Drug-induced arterial pressure elevation is associated with arousal from NREM sleep in normal volunteers

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Kesler, Branko, Amit Anand, Sandrine H. Launois, and J. Woodrow Weiss. Drug-induced arterial pressure elevation is associated with arousal from NREM sleep in normal volunteers. J. Appl. Physiol. 87(3): 897-901, 1999.—Abrupt changes in arterial pressure produce arousal in sleeping animals. To determine whether arterial pressure elevations can cause arousal from sleep in humans, we studied five healthy individuals without sleep complaints or cardiac abnormalities. Monitoring included electroencephalogram, electrooculogram, and electromyogram to determine stage sleep; finger cuff to measure arterial pressure; and electrocardiogram to measure heart rate. We administered intravenous bolus doses of either phenylephrine or saline after performing a dose-response curve to establish the amount of phenylephrine that produced a 20-mmHg increase in mean arterial pressure. Ten boluses of phenylephrine and ten boluses of saline were then administered in random order during stable non-rapid-eye-movement sleep. An observer blinded to the order of drug administration identified arousals using a standard definition. Arousals were five times more likely to occur after phenylephrine than after saline (58 vs. 12%; P = 0.0071). Phenylephrine administration produced heart rate slowing, indicative of baroreflex stimulation. We conclude that pharmacologically induced arterial pressure elevation is associated with arousal from sleep in normal volunteers.

hypertension; phenylephrine; non-rapid-eye-movement sleep

UPPER AIRWAY OBSTRUCTION during sleep is characterized by hemodynamic oscillations and by changes in state. Termination of obstructive apneas is associated with abrupt increases in systemic arterial pressure and heart rate (23), which occur coincidently with decreases in left ventricular stroke volume (10). Apnea termination is also associated with arousal from sleep, defined as an abrupt change in sleep state.

A number of lines of evidence suggest that arousal contributes to the increase in arterial pressure that follows the end of an apnea. Ringler et al. (21) used acoustic stimuli to induce arousals in obstructive sleep apnea patients sleeping without obstructions while they were on nasal continuous positive airway pressure (CPAP). These nonrespiratory arousals were followed by arterial pressure increases of the same magnitude as the changes in arterial pressure that followed naturally occurring apneas in the same patients. In a complementary study, Ali and co-workers (1) reported a woman with narcolepsy and periodic movements in sleep syndrome who had regular increases in arterial pressure when aroused by the leg movements. Finally, O'Donnell and colleagues (19), working with an animal model of induced tracheal occlusion during sleep, showed that occlusions associated with arousal resulted in greater increases in systemic pressure than did occlusions of the same duration that were terminated before any visible change in the electroencephalogram (EEG).

These studies suggest that arousal from sleep results in abrupt increases in arterial pressure, but other studies suggest that changes in arterial pressure may conversely contribute to arousal from sleep. Fewell and Johnson (9) produced abrupt increases in arterial pressure in sleeping lambs by suddenly inflating a balloon in the aorta. These surges in pressure reliably resulted in arousal of the animal from sleep. Horne et al. (14) used a similar model to examine whether the effect of arterial pressure swings on sleep state is mediated through arterial baroreceptors. In that study, baroreceptor denervation prevented the change in state that followed aortic balloon inflation in intact animals.

On the basis of these data, we hypothesized that pharmacologically induced increases in arterial pressure might cause arousal from sleep in humans. To test this hypothesis, we administered phenylephrine by bolus to sleeping human volunteers.

METHODS

Subjects. We recruited eight healthy adult volunteers (6 men, 2 women) to serve as subjects. All subjects were without sleep complaints. Subjects were excluded if they had diabetes or autonomic dysfunction. We also excluded subjects taking vasoactive medications or with evidence of preexisting chronic disease, including hypertension, cardiovascular, or intrinsic lung disease. Each subject had a medical history and physical examination before participation. All subjects gave informed consent before participation, as dictated by the hospital Committee on Clinical Investigation.

All subjects were asked to partially sleep deprive themselves the night before participation (maximum 5 h). Despite this, three subjects were unable to sleep under the conditions of the study. As a result, five subjects completed the entire protocol and were included in the final data analysis.

Protocol. We studied each subject on a single occasion, overnight, beginning between 10 PM and 12 AM. When the subjects arrived in the laboratory, we placed electrodes on the scalp and face to monitor EEG, electromyogram, and electro-
oculogram. In addition, we placed electrodes on the chest to monitor the electrocardiogram. We placed a digital cuff on the second digit to monitor arterial pressure noninvasively, by using digital photoplethysmography (Finapres, Ohmeda). This technique has been shown to correlate well with invasive blood pressure measurements during phenylephrine injection, although absolute changes in arterial pressure are underestimated (12). After placement of these monitoring devices, the subject was asked to recline, and we inserted an 18-gauge catheter into the basilic vein for administration of drug and saline boluses.

We then turned out the lights and asked the subject to sleep. Subjects slept supine with the hand on which the pressure cuff was placed fixed at the level of the midaxillary line. We performed no interventions until the subject displayed stable stage 2 non-rapid-eye-movement (NREM) sleep for 20 min. All trials were conducted during stage 2 NREM sleep, and only two subjects achieved rapid-eye-movement (REM) sleep during the protocol. Once we observed stable sleep, we administered intravenous boluses of phenylephrine every 5 min, beginning at 50 µg and increasing in 50-µg increments until we observed a rise in mean arterial pressure (MAP) of 20 mmHg or we reached a maximum dose of 250 µg. The change in pressure was calculated from a stable 30-s baseline to the three beats surrounding the peak pressure. The desired dose was typically between 150 and 250 µg. We then administered in random order 10 boluses of this maximal dose and 10 boluses of saline, matched for volume and attempting to match for speed of injection. Bolus volume was between 3 and 5 ml, and we followed each bolus with a volume of saline calculated to equal the dead space of the intravenous tubing (8 ml). We allowed at least 10 min between trials to allow arterial pressure and heart rate to return to baseline. We administered boluses only after 4 min (or more) of stable stage 2 NREM sleep. An infrared video camera permitted continuous visual monitoring during the protocol, but subjects were physically and acoustically isolated from the investigators during the protocol by a soundproof door and a sound-baffled pass-through specially constructed to allow for passage of intravenous tubing and monitoring wires.

EEG, electrooculogram, and electromyogram were recorded on a polygraph (model 8-24, Grass) permitting later review of sleep stage without hemodynamic variables. Hemodynamic variables were recorded on a thermal array recorder (Western Graphtec) and on digital tape (TEAC) where EEG was simultaneously displayed.

Data analysis. A board-certified sleep specialist scored the polygraph recordings for sleep stage and for arousals. At the time of the scoring, the reviewer was aware of the points at which a bolus was administered but was blind to the drug administered with each bolus (phenylephrine or saline). The reviewer used a standard definition for arousals: “an abrupt shift in EEG frequency which may include theta, alpha, or higher frequency bursts but not spindles, lasting 3 s and following a period of continuous sleep of at least 10 s” (2). A trial was considered to have resulted in arousal if an arousal occurred within 90 s of bolus administration.

We calculated MAP by using the formula

\[
MAP = \frac{1}{3} \text{diastolic pressure} + \frac{2}{3} \text{systolic pressure}
\]

We derived heart rate from the R-R interval.

We used McNemar’s test to assess the statistical difference between the frequency of arousals after saline boluses compared with phenylephrine boluses. We present data as means ± SD.

**RESULTS**

We present subject characteristics and baseline hemodynamic values in Table 1. As expected, we observed a decrease in heart rate and arterial pressure in all subjects from wakefulness to sleep.

We calculated the maximal change in MAP and heart rate after each bolus, before any change in state. Phenylephrine infusion increased MAP by 24 ± 7 mmHg. This increase in arterial pressure was accompanied by a decrease in heart rate with the mean decrease 16 ± 5 beats/min. Saline boluses produced no change in heart rate or arterial pressure. Figure 1 displays a representative tracing depicting the hemodynamic and physiological variables during the protocol.

![Representative tracing from a subject sleeping in stable stage 2 non-rapid-eye-movement (NREM) sleep when given an intravenous bolus of phenylephrine (first arrow). EEG, ECG, and arterial pressure by finger cuff (AP) are displayed. Bolus of phenylephrine results in an increase in AP, which is accompanied by heart rate slowing several seconds before EEG arousal (second arrow).](image)
EEG response to phenylephrine in an individual subject.

Table 2 represents the proportion of boluses, saline, and phenylephrine that were followed by arousal in each subject. For the group, phenylephrine was followed by arousal in 58% of trials, whereas saline was followed by arousal in 12% of trials. This difference in arousal frequency is highly significant ($P = 0.007$).

**Table 2. Proportion of trials associated with electroencephalographic arousal after bolus administration of saline and phenylephrine**

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Saline</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0.6</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.7</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>$0.12 ± 0.08$</td>
<td>$0.58 ± 0.08$</td>
</tr>
</tbody>
</table>

DISCUSSION

Obstructive apneas during sleep are associated with oscillations in arterial pressure and changes in sleep state (23). Considerable evidence indicates that arousal, the abrupt change in sleep state, contributes to the increase in arterial pressure that follows termination of obstructive apneas (19, 21). This study suggests that in sleeping normal volunteers pharmacologically induced changes in arterial pressure also contribute to arousal.

Several aspects of our study warrant comment. First, because arousal invariably resulted in an increase in arterial pressure beyond that seen before arousal, we cannot accurately compare the arterial pressure response in those trials resulting in arousal with the pressure response in those trials that did not result in arousal. Nevertheless, because the phenylephrine dose was fixed throughout the protocol, and because the trials without arousal resulted in substantial changes in pressure, we believe that there were phenylephrine trials that produced near-identical hemodynamic responses that nevertheless differed in the EEG response. This is not surprising because many factors may influence arousability to external stimuli. For example, although we performed all trials during stage 2 sleep, there may be differences in depth of sleep that are not reflected in sleep staging.

A second aspect of our study that deserves comment is the use of the American Sleep Disorders Association definition of arousal (2). We acknowledge that subtle changes in EEG frequency, not detectable by visual inspection, may occur after acoustic stimuli. Thus our use of a restrictive definition may have missed more subtle episodes of EEG arousal in other trials. We used the American Sleep Disorders Association definition precisely because it is restrictive, however. We believe the episodes of arousal we identified were unequivocal.

Of interest, reviewing our data we did not appreciate other "less-intense" arousals in our trials. In our subjects, the arousals that occurred were frequently several seconds in duration, making them clearly identifiable to visual inspection.

A third aspect of our study that deserves comment is the 90-s window we used to identify arousals. This time period was chosen arbitrarily, on the basis of prior experience in normal volunteers in whom acoustic tones were followed by arousals up to 45 s after administration of the tone. We recognize that this broad time window allows for some arousals not associated with the phenylephrine administration to be included in our data analysis. Nevertheless, our study design should control for this possibility because random arousals should occur equally frequently after saline and after phenylephrine.

A fourth aspect of our study that deserves comment is the method by which we measured arterial pressure. Although digital photoplethysmography has been used extensively to monitor arterial pressure noninvasively on a beat-by-beat basis, this method may underestimate arterial pressure changes during drug-induced peripheral vasoconstriction (12). Thus we may have underestimated the absolute pressure change in our subjects. Nevertheless, we believe the noninvasive measurement adequately demonstrates engagement of the arterial pressure-heart rate baroreflex response.

A number of studies have investigated the relationship of arousal and arterial pressure changes. Ringler et al. (21) studied patients with obstructive sleep apnea while they slept with, and without, nasal CPAP. Five to seven seconds after termination of naturally occurring apneas, MAP increased ~20 mmHg above the waking baseline. When the same subjects were aroused with an acoustic tone while sleeping without obstructions on CPAP, arterial pressure increased almost precisely the same amount. Ringler et al. concluded that arousal was sufficient to duplicate the hemodynamic changes that occur after the end of obstructive apneas during sleep. Ali and colleagues (1) also suggested a causal relationship of arousal to increased pressure, reporting that nonrespiratory arousals associated with periodic limb movements in a patient with narcolepsy were associated with significant increases in arterial pressure. Davies et al. (6) further examined the connection of arousal to arterial pressure by producing tactile arousals in normal individuals sleeping in NREM sleep. These investigators (6) observed increases in arterial pressure that were proportional to the degree or intensity of arousal. Morgan and colleagues (18) attempted to define the mechanism for the arterial pressure changes after acoustic arousal by monitoring sympathetic nerve activity by peroneal microneurography. Stimuli that resulted in abrupt arterial pressure changes also elicited one to two large sympathetic bursts in the peroneal nerve. They concluded that arousal increases arterial pressure by causing sympathetically mediated peripheral vasoconstriction. Finally, O’Donnell and co-workers (19) induced tracheal occlusions in sleeping dogs. Occlusions that were maintained until EEG arousal was observed were matched to occlusions of the same duration after which no arousal was identified. Occlusions with arousal were
followed by significantly greater increases in systemic pressure than were occlusions without arousal.

Fewell and Johnson (9) were among the first investigators to propose that changes in arterial pressure might, conversely, contribute to arousal from sleep. Working with lambs, they manipulated arterial pressure by inflating a balloon-tipped catheter previously implanted in the aorta of the animals. An increase in arterial pressure of 28 mmHg in NREM sleep and 24 mmHg in REM sleep followed sudden balloon inflation. These abrupt changes in pressure were followed by arousal in both sleep states, although arousal after inflation was delayed in REM compared with NREM sleep. Horne et al. (14) built on this work to investigate the mechanism of the state change. Episodes of increased arterial pressure were created in newborn lambs with, and without, sinoaortic denervation. In the intact lambs, pressure elevations were followed by arousal from sleep after one-half the trials in both REM and NREM sleep. After denervation, abrupt increases in arterial pressure resulted in arousal in 31% of NREM trials and 10% of trials in REM. These differences were significant. Using a similar model, Horne et al. (13) found that intact baroreflexes were also important for the arousal response to decreases in pressure. These animal studies may reconcile our findings with previous human studies. Cole (5) studied normal volunteers exposed to tilt, with and without leg pressure. Heart rate changes suggested that tilt without leg pressure substantially reduced baroreceptor activity. This condition both inhibited sleep and caused a persistent increase of EEG beta frequency activity, suggesting EEG arousal. Taken with our findings, the results of Cole suggest that in humans, as in animals, both baroreceptor activation and deactivation result in cortical activation.

In contrast to these findings, Saupe and colleagues (22) examined the consequences of isolated changes in carotid sinus pressure in unanesthetized, sleeping dogs. These investigators reported no change in EEG frequency in response to large carotid pressure changes. Several aspects of this study might account for the differences in the observed outcomes compared with our investigation. First, the carotid sinus pressure increases were associated with substantial decreases in systemic pressure (MAP decreasing from ~85 to 60 mmHg). This systemic pressure decrease could alter cerebral perfusion and might thus mitigate any baroreflex-induced change in arousal. Another difference is that Saupe et al. measured EEG frequency for 20 s after the induced change in carotid sinus pressure. Thus some delayed cortical response might have been missed. Additionally, there may be species differences in the cortical response to baroreceptor stimulation. Finally, although we believe that baroreceptor stimulation is the most likely mechanism for the responses we observed, it is possible that phenylephrine-induced increases in arterial pressure produce arousal through some other mechanism.

This study does not definitely establish a link between arterial pressure increases and arousal in humans. We cannot exclude some other indirect effect of phenylephrine that might have contributed to arousal in our subjects. In addition, we did not perform a dose-response study that might have related the magnitude of the arterial pressure change to the change in state. Nor did we use another pharmacological agent to alter pressure, which might have strengthened the connection of the hemodynamic events to the arousals we observed. In this human study we were unable to manipulate arterial pressure nonpharmacologically, and interventions such as neck suction, which stimulates carotid baroreceptors mechanically, might also contribute to arousal through tactile stimulation. Despite these weaknesses, the connection between baroreflex stimulation and arousal from sleep is physiologically plausible.

The present study is unable to shed light on the mechanism by which abrupt increases in arterial pressure contribute to arousal. The arousal response we observed is unlikely, however, to be related to direct actions of phenylephrine in the central nervous system. Phenylephrine is a direct α1-agonist that is not thought to cross the blood-brain barrier (7). Autoradiographs with 2-deoxyglucose done in rats given pressor doses of phenylephrine did not show enhanced uptake in numerous brain stem locations, including nucleus accumbens, paraventricular nucleus of the hypothalamus, hippocampus, and the intermediolateral nucleus, among others (4). Furthermore, phenylephrine has been used for many years to test baroreflex function because of the belief that its actions are exclusively on the peripheral vessels (7).

Although phenylephrine does not act directly in the brain after intravenous administration, considerable evidence now suggests that sustained changes in arterial pressure may cause specific patterns of neuronal activation in the central nervous system. Miura and co-workers (17) measured expression of Fos protein in rats after repeated stimulation of baroreceptors by the pressor responses to phenylephrine. Fos protein is a marker of neuronal activation. The correlation coefficient of the dose-response relationship was significant only in the medial part of the nucleus of the solitary tract in the medulla and in the periaqueductal gray in the midbrain. Li and Dampney (16) also used neuronal expression of Fos to measure the activation of neurons of the brain stem and forebrain in rabbits experiencing hypertension and hypotension induced by phenylephrine and nitroprusside, respectively. Neuronal activation to hypertension was demonstrated in the nucleus of the solitary tract, in the caudal and intermediate parts of the ventrolateral medulla, as well as in supramedullary regions: the central nucleus of the amygdala, the bed nucleus of the stria terminalis, and the parabrachial complex of the pons. Potts and co-workers (20) followed these observations by showing that sectioning of the carotid and aortic depressor nerves led to a 90% reduction in Fos expression in the nucleus of the solitary tract and in the caudal and intermediate parts of the ventrolateral medulla. Lesser reductions oc-
curred in the central nucleus of the amygdala and in the bed nucleus of the stria terminalis.

Although these studies indicate pathways through which baroreflex stimulation may activate central nervous system centers, these studies do not identify the mechanism by which baroreflex stimulation contributes to arousal. Anatomic evidence identifying connections between brain stem structures and forebrain arousal systems suggests that the necessary pathways exist, however.

Any contribution of hypertension to the sleep disruption experienced by patients with sleep apnea remains uncertain. Typically, the highest arterial pressure of the apnea-recovery cycle occurs 5–7 s after arousal from sleep (21), but arterial pressure increases as the apnea progresses and the highest apneic arterial pressure occurs immediately before arousal (10). Numerous other events associated with airway obstruction during sleep have been shown to contribute to sleep disruption, including hypoxemia (3), hypercapnia (8), upper airway stimulation (15), and thoracic pressure swings (11). Thus there are redundant mechanisms capable of contributing to arousal, so the relative importance of each mechanism is difficult to define. Although we think it unlikely that increased arterial pressure during the obstruction contributes to arousal, the pressure rise that follows apnea termination may increase the degree of arousal produced by the event. Thus it seems likely that the increase in pressure that occurs after apnea termination may amplify the arousal response to the preceding obstruction.

In summary, our studies shows that arterial pressure elevation induced by bolus administration of phenylephrine is significantly more likely to result in arousal from sleep than is bolus administration of saline to the same sleeping normal volunteers. We speculate that abrupt increases in arterial pressure after apnea termination in patients with obstructive sleep apnea may amplify the arousals that occur at the end of obstructive events during sleep.

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