analyzers has led to a broader application of oxygen and carbon dioxide monitoring in clinical practice. This is particularly the case in the exercise laboratory, where oxygen uptake (\(V_{O_2}\)) and carbon dioxide production (\(V_{CO_2}\)) can be easily monitored using either intermittent or breath-by-breath sampling techniques. We term the monitoring of these respiratory gases during various forms of muscular work as cardiopulmonary exercise (CPX) testing to distinguish it from traditional stress testing and to indicate that heart and lung function can be assessed simultaneously. Hence, CPX testing makes it possible to assess the exercise response in patients with cardiovascular or respiratory disease, or in patients with coexistent heart and lung disease. Clinically relevant issues that heretofore could not be adequately addressed from the response in exercise heart rate or blood pressure alone, can now be examined in objective and quantitative terms. Specifically, one can determine aerobic capacity, anaerobic threshold, the ventilatory response, and the appearance of hypoxemia and use this information to address the nature and severity of disease, its progression over time, and its response to therapy. The CPX testing is therefore gaining in popularity while an increasing number of clinical applications are being identified to ensure its role as a valuable clinical tool in the future.

The purpose of this brief review is to provide an overview of physiologic concepts relevant to CPX testing. We then will discuss our approach to using CPX testing in the assessment of common clinical problems that include evaluating the severity of cardiac or circulatory failure, identifying the cause of exertional dyspnea, and finally monitoring the response to medical therapy in patients with chronic cardiac failure. For a more detailed discussion of these topics, the interested reader is referred to several recently published texts.\(^1,2\)

**Physiologic Concepts Underlying Clinical Application of CPX Testing**

The heart and lungs, working as an integrated cardiopulmonary unit together with hemoglobin, are responsible for sustaining \(O_2\) availability within metabolizing tissues. They also aid in eliminating the \(CO_2\) produced by oxidative metabolism and that formed by the buffering of lactic acid produced during periods of accelerated lactate production. A functional defect within the cardiopulmonary unit that results from a particular disease process has the potential to compromise the unit's ability to fulfill its purpose. For example, during the physiologic stress of exercise, where \(O_2\) requirements and \(V_{CO_2}\) of the tissues are each increased, the compromised cardiopulmonary unit may be unable to sustain respiratory gas transfer and delivery. Accordingly, patients with heart or lung disease, or both, may find their exercise capacity impaired; they may also experience distressing symptoms of breathlessness or fatigue or both. The monitoring of respiratory gas exchange during an incremental upright exercise test therefore represents an attractive method to detect such abnormalities. Moreover, the early detection of less severe expressions of heart and lung disease may now be possible.

**Maximal \(O_2\) Uptake (\(V_{O_2}\max\))**

We prefer incremental (two minute stages) treadmill exercise (Table 1) to maximally stress the cardiopulmonary unit. Walking uses a large muscle mass and is not a specialized skill for the broad spectrum of patients we commonly see in our hospital. Upright cycle ergometry can also be used for this purpose, and in fact, may be preferred in obese patients and those with very severe ventilatory disease.

The incremental exercise test is designed to have the patient reach his/her aerobic capacity or plateau in \(O_2\) uptake. It is clear that patients do not usually
perform work at \( \dot{V}O_2 \text{max} \) during daily living. However, our purpose in the laboratory is to derive an objective and quantifiable measure of the severity of disease. According to the Fick principle, maximal \( \dot{V}O_2 \) uptake is determined by the patient's maximal cardiac output and the maximal extraction of \( \dot{V}O_2 \) by the tissues (or maximal arteriovenous \( \dot{V}O_2 \) difference). An inability of the heart to raise its cardiac output adequately or an inability of the tissues to extract \( \dot{V}O_2 \) sufficiently will reduce \( \dot{V}O_2 \text{max} \) below the expected normal level for the type of exercise performed and for the individual's age, gender, and level of training. In patients with impaired \( O_2 \) delivery, such as those with cardiac or circulatory failure secondary to myopathic or valvular heart disease, respectively, \( \dot{V}O_2 \text{max} \) can be obtained with firm encouragement and exercising the patient to exhaustion. We have not found such maximal workloads to have a deleterious effect on the patient. Such a maximal effort is analogous to deriving the patient's maximal voluntary ventilation (MVV) during standard pulmonary function studies. The \( \dot{V}O_2 \text{max} \) is a reproducible measurement of aerobic capacity. The breath-by-breath monitoring of respiratory gas exchange and its visual display during the test allows us to quickly and reliably identify the plateau in \( \dot{V}O_2 \) (see Fig 1). We define \( \dot{V}O_2 \text{max} \) as a change in \( \dot{V}O_2 \) of <1 ml/min/kg that is sustained for a minimum of 30 seconds into the next stage of incremental treadmill work, but preferably a full stage or two minutes. As we will indicate further below, \( \dot{V}O_2 \text{max} \) is a reliable measure of the impairment in \( O_2 \) delivery, and thereby, the severity of heart failure, irrespective of its cause. The \( \dot{V}O_2 \text{max} \), however, is not diagnostic in that it will not identify the cause of the impairment in exercise cardiac output.

**Anaerobic or Lactate Threshold**

The metabolizing tissues normally produce a small amount of lactate. In our laboratory, the normal resting lactate concentration found in mixed venous blood is 7 to 8 mg/dL (2 standard deviations above this level is

### Table 1—Incremental Treadmill CPX Protocol and Normal Response

<table>
<thead>
<tr>
<th>Stage</th>
<th>Speed/Grade (mph/%)</th>
<th>Speed/Grade (mph/%)</th>
<th>HR (bpm)</th>
<th>SBP/DBP (mm Hg)</th>
<th>( \dot{V}E ) (L/min)</th>
<th>( \dot{V}T ) (ml)</th>
<th>( f ) (bpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0/0</td>
<td>2.6</td>
<td>96 ± 15</td>
<td>140 ± 13</td>
<td>18 ± 6</td>
<td>1153 ± 417</td>
<td>17 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>1.5/0</td>
<td>3.1</td>
<td>98 ± 14</td>
<td>141 ± 12</td>
<td>20 ± 5</td>
<td>1162 ± 450</td>
<td>19 ± 4</td>
</tr>
<tr>
<td>3</td>
<td>2.0/3.5</td>
<td>3.8</td>
<td>104 ± 13</td>
<td>145 ± 13</td>
<td>24 ± 7</td>
<td>1270 ± 368</td>
<td>20 ± 4</td>
</tr>
<tr>
<td>4</td>
<td>2.0/7.0</td>
<td>4.7</td>
<td>110 ± 13</td>
<td>150 ± 13</td>
<td>29 ± 9</td>
<td>1388 ± 394</td>
<td>22 ± 4</td>
</tr>
<tr>
<td>5</td>
<td>2.0/10.5</td>
<td>5.4</td>
<td>118 ± 14</td>
<td>155 ± 13</td>
<td>33 ± 9</td>
<td>1468 ± 405</td>
<td>24 ± 3</td>
</tr>
<tr>
<td>6</td>
<td>3.0/7.5</td>
<td>6.2</td>
<td>126 ± 13</td>
<td>159 ± 21</td>
<td>40 ± 12</td>
<td>1628 ± 458</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>7</td>
<td>3.0/10.0</td>
<td>6.9</td>
<td>135 ± 15</td>
<td>168 ± 19</td>
<td>46 ± 14</td>
<td>1776 ± 502</td>
<td>27 ± 6</td>
</tr>
<tr>
<td>8</td>
<td>3.0/12.5</td>
<td>7.9</td>
<td>144 ± 15</td>
<td>166 ± 21</td>
<td>52 ± 17</td>
<td>1921 ± 502</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>9</td>
<td>3.0/15.0</td>
<td>8.7</td>
<td>155 ± 14</td>
<td>169 ± 25</td>
<td>61 ± 10</td>
<td>2155 ± 681</td>
<td>28 ± 7</td>
</tr>
<tr>
<td>10</td>
<td>3.4/14.0</td>
<td>9.2</td>
<td>162 ± 15</td>
<td>179 ± 21</td>
<td>72 ± 25</td>
<td>2261 ± 700</td>
<td>33 ± 10</td>
</tr>
</tbody>
</table>

*HR is heart rate; Met, metabolic equivalent (1 met = 3.5 ml/min/kg \( O_2 \) uptake); SBP/DBP, systolic and diastolic blood pressure; \( \dot{V}E \), minute ventilation; \( \dot{V}T \), tidal volume; and \( f \), respiratory rate.
During incremental exercise when O$_2$ delivery is inadequate to sustain oxidative metabolism as the primary source of energy, as is the case in heart failure, anaerobic pathways are used to a greater extent leading to lactate production above the baseline value >12 mg/dL. An exponential rise in mixed venous lactate concentration can be found in patients with heart failure during exercise. The appearance of lactate production has been shown by a number of investigators monitoring lactate concentration in the systemic circulation\(^3^4\) and in regional venous blood of the exercising limb\(^5^7\) in such patients.

The lactate threshold can also be detected noninvasively from the response in respiratory gas exchange. Wasserman et al\(^8\) have recommended that five criteria be used for this purpose. These include the following:

1. the disproportionate rise in VCO$_2$ relative to VO$_2$, (see Fig 1);
2. the disproportionate rise in minute ventilation (VE) relative to VO$_2$;
3. the disproportionate rise in the ratio of VCO$_2$/VO$_2$ relative to VO$_2$;
4. the disproportionate rise in the ratio of VE/VO$_2$ relative to VO$_2$ and finally;
5. the rise in end tidal O$_2$ relative to end-tidal CO$_2$.

We monitor VO$_2$ and VCO$_2$ continuously throughout exercise (Fig 1) using a specialized system (Medical Graphics System 2001). This allows us to immediately determine when the anaerobic threshold (AT) has been attained. Following the exercise test, we further determine AT using the remaining criteria cited above. In patients with heart failure of diverse etiology and severity, we have found AT to generally occur at 60 to 70 percent of VO$_2$max.\(^1\) The anaerobic threshold also provides us an additional landmark with which to push our patients to an additional 30 to 40 percent increment in VO$_2$ so that they will reach their VO$_2$max.

### Ventilatory Response to Incremental Exercise

It is not possible to sustain O$_2$ delivery during exercise without the integrated rise in both cardiac output and VE. For aerobic work, VE rises in proportion to both VO$_2$ and VCO$_2$. With the appearance of anaerobic work and the buffering of lactic acid, there is an additional source of CO$_2$ production, and hence, an additional drive to ventilation. Accordingly, exercise VE is most closely related to exercise VCO$_2$.

In normal subjects, the maximal VE attained at VO$_2$max normally represents <50 percent of the ventilatory reserve, or MVV. This pattern of ventilation relative to the ventilation reserve is also seen in patients with chronic cardiac failure.\(^1\) The VE at a higher proportion of MVV cannot be sustained for any significant length of time. This is the case in interstitial lung disease, where >50 percent of the MVV is used during exercise and the patient experiences dyspnea.\(^8\)

For most patients seen in clinical practice, where maximal levels of VO$_2$ are typically <30 ml/min/kg, the increment in VE is derived primarily from an increment in both tidal volume and respiratory rate. In athletes working at much higher levels of work or in patients with an abnormality in lung compliance, the tidal volume response to exercise may plateau, making it necessary for further increments in VE to be derived solely from a rise in respiratory rate.

### Clinical Applications of CPX Testing

#### Severity of Heart Failure

Heart failure may be defined in physiologic terms as that circumstance in which the heart is unable to provide the tissues with O$_2$ at the rate which is in keeping with their aerobic requirements. Heart failure should be subdivided into *cardiac* (or myocardial) failure and *circulatory* failure. In cardiac failure, myocardial injury (eg, myocardial infarction or myopathic process) is responsible for the abnormality in cardiac output which may be present at rest or only during exercise. Valvular heart disease, pulmonary vascular disease, or pericardial disease are examples of circulatory failure. In either cardiac or circulatory failure, the defect in cardiac output may be quite severe, and therefore, the patient has heart failure for the modest levels of VO$_2$ seen at rest. In less severe disease, the defect in O$_2$ delivery may only become apparent during the physiologic stress of exercise or a pathologic stress, such as infection or anemia. In keeping with the physiologic definition of heart failure cited above, the impairment in the cardiac output response to exercise can be used to gauge the severity of cardiac or circulatory failure.

We therefore categorize the severity of cardiac or circulatory failure according to the patient’s aerobic capacity: Class A represents patients achieving a VO$_2$ of >20 ml/min/kg body weight, which is in keeping with their having only a mild impairment in aerobic capacity; class B includes patients reaching VO$_2$max of 16 to 20 ml/min/kg, or a mild to moderately severe impairment; class C represents a moderately severe degree of failure because their VO$_2$max is 10 to 16 ml/min/kg; and class D patients have a severe reduction in VO$_2$max of <10 ml/min/kg.

When the cardiac output response to exercise was measured directly by either Fick principle or thermodilution technique in patients with cardiac or circulatory failure of diverse etiology, we found that the maximum exercise cardiac output attained was as follows: class A, >8 L/min/m$^2$; class B, 6 to 8 L/min/m$^2$; class C, 4 to 6 L/min/m$^2$; and class D, <4 L/min/m$^2$. A defect in the ability of working skeletal muscle to extract O$_2$ was not apparent with systemic O$_2$ extraction exceeding 80 percent at maximal exercise.
Hence, the primary defect responsible for the impairment of \( \dot{V}O_2 \max \) will be a function of the impaired cardiac reserve and thereby the severity of heart failure.

Similarly, the anaerobic threshold is a measure of the severity of heart failure. This is so because the onset of lactate production will be determined by the response in \( O_2 \) delivery. When exercise cardiac output is severely limited, as is the case in class D patients, mixed venous lactate concentration exceeds 12 mg/dL at a \( \dot{V}O_2 \) of <8 ml/min/kg. In class A patients, on the other hand, lactate rises above 12 mg/dL only when \( \dot{V}O_2 \) is >14 ml/min/kg. In class B and C patients, the lactate threshold occurs for \( \dot{V}O_2 \) ranging between 11 to 14 and 8 to 11 ml/min/kg, respectively. These findings, based on mixed venous lactate concentration (Fig 2), were also observed for the noninvasive determination of lactate threshold by respiratory gas exchange analysis and both the direct and indirect determinations of AT were reproducible in these patients. Table 2 summarizes our classification of heart failure according to \( \dot{V}O_2 \max \) and anaerobic threshold and also indicates the predicted maximum exercise cardiac output.

### Evaluation of Exertional Dyspnea

Patients with heart disease, lung disease, or coexistent heart and lung disease frequently experience breathlessness on exertion. It is oftentimes difficult to evaluate the severity of dyspnea in these patients because of affective or cognitive factors attendant with eliciting historical information pertaining to this sensation. The situation becomes even more complex in patients with coexistent heart and lung disease, where the primary cause of dyspnea may be unclear.

We utilize CPX testing to address these issues. Specifically, we determine the level of work or \( \dot{V}O_2 \), at which limiting dyspnea occurs. This aids us in clarifying the severity of exertional dyspnea. To distinguish cardiac vs ventilatory causes of dyspnea, we ask the following questions of the exercise response: (a) Did
the patient attain their lactate threshold and $\dot{V}O_2\text{max}$?

(b) What was the ratio of the maximum exercise $V_R$ to the patient's MVV measured during recent pulmonary function studies? (c) Did arterial hypoxemia occur during the exercise test as measured by ear oximetry or direct arterial sampling? From the answers to these questions, we can pinpoint the organ system primarily responsible for exertional dyspnea. The distinguishing features of cardiac and ventilatory system related dyspnea are shown in Table 3. Patients with heart disease are able to cross their anaerobic threshold and attain a MVV with or without arterial hypoxemia appearing and without utilizing more than 50 percent of their MVV. Patients with a primary ventilatory limitation to exercise rarely cross their lactate threshold and will not attain their $\dot{V}O_2\text{max}$ because they utilize such a large percentage (>70 percent) of their ventilatory reserve. These patients are also quite likely to develop hypoxemia (arterial $O_2$ saturation <90 percent) with exercise.

**Monitoring Response to Therapy in Cardiac Failure**

In patients with chronic cardiac failure, pharmacologic interventions are intended, for the most part, to improve $O_2$ delivery relative to $O_2$ requirements and in keeping with physiologic priorities. Hence, an improvement in cardiac output and the delivery of blood flow to the appropriate tissues, based on need, is an expected end point. If this occurs, then one would expect a delay in the anaerobic threshold and an improvement in $\dot{V}O_2\max$ with therapy. Regrettably, this may not always be the case. A discrepancy occurs in raising cardiac output without regard to blood flow distribution. A shunting of blood flow to the splanchnic circulation, for example, will not improve aerobic capacity of working skeletal muscle. We have found that certain drugs did improve the lactate response to exercise as well as exercise performance, while others did not despite having a salutary hemodynamic effect on the failing heart.9,10

Our experience with monitoring the response to therapy has also shown that the simple measurement of treadmill exercise time, or the duration of exercise to a symptomatic maximum, is flawed with a great deal of variability and is without objective end points. Therefore, we recommend using the objective parameters of anaerobic threshold and $\dot{V}O_2\text{max}$; in addition, these parameters are free of both patient and physician bias. It is encouraging to note that many large scale controlled trials that are designed to establish the efficacy of any given therapy for the treatment of chronic cardiac failure have taken the same viewpoint. An additional positive feature of these trials is that CPX testing has come to the attention of many cardiologists who might not otherwise have had the opportunity to consider this important new approach.

**REFERENCES**