Patients with COPD usually are limited in their exercise tolerance by a limited ventilatory capacity. Lactic acidosis induced by exercise increases the stress on the ventilatory system due to CO₂ generated by bicarbonate buffering and hydrogen ion stimulation. Patients with COPD are often observed to increase blood lactate levels at low levels of exercise. We wished to determine whether patients with COPD who experience lactic acidosis do so because of respiratory muscle production of lactate. Eight patients with moderate to severe COPD (FEV₁=43.5±11.6% predicted) and 5 healthy subjects performed 10 min of moderate constant work rate exercise either spontaneously or volitionally increasing their ventilation for 5 min to approximate the peak minute ventilation seen during incremental exercise. During volitional increased ventilation, 3% CO₂ was added to the inspirate to prevent alkalosis and hypocapnia. In neither the healthy subjects nor the COPD group was the end-exercise lactate level significantly higher during volitional ventilation increase than during spontaneous ventilation. Further, in the COPD patients, the blood lactate levels during volitional ventilation increase were much lower than during maximal exercise (averaging 2.4 vs 5.3 mmol/L) despite similar ventilation levels (averaging 50 and 53 L/min). We conclude that it is unlikely that the respiratory muscles have an important influence on the blood lactate level elevation seen during maximal exercise in COPD patients.

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Key words: COPD; lactic acidosis; respiratory muscles

The level of ventilation that can be sustained is often the primary factor limiting exercise tolerance in patients with COPD. In these patients, the ventilatory requirement is increased for a given level of exercise. Inefficient ventilation of the lungs is evidenced by an increase in the ratio of physiologic dead space to tidal volume. Another important factor that has an influence on the exercise ventilation is CO₂ production, which is generated both by aerobic metabolism and by buffering of lactic acid, which is formed anaerobically when oxygen demand exceeds supply to exercising muscles. The aerobic CO₂ production for a given rate of O₂ consumption is dependent on the respiratory quotient of the metabolic substrate. The production of lactic acid by exercising muscles depends on the ability of the muscle to create adequate energy from a given supply of oxygenated blood. Lactic acidosis puts a particular stress on the ventilatory system. In addition to generating CO₂, hydrogen ion itself elevates ventilation by stimulation of the carotid bodies. Both the increase in CO₂ generated by buffering and the respiratory stimulation by the hydrogen ion act as breathing stimuli.

It has been observed that many patients with COPD experience lactic acidosis at work rates that would not produce lactic acidosis in healthy subjects. There is little information regarding the aerobic capacity of the respiratory muscles and the contribution of the respiratory muscles to the lactic acidosis observed in COPD patients. However, there is indirect evidence that suggests that the respiratory muscles might be capable of generating a sufficient quantity of lactate with exercise to alter blood lactate levels. In 1966, Eldridge demonstrated that, in a group of normal subjects, blood lactate levels could be elevated when the respiratory muscles are sufficiently stressed and if the blood oxygen level is slightly reduced. More recently Freedman et al demonstrated that normal subjects can raise their blood lactate levels solely with isocapnic increase in ventilation, although the degree of elevation was mild. In COPD patients in whom the work of breathing is much greater and hypoxemia from ventilation/perfusion mismatching is more likely, anaerobic metabolism
and therefore lactate production might be expected at a lower level of ventilation than in normal subjects. If lactic acid were produced by the respiratory muscles in sufficient quantities to alter acid-base balance, the ventilatory requirement during exercise would be increased and exercise tolerance reduced. However, direct evidence demonstrating that elevated blood lactate levels result from respiratory muscle lactate production in COPD is lacking.

The primary objective of this investigation was to determine whether patients with COPD who experience lactic acidosis during exercise do so because of respiratory muscle production of lactate. In this study, patients who performed moderate exercise voluntarily increased ventilation to levels approximating peak levels seen during maximal exercise while inspiring a low level of CO₂ to minimize hypocapnia. The effect of this maneuver on blood lactate level was determined. Because respiratory alkalosis is known to elevate lactate levels, a group of healthy subjects underwent a similar voluntarily increased ventilation protocol with and without a low level of inspired CO₂.

**METHODS**

**Patients**

A group of eight patients with moderate to severe COPD (FEV₁ <65% of predicted) took part in this study after giving written informed consent. Before entering the study, full pulmonary function testing and incremental cardiopulmonary exercise testing were performed. Patients were included when they fulfilled the following criteria: (1) irreversible obstructive airway disease (<10% improvement in FEV₁ after inhalation of B₂-agonist); (2) ability to exercise beyond the lactic acidosis threshold (LAT) on incremental exercise testing (peak blood lactate level >3 mmol/L); and (3) no recent exacerbation in COPD symptoms. None of the participants were known to be impaired by a disease process other than their lung disease. Clinical evidence of cardiovascular, endocrine, or orthopedic disorders was not present.

**Healthy Subjects**

Five young, healthy nonsmoking volunteers with no known cardiac or pulmonary disease also participated in this study. They were determined to be healthy on the basis of normal history, physical examination, and incremental exercise testing and were taking no medication.

**Resting Respiratory Function Tests**

Before the start of the exercise tests, resting spirometry (SensorMedics 2200; Torba Linda, CA) was performed in the patient population. The FEV₁, FVC, and maximal voluntary ventilation (MVV) were determined from the best of at least three adequate performed maneuvers. Total lung capacity (TLC) was also measured by body plethysmography. Spirometry results were compared with the normal values derived by Knudson et al. Normal values of TLC were those derived by Goldman and Becklake.

**Exercise Tests**

An incremental exercise test on an electrically braked cycle ergometer (Lode; Excalibur Sport; Groningen, Netherlands) was performed by both patients and healthy subjects to determine their peak minute oxygen uptake (Vo₂) and LAT, as previously described. After 3 min of rest and 3 min of unloaded cycling, work rate was increased at either 5 or 10 W/min in the patients and 20 or 25 W/min in the healthy subjects until volitional fatigue was signaled by the subject. Subjects were verbally encouraged to exercise as long as possible.

In the patients, 2 min after peak exercise, antecubital venous blood was drawn for measurement of whole blood lactate level. Antecubital venous blood lactate levels drawn during or shortly after incremental exercise testing have been shown to underestimate arterial[12] or arterialized venous[13] lactate levels. Patients were excluded from further study if the lactate level did not exceed 3 mmol/L. Blood was not drawn from the healthy subjects following the incremental exercise test. From the incremental exercise test, the work rate for the constant work rate exercise tests was determined as the work rate at or slightly above the LAT of each subject. The LAT was determined from a plot of minute carbon dioxide output (VCO₂) vs Vo₂ as the point at which VCO₂ increases out of proportion to Vo₂ (V-slope method).[5] On a subsequent day, or at least 2 h after the incremental exercise test, all subjects performed two constant work rate (CWR) tests. Each test consisted of 3 min of rest, 10 min of exercise, and 2 min of rest recovery. One CWR test was carried out while respiring room air with a ventilation chosen spontaneously. The other test was a volitionally increased ventilation experiment in which subjects resired room air with a spontaneous level of ventilation for the first 5 min of exercise and then were coached to breathe as deep and fast as possible for 5 min. At the moment the subjects started to volitionally increase ventilation, the inhalate was switched to a gas mixture.

**Figure 1.** Plots of the averaged time course of ventilation (Ve) and arterialized venous PCO₂, pH, and lactate for the five healthy subjects during 10 min of CWR exercise. Following 5 min of spontaneous ventilation, the subjects performed at random three test conditions: spontaneous ventilation (open circles), voluntarily increased ventilation while respiring room air (open triangles), and while inspiring CO₂ (closed circles). Significant differences in the variables were calculated between before (minute 4) and at the end (minute 10) of each test condition. Asterisks=p<0.05.
consisting of 3% CO₂ and 21% O₂. This was done in an attempt to prevent respiratory alkalosis.

The normal subjects performed an additional test in which ventilation was volitionally increased and which was identical to the previously described test except that CO₂ was not added to the inhalate during the increased ventilation period. These CWR tests were done in a random order.

The CWR studies were preceded by placement of a venous cannula, inserted into a vein on the back of the hand. The hand was kept warm with a heat lamp to arterialize the blood specimens.14 Arterialized venous blood was sampled at rest, during the CWR exercise at 4, 7, 8.5, and 10 min, and at the second minute of recovery; samples were drawn into heparinized syringes. Each sample was analyzed for lactate (Yellow Springs; model 2300; Yellow Springs, Ohio) and underwent blood gas and pH analysis (Instrumentation Laboratories; model 1306; Lexington, Mass).

In all tests, the subjects were asked to maintain the pedaling frequency constant at approximately 60 rpm. During the exercise tests, subjects respired through a mouthpiece with noseclip in place. Respired air was directed through a breathing valve (dead space=0.1 L). The time course of ventilation and gas exchange was measured on-line and the results stored for later analysis by one of two computerized systems. In five patients and four normal subjects, the data processing was done by a desktop calculator, as previously described.15 In the remaining three patients and one normal subject, a commercial exercise system was used (SensorMedics; model 2900). Heart rate was measured from the R to R intervals using a three-lead ECC configuration (Hewlett Packard; model 78332A; Cupertino, Calif).

Statistical Methods

To evaluate the differences in the parameters of interest between the test conditions, analysis of variance was done for each subject group. When significant differences were found, these were further evaluated by post hoc analysis (Duncan’s Multiple Range Test). Within each test condition, the average change in the variables between minute 4 and 10 of exercise was determined using paired t test. Differences were declared to be significant when p was less than 0.05. All average values are expressed ±1 SD, unless otherwise indicated.

RESULTS

Healthy Subjects

Average physical characteristics of the healthy subjects were as follows: age, 28.3±4.7 years; height, 174.4±4.7 cm; and weight, 78.6±13.9 kg. There were two women and three men in this group. In the incremental exercise test, average peak V̇O₂ was 2.32±0.56 L/min and peak minute ventilation (V̇E) was 89.4±16.7 L/min. The lactic acidosis threshold averaged 1.27±0.37 L/min.

The work rate chosen for the CWR averaged 94±22 W. The upper panel in Figure 1 shows the ventilatory time courses for the three CWR tests. In the test in which subjects respired at spontaneously chosen levels throughout the test, V̇E reached a steady state, averaging approximately 38 L/min within the first 5 mins; V̇E did not change appreciably over the subsequent 5 min of exercise. In the other two tests, subjects were able to roughly double V̇E (to an average of 70 to 80 L/min) volitionally. The middle two panels of Figure 1 show the effects of the experimental intervention on arterialized venous PCO₂ and pH. When spontaneously ventilating, PCO₂ stayed near 40 mm Hg and pH stayed near 7.40 through the exercise period. When the subjects volitionally increased ventilation while respiring air, PCO₂ fell and pH rose (reaching an average of 32 mm Hg and 7.43, respectively). Adding 3% CO₂ to the inspirate during volitionally increased ventilation prevented changes in PCO₂ and pH; levels were indistinguishable from those seen during spontaneous ventilation.

The lower panel of Figure 1 shows the effect of these maneuvers on arterialized venous lactate levels. As intended, exercise produced only a modest increase in lactate level in the test featuring spontaneous V̇E for 10 min. There was a small rise in average lactate level between minute 4 and 10 of exercise (from 1.6 to 2.1 mEq/L). In the two tests featuring volitionally increased ventilation during the last 5 min of exercise, the average time courses of blood lactate were quite similar to the spontaneous ventilation study. Specifically, it was apparent that increasing ventilation while respiring room air did not yield an elevation in lactate values. Apparently, under the conditions of this experiment, hypocapnia and alkalosis did not yield higher blood lactate levels.

COPD Patients

Average physical characteristics of the patients were as follows: age, 64±5.7 years; height, 169.1±5.8 cm; and weight, 67.4 ±12.1 kg. There were six men and two women in this group. Resting spirometry demonstrated FEV₁ of 1.21±0.32 L, which was 43.5±11.6% of predicted values; FEV₁/FVC averaged 46.1±12.7%. The degree of airways obstruction ranged from moderate to severe. MVV was 50.3±23.5 L/min. TLC averaged 6.95±1.18 (123.9±24.6% predicted).

In the incremental exercise test, peak V̇O₂ averaged 1.26±0.35 L/min and the lactic acidosis threshold averaged 0.84±0.31 L/min. The peak V̇E observed was 55.4±19.3 L/min (ie, on average, 10% higher than MVV, consistent with a ventilatory limitation to exercise1,2). The peak lactate level observed during the incremental exercise test was 5.3±2.8 mEq/L, consistent with our intention to select patients in whom exercise was associated with appreciable elevations in blood lactate levels.

Figure 2 shows the responses to the two CWR tests; work rate averaged 26.9±19.4 W. As seen in the upper panel, V̇E reached a plateau averaging 35 L/min during exercise, when V̇E was spontaneously chosen. When asked to increase ventilation during the last 5 min of exercise, V̇E averaged 48 L/min, an increase of 37%. Further, V̇E during volitional increase in ventilation approached the V̇E seen during incremental exercise (hatched area). The middle two panels of Figure 2 demonstrate that, during spontaneous venti-
incremental exercise test (hatched area of lower panel). Thus, these data yield no evidence that the increase in blood lactate level seen in these patients during maximal exercise is related to lactate generation by the muscles of respiration.

We sought to determine whether the more severely obstructed patients demonstrated a larger lactate increase during volitionally increased ventilation. Plotted on the abscissa of Figure 3 is the severity of obstruction (expressed as percent predicted FEV₁). On the ordinate is the difference in lactate level at the tenth minute of exercise between the spontaneous and volitionally increased ventilation studies (normalized to the difference in Ve between the two studies). The significant negative correlation (r = -0.72) suggests that the more severely obstructed patients may experience a small increase in blood lactate level during volitional ventilation increase. However, this analysis suggests that, in the most severely obstructed patient (FEV₁ = 26% predicted), volitional ventilation increase is associated with an increase in blood lactate level of only 0.5 mEq/L.

**DISCUSSION**

Impaired exercise tolerance is a prominent complaint of patients with obstructive lung disease. Unlike healthy subjects, patients with obstructive lung disease are often limited in their exercise tolerance by the level of ventilation they are able to sustain. Strategies to improve exercise tolerance have focused on either reducing the high ventilatory requirement for a given level of exercise or increasing the amount of ventilation that can be sustained. Improving the function of the respiratory muscles, for example through respiratory muscle training, has been seen as a logical strategy for improving exercise tolerance. The most apparent benefit of improving respiratory muscle function would be to better sustain the high work of breathing that
these patients experience during exercise. However, it also seemed possible that inadequate oxygen supply to the respiratory muscles, either due to insufficient blood flow or to relatively low O₂ content of the arterial blood supply, might contribute to the elevated ventilatory requirement for exercise. If lactic acid production by the respiratory muscles during exercise was sufficient to raise blood lactate levels appreciably, this would be a superimposed ventilatory stimulus.

In resting healthy subjects, maximal isocapnic volitional ventilation increase has been shown to modestly increase blood lactate levels (in the order of 1 mmol/L). Extrapolating these findings to COPD is complex. For a given level of ventilation, the work of breathing would be higher in the patient with obstructive disease; however, the achievable ventilation would be lower in the COPD patient. Further, because of chronically high work of breathing, the respiratory muscles of COPD patients may have a high capacity for aerobic work; endurance training programs have recently been shown to increase the level of aerobic enzymes in rat diaphragm and intercostal muscles. Complicating matters further, it has recently been shown in the pony that the diaphragm produces no lactate even during maximal exercise. Intercostal muscle lactate production has not been investigated.

Cooke et al. reported that a resting MVV maneuver failed to increase blood lactate levels significantly in five patients with COPD. We reasoned that voluntarily increasing ventilation against a background of exercise might be more relevant; blood flow demands of the exercising muscles might tend to impair blood flow to the respiratory muscles and increase the likelihood of anaerobic metabolism. Further, the patients of Cooke et al failed to increase blood lactate levels during maximal exercise.

The plausibility of respiratory muscle lactate production in COPD patients is enhanced by the observation that these patients often experience elevated blood lactate levels at work rates that do not elicit elevated blood lactate levels in healthy subjects. However, other explanations for early onset of lactic acidosis have been postulated. Pulmonary vascular disease that often accompanies COPD can limit blood flow to the exercising muscles and decrease the aerobic exercise capacity. Further, most COPD patients are extremely sedentary and deconditioned individuals produce lactic acid at low work rates. In fact, it has been demonstrated that exercise training of COPD patients reduces blood lactate levels at a given level of exercise.

The data presented in Figure 2 show that it is unlikely that the respiratory muscles are responsible for an appreciable fraction of the blood lactate levels seen at peak exercise. Volitionally increasing ventilation to levels near those seen during maximal exercise did not result in a significant increase in blood lactate level. It should be noted that we failed in our goal of precisely compensating for the effect of hyperventilation on arterial Pco₂ and pH. In fact, inhalation of 3% CO₂ overcompensated for the increased alveolar ventilation during the volitionally increased ventilation study, yielding a mild hypercapnia and acidosis. Since it has been shown that (at rest) hypocapnia results in mildly increased lactate levels, we must consider whether hypercapnia might suppress any lactate increase associated with the volitional increase in ventilation. This seems highly unlikely, however, because the healthy subjects (Fig 1) did not have a measurable alteration in blood lactate levels when a substantial hypocapnia and alkalosis resulted from ventilation increase without supplemental inhaled CO₂.

This is not to say that we obtained no evidence that the respiratory muscles were a source of blood lactate elevation in these COPD patients. There was a significant tendency for the more severely obstructed patients to increase blood lactate levels as a result of volitional increases in ventilation (Fig 3). We speculate that if we had studied only patients with very severe obstruction (FEV1=20 to 30% predicted) we might have detected significant increases in blood lactate levels during volitional ventilation increase. However, in the case of the more severely obstructed patients we studied, the increase in blood lactate level that can be ascribed to the respiratory muscles is a very small fraction of the increase seen during maximal exercise.

We conclude that lactate production by respiratory muscles is unlikely to contribute appreciably to the lactic acidosis of heavy exercise in patients with COPD. The exercising muscles are likely the source of the relatively high blood lactate levels seen in these patients at peak exercise. Further studies will be required to fully explain why many COPD patients experience high blood lactate levels at the relatively low work rates they are able to tolerate.

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