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Differential Inhibition of the Diaphragm and Posterior Cricoarytenoid Muscles Induced by Transient Hypertension across Sleep States in Intact Cats

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Arterial pressure was transiently elevated by intravenous infusion of phenylephrine in intact, freely moving cats during sleep and waking states to determine pressure effects on diaphragmatic and laryngeal abductor EMG activity. Transient hypertension caused respiratory cycle duration to increase and integrated EMG area to decrease for several breaths in both the diaphragm and posterior cricoarytenoid, the integrated inspiratory area of which decreased to a greater extent than did that of the diaphragm. Cycle duration increases resulted from increases in expiratory duration. Expiratory duration of the posterior cricoarytenoid initially increased proportionately more than that of the diaphragm, causing a transient phase disassociation between that upper airway muscle and diaphragmatic timing. This disassociation disappeared after several breaths. Changes in posterior cricoarytenoid expiratory duration and integrated inspiratory area were sleep state-dependent: area decreases were greatest in rapid eye movement sleep; expiratory duration increases were greatest in quiet sleep. Neural mechanisms underlying laryngeal abductor activity are sleep state-dependent and appear to be affected more than diaphragmatic mechanisms by baroreceptor stimulation.

INTRODUCTION

Increased baroreceptor stimulation, produced either mechanically or pharmacologically, transiently decreases respiratory rate and tidal volume in

Abbreviations: PCA—posterior cricoarytenoid, QS—quiet sleep, REM—rapid eye movement sleep, AW—waking, RMS—root-mean-square, T_{tot}—respiratory duration, T_i—inspiratory duration, T_e—expiratory duration.

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anesthetized animals (6, 8, 16, 35). In unanesthetized animals, both respiratory rate and peak diaphragmatic EMG amplitude decrease during transient hypertension, and this effect is maximal during quiet sleep (QS) (34). These observations suggest that baroreceptor afferent information directly affects respiratory control mechanisms, and that these effects are sleep state-dependent.

The effects of transient baroreceptor stimulation on upper airway musculature are not well understood, but there are suggestions that these muscles may behave differently in general from the diaphragm, both across sleep–waking states and in response to a variety of stimuli. Phasically active upper airway muscles, including the alae nasae at the nares (32, 33), the genioglossi in the oropharynx (2, 26), and the cricothyroids and posterior cricoarytenoids (PCA) in the larynx (14, 29), control upper airway caliber, compliance, and resistance at critical, flow-limiting locations in the upper airway (31). Upper airway resistance increases in the cat during QS (21), perhaps because of decreases in PCA activity (20). In the human, a decline in genioglossal activity during rapid eye movement sleep (REM) (25) could similarly enhance airway resistance. Upper airway musculature timing differs from that of the diaphragm such that muscles situated more distally in the airway are activated increasingly before the diaphragm (18, 28, 32). Upper airway muscles respond to hypoxia and hypercapnia with increased preactivation and increase their activity differently from the diaphragm (18, 19, 32).

Baroreceptor stimulation decreases hypoglossal nerve activity significantly more than either phrenic or recurrent laryngeal nerve activity in anesthetized, paralyzed, and intubated dogs (23). This finding suggests that the upper airway may be more sensitive than the diaphragm to the respiratory depressant effects of baroreceptor stimulation. The use of anesthesia, however, precludes assessing how sleep states may contribute to upper airway responses to transient hypertension. In addition, the depressant effects of decreased airway resistance on PCA activity (24), such as may be afforded by an endotracheal tube, and the depressant action of barbiturates on upper airway muscles (10), suggest that the effects of transient hypertension might be clarified in an intact, drug-free preparation.

A major clinical problem involving upper airway muscle control is the obstructive sleep apnea syndrome, where apnea is associated with changes in upper airway muscle activity (1, 11, 22). Whereas obstructive events may be initiated by an acute loss of tone in an upper airway dilator muscle (22), the respiratory depressant effects of an acute elevation in blood pressure secondary to hypoxia may be significant. The effects of an arterial pressure increase on upper airway musculature in different sleep and waking states analogous to the pressor response associated with upper airway obstruction are not known.

The hypothesis for the present study was that upper airway muscles would respond to transient hypertension differently from the diaphragm, and that this response would depend on the sleep–waking state. Moreover, because sleep states differentially alter diaphragmatic responses to transient hypertension (34), a test of upper airway muscle control in intact preparations was conducted during different states to delineate baroreceptor/respiratory/arousal relationships. This study examined the effects of transient hypertension on an upper airway muscle, the PCA, and the diaphragm across sleep–waking states.

METHODS

Five female cats (2.9 to 3.2 kg) were prepared for chronic recording under halothane–nitrous oxide anesthesia. Electrodes were inserted into the orbital plate of the frontal bone and into the calvarium overlying sensorimotor cortex for recording eye movements and the sensorimotor EEG, respectively. A concentric bipolar electrode was placed stereotaxically into the lateral geniculate body for later recording of pontogeniculooccipital waves characteristic of REM sleep. Stainless-steel wires were sutured into the nuchal musculature. Activity from these four measures permitted electrophysiological classification of the animal's state into awake (AW), QS, and REM.

Stainless-steel wires were sutured under direct vision into the left lateral costal diaphragm after a midline laparotomy. Paired, stainless-steel fine wires were sutured into the PCA after a midline anterior cervical incision followed by laryngeal rotation and opening of the superior pharyngeal constrictor following the method of Sherrey and Megirian (29). Electrode leads were soldered to a 20-pin miniature connector which was fixed to the skull with dental acrylic. Catheters were placed in the abdominal aorta through a transfemoral approach and in the right atrium through an internal jugular cutdown, for monitoring arterial pressure and infusing phenylephrine, respectively. The vascular lines were passed subcutaneously to exit beside the electrode connector, and were kept patent by daily flushing with heparinized normal saline (4 U/ml). During a 1-week recovery period, the animals became adapted to sleeping in a shielded recording chamber ($60 \times 60 \times 60$ cm).

During recording, aortic pressure was monitored by connecting the arterial catheter to a transducer mounted outside the chamber. Blood pressure and electrophysiologic data were amplified by a Grass polygraph. The respiratory EMGs were bandpass filtered (100 to 10,000 Hz), and passed through an analog signal processor which calculated the root-mean-square (RMS) of the signal amplitudes. Data were simultaneously recorded onto polygraph paper and FM tape, and digitized on-line onto magnetic tape by a PDP-11 minicomputer, along with event markers which indicated onset of phenylephrine infusion.

Transient baroreceptor stimulation was induced during AW, QS, and REM by infusing phenylephrine hydrochloride 30 μg/kg as a 0.2-ml bolus in normal saline through the central venous catheter. Blood pressure was returned to prestimulus values and remained there for at least 5 min before another trial was assayed.

One-minute segments of the digitized record starting three breaths before the pressor response were extracted for analysis. A computer program analyzed the integrated respiratory EMG and provided a breath-by-breath printout of the following parameters for the diaphragm and PCA: breath duration (T_{tot}), inspiratory duration (T_i), expiratory duration (T_e), peak height of the EMG, and the integrated areas under the RMS inspiratory and expiratory portions of the curve. Inspiration was considered to begin with the onset of an EMG burst. Expiration was considered to begin with attainment of peak EMG amplitude. The portion of the EMG burst that came after attainment of peak amplitude was assigned to the expiratory phase of the respiratory cycle, and was attributed to expiratory braking.

For each respiratory parameter, a prestimulus average of three breaths was calculated. The percentage change from the prestimulus average was calculated for each breath during the pressor response. Phase relationships between timing of diaphragmatic and PCA activity were assessed by superimposing plots of percentage changes from control of T_{tot}, T_i, and T_e on a breath-by-breath basis.

Multiple trials were averaged on a breath-by-breath basis within each animal in each sleep–waking state. Statistical analysis of each respiratory parameter in terms of average percentage change of each breath from control was carried out using a randomized block factorial analysis of variance with breath and sleep state as independent variables.

RESULTS

After phenylephrine infusion, blood pressure increased 20 to 50 mm Hg, and heart rate decreased. Figure 1 shows polygraph examples of phenylephrine-induced pressor responses in one animal across sleep–waking states. Peak diaphragmatic RMS EMG amplitude decreased significantly from control ($P < 0.01$) over the first three breaths of the response in all sleep–waking states. Peak posterior cricoarytenoid RMS EMG amplitude also decreased significantly from control ($P < 0.01$) in all states, maximally in the second breath of the response. Peak PCA EMG amplitude decreased to 75% (±5.4% SE) of control ($P < 0.01$). Peak diaphragmatic EMG amplitude decreased to 81% (±1.8% SE) of control ($P < 0.01$).

During the first three breaths of the pressor response, both diaphragmatic and PCA RMS total EMG area decreased significantly from control. PCA

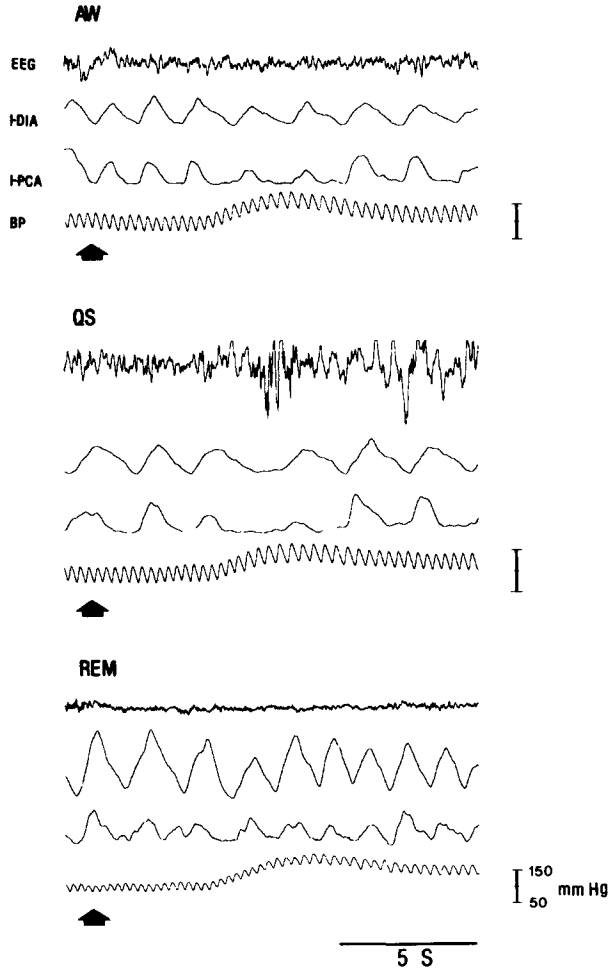

FIG. 1. Diaphragmatic and posterior cricoarytenoid (PCA) responses to transient hypertension across sleep–waking states in one cat. Note decreased amplitude of PCA compared with diaphragm in all three states. Note also increased expiratory duration that was most prominent in quiet sleep. Arrows: phenylephrine infusion. EEG—electroencephalogram, I-DIA—integrated diaphragmatic EMG activity, I-PCA—integrated PCA EMG activity, BP—blood pressure, AW—waking, QS—quiet sleep, REM—rapid eye movement sleep.

total EMG area decreased maximally to 63% (±4.0% SE) of control ($P < 0.001$). Diaphragmatic total EMG area decreased maximally to 79% (±2.2% SE) of control ($P < 0.001$). There was no significant difference in the decrease in total EMG area of either muscle that could be attributed to sleep state (Fig. 2).

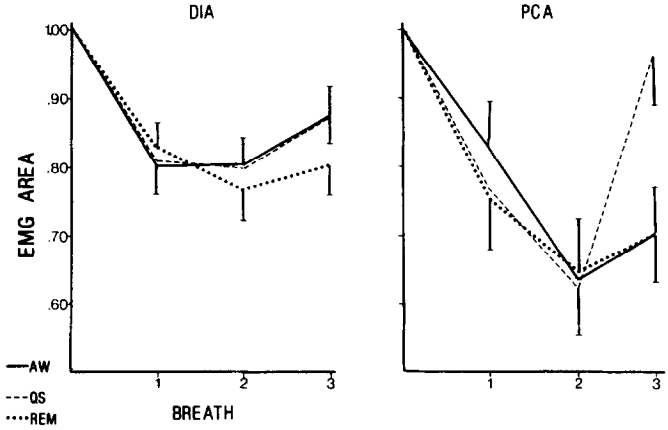

FIG. 2. Mean percentage change from control in diaphragm (DIA) and PCA integrated EMG area in the first three breaths of the response to transient hypertension across sleep–waking states. Error bars are 1 SE. Abbreviations as in Fig. 1.

Partitioning total EMG area of each muscle into inspiratory area and expiratory area revealed a significant ($P < 0.01$) state dependency in PCA inspiratory area that was not apparent for the diaphragm. Over the first three breaths of the response, PCA inspiratory area decreased to 76.7% of control in AW, 83% in QS, and 55.7% in REM (±8.5% SE, $P < 0.01$). Over the first three breaths of the response, diaphragmatic inspiratory area decreased to between 75% and 78% of control in all three states (±4.5% SE, not significant).

During AW and QS phenylephrine trials, respiratory rate transiently decreased for approximately two breaths ($P < 0.01$). In REM, respiratory rate did not change significantly in the initial breaths of the response. However, the respiratory rate transiently decreased later in the response, at approximately the seventh breath from the beginning of the blood pressure rise. Figure 3 shows longer polygraph records of representative ventilatory responses to baroreceptor stimulation in one animal across sleep–waking states.

Diaphragmatic T_{tot} increased significantly during the first two breaths of the response ($P < 0.01$), and then returned to approximate control values for the remainder of the response period. Although there was a tendency for diaphragmatic T_{tot} to be longer in AW and QS than in REM sleep, this increase in length was not significant. PCA T_{tot} increased to 144% of control in AW and 140% of control in QS (±9.5% SE, $P < 0.01$) in the first breath of the pressor rise and to 108% of control in REM (not significant). In REM, PCA T_{tot} increased to 124% in breath 7 and 123% in breath 9 of control (±9.5% SE, $P < 0.05$), compared with diaphragmatic values of 105% and

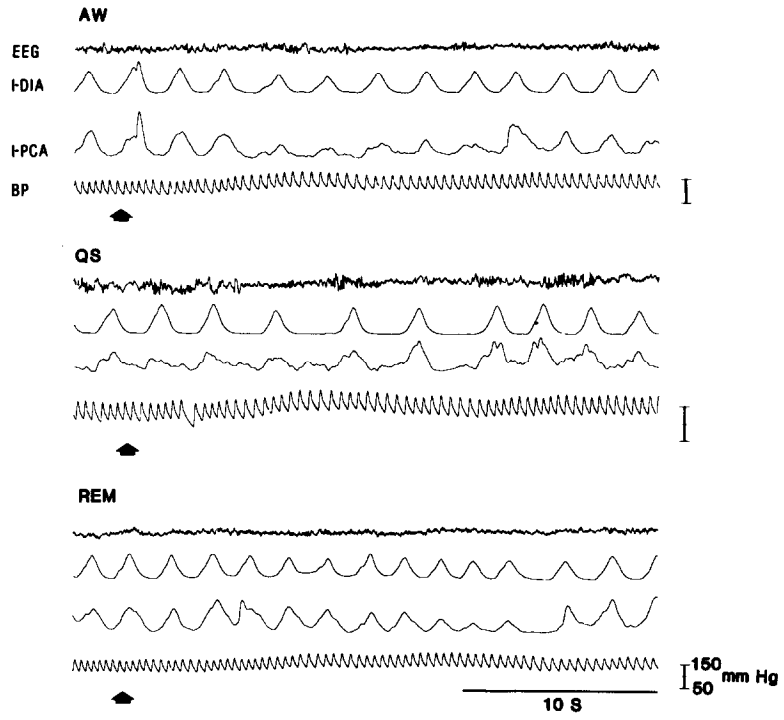

FIG. 3. Diaphragmatic and PCA respiratory cycle timing responses to transient hypertension in one cat across sleep–waking states. Note the initial respiratory slowing in waking and quiet sleep, and the delayed slowing in REM. Abbreviations as in Fig. 1.

99.5% of control in breaths 7 and 9, respectively (±4.5% SE, not significant). Neither diaphragmatic nor PCA T_i differed significantly from control during blood pressure elevations, and there was no significant difference between sleep states for these parameters.

Both diaphragmatic and PCA T_e increased significantly ($P < 0.01$) during the first three breaths of the response and then returned to approximate control values for the remaining seven breaths of the response period (Fig. 4). Increases were greatest in the first breath of the response. There were no significant differences attributable to sleep state across the first three breaths of the response in either the diaphragm or PCA. In REM, PCA T_e increased to 151% of control in breath 7 and 142% in breath 9 (±18% SE, $P < 0.05$). Diaphragmatic T_e was not significantly different from control at that point of the REM response.

To examine the phase relationships between the diaphragm and PCA during the pressor response, the diaphragmatic and PCA percentage change

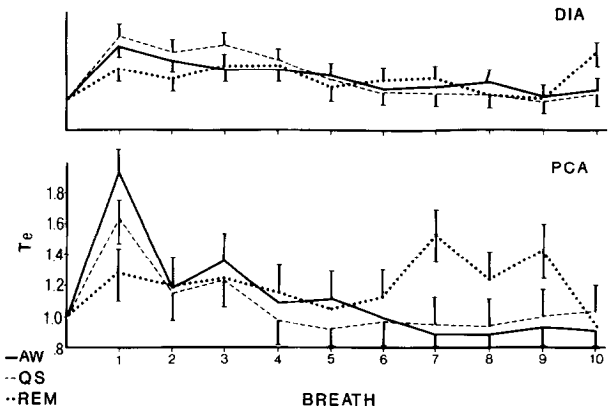

FIG. 4. Mean percentage change from control in diaphragm (DIA) and PCA expiratory duration (T_e) in the first 10 breaths of the response to transient hypertension across sleep–waking states. Error bars are 1 SE. Abbreviations as in Fig. 1.

plots for T_{tot} were superimposed within each state. In AW, PCA T_{tot} increased disproportionately in breath 1 with respect to the diaphragmatic increase (striped area, top trace, Fig. 5), then decreased in approximate proportion with the diaphragm in breaths 2 through 6. In breath 7 and subsequently, PCA T_{tot} decreased proportionately more than the diaphragmatic T_{tot} (stippled area, top trace, Fig. 5). This pattern was apparent in both AW and QS, but not in REM. The pattern for changes in T_e was identical to the T_{tot} pattern. For inspiration, the changes in PCA duration were proportional to the diaphragm changes.

DISCUSSION

This study used EMG as a measure of central neural activation of respiratory musculature, and viewed respiratory EMG depression as a neural analog of respiratory depression. The relationship between the integrated EMG activity and force output of a particular respiratory muscle remains to be clarified, as does the sensitivity and specificity of the EMG in detecting significant differences in the contractile response of a muscle. However, our aim was to clarify the differential distribution of central neural respiratory motor outflow to the diaphragm and larynx in response to transient baroreceptor stimulation. We were therefore interested in determining the differential changes from baseline neural activation of these respiratory muscles, whatever the ultimate correlation with actual force transduction may be.

Our results suggest that neural mechanisms underlying laryngeal abductor timing and activation are more affected by inhibitory baroreceptor responses

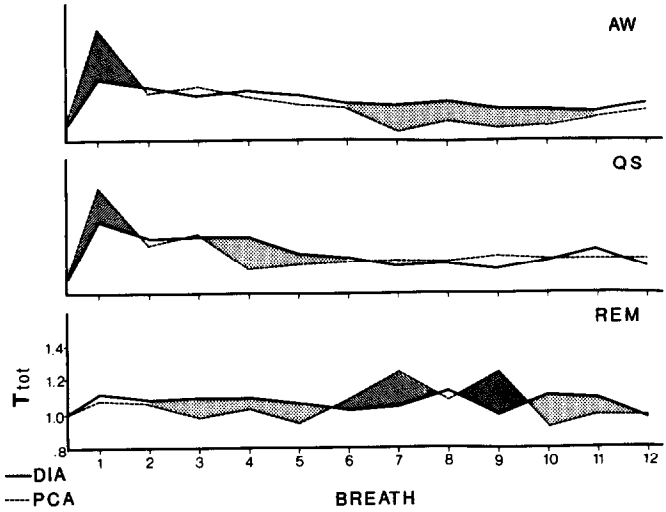

FIG. 5. Phase relationships between diaphragm (DIA) and PCA respiratory duration (T_{tot}) in the first 12 breaths of the response to transient hypertension. Percentage change plots for each muscle are superimposed. The striped area highlights the initial disproportionate increase in PCA respiratory period over that of the diaphragm suggestive of a phase disassociation between the two muscles. The stippled area highlights the later disproportionate decrease in PCA respiratory period over that of the diaphragm during which the PCA may "catch up" to the diaphragm. Abbreviations as in Fig. 1.

to transient hypertension than are diaphragmatic control mechanisms. Response differences between the upper airway and the diaphragm have been demonstrated by others under a variety of circumstances (4, 5, 7, 10). The increased sensitivity of the PCA to baroreceptor input suggests that neural integration of upper airway respiratory musculature differs from that of the diaphragm. Although we show differential responses to baroreceptor input, altered responses to chemoreceptor input have also been reported (10). The etiology of this differential control is unknown. The nucleus tractus solitarius, which receives carotid sinus afferent fibers (9), projects to the nucleus ambiguus (12), which contains a major pool of laryngeal motoneurons (15). The differential sensitivity of upper airway motoneurons over that of the phrenic motor pool may result from the nature of functional connectivity between the nucleus tractus solitarius and the nucleus ambiguus, or perhaps from a more general influence on laryngeal motoneurons from another, as yet unknown, central nervous system source in response to hypertension.

The pattern of decreased activity in the PCA after baroreceptor stimulation was sleep state-dependent. The finding that state dependencies differed for T_e and inspiratory area suggests that baroreceptor influences on neural

mechanisms affect respiratory effort differently from respiratory rate. In REM, there was little decrease in respiratory effort during baroreceptor stimulation, but a significant respiratory timing effect developed from the blood pressure stimulus. This timing effect, however, was delayed from where it appeared in AW and QS. Although we have no information on the nature of the delay in the timing effect, the slowing of rate in REM in the absence of a significant decrease in effort suggests that baroreceptor stimulation mediates two separate respiratory responses in the intact preparation.

The state dependency shown by the PCA, in contrast to the effects observed in the diaphragm, suggests that upper airway musculature is more subject to sleep state influences than is the diaphragm. Sleep states have the potential to alter airway resistance by influencing discharge in the alae nasae (33), genioglossi (25), and jaw protruder muscles in the human, and a number of laryngeal muscles in the rat (13, 28). Although many diaphragmatic units cease firing during REM (30), this decrease appears to be less than in the upper airway.

The neural substrate for the increased sensitivity of the upper airway to sleep state is unknown. Direct central nervous system influences on membrane potentials of the laryngeal motoneuron pool may differ from those of the phrenic spinal cord pool during different sleep states. Because of the difficulties in recording membrane potentials in the intact, drug-free cat, evidence on that issue is not yet available. However, state influences on membrane potentials of at least a subset of trigeminal motoneurons (which, because they control jaw protrusion, affect upper airway patency) show only minor differences from the patterns observed in the lumbar motoneurons of the spinal cord (3). State-related properties of lumbar motoneurons may differ greatly from phrenic motoneurons, however.

Analysis of T_i and T_e changes during baroreceptor stimulation suggests that the transient respiratory rate decrease resulted solely from transient increases in T_e. Because both tidal volume and respiratory rate decrease during baroreceptor stimulation (6), it is important to ascertain whether respiratory timing mechanisms are directly affected by changes in baroreceptor firing, or whether respiratory rate changes occur secondarily to tidal volume changes, via vagal reflexes. Grunstein *et al.* (6) found that the respiratory rate decrease observed during baroreceptor stimulation disappeared after vagotomy and was dependent on the concomitant tidal volume decreases. However, Nishino and Honda (17), working with anesthetized cats, and Trelease *et al.* (34), using intact, unanesthetized cats, found that the respiratory rate decrease was due to an increase in T_e, suggesting that baroreceptor stimulation directly affected respiratory timing mechanisms. Our results support those of these latter two studies, and we extend the findings to another airway muscle, the PCA.

Analysis of the T_e changes in the diaphragm and PCA revealed that, initially, T_e increased proportionately more in the PCA than in the diaphragm. After a period of isoproportionally decreasing T_e, PCA T_e decreased proportionately more than diaphragmatic T_e. Baroreceptor stimulation may thus cause a transient phase dissociation between upper airway and diaphragmatic timing mechanisms: the initially disproportionate T_e increase in PCA delayed the onset of activity in the subsequent breath in relation to diaphragmatic onset. Because diaphragmatic and PCA T_e changed proportionately during the subsequent few breaths, we assume that this new phase relationship is maintained until PCA T_e decreases proportionately more than diaphragmatic T_e at about breath 7. Presumably, this last set of T_e changes allowed the diaphragm to "catch up" and thereby restore the normal phase relation between the PCA and diaphragm.

The nature of the neural mechanisms underlying this transient phase disassociation is unknown. Normal timing of activity of upper airway musculature differs from that of the diaphragm (19, 28, 32). Thus, pattern generation mechanisms for respiratory cycling must incorporate differential activation timing of muscles in the path of airflow. Central tegmental field stimulation in anesthetized cats causes an increased interval between laryngeal and diaphragmatic onset of activity (20), suggesting a possible phase change between larynx and diaphragm. In addition, airflow resistance is greatly increased when upper airway contraction is out of phase with chest wall contraction (27). As phase disassociation resulting from transient hypertension does not appear in REM, tonic inhibitory influences found in REM may override normal timing influences observed in other studies.

The differential sensitivity of upper airway and diaphragmatic musculature may contribute to the mechanisms underlying sleep-related obstructive apnea. Obstructive sleep apnea events typically are mediated by a restriction in the upper airway of a predisposed individual (22, 25), typically by relaxation of one or more airway dilator muscles (31). Sleep-related airflow restriction can readily result from atonia in the genioglossi or lateral pterygoid muscles which protrude the tongue and jaw, respectively. The present finding of a large PCA activity decrease during transient hypertension, particularly in REM, suggests a possible laryngeal role in the maintenance of an obstructive episode. The rapid arterial pressure rise after phenylephrine administration shows more similarities to the pressure increase observed to follow obstruction of the upper airway during acute hypoxia. Laryngeal patency may be acutely compromised during the resultant hypoxic hypertension, due to decreased PCA activity, regardless of the upper airway site of obstruction. Assuming laryngeal adductor activity was unaffected by episodic hypertension, compromised laryngeal patency could prolong the original obstruction, exacerbate the hypoxia, and thereby maintain the hypertension. Activity of

the laryngeal adductors during such a scenario is unknown; if adductors were equally affected as is the PCA, the net effect would be less disruptive to airway resistance in the human, since relaxation of both laryngeal abductors and adductors may provide adequate airway patency.

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