Reduced respiratory-related evoked activity in subjects with obstructive sleep apnea syndrome

METIN AKAY,1 J. C. LEITER,2,3 AND J. ANDREW DAUBENSPECK1,2
1Thayer School of Engineering, Dartmouth College, and the Departments of 2Physiology and 3Medicine, Dartmouth Medical School, Hanover, New Hampshire 03756

Submitted 9 January 2001; accepted in final form 6 September 2002

Akay, Metin, J. C. Leiter, and J. Andrew Daubenspeck. Reduced respiratory-related evoked activity in subjects with obstructive sleep apnea syndrome. J Appl Physiol 94: 429–438, 2003; 10.1152/japplphysiol.00018.2001.—Midlatency respiratory-related evoked potentials were measured during wakefulness by using a 60-electrode array placed over the cortical region of the scalp. We studied the responses evoked by 200-ms pressure pulses at −5 and −10 cmH2O applied at inspiratory onset and during control tests (no pressure applied) in 14 subjects with obstructive sleep apnea syndrome (OSAS) and 18 normal subjects. Wavelet decomposition was used to smooth and dissect the respiratory-related evoked potentials in frequency and time in 8 frequency bands. After denoising, selected wavelet scales were used to reconstruct the respiratory-related evoked potentials, which were quantified by using global field power estimates. The time course of the global field power activity in OSAS subjects compared with normal subjects was significantly depressed in the period 55–70 ms poststimulus onset, a time when afferent traffic from upper airway receptors arrives in normal subjects. The reduced evoked response in subjects with OSAS suggests that these subjects receive less afferent input from upper airway mechanoreceptors. This may reflect reduced sensitivity of mechanoreceptors or reduced mechanoreceptor stimulation due to decreased upper airway compliance during wakefulness in OSAS.

respiratory mechanoreceptors; mechanoreceptor afferent activity; event-related potentials; sleep disordered breathing; global field power; time-frequency analysis; wavelet analysis

RESPIRATORY-RELATED CORTICAL ACTIVITY may be evoked by airflow occlusion (13, 16, 37) or in response to small, brief negative pressure pulses (9, 27, 40). The evoked activity may be quantified by using individual electrode pairs and a common reference (13, 16, 27, 37, 40), or activity from multiple electrodes may be analyzed by using the global field power (GFP) (2, 3, 9–11). The midlatency components (20–100 ms poststimulus) of respiratory-related evoked activity, as estimated by the GFP, reflect respiratory mechanoreceptor afferent activity (9). GFP is analogous to a spatial standard deviation computed from multiple electrodes arrayed on the scalp bilaterally over the cortex, and temporal variation of the GFP is correlated with activation of the somatosensory cortex. In contrast, the analysis of activity from individual paired electrodes has some disadvantages (9, 16). Airway occlusion and applied pressure pulses not only activate the somatosensory cortex but also stimulate facial and upper airway muscle activity that contaminates electroencephalogram (EEG) signals derived from somatosensory activation. As a result, evoked activity analyzed from electrode pairs and a reference electrode includes both EEG and electromyogram (EMG) activation (9, 16). GFP is, however, reference independent and partially insulated from electrical contamination due to concurrent activation of facial and upper airway muscles excited by pressure pulse stimuli (9). Evoked responses estimated by GFP closely reflect the activation of mechanoreceptors throughout the respiratory system and provide an index of mechanoreceptor afferent activity available to central respiratory control mechanisms.

The midlatency components of GFP activity between 50 and 80 ms poststimulus are dominated by information from receptors in the upper airway above the larynx in normal subjects (2, 10). The magnitude of this midlatency GFP activity varies directly with the amplitude of the applied pressure pulse, and its spectral power is concentrated in the frequency range between 15 and 250 Hz (3). Midlatency activity is exogenous in that it does not reflect endogenous cognitive processing of the stimulus. However, attention to the stimulus reduces the latency of one component of respiratory-related evoked responses within 100 ms of stimulus onset (44), and sleep has been shown to affect some components of somatosensory-evoked potentials with latencies of <100 ms elicited by peripheral nerve electrical stimulation (1, 35, 48) or inspiratory occlusion (43). These results indicate that state-related modulation of midlatent, exogenous activity can occur, but if the state of consciousness and the level of attention are similar between conditions, respiratory-related evoked potential (RREP) responses with latencies of <100 ms can be used effectively to evaluate the magnitude of exogenous activation of the somatosensory cortex.

Patients with obstructive sleep apnea syndrome (OSAS) have reduced temperature sensation in their
upper airways (24), reduced oropharyngeal mechanosensation (23), and decreased conduction velocity in nonrespiratory peripheral sensory nerves during anoxia (29). There is substantial evidence that, during sleep, respiratory mechanoreceptors play an important role in maintaining airway patency (31), and stimulation of mechanoreceptors contributes to arousal after airway obstruction (4, 22). Deficits in afferent activity before or concurrent with airway obstruction during sleep could promote apnea in OSAS patients by reducing or delaying reflex mechanisms that promote airway patency and stabilize the upper airway in normal subjects.

The goal of the research reported here was to evaluate respiratory-related evoked activity in response to small, brief oral pressure pulses during wakefulness in OSAS subjects to determine whether GFP differed compared with responses from a normal group of subjects. If a deficit in mechanoreceptor activation could be identified, it would support the hypothesis that OSAS is characterized by abnormal afferent information from respiratory mechanoreceptors.

METHODS

Subjects. We studied 18 normal subjects ranging in age from 18 to 72 yr, who were recruited from within the medical center. None of the normal subjects had any history of daytime somnolence, loud snoring, or observed apnea, and none reported having any respiratory illnesses. We recruited 15 subjects with OSAS, aged 32–82 yr, from the Dartmouth Hitchcock Sleep Clinic. All of the patients had complete diagnostic polysomnography at Dartmouth-Hitchcock Medical Center (DHMC), and all but one had been treated with nasal continuous positive airway pressure (nCPAP) at an effective pressure for varying lengths of time. None of the patients or subjects had any active intercurrent illness at the time they participated in this study. Neither normal nor OSAS subjects had any knowledge of respiratory physiology. OSAS subjects were usually studied the morning after a night of sleep in the DHMC sleep clinic, which was part of the evaluation of their therapy. Subjects in the control group were given no explicit instructions in respect to their sleep routine before the study, and they were studied at the same time of day as the OSAS subjects. The study was approved by our Institutional Review Board, and all of the subjects gave written, informed consent to participate in the study.

Experimental procedures. RREPs were recorded from 60 scalp electrodes fixed on an appliance (Electro-Cap, Eaton, OH) overlying the cortex bilaterally. Cortical somatosensory responses were elicited by applying 200-ms duration pressure pulses of –5 or –10 cm H2O at the mouth at the onset of inspiration. Control responses were measured in each subject in identical experimental protocols except that the vacuum source was turned off. The procedures and experimental details have been described previously (9, 10).

Subjects sat on a dental chair within a Faraday cage with head and neck comfortably supported. Each subject breathed on a custom-made mouthpiece attached to the apparatus used to apply the pressure stimuli. During data collection, each subject kept his/her eyes open in a fixed position and watched movies to maintain wakefulness. EEG data were obtained by using closely matched, low-noise isolated amplifiers with a gain of 40,000 and bandpass filtering (10–500 Hz, 8-pole, linear phase filters; EPA-6, Sensorium, Charlotte, VT). Each subject wore a 60-electrode array designed to extend bilaterally over the cortex between approximately the F (anterior) and P (posterior) bands, as defined in the international 10–20 electrode nomenclature. The interelectrode spacing was ~3 cm. A spatial tracking system (FastTrak, Polhemus, Colchester, VT) was used to orient the electrode array so that the rectangular grid was aligned to the inion and right ear-to-left ear directions and to determine the relative spatial positions of the electrodes. Electrode impedance of each of the 60 electrodes was maintained at or below 8 kΩ. Mouth pressure was measured by using a pressure transducer (Validyne MP45, Northridge, CA). The 60-channel EEG and pressure pulse data were sampled at 2 kHz/channel for 35 ms before the pressure pulse (the time required to activate the balloon valves) plus 200 ms during each pressure pulse trial.

Rapidly acting, computer controlled balloon valves (Hans Rudolph, Kansas City, KS) were used to connect the subject’s airway to room air or to a vacuum source, a small vacuum cleaner controlled by a rheostat. The duration of each pressure pulse and any delay from the onset of inspiration were controlled by a Macintosh-based virtual instrument created with LabVIEW (National Instruments, Austin, TX). The stimulus was usually presented on every other breath at the start of inspiration once the mouth pressure dropped below a preset threshold (~0.2 cm H2O subatmospheric). Each trial was displayed for review and, if free from artifact (eye movement, airway collapse, excessive EMG contamination, etc.), it was saved to disk, provided that other aspects of the trial were acceptable. Both the EEG and mouth pressure data were also monitored continuously with a separate computer. Mouth pressure and EEG data were screened online for obvious artifacts, and acceptable trials were saved for offline analysis. Based on our previous results (2, 3) and more recent experience, acquisition of 30–100 trial sequences was sufficient to obtain reliable cortical evoked responses.

Analytical methods. We ensemble averaged RREPs from each trial and condition for each of the subjects, and these signals were subjected to wavelet filtering. The wavelet transform is a recent development in signal processing that enables one to determine the frequency content of a signal even as the frequency content varies with time. We used wavelet decomposition to determine the frequency content of each ensemble-averaged evoked response according to a dyadic sequence based on the Nyquist frequency (half the sampling frequency of 2 kHz) and obtained signal components at eight wavelet scales (frequency bands): 1 (500–1,000 Hz), 2 (250–500 Hz), 3 (125–250 Hz), 4 (62.5–125 Hz), 5 (31.25–62.5 Hz), 6 (15.6–31.25 Hz), 7 (7.81–15.62 Hz), 8 (3.9–7.81 Hz). Filtering is implemented by omitting information from scales previously determined to contribute little to the evoked response waveshape (scales 1–2 and 7–8) and then reconstructing the filtered signal. We have described this process elsewhere (2, 3) and refer the reader there for further details. After filtering, the signals were subject to GFP analysis.

GFP. GFP is analogous to a spatial standard deviation and has been used to assess the degree of spatial variation of the evoked potential field due to local currents by taking the square root of the sum of the squares of all possible potential differences in the field at each moment in time and normalizing for the number of differences computed (25), as shown in Eq. 1 for scalp potentials (u) measured at n (= 60 here) electrodes at time t_k.

J Appl Physiol • VOL 94 • FEBRUARY 2003 • www.jap.org
If all the potentials were homogeneous over the spatial domain at any time, GFP would be small. Local potentials attributable to radial currents at a particular time result in a larger GFP. GFP is a reference-independent measure of respiratory-related evoked activity and has the further advantage of reducing the contamination of facial EMG responses evoked by the pressure stimulus (9). GFP was calculated from the set of 60 reconstructed RREP signals at each 0.5-ms interval for the period 20 ms before stimulus onset to 100 ms poststimulus (2, 3, 9, 10). GFP has some finite value even in the control condition, and to account for this control background activity, we normalized GFP during the test conditions by calculating the ratio of the GFP responses at each stimulus level (−5 or −10 cmH2O) to the GFP in the control condition, and the normalized GFP is referred to hereafter as nGFP.

Statistical analysis. We analyzed the nGFP responses by using a three-way ANOVA in which disease state (normal vs. OSAS) and gender (male vs. female) were between-subjects factors and pressure was a repeated, within-subject factor with two levels (−5 and −10 cmH2O). We tested the hypotheses that nGFP responses varied linearly with subject age or weight by adding these variables to the ANOVA as covariates. In addition, we analyzed the effects of age and weight within each population separately by using a general linear model. Data are reported as means ± SE unless otherwise stated.

RESULTS

One OSAS subject was unable to withstand the higher pressure pulse, and we did not include this subject in the final analyses. This reduced the number of OSAS subjects to 14. The characteristics of the remaining subjects are shown in Table 1. The control group is younger than the OSAS group: 44.6 ± 3.6 yr for normal and 57.4 ± 3.4 yr for OSAS subjects; P < 0.02 (t-test). OSAS is a disease highly correlated with obesity and age, and it is difficult to find older, overweight subjects who do not have OSAS. Therefore, our subject groups are not closely matched for weight as estimated by body mass index (BMI): 27.9 ± 6 kg/m2 for normal and 34.7 ± 8 kg/m2 for OSAS subjects; P < 0.01 (t-test).

The average apnea-hypopnea index in the OSAS group before nCPAP treatment was 57.5 ± 11.2 and after treatment was 9.7 ± 2.1, indicating that OSAS patients had mild to moderate OSAS. The Epworth score was elevated (normal < 10) and indicates that patients with OSAS had significant excessive daytime sleepiness at the time of diagnosis. We did not re-administer the Epworth sleepiness test at the time of study, which occurred days to months after the initial sleep evaluation in these patients. We do not have similar Epworth data in the control group, but control subjects were questioned about sleepiness, snoring, and sleep habits, and they described no symptoms of excessive daytime sleepiness.

Figure 1 shows the RREPs reconstructed from wavelet scales 3–6 (15.6–250 Hz) for each of the 60 individual channels in the EEG montage along with the EEG montage and the ensemble-averaged mouth pressure pulse (−10 cmH2O) for a normal subject (Fig. 1). To demonstrate the quality of the reconstruction, Fig. 2 shows reconstructed RREPs for a single representative channel of the 60-channel montage used to produce the responses in Fig. 1. The raw EEG signal and the

Table 1. Subject population characteristics

<table>
<thead>
<tr>
<th>Normal Subjects</th>
<th>OSAS Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>BMI</td>
</tr>
<tr>
<td>-------</td>
<td>----</td>
</tr>
<tr>
<td>23</td>
<td>22.31</td>
</tr>
<tr>
<td>58</td>
<td>25.90</td>
</tr>
<tr>
<td>44</td>
<td>25.88</td>
</tr>
<tr>
<td>57</td>
<td>32.27</td>
</tr>
<tr>
<td>55</td>
<td>27.34</td>
</tr>
<tr>
<td>18</td>
<td>30.86</td>
</tr>
<tr>
<td>57</td>
<td>31.83</td>
</tr>
<tr>
<td>59</td>
<td>34.05</td>
</tr>
<tr>
<td>34</td>
<td>27.94</td>
</tr>
<tr>
<td>72</td>
<td>29.22</td>
</tr>
<tr>
<td>27</td>
<td>26.58</td>
</tr>
<tr>
<td>46</td>
<td>33.93</td>
</tr>
<tr>
<td>29</td>
<td>22.40</td>
</tr>
<tr>
<td>37</td>
<td>25.04</td>
</tr>
<tr>
<td>64</td>
<td>33.71</td>
</tr>
<tr>
<td>47</td>
<td>25.11</td>
</tr>
<tr>
<td>32</td>
<td>24.55</td>
</tr>
<tr>
<td>43</td>
<td>22.81</td>
</tr>
</tbody>
</table>

Mean ± SE 44.6 ± 3.6 27.9 ± 1.0 9M/9F 57.4 ± 3.4 34.6 ± 2.1 10M/4F 57.5 ± 11.2 14.0 ± 1.2 90.3 ± 1.0 78.0 ± 2.2

OSAS, obstructive sleep apnea syndrome; M, male; F, female; BMI, body mass index; AHI, apnea-hypopnea index scored by using standard techniques during the OSAS subject’s evaluation sleep night; Epworth, Epworth sleepiness score evaluated by the sleep clinic using a standard questionnaire at the first visit of the patient to the sleep clinic; minSaO2, minimum arterial O2 saturation observed during the sleep night; t, continuous positive airway pressure titration study; sn, split-night in which continuous positive airway pressure titration was performed during the second half of the night.
reconstructed composite single-channel responses to control, and −5 and −10 cmH₂O stimuli in a typical normal subject are shown. The fidelity of the filtering obtained by wavelet processing is apparent, but note that the raw signal has more high-frequency noise, as mentioned above.

RREP activity was present between 25 and 100 ms poststimulus in some electrodes in all subjects, although this was more apparent in normal subjects compared with OSAS subjects. GFP activity, reflecting inhomogeneity caused by distortion of the scalp potential field by evoked activity, is apparent as early as 30 ms poststimulus at the higher stimulus level, and this is true for GFP signals from the wavelet-filtered RREPs for both normal and OSAS subjects. Figure 3 shows GFP responses for the normal subject whose filtered RREPs are shown in Fig. 1, and Fig. 4 shows GFPs computed for an OSAS subject during the same treatment condition. In both subjects, GFP responses varied directly with the amplitude of the stimulus. These two subjects represent nearly the extremes of the responses, but there was a striking and consistent reduction in amplitude of GFP activity in the OSAS population compared with normal subjects.

GFP temporal responses for each subject at each stimulus level were normalized to account for the large variation in control activity by dividing each subject’s responses to the −5 and −10 cmH₂O stimuli by that subject’s control GFP (no stimulus applied) at each point in time. Responses of the individual nGFP time courses were averaged, and 90% confidence intervals were computed for responses from the 18 normal and 14 OSAS subjects. Figure 5 shows the likely response regions for normal and OSAS subjects for the −5 cmH₂O stimulus, and Fig. 6 shows the expected response regions for the −10 cmH₂O stimulus. It is apparent in both Figs. 5 and 6 that the normalized OSAS responses are reduced compared with the normal population in the span between −55 and 70 ms where the 90% confidence regions do not overlap.

In a previous study (10), our laboratory tested normal subjects with and without stimulation of supralaryngeal mechanoreceptors by using a laryngeal mask airway to restrict stimulation to the lower airways and found that absence of upper airway mechanoreceptor information produced a similar deficit in the GFP responses to oral pressure pulses in the time window of 55–70 ms poststimulus. To test the hypothesis that upper airway mechanoreceptor information reflected in the GFP differed in normal subjects and OSAS subjects, we plotted each subject’s nGFP trace for the period 55–70 ms poststimulus. The results are shown for the −10 cmH₂O stimulus in Fig. 7. OSAS responses are plotted in heavy lines to make it easier to see that individual OSAS responses crowded toward the low end of the scale. Similar, although less dramatic differences were seen at the lower stimulus level.

To evaluate the effects of gender, age, and weight on the apparent differences seen in Fig. 7, we used the sum of the GFP activity between 55 and 70 ms poststimulus (ΣnGFP₅₅₋₇₀) to produce a single number representative for each subject of the effect of pressure pulse amplitude on the evoked response. The resulting measures of evoked activity were analyzed further by using ANOVA.

We performed a repeated-measures (RM) ANOVA to analyze the reconstructed ΣnGFP₅₅₋₇₀ responses to determine whether the effects of disease state on respiratory-related evoked activity were modulated by the gender, age, and weight (BMI) characteristics of the subject populations. We included BMI and age as co-variates, and in this way we accounted partially for our
inability to construct a matched control group adequate to account for these factors. Between-subject results of the RM-ANOVA on the reconstructed $\Sigma nGFP_{55-70}$ responses indicated a significant influence of disease on GFP ($P < 0.044$) but no significant main effects of gender, weight, or age. In addition, we regressed the $\Sigma nGFP_{55-70}$ responses against age and weight within each subject classification and found no significant effect of either variable on the responses. We therefore dropped gender as a factor and age and weight as covariates and repeated the RM-ANOVA. We found a significant between-subject effect of disease ($P < 0.005$) plus a within-subject significant effect of pressure pulse amplitude ($P < 0.002$), and no significant amplitude-disease interaction ($P < 0.19$). In view of these ANOVA results, we conclude that there is an effect of disease to reduce the $\Sigma nGFP_{55-70}$ by a similar amount at each level of the pressure pulse stimulus, and as the magnitude of the pressure pulse increases, the size of the GFP increases. However, there is no significant effect of gender, age, or weight on this result. The effect of disease on the mean $\Sigma nGFP_{55-70}$ responses within each group is shown in Fig. 8. Although the slopes of the responses between the two levels suggest that OSAS patients do not respond to

Fig. 2. Ensemble averages of raw and reconstructed (temporally denoised/enhanced by wavelet techniques) RREPs taken from a single channel and recorded from the same normal subject shown in Fig. 1 under control conditions with no pressure pulse (A) and in response to the $-5$ (B) and $-10$ cmH$_2$O (C) pressure pulses applied at inspiratory onset. EEG, electroencephalogram; P, pressure.

Fig. 3. Global field power (GFP; in $\mu$V) estimates from the reconstructed, wavelet-filtered RREPs for control (broken line) and at $-5$ (thin line) and $-10$ cmH$_2$O (thick line) pressure pulse stimuli for the same normal subject shown in Fig. 1.

Fig. 4. GFP estimates from the reconstructed, wavelet-filtered RREPs for control (broken line) and at $-5$ (thin line) and $-10$ cmH$_2$O (thick line) pressure pulse stimuli for an obstructive sleep apnea syndrome (OSAS) subject.
changes in stimulus amplitude as sensitively as normal patients, the lack of a significant amplitude-disease interaction noted above indicates that this response characteristic is not significant in our sample population. The effect of disease, however, is significant, as indicated above and shown in Fig. 8.

Within the OSAS group, we also examined the effect of weight, disease severity as reflected by the apnea-hypopnea index, and sleepiness as reflected by the Epworth score at the time of diagnosis. We regressed weight (BMI), apnea-hypopnea index, and the Epworth sleepiness scale against $\Sigma nGFP_{55-70}$ responses at the two level of stimulus. When all factors were considered together, none served to explain a significant component of the variation of OSAS responses. When separate regressions were performed with each independent variable, only the Epworth sleepiness scale at the higher level of stimulation emerged as a significant factor ($P < 0.022$) with a negative slope (i.e., as the subject was sleepier, the $\Sigma nGFP_{55-70}$ response tended to be smaller). It should be noted that the Epworth questionnaire was administered at the time of clinical evaluation, which was before the time we tested the subjects by many days to weeks.

**DISCUSSION**

We used specific frequency bands to filter the cortical activity evoked by brief, oral pressure pulses, and we
calculated the GFP over the somatosensory cortex. GFP permits reliable quantitative characterization of respiratory-related evoked activity, and we analyzed GFP responses to brief pressure pulses at −5 and −10 cmH2O in 18 normal and 14 OSAS subjects. We compared the normalized responses 55–70 ms poststimulus in these groups. The most important finding is that the apparent activation of the somatosensory cortex in the time period of 55–70 ms after application of a standard respiratory stimulus is significantly less in patients diagnosed with OSAS than in the group of normal subjects. Reduced somatosensory activity at this time is significant since, as we have previously shown, supralaryngeal mechanoreafferent information appears in the GFP response to pressure pulses at this time in normal subjects (10). Hence, OSAS patients appear to receive deficient mechanoreafferent information from receptors located in the airway above the larynx. Although we were not able to match closely the ages and weights of the subjects in the two study groups, we found no statistical evidence to attribute the sensory insensitivity of patients with OSAS to weight, age, or gender.

**Influence of sleep.** The possible roles of sleepiness and sleep deprivation in the responses we observed are difficult to resolve. All but one of the OSAS patients had received nCPAP treatment for weeks to months before being tested and were sleeping satisfactorily as best we can tell. However, even while using nCPAP, many OSAS patients had significant sleep fragmentation and low sleep efficiency when studied in the sleep lab (Table 1). Moreover, compliance with nCPAP therapy is often poor, and patients with OSAS may have been sleep deprived compared with the normal subjects. We saw an overt tendency toward sleepiness in one of the OSAS subjects at the time we performed our testing. Normal subjects had no evidence of excessive sleepiness when we studied them. Thus it is our working assumption that OSAS subjects were significantly sleepier than normal subjects.

**Sleepiness effect.** In assessing the likely effect of sleepiness on our results, two possibilities merit consideration. First, to the extent that subjects fell asleep during the study, we might expect to see the effects of sleep on evoked somatosensory activity manifest during our study of waking subjects. Second, we might expect to see an effect of sleep deprivation independent of the effect of sleep itself on evoked activity. Wheatley and White (45) reported that the earliest component (P1) of the cortical evoked responses stimulated by inspiratory negative pressure pulses was delayed during sleep from a wakefulness latency of 72 ± 8 ms postocclusion to a non-rapid eye movement (NREM) sleep value of 116 ± 16 ms (45). Genioglossal reflex activation by similar stimuli was delayed from 53.8 ± 11.5 ms in wakefulness to 132.7 ± 24.5 ms during NREM sleep. Our laboratory and others (9, 16) demonstrated the possibility of artifact in the scalp-measured evoked responses connected to upper airway and facial muscle activation, and it is possible that the effect of sleep on RREPs partially reflects the effect of sleep on muscle reflexes and the associated artifact as opposed to direct effects on exogenous components of the evoked EEG response.

Webster and Colrain (43) reported effects of the state of consciousness from wakefulness through stage 2 sleep on RREPs evoked by inspiratory occlusions for components in the midlatency range and later. Components with wakeful latencies of ~25 and ~43 ms (their P1a and Nf components) were delayed by the transition from wakefulness to stage 1 sleep and were further delayed by entering stage 2 sleep (~3 ms for wakefulness-to-stage 1 transition and ~7 ms for wakefulness-to-stage 2 comparison). For the P1 component, with a wakeful latency of ~58 ms and thus in the range of interest here, there was no effect of the wakefulness-to-stage 1 transition on latency, although the stage 1-to-stage 2 transition prolonged that component by ~2–4 ms; there was no effect on the amplitude of the P1 component. An effect of sleepiness was exhibited in their N1 component (latency of ~110 ms), the amplitude of which was diminished from wakeful levels as sleep deepened with no effect on latency. In addition, Gora et al. (18) studied the effect on RREPs produced by midinspiratory occlusions at the transition from alpha to theta rhythm within stage 1 sleep and from wakefulness through stage 2 sleep. The shortest latency component that they observed, N1 with a wakeful latency as short as 98 ms postocclusion (location CPz referenced to linked ears), also showed a progressive decrease in amplitude as sleep deepened.

Although there are reports of the effect of sleep on short-latency (<20 ms), somatosensory-evoked responses to median nerve stimulation (1, 34), the effects were rather small (~5% increase in latency), and effects on components with longer latencies were not evaluated. In summary, none of the studies of the effect of sleep state on RREPs has shown an influence of sleep in the 55–70 ms time span that could explain the differences we found between normal and OSAS subjects, so the reduction in midlatency somatosensory cortical activation in our OSAS subjects does not resemble the effect of sleep per se on RREPs. Although we cannot rule out that some of the OSAS subjects may have been drowsy, it is unlikely that any actually entered stage 2 sleep, and, if they had, this would not be expected to have a profound effect on the summed GFP activity in the 55- to 70-ms span.

**Sleep deprivation effect.** There is little information in the literature relevant to the effect of sleep deprivation on midlatency (55–70 ms)-evoked activity. Rats showed no effect of sleep deprivation on the amplitudes or latencies of response components in the 14- to 22-ms range produced by electrical stimulation of the trigeminal nerve (15). Broughton (7) reported no significant difference in auditory evoked potential components with latencies near 50–55 ms from sleep-deprived and normal populations. A report of the effects of sleep deprivation on responses in the midlatency range evoked by visual stimuli indicated a reduction in latency of the P1 component from ~67 to ~63 ms but no effect on the amplitudes of P1 relative to neighboring
components outside the time frame of interest here (33). Thus there is no convincing evidence that sleep deprivation reduces the amplitude of evoked responses from any modality in the time 55–70 ms poststimulus.

*Mechanism of the decreased afferent signal.* The reduction in the \(\Sigma n\text{GFP}_{55–70}\) in patients with OSAS compared with normal subjects implies that substantially less afferent information arrives at the somatosensory cortex in patients with OSAS in this period. We have shown previously that, on average, \(\sim 50\%\) of the GFP signal generated in the period 25–100 ms poststimulus is attributable to mechanoreceptors above the larynx in normal subjects and that the deficit is most apparent in the span 55–70 ms poststimulus (10). There are at least two explanations for reduced activation of upper airway mechanoreceptors: 1) the airway structure in which the receptors lie may be less compliant in OSAS subjects and/or 2) the receptors may show less sensitivity to distortion in OSAS.

**Difference in airway compliance.** OSAS is generally characterized by a more, not a less, compliant upper airway (39, 41). However, it is important to consider the phase of breathing when the pressure pulse is delivered. Schwab et al. (39) showed that, at the start of inspiration (the time we applied each pressure pulse stimulus), the upper airway tends to increase in area during wakefulness in patients diagnosed with OSAS despite the increasing tendency for airway negative pressure to narrow the lumen. This airway widening is associated with augmented genioglossal EMG activity in OSAS patients (32) and could reduce the compliance of the upper airway at inspiratory onset (IO). The effect of this stiffening of the upper airway would be to reduce the distensibility of the airway, thereby reducing the output of upper airway mechanoreceptors in response to a given pressure pulse.

The changes in airway distensibility outlined above predict effects on mechanoreceptor activation that match the observed changes in the \(\Sigma n\text{GFP}_{55–70}\) results for the OSAS subjects compared with the normal subjects shown in Figs. 5–8. To test the hypothesis that reduced upper airway compliance at IO caused the reduction of somatosensory cortical activation observed, we recalled two of the previously tested OSAS subjects and recruited a third patient with OSAS for further tests in which we applied pressure pulses either during late expiration (LE) or at IO, as previously described. If changes in upper airway compliance significantly modify the nGFP responses, then the \(\Sigma n\text{GFP}_{55–70}\) obtained at IO should be smaller in each subject than the \(\Sigma n\text{GFP}_{55–70}\) obtained during LE when genioglossal EMG activity is negligible. We performed these tests with procedures that were otherwise identical to those previously described.

Table 2 shows the normalized \(\Sigma n\text{GFP}_{55–70}\) responses in each of the four conditions for each of the three subjects. The numbers of subjects here are too small to permit statistical analysis, but the number of cases in which LE response was smaller than IO response is equal to the number of cases in the LE response exceeded IO response. Thus there is no compelling reason to conclude that stiffening of the upper airway at the start of inspiration is sufficient to reduce receptor distension and account for the observed reduction in somatosensory activation in OSAS subjects.

**Difference in mechanoreceptor sensitivity.** An alternative explanation for our finding of reduced somatosensory cortical activation lies in the possibility that respiratory mechanoreceptors in OSAS subjects are less sensitive to mechanical stimulation. Temperature sensation in the upper airway of OSAS subjects may be reduced, and this may result from repeated exposure of mucosal receptors to the mechanical trauma of snoring, thereby causing receptor damage (24). The recent report of Kimoff et al. (23) showing reduced perception of vibratory stimuli applied directly to upper airway structures in snorers and patients with OSAS further supports the hypothesis that OSAS subjects have reduced mechanosensory responses. Therefore, reduced mechanoreceptor sensitivity seems more likely than decreased airway compliance as an explanation for our findings.

**Consequences of reduced sensory afferent information.** Our results suggest that OSAS subjects receive less afferent information from upper airway mechanoreceptors during wakefulness than do normal subjects. Despite this, tonic genioglossal activation seems to be higher during wakefulness in patients with OSAS than in normal subjects (14). Upper airway muscle activity, which is normally phasic with inspiration during wakefulness, is attenuated during NREM sleep and the various components of rapid eye movement sleep in dogs and humans (17, 38, 47). Reduction in upper airway muscle activation is thought to be the basis for the increase in upper airway resistance during sleep in normal humans (46). Reflex activation of an important airway dilator, the genioglossus muscle, by negative upper airway pressure is well established in awake humans (20, 26), and NREM sleep attenuates this reflex (19, 45). Similar reflex activation may not occur in other upper airway muscles, but the activity of these muscles may be quite low during NREM sleep (28). Because upper airway anesthesia reduces phasic genioglossal activity in patients with OSAS (6) and exacerbates OSAS (8), there is reason to suspect that upper airway mechanoreceptors play a role in maintaining airway patency reflexively during sleep in OSAS patients. To the extent that the reduced somatosensory

<table>
<thead>
<tr>
<th>Subject</th>
<th>(-5 \text{ cmH}_2\text{O})</th>
<th>(-10 \text{ cmH}_2\text{O})</th>
</tr>
</thead>
<tbody>
<tr>
<td>IO LE</td>
<td>IO LE</td>
<td>IO LE</td>
</tr>
<tr>
<td>1</td>
<td>92.9 70.2</td>
<td>62.7 149.8</td>
</tr>
<tr>
<td>2</td>
<td>45.0 40.2</td>
<td>125.6 58.6</td>
</tr>
<tr>
<td>3</td>
<td>29.7 35.6</td>
<td>39.3 44.5</td>
</tr>
</tbody>
</table>

Mean ± SE IO: 55.6 ± 18.7; LE: 48.7 ± 10.9; 5 cmH2O: 75.9 ± 25.8; 10 cmH2O: 84.3 ± 33.0.

IO, inspiratory onset; LE, late expiration; \(\Sigma n\text{GFP}_{55–70}\), sum of global field power activity between 55 and 70 ms poststimulation.
activation we found in wakeful OSAS subjects persists in sleep, activation of reflexes enhancing upper airway patency may be compromised in OSAS. OSAS is often seen as a deficiency of upper airway activation arising centrally as a consequence of sleep onset (36), but the reduced somatosensory activation we found raises the possibility that deficient efferent upper airway muscle activity during sleep may partly result from deficient afferent activation from upper airway mechanoreceptors. Moreover, patients suffering from OSAS may lack normal upper airway load-compensating reflexes when awake, and this too could be due to impaired upper airway sensation (42).

In addition to altering reflex control of upper airway muscle activity, reduced afferent information from peripheral mechanoreceptors may alter perception of respiratory stimuli. For example, OSAS patients have a reduced ability to detect the application of inspiratory flow resistance loads (30). Conscious perception is a complex process that depends on afferent sensory information and on central cognitive processing. Thus reduced perceptual acuity in OSAS and other respiratory illnesses, such as life-threatening asthma (21), may derive in part from deficits in afferent sensory information (12), but altered central cognitive processes may enhance or mitigate any deficits in afferent information. For example, we recently found that normal subjects perceive pressure pulse stimuli relatively uniformly, although the afferent information they receive, estimated by GPP, varies over a wide range (11). Hence, it would not be surprising if the perceptual deficits described by McNicholas et al. (30) resulted from both reduced afferent information and altered cognitive processing. Similarly, there may be dual mechanisms in more complex reflex respiratory responses. Berry and Gleeson (5) suggested that impaired arousal in OSAS patients during NREM sleep could be explained by two mechanisms: an increased arousal threshold (reflecting a central mechanism) or abnormal upper airway mechanoreceptor function (reflected by deficient sensory afferent information). Our results lend support to the latter explanation but in no way deny the importance of the former.

In summary, we found that patients diagnosed with OSAS have significantly less midlatency somatosensory activation in response to small pressure pulses applied at IO than is the case for normal subjects. We cannot rule out a contribution of sleep-related factors to the results we obtained, but other studies of the effects of sleep on sensory-evoked activity do not indicate significant changes in the nature of evoked activity in the midlatency time range we studied. Therefore, our results imply that differences in mechanoreceptor characteristics or in airway compliance exist between normal subjects and patients with OSAS. The net effect, regardless of the cause, is that OSAS subjects get less information about the applied stimulus than do normal subjects, and we feel that the relative poverty of upper airway sensory information available to patients with OSAS may contribute to the pathogenesis of this syndrome.

We thank R. Hamlin for excellent technical assistance. This research was supported in part by National Heart, Lung, and Blood Institute Grant HL-29068 and Whitaker Foundation Grant 97-0530.

REFERENCES

22. Kimoff RJ, Cheong TH, Olha AE, Charboneau M, Levy RD, Cosio MG, and Gottfried SB. Mechanisms of apnea ter-