Arousal responses to added inspiratory resistance during REM and non-REM sleep in normal subjects

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Abstract

Background **Arousal in response to increased airflow resistance during sleep, especially rapid eye movement sleep (REM), could be an important protective mechanism against asphyxia.**

Methods **The arousal response to the application of an external inspiratory resistance of 25 cm H_2O/l/s was determined during REM and non-REM sleep in ten healthy men.**

Results **The number of arousals occurring within two minutes of the load application was significantly higher during REM sleep than during either of the non-REM sleep stages 2 and 3/4, and was similar to that during stage 1. The proportion of arousals to non-arousals decreased significantly from stage 1 to stage 4. The mean time to arousal in REM was significantly shorter than in non-REM stages 1, 2 or 3/4 and increased significantly from stage 1 to stage 3/4. The duration of sleep (comparing the results of the first with the second half of the sleep period time) did not modify the arousal response in stages 2 and 3/4.**

Conclusions **The results show a significantly increased arousal response to an added inspiratory resistive load in REM sleep compared with non-REM sleep stages 2, 3 or 4 in normal men. In the context of previous studies these data could add support to the hypothesis that the decreased arousal response during REM sleep in patients with sleep apnoea might be due to an impairment of the normal "central processing" of this stimulus.**

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Airways resistance increases during sleep in normal subjects, mainly as a result of narrowing of the upper airways.[1] In patients with obstructive sleep apnoea upper airway narrowing may be severe, and complete occlusion may occur. In asthmatic patients, total airway resistance increases because of bronchoconstriction and upper airway narrowing. Arousal in response to increased airflow resistance would be a beneficial protective mechanism. In patients with obstructive sleep apnoea, breathing abnormalities are known to be worst during rapid eye movement (REM) sleep.[2–4] Arousal as a response to increased airflow resistance in REM sleep has not been adequately assessed. The arousal response to inspiratory resistive loading in normal subjects has been shown to be lowest during sleep stage 3/4.[5] Asthmatics were found to waken less frequently with wheeze during stage 3/4,[6 7] although this was not confirmed in another study.[8] There is also evidence that asthmatic bronchoconstriction increases throughout the night and reaches its maximum towards the end of the night.[9] Whether the arousal response to increased airflow resistance changes throughout the night, and whether a decreased arousal response might be dangerous or potentially helpful, has not been determined.

This study was designed to investigate whether an added inspiratory resistance of 25 cm H_2O/l/s caused any differences in the arousal response and the time to arousal between REM sleep and stages 1–4 non-REM sleep. Furthermore, we investigated whether there is a difference in the arousal response to resistive loading between non-REM sleep during the first and second halves of the sleep period.

Methods

SUBJECTS

We studied 10 normal men aged 22–29 (mean 25·3) years. None of the subjects was obese or taking any medication (or alcohol the day before the study) or had any sleep complaints. Each subject was a regular nocturnal sleeper. The subjects gave informed consent to the study, which had the prior approval of the local ethical committee.

SLEEP STUDIES

All studies were performed between 22·00 hours and 7·00 hours. Data collection was performed in a quiet, purpose built sleep laboratory after recording equipment was attached. All measurements were recorded on a 20-channel Van Gogh polygraph. Sleep was monitored with standard silver electrodes recording electroencephalographic, electrooculographic and electromyographic signals.[10] Sleep stage was determined by standard criteria[11] with 30 second epochs. All studies were conducted with a sealed face mask (Speakeasy, Respironics Inc, Murrysville,

Pennsylvania) with built in inspiratory and expiratory valves. Before the study, all subjects wore the face mask during sleep at home for adaptation. The mask dead space was approximately 50–70 ml depending on individual facial configuration. A leak detector was attached to the circumference of the face mask cushion, consisting of a perforated polyethylene catheter connected to a CO_2 analyser set at maximum gain[12] which detects an expiratory leak of 1·2% ventilation (no subject had a beard). Resistive loading was accomplished by the addition of a 25 cm H_2O/l/s linear resistive load to the inspiratory line by turning a three way tap. Care was taken that the tap was turned only during expiration to avoid disruption of the breathing cycle. Turning the tap was absolutely silent. While manipulations were undertaken, scrupulous attention was paid to avoiding any noise or contact capable of disturbing sleep. Both the tap and the observer were in a different room from the subject. The resistance was not applied until the subject had slept for at least 10 minutes. Thereafter the load was applied every two to four minutes, but was not reapplied for at least two minutes after spontaneously occurring arousals or sleep stage changes. When the subject had an arousal or awakening during the resistive breathing, the resistance was switched off and not reapplied until the subject had slept for at least two minutes. An arousal was defined as an episode lasting 1·5 seconds or longer in which there was a return of alpha or theta activity associated with unequivocally increased electromyographic activity.[3,5] When no arousal or awakening occurred, the resistance was switched off after two minutes and again not reapplied for at least two minutes. Switching the resistance on or off was recorded with an event marker on the polygraph.

DATA ANALYSIS AND STATISTICS

The results are presented as mean (SD). The numbers of arousals and non-arousals were compared in the different sleep stages and in the first and the second half of the sleep period with χ^2 and heterogeneity tests (tests of independence: two way tables).

The time to arousal and the individual arousal frequencies between the different sleep stages were compared by analysis of variance and a Tukey post hoc test.

Results

The ten subjects were awake for 17·1 (9·9)% of a mean sleep period time of 6·48 (0·4) hours. Of the mean total sleep time of 5·39 (0·7) hours, 20·1 (11·6)% was stage 1, 46·7 (8·6)% stage 2, 10·4 (4·5)% stage 3, 12·5 (7·4)% stage 4 and 9·4 (5·4)% stage REM. Every subject reached stage REM and the mean (SD) time spent in REM was 31 (20·8) minutes.

AROUSAL FREQUENCY

Pooled data Comparing the number of times that arousal occurred within two minutes of the application of the inspiratory resistance with the number of non-arousals between all five stages together showed that there were significant differences between the stages ($p < 0·001$). There was a significantly higher number of arousals from stage REM (96 (91%) arousals, nine non-arousals) than from either stage 2 (82 (45%) arousals, 99 non-arousals; $p < 0·001$), stage 3 (13 (22%) arousals, 47 non-arousals; $p < 0·001$) or stage 4 (eight (10%) arousals, 69 non-arousals; $p < 0·001$) (fig 1). The proportions of arousals and non-arousals in stage REM (96 (91%) arousals, nine non-arousals) and stage 1 (38 (88%) arousals, five non-arousals) were similar (fig 1).

The percentage of arousals (as a percentage of total number of tests) decreased significantly from stage 1 to stages 2, 3 and 4, and from stage 2 to stages 3 and 4 ($p < 0·001$) (fig 1). The difference between stages 3 and 4 was not significant.

INDIVIDUAL DATA

In order to check the pooled data for any possible bias caused by doing a disproportionate number of tests in each subject in each sleep stage, we also looked at the individual arousal frequencies in each sleep stage (table). This analysis resulted in a loss of significance of

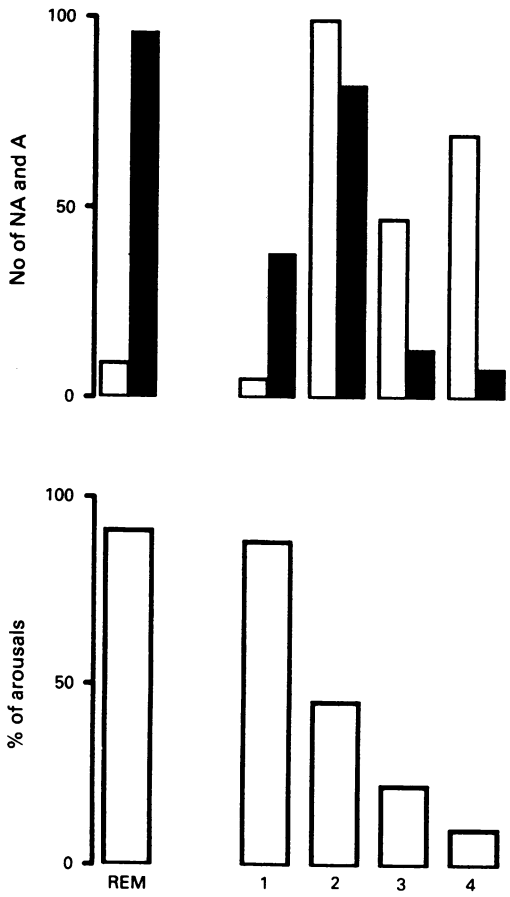

Figure 1 Upper panel: Number of non-arousals (open bars) and arousals (black bars) within two minutes of application of an inspiratory resistive load in each sleep stage. Lower panel: Arousals within two minutes of inspiratory loading as percentage of the total number of tests performed in each sleep stage. NA—non-arousal; A—arousal; REM—rapid eye movement sleep; 1, 2, 3, 4—non-REM sleep stages.

Arousals as percentage of total number of tests for each subject in each sleep stage

	Stage				
Subject	*1*	*2*	*3*	*4*	*REM*
1	50	60	0	25	100
2	100	24	33	0	100
3	86	35	29	0	34
4	83	74	57	33	83
5	92	33	25		100
6	100	45	11	17	75
7	100	44	0	11	100
8	100	53	75	25	75
9	100	42	13	0	94
10	50	42	0	13	96
Mean	86·1	44·4	24·3	13·8	85·7
SD	20·0	14·7	25·4	12·3	20·8

REM—Rapid eye movement sleep.

the difference between stages 2 and 3, indicating no relevant effect of amalgamating the data from all ten subjects.

The mean (SD) time to arousal within two minutes of application of the inspiratory resistance was 34 (35) seconds in stage 1, 46 (30) seconds in stage 2, 59 (35) seconds in stage 3/4 and 29 (30) seconds in stage REM. The levels of significance of the differences are shown in fig 2. (As only a few arousals occurred in stages 3 and 4 and these stages tend to intermingle, the data from stages 3 and 4 were amalgamated for this analysis and the analysis below.)

In stage 2 there were 40 arousals and 41 non-arousals in the first half of the sleep period, and 41 arousals and 59 non-arousals during the second half ($p = 0{\cdot}196$); in stage 3/4 there were 16 arousals and 83 non-arousals in the first half of the sleep period, and five arousals and 33 non-arousals in the second half ($p = 0{\cdot}662$) (fig 3).

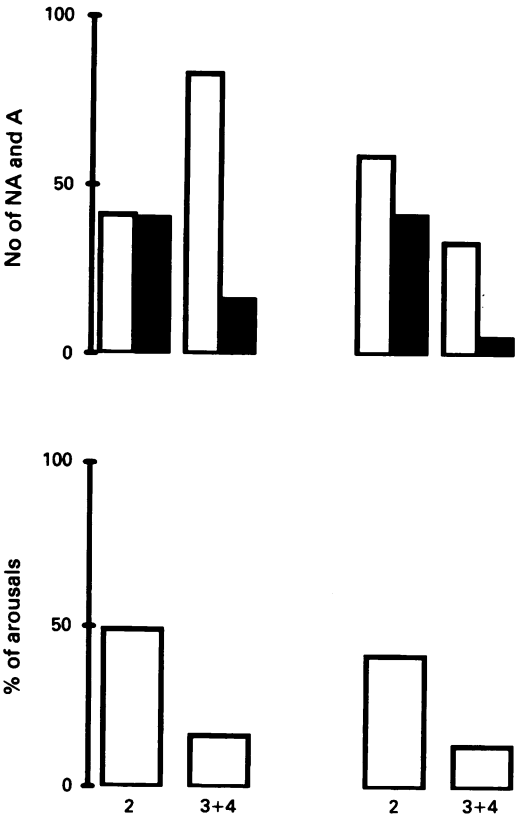

Figure 3 Upper panel: Number of non-arousals (open bars) and arousals (black bars) within two minutes of application of an inspiratory resistive load during the first (left side) and second half (right side) of the sleep period time. Lower panel: Arousals within two minutes of inspiratory loading as percentage of the total number of tests performed during the first (left side) and second half (right side) of the sleep period time. NA—non-arousal; A—arousal; 2, 3/4—non-REM sleep stages; 1st—first half of the sleep period time; 2nd—second half of the sleep period time.

Discussion

The aim of this study was to investigate the arousal response to resistive loaded breathing in REM sleep and to determine whether the arousal response to inspiratory loading is modified by duration of sleep.

The main findings of this study were that (1) the arousal response during REM sleep was significantly higher than in non-REM sleep stages 2, 3 or 4 (fig 1); (2) the arousal response decreased significantly from stage 1 to stage 2, from stage 1 to 3/4, and from stage 2 to 4 (fig 1); (3) the time to arousal was significantly shorter during REM sleep than during stage 2 or stage 3/4 (fig 2); (4) the time to arousal increased significantly from stage 1 to stage 3/4 (fig 2); (5) in stage 2 and stage 3/4 sleep there was no difference in the arousal response when the results obtained from the first half of the sleep period time were compared with those obtained during the second half (fig 3).

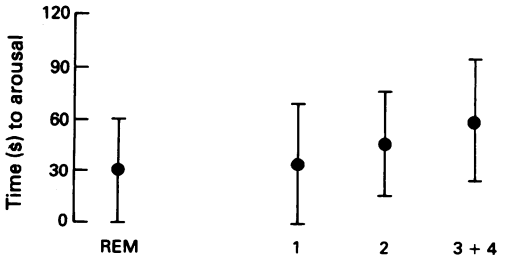

Figure 2 Mean (SD) time to arousal after application of an inspiratory resistive load in each sleep stage. The difference was significant between REM and stage 2 ($p < 0{\cdot}005$), REM and stage 3/4 ($p < 0{\cdot}001$) and stage 1 and stage 3/4 ($p < 0{\cdot}002$). REM—rapid eye movement sleep; 1, 2, 3/4—non-REM sleep stages.

As the sleep disturbing effects of equipment often impair data collection, particularly during REM sleep, the instrumentation was restricted to the minimum required for investigating the questions outlined in the introduction. We used only a single level of resistance to get comparable data in the different sleep stages. To reduce the sleep disturbing effect of the tests we did not use complete occlusion of the inspiratory airflow. Although we realised that the response might be affected by both resistive loading itself and also the speed of deterioration in blood gases as a result of loading in non-REM and REM sleep, blood gases were not measured in this study.

Since sleep stages are not evenly distributed throughout the night (REM sleep mainly occurring in the early morning), and because of the number of tests in stage 1, comparison of the number of arousals occurring within two minutes of application of the resistance with the number of non-arousals during the first and second halves of the sleep period time was only possible for stages 2 and 3/4. As nocturnal bronchoconstriction reaches its maximum during the early morning,[9] a change in the arousal response could be important. However, the duration of sleep did not modify the arousal response to external resistive loading in normal subjects.

The results obtained in this study confirm the decreased arousal response to inspiratory resistive loading in stage 3/4 sleep compared with stage 2.[5] In two previous studies there were no data available from REM sleep.[13,14] In another study arousal was significantly more frequent from REM than from stage 3/4 sleep, but showed no significant difference between stage 2 and REM sleep.[5] The failure of this previous study to demonstrate a difference between REM and stage 2 sleep in this regard was likely to be due to a type II error.

The finding of a shorter time to arousal in REM compared with non-REM sleep in this study is in agreement with a similar study of Issa and Sullivan in normal men.[15] Using complete external occlusion of inspiratory airflow as a stimulus, they found that arousal occurred more rapidly from REM than from stage 3/4 sleep (no data collection during stage 1 or 2).

The finding of brisker arousal response to external loading in REM sleep than in non-REM sleep stages 2, 3, and 4 in normal men is in contrast to the findings of Sullivan and Issa in patients with obstructive sleep apnoea.[2] They found that arousal in response to spontaneous upper airway occlusion occurs more rapidly from non-REM than REM sleep. This discrepancy could be explained either by stimulation of different receptors or by a difference in arousal threshold due to impaired load perception. Issa *et al* have shown that, following tracheal occlusion in dogs, the arousal response was slower than in tests using nasal occlusion.[16] They concluded that upper airway mechanoreceptors might have an important role in the induction of arousal from nasal occlusion. These receptors could be located above the site of airway occlusion in apnoeic subjects. The finding of a larger number of more prolonged episodes of apnoea and more arousals in normal subjects as a result of nasal obstruction[17] does not help to localise these potential receptors. The studies of Gleeson *et al* in normal subjects and Yasuma *et al* in dogs, however, suggest that mechanoreceptor stimuli arising from the ventilatory apparatus (chest wall and lungs) might be the major stimulus for arousal, independent of the source of the rising drive to breathe.[18-20] Gleeson's group has demonstrated that arousal produced by hypoxia, hypercapnia and external resistive loading occurred quite uniformly at a peak negative oesophageal pressure of around 15 cm H_2O.[18] Mechanoreceptors of the chest wall and lungs would be stimulated by naturally occurring episodes of apnoea in patients with sleep apnoea, nasal obstruction, and external resistance or airway occlusion. The different arousal response in normal and apnoeic subjects could then no longer be explained by the stimulation of different receptors. We sympathise therefore with a hypothesis put forward many years ago by Phillipson and Sullivan[21] that suggested that patients with sleep apnoea might have a different arousal threshold. This hypothesis is indirectly supported by the data of McNicholas *et al*, who observed an impaired detection of added inspiratory resistance in patients with obstructive sleep apnoea during wakefulness.[22] A study by Calverley *et al*, although performed in patients with chronic obstructive lung disease and using hypoxia as a stimulus, further supports the idea that "differences in the ability to arouse from sleep" exist in response to respiratory stimuli.[23] The discrepant results between normal subjects and patients with sleep apnoea with respect to arousal during REM sleep as a response to increased inspiratory resistance appears, therefore, to be the result of a different "central processing" of the stimulus, although reduced reflex activity from the pharynx cannot be ruled out as an explanation.

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