Within-night variation in respiratory effort preceding apnea termination and EEG delta power in sleep apnea

RICHARD B. BERRY, MUSA A. ASYALI, MICHAEL I. MCNELLIS, AND MICHAEL C. K. KHOO

AROUSAL FROM non-rapid-eye-movement (NREM) sleep within-night variation in respiratory effort preceding apnea termination and EEG delta power in sleep apnea. J. Appl. Physiol. 85(4): 1434–1441, 1998.—We studied the within-night variability of the maximum esophageal pressure deflection before apnea termination (DPmax) in nine patients with severe obstructive sleep apnea as an index of the arousal threshold and the mean electroencephalogram (EEG) delta power for each 30 s as an index of the timing of sleep cycles. Periodicity in the time variation of delta power and DPmax was analyzed by determining their power spectral density and their relationship determined by cross correlation. DPmax and delta power varied cyclically and in phase with a major periodicity (major peak in power spectral density) of 117.6 ± 8.8 (SE) min. The correlation between the values of DPmax and delta power was significant (P < 0.001) in each subject (mean r = 0.47 ± 0.03), and the coherence between DPmax and delta power at their dominant frequency was high. Within cycles of non-rapid-eye-movement sleep, DPmax and delta power increased, reaching peak values on average at or after midcycle. These findings suggest that the arousal threshold to airway occlusion in patients with obstructive sleep apnea varies cyclically during the night synchronous to the underlying cycles of sleep.

Methods

Nine patients with severe OSA, defined as an apnea + hypopnea index >40 events/h on a previous study, were studied on a single night in the sleep laboratory. The project was approved by the Human Studies Subcommittee of our hospital. Written informed consent was obtained from all subjects before they participated in the study.

Sleep was monitored using two pairs of EEG leads (C4-A1 and O2-A1), two pairs of electrooculogram leads, and chin electromyogram leads using standard techniques (23). An electrocardiogram lead was also monitored. The arterial O2 saturation was also measured continuously using pulse oximetry (model 3700, Ohmeda, Boulder, CO). Airflow was detected using a mask with a built-in pneumotachograph worn over the nose and mouth and kept in place with head straps. Deflections in esophageal pressure during occluded efforts were determined using a soft fluid-filled catheter (12). The catheter, a 5-Fr polyurethane pediatric feeding tube (Sherwood Medical, St. Louis, MO), was inserted through one nostril and swallowed into the esophagus. The tip was positioned 34–36 cm from the nares to obtain tracings with the smallest amount of cardiac artifact. Before insertion of the catheter, 1–2 ml of 4% lidocaine was dripped into one nostril to minimize discomfort during catheter insertion. The application of lidocaine occurred 1 h before sleep monitoring began. The catheter was well tolerated without additional anesthesia. The catheter was connected to a disposable Transpac II pressure transducer (Abbott Critical Care, North Chicago, IL). The system was calibrated with a water manom-
eter. The transducer system contained a valve that allowed a slow infusion of fluid (normal saline) at 3–4 ml/h to maintain catheter patency.

All measured variables were recorded on a 12-channel polygraph (model 78D, Grass Instrument, Quincy, MA) using a paper speed of 10 mm/s. The central EEG amplifier was calibrated so that 50 µV resulted in a pen deflection of 1 cm. Low- and high-frequency filter settings (one-half amplitude frequency) of 0.3 and 100 Hz, respectively, were used as well as a 60-cycle notch filter. The data were also acquired digitally by recording the output of the polygraph amplifier (J6 output jack) at a sampling rate of 100 Hz using an analog-to-digital board (Datag Instrument, Akron, OH) and stored on an IBM-compatible computer. Before patient recording, calibration signals were also digitally acquired for the central EEG channel. The digitally acquired signal was multiplied by an appropriate factor for conversion to microvolts.

Data analysis. Sleep was staged in 30-s epochs from the polygraph tracings according to standard criteria (23). Total sleep time was the minutes of stages 1–4 and REM sleep. The sleep period time was total sleep time plus wakefulness after sleep onset, i.e., the time after sleep onset but before the final awakening. We defined an arousal on the basis of criteria proposed by the American Sleep Disorders Association (1). An obstructive apnea was defined as an absence of flow signal from the mask covering the nose and mouth for ≥10 s associated with continued evidence of respiratory effort (esophageal pressure deflection). A hypopnea was defined as a reduction in airflow to <50% of baseline lasting for ≥10 s. Obstructive hypopnea was defined as a hypopnea associated with an increase in esophageal pressure deflection.

The esophageal pressure deflection during obstructive events was assumed to reflect the level of inspiratory effort. The maximum esophageal pressure deflection before apnea or hypopnea termination was designated DPmax. This pressure deflection occurred on the final or next-to-final breath preceding apnea or hypopnea termination. Prior studies have suggested that DPmax is an index of the arousal threshold (2–5). However, the DPmax values from events not meeting American Sleep Disorders Association criteria for arousal were still included in the analysis.

EEG signal processing. Spectral analysis of the central EEG was performed by analyzing the data in sequential nonoverlapping 1-s windows using the autoregressive model (6, 14). The advantage of this method over the conventional Fourier transform is that it is not critically dependent on data at the borders of the time window being analyzed. The delta power was defined as the power from 1 to 4 Hz. Using this method, we computed a delta power for each second (delta power-s) over the entire night. An average delta power was then determined for each sequential 30-s of the data file by averaging the delta power-s values for that time interval. The digital data (EEG, electrooculogram, electromyogram, airflow, and esophageal pressure) were manually viewed against elapsed time using a computer program (Windaq, Datalog Instrument). This allowed precise timing of all events (apnea onset/cessation, arousals, artifacts) including the time at which an arousal was identified on the basis of criteria.

Spectral analysis of the EEG sleep. Correlation by linear regression was also performed between DPmax and delta power in NREM sleep for the actual and detrended data. To further enhance our determination that the major periodicities in DPmax and delta power were linearly correlated, we also computed the mean-squared coherence (γ²) between these two time series (25). Coherence at any frequency (f) is defined as follows:

$$\gamma^2(f) = \frac{|P_{\text{DPmax-deltaPwr}}(f)|^2}{P_{\text{DPmax}}(f) \cdot P_{\text{deltaPwr}}(f)}$$

where $P_{\text{DPmax-deltaPwr}}$ is the cross spectrum between DPmax and delta power, and $P_{\text{DPmax}}$ and $P_{\text{deltaPwr}}$ are the power spectral densities of DPmax and delta power, respectively. $P_{\text{DPmax-deltaPwr}}$ was computed by applying fast Fourier analysis to the cross-correlation function between DPmax and delta power. A coherence value of unity at the periodicity in question would indicate a perfect linear correlation between the two signals at that frequency. This is not achievable in practice because of the presence of noise or nonlinearity in the relationship. However, coherence values >0.7 are generally regarded as “high.”

We also analyzed the variability in DPmax and delta power over NREM sleep cycles by dividing each cycle of NREM sleep into thirds. We defined an NREM sleep cycle as an episode of NREM sleep followed by a subsequent REM episode with the following exceptions. In some cases, the final episode of NREM sleep (preceded by an REM episode) was followed by morning awakening. Such episodes of NREM sleep were also considered a cycle of NREM sleep. In two patients the initial episode of NREM sleep was terminated by a period of prolonged wakefulness (>15 min) rather than REM sleep. These initial periods of NREM sleep were also considered cycles of NREM sleep. The mean values of DPmax and delta power for each one-fifth of a cycle were determined and expressed as a percentage of the mean value for the cycle. These values were then averaged over all NREM cycles for each patient. Thus we obtained mean percent values for DPmax and delta power for five equal segments of the NREM cycle. These values were then analyzed by ANOVA for re-
peated measures to determine whether a difference over time within NREM cycles was present. Differences between individual portions of the NREM cycles were determined by the Student-Newman-Keuls test.

Underlying trends over the entire night in \( \text{DP}_{\text{max}} \) and delta power were determined by obtaining mean values of quarters of the data by cumulative NREM sleep. This method was used rather than linear regression, inasmuch as one could detect trends that were not linear throughout the night. For example, a parameter could peak at the second quarter and then decrease over the next two quarters. The significance of changes in \( \text{DP}_{\text{max}} \) and delta power over the quarters of NREM sleep were determined using the analysis of variance. If appropriate, individual time period values were compared using the Student-Newman-Keuls test. Values are means ± SE unless otherwise stated. \( P < 0.05 \) was considered to show statistical significance.

RESULTS

The patients were 46.8 ± 7.7 (SD) yr of age and 163.9 ± 134% of ideal body weight (24). The amount and architecture of recorded sleep are summarized in Table 1. The pattern of sleep disturbance is typical for patients with OSA, showing almost no stage 3/4 sleep, reduced REM sleep, and a high arousal index. The patients as expected had a very high apnea + hypopnea index. About 90% of all apnea terminations were associated with evidence of cortical arousal. The mean values of \( \text{DP}_{\text{max}} \) and delta power (30-s averages) and their coefficients of variation are shown for NREM and REM sleep in Table 2. There was considerable variability of \( \text{DP}_{\text{max}} \) during the night within NREM sleep, which was composed almost entirely of stages 1 and 2 sleep. The mean values of delta power in NREM and REM sleep for the subject group are also shown in Table 2. Mean \( \text{DP}_{\text{max}} \) and delta power were significantly lower in REM sleep.

The \( \text{DP}_{\text{max}} \) and delta power (30-s averages) fluctuated in cycles during the night in all patients. A plot of the values for one subject is shown in Fig. 1. In this subject, delta power and \( \text{DP}_{\text{max}} \) varied synchronously and in phase over the night. The amplitude of the delta power tended to decrease over the night in this subject. Plots of the power spectral density of \( \text{DP}_{\text{max}} \) and delta power for this same subject are shown in Fig. 2. The major periodicity of the data by cumulative NREM sleep. This method was used rather than linear regression, inasmuch as one could detect trends that were not linear throughout the night. For example, a parameter could peak at the second quarter and then decrease over the next two quarters. The significance of changes in \( \text{DP}_{\text{max}} \) and delta power over the quarters of NREM sleep were determined using the analysis of variance. If appropriate, individual time period values were compared using the Student-Newman-Keuls test. Values are means ± SE unless otherwise stated. \( P < 0.05 \) was considered to show statistical significance.

Table 1. Sleep architecture and events

| TST, min | 323.7 ± 15.2 |
| SPT, min | 370.4 ± 16.0 |
| WASO, %SPT | 12.5 ± 2.1 |
| Stage 1, %SPT | 21.6 ± 3.1 |
| Stage 2, %SPT | 56.0 ± 3.9 |
| Stage 3/4, %SPT | 0.8 ± 0.4 |
| REM, %SPT | 9.1 ± 1.7 |
| Arousal index, events/h | 77.7 ± 2.2 |
| Apnea + hypopnea index, events/h | 865.9 ± 30.0 |

Values are means ± SE. TST, total sleep time; SPT, sleep period time; WASO, wake after sleep onset; REM, rapid-eye-movement sleep.

Table 2. \( \text{DP}_{\text{max}} \) and delta power

<table>
<thead>
<tr>
<th></th>
<th>NREM</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{DP}_{\text{max}} ), cmH(_2)O</td>
<td>45.9 ± 5.4</td>
<td>31.8 ± 3.7*</td>
</tr>
<tr>
<td>Coeff of variation of ( \text{DP}_{\text{max}} )</td>
<td>0.29 ± 0.02</td>
<td>0.23 ± 0.03</td>
</tr>
<tr>
<td>Delta power, µV(^2)</td>
<td>25.9 ± 3.2</td>
<td>16.2 ± 2.2*</td>
</tr>
<tr>
<td>Coefficient of variation of delta power</td>
<td>0.37 ± 0.02</td>
<td>0.34 ± 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE for subject group. \( \text{DP}_{\text{max}} \), maximum esophageal pressure deflection; Coeff, coefficient; NREM, non-rapid-eye-movement sleep; REM, rapid-eye-movement sleep. *\( P < 0.001 \), REM vs. NREM.

shows that the maximum correlation \( (r = 0.56, P < 0.001) \) occurred at a lag of 0 epochs (no phase shift).

The major power spectral density peaks of \( \text{DP}_{\text{max}} \) and delta power occurred at the same frequency in all subjects and were highly significant \((P < 0.001)\). The periods corresponding to these frequencies ranged from 68 to 146 min with a mean for the group of 117.6 ± 8.8 min. The maximum correlation between the \( \text{DP}_{\text{max}} \) and delta power time series (cross-correlation analysis) occurred at a lag of zero epochs (no phase shift).

The correlations between \( \text{DP}_{\text{max}} \) and delta power (detrended data) for NREM and REM sleep for each subject are shown in Table 3. All these correlations were highly significant \((P < 0.001)\). The \( \gamma^2 \) values between the \( \text{DP}_{\text{max}} \) and delta power time series (detrended data) evaluated at their major periodicity are also shown in Table 3. The values reveal a high coherence \((>0.7)\) between fluctuations in \( \text{DP}_{\text{max}} \) and delta power.

Significant correlations between \( \text{DP}_{\text{max}} \) and delta power were also present for the data for REM sleep were excluded. The correlation between \( \text{DP}_{\text{max}} \) and delta power during NREM sleep (actual and detrended data) for each subject is shown in Fig. 4. All these correlations were significant \((P < 0.001)\). For the entire group, the mean correlations between \( \text{DP}_{\text{max}} \) and delta power in NREM sleep were 0.41 ± 0.04 (actual) and 0.44 ± 0.03 (detrended data).

The mean time course of \( \text{DP}_{\text{max}} \) and delta power within cycles of NREM sleep is illustrated in Fig. 5. Here, mean values of \( \text{DP}_{\text{max}} \) and delta power are plotted for each one-fifth of cumulative sleep within an NREM cycle. The values of \( \text{DP}_{\text{max}} \) and delta power for each NREM cycle were expressed as a percentage of the corresponding mean value for that cycle. The data shown represent the average of 35 cycles of NREM sleep in the 9 patients. \( \text{DP}_{\text{max}} \) and delta power initially increased, reaching peak values near midcycle, and then decreased slightly toward the end of the cycle.

Although \( \text{DP}_{\text{max}} \) and delta power values for the entire night in NREM sleep were significantly correlated, their overnight trends differed. When each subject's data were expressed as a fraction of the all-night mean, separation into the night by quarters of cumulative NREM sleep showed that the delta power decreased significantly during the night (Fig. 6), whereas the \( \text{DP}_{\text{max}} \) showed a trend for an increase for the group as a whole through the third quarter. Although all patients showed a decrease in delta power, only six showed a
definite increase in $D_{\text{max}}$ during the night in NREM sleep.

**DISCUSSION**

This study demonstrates that, in patients with severe OSA, $D_{\text{max}}$ varies over the night in a cyclical fashion. We also found that, despite almost continuous apnea, the EEG delta power also varied in cycles throughout the night. The cyclic variation in $D_{\text{max}}$ was synchronous, with similar variation in the delta power of the central EEG. This variation was not simply secondary to a reduction in delta power and $D_{\text{max}}$ during periods of REM sleep. Analysis of cycles of NREM sleep showed that $D_{\text{max}}$ and delta power initially increased, reaching a maximum value on average at or after midcycle. Further analysis showed that the major period of the cycles of $D_{\text{max}}$ and delta power is approximately what one sees in the normal sleep cycles. We also found a significant correlation between the delta power and the $D_{\text{max}}$ for the entire night and for NREM sleep. A higher $D_{\text{max}}$ was associated with a higher delta power of the EEG. However, the EEG delta power decreased across the night (as in normal subjects), whereas the mean $D_{\text{max}}$ during NREM sleep varied cyclically and synchronously during night.
sleep tended to increase slightly overnight in most patients.

Studies in patients with OSA (19, 28, 29) and in normal subjects using mask occlusion (5) or induced hypoxia-hypercapnia (15) have found that arousal from NREM sleep occurs once a given level of inspiratory effort is reached independent of the values of hypoxia and hypercapnia stimulating ventilatory effort at the time of arousal. Central nervous system depressants (2, 3) or prior sleep fragmentation (4, 9, 22) increases the level of inspiratory effort associated with arousal. The level of effort triggering arousal is then an index of the arousal threshold (arousability). As might be expected, the arousal threshold (or maximum inspiratory effort before arousal) in a given individual varies during the night (18, 20, 28, 29). In fact, the above studies of the effects of hyperoxia and hypercapnia on arousal (5, 15, 19) controlled for this within-night variation by randomly alternating conditions over a night so that equivalent states of arousability would be present in each condition. However, little is known about the nature and mechanisms responsible for the within-night variation in the arousal threshold to respiratory stimuli.

Table 3. Relationship between DP_max and delta power for NREM and REM sleep

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Correlation*</th>
<th>Coherence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.56</td>
<td>0.93</td>
</tr>
<tr>
<td>2</td>
<td>0.42</td>
<td>0.95</td>
</tr>
<tr>
<td>3</td>
<td>0.44</td>
<td>0.73</td>
</tr>
<tr>
<td>4</td>
<td>0.47</td>
<td>0.93</td>
</tr>
<tr>
<td>5</td>
<td>0.38</td>
<td>0.71</td>
</tr>
<tr>
<td>6</td>
<td>0.55</td>
<td>0.90</td>
</tr>
<tr>
<td>7</td>
<td>0.47</td>
<td>0.72</td>
</tr>
<tr>
<td>8</td>
<td>0.35</td>
<td>0.99</td>
</tr>
<tr>
<td>9</td>
<td>0.58</td>
<td>0.93</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>0.47 ± 0.03</td>
<td>0.87 ± 0.04</td>
</tr>
</tbody>
</table>

*All correlations were significant (P < 0.001).
found a higher arousal threshold in sleep stages 3 and 4 than in sleep stages 1 and 2. However, there are several difficulties with using traditional sleep staging as a marker of the depth of sleep in patients with severe OSA. First, separation of NREM sleep into only four stages would allow for only a very crude characterization of sleep depth. Second, the NREM sleep of patients with severe OSA usually comprises only stages 1 and 2. Even applying the usual rules for sleep staging may be problematic in these patients, inasmuch as only short periods of sleep are spaced between periods of arousal and ventilation. An alternative is to use a continuous characteristic of the EEG as a marker for sleep stage and perhaps the depth of sleep. The delta power of the EEG is a continuous marker of the sleep cycles, increasing at the start of each NREM cycle and falling with the onset of REM sleep. Inasmuch as the delta power is highest in stage 3/4 sleep, one might also hypothesize that a higher delta power would be associated with a higher arousal threshold. In fact, Neckelman and Ursin (21) found a correlation between the arousal threshold to acoustic stimuli and the EEG delta power in rats. This led us to correlate changes in the EEG delta power with variation in DP$_{max}$. In our study, we also found a significant correlation between the delta power of the EEG and the arousal threshold to airway occlusion (as reflected by DP$_{max}$) in NREM sleep. However, correlation does not prove causality. Furthermore, although the cyclic variation in DP$_{max}$ and the EEG delta power were synchronous, the overnight trends differed. Thus the delta power, rather than being an absolute marker for the depth of sleep (arousal threshold) across the entire night, is a marker for the time course of arousability within a cycle of NREM sleep. As a given cycle of sleep progresses, DP$_{max}$ and delta power increase, reach a plateau, and then fall at or just before the start of the subsequent REM cycle.

Despite severe sleep fragmentation and a virtual absence of slow-wave sleep in our patients, we demonstrated that an underlying rhythm of cycles of delta activity was still present. The delta power also decreased during the night as in normal subjects. In contrast, DP$_{max}$ in NREM sleep for the group showed an increasing trend at least through the third quarter of cumulative NREM sleep. However, at least two of our patients had a downward trend in DP$_{max}$. O'Donnell and co-workers (22) did not find a progressive within-night increase in the maximum suction pressure triggering arousal in a study of airway occlusion in dogs after a previous night of sleep deprivation. Montserrat and co-workers (20) found that the maximum tension-time index of the diaphragm before apnea termination (another index of the arousal threshold) increased from the first to the final portion of the night in NREM sleep. In this study, 10 consecutive apneas from the earliest and latest portions of the night showing stable NREM sleep (and not contiguous with REM periods) were analyzed. This result is not necessarily inconsistent with our findings. The earlier period undoubtedly occurred during an upswing of a cycle of DP$_{max}$ and the final period prior to a downsing before a REM period. In that study two esophageal balloons were utilized, whereas our study employed a small fluid-filled catheter. The latter system is much more comfortable and causes minimal changes in sleep architecture (10). Thus our patients may have adapted to the monitoring system better and slept more deeply in the earlier portions of the night. However, we still found a trend for a small overnight increase in DP$_{max}$ during NREM sleep in most of our patients. Our findings do suggest that evaluations of trends in the arousal threshold (or maximum respiratory effort preceding apnea termination) during the night must consider the cyclic behavior of this threshold. Comparisons of small segments of the night must therefore be performed with caution.

In our spectral analysis of DP$_{max}$ vs. time during the night, we included values during REM as well as NREM sleep. There is no evidence to support DP$_{max}$ as an index of the arousal threshold during REM sleep. Although respiratory effort progressively increases near
apnea termination in NREM sleep, this is often not the case in REM sleep (22). We included the REM values so that $DP_{\text{max}}$ would be a continuous function and the period of the fluctuations would reflect the actual time course during the night. However, one might object that our finding of cyclical variation in $DP_{\text{max}}$ and EEG delta power was simply the result of the low values of $DP_{\text{max}}$ and delta power associated with periods of REM sleep. This is not the case, inasmuch as we also analyzed cycles of NREM alone and demonstrated a significant correlation between $DP_{\text{max}}$ and the EEG delta power in NREM sleep as well as a synchronous variation in both during cycles of NREM sleep.

To obtain continuous values of $DP_{\text{max}}$ and delta power throughout the night, we had to deal with the problem of intervening periods of wakefulness. As discussed in METHODS, we added interpolated values of $DP_{\text{max}}$ and delta power for short periods of intervening wakefulness and deleted longer periods by time shifting the data. The latter procedure could alter the major periodicity of the time series. However, although on average 12.5% of the sleep period time was composed of epochs scored as wakefulness, 77% of these periods of wakefulness were $<5$ min in duration and 88% were $<10$ min in duration. Values for these segments were added by interpolation. In only three patients were major data shifts (≥15 min) required (1 shift each in 2 subjects and 2 shifts in 1 subject). If we eliminated these patients, the mean periodicity for the remaining group differed only slightly from the entire group. In addition, inasmuch as such shifts were performed on the delta power and the $DP_{\text{max}}$ data, the ability of our analysis to detect synchronous variation in these two signals was not altered, even in these three subjects.

Other interpretations of our results are certainly possible. One could argue that the cyclic variation in the delta power in our patients was not a marker for events controlling arousability but simply an effect of variations in the arousal threshold. That is, a higher arousal threshold produced a longer apnea, which produced an opportunity for deeper sleep (greater delta power) to develop. Svanborg and Gulimenvault (27) demonstrated an increase in delta power from the initial to the final portion of apnea. In their study the delta power of the EEG started to rise on average $\sim 13$ s after apnea onset. The EEG delta power of the final 2 s of the apnea was double that of the initial 2 s. However, we do not believe that the cyclic variation in the delta power was simply secondary to a cyclic variation in the arousal threshold. First, this logic cannot explain the progressive fall in the amplitude of delta power over the night (without a decrease in the arousal threshold). Second, when we repeated the calculations averaging over NREM cycles (Fig. 5) using only the delta power from events from 20–25 s, we still noted the same cyclic behavior in delta power increasing over the initial part of the cycle, reaching a maximum value, and then decreasing slightly at the end of the cycles. Thus, although the delta power may increase during apnea, other factors in addition to event length are responsible for the cyclic variation in delta power.

In summary, we found that $DP_{\text{max}}$ varied in cycles during the night in a group of patients with severe OSA. During each cycle of NREM sleep, $DP_{\text{max}}$ initially increased and reached peak values on average near or after midcycle. Inasmuch as $DP_{\text{max}}$ is an index of the arousal threshold in NREM sleep, this suggests a cyclic variation in arousability. Despite severe sleep fragmentation, we also found a cyclic variation in the EEG delta power. $DP_{\text{max}}$ varied synchronously with the delta power of the EEG; a higher $DP_{\text{max}}$ was associated with a higher value of delta power. Although the overnight trends in $DP_{\text{max}}$ and the EEG delta power differed, their synchronous variation during the night and within cycles of NREM sleep suggests that they have some common controlling influences. We propose that the mechanisms controlling the cycles of sleep are responsible for the cyclic variability of the arousal threshold to airway occlusion.

Address for reprint requests: R. B. Berry, Pulmonary Section, Long Beach VAMC, 5901 East 7th St., Long Beach, CA 90822.

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