AROUSAL DOES NOT LEAD TO REDUCED DILATOR MUSCLE ACTIVITY IN THE HEALTHY

Arousal from Sleep Does Not Lead to Reduced Dilator Muscle Activity or Elevated Upper Airway Resistance on Return to Sleep in Healthy Individuals

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Study Objectives: To compare changes in end-tidal CO2, genioglossus muscle activity and upper airway resistance following tone-induced arousal and the return to sleep in healthy individuals with small and large ventilatory responses to arousal.

Design: Observational study.

Setting: Two sleep physiology laboratories.

Patients or Participants: 35 men and 25 women with no medical or sleep disorders.

Interventions: Auditory tones to induce 3-s to 15-s cortical arousals from sleep.

Measurements and Results: During arousal from sleep, subjects with large ventilatory responses to arousal had higher ventilation (by analytical design) and tidal volume, and more marked reductions in the partial pressure of end-tidal CO2 compared to subjects with small ventilatory responses to arousal. However, following the return to sleep, ventilation, genioglossus muscle activity, and upper airway resistance did not differ between high and low ventilatory response groups (Breath 1 on return to sleep: ventilation 6.7 ± 0.4 and 5.5 ± 0.3 L/min, peak genioglossus activity 3.4% ± 1.0% and 4.8% ± 1.0% maximum, upper airway resistance 4.7 ± 0.7 and 5.5 ± 1.0 cm H2O/L/s, respectively). Furthermore, dilator muscle activity did not fall below the pre-arousal sleeping level and upper airway resistance did not rise above the pre-arousal sleeping level in either group for 10 breaths following the return to sleep.

Conclusions: Regardless of the magnitude of the ventilatory response to arousal from sleep and subsequent reduction in PETCO2, healthy individuals did not develop reduced dilator muscle activity nor increased upper airway resistance, indicative of partial airway collapse, on the return to sleep. These findings challenge the commonly stated notion that arousals predispose to upper airway obstruction.

Keywords: upper airway collapse, pharyngeal airway, genioglossus, obstructive sleep apnea

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INTRODUCTION

The pathogenesis of obstructive sleep apnea (OSA) is only partially understood; in particular, the potential role of arousals from sleep in destabilizing upper airway function is controversial.1 Arousals from sleep commonly occur at the termination of respiratory events in OSA2,3 and have been suggested by some authors to predispose to further upper airway collapse on the return to sleep.2 The adverse effect of arousal on airway function has been proposed because the brief period of hyperventilation which accompanies arousal lowers the partial pressure of end-tidal CO2 (PETCO2). As upper airway dilator muscles such as the genioglossus are known to vary their activity in response to both chemical and mechanical drives,4–6 the arousal-induced hypocapnia could lower airway dilator muscle activity on the return to sleep, predisposing to upper airway collapse. Despite this commonly described sequence of events and evidence indicating hypocapnia can lead to dilator muscle hypotonia6 and increased airways resistance6–8 during stable sleep in susceptible individuals, there are in fact very limited data supporting such a role of arousals from sleep, as is outlined below.

Five studies have investigated the activity of one or more upper airway dilator muscles following arousal from sleep in either patients with OSA or healthy controls.9–13 Regardless of whether the arousals were induced with auditory tones, occurred spontaneously, or followed respiratory events, dilator muscle activity was not reduced below pre-arousal baseline levels following arousal or on the return to sleep. In addition, several studies have assessed upper airway resistance changes following arousal and have not reported a period of increased resistance,9,10,14 suggesting that the airway is not predisposed to collapse on return to sleep immediately after an arousal.

The magnitude of the increase in ventilation following arousal varies considerably between individuals.15 Thus, it is possible that only individuals with marked hyperventilation at arousal show the expected reduction in dilator muscle activity and increase in resistance following the return to sleep. This may explain why prior studies, which have examined group responses, did not observe the expected changes following arousal and return to sleep. Therefore, the aim of the current study was to investigate the changes in PETCO2, genioglossus muscle activity, and upper airway resistance following arousal and on the return to sleep in individuals with small and large ventilatory responses to arousal. We hypothesized that healthy individuals with a large ventilatory response to arousal would have greater hypocapnia and therefore lower genioglossus...
muscle activity and higher upper airway resistance on return to sleep following brief auditory induced arousal than individuals with a small ventilatory response to arousal. Data from some of the subjects included in this study contributed to prior publications addressing different aims and hypotheses.

METHODS

Subjects
Sixty healthy, non-obese individuals were recruited by advertisements placed at 2 sites: 27 subjects at the University of Melbourne Sleep Laboratory (UoMSL) and 33 subjects at the Adelaide Institute for Sleep Health (AISH). All subjects were aged between 18 and 60 years, did not smoke, had no history of cardiorespiratory disease or sleep disorders, and did not regularly take medications. Female participants were all premenopausal and studied in the follicular menstrual phase. All participants gave informed written consent, and the study was approved by the ethics committees in both locations.

Instrumentation and Measurements
In order to stage sleep and arousals, 2 EEG (UoMSL: C3-A2 and F3-A2; AISH: C3-A2 and C4-A1), left and right EOG, and chin EMG (UoMSL: mentalis muscle, AISH: submental) were recorded (Compumedics S series, Abbotsford, Victoria, Australia). Subjects were also instrumented with a nasal mask (modified Respironics Profile Lite, Philips Respironics, Murrysville PA) that was connected to a pneumotachograph (UoMSL: model 3700 Hans Rudolph, Shawnee, KS; AISH: PT36, Erich Jaeger, Germany) for measurement of inspired airflow and calculation of tidal volume ($V_t$), breathing frequency ($F_b$), and inspired minute ventilation ($V_{\text{I}}$). Mask gas was continuously sampled from a port in the mask and the end-tidal partial pressure of CO$_2$ ($\text{PETCO}_2$) determined (UoMSL: CD-3A analyzer; Ametek, Berwyn, PA; AISH: POET II model 602-3, Criticare systems Berwyn, PA) as well as mask pressure ($P_{\text{mask}}$; UoMSL: DP45; Validyne, Northridge, CA; AISH: Spectramed DXT, Oxnard, CA). Pressure at the level of the epiglottis ($P_{\text{epiglottis}}$) was determined by advancing a pressure catheter (UoMSL and some AISH patients: model MCP-500; Millar, Houston, TX; remaining AISH patients: Spectramed DXT, Oxnard, CA, attached to an air perfused catheter) 1.5 to 2 cm below the tongue base under direct visualization after nasal anesthesia (both laboratories: lignocaine) and nasal decongestion (AISH only: oxymetazoline HCl). Genioglossal muscle EMG (EMG$_{GG}$) was recorded with intramuscular electrodes inserted orally in the AISH laboratory (316SSST wire, Medwire, Mt Vernon, NY) and percutaneously at UoMSL (000-318-30; Motion Lab Systems, Baton Rouge, LA). The EMG$_{GG}$ signals were amplified and band-pass filtered from 30 to 1,000 Hz at UoMSL and 22–500 Hz at AISH (model P511, Grass TeleFactor; Grass Technologies, West Warwick, RI) before being scaled between electrical zero and each subject’s voluntary maximal activity (see protocol for maneuvers used).

All data were recorded on a personal computer using an analogue to digital converter (UoMSL: 1401plus and Spike2 software; AISH: DATAQ Instruments Inc, OH). Genioglossus EMGs were recorded at 1 kHz; EEGs were recorded at 250 Hz. The sampling rate of the other respiratory variables and EOGs ranged from 200 to 500 Hz, respectively.

Protocol
Subjects attended the sleep laboratory in the evening 2 h before their usual bedtime after abstaining from alcohol and caffeine for ≥ 8 hours. Subjects were instrumented with the recording equipment and then lay on a bed. The following maneuvers were performed to determine the maximum activity of the genioglossus muscle: 3 swallows, 3 deep breaths, and 3 tongue protrusions. Following this, 5–10 min of resting breathing during wakefulness was recorded before the lights were switched off and the subject was allowed to fall asleep. Subjects slept in both the supine and lateral body positions. However, only data collected in the supine position were included in this analysis. Once ≥ 5 min of stable stage N2 or N3 sleep had been achieved, auditory tones (1,000 Hz, 0.5 s, 45–105 dB) were played during expiration in order to induce brief arousals from sleep. Two minutes of N2 or N3 sleep was required to intervene between tone-induced arousals. Tones were played through ear insert headphones in the AISH laboratory and via speakers mounted above the bed in the UoMSL. The tone volume was targeted to induce 3-s to 15-s arousals from sleep. Tone presentation continued in all sleep stages and body positions until sufficient data were collected, the subject reached the end of their natural sleep period, or the subject requested the study be terminated.

Data and Statistical Analysis
Trained technicians identified 3-s to 15-s arousals throughout the whole recording while blinded to all signals except EEGs, EOGs, and chin EMG. The times at which tones were played were then displayed, and arousals that occurred within 5 s after a tone were considered to be tone-induced. Only arousals arising from and returning to NREM sleep were analyzed. After creating a rectified and moving time averaged (100 msec centered around each sample to avoid time skewing) genioglossus EMG trace scaled between maximum activity and electrical zero, custom written software was used to extract breath-by-breath data ($V_t$, $V_{\text{I}}$, $F_b$, mean inspiratory flow [$V_t/T_t$], duty cycle [$T_{\text{I}}/T_{\text{TOT}}$], nadir $P_{\text{EPI}}$, airway resistance [$R_{\text{UA}}$] calculated from mask, and epiglottic pressure at 0.2 L/s, $\text{PETCO}_2$, peak inspiratory [Peak] $\text{EMG}_{GG}$ and expiratory tonic [Tonic] $\text{EMG}_{GG}$) for 60 s before and 60 s after the onset of each tone-induced arousal from sleep. For each subject, the following breathes were averaged across arousals: the 5 breaths prior to tone presentation (baseline), the breaths during arousal from sleep (averaged by breath number, which ranged from 1 to 5), and the first 10 breaths on resumption of sleep following the arousal. All data were then expressed as a percentage change from the baseline level. Each subject’s peak ventilatory response to arousal (VRA) was calculated as the highest level of ventilation observed during the arousal (based on each subject’s average response) and expressed as a percentage of that subject’s average baseline ventilation. A median split was performed on the peak VRA data in order to allocate subjects to high and low VRA groups. Repeated measures ANOVAs were then performed to compare breath-by-breath respiratory and muscle data between the high and low VRA groups both during arousal (3 breaths × 2 groups, with missing data [not all subjects had 3 breaths during arousal] replaced by group mean data) and on return to sleep (10 breaths × 2 groups).
significant ANOVA effects were identified, Student t-tests were used to identify the location of the difference.

**RESULTS**

Thirty-three of 60 subjects (13 subjects from UoMSL and 20 subjects from AISH) had adequate data for analysis. Thirteen subjects slept poorly with the experimental equipment and had no brief tone-induced arousals. A further 7 subjects did not have any suitable arousals while in the supine position. Five subjects had signs of sleep disordered breathing such as heavy snoring and hypopneas and were excluded to avoid potential confounding by unstable breathing and non-auditory arousal responses. Finally, 1 subject slept extremely deeply and did not arouse following tones even at the highest volume, and another subject had persistent mask leaks such that the ventilatory response to arousal could not be reliably determined.

A total of 222 arousals were analyzed in the 33 subjects. The peak ventilatory response to arousal was normally distributed (Shapiro-Wilk P = 0.281, Figure 1). The median Peak VRA was 131.9% of the minute ventilation level observed during stable sleep prior to arousal. The participant with the median Peak VRA was omitted from further analyses, leaving 16 participants in each of the low and high VRA groups. The high and low VRA groups did not differ in terms of age, BMI, height, average tone used to induce arousal, or average arousal duration (Table 1). There were also similar numbers of men and women in the 2 VRA groups, and the proportion of studies performed during arousal breaths. No other variables differed between groups or over breaths during arousal (including total breath time, data not shown), and no breath-by-group interactions existed for any variable other than PETCO₂ during arousal.

Following the return to sleep, the respiratory variables (minute ventilation, tidal volume, mean inspiratory flow, and PETCO₂) showed similar results with significant or near significant main effects for breath, and breath by group interactions. Specifically, ventilation, tidal volume, and mean inspiratory flow gradually declined, and PETCO₂ rose over the 10 sleep breaths (Figure 2, breaths S1 to S10). All 4 variables were initially different between groups on the return to sleep, with the high ventilatory response to arousal group showing more extreme changes, but the groups had converged by the 10th sleep breath. PETCO₂ showed a significant breath-by-group interaction, falling more in the high VRA group across the arousal breaths. No other variables differed between groups or over breaths during arousal (including total breath time, data not shown), and no breath-by-group interactions existed for any variable other than PETCO₂ during arousal.

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Table 1—Participant demographics.

<table>
<thead>
<tr>
<th></th>
<th>High VRA</th>
<th>Low VRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23.7 ± 1.2</td>
<td>22.6 ± 1.4</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.02</td>
<td>1.77 ± 0.02</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.3 ± 0.7</td>
<td>21.6 ± 0.7</td>
</tr>
<tr>
<td>Men: Women</td>
<td>9:7</td>
<td>7:9</td>
</tr>
<tr>
<td>UoMSL: AISH (study location)</td>
<td>6:10</td>
<td>6:10</td>
</tr>
<tr>
<td>Tone volume (dB)</td>
<td>65.0 ± 2.9</td>
<td>64.5 ± 2.2</td>
</tr>
<tr>
<td>Average arousal duration (s)</td>
<td>7.3 ± 0.4</td>
<td>6.8 ± 0.5</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. No significant differences between groups.

Table 2—Pre-arousal respiratory data.

<table>
<thead>
<tr>
<th></th>
<th>High VRA</th>
<th>Low VRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>V₁ (L/min)</td>
<td>5.95 ± 0.14</td>
<td>5.55 ± 0.23</td>
</tr>
<tr>
<td>V₁ (L)</td>
<td>0.43 ± 0.01</td>
<td>0.41 ± 0.003</td>
</tr>
<tr>
<td>T₉₀ (%)</td>
<td>4.34 ± 0.12</td>
<td>4.44 ± 0.17</td>
</tr>
<tr>
<td>V₁/T₁ (%)</td>
<td>0.23 ± 0.003</td>
<td>0.24 ± 0.002</td>
</tr>
<tr>
<td>T₁/T₉₀ (%)</td>
<td>0.45 ± 0.01</td>
<td>0.43 ± 0.02</td>
</tr>
<tr>
<td>PETCO₂ (mm Hg)</td>
<td>43.5 ± 0.1</td>
<td>43.4 ± 0.1</td>
</tr>
<tr>
<td>Pₚₑᵢ (cm H₂O)</td>
<td>-4.8 ± 0.1</td>
<td>-4.6 ± 0.1</td>
</tr>
<tr>
<td>Rₛₑ (cm H₂O/(L/s))</td>
<td>7.14 ± 0.4</td>
<td>6.28 ± 0.1</td>
</tr>
<tr>
<td>GG Peak (%max)</td>
<td>3.24 ± 0.1</td>
<td>4.22 ± 0.1</td>
</tr>
<tr>
<td>GG Tonic (%max)</td>
<td>1.5 ± 0.03</td>
<td>1.9 ± 0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. No significant differences between groups.
Figure 2—Respiratory and EMG$_{GG}$ data during tone induced arousal and the subsequent return to sleep. Inspired minute ventilation ($V_i$), tidal volume ($V_t$), mean inspiratory flow ($V_t/T_i$), duty cycle ($T_i/T_{TOT}$), partial pressure of carbon dioxide (PETCO$_2$), expiratory tonic and peak inspiratory genioglossus EMG (Tonic EMG$_{GG}$ and Peak EMG$_{GG}$, respectively), and upper airway resistance ($R_{UA}$) during the first 3 breaths of arousal (Breaths Ar1 to Ar3) and following the return to sleep (Breaths S1 to S10). All data are expressed as a percent of the pre-arousal sleeping level (%baseline) except PETCO$_2$, which is in mm Hg change from the pre-arousal sleeping level. Means ± SEM are presented and $P < 0.05$ was considered significant. * Significant breath effect during arousal, § significant group effect during arousal, # significant breath-by-group interaction during arousal, † significant breath effect on return to sleep, ‡ significant group effect on return to sleep, § significant breath-by-group interaction on return to sleep. VRA, ventilatory response to arousal.
group (P = 0.004) effects being lower in subjects in the high VRA group and gradually increasing over the sleep breaths.

While $P_{\text{aw}}$ (data not shown), Peak EMG$_{\text{GG}}$, and Tonic EMG$_{\text{GG}}$ all showed significant breath effects (all $P < 0.002$) following the return to sleep, in contrast to the respiratory variables no group or interaction effects were present for these variables. $R_{\text{UA}}$ also showed significant breath (P < 0.001) and group (P = 0.02) effects being lower in the high VRA group on return to sleep and gradually increasing over the 10 sleep breaths.

**DISCUSSION**

This study has demonstrated that, contrary to our hypothesis, healthy individuals with large ventilatory responses to tone-induced arousal do not show reduced upper airway dilator muscle activity or higher airway resistance on return to sleep when compared to individuals with small ventilatory responses to arousal. Furthermore, the activity of the upper airway dilator muscle genioglossus did not fail below pre-arousal sleeping levels in either group for ten breaths following the return to sleep after arousal. This occurred despite the high ventilatory response to arousal group experiencing lower PETCO$_2$ levels than the low ventilatory response to arousal group. These findings call into question the validity of the commonly described sequence of events following arousal from sleep which maintain that arousal-induced hyperventilation induces hypocapnia, which on the return to sleep causes a reduction in activity of the upper airway dilator muscles predisposing the upper airway to collapse. Our data indicate that, if anything, airway resistance was reduced following the return to sleep in individuals with a large ventilatory response to arousal indicating improved airway patency.

**Implications for Sleep Related Breathing Disorders**

The magnitude of ventilatory responses observed in this study ranged from no change, to a doubling of ventilation, and is similar to what we and others have previously noted in patients with OSA while studied on CPAP.$^{17,18}$ However, arousals that occur with the termination of respiratory events are associated with more marked hyperventilation due to the blood gas abnormalities present at the time of arousal. Whether this additional hyperventilation is excessive (and results in more marked hypocapnia) or appropriate (and just lowers PETCO$_2$ back to the eupneic level) is unclear. However, should the resulting PETCO$_2$ (and genioglossus muscle activity) changes in OSA be similar to those observed in the healthy normal individuals studied in this paper, then arousals may, in contrast to common thinking, not worsen upper airway function even if hypocapnia is induced. In fact, arousals could even improve airway function for a few breaths following the return to sleep, as we found a small increase in genioglossus activity and reduced airway resistance in the current study. That arousals could result in a period of reduced airway resistance is consistent with our prior study conducted in OSA patients on sub-therapeutic CPAP treatment, in whom we saw reduced upper airway resistance for 60 s following tone-induced arousals.$^{17}$ However, the differences in stimuli causing arousal, as well as the absence of blood gas disturbance preceding arousal, limit our ability to extrapolate these findings to patients with OSA.

Further direct investigation in patients with sleep disordered breathing is required.

Several sedative trials have been conducted in patients with OSA,$^{19,20}$ two with the intent of preventing the proposed adverse effects of arousal on upper airway dilator muscle activity and upper airway function. One of these trials$^{19}$ showed a small but statistically significant reduction in AHI, whereas no change in AHI was observed in the seven other studies. While this may reflect that arousals do not have the commonly stated adverse effects of lowering dilator muscle activity and predisposing to airway obstruction, several trials have noted that some individual patients had reduced AHI.$^{19,21,22}$ Based on the findings of the current study we believe that additional trials investigating participant characteristics that predict successful sedative treatment, as well as further studies examining the mechanism of action of sedatives are warranted. Clearly, sleep fragmentation and repeated cardiovascular activation with arousals in OSA likely contribute to excessive daytime sleepiness, neurocognitive deficits, and increased risk of cardiovascular disease seen in the disorder. Also, arousals likely contribute to central respiratory instability by bringing patients closer to the apneic threshold. Therefore, reducing arousals may still have symptomatic benefit for patients with OSA, particularly those with a large central respiratory control instability component, even if the effects on upper airway collapsibility are less clear.

**Airway Physiology Changes Following Arousal**

A progressive rise of tonic genioglossus muscle activity following arousal was observed, which persisted for several breaths after the return to sleep. To our knowledge this has not previously been noted, potentially because the breaths during arousal and on the return to sleep have not been separated in most prior studies. The mechanism responsible for this gradual change is of interest, because if it could be harnessed or pharmacologically induced in sleep it may result in improved airway patency. The gradual increase in tonic genioglossus activity is unlikely to be a result of the wakefulness stimulus, which is generally thought to return almost instantly at the time of the arousal. Indeed in this study ventilation and peak genioglossus activity showed the usual rapid increase on the first breath following arousal consistent with the wakefulness stimulus concept. Rather, it is possible the slow increase in tonic genioglossus activity reflects a previously unreported stimulus which gradually develops following arousal. Alternatively, it may represent a form of neural potentiation in which a greater EMG results from constant neural drive such as the development of a plateau potential.

It should be noted that although upper airway resistance was significantly lower during arousal and on return to sleep in the high ventilatory response to arousal group, the 20% of baseline difference corresponds to approximately a 1 cm H$_2$O/ (L/s) difference in resistance which may not be of physiological importance. However, it is possible that the greater change in resistance with a similar change in genioglossus muscle activity indicates that the genioglossus muscle is more efficient in participants with a high ventilatory response to arousal, and further, part of the reason this group exhibits a high ventilatory response to arousal may relate to differences in upper airway mechanics as opposed to central drive changes. We are unable
to separate the central drive vs airway mechanics components of the ventilatory response to arousal in this study, but Khoo et al.\textsuperscript{14} have previously suggested that post-arousal changes in ventilation are dominated by resistance changes as opposed to central drive changes, supporting this concept.

**Limitations**

The participants studied in this experiment were relatively young, with a mean age of 23 years. Although Goff and colleagues\textsuperscript{27} have previously demonstrated that the ventilatory response to arousal did not differ between a young and older group, they did show a trend towards a difference in upper airway resistance. Therefore, extrapolation of our results to healthy older individuals must be made with caution. We also excluded five participants who exhibited hypopneas and loud snoring to ensure a homogeneous healthy study population. However, this group could show different responses compared to patients with sleep disordered breathing. We also observed a relatively high dropout rate, with 13 subjects unable to sleep adequately with all experimental equipment in place. This may have resulted in a selection bias of “good sleepers.”

A further consideration with nonsignificant findings is whether the comparisons were adequately powered. We determined that 166 subject would be required to detect the observed difference in genioglossus activity of 6% of the stable sleeping baseline with 80% power and \( \alpha \) of 0.05. However, a difference of 6% of the sleeping baseline corresponds to a difference of approximately 0.5% maximum activity, which is unlikely to be physiologically important. In order to detect a 2% of maximum increase in genioglossus activity, which might be important physiologically, only 6 subjects would be required. Therefore, even though genioglossus activity appears slightly lower in the high ventilatory response group, the magnitude of the difference is likely to be unimportant and inadequate power is unlikely to explain the main findings.

We performed a median split and included all participants except the median subject in the analysis. While this analysis maximizes subject numbers, it potentially biases toward the null hypothesis by including patients near the median in both groups. We therefore also compared arousal responses between participants in the upper and lower quartiles with very similar findings. Therefore, we do not believe that the method of analysis significantly influenced the interpretation of the data. Finally, although data were collected in two locations and each laboratory used slightly different equipment and methodologies, the proportion of subjects from each laboratory did not differ between the high and low ventilatory response to arousal groups. Therefore, the two locations and slight methodological differences are unlikely to have substantially influenced the study findings.

**CONCLUSION**

This study has demonstrated that healthy individuals with an inherently large ventilatory response to tone-induced arousal do not have physiological signs of an increased predisposition to airway collapse (neither lower upper airway dilator muscle activity nor increased upper airway resistance) on the return to sleep when compared to individuals with a low ventilatory response to arousal. Furthermore, upper airway dilator muscle activity gradually declined following the return to sleep but did not fall below the level observed during stable sleep in either low or high ventilatory response to arousal groups. While it is important to note that the participants studied were healthy volunteers and no blood gas abnormalities were present at the time of arousal, should these findings also be present in patients with obstructive sleep apnea, then it would suggest that the arousals that commonly occur at the end of respiratory events may not worsen airway function on the subsequent return to sleep and could potentially improve airway function.

**DISCLOSURE STATEMENT**

This was not an industry supported study. This work was supported by grants from the Australian Research Council (FT100100203), National Health and Medical Research Council of Australia (138403 and 430300) and the University of Melbourne Faculty Research Grant Support Scheme. The data was collected at both the Adelaide Institute for Sleep Health, Daw Park, SA, Australia and University of Melbourne, Parkville VIC, Australia. The authors have indicated no financial conflicts of interest.

**REFERENCES**


