Occlusion of the upper airway does not augment the cardiovascular response to arousal from sleep in humans

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O’Driscoll, Denise M., Konstantinos Kostikas, Anita K. Simonds, and Mary J. Morrell. Occlusion of the upper airway does not augment the cardiovascular response to arousal from sleep in humans. J Appl Physiol 98: 1349—1355, 2005. First published December 3, 2004; doi:10.1152/japplphysiol.00706.2004.—The cardiovascular response to an arousal from sleep at the termination of an obstructive apnea is more than double that to a spontaneous arousal. We investigated the hypothesis that stimulation of respiratory mechanoreceptors by inspiring against an occluded airway during an arousal from sleep, augments the accompanying cardiovascular response. Arousals (>10 s) from stage 2 sleep were induced by a 1-s auditory tone (85 dB) during a concomitant 1-s inspiratory occlusion (O) and without an occlusion [i.e., control arousal (C)] in 15 healthy men (mean ± SE: age, 25 ± 1 yr). Arousals were associated with a significant increase in mean arterial blood pressure (MAP) at 4 s (P < 0.001) and a significant decrease in R-R interval at 3 s (P < 0.001). However, the magnitude of the cardiovascular response was not different during C compared with O (MAP: C, 86 ± 3 to 104 ± 3 mmHg; O, 86 ± 3 to 105 ± 3 mmHg; P = 0.99. R-R interval: C, 1.12 ± 0.03 to 0.89 ± 0.04 s; O, 1.11 ± 0.02 to 0.87 ± 0.02 s, P = 0.99). Ventilation significantly increased during arousals under both conditions at the second breath (P < 0.001); this increase was not different between the two conditions (C: 4.40 ± 0.29 to 7.67 ± 0.61 l/min; O: 4.35 ± 0.34 to 7.65 ± 0.73 l/min; P = 0.31). We conclude that stimulation of the respiratory mechanoreceptors by transient upper airway occlusion is unlikely to interact with the arousal-related autonomic outflow to augment the cardiovascular response in healthy young men.

blood pressure; heart rate

SPONTANEOUS AROUSAL FROM SLEEP is associated with large surges in both heart rate and blood pressure (13, 42, 49). In patients with obstructive sleep apnea (OSA), the surges in sympathetic activity that occur during an arousal from sleep at the termination of an apnea are more than double in size compared with a spontaneous arousal (2, 29, 40). Frequent cardiovascular surges in OSA have been implicated in the increased prevalence of both nocturnal and diurnal hypertension associated with OSA (37, 41). The mechanisms responsible for the augmentation of the cardiovascular response to arousal at the termination of an apnea potentially include stimulation of the chemoreceptors (hypcapnia, hypoxia), stimulation of upper airway (UA) mechanoreceptors (occlusion), stimulation of the pulmonary stretch receptors (increasing negative intrathoracic pressure, lung inflation), or arousal-related central activation of autonomic centers. Our laboratory has previously reported in this journal that combined stimulation of the central and peripheral chemoreceptors (using hypcapnic hypoxia) does not significantly augment the cardiovascular response to arousal from sleep in healthy human subjects (39).

Brief inspiratory occlusion evokes cortical activity during wakefulness (12, 15) and sleep (1, 51). Additionally, during sleep, complete airway occlusion can rapidly induce arousal, most likely as a result of afferent activity from UA mechanoreceptors to the brain stem respiratory centers (24). Altering this afferent activity, by topical anesthesia, has been shown to prolong the time to arousal (6). Taken together, these studies support the idea that occlusion of the UA may induce arousal from sleep. Furthermore, we speculate that occlusion may also augment the cardiovascular response to arousal from sleep.

Mechanoreceptors located in the UA are stimulated by application of negative intraluminal pressure (21, 23). This afferent sensory activity is likely to be transmitted to the respiratory control center in the medulla, coinciding with the dilator reflex (genioglossal muscle) to reestablish airway patency (22, 27, 44). In animal models, sites within the medulla receiving afferent information from the mechanoreceptors are also known to be involved in the regulation of sympathetic outflow to the heart and blood vessels, and involved with areas associated with the alerting response. Specifically, peripheral nerves from the UA terminate in the nucleus tractus solitarius, an area acknowledged to mediate cardiovascular reflexes (11, 35, 36, 47). We therefore reasoned that stimulation of the UA mechanoreceptors could interact centrally with the arousal-related sympathetic outflow to augment the cardiovascular response.

Previous studies investigating the effect of UA occlusion during sleep have primarily focused on replicating an obstructive apnea (i.e., occlusion maintained over several breaths) (38, 45). However, this approach does not separate the effect of UA mechanoreceptor stimulation from the hypcapnia and hypoxia. The aim of the present study was to test the hypothesis that stimulation of the UA mechanoreceptors alone interacts with the arousal-related sympathetic outflow to augment the accompanying cardiovascular response. Specifically, we compared the cardiovascular response to auditory-induced arousals in healthy young men with and without a concomitant inspiratory occlusion.

METHODS

Subjects. Fifteen healthy male subjects recruited from the general population were studied (means ± SE: age, 25 ± 1 yr; body mass...
index, 22.9 ± 0.5 kg/m²; neck circumference, 38 ± 0.5 cm). No subject had a history of cardiovascular disease, snoring, or other sleep pathology associated with excessive daytime somnolence (Epworth sleepiness scale, 5.5 ± 0.5). No subject reported any limitations of hearing. All were normotensive (office blood pressure: systolic 121 ± 2 mmHg; diastolic, 65 ± 2 mmHg) and had normal lung function as determined by forced spirometry (ratio of forced expiratory volume in 1 s to forced vital capacity, 87 ± 1.7%).

Protocol. Subjects were asked to abstain from caffeine and alcohol consumption on the day of testing. Each subject arrived at the sleep laboratory at 2000, and the monitoring equipment was attached for overnight polysomnography. During stage 2 non-rapid eye movement sleep, an auditory tone was sounded to induce arousals during a concomitant 1 s inspiratory occlusion (O) and without an occlusion [i.e., control arousal (C)]. The auditory stimulus consisted of a tone delivered remotely via an audio speaker placed at the end of the subject’s bed (85 dB measured at the subject’s ear). Each recorded tone was swept linearly over a frequency modulation of 500–1000 Hz (39). The ambient room noise was measured as 50 dB. The Brompton and Harefield Ethics Committee approved this study, and all subjects gave written, informed consent.

Physiological measurements. Electroencephalograms (EEG; C3/A2, O1/A2), electrocorticograms (EOG; F7/F8), and an electromyogram (EMG; submentalis muscle) were recorded (Grass Instrument) to determine sleep stage according to standard criteria (43). Continuous electrocardiography (ECG) was recorded (Lifetrak, HME), and continuous blood pressure was measured via finger plethysmography (Finapres, Ohmeda). Arterial oxygen saturation (SaO₂) was measured by using a rapidly responding gas analyzer (model CD3A, AEI Technologies). Ventilation was measured via a pneumotachograph (model 4700A, Hans Rudolph) and a differential pressure transducer (model MC1-3, Validyne) attached to a tightly sealed full-face mask (B&D Electromedical). Esophageal pressure (Pes) was recorded from a pressure sensor (model CTO-2, Gaeltec) connected to a pressure transducer (model S7b/2, Gaeltec) to measure respiratory effort. The pressure sensor was inserted nasally into the middle one-third of the esophagus with minimal cardiac artifact (~40 cm from the nares), after topical anesthesia was applied to the nose and throat (lignocaine hydrochloride gel 2%, Biorex Laboratories). All physiological parameters were recorded by using a computerized data system (CED 1401, Spike 2, Cambridge Electronic Design).

Sleep studies. All sleep studies were commenced between 2300 and 0000, at least 90 min after the topical anesthesia was applied. After 5 min of stable stage 2 sleep, the auditory tone was sounded at end expiration (mean onset 0.26 ± 0.03 s). This served as the C condition. The O condition consisted of the tone being sounded simultaneously with a 1 s inspiratory occlusion. An external occlusion was induced during inspiration by an inflatable balloon (balloon assembly 9308, Hans Rudolph) located in the inspiratory limb of a two-way nonre-breathing valve (2600 series, Hans Rudolph) attached to the full-face mask. The balloon was regulated by an automated pneumatic controller (Biomedical Engineering Department, Royal Brompton Hospital), which was armed remotely by the experimenter during the preceding expiration. The balloon inflated rapidly at inspiration (mean onset 0.38 ± 0.03 s). The mean duration between the occlusion and the auditory tone was 0.29 ± 0.02 s. The two conditions were presented in a random order during stage 2 sleep, separated by a minimum of 2 min of stable sleep, until morning wake time.

Data analysis. Cardiovascular and ventilatory responses were analyzed for every induced arousal. Beat-by-beat blood pressure and R-R interval were analyzed from 15 s before to 15 s after the auditory stimulus. All cardiovascular data were resampled at 1 s intervals, by using linear interpolation, to enable comparison between interventions. (This process estimates data points at 1 s intervals by using the range of data collected.) Respiratory parameters [ventilation, tidal volume (VT), total breath duration (Tt), SaO₂, PETCO₂, total inspiratory pulmonary resistance (RL), and peak negative intrathoracic pressure] were analyzed from six breaths before to six breaths after the auditory stimulus. RL was calculated from the Pes signal (an indirect measure of pleural pressure) and the airflow signal (32). A continuous inspiratory resistance measurement for each breath was divided into 10 equal sections, the middle eight of which were averaged to provide the final resistance measurement for that breath. This method has been used previously to measure RL during sleep (5, 8, 17, 34). Peak negative intrathoracic pressure was derived indirectly from the Pes signal (7, 31).

Sleep state was determined from the EEG, EOG, and EMG by a researcher blinded to other physiological data. Arousals were graded into one of five previously described categories (39) according to the type and duration of the shift in EEG frequency: 1) no discernible change, 2) an increase in the amount of slow-wave activity, 3) an abrupt shift in EEG frequency lasting between 1.5 and 3 s (including any combination of theta, alpha, or other activity >16 Hz but not spindle or delta frequencies), 4) an abrupt shift in EEG frequency lasting between 3 and 10 s, and 5) an abrupt shift in EEG frequency lasting >10 s. Only data from category 5 arousals are presented.

Statistical analysis. All data are presented as means ± SE. For all variables, within-condition responses for each subject were averaged for between-condition comparisons to ensure that each subject contributed equally to the group mean. The effects of time and of C vs. O on cardiovascular and ventilatory responses to arousal were tested by using ANOVA with repeated measures. Statistical analysis was performed on all postarousal data, specifically breaths 1–6 and seconds 1–15. A paired t-test was used to compare the mean peak negative intrathoracic pressure measured on the first breath postarousal between the two conditions. Null hypotheses were rejected when P < 0.05.

RESULTS

All data presented are from arousals lasting >10 s. A total of 102 arousals were achieved during C (3–16 per subject) and 105 during O (3–14 per subject). Figure 1 shows original traces from one subject with arousals induced under C and O conditions.

Cardiovascular parameters. Group data mean arterial blood pressure increased significantly during arousals under both conditions, peaking at 4 s (C, 86 ± 3 to 104 ± 3 mmHg; O, 86 ± 3 to 105 ± 3 mmHg; P < 0.001), followed by a decline close to prearousal levels at 15 s. However, the magnitude and time course of the increase were not significantly different during C compared with O (P = 0.99; Fig. 2A). Mean R-R interval decreased significantly during arousals under both conditions at 3 s (C, 1.12 ± 0.03 to 0.89 ± 0.04 s; O, 1.11 ± 0.02 to 0.87 ± 0.02 s; P < 0.001), returning to prearousal levels at 6 s. However, again, the magnitude and time course of the decrease were not significantly different between C compared with O (P = 0.99; Fig. 2B).

Respiratory parameters. Arousals were associated with a significant increase in mean ventilation at the second breath (C, 4.40 ± 0.29 to 6.76 ± 0.61 l/min; O, 4.35 ± 0.34 to 7.65 ± 0.73 l/min; P < 0.001), decreasing toward prearousal levels at breath 6. However, the magnitude and time course of the increase were not significantly different between the two conditions (P = 0.31; Fig. 3A), despite the increase appearing to be more sustained during O compared with C.

The arousal-related increase in ventilation was produced by an increase in VT. VT increased significantly at the second breath postarousal (C, 0.32 ± 0.02 to 0.46 ± 0.04 liter; O,
0.32 ± 0.03 to 0.53 ± 0.05 liter; \( P < 0.001 \)), although this increase was not significantly different between the two conditions \( (P = 0.33; \text{Fig. 3B}) \). Tr significantly decreased at the first breath (C, 4.4 ± 0.1 to 3.7 ± 0.1 s; O, 4.4 ± 0.1 to 3.6 ± 0.3 s; \( P < 0.001 \)) after arousal, but again this decrease was not significantly different between conditions \( (P = 0.91) \).

Arousals were associated with a significant decrease in PETCO2 at the second breath (C, 43.1 ± 0.5 to 41.8 ± 0.5 Torr; O, 43.0 ± 0.6 to 41.4 ± 0.7 Torr; \( P < 0.001 \)), but this was not significantly different between conditions \( (P = 0.94) \). Mean SaO2 remained stable throughout all arousals (C, prearousal: 97.7 ± 0.2%, postarousal: 97.6 ± 0.2%; O, prearousal: 97.8 ± 0.2%, postarousal: 97.7 ± 0.2%).

Data presented for RL and peak negative intrathoracic pressure are from 14 subjects, because one subject could not tolerate the Pes sensor. Mean RL significantly decreased at the third breath during arousals under both conditions (C, 11.44 ± 1.31 to 7.48 ± 0.90 cmH2O·l⁻¹·s⁻¹; O, 11.61 ± 1.59 to 7.39 ± 0.99 cmH2O·l⁻¹·s⁻¹; \( P < 0.001 \)), but this was not significantly different between conditions \( (P = 0.90; \text{Fig. 4A}) \). Mean peak negative intrathoracic pressure became significantly more negative at the second breath during arousals under both conditions (C, -4.45 ± 0.55 to -5.74 ± 1.21 cmH2O; O, -4.59 ± 0.62 to -7.72 ± 1.68 cmH2O; \( P < 0.001 \)), but again this was not significantly different between conditions \( (P = 0.37; \text{Fig. 4B}) \). However, mean peak negative intrathoracic pressure measured on the first breath postarousal was significantly more negative during O (occluded breath) compared with C (C, -3.18 ± 0.36 cmH2O; O, -4.43 ± 0.66 cmH2O; \( P < 0.05 \)). This shows that the occlusion produced a significant increase in negative intraluminal pressure on the first breath postarousal.

**DISCUSSION**

The main finding of the present study was that stimulation of the UA mechanoreceptors, using a 1-s inspiratory occlusion, does not interact with the arousal-related sympathetic outflow to augment the accompanying cardiovascular response in healthy young men. As with previous studies detailing the cardiovascular response to auditory-induced arousals from sleep, arousals in the present study were associated with a surge in blood pressure and heart rate (measured by R-R interval) peaking at 4 and 3 s, respectively \( (10, 13, 39, 42) \). However, the magnitude and time course of the blood pressure and heart rate responses were not different when arousals...
occurred in association with an inspiratory occlusion compared with the control condition.

Our results are consistent with the findings of Eastwood et al. (14). These researchers found that, in sleeping dogs, the blood pressure response during sustained airway occlusion was similar when the UA was exposed to negative pressure compared with when it was effectively isolated by applying the negative pressure below the UA via a tracheostomy tube. Furthermore, they showed that the magnitude of the blood pressure response was similar whether or not it was accompanied by an arousal from sleep.

The overall findings of the present study are based on the premise that the 1-s inspiratory occlusion was sufficient to significantly stimulate the UA mechanoreceptors. In this respect, the peak negative intrathoracic pressure was more negative during the first breath postarousal during O (occluded breath) compared with C, with a trend for this difference to continue during subsequent breaths. The more negative intraluminal pressure, generated by the abrupt more negative intrathoracic pressure, would have stimulated the UA mechanoreceptors to a greater extent (21–23), most likely causing a small but significant increase in genioglossal activity (27). The UA negative pressure reflex is typically stimulated at 2–5 cmH₂O (50). The occlusion in the present study produced an intrathoracic pressure change >3 cmH₂O postarousal.

Further evidence of the stimulation of the UA mechanoreceptors is the trend for the ventilatory response postarousal during O to be increased compared with C. The rapid feedback from the UA mechanoreceptors has been reported previously. Issa and Sullivan (24) found that arousal could, on occasion, be induced from sleep during a single occluded breath when hypercapnic and hypoxic stimuli would have been negligible, just as in the present study.

Finally, as mentioned earlier, the peak negative intrathoracic pressure was more negative during the first breath postarousal during O compared with C. This was associated with the trend for the ventilatory response postarousal during O to be increased compared with C. The unchanged ventilation during the first breath of the C arousal could be due to a transient inhibitory response, attributed to the orienting reflex (25). Badr
et al. (4) reported that ventilation was unchanged during the first breath of an auditory-induced arousal and that the arousal-related increase in ventilation occurred during the second breath of the arousal. First-breath inhibition of ventilation after arousal has also been demonstrated in dogs (19). In our study, the fact that the inhibition occurred to a lesser extent during the occlusion arousals, as demonstrated by the peak negative intrathoracic pressure (also shown in Fig. 1), indicates increased respiratory effort due to stimulation of the UA mechanoreceptors. Taken together, all of these arguments suggest that, although the inspiratory occlusion was brief, it was sufficient to stimulate the UA mechanoreceptors. However, the mechanoreceptor stimulation achieved in this study may not have produced equivalent afferent activity as the collapse or deformation of the UA that occurs during an obstructive apnea.

Young healthy nonsnoring men were chosen as subjects for the present study, instead of OSA patients, to ensure that UA sensation would be unimpaired. OSA patients are known to have a dampened response to UA stimulation compared with healthy individuals. Sensitivity thresholds to vibration (26) and temperature (28) in the UA have been found to be altered in snorers and patients with OSA. In addition, and perhaps more importantly, OSA patients have been shown to have a blunted cortical response to inspiratory occlusion during sleep (1). Therefore, we anticipated that, by testing a young healthy subject group, we would have achieved the maximal autonomic response when stimulating the UA during an auditory-induced arousal. Similarly, only data from the largest induced arousals (>10 s) are shown for the present study because the length of the arousal from sleep is known to be related to the associated autonomic response (42, 48). However, this arousal grading does include arousals >15 s in length, which may be considered as awakenings and as such may be associated with a different autonomic response. We do not believe that our results were unduly affected by arousal length because the two conditions included similar percentages of arousals >15 s: control arousals 47%, occlusion arousals 60%.

Previous studies investigating the effect occlusion has on arousal from sleep and the associated autonomic responses have focused on replicating an obstructive apnea. O'Donnell et al. (38) found that airway obstruction maintained for a number of breaths increases digital vasoconstriction in OSA patients, measured by peripheral arterial tonometry. Ringler et al. (45) demonstrated large blood pressure surges after occlusion during sleep in healthy subjects, again maintained for several breaths. However, an occlusion over this increased time period would have allowed hypercapnic, hypoxic, and increasing negative intrathoracic pressure influences to come into effect. The occlusion method in the present study employed a brief restriction of inspiratory airflow coincident with an auditory-induced arousal, followed by its abrupt release. This does not reproduce an apnea but attempts to isolate the stimulation of the UA mechanoreceptors. To our knowledge, this is the first demonstration of the effect that stimulation of the UA mechanoreceptors alone has on the cardiovascular response to arousal.

The external occlusion used in this study exposed the entire UA to increased suction pressure. During an obstructive apnea, the nasal cavity is not exposed to pressure changes because the airway collapse occurs at the oropharynx (44). However, pressure-sensitive receptors have also been identified in the nasal cavity (30). In the present study, occlusion of the UA did not augment the cardiovascular response to an induced arousal, despite the likely addition of stimulation of receptors in the nose.

Although auditory stimuli have been widely used in studies investigating the autonomic response to arousal (4, 10, 13, 33, 42), it is unlike the endogenous stimuli that induce arousal at the termination of an obstructive apnea. We chose to use the auditory stimulus because occlusion alone is unlikely to induce arousal on all occasions, and it was a standardized method of rapidly inducing cortical arousal during the two conditions. The effects of occlusion alone were not examined in this study. Had we studied occlusion alone, the time to arousal would have been variable (24) and would have also resulted in chemoreceptor stimulation. The effect of chemostimulation on the cardiovascular response to arousal from sleep has been previously studied by our group and others (10, 39).

The mechanism responsible for the increased cardiovascular response that occurs at the termination of an apnea remains
unclear. Hypercapnia and hypoxia are known to produce large increases in sympathetic nerve activity (46). Despite this, our laboratory has previously reported that combined central and peripheral chemoreceptor stimulation (using hypercapnic hypoxia) did not significantly augment the blood pressure or heart rate response to induced arousals in healthy young men (39). A remaining potential mechanism is the increasing negative intrathoracic pressure that occurs as the apnea progresses. Glessen et al. (16) found that arousal from sleep occurred at similar levels of respiratory effort irrespective of the levels of hypercapnia or hypoxia. Negative intrathoracic pressure is also known to directly affect left ventricular function and thereby alter cardiac output (9). It is possible then that the increasing negative intrathoracic pressure contributes to the arousal-related sympathetic activity to augment the cardiovascular response.

On the other hand, there is evidence indicating that central arousal mechanisms have an important role in determining the autonomic response to arousal from sleep. Arousal is known to represent a unique state of heightened preparedness to evaluate and react to the new environment, a form of reflex response (18, 20). Ringler et al. (45) concluded that arousal itself contributed to the blood pressure surges after airway occlusion, because apneas induced during sleep elicited a much larger blood pressure response than those induced during wakefulness. In addition, Trinder et al. (49) found that sleep-related respiratory stimuli may not be necessary for the cardiovascular response to occur. These authors found that the large heart rate and blood pressure responses to spontaneous arousals were still present in individuals breathing passively on a ventilator.

Conclusion. This study does not support the hypothesis that stimulation of the UA mechanoreceptors interacts with the arousal-related sympathetic outflow to augment the accompanying cardiovascular response. Whether the increased cardiovascular response to arousal from sleep at the termination of an apnea is due to increasing negative intrathoracic pressure, stimulation of the pulmonary stretch receptors or central activation of autonomic centers requires further investigation.

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REFERENCES


