Theophylline Improves Measurements of Respiratory Muscle Efficiency*

Michael S. Sherman, MD, FCCP; David M. Lang, MD; Amir Matityahu, BA; and Dave Campbell, BS, RPFT

To determine the effect of theophylline on respiratory muscle efficiency (RME), 12 normal subjects were given theophylline vs placebo in a double-blind, randomized crossover protocol. Spirometry, resting energy expenditure, minute ventilation, RME, and oxygen cost of breathing were measured at baseline, after taking theophylline, and after placebo. RME was calculated by dividing the added work required to breathe through a threshold load by the added energy consumed during loaded breathing. Oxygen cost of breathing was calculated by dividing the increase in oxygen consumption induced by breathing an air/carbon dioxide mixture by the associated increase in minute ventilation. RME increased from 3.3±1.6% at baseline to 7.9±3.2% after theophylline (p<0.01) but did not change significantly after placebo (4.8±2.4%). Oxygen cost of breathing decreased from 3.9±2.4 mL O2 per liter at baseline to 1.7±0.7 mL O2 per liter after theophylline (p<0.05) but did not change significantly after placebo (2.8±1.3 mL O2 per liter). Theophylline use was also associated with an 18% increase in minute ventilation (p<0.01) and a 15.7% increase in resting energy expenditure (p<0.01). Theophylline improves measured RME and reduces oxygen cost of breathing in normal subjects. These effects are offset by increases in resting energy expenditure and minute ventilation.

Key words: oxygen consumption; oxygen cost of breathing; respiratory muscles; resting energy expenditure; theophylline; work of breathing

Abbreviations: ATP=adenosine triphosphate; REE=resting energy expenditure; RME=respiratory muscle efficiency; VCO2=carbon dioxide production; Ve=minute ventilation; VO2=oxygen consumption

Theophylline is the most widely prescribed bronchodilator worldwide. In addition to its effect on airway muscle tone, theophylline is thought to owe some of its therapeutic efficacy to actions on the respiratory muscles. Theophylline has been reported to have an inotropic effect on the diaphragm and to decrease fatigability in both human and animal models. Although controversial, this effect has been demonstrated to improve respiratory muscle performance in patients with COPD and in patients with neuromuscular dysfunction. Whether an improvement in contractility occurs at the expense of increased respiratory muscle tissue oxygen consumption or whether theophylline actually improves respiratory muscle efficiency is not known.

We evaluated the effect of theophylline on measurements of respiratory muscle efficiency (RME) and oxygen cost of breathing in a group of normal subjects.

Normal subjects were studied to minimize any bronchodilator action of theophylline that could potentially reduce respiratory muscle demand or change the length-tension relationship of the diaphragm. We demonstrated a significant improvement in measured RME and oxygen cost of breathing during theophylline administration; however, this effect was associated with a significant increase in resting energy expenditure (REE) and minute ventilation (Ve).

Materials and Methods

Ten healthy subjects were recruited for the study. Subjects were excluded if they had a history of asthma, COPD, or if they had a smoking history. Informed consent was obtained after approval by the Hahnemann University Investigational Review Board.

Subjects were asked to refrain from drinking caffeinated beverages for the duration of the study. Subjects were also asked to refrain from eating or drinking for 8 h prior to the study time. Measurements were obtained on each study day in the following order: Ve with Ve, RME, repeated baseline Ve, oxygen cost of breathing, and spirometry, with a 40-min recovery period between the RME and the repeated baseline Ve measurements, and a 15-min recovery period before spirometry. The initial Ve measurement was used for analysis; the repeated Ve was used as part of the oxygen cost of breathing calculation. Subjects were withdrawn from the study if they were unable to produce steady-state values of Ve. Steady-state was defined as a continuous 5-min period in which there was less than a 5% change in the respiratory exchange ratio.
Table 1—Patient Characteristics and Pulmonary Function*

<table>
<thead>
<tr>
<th>Subject/Age, yr/sex</th>
<th>Baseline, L</th>
<th>Placebo (% Δ)</th>
<th>Theophylline (% Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁</td>
<td>FVC</td>
<td>FEV₁</td>
</tr>
<tr>
<td>1/A30/F</td>
<td>4.03</td>
<td>5.09</td>
<td>0</td>
</tr>
<tr>
<td>2/#37/M</td>
<td>4.33</td>
<td>5.54</td>
<td>-1.4</td>
</tr>
<tr>
<td>3/A39/M</td>
<td>3.66</td>
<td>4.54</td>
<td>-1.9</td>
</tr>
<tr>
<td>4/#27/M</td>
<td>3.72</td>
<td>5.03</td>
<td>0</td>
</tr>
<tr>
<td>5/#39/F</td>
<td>2.77</td>
<td>3.63</td>
<td>2.9</td>
</tr>
<tr>
<td>6/#31/M</td>
<td>3.30</td>
<td>4.30</td>
<td>-2.7</td>
</tr>
<tr>
<td>7/#30/F</td>
<td>3.10</td>
<td>3.75</td>
<td>6.5</td>
</tr>
<tr>
<td>8/#29/M</td>
<td>3.63</td>
<td>4.50</td>
<td>0</td>
</tr>
<tr>
<td>Mean, 32.8</td>
<td>3.57</td>
<td>4.55</td>
<td>0.4</td>
</tr>
<tr>
<td>SD, 4.8</td>
<td>0.46</td>
<td>0.63</td>
<td>3.0</td>
</tr>
</tbody>
</table>

*Baseline values are given in liters. Placebo and theophylline values are presented as percent change from baseline. Symbols are given to identify specific individuals in Figures 1-3.

and less than a 10% change in oxygen consumption (\( \dot{V}O_2 \)) and carbon dioxide production (\( \dot{V}CO_2 \)). Continuous data points were added if they were within 5% of the mean respiratory exchange ratio, 10% of the mean \( \dot{V}O_2 \), and 10% of the mean \( \dot{V}CO_2 \) of the 5-min steady-state period.

Subjects underwent baseline measurements of REE, RME, \( \dot{V}E \), and oxygen cost of breathing on the morning of the first study day. Subjects were then randomly assigned to receive either sustained-release theophylline, 300 mg twice daily for 48 h, or placebo. Treatment with medication was started the evening of day 1. Measurements were then repeated on the morning of day 3, after the fourth dose of medication. After a 2- to 4-d washout period, subjects were then assigned to the alternative agent and measurements were again repeated after the fourth dose of the alternative medication. Measurements were performed at the same time of day in each patient, usually in the early morning, and in the same order. Subjects maintained the same posture and used the same chair for each study day. Neither the investigator nor the subject knew the medication assigned. Theophylline levels were drawn at the end of both assigned medication study days.

Spirometry was performed (Medgraphics 1700; Medical Graphics Corporation, St. Paul, Minn.). RME was measured using a method adapted from Campbell et al.\(^{14-17}\) Subjects were asked to breathe normally while wearing a face mask sealed tightly around the nose and mouth. The face mask included inspiratory and expiratory valves that were connected using low-resistance tubing to an automated portable system of indirect calorimetry (Cybermedic Metascope; Metabolic Cart; Louiseville, Colo.).

After a 3-min calibration period, subjects were asked to breathe normally for a 20-min period while seated in a reclining chair in a darkened, quiet room. After a 5-min period of observation to ensure that steady-state was present, a continuous steady-state interval of 5 to 15 min was used for analysis. REE was calculated using the Weir\(^{18}\) equation:

\[
\text{Energy expenditure} = [3.9(\dot{V}O_2) + 1.1(\dot{V}CO_2)] \times 1.44
\]

where \( \dot{V}O_2 \) and \( \dot{V}CO_2 \) are measured in milliliters of gas per minute and energy expenditure is in kilocalories per day. A threshold load of between 1.47 and 1.96 kilopascals (15 to 20 cm H₂O) was then placed along the inspiratory limb of the face mask (the exact magnitude of the load was previously selected based on individual subject tolerance). The magnitude of the inspiratory pressure load was verified using a water manometer. Subjects were asked to continue to breathe in a steady rhythm for an additional 20-min period. Energy expenditure was measured as above, with a continuous 5- to 15-min steady-state interval used for analysis.

Added mechanical work per minute was calculated by multiplying the \( \dot{V}E \) during loaded breathing by the added threshold inspiratory pressure.\(^{14-17}\) Metabolism of respiratory muscles was calculated by determining the difference in \( \dot{V}O_2 \) between the resting state and when breathing against the threshold load. The added \( \dot{V}O_2 \) was then converted to its caloric energy equivalent (assuming a respiratory quotient of 0.82). Efficiency was then calculated by dividing the added mechanical work by the added energy expenditure:

\[
\text{RME} = \frac{\dot{V}E \times P}{(\dot{V}O_2 - \dot{\dot{V}}O_2) \times 4.825 \times 4.184}
\]

where \( \dot{V}E \) is ventilation during loaded breathing; \( P \) is the inspiratory threshold pressure in kilopascals; \( \dot{V}O_2 \) is oxygen consumption during loaded breathing in mL/min; \( \dot{V}O_2b \) is baseline oxygen consumption in mL/min; and 4.825 is the caloric equivalent of oxygen when \( R \) is 0.82, and 4.184 is Joule's equivalent.

Oxygen cost of breathing was determined using a variation of a technique developed by Levinson and Cherniack.\(^{19}\) Subjects were asked to breathe a mixture of 5% \( CO_2 \), 95% air. After a 5-min reequilibration period, \( \dot{V}O_2 \) and \( \dot{V}E \) were measured using the metabolic cart for an additional 15-min period. A 5- to 10-min period of steady-state was used for analysis. Oxygen cost of breathing was calculated as the ratio of the increase in \( \dot{V}O_2 \) during \( CO_2 \) breathing over the increase in \( \dot{V}E \) and expressed as mL \( O_2 \) per liter ventilation.

Statistics

Results are presented as mean ± SD. Differences among baseline, placebo, and theophylline treatment arms were compared using the multiple measures Friedman test. Pairwise comparisons were then performed using a Bonferroni \( t \) test, using a critical value for the \( t \) statistic corrected for the multiple comparisons. Differences were considered significant at \( p \le 0.05.\(^{20}\)

RESULTS

Two subjects were unable to maintain steady-state conditions and were not randomized. Subject characteristics of the eight subjects who completed the protocol are shown in Table 1. Baseline FEV\(_1\) and FVC measurements were all above 90% of the predicted normal for our laboratory. The spirometric responses to placebo and theophylline are also shown in Table 1. There was no significant increase in the mean FEV\(_1\) or...
mean FVC when subjects received either placebo or theophylline. No subject had more than a 15% improvement in FEV1 or vital capacity after either medication. Only 1 subject had more than a 5% improvement in FEV1 after placebo; 2 subjects had more than a 5% improvement in FEV1 after theophylline. Theophylline levels ranged from 6.2 to 11.4 µg/mL (mean, 8.6 µg/mL; 5 to 15 µg/mL is considered the therapeutic range21) after subjects took theophylline and were undetectable after subjects received placebo.

RME increased significantly when subjects were given theophylline (Fig 1, Table 2). There was a significant difference among baseline, placebo, and theophylline treatment arms ($\chi^2=9.75, p<0.005$). There was no significant difference between baseline and placebo treatments; however, there were significant differences between baseline and theophylline (mean difference, 4.6%; p<0.01), and between placebo and theophylline treatments (mean difference, 3.1%; p<0.05). The improvement in efficiency was due to a smaller rise of $\text{VO}_2$ during loaded breathing ($150\pm69\ \text{mL O}_2$ per minute at baseline vs $179\pm141\ \text{mL O}_2$ per minute after placebo vs $69\pm54\ \text{mL O}_2$ per minute after theophylline); mean work performed against the threshold load was similar in the three groups ($12.1\pm2.9\ \text{J vs 12.9}\pm3.9\ \text{J vs 13.6}\pm2.4\ \text{J}$, respectively; NS).

Oxygen cost of breathing decreased when subjects were given theophylline (Fig 2, Table 2). There was a significant difference among the three treatment arms ($\chi^2=6.25, p<0.05$) and there was no significant difference between placebo and baseline. The trend to lower oxygen cost of breathing between placebo and theophylline did not reach significance (mean difference=1.03 mL O2 per liter; p=0.13), however, the decrease in oxygen cost of breathing between baseline and theophylline arms was significant (mean difference=2.16 mL O2 per liter; p<0.05).

Figure 3 illustrates that theophylline increased $\text{Ve}$ by an average of 18% over baseline. The three treatment arms differed significantly ($\chi^2=7.313, p<0.03$). There was no significant difference in $\text{Ve}$ between baseline and placebo treatments (Table 2). The increase in $\text{Ve}$ was significant for both placebo vs theophylline (p<0.01) and baseline vs theophylline (p<0.01).

REE measurements at baseline, when receiving placebo, and when receiving theophylline are illustrated in Figure 4. There was a significant increase in REE in the theophylline treated arm compared to either placebo or to baseline ($\chi^2=9.25, p<0.01; p<0.03$, respectively).
Our measurement of efficiency is the ratio of added workload to the caloric cost of the increased work. Our efficiency measurement would increase if either (1) the amount of work performed was actually less when subjects received theophylline than when they received placebo, or (2) the caloric cost for the added work actually decreased.

The first alternative is not likely. Although theophylline has been shown to decrease work of breathing in patients with COPD, this is believed to occur by a decrease in airways resistance and by improved lung compliance. Since FEV₁ and FVC did not change significantly in our normal subjects, theophylline would be unlikely to have improved either resistance or compliance.

RME may increase if the length-tension relationship changed. However, since pulmonary function was unchanged, it is doubtful that a significant effect on the functional residual capacity (and thus length-tension relationship of the diaphragm and chest wall muscles) occurred. Moreover, we found no relationship between the magnitude of improvement in FEV₁ and the magnitude of improvement in RME.

We postulate two reasons for the increase in measured efficiency. It is known that methylxanthines stimulate the ryanodine receptors of the sarcoplasmic reticulum, increasing the calcium flux into the muscle cytoplasm. Increases in cytoplasmic calcium concentrations can cause an increase in glucose transport into the cell, by a pathway that does not consume oxygen or require adenosine triphosphate (ATP). We postulate that a further savings in VO₂ would occur if this added glucose were utilized during the loaded breathing and CO₂ stimulation trials, since consumption of 1 mol of oxygen would produce 6.3 ATP for glucose vs 5.6 ATP for fat. However, in vitro studies demonstrating these effects on the ryanodine receptor utilize intracellular drug concentrations that greatly exceed normal therapeutic serum levels. It is not known whether these effects occur in vivo at these lower serum levels.

A second reason for the improved efficiency may be an effect of theophylline on expiratory muscles. Electromyographic studies have demonstrated recruitment of expiratory muscles during aminophylline administration in a canine model. The respiratory pattern

### Table 2—Effect of Theophylline on Respiratory Muscles*

<table>
<thead>
<tr>
<th></th>
<th>RME, %</th>
<th>Oxygen Cost of Breathing, mL O₂/L</th>
<th>Vₑ, L/min</th>
<th>REE, kcal/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3.3±1.6⁴</td>
<td>3.9±2.4⁴</td>
<td>7.07±1.31⁴</td>
<td>1623±303⁴</td>
</tr>
<tr>
<td>Placebo</td>
<td>4.8±2.4⁴</td>
<td>2.8±1.3⁴</td>
<td>6.99±1.58⁴</td>
<td>1643±436⁴</td>
</tr>
<tr>
<td>Theophylline</td>
<td>7.9±3.2⁴</td>
<td>1.7±0.7⁴</td>
<td>8.34±1.50⁴</td>
<td>1876±381⁴</td>
</tr>
</tbody>
</table>

*Data given as means±SDs.

Differences between groups are significant at ¹p<0.005, ²p<0.05, ³p<0.03, and ⁴p<0.01, respectively, by Friedman test. Fairwise comparisons are described in the text.
During aminophylline administration was characterized by a sudden relaxation of the expiratory muscles which causes an increase in thoracic cage volume that occurs prior to the activation of the inspiratory muscles. This mechanism may, in part, explain our paradoxical findings of increasing \( \text{VO}_2 \) overall, but a decrease in the added utilization of oxygen that occurs during loaded breathing. Recruitment of the expiratory muscles increases overall energy expenditure. The relaxation of the expiratory muscles during inspiration (and, presumably, during inspiratory loading) causes an increase in inspiratory volume that has a "hidden" oxygen cost. The cost is actually a part of the increased baseline energy expenditure. Thus, the added \( \text{VO}_2 \) required to overcome the inspiratory load may be less during inspiration when the subject is receiving theophylline, and so our measured efficiency shows an improvement. Gorini et al.\(^{28}\) did not find expiratory muscle recruitment in humans receiving theophylline, but electromyography of expiratory muscles was not performed in this study.

Our results showing a theophylline-induced increase in \( \dot{V}e \) of 18\% is in close agreement with earlier studies. Morice et al.\(^{29}\) also demonstrated an 18.6\% increase in \( \dot{V}e \) in normal subjects given theophylline. Gorini et al.\(^{28}\) also found a similar increase in \( \dot{V}e \) in normal subjects, which was mostly due to an increase in tidal volume. \( \text{CO}_2 \) production increased 11.4\% in our subjects when they took theophylline, suggesting that increased metabolic activity may have accounted for some of this rise in \( \dot{V}e \); the remainder of this increase is likely due to an increase in central respiratory drive.\(^{29,30}\)

Our finding that theophylline increases total body \( \text{VO}_2 \) is also in agreement with earlier studies. Indeed, attempts have been made to use this property of methylxanthines to promote weight loss.\(^{31,32}\) Donahoe et al.\(^{33}\) have shown that patients with COPD have increased caloric requirements compared with normal subjects, and have suggested that the increased work of breathing may be a cause; however, medication usage was not described in this report. Our data suggest that theophylline may be contributing to the increase in energy expenditure in this patient population, by its direct effect on basal metabolism and by the increased work of breathing incurred by the higher \( \dot{V}e \). Since there is an association between weight loss and increased mortality in patients with COPD,\(^{34}\) this thermogenic effect of theophylline may have potentially deleterious effects.

Our results differ from a recent study by Janssens et al.\(^{35}\) While they also observed an increase in total body \( \text{VO}_2 \), they found an increase in diaphragmatic \( \text{VO}_2 \) during inspiratory resistive loading. This study measured \( \text{VO}_2 \) in the canine diaphragm using blood samples drawn from catheters in the abdominal aorta and phrenic vein, while our measurements were indirect measurements of the increase in \( \text{VO}_2 \) that occurred during respiratory loading. If some of the effects that we are seeing are indeed due to theophylline-induced relaxation of expiratory muscles, then such an effect would not be detected in studying the effect on the isolated diaphragm alone. In addition, there are differences in fiber composition between canine and human diaphragms that may respond differently to theophylline.\(^{36}\)

There are two limitations of this study that merit mention. (1) Our measurement of RME may underestimate the amount of mechanical work performed during loaded breathing—it does not measure the work performed by respiratory muscles to compress alveolar gas\(^{37}\) or the work associated with changes in abdominal and thoracic partitioning.\(^{38}\) However, Jaeger and Otis\(^{37}\) note that the increase in the rate of work due to compressibility was not measurable unless breathing through a resistance of at least 38 cm H\(_2\)O, a much greater resistance than our subjects used. Goldman et al.\(^{38}\) observed that little or no chest wall distortion occurs in unloaded breathing unless \( \dot{V}e \) was significantly increased through exercise or carbon dioxide rebreathing; \( \dot{V}e \) did not increase in our subjects during loaded breathing. Agostoni et al.\(^{39}\) suggested that work of deformation is probably negligible unless flow resistance is high, at levels where the work of alveolar gas compression also becomes appreciable.\(^{39}\) Since our threshold load was relatively low, the effect of these errors is likely to be small. For this reason, we believe that it is unlikely that our measurement of efficiency was significantly affected. This error should also be similar when subjects take placebo or theophylline. (2) Side effects of tremulousness, nausea, tachycardia, and nervousness were often recognized by subjects when they took theophylline. Although this may have alerted participants to drug exposures, subjects would be unable to manipulate measures of RME or oxygen cost of breathing. We therefore do not believe possible recognition of theophylline exposure explains our findings.

We conclude that theophylline increases measurements of RME during inspiratory muscle loading in normal subjects. These effects are offset by an increase in REE and \( \dot{V}e \). Further studies are needed to investigate the effects of higher theophylline doses and serum levels, establish whether the effects persist with long-term use, and determine whether these findings could adversely affect patients with COPD or asthma.

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