Influence of Posture on Expiratory Flows and Airway Responsiveness to Methacholine in Asthma*

Majd Tahan, M.D.; and Louis-Philippe Boulet, M.D., F.C.C.P.

This study looked at the effects of posture on the morning/evening expiratory flows and airway responsiveness to methacholine. Fourteen nonsmoking subjects with stable asthma (eight men, six women) were included in the study. Subjects were randomly allocated to spend 4 h in the supine or seated position on separate days, in the morning from 8 to 12 AM and in the evening from 8 to 12 PM. The FEV₁ was measured hourly in the assigned position. Before and after each 4-h period, a methacholine inhalation test was done in the sitting position. In the morning study, baseline FEV₁ measurements on the supine and seated days were not different. There was no significant difference between the baseline and postsession FEV₁ on both days (baseline and postsession FEV₁, percent predicted ± SEM; seated: 83.6 ± 2.9, 83.8 ± 3.3; supine: 83.8 ± 2.8, 85.4 ± 3.7; n = 13). ΔFEV₁ (baseline/postsession) was not different between the two evening sessions. In the morning, after the seated position, PC20 methacholine was unchanged (mean PC20 [mg/ml]: beginning = 1.00, end = 1.02) while after the supine position it was slightly reduced from a mean of 0.97 to 0.73 mg/ml. This last reduction was mainly observed in the most hyperresponsive subjects and its magnitude was significantly correlated with baseline PC20 (r = 0.637, p = 0.024). The increase in methacholine response (ΔPC20) after the supine session was significantly higher than after the seated session. In the evening study, there was a slight reduction in PC20 after both sessions, but this was only significant after the supine position (mean PC20 baseline and postsession [mg/ml]; seated: 0.63, 0.47, p = 0.08; supine: 0.62, 0.44, p = 0.04). No difference was found between ΔPC20 of the two sessions. We conclude that the supine position does not have persistent effects on FEV₁, but it may increase airway responsiveness in the most hyperreactive subjects.

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Nocturnal asthma is frequently reported by asthmatic patients and usually suggests that asthma is not optimally controlled. Up to 75 percent of asthmatics admit to having nocturnal or early morning awakening with dyspnea and wheezing.¹ ² Many pathogenetic factors have been proposed to explain this nocturnal bronchoconstriction, including the possibility of a late-phase allergic reaction, accumulation of metabolic toxins, impaired mucociliary clearance, gastroesophageal reflux with gastric acid aspiration, sleep stages, timing of drug administration, airways cooling and dryness, hormonal circadian rhythms, and the supine position (SP).³ ⁴ However, up to now, no single factor itself by explains this phenomenon.

The effect of recumbency on airway function is still uncertain. Expiratory volumes are reduced when measured in the SP in asthmatics or normal subjects, but data are somewhat conflicting about the effects of prolonged SP on airway caliber.⁷

Jonsson and Mossberg⁶ have shown that in asthmatics, daytime SP for 4 h induces a progressive increase in airflow obstruction that persists even after resumption of the upright position. On the other hand, Whyte and Douglas⁹ reported that daytime SP for 4 h was not associated with a persistent obstruction. Furthermore, we still do not know if prolonged recumbency can influence airway responsiveness.

During the night, we may observe a fall in expiratory flows, more pronounced in asthmatics than in nonasthmatics.¹⁰ Recent observations suggest that airway inflammation may increase during the night. Martin et al¹¹ described an increase in inflammatory cells on bronchoalveolar lavage, mainly eosinophils, at 4 AM compared with 4 PM, in patients with nocturnal asthma. The mechanisms by which this nocturnal inflammation occurs are unknown, but these observations suggest that it may play a role in nocturnal bronchoconstriction.

The reports that nocturnal asthma can be blocked by a single dose of prednisone at bedtime or by increasing or introducing inhaled steroids further support this role.¹² ¹³ This study was set to look at the effects of SP on airway responsiveness and airflow obstruction over a
Table 1—Subject Characteristics

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Age, yr</th>
<th>Sex</th>
<th>FEV\textsubscript{1}, L (% pred)</th>
<th>PC20, mg/ml</th>
<th>Medication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/36/F</td>
<td>24</td>
<td>F</td>
<td>2.50 (86.8)</td>
<td>0.40</td>
<td>(\beta_2)</td>
</tr>
<tr>
<td>2/22/M</td>
<td>49</td>
<td>M</td>
<td>3.55 (83.7)</td>
<td>3.37</td>
<td>(\beta_2)</td>
</tr>
<tr>
<td>3/24/M</td>
<td>18</td>
<td>M</td>
<td>3.26 (71.5)</td>
<td>0.24</td>
<td>(\beta_2), IS</td>
</tr>
<tr>
<td>4/25/F</td>
<td>42</td>
<td>F</td>
<td>2.75 (87.6)</td>
<td>0.81</td>
<td>(\beta_2), IS</td>
</tr>
<tr>
<td>5/27/M</td>
<td>38</td>
<td>M</td>
<td>4.00 (96.2)</td>
<td>0.33</td>
<td>(\beta_2), IS</td>
</tr>
<tr>
<td>8/37/F</td>
<td>52</td>
<td>F</td>
<td>2.69 (95.2)</td>
<td>1.04</td>
<td>(\beta_2)</td>
</tr>
<tr>
<td>10/11/F</td>
<td>36</td>
<td>M</td>
<td>2.66 (83.9)</td>
<td>8.19</td>
<td>(\beta_2), IS</td>
</tr>
<tr>
<td>11/48/M</td>
<td>29</td>
<td>M</td>
<td>2.51 (76.5)</td>
<td>0.50</td>
<td>(\beta_2), IS</td>
</tr>
<tr>
<td>12/47/M</td>
<td>45</td>
<td>M</td>
<td>2.04 (63.6)</td>
<td>0.51</td>
<td>(\beta_2)</td>
</tr>
<tr>
<td>13/47/M</td>
<td>48</td>
<td>M</td>
<td>3.54 (90.2)</td>
<td>3.87</td>
<td>(\beta_2)</td>
</tr>
<tr>
<td>14/27/F</td>
<td>21</td>
<td>M</td>
<td>2.72 (100.0)</td>
<td>1.22</td>
<td>(\beta_2)</td>
</tr>
</tbody>
</table>

\(\beta_2\) = inhaled \(\beta_2\)-agonist on demand; IS = inhaled steroid.

4-h period, in the morning and the evening, in subjects with mild to moderate asthma.

Methods

Subjects

Fourteen nonsmoking subjects (eight men, six women) with a diagnosis of asthma corresponding to the American Thoracic Society criteria, aged 18 to 49 years (mean = 32.1) were recruited from the Laval Hospital Asthma Clinic. Subject characteristics are shown in Table 1. None had a recent (<4 weeks) respiratory infection or allergic reaction. One patient, subject 14, had an asthma exacerbation during the study and was excluded from the analysis. Eight of these subjects agreed to come back in the evening to repeat the same procedures, (subjects 1 to 8).

Their airway hyperresponsiveness to methacholine was mild to moderate, with a PC20 (the provocation concentration of methacholine giving a 20% fall in FEV\textsubscript{1}) ranging from 0.34 to 8.19 mg/ml. All used an inhaled \(\beta_2\)-agonist on demand. Six also used additional inhaled steroids, beclomethasone (mean daily dose: 540 \(\mu\)g, \(n = 4\)) or flunisolide (mean daily dose: 1250 \(\mu\)g, \(n = 2\)), to control their asthma symptoms. The study was approved by our local Ethics Committee and all patients signed an informed consent form.

Study Design

Subjects were investigated on two days for the morning study and two other days for the evening study. The two morning or evening visits were made within a week, and the study was completed within a month. In the morning study, all visits began at 7 AM. No medication was taken within 8 h of each visit. The subjects were randomly allocated to remain 4 h in SP on one day, and 4 h in seated position (ST) on the other day. Supine position means lying comfortably on the back with short periods on the sides, the subjects being kept awake during the whole study. Seated position means staying comfortably in a straight back chair, and walking around for short periods. The FEV\textsubscript{1} was measured hourly in the position assigned with a spirometer (PFT Vitalograph spirometer). Expiratory flow measurements and methacholine inhalation tests (MIT) were done before and after each 4-h session (MIT1 = baseline, MIT2 = postsession), according to the method described by Juniper et al. Briefly, a solution of control saline solution (0.9 percent) was inhaled for 2 min, followed by progressive doubling concentrations of methacholine (0.03 to 8 mg/ml) to obtain a 20 percent fall in FEV\textsubscript{1}. All baseline and postsession expiratory flows and methacholine challenges were done seated. After the baseline provocation test (MIT1), the 4-h session did not begin until the FEV\textsubscript{1} had recovered >80 percent of baseline, which means generally no more than 1 h (Table 2). No beverages containing caffeine were allowed before or during the tests. In the evening study, the same design was followed, the tests beginning at 7 PM.

Data Analysis

Data analysis was done on the results obtained from the 13 subjects who completed the morning study and on 8 of those subjects who agreed to come back for the evening study. Baseline and postsession FEV\textsubscript{1} or PC20 were compared by paired t test. Mean PC20 values were obtained after logarithmic transformation of data. A Spearman’s correlation test was made between baseline PC20 and the change in number of doubling concentrations of methacholine observed after each session. The level of statistical significance was established at \(p < 0.05\).

Results

Expiratory Volumes (FEV\textsubscript{1})

Morning Study: There was no significant difference

Table 2—Study Design*

<table>
<thead>
<tr>
<th>Subject</th>
<th>FEV\textsubscript{1}, 0 h</th>
<th>FEV\textsubscript{1}, 1 h</th>
<th>FEV\textsubscript{1}, 2 h</th>
<th>FEV\textsubscript{1}, 3 h</th>
<th>FEV\textsubscript{1}, 4 h</th>
<th>Postsession</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP</td>
<td>X</td>
<td>X</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>X</td>
</tr>
<tr>
<td>ST</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*SP = supine position; ST = seated position; X = tests done in seated position; Y = tests done in supine position.

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Figure 1. FEV\textsubscript{1} (mean of 13 subjects, percent predicted ± SEM) during the two morning visits, supine and seated. In the supine position, there was an immediate fall in FEV\textsubscript{1} but no further reduction during the next 4 h. After the end of the supine position, when the seated position is resumed, FEV\textsubscript{1} immediately comes back to baseline.

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between baseline premethacholine FEV₁ of both visits (mean ± SEM, percent predicted: SP = 85.8 ± 2.8; ST = 83.6 ± 2.9) nor between the FEV₁, measured seated, before the beginning of the 4-h sessions, when FEV₁ was back >80 percent of baseline (mean ± SEM, percent predicted: SP = 74.9 ± 2.6; ST = 75.4 ± 3.2; Fig 1).

During the 4-h session in the SP, FEV₁ measured supine fell immediately when the subject lay down. A subsequent increase in FEV₁ was found during the first hour, corresponding to full recovery from the baseline methacholine test. The FEV₁ remained unchanged during the next 3 h. At the end of the supine session, when the ST was resumed, FEV₁ immediately returned to its baseline value, so that no significant difference was found between baseline and postsession FEV₁, both measured seated (mean ± SEM, percent predicted: baseline = 85.8 ± 2.8; after SP = 85.4 ± 3.7).

During the 4-h session in the ST, FEV₁ increased during the first hour, corresponding to full recovery from the baseline methacholine test, then remained unchanged during the next 3 h. No significant difference was found between baseline and postsession FEV₁ (mean ± SEM, percent predicted: baseline = 83.6 ± 2.9; after ST = 83.8 ± 3.3).

There was no significant difference between the two sessions Δ FEV₁ (initial/postsession). The subgroup of eight subjects who took part in the evening study showed the same pattern and degree of change as the whole group.

**Evening Study:** There was no significant difference between baseline FEV₁ at the beginning of both visits (mean ± SEM, percent predicted: SP = 90.7 ± 3.1; ST = 90.0 ± 4.1) nor between the FEV₁, measured seated, before the beginning of the 4-h sessions, when FEV₁ was back >80 percent of baseline (mean ± SEM, percent predicted: SP = 75.6 ± 5.2; ST = 76.2 ± 5.1; Fig 2).

During the 4-h session in SP, FEV₁ fell immediately when the subject lay down. A subsequent increase in FEV₁ was found during the first hour, corresponding to full recovery from the baseline methacholine test. FEV₁ remained unchanged for the next 3 h. At the end of the supine session, when the ST was resumed, the FEV₁ increased immediately, but not up to the initial values, so that a significant reduction was found.
Changes in airway responsiveness following the morning and evening sessions are shown on Figures 3 and 4.

Morning Study: Geometric mean baseline PC20 values for the 13 subjects before either the seated or supine sessions were not significantly different (1.00 and 0.97 mg/ml, respectively; Fig 3). After 4 h in the ST, there was no significant change in PC20 (1.00 and 1.02 mg/ml, respectively). PC20 measured after the supine session was slightly reduced (from 0.97 to 0.73 mg/ml), but was not statistically significant.

Comparing the two sessions ΔPC20, we found a statistically significant difference (p<0.05) showing that the increase in methacholine response was greater after the SP. Furthermore, there was a significant correlation between the baseline PC20 and the magnitude of the PC20 reduction after the 4-h supine session (p = 0.024; Fig 5).

The subgroup of eight subjects who took part in the evening study showed the same pattern of change as the whole group (supine/seated ΔPC20: p<0.05).

Evening Study: Geometric mean baseline PC20 values for the eight subjects before either seated or supine session were not significantly different (0.63 and 0.62 mg/ml, respectively; Fig 4). The PC20 reduction after the seated session just failed to reach statistical significance (from 0.63 to 0.47 mg/ml; p = 0.08). However, after the SP, this reduction in PC20 was statistically significant (from 0.62 to 0.44 mg/ml).

Figures 4 and 5. Influence of posture on airway responsiveness.
mg/ml; p = 0.04). No significant difference was found between the two sessions ΔPC20.

DISCUSSION

This study shows that in the morning, a 4-h period in the SP may induce an increase in nonallergic airway responsiveness in the most hyperreactive subjects, without influencing expiratory flow. The magnitude of this increase correlates directly with the baseline level of airway responsiveness. However, in the evening, changes in expiratory flow and airway responsiveness were not different between the two positions.

When unstable, asthmatics typically develop early-morning asthma and many of them experience symptoms immediately on recumbency at bedtime in the evening. We postulated that recumbency was one of many factors leading to this nocturnal or early-morning exacerbation of asthma. An important factor in the evaluation of changes in airway resistance or responsiveness is the position in which the tests are done.17 With recumbency, expiratory flows decrease immediately in asthmatics as well as in nonasthmatics.4,18,19 However, airway responsiveness does not seem to change acutely when measured in SP in normal subjects.19 We chose to measure baseline and postsession expiratory flows and methacholine responsiveness in the ST position to be able to compare these results without interference with the acute change in position, and to document any persistent effects of recumbency. Furthermore, we chose to study these subjects both in the morning and in the evening to obtain a maximal time difference (12 h) between the two tests while avoiding the interference of sleep or other night-time factors that may modify the effect of posture. Our results show that recumbency has a modest influence on expiratory flows in most subjects but may significantly change airway responsiveness to different degrees according to the timing of the tests and to baseline airway responsiveness. During the 4-h session in the SP or ST, no significant change in FEV1 was observed except for an increase during the first hour in relation to full recovery from the first MIT.

Up to now, to our knowledge, no study has looked at the influence of prolonged SP on airway responsiveness or at the influence of circadian variations of posture on airway responsiveness in asthmatics. In our study, in the morning, after the 4-h supine session, the most hyperreactive subjects showed an increase in their methacholine response, and a significant correlation between the degree of increase in airway responsiveness and baseline PC20 was found. This increase in bronchial responsiveness cannot be attributed to changes in airway caliber since the FEV1 after 4 h in the SP was not significantly different from baseline. The evening study showed the same pattern, although it did not reach statistical significance, pos-}

sibly because of interference from other factors not present in the morning.

The observed increase in methacholine response after recumbency can be due to changes in the water content of the airway wall or to an increase in vascular volume of the bronchial circulation. In SP, blood redistribution promotes bronchial vascular congestion. Increased hydrostatic blood pressure enhances fluid extravasation, then potentially increasing the airway wall thickness. Blood velocity may decrease in the bronchial vascular plexus and cell migration into the airway wall can be enhanced.30 Moreno et al31 showed that moderate thickening of the airway wall could produce large effects on the maximal response to agonists with only moderate increase in baseline airway resistance. Thus, the edema and vascular congestion resulting from SP could minimally influence expiratory airflows but amplify the response to agonists such as methacholine. Different observations support this hypothesis. Cabanes et al32 showed that most patients with severe impairment of left ventricular function had marked airway hyperresponsiveness to methacholine compared with others with coronary artery disease, even though the mean FEV1 values in the two groups were not significantly different. Regnard et al33 showed that when antishock trousers were inflated at venous occlusion pressure to lower limbs in healthy subjects in the standing position, lung volumes did not change but bronchial response to methacholine increased.

More information is needed on the influence of posture during sleep. Bronchoconstriction and airway responsiveness increase in the evening, in asthmatics, to reach a nadir at 4 AM.44 Our study suggests that the SP, in stable asthmatics, may play a role in the pathogenesis of nocturnal bronchoconstriction and hyperresponsiveness, although it is not the sole determinant.

Further studies should look at the possibility of an enhanced role of recumbency in nocturnal asthma and following stimuli that increase airway inflammation such as antigenic exposure or respiratory infection.

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