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Ventilatory Response to Induced Auditory Arousals During NREM Sleep

M. Safwan Badr, Barbara J. Morgan, Laurel Finn, Fredy S. Toiber, David C. Crabtree, Dominic S. Puleo and James B. Skatrud

Medical Service, William S. Middleton Memorial Veterans Hospital, Departments of Medicine and Kinesiology, University of Wisconsin Medical School, Madison, Wisconsin, U.S.A.

Summary: Sleep state instability is a potential mechanism of central apnea/hypopnea during non-rapid eye movement (NREM) sleep. To investigate this postulate, we induced brief arousals by delivering transient (0.5 second) auditory stimuli during stable NREM sleep in eight normal subjects. Arousal was determined according to American Sleep Disorders Association (ASDA) criteria. A total of 96 trials were conducted; 59 resulted in cortical arousal and 37 did not result in arousal. In trials associated with arousal, minute ventilation ($\dot{V}_E$) increased from 5.1 ± 1.24 minutes to 7.5 ± 2.24 minutes on the first posttone breath ($p = 0.001$). However, no subsequent hypopnea or apnea occurred as $\dot{V}_E$ decreased gradually to 4.8 ± 1.5 l/minute ($p > 0.05$) on the fifth posttone breath. Trials without arousal did not result in hyperpnea on the first breath nor subsequent hypopnea. We conclude that 1) auditory stimulation resulted in transient hyperpnea only if associated with cortical arousal; 2) hypopnea or apnea did not occur following arousal-induced hyperpnea in normal subjects; 3) interaction with fluctuating chemical stimuli or upper airway resistance may be required for arousals to cause sleep-disordered breathing. **Key Words:** Arousal—Sleep discontinuity—NREM sleep.

Apneas and hypopneas are common during sleep even in otherwise healthy individuals (1). Apnea rarely occurs as a single event; instead, repetitive cycles of apnea and hypopnea alternate with hyperpnea and are often accompanied by transient electroencephalographic (EEG) signs of arousal. The hyperpnea associated with arousal is thought to contribute to the subsequent apnea or hypopnea (2) via hypocapnia (3) or volume-mediated inhibition of ventilatory motor output (4). Thus, transient arousal may be a key factor in perpetuating breathing instability during sleep. The sequence of arousal-hyperpnea-hypocapnic inhibition of ventilatory motor output has been proposed as a primary mechanism for breathing instability in older adults (5) and for periodic breathing at sleep onset (6). However, there are both clinical and empiric concerns about this postulate. For example, there is no evidence that individuals with repetitive nonrespiratory-mediated arousal, such as patients with periodic leg movements during sleep, develop apnea or hypopnea during sleep following leg movements. Furthermore, induction of posthyperventilation apnea during non-rapid eye movement (NREM) sleep requires sustained (3–5 minutes) hyperpnea with hypoxia (7) or prolonged nasal mechanical ventilation (3,8). In contrast, termination of brief (1 minute) nasal mechanical hyperventilation is associated with hypopnea and not apnea, even when $P_{ET}CO_2$ is reduced by 4 mmHg or more (9). Likewise, transient hypoxic hyperpnea for 30 seconds is not followed by apnea or hypopnea (7). The key question is whether arousal-associated hyperpnea is of sufficient magnitude and duration to induce subsequent inhibition of ventilatory motor output and hence apnea or hypopnea. The present study investigated the ability of transient, auditory-induced arousals to cause sufficient hyperpnea to result in subsequent apnea or hypopnea.

METHODS

Subjects

Six men and two women, aged 32 < 6 [standard deviation (SD)] years with a body mass index of 25.4 < 3.1 (SD) kg/m^2, were studied. All subjects were healthy nonsnorers with no evidence of excessive daytime sleepiness. All subjects provided informed consent. The experimental protocol was approved by the University of Wisconsin Center for Health Sciences

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Address correspondence and reprint requests to M. Safwan Badr, M.D., Veterans Administration Medical Center, Pulmonary Section (111A), 4646 John R, Detroit, MI 48201, U.S.A.

Human Subjects Committee. All studies were performed with the subject lying supine in a quiet, darkened laboratory between 2300 and 0330 hours. Subjects were asked to restrict their sleep to 6 hours or less on the previous night.

Measurements

Tidal volume (V_T) was measured by inductance plethysmography (Respitrace, Ambulatory Monitoring, Ardsley, NY) rather than by a pneumotach to ensure unencumbered sleep. The inductance plethysmography output was calibrated by the isovolume technique of Konno and Mead (10) in conjunction with a rolling seal spirometer (Ohio 800, Ohio Instruments, Madison, WI). Respiratory cycle timing was measured using the inductance plethysmograph signal. Electroencephalogram (EEG) was recorded using two leads (C_4/A_1 and O_1/A_2); chin electromyogram (EMG) and electrooculogram (EOG) were also recorded. Sleep staging and identification of K complexes were performed according to conventional scoring criteria (11). Additional neurocirculatory measurements were performed, including peroneal nerve microneurography and impedance cardiography, as part of a concurrent protocol reported separately (12).

Auditory stimuli

A computer-generated tone (1,000 Hz, 0.5 second) was input to an audio amplifier for loudness modulation. The amplified signal drove a 2-inch diameter audio speaker, which was positioned 15 cm above the forehead of the supine subject. A sound level meter placed 25 cm from the speaker was used to calibrate the gain control on the amplifier so that a range of audio stimuli at 45–85 dB was produced. The first trial was at 45 dB, if no arousal was induced; the next trial was at 68 or 85 dB, which was kept constant.

Experimental protocol

An auditory stimulus was delivered during stable NREM sleep (stages 2–4); no trials were performed during stage 1 given the intrinsic instability of stage 1 sleep. Slow-wave sleep was achieved by only two subjects. The tone was delivered only during inspiration, and the corresponding breath was designated as breath 0. The auditory signals were presented in order of ascending intensity because we were concerned that the more intense stimuli would interfere with the subject's ability to return to sleep. A minimum of 45 seconds of stable sleep was required prior to delivering the next tone.

TABLE 1. *Summary of number of auditory arousal trials and classifications per subject*

Subject no.	Arousal A	Arousal B	No arousal	Total
1	1	2	2	5
2	2	5	0	7
3	7	1	22	30
4	5	0	0	5
5	9	6	0	15
6	3	5	2	10
7	3	1	1	5
8	7	2	10	19
Total	37	22	37	96

Data analysis

The response to the auditory stimulus was classified as *arousal* or *no arousal*; an arousal was defined according to the American Sleep Disorders Association (13) definition as an abrupt shift in EEG frequency lasting at least 3 seconds. Arousals were then graded according to the presence or absence of chin EMG activation (14); grade A arousal occurred if isolated EEG change was present, and grade B arousal was defined by the increased EEG frequency and the activation of chin EMG. Classification of each evoked arousal was determined independently by two observers. In cases of disagreement, a third observer was consulted to achieve consensus.

The total number of auditory stimulus trials and classifications varied between subjects. Table 1 gives a breakdown of the trials for each individual as well as the overall totals.

The results of all trials for a given subject and for each arousal type were averaged, and the mean value was used in computation of group mean values. Thus, arousal grade A occurred in eight subjects, arousal grade B occurred in seven subjects, and no arousal occurred in five subjects. The control period consisted of the average of five breaths preceding the auditory stimulus. The breath corresponding to the tone was designated as breath 0 and was excluded from the analysis. The posttone period was analyzed on a breath-by-breath basis.

A two-way repeated measures analysis of variance (ANOVA) was used to investigate the effects of arousal type, breath effect, and the interaction of the two. This analysis used only subjects having both arousal type trials, hence allowing self-comparison of each subject. Because of the repeated measures in this data, a Huynh-Feldt adjustment was made to the degrees of freedom, which corrected for the loss of independence of the observations due to the correlation among them. The two-way repeated measures ANOVA revealed significant interactions between arousal type and breath effect. This implied that the effect of breath over time was not the same for each arousal type. Because of

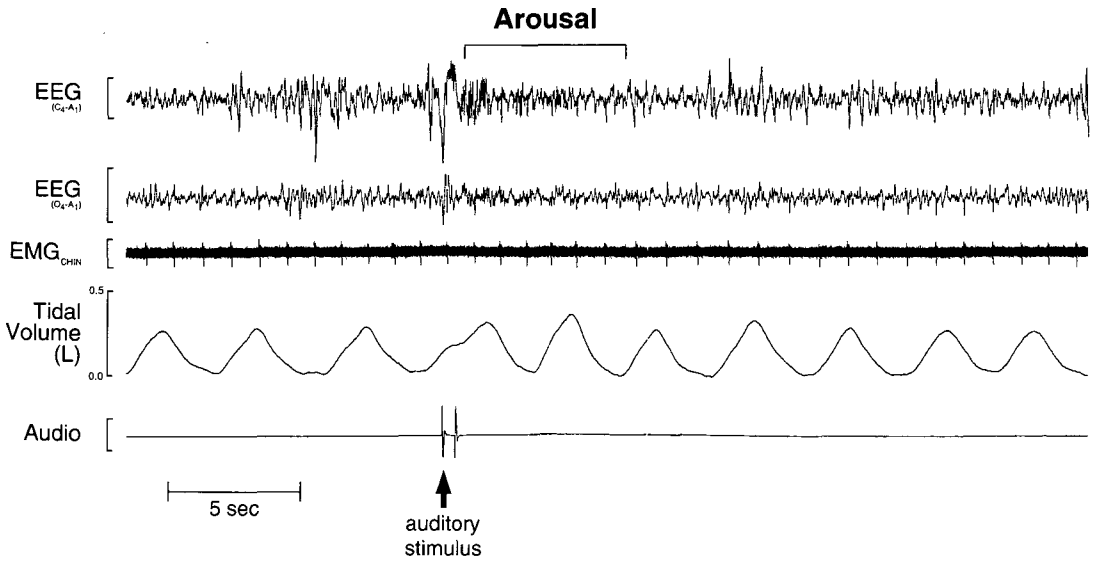

FIG. 1. Polygraph record showing grade A arousal. Electroencephalogram (EEG), chin electromyogram (EMG), surface chin EMG. Note the increased EEG frequency without change in chin EMG. Also note the mild hyperpnea without subsequent hypopnea.

this interaction, a repeated measures one-way stratified analysis was deemed appropriate to assess the effect of breath within each arousal type. In addition, a one-way ANOVA allowed us to use all subjects and not just subjects who experienced both arousal type trials. Huynh-Feldt adjustments were made for each one-way ANOVA as well. If the overall one-way Huynh-Feldt adjusted test for a breath effect was significant, each breath was then compared to the control breath using paired *t* tests. To further characterize the effect of acoustic stimulation on respiration, we tested whether arousal per se predicted the occurrence of hyperpnea after the stimulus. To this end, we defined hyperpnea as peaks $\dot{V}_E$ exceeding 125% of control during the poststimuli period. A two-by-two contingency table was constructed with arousal/no arousal as the independent variables and hyperpnea/no hyperpnea as the dependent variables.

RESULTS

NREM sleep resulted in significant changes in ventilation compared to wakefulness. Minute ventilation ($\dot{V}_E$) decreased from 6.7 ± 0.7 l/minute during wakefulness to 5.1 ± 0.4 l/minute ($p = 0.05$), primarily because tidal volume (V_T) decreased from 0.44 ± 0.05 l to 0.36 ± 0.04 l ($p = 0.05$). Breathing frequency (F) also decreased, albeit not to a statistically significant level, from 15.6 ± 1.1 to 14.2 ± 1.0 breath/minute ($p = 0.08$). There was no significant change in inspiratory time (T_I) or expiratory time (T_E) from wakefulness to NREM sleep.

A total of 96 auditory stimulation trials were conducted; 59 resulted in cortical arousal (37 grade A and 22 grade B), and 37 were not associated with cortical arousal. In trials associated with arousal, a typical EEG response consisted of a K-complex or high-voltage activity immediately after the tone, followed by abrupt increase in EEG frequency. Figure 1 is an example of a trial with grade A arousal (without chin EMG recruitment). Note the occurrence of a K-complex, increased EEG frequency, increased respiratory frequency, and the slightly increased V_T following the tone; also note the return to sleep, the return of V_T to prestimulus control, and the absence of sustained hypopnea. Figure 2 is an example of grade B arousal. Note the recruitment of chin EMG, the immediate increase in F, and the absence of hypopnea in the recovery period. Group data for all trials associated with arousal are shown in Fig. 3 for $\dot{V}_E$, V_T, and F (closed circles). $\dot{V}_E$ increased immediately, reaching a peak on the first posttone breath from a control value of 5.1 ± 1.2 l/minute to 7.5 ± 2.2 l/minute (148% of control, range 75–400%, $p < 0.01$), primarily because V_T increased from 0.36 ± 0.12 l to 0.49 ± 0.15 l (136% of control, $p < 0.01$) and F increased (14.4 ± 2.8 breaths/minute to 15.8 ± 2.3 breaths/minute, $p < 0.01$). The peak values reached on the first posttone breath were not statistically different from awake values. Gradual decline in $\dot{V}_E$ was noted following the peak breath reaching a nadir $\dot{V}_E$ of 4.8 ± 1.5 l/minute (94% of control, $p > 0.05$) and a nadir V_T of 0.34 ± 0.13l (94% of control, $p > 0.05$).

Contrary to auditory stimulation with arousal, no hyperpnea was noted in trials without evidence of cortical arousal. Typically, no EEG change was noted,

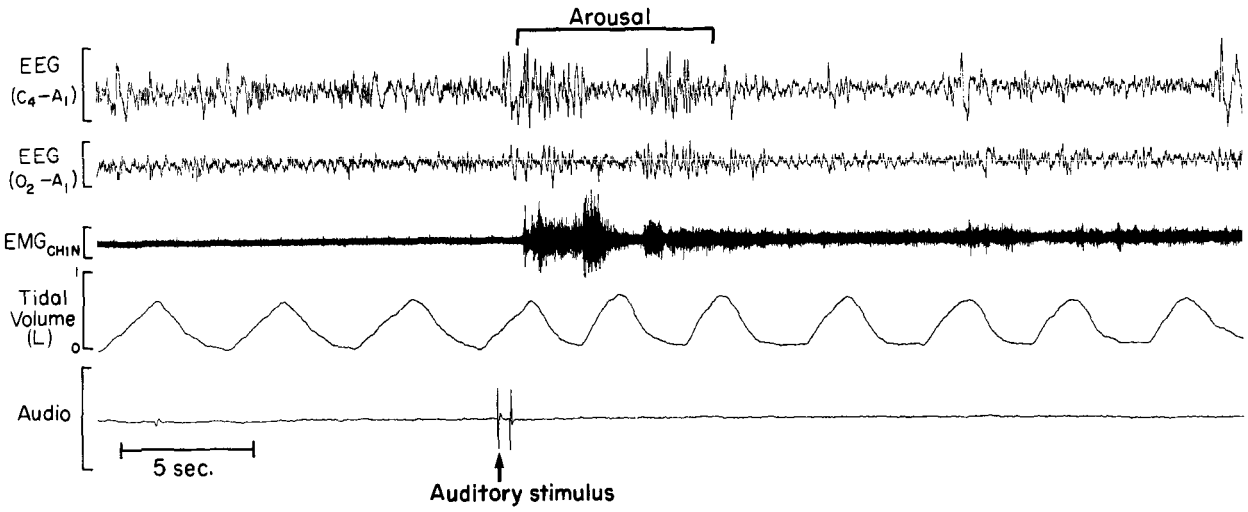

FIG. 2. Polygraph record showing grade B arousal. For abbreviations, see Fig. 1. Note the augmentation of chin EMG with the occurrence of arousal.

including the absence of K-complex. A representative example is shown in Fig. 4; note the absence of any change in EEG, chin EMG, or ventilation following auditory tone. Group data are shown in Fig. 3 (no arousal = open circles). Note the negligible increase in ventilation as $\dot{V}_E$ reached 105 and 109% of control on posttone breaths one and two, respectively ($p > 0.05$). When arousal and no arousal were compared in two-by-two contingency table analysis, arousal was associated with hyperpnea and no arousal with the absence of hyperpnea (defined as $\dot{V}_E$ exceeding 125% of control; $p = 0.001$). In addition, no hypopnea was noted as the subsequent nadir was 90% of control ($p > 0.05$). Thus, auditory stimulation without arousal was not associated with hyperpnea or subsequent hypopnea.

To ascertain whether sleep state influenced the response to auditory stimulation, we repeated the analysis using trials conducted during stage 2 NREM sleep only. Table 2 shows $\dot{V}_E$, V_T, and F for the control breath and six postauditory stimulus breaths. Note that $\dot{V}_E$, V_T, and F increased after the stimulus in trials associated with arousal only. No poststimulus hyperpnea was noted in trials with no arousals. Likewise, no hypopnea occurred regardless of the occurrence of arousal. Thus, the response in stage 2 NREM sleep was similar to the overall response.

To ascertain a potential relationship between the grade of EEG response and postarousal ventilation, we separated trials with grade A and grade B arousal as shown in Fig. 5. Note that the postarousal $\dot{V}_E$ was higher than control, in both grades of arousal, but did not decrease below control in either grade. Thus, more pronounced hyperpnea noted in grade B arousal did not cause a subsequent hypopnea.

DISCUSSION

The major findings of our study are as follows: 1) auditory stimulation resulted in transient hyperpnea only if associated with arousal, and 2) hypopnea or apnea did not occur following arousal-induced hyperpnea in normal subjects.

Limitation of methods

Several factors should be considered for proper interpretation of our data. First, our experimental apparatus did not allow detection of changes in $P_{ET}CO_2$ because no mask was used to minimize instrumentation. However, even if $P_{ET}CO_2$ had been measured, the measurement may not have accurately reflected chemoreceptor PCO_2, given the transient nature of arousal-associated hyperpnea (15). Although our conclusions are not affected by the lack of data on the magnitude of hypocapnia, we are limited in our ability to define the mechanisms underlying the absence of hypopnea in the recovery period. Second, our findings are critically dependent on the accuracy of noninvasive measurement of ventilation using respiratory inductance plethysmography (RIP). To ensure accurate detection of the relative changes, the device was meticulously calibrated and the subjects slept in the supine position throughout the experiment. In addition, we have previously shown accurate representation of ventilatory data when V_T obtained from RIP was compared to the simultaneously obtained measurements using a pneumotachometer. Thus, we are confident in the accuracy of the detected ventilatory changes. Finally, auditory stimulation is a contrived intervention that may not faithfully simulate either spontaneously

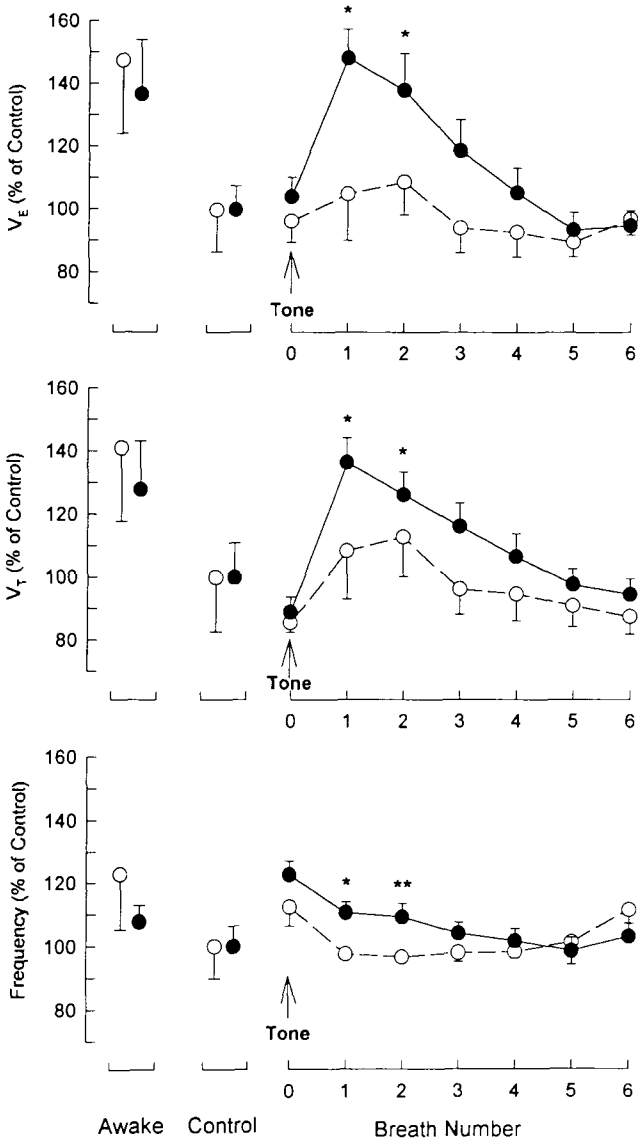

FIG. 3. Group data showing breath-by-breath response to auditory stimulus as percent of non-rapid eye movement (NREM) control. Closed circles, trials with arousal; open circles, trials without arousal. $\dot{V}_E$, minute ventilation; V_T, tidal volume; F, respiratory frequency; asterisk (*) indicates a statistically significant difference from control at $p < 0.01$; double asterisk (**) indicates statistically significant difference at $p < 0.05$. Note the increase in $\dot{V}_E$ and V_T in trials associated with arousal only. Also note the absence of hypopnea regardless of whether arousal occurred.

occurring or respiratory-related arousals. However, arousals occurring upon termination of apnea or hypopnea are not "pure" given the confounding contribution of asphyxia and relief of upper airway obstruction. Furthermore, we found that auditory stimulation had no effect on ventilation unless accompanied by arousal, which argues for arousal and not the auditory stimulation per se, as the cause of observed ventilatory changes. Thus, we believe that auditory arousals are appropriate tools to study the independent effect of cortical arousal on ventilation.

Immediate consequences of arousals

We noted that the presence of arousal predicted the occurrence of hyperpnea following the auditory stimulus; in the majority of trials, no hyperpnea was noted without cortical arousal. Our data corroborate previous studies, which have shown that induced auditory arousals result in increased ventilation and recruitment of upper airway dilating muscles (16) and in shortening of apnea length in patients with sleep apnea (17). Conversely, hyperpnea due to induced arousals was mild (150% of eupnea), in contrast to the pronounced hyperpnea noted by Xie et al. (14) when arousal occurred coincident with termination of central apnea as peak $\dot{V}_E$ increased above 200% of control upon termination of central apnea, regardless of the occurrence of arousal (14). This is not surprising if we consider the overlapping stimuli immediately prior to termination of apnea including asphyxia and upper airway narrowing/occlusion (18).

Alternatively, arousal following apnea may be a consequence rather than a cause of hyperpnea. Support for this notion comes from studies showing that arousal occurred when hyperpnea was induced with hypercapnia or adenosine infusion (19), resulting in arousal at the same $\dot{V}_E$, regardless of the modality of hyperpnea. Hyperpnea-induced arousal may be due to augmented respiratory effort (20). In conclusion, hyperpnea upon induced arousal is generally mild, which may explain the minimal occurrence of subsequent inhibition of ventilatory motor output (see below).

We were intrigued by the discrepancy between the findings of our study and those of other investigators who have found that EEG arousal is not a prerequisite for postauditory stimulation hyperpnea. Carley et al. (21) found that auditory stimulation was associated with hyperpnea even in the absence of electrocortical arousal. Likewise, Basner et al. (17) found that auditory stimulation may terminate an obstructive apnea even if arousal does not occur. The reasons for the difference in findings is not clear. The only apparent methodological difference is the timing of the stimulus; we delivered the tone during inspiration only, whereas the other two studies did not attempt to control for the timing of the tone. Nevertheless, our data agree with the other two studies insofar as there is a clear difference in the magnitude of ventilatory response between trials associated with arousals versus no arousal.

The lack of hyperpnea when auditory stimulation did not induce cortical arousal is in contrast with our findings on the neurocirculatory response to auditory stimulation. In the same group of subjects (12), auditory stimulation increased blood pressure and heart rate, even when cortical arousals were not present. The

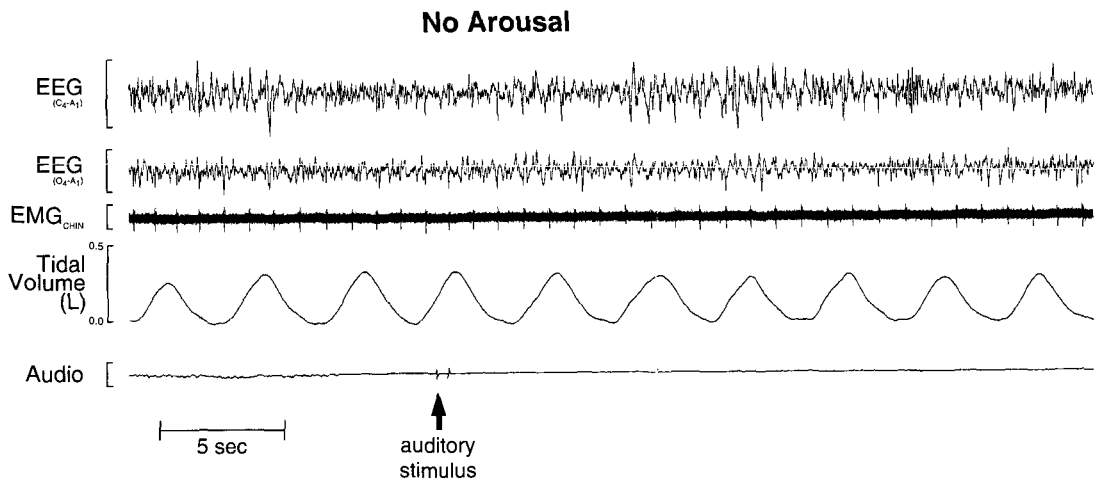

FIG. 4. Polygraph record showing auditory stimulus not followed by arousal. Note the lack of change in ventilation. For abbreviations, see Fig. 1.

noted cardiovascular response to auditory stimulation, without EEG change, is often referred to as a subcortical or autonomic arousal. Our present study suggests that "autonomic" arousals may occur without a ventilatory component. The discrepancy between cardiovascular and respiratory responses to auditory stimulation is intriguing and cannot be readily explained by our data. Nevertheless, we interpret our findings as an indication of a hierarchical arousal response. Thus, neurocirculatory responses occur at lower intensity stimulation than do ventilatory responses, which may be closely linked to cortical arousals. The presence and importance of such a postulated hierarchy remains uncertain.

Is cortical arousal a cause of hypopnea?

We considered several possibilities to explain the rarity of apnea or hypopnea following induced auditory arousals. First, several studies have shown that brief hyperpnea during sleep does not cause significant ventilatory inhibition. We have previously shown that brief hypoxic hyperpnea (15–30 seconds) with peak $\dot{V}_E$ of 150% was not followed by hypopnea, despite hypocapnia ranging between 2–3 mmHg (7). Likewise, central apnea rarely occurred upon termination of 1 minute of mechanical ventilation even when $P_{ET}CO_2$ decreased by 4–6 mmHg (9). Similarly, Gleeson et al. demonstrated that apnea rarely occurred following release of induced brief upper airway obstruction in sleeping humans despite hypocapnia as low as 9 mmHg (22). It is likely that the brief duration of arousal-associated hyperpnea in our study was insufficient to decrease chemoreceptor PCO_2 and hence was insufficient for hypopnea to occur.

The preservation of ventilatory motor output following arousal-associated hyperpnea could also be explained by the activation of short-term potentiation. It is known that actively induced hyperpnea (as in our study) is associated with a central nervous system phenomenon referred to as "short-term potentiation", which augments ventilatory motor output for a given stimulus. Cessation of the stimulus leaves behind a trailing excitatory effect, referred to as "after-dis-

TABLE 2. *Effect of auditory stimulation during stage 2 NREM sleep on ventilation*

	$\dot{V}_E$ (l/minute) Mean (% of control)		V_T (l) Mean (% of control)		F (breath/minute) Mean (% of control)	
Poststimulus breath no.	No arousal (n = 5)	Arousal (n = 8)	No arousal	Arousal	No arousal	Arousal
Control	4.57 (100)	5.02 (100)	0.33 (100)	0.34 (100)	14.3 (100)	14.5 (100)
1	4.14 (91)	7.39 (147)[a]	0.31 (94)	0.48 (141)[a]	13.8 (97)	15.8 (109)[a]
2	4.79 (105)	6.95 (138)[a]	0.37 (112)	0.45 (132)[a]	13.7 (96)	15.7 (108)
3	4.11 (90)	6.00 (120)	0.31 (94)	0.41 (121)	13.6 (95)	15.0 (103)
4	4.10 (90)	5.38 (107)	0.31 (94)	0.38 (112)	13.9 (97)	14.6 (101)
5	4.22 (92)	4.75 (95)	0.31 (94)	0.35 (103)	14.3 (100)	14.1 (97)
6	4.21 (92)	4.77 (95)	0.28 (85)	0.34 (100)	15.5 (108)	14.8 (102)

NREM, non-rapid eye movement; $\dot{V}_E$, minute ventilation; V_T, tidal volume; F, breathing frequency.
Values are mean ± SD. Numbers in parentheses are normalized relative to control.
[a] Breath is significantly different from control ($p < 0.05$).

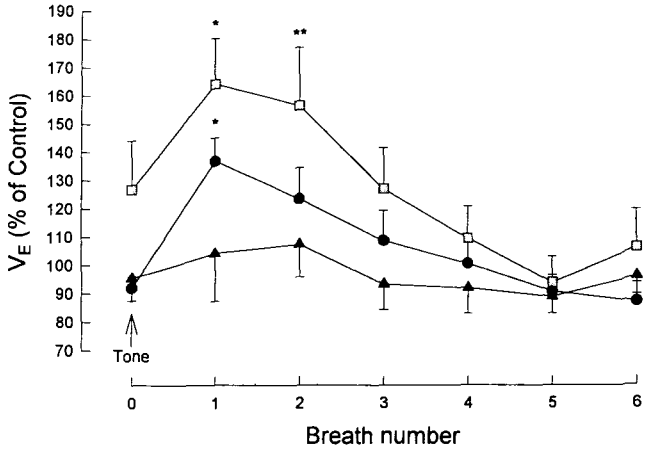

FIG. 5. Group data showing breath-by-breath $\dot{V}_E$ change following auditory stimulation in arousal grades A and B. Values are expressed as percent of control. Closed triangle, no arousal; closed circle, grade A arousal; closed square, grade B arousal; asterisk (*) indicates statistically significant difference from control at $p < 0.01$; double asterisk (**) indicates statistically significant difference from control at $p < 0.05$.

charge", manifested as posthyperventilation hyperpnea despite hypocapnia (7,23,24). Previous studies showing posthyperventilation apnea in humans used sustained passive hyperventilation, which does not activate short-term potentiation (3,8), or sustained hypoxia, which is thought to abolish short-term potentiation (7). Thus, the lack of significant hypopnea in the recovery period may be explained by the brief duration of hyperpnea and/or the activation of short-term potentiation. The relative contribution of each mechanism cannot be determined from our data.

The lack of apnea or hypopnea following arousal-induced hyperpnea suggests that transient arousals alone do not explain the pathogenesis of sleep-disordered breathing in older adults, periodic breathing at sleep onset, or idiopathic central sleep apnea syndrome. However, the results of our study may not be readily applicable to clinical conditions associated with central sleep apnea. Specifically, hypocapnia secondary to chronic hyperventilation (14) is common in patients with idiopathic central sleep apnea syndrome, and hence they are closer to the apneic threshold, even following modest hyperventilation. Furthermore, short-term potentiation may be abolished by repetitive or chronic hypoxia (7), leaving unmitigated hypocapnic inhibition as the main influence on ventilatory motor output following transient arousals. In addition, we cannot exclude the possibility that frequent, repetitive arousals may trigger periodic breathing by recurrent hyperpnea and hypocapnia. This possibility is purely speculative at the present time. Thus, caution is mandated when extrapolating the findings of our study to patients with sleep apnea who may be more susceptible than normal subjects to the development of apnea/hypopnea following transient arousals. Nevertheless, our data indicate that arousal alone is insufficient to initiate apnea or hypopnea unless other factors amplify the magnitude of hyperpnea (e.g. upper airway obstruction or asphyxia), prolong the hyperpnea (e.g. longer arousals), or impair excitatory mechanisms (e.g. the impairment of short-term potentiation with sustained hypoxia).

In summary, we have shown that cortical arousals induced by auditory stimulation are associated by transient hyperpnea but do not lead to hypopnea or apnea in the recovery period. Thus, repetitive arousal is insufficient to cause sleep-disordered breathing unless aided by the interaction with fluctuating chemical stimuli or upper airway resistance.

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