Arterial Blood Pressure Response to Transient Arousals From NREM Sleep in Nonapneic Snorers With Sleep Fragmentation*

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Study objectives: To assess the hemodynamic effects of graded arousals during nonrapid eye movement (NREM) sleep in patients with partial upper airway obstruction during sleep without obstructive sleep apnea/hypopnea, overnight beat-to-beat BP was recorded in six patients.

Setting: At the end of each nonapneic obstructive event, EEG responses were graded as follows: grade 2, grade 1, and grade 0 were defined as increased high-frequency EEG lasting >15 s, 3 to 15 s, and no EEG arousals according to the American Sleep Disorders Association, respectively.

Measurements and results: The following were observed during grade 0, 1, and 2 EEG patterns (mean±SD): systolic pressure increased by 7.1±1.5, 11.7±1.9, and 14.2±3.4 (p<0.005), respectively; diastolic pressure increased by 4.6±0.6, 6.7±1.7, and 9.4±3.0 (p<0.005), respectively; heart rate increased by 2.9±0.4, 3.9±2.2, and 8.6±4.6 (p<0.005), respectively.

Conclusions: We conclude that nonapneic-nonhypopneic obstructive events are followed by arterial systemic pressure increases whose magnitude varies with the grade of the arousal.

(CHEST 1998; 113:985-91)

Key words: arousal; blood pressure; snoring; upper airway resistance

Abbreviations: ASDA=American Sleep Disorders Association; NREM=no rapid eye movement; OSAS=obstructive sleep apnea syndrome; REM=rapid eye movement

It has long been recognized that the obstructive sleep apnea syndrome (OSAS) is associated with acute increases in arterial BP at the termination of respiratory events.1 This phenomenon has been ascribed to hypoxemia,2,3 to the hemodynamic effects of intrathoracic pressure changes,4-6 to interruptions in respiration,7-9 and to disruption of sleep.10-14 For others, the magnitude of the increase in arterial BP does not vary with the grade of the arousal.15

Recent reports have demonstrated that an abnormal amount of breathing effort due to partial upper airway obstruction, even in the absence of sleep apnea or oxygen desaturation, can disrupt sleep architecture by causing arousals.16,17 The purpose of this study was to examine whether the termination of nonapneic-nonhypopneic obstructive events coincides with an abrupt increase in arterial BP similar to that seen in OSAS, despite the absence of oxygen desaturation and interruption of ventilation. In addition, the relationship between the magnitude of the arterial BP increase and the change in the EEG pattern was examined. We recorded acute increases in systemic arterial BP at the time of the abrupt reduction in upper airway obstruction, and found that this BP rise was primarily due to sleep disruption.

Materials and Methods

Patients

Six men were studied. Mean age was 45±11 years (range, 33 to 65 years). Mean body mass index was 27±3 kg/m². All six subjects had heavy snoring confirmed by a roommate or bed partner and daytime sleepiness with an Epworth sleepiness scale18 >10.

Patients were included in the study after a home polysomnography study, including EEG (C4-A1, C3-A2), electro-oculography, chin electromyography, electromyography of the tibialis anterior muscle of both legs, oronasal airflow recordings, rib cage movement recordings (Multi-Parameter Analysis recorder 2/Medilog 9200; Oxford Medical Instruments; Abingdon, England), and arterial pulse oximetry (Nellcor BS; Nellcor Inc; Hayward Calif).
To be eligible for the study, subjects had to have an at-home polysomnography study that met the following criteria: apnea-hypopnea index <5/h of sleep (apnea was defined as cessation of airflow lasting ≥10 s and hypopnea as a ≥50% fall in oronasal airflow for 10 s or a fall in oronasal airflow with an oxygen desaturation ≥3% of the preceding baseline level); and arousal index >10/h of sleep (arousals were detected on the basis of an abrupt shift in EEG frequency, including alpha and/or frequencies >16 Hz but not spindles, and were scored according to standard criteria[23]). To relate clinical complaints and sleep fragmentation to an upper airway obstruction without obstructive sleep apnea/hypopnea, a sleep polygraphic investigation, including respiratory effort evaluation, was performed as recommended.[28] The study was approved by the Research Ethics Committee of our institution, and each subject gave consent in accordance with the committee’s requirements.

Clinical Trial

The clinical trial consisted of a repeat polysomnography study, including EEG (C3-A1, C3-A2), electro-oculography, chin electromyography, thoracic and abdominal movement recording, and arterial pulse oximetry (Nellcor BS, Nellcor Inc.). During the study night, oronasal airflow was quantified using a tight-fitting facial mask and a No. 2 pneumotachograph (Fleisch; Lausanne, Switzerland) connected to a differential pressure transducer (Validyne MP14S ±5 cm H2O; Northridge, Calif.). In addition, respiratory effort was monitored by measuring esophageal pressure (Gaeltec; Duvnevan, Isle of Skye, UK), and BP and heart rate were monitored by recording digital arterial beat-to-beat systolic/diastolic pressure at the third finger of the left hand using an infrared plethysmographic volume clamp method (Finapres; Ohmeda; Maurepas, France). As previously proposed,[11,12] the left hand was taped to the epigastic area to avoid artifactual BP modifications caused by changes in hydrostatic pressure associated with hand movement. All signals were recorded using a 14-channel paper recorder (Electroencephalograph; Nihon Kohden; Tokyo, Japan) digitized at 128 Hz and sampled using an analogic/numerical system (MP100, Biopac System; Goleta, Calif.) for subsequent analysis.

Data Analysis

A nonapneic-nonhypopneic obstructive event was defined as the occurrence, in the absence of hypopnea (airflow drop <50% of the preceding baseline during 10 s or airflow drop with desaturation <3% of the preceding baseline level), of a progressive change in the shape of the inspiratory flow contour characterized by increasing limitation[23] and of a concomitant increase in the esophageal pressure swing, with termination of the vent as abrupt normalization of both the inspiratory flow contour and the esophageal pressure swing. Esophageal pressure swings were calculated as the difference between the minimal inspiratory value and the minimal inspiratory value. Esophageal pressure swing decrease was quantified as the decrease in esophageal pressure swing at the termination of the respiratory event, i.e., the difference between esophageal swings immediately before and after the termination of the respiratory event. BP parameters and heart rate were analyzed over two 10-s periods before and after the termination of the respiratory event. BP parameters were taken into account only during the respiratory phase of the breathing cycle. They corresponded to at least three data points for each 10-s period.

Sleep staging was performed according to standard criteria.[24] Only respiratory events from nonrapid eye movement (NREM) sleep periods were used. EEG changes during the 10 s before and after the end of respiratory events were looked for. Arousal scoring analysis was performed by one of us (F.G.), who was aware of the time at which respiratory events were terminated, but was not aware of the changes in respiratory effort and in BP at the time of the respiratory event. EEG changes were graded as follows: grade 2, shift in EEG frequency lasting ≥15 s and including alpha activity and/or frequencies ≥16 Hz, according to the standard criteria of awakening;[23] grade 1, shift in EEG frequency lasting from 3 to 15 s and including alpha activity and/or frequencies ≥16 Hz, except spindles, according to standard criteria of arousal;[19] grade 0, no EEG changes or minor EEG changes, usually not classified as arousals in the American Sleep Disorders Association (ASDA) criteria.[19] Grade 0 EEG changes were further classified as follows: grade 0a, shift in EEG frequency lasting <3 s and including alpha activity and/or frequencies ≥16 Hz, except spindles; grade 0b, low-frequency EEG changes (K-complexes and/or delta wave burst) without any increase in EEG frequency except spindles; grade 0c, no increase in cortical high frequency and no occurrence of K-complexes or delta wave bursts.

Statistical Analysis

For each patient and each type of EEG change, the changes in respiratory pressure and in esophageal pressure at the end of the nonapneic-nonhypopneic respiratory events were averaged and Friedman’s two-way analysis of variance was performed. Where appropriate (p value <0.05), pairwise comparisons were performed using a Wilcoxon matched-paired test. The level of significance was set at 5%.

RESULTS

Epworth sleepiness scale[18] and main sleep and respiratory parameters during the polysomnography with arterial BP measurement are presented in Table 1. A mean (±SD) of 167 (±145) nonapneic-nonhypopneic respiratory events were observed per patient during NREM sleep. Distribution of EEG patterns during these nonapneic-nonhypopneic respiratory events is presented in Table 2.

Systolic and diastolic BPs and heart rate rose after the end of the respiratory events, reaching a peak within 10 s after event termination (Fig 1).

BP and heart rate changes in response to different grades of EEG modifications are shown in panels A (top) and B (center) of Figure 2, respectively. The following were observed during grade 0, 1, and 2 EEG patterns (mean±SD): systolic pressure increased by 7.1±1.5, 11.7±1.9, and 14.2±3.4 (p<0.005) respectively; diastolic pressure increased by 4.6±0.6, 6.7±1.7, and 9.4±3.0 (p<0.005), respectively; heart rate increased by 2.9±0.4, 3.9±2.2, and 8.6±4.6 (p<0.005), respectively.

No differences were observed across the three grade 0 subclasses (0a, 0b, and 0c). Systolic and diastolic BP increases were significantly higher for grade 2 and grade 1 than for grade 0. The heart rate increase was significantly higher for grade 2 than for grade 0.
Esophageal pressure swing decreases in response to different grades of arousals are shown in panel C (bottom) of Figure 2. No differences in esophageal pressure swing changes were observed across grades. The mean fall in arterial oxygen saturation was <0.3% for each grade of arousal, with no significant differences across grades.

**Discussion**

Patients with upper airway obstruction without obstructive sleep apnea/hypopnea exhibit increased respiratory efforts during NREM sleep, often with EEG pattern changes. We found that termination of these nonapneic-nonhypopneic obstructive events was consistently followed by a rise in BP, and that the magnitude of this rise increased with the intensity of EEG arousal, although significant but smaller rises were detectable in the absence of apparent EEG arousal.

In this study, as previously proposed, BP was analyzed by infrared plethysmography. Because this noninvasive indirect method may overestimate BP, we measured only arterial BP changes. However, increased arteriolar constriction at the periphery could increase systolic BP measured at the finger by a phenomenon of reflectance of the pressure wave at the resistance vessels causing amplification and rise in systolic BP. However, diastolic BP is virtually unaffected by this phenomenon. We found that magnitude of diastolic pressure increases also varied with the grade of arousal. This indicates that the BP rises that we observed cannot be due solely to this artifact of pulse wave amplification.

Although we analyzed both rapid eye movement (REM) and NREM data, the amount of data was too small to allow comparisons of the different grades of arousal during REM sleep. Only two patients experienced nonapneic-nonhypopneic obstructive events both with and without awakening/arousal during REM sleep. This is due in part to the fact that apneas/hypopneas were predominant in REM sleep, whereas nonapneic-nonhypopneic obstructive events were observed less frequently.

The age range in our six patients was quite large, but only one patient was >50 years (patient E, 65 years). Interestingly, he was the patient who had the lowest arterial BP response to the different levels of arousal. During grade 2, 1, and 0 EEG patterns, systolic pressure increased by only 10, 9, and 4 mm Hg, respectively. This result corroborates the study of Hajduczok et al that demonstrated that sympathetic activity is impaired with senescence.

The cardiovascular consequences of OSAS include a rise in systemic BP after each episode of apnea. These postapneic BP elevations contribute signifi-

**Table 1—Epworth Sleepiness Score and Sleep and Respiratory Data During Polysomnography With Arterial BP Measurements**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Epworth Sleepiness Scale</th>
<th>TST, min</th>
<th>WASO, min</th>
<th>Stages 1+2, % TST</th>
<th>Stages 3+4, % TST</th>
<th>REM, % TST</th>
<th>AHI, Events per Hour of Sleep</th>
<th>Nonapneic-Nonhypopneic Respiratory Events per Hour of Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>20</td>
<td>426</td>
<td>80</td>
<td>93</td>
<td>0</td>
<td>7</td>
<td>4</td>
<td>59</td>
</tr>
<tr>
<td>B</td>
<td>21</td>
<td>398</td>
<td>112</td>
<td>72</td>
<td>17</td>
<td>11</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>C</td>
<td>11</td>
<td>279</td>
<td>146</td>
<td>54</td>
<td>16</td>
<td>0</td>
<td>3</td>
<td>54</td>
</tr>
<tr>
<td>D</td>
<td>12</td>
<td>362</td>
<td>163</td>
<td>77</td>
<td>13</td>
<td>10</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>E</td>
<td>11</td>
<td>360</td>
<td>160</td>
<td>65</td>
<td>25</td>
<td>10</td>
<td>1</td>
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<td>152</td>
<td>102</td>
<td>58</td>
<td>19</td>
<td>17</td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

*TST=total sleep time; WASO=wake after sleep onset; AHI=apnoea-hypopnoea index; UAR=upper airway resistance.

**Table 2—EEG Patterns at the End of Nonapneic-Nonhypopneic Respiratory Events During NREM Sleep**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Nonapneic-Nonhypopneic Respiratory Events</th>
<th>Grade 2, %</th>
<th>Grade 1, %</th>
<th>Total Grade 0</th>
<th>Grade 0a</th>
<th>Grade 0b</th>
<th>Grade 0c</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>421</td>
<td>16</td>
<td>66</td>
<td>18</td>
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<td>3</td>
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<td>12</td>
<td>48</td>
<td>40</td>
<td>2</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>C</td>
<td>250</td>
<td>8</td>
<td>81</td>
<td>11</td>
<td>1</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>D</td>
<td>59</td>
<td>12</td>
<td>27</td>
<td>61</td>
<td>9</td>
<td>49</td>
<td>13</td>
</tr>
<tr>
<td>E</td>
<td>73</td>
<td>26</td>
<td>53</td>
<td>21</td>
<td>3</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>F</td>
<td>59</td>
<td>2</td>
<td>72</td>
<td>26</td>
<td>2</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Mean</td>
<td>167</td>
<td>13</td>
<td>57</td>
<td>30</td>
<td>3</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>SD</td>
<td>145</td>
<td>8</td>
<td>23</td>
<td>18</td>
<td>3</td>
<td>15</td>
<td>6</td>
</tr>
</tbody>
</table>
Figure 1. Continuous polysomnographic recordings obtained in a patient, showing BP changes in response to various grades of EEG arousals due to nonapneic-nonhypopneic respiratory events. The EEG, electro-oculogram (EOG), chin electromyogram (EMG), air flow (Flow) pneumotachograph recording, esophageal pressure (Peso) recording, and arterial BP recordings are shown.

Slightly to the nocturnal hypertension and perhaps also to the diurnal hypertension seen in patients with obstructive sleep apnea. A recent study demonstrated that acute increases in systemic arterial BP also occur after each respiratory event in the patients with upper airway obstruction without obstructive sleep apnea/hypopnea. We found that the magnitude of these BP increases is related to the intensity of EEG arousal.

Both arterial hypoxemia and arousal from sleep have been suggested as the main causes of the nocturnal hemodynamic oscillations seen in patients with OSAS, although Rees et al found no relationship between the rise in BP and the occurrence of EEG change. To evaluate the respective contributions of hypoxia and arousal, investigators have used a variety of approaches to isolate these two factors from each other. To maintain arterial oxygen saturation >90% at the end of apneas, Ringler et al and Ali et al provided supplementary oxygen to OSAS patients undergoing polysomnography. They found that oxygen supplementation did not alter the
induce arousal, auditory stimulation in normal subjects. In their study, the magnitude of the BP increase was proportional to the degree of arousal, as defined by the duration of the increase in high-frequency EEG activity. In our study, in patients with upper airway obstruction without obstructive sleep apnea/hypopnea, we also found that the magnitude of the BP rise was closely related to the degree of arousal. These data corroborate the findings from the studies on OSAS, providing additional evidence that arousals related to obstructive respiratory events may be accompanied by significant BP rises even in the absence of oxygen desaturation.

Other factors than arousal or hypoxia have been suggested as possibly being responsible for the BP elevation in OSAS. These factors include reinflation of the lung, which may change cardiovascular performance via a number of mechanisms, and termination of deep negative pleural pressure dips generated by frustrated inspiratory efforts during obstructive apnea. These factors may also be involved in patients with upper airway obstruction without obstructive sleep apnea/hypopnea, either in combination with arousals or alone, since we observed some increase in BP in the absence of arousals (EEG pattern scored as grade 0). In a discussion of the lung volume changes in patients with upper airway obstruction without obstructive sleep apnea/hypopnea, Stoohs and Guilleminault pointed out that the mean decrease in tidal volume during nonapneic-nanhypopneic respiratory events was only 100 mL. It can be postulated that such a small increase in end-inspiratory thoracic volume at the end of a respiratory event will result in insignificant inflation-associated cardiovascular responses. A second factor may be intrathoracic pressure changes, which are known to influence BP. BP decreases from expiration to inspiration, and when pleural pressure becomes more negative during inspiration, such as in patients with asthma, inspiratory arterial pressure decreases further. Because part of the increase in BP occurring at the end of respiratory events may be ascribable to a reduction in the inspiratory decline of arterial BP, we decided to avoid this possible mechanical effect by measuring arterial BP during expiration. However, because mean intrathoracic pressure is more negative during an obstructive respiratory event, left ventricular ejection may decrease following increases in left ventricular afterload and in venous return, which increase end-diastolic volume of this cardiac chamber; this increase of end-diastolic volume of right ventricle can also decrease the left ventricular diastolic compliance and therefore the left ventricular preload through the mechanisms of the ventricular interde-

Fig. 2. Systolic pressure (squares) and diastolic pressure (diamonds) changes (top, A), heart rate changes (center, B), and esophageal pressure swing decrease (bottom, C) in response to various grades of arousal at the end of nonapneic respiratory events. The left-sided panels show the values observed during grade 2, 1, and 0 arousals. In the right-sided panels, grade 0 arousals are divided into three subgroups (see “Materials and Methods” for definition). No differences were observed across grade 0 subtypes. Systolic and diastolic BP increases were significantly higher for grade 2 and grade 1 than for grade 0. Heart rate increases were significantly higher for grade 2 than for grade 0. No differences in esophageal pressure swing changes were observed across grades. Values are means ± SEM.
pendsence.\textsuperscript{27} Thus, a return to normal intrathoracic pressure after the end of the obstructive respiratory event may increase BP by raising left ventricular ejection. Such a phenomenon may explain the increase in BP that occurred in our study after the end of nonapneic-nonyhypopneic respiratory events, even in the absence of visible EEG changes. However, the putative role of a decrease in intrathoracic pressure in decreasing left ventricular ejection under conditions appropriate to sleep apnea syndrome has not yet been confirmed by experimental studies.\textsuperscript{27} In addition, in our study, although esophageal pressure did become more negative during these respiratory events, the mean esophageal pressure swing increase was \(<10 \text{ cm H}_2\text{O}\), a value much lower than in the sleep apnea syndrome.

Since none of these previous hypotheses is satisfactory, we suggest that an increase in BP (during grade 0c arousals) may occur as a result of brainstem activation caused by the respiratory event and sufficiently marked to produce an autonomic response but not cortical arousal. This hypothesis has been suggested previously by Davies et al,\textsuperscript{13} who observed that auditory stimuli could also induce BP increases (with magnitudes similar to those in our study during grade 0 arousals) without causing EEG arousal.

A recent study investigated a subpopulation of patients with upper airway obstruction without obstructive sleep apnea/hypopnea and without detectable EEG arousals.\textsuperscript{20} In our study, one third of nonapneic-nonyhypopneic respiratory events were not associated with arousals according to ASDA criteria (grades 0), but were associated with abrupt BP increases. Among these respiratory events without arousal, many (80\%) were associated with EEG changes, which were usually of low frequency (grade 0b: K-complexes and/or delta wave bursts). Since it has been demonstrated that a minimal EEG event, such as a K complex, may induce an increase of the sympathetic discharge,\textsuperscript{28} we checked whether these events with minimal EEG changes (grades 0a and 0b) were associated with larger arterial BP elevations than events with no EEG changes (grade 0c). We found no differences, suggesting that use of arousability criteria that are more sensitive than ASDA criteria does not provide any additional clinical information on the cardiovascular consequences of upper airway obstruction without obstructive sleep apnea/hypopnea.

In conclusion, we found that, similar to OSAS patients, snorers with upper airway obstruction without obstructive sleep apnea/hypopnea exhibited abrupt transient systemic BP elevations at termination of respiratory events. In addition, the magnitude of the transient BP increases during NREM sleep varied with the grade of the arousal associated with the nonapneic-nonyhypopneic respiratory event. However, BP increases were also seen in the absence of detectable EEG arousal. Because the other factors generally believed to produce postapneic BP elevation in OSAS are absent or insignificant in patients with upper airway obstruction without obstructive sleep apnea/hypopnea, we believe that arousal is the main cause of the systemic BP increases seen after termination of nonapneic-nonyhypopneic obstructive events. In addition, given that BP increases also occurred without apparent EEG arousal, beat-to-beat BP evaluation may be a more sensitive means of identifying nonapneic-nonyhypopneic respiratory events than conventional evaluation of EEG changes.
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