Use of the Gas Exchange Threshold to Noninvasively Determine the Lactate Threshold in Patients With Cystic Fibrosis*

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Objective: The anaerobic threshold (AT) is a submaximal index related to endurance exercise performance, which is usually determined by the measurement of blood lactate concentration during an incremental exercise test (lactate threshold [LT]). The LT, and thus the AT, can also be detected noninvasively in normal subjects by means of the gas exchange threshold (GET). This study was undertaken to validate the use of GET in patients with cystic fibrosis (CF) with a wide range of disease severity, and to assess the reproducibility of this index.

Methods: In patients with CF (FEV₁ range, 23 to 118% of predicted) and control subjects, gas exchange was measured breath by breath during the incremental exercise tests to allow determination of the GET. Arterialized-venous blood was sampled for determination of the LT. The GET and LT were determined in a blinded manner.

Results: The mean differences (GET – LT) for control subjects (n = 18) and patients with CF (n = 23) were −40 mL/min and +10 mL/min, respectively, neither being significantly different from zero. The limits of agreement were ±550 mL/min and ±410 mL/min, respectively. The mean test-retest differences in GET for control subjects (n = 14) and patients with CF (n = 12) were −50 mL/min and 0 mL/min, respectively, neither being significantly different from zero; the respective limits of reproducibility were ±450 mL/min and ±350 mL/min.

Conclusions: This study demonstrates that in patients with CF, the GET can be used to obtain an unbiased estimate of the LT, and that the GET is reproducible.

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Key words: cystic fibrosis; gas exchange threshold; lactate threshold; noninvasive; submaximal

Abbreviations: AT = anaerobic threshold; CF = cystic fibrosis; CI = confidence interval; GET = gas exchange threshold; LT = lactate threshold; MVV = maximum voluntary ventilation; PAVCO₂ = arterialized-venous PCO₂; VO₂ = carbon dioxide output; VE = minute ventilation; VenT = ventilatory threshold; VE/VO₂ = ventilatory equivalents for carbon dioxide; VE/O₂ = ventilatory equivalents for oxygen; VO₂ = oxygen uptake; WR = work rate

Higher levels of aerobic fitness (peak oxygen uptake [VO₂]) in patients with cystic fibrosis (CF) have been found to be associated with increased longevity.¹ More recently, it has been reported that regular exercise attenuates the progressive decline in lung function.² Physical activity also promotes sputum clearance,³ improves aerobic fitness,⁴⁻⁵ and has psychological benefits.⁶ For these reasons, it is recommended that regular exercise should form an important part of a CF treatment program.⁶⁻⁸ In order to monitor responses to training programs and to investigate the mechanisms by which aerobic exercise exerts its beneficial effects, methods of quantifying aerobic fitness in patients with CF are required that are not excessively stressful and are readily acceptable to patients.

The anaerobic threshold (AT) is a submaximal index of aerobic fitness that is closely related to endurance performance.⁹⁻¹¹ The AT may be determined both by the measurement of blood lactate
concentration (the lactate threshold [LT]) and non-invasively by a hyperventilatory response to the exercise-induced metabolic acidosis (the ventilatory threshold [VentT]). Subjects with significant obstructive lung disease are frequently unable to produce this hyperventilatory response. However, in these subjects, it may be still possible to detect an increase in the rate of carbon dioxide output (\(\dot{V}_{\text{CO}_2}\)) over the rate of \(\dot{V}_\text{O}_2\) (the gas exchange threshold [GET]).\textsuperscript{13–15}

The response of patients with CF to exercise is characterized by an increased ventilatory equivalents for oxygen (minute ventilation [\(\dot{V}_\text{E}/\dot{V}_\text{O}_2\)]) and an increased ventilatory equivalents for carbon dioxide (\(\dot{V}_\text{E}/\dot{V}_{\text{CO}_2}\)), and an elevated physiologic dead space to tidal volume ratio.\textsuperscript{16–18} Despite this inefficiency of carbon dioxide excretion, it has been demonstrated in CF patients with mild lung disease that the GET may be used to detect the AT noninvasively, as indicated by the agreement between GET and the invasively determined LT.\textsuperscript{19} Although in patients with mild CF ventilatory capacity is normal, with declining lung function there is evidence of ventilatory limitation.\textsuperscript{20} As the ventilatory and gas exchange abnormalities worsen with disease progression, it may no longer be possible to use the GET to detect the AT in these subjects. Furthermore, if the GET is to be used to monitor changes in aerobic fitness on an individual basis, then information on the reproducibility of the GET is required—in particular, how large the difference between two separate determinations of the GET performed in the same laboratory must be before one can be confident that a real change has occurred.\textsuperscript{21}

We hypothesized that the GET could be used to provide an accurate estimate of the LT in patients with CF, even when lung disease is severe. The present study was therefore undertaken to determine if the onset of exercise-induced lactic acidosis during an incremental exercise test could be detected noninvasively by means of the GET in CF patients with more severe lung disease, thereby providing an easily determined index of aerobic fitness in this patient group. We also assessed, using the technique of Bland and Altman,\textsuperscript{21} the reproducibility of the GET in patients with CF.

**Materials and Methods**

Patients with CF diagnosed on the basis of clinical history and abnormal sweat electrolyte measurements (chloride level > 60 mmol/L) were recruited from the National Referral Center for Adult Cystic Fibrosis, St. Vincent’s University Hospital. All patients were free of acute pulmonary exacerbations for at least 2 months. Nonsmoking subjects with no history of lung or cardiovascular disease were recruited as control subjects. The study protocol was approved by the Ethics Committee of St. Vincent’s University Hospital, and all subjects gave written informed consent.

Anthropometric measurements were undertaken, and spirometry was performed using the spirometry module of the Vmax 229 (Sensor Medics; Yorba Linda, CA). Predicted maximum voluntary ventilation (MVV) was estimated as 37.5 times FEV\textsubscript{1}.\textsuperscript{22} The CF subjects were classified into groups according to the severity of their lung disease as follows: mild CF, FEV\textsubscript{1} > 70% of predicted; moderate CF, FEV\textsubscript{1} > 40% and ≤ 70% of predicted; and severe CF, FEV\textsubscript{1} ≤ 40% of predicted.

The cycle ergometer (Excalibur; Lode BV; Groningen, the Netherlands) was electromagnetically braked, and the subjects were able to select their own cadence, anywhere from 50 to 80 revolutions per minute. The exercise protocol consisted of 1 min of unloaded cycling, a 4-min warm-up period, and then a continuous work rate (WR) ramp to volitional exhaustion, selected for the CF patients according to stature, FEV\textsubscript{1} percent predicted, and level of habitual physical activity. Bipolar ECG and earlobe pulse oximetry (Sat-Trak; SensorMedics) were monitored and recorded throughout the test. Subjects wore a nose clip and a mouthpiece connected to a hot-wire anemometer for measurement of flow that was digitally integrated to obtain tidal volume. Oxygen and carbon dioxide were measured continuously using fast-response paramagnetic oxygen and nondispersive infrared carbon dioxide analyzers (Vmax 229; SensorMedics). All signals were digitized and stored on a breath-by-breath basis for later analysis. Calibration was carried out before each test using a calibration syringe and precision oxygen and carbon dioxide mixtures.

Arterialized-venous blood was drawn (4 to 5 mL) over the last 10 s of each completed minute as previously described.\textsuperscript{23} In brief, a Teflon cannula was inserted into a vein on the dorsum of the hand, and an extension catheter and a three-way tap attached. The hand was then immersed in a water bath maintained at 42°C for the duration of the test, with 10 min allowed to elapse before sampling began. Patency was maintained by intermittent flushing with heparinized saline solution. Two milliliters of each sample were immediately aliquoted into glass tubes containing 12.5 mg of sodium fluoride and 10 mg of potassium oxalate (Gray Vacutainer; Becton Dickinson; Meylan, France) for the measurement of blood lactate concentration. The assay was performed on an automated spectrophotometric analyzer (Cobas Mira Bio; Roche; Basel, Switzerland) as previously described.\textsuperscript{24} An increase in blood lactate concentration of > 2 mmol/L above the resting value was considered to indicate that an exercise intensity above the LT had been achieved. The remainder of each sample was stored anaerobically on ice for measurement of arterialized-venous \(P_{\text{CO}_2}\) (\(P_{\text{avCO}_2}\)) within 90 min using an automated, self-calibrating blood gas analyzer (Model IL 1312 Blood Gas Manager; Allied Instrumentation Laboratory UK; Cheshire, UK). This method of arterialized-venous blood yields \(P_{\text{avCO}_2}\) PH, and blood lactate concentration values that are in close agreement with arterial values.\textsuperscript{21}

**Calculations**

Peak WR was taken as the highest value achieved during the test. Peak VE and peak \(\dot{V}_\text{O}_2\) were calculated as the average of the 30 s breath-by-breath data immediately prior to the peak WR. Peak \(\dot{V}_\text{O}_2\) was expressed as a percentage of predicted value,\textsuperscript{25} since the expression of these indexes per unit of body mass may be affected by nutritional status, particularly in CF patients with more severe lung disease. One patient with CF (FEV\textsubscript{1} 97% of predicted) exhibited intermittent breath holding at maximal exertion; therefore, in order to obtain more representative values...
for peak VE and peak VO\textsubscript{2} in these patients, they were calculated on the basis of the highest values obtained from a seven-breath running average.

**Threshold Determination**

All thresholds were determined by a reviewer in a blinded manner using plots approximately 15 × 15 cm. In addition to not identifying the subjects, no information was given on corresponding threshold determinations. The LT was determined using the log-log transform method.\textsuperscript{26} Log(blood lactate concentration) is plotted against log\(\dot{V}\text{CO}_2\), and the point of inflection was chosen visually (Fig 1, top, A). Using least-squares regression, a straight line was fitted to data points below and including the chosen inflection point, and a separate line to data points above and including the inflection point. The intersection of these two lines indicates the LT. The GET was determined manually using the modified V-slope method,\textsuperscript{14} and is illustrated in Figure 1, bottom, B. V\textsubscript{CO}_2 is plotted against \(\dot{V}\text{CO}_2\), and a line parallel to the line of identity is plotted through the lower data points. This maneuver identifies the point during the exercise test where \(\dot{V}\text{CO}_2\) begins to rise disproportionately faster than \(\dot{V}\text{O}_2\) due to the bicarbonate buffering of the lactic acidosis. Any inflection point occurring < 2 min into the WR ramp was rejected on the basis that it may represent a “pseudothreshold”\textsuperscript{27} due to transient changes in body carbon dioxide stores.\textsuperscript{25,26} The Vent\textsuperscript{T} was determined by identifying the point at which VE/VO\textsubscript{2} began to increase after a period when they had been unchanging or progressively falling and without a concomitant increase in VE/V\textsubscript{CO}_\textsubscript{2}.\textsuperscript{12}

**Comparison of the Exercise Data at Physiologically Equivalent Workloads**

In order to compare the relative impairment of gas exchange during exercise in the three CF groups, blood lactate concentration and \(\text{PavCO}_2\) data were compared at physiologically equivalent workloads: (1) rest, (2) 70% LT, (3) LT, (4) the last blood sample (peak exercise), (5) halfway between LT and the last blood sample (peak exercise). As workloads at 70% LT, LT, and halfway between LT and the last blood sample (peak exercise) were defined for each individual in terms of \(\dot{V}\text{O}_2\), they do not necessarily correspond to times when blood samples were obtained. Therefore, blood lactate concentration and \(\text{PavCO}_2\) were plotted against \(\dot{V}\text{O}_2\), and the value of these variables at the defined physiologically equivalent workloads were obtained by interpolation.

**Reproducibility of the GET**

The reproducibility of the GET in patients was assessed by means of two additional incremental exercise tests separated by 4 to 8 days as described above except without blood sampling. The control subjects underwent a second identical exercise test 1 week later (except one subject for whom the interval was 2 weeks). Each exercise test took place at the same time of day, and subjects were instructed not to change their diet or pattern of physical activity between tests. Anthropometric measurements were undertaken, spirometry was performed, peak exercise variables were calculated, and GET was determined in a blinded manner, as described above.

**Statistical Tests**

Agreement between the determined GETs and LTs was assessed using the technique of Bland and Altman.\textsuperscript{21} For each subject, the difference between the \(\dot{V}\text{O}_2\) at the GET and that at the LT is plotted against the average of the two values. The mean of all the differences was calculated. If the GET provided an unbiased estimate of the LT, then the mean of these differences would not have been significantly different from zero. This null hypothesis was tested using a t test. The limits of agreement were...
calculated by adding and subtracting from the mean value 1.96 times the SD of the differences. These limits indicate the 95% confidence interval (CI) for the size of the difference between the two methods of determining the AT. This provides an estimate of the maximum amount by which the GET may differ above or below the LT in 95% of determinations.

Statistical analysis between the groups was undertaken using analysis of variance in both single and repeated-measures forms. Where the variance increased with the size of the mean (Ve and blood lactate concentration), a logarithmic transformation was performed to normalize the distribution of the data. When the overall analysis of variance was statistically significant, the significance of the differences between specific means was assessed using Student Newman-Keul post hoc testing. Test-retest comparisons within groups were made using a paired t test.

The reproducibility of the GET was again assessed using the technique of Bland and Altman. 21 For each subject, the GET test-retest difference was plotted against the average of the two values. If there was no systematic difference between the two tests undertaken on separate occasions (ie, the GET was reproducible), then the mean of the test-retest differences should not have been significantly different from zero. This hypothesis was tested using a t test. The limit of reproducibility, defined as the 95% CI for the differences (1.96 SD of the differences), was then calculated. This interval indicates the 95% CI for no systematic change in the GET. Conversely, in order to be confident at the 95% level that two separate determinations of the GET indicate a real change, the measured difference must exceed either the lower or upper limit. The reproducibility of peak VO2 was also assessed in the same manner.

RESULTS

Profile of Subjects

In total, 36 patients with CF and 18 control subjects were recruited to one or both of the protocols involving the assessment of the agreement between the GET and the LT, and the assessment of the reproducibility of the GET. Six patients were not included in the analyses for a variety of reasons detailed below. In addition, one patient was included in the reproducibility part of the study and at a later stage underwent the agreement part, but was excluded from the analysis of the agreement between the GET and the LT. Anthropometric and pulmonary function data relating to the 18 control subjects and remaining 30 CF patients are shown in Table 1. There were no significant differences between the mean age and height of the CF and control groups (Table 1). The mean body mass index of the moderate and severe CF groups was significantly less than that of the control group and the mild CF group. As the CF patients were classified according to FEV1 percent predicted, and since other spirometric indexes correlate with this variable, no statistical analysis of the spirometric data presented in Table 1 was undertaken. Furthermore, there were no significant postexercise falls in FEV1 in any of the subjects.

Data relating to the peak exercise capacity of each group are shown in Table 2. Mean peak WR, peak Ve, peak VO2, and peak VO2 percent predicted were all significantly lower in all CF groups than in the control group, and also significantly lower in the severe CF group than in the mild CF group. Conversely, peak Ve expressed as a percentage of predicted MVV was systematically higher as lung function declined.

Agreement Between GET and LT

Altogether, 28 CF patients and 18 control subjects initially participated in the assessment of the agreement between the GET and LT. Data from a single CF subject (FEV1 71% of predicted) had to be excluded because of a technical problem with the measurement of breath-by-breath gas exchange. Two CF subjects (FEV1 39% and 72% of predicted, respectively) terminated the exercise test before the development of exercise-induced lactic acidosis and were also excluded. Two additional CF subjects (FEV1 80% and 88% of predicted, respectively), who both develop significant exercise-induced lactic acidosis, demonstrated a pseudothreshold and no GET could be identified; they too were not included in the analysis.

The VO2 value at the determined GET was plotted

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Table 1—Anthropometric Data Classified by Disease Severity*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Mild CF</th>
<th>Moderate CF</th>
<th>Severe CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female gender</td>
<td>16/2</td>
<td>7/2</td>
<td>11/4</td>
<td>5/1</td>
</tr>
<tr>
<td>Age, yr</td>
<td>24.5 (2.4)</td>
<td>24.3 (6.0)</td>
<td>23.2 (5.5)</td>
<td>25.3 (3.2)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.77 (0.10)</td>
<td>1.75 (0.09)</td>
<td>1.70 (0.10)</td>
<td>1.71 (0.08)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.6 (2.7)</td>
<td>23.2 (2.1)</td>
<td>21.0 (2.3)</td>
<td>19.7 (1.4)</td>
</tr>
<tr>
<td>FVC % predicted</td>
<td>108 (15)</td>
<td>101 (10)</td>
<td>78 (10)</td>
<td>58 (7)</td>
</tr>
<tr>
<td>FEV1 % predicted</td>
<td>107 (13)</td>
<td>91 (17)</td>
<td>58 (9)</td>
<td>34 (6)</td>
</tr>
<tr>
<td>FEV1/FVC %</td>
<td>84 (6)</td>
<td>75 (8)</td>
<td>64 (8)</td>
<td>50 (7)</td>
</tr>
</tbody>
</table>

*Data are shown as mean (SD). Mild CF = FEV1 > 70% of predicted; Moderate CF = FEV1 > 40% and ≤ 70% of predicted; Severe CF = FEV1 ≤ 40% of predicted.

†Significantly lower compared to control and mild CF groups (p < 0.05). No statistical analysis was performed on the spirometry data as the CF subjects were classified according to lung function (see text for details).
against that at the LT for the control subjects (Fig 2, top left, A) and for the patients with CF (Fig 2, bottom left, B). The mean values of the GET and LT determined in each group declined with increasing severity of lung disease and are shown in Table 3. Figure 2, top right, C, and bottom right, D shows the difference between the \( \dot{V}O_2 \) at the GET and that at the LT for each subject, plotted against the average severity of lung disease and are shown in Table 3.

For the control subjects, the mean difference (GET − LT) was −40 mL/min, a value not significantly different from zero, and the limits of agreement were ±550 mL/min. The mean difference for the CF subjects was +10 mL/min, a value not significantly different from zero, and the limits of agreement were ±410 mL/min.

There was no correlation between the individual GET − LT differences in the CF subjects and FEV\(_1\) percent predicted. In addition, none of the mean differences separately calculated for the mild, moderate, and severe CF groups ( +60, +10, and −50 mL/min, respectively) were significantly different from zero.

**Performance of the VentT**

In many patients with CF, no increase in \( \dot{V}E/\dot{V}O_2 \) was seen, and thus the VentT could not be identified. A typical plot illustrating the absence of a rise in \( \dot{V}E/\dot{V}O_2 \) is shown in Figure 3. A VentT was only detected in 11 of 23 patients with CF (48%) compared to 16 of 18 control subjects (89%). Furthermore, a VentT was not detected in any of the patients in the severe CF group. The high failure rate in the detection of the VentT in the patients with CF meant that agreement between the VentT and the LT could not be meaningfully assessed.

**Comparison of the Exercise Data at Physiologically Equivalent Workloads**

Comparisons of the exercise data at physiologically equivalent workloads are shown in Figure 4. In all groups, mean blood lactate concentration values were elevated at peak exercise. The mean value in the control group was significantly greater than that in the severe CF group, but not significantly different from the other two groups. At peak exercise, the control group displayed a fall in PavCO\(_2\) below the value at the LT. There was no significant reduction in PavCO\(_2\) in the mild and moderate CF groups, while in the severe CF group, the mean PavCO\(_2\) rose significantly above the value at the LT. These data indicate a lack of respiratory compensation for the exercise-induced metabolic acidosis in the CF subjects.

**Reproducibility of the GET**

Fourteen of the control subjects also participated in the assessment of the reproducibility of the GET. Fourteen CF patients were also incorporated into this part of the study, 5 of whom were included in the analysis of the agreement between the GET and the LT. One CF patient (FEV\(_1\) 89% of predicted) was withdrawn from the study due to Pseudomonas cepacia infection, and data from one CF patient (FEV\(_1\) 36% of predicted) had to be excluded because of a technical problem with the measurement of breath-by-breath gas exchange, leaving 12 CF patients included in the analysis of the reproducibility of the GET. In eight of the these CF subjects, the data were obtained during the course of a previously published study.30

Mean FEV\(_1\) and FVC were not different between the two occasions, in either the control or CF groups (data not shown), indicating that the CF patients were in clinically stable condition for the period of testing. Bland and Altman plots assessing the reproducibility of the GET in the control and CF groups are shown in Figure 5. In both groups, the mean test\(_2\) − test\(_1\) differences, shown by the solid lines, were not statistically significantly different from zero. The reproducibility of peak Vo\(_2\) was also assessed, and the mean test\(_2\) − test\(_1\) differences for the control subjects and patients with CF were −50

### Table 2—Peak Exercise Data Classified by Disease Severity*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Mild CF</th>
<th>Moderate CF</th>
<th>Severe CF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>((n = 18))</td>
<td>((n = 9))</td>
<td>((n = 15))</td>
<td>((n = 6))</td>
</tr>
<tr>
<td>Peak WR, W</td>
<td>305(62)</td>
<td>202(59)</td>
<td>164(47)</td>
<td>127†(42)</td>
</tr>
<tr>
<td>Peak V(_t), L/min</td>
<td>106.3(33.0)</td>
<td>78.3(25.2)</td>
<td>65.01(18.3)</td>
<td>49.7†(8.4)</td>
</tr>
<tr>
<td>Peak V(_t)/predicted MVV, %</td>
<td>62(18)</td>
<td>53(10)</td>
<td>78±2(21)</td>
<td>100±11(11)</td>
</tr>
<tr>
<td>Peak Vo(_2), L/min</td>
<td>3,120(630)</td>
<td>2,140(810)</td>
<td>1,650±(540)</td>
<td>1,290±(370)</td>
</tr>
<tr>
<td>Peak Vo(_2) % predicted</td>
<td>102(18)</td>
<td>71(16)</td>
<td>62(13)</td>
<td>50†(14)</td>
</tr>
</tbody>
</table>

*Data are shown as mean (SD). See Table 1 for definitions.
†Significantly different compared to control group (p < 0.05).
‡Significantly different compared to mild CF group (p < 0.05).
§Significantly different compared to moderate CF group (p < 0.05).
mL/min and +80 mL/min, respectively, and were not statistically significantly different from zero. The limits of reproducibility were 520 mL/min and 350 mL/min, respectively.

**Discussion**

We have demonstrated that the noninvasive GET can be used to obtain an unbiased estimate of the LT in CF patients with mild, moderate, and severe lung disease, and therefore is a useful submaximal index of aerobic fitness. In contrast, the VentT cannot be used to reliably assess fitness in patients with CF. In addition, we have also shown that GET was reproducible in patients with CF.

**Rate of Successful GET Determination**

It is well recognized that inflection points in the plot of V\(_{\text{CO}}\)\(_2\) against V\(_{\text{O}}\)\(_2\) that occur very early (<2 min) into an incremental exercise test frequently do not result from the onset of lactic acidosis\(^{15,27}\); rather, such inflection points may reflect the end of

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**Figure 2.** Assessment of the agreement between the GET and the LT for the control subjects (top left, A, and top right, C) and the patients with CF (bottom left, B, and bottom right, D). □ = control subjects (n = 18); □ = mild CF (FEV\(_1\) > 70% of predicted; n = 6); △ = moderate CF (FEV\(_1\) > 40% and ≤70% of predicted; n = 11); ○ = severe CF (FEV\(_1\) ≤40% of predicted; n = 6). **Top left, A, and bottom left, C:** V\(_{\text{O}}\)\(_2\) values at the determined GET plotted against that at the LT for the two groups. **Top right, C, and bottom right, D:** Difference between the V\(_{\text{O}}\)\(_2\) at the GET and that at the LT for each subject, plotted against the average of the two values. The mean of the differences, indicated by the solid line, is not significantly different from zero. Dashed lines indicate limits of agreement (ie, ±1.96 SD of the differences; see text for details).
an initial rapid filling of body carbon dioxide stores, and have been termed pseudothresholds.\textsuperscript{27} In normal subjects, the LT is expected to occur beyond this point in the test, and the associated GET would be more readily apparent than any pseudothresholds. If, however, the onset of lactic acidosis occurs within this critical period, retention of the carbon dioxide produced by bicarbonate buffering prevents detection of the LT by gas exchange measurements. It is for this reason that the three patients who demonstrated an early inflection point were excluded, as previously recommended.\textsuperscript{15}

In the present study, the frequency with which the GET could be detected in the CF patients (approximately 85\%) was substantially higher than 31\%\textsuperscript{31} and 60\%\textsuperscript{14} in studies with COPD patients. There appear to be two major reasons for this greater success rate. First, in COPD patients, a common cause of failure to identify a GET is because patients do not have lactic acidosis develop before the exercise test is terminated.\textsuperscript{14,31} This is presumably because exercise is limited by dyspnea\textsuperscript{32} or other factors that cause the subject to stop prematurely. In contrast, in the present study, only two individuals (ie, approximately 7\%) with FEV\textsubscript{1} of 39\% and 72\% of predicted, respectively, did not have exercise-induced lactic acidosis develop. Furthermore, in neither case was a valid GET identified.

![Figure 3](image1.png)

**Figure 3.** Sample plot of ventilatory equivalents for oxygen plotted against \(V\textsubscript{O_2}\) for a patient with CF (FEV\textsubscript{1} 36\% of predicted) in whom it was not possible to determine a VentT. \(\bullet = \text{Ve/Vo}_2; \bigcirc = \text{Ve/VCO}_2\).

![Figure 4](image2.png)

**Figure 4.** Plot of blood lactate concentration (top) and \(P\text{aco}_2\) (bottom) at physiologically equivalent workloads (see text for details of calculations). Data are shown as group means with error bars indicating SEM. \(\bullet = \text{control subjects (n = 18); } \square = \text{mild CF (FEV}1 > 70\% \text{of predicted; n = 6); } \Delta = \text{moderate CF (FEV}1 > 40\% \text{and } \leq 70\% \text{of predicted; n = 11); } \oplus = \text{severe CF (FEV}1 \leq 40\% \text{of predicted; n = 6); } * = \text{significantly different from severe CF group (p < 0.05); } \dagger = \text{significantly different from rest and all submaximal workloads (p < 0.05); } \ddagger = \text{significantly different from all other groups (p < 0.05); } \S = \text{significantly different from LT (p < 0.05); } 50\% \text{Delta} = \text{halfway between LT and the last blood sample.}

Table 3—Mean LT and GET Data Classified by Disease Severity\textsuperscript{*}

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control</th>
<th>Mild CF</th>
<th>Moderate CF</th>
<th>Severe CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT, mL/min</td>
<td>1,829 (536)</td>
<td>1,138 (435)</td>
<td>992 (224)</td>
<td>787 (281)</td>
</tr>
<tr>
<td>GET, mL/min</td>
<td>1,787 (312)</td>
<td>1,202 (562)</td>
<td>995 (216)</td>
<td>742 (245)</td>
</tr>
</tbody>
</table>

*Data are shown as mean (SD). See Table 1 for definitions.
development, blood lactate concentration rose significantly before 2 min had elapsed in approximately 25% of cases. In the present study, the early onset of lactic acidosis was evident in only two CF patients (approximately 7%). Both of these patients had only mild abnormalities of lung function (FEV1, 80% and 88% of predicted, respectively), and therefore a WR increment of 15 W/min was selected. It is likely that use of a lower WR increment may have allowed successful GET identification in these two individuals.

Size of the Limits of Agreement

The sizes of the limits of agreement between GET and the LT were similar in the CF and control subjects (Fig 2) and similar to those that we have previously reported in CF patients with relatively mild lung disease. Furthermore, as lung function declined in the CF patients, there was no evidence of a failure of agreement between the GET and the LT (Fig 2, bottom left, B and bottom right, D). This indicates that the GET can be used to noninvasively determine the AT, and hence provides a useful index of aerobic fitness in CF patients with a wide severity of lung disease.

In a report assessing the agreement between the GET and the LT in patients with documented myocardial infarction, the SD of the differences was reported, which gives an estimate of ±300 mL/min for the size of the limits of agreement, and is comparable to those in the present study. In patients with COPD, after removal of those patients with pseudothresholds, the agreement between the GET and the inflection point on a log-log plot of standard bicarbonate vs V\(\dot{O}_2\), the limits of agreement were ±180 mL/min. Although this value is somewhat smaller than the estimates in the present study, the two values are not significantly different.

The GET and LT are two independent methods of determining AT. The present study shows that the two methods agree with one another in both control subjects and CF patients. The variability inherent in each method limits the amount of agreement that is possible between the two methods. In normal subjects, we have found the reproducibility of the LT and GET to be identical (unpublished data), implying that the random variability of each method is equal. Therefore, neither method provides a more precise estimate of the AT. Thus exercise prescriptions based on the GET are as useful as those based on the LT. If a more precise estimate of AT is required, then repeated testing with either method could provide this. Obviously, the noninvasive nature of the GET permits repeated testing to be carried out easily and conveniently. While it must be recognized that any single GET determination may underestimate or overestimate the AT, our results suggest that regular repeated assessment of the GET will allow a more precise determination of AT. This will permit training intensity to be optimized throughout an exercise program.
Absence of VentT in CF

There was no evidence of respiratory compensation for the exercise-induced metabolic acidosis in the moderate and severe CF groups, as indicated by the absence of a fall in Pavco2 (Fig 4, bottom). Indeed, the increase in Pavco2 above the LT in these two groups is indicative of a degree of alveolar hypoventilation leading to carbon dioxide retention. The failure to detect a VentT in more than half of the CF patients can therefore be attributed to the absence of a significant hyperventilatory response in many of these patients.

Reproducibility of the GET in CF

The CF patients were in clinically stable condition over the period of testing, as indicated by the absence of any change in spirometric indexes (Table 4). There are a small number of studies that have reported either the individual test results34,35 or SD of the differences36–39 for the LT, GET, or VentT. Similar to above, the results from these reports can be used to calculate limits of reproducibility. The results of this analysis yield estimates for the invasive and noninvasive thresholds ranging 200 to 580 mL/min, and are of a similar size to those obtained in the present study.

Conclusion

This study has demonstrated that in CF patients with mild, moderate, and severe lung disease, the GET may be used to identify the LT, providing inflection points occurring < 2 min into the WR ramp are rejected. In contrast, the VentT cannot be used to reliably assess fitness in these patients due to the absence of a respiratory compensation for the exercise-induced metabolic acidosis. The noninvasive nature of the GET makes it more acceptable to patients than the determination of the LT, which requires blood sampling. Furthermore, an assessment of the reproducibility of the GET indicated that the limits of reproducibility are similar in CF and control subjects.


