Invited Editorial on “Respiratory-related heart rate variability persists during central apnea in dogs: mechanisms and implications”

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RICHARD HORNER ET AL. (5) have used mechanical ventilation in unanesthetized dogs to show that the respiratory sinus arrhythmia (RSA) present during hypocapnic mechanical ventilation persists during the apneic period following cessation of the mechanical ventilation. During this postmechanical ventilation apneic period, RSA was clearly present in the same time period (as during mechanical ventilation breaths) in the first one or two “phantom” breaths of the apnea, although the RSA amplitude was reduced and phase was altered. Thereafter, as apnea proceeded, the RSA was markedly reduced in amplitude but then came back strongly toward the termination of the apneic period and was in phase with the postapneic spontaneous breaths. This persistent RSA at the onset of central apnea was perceived as a lingering time-dependent “memory” effect from the preceding respiratory-related events.

The concept of memory in the respiratory control system has been demonstrated under a variety of conditions and should be considered an integral part of the total response to excitatory or inhibitory influences that affect ventilatory control. The excitatory short-term potentiation (STP) of phrenic nerve activity that follows withdrawal of heightened chemoreceptor input was described over 50 years ago (2). Eldridge and Millhorn (2) have added substantially in the past two decades to our understanding of this phenomenon by demonstrating that the STP occurs in response to a variety of sensory stimuli and that it represents an important component of the behavior of the brain stem respiratory control mechanism. This STP is also manifested in a slowly dissipating enhanced ventilatory output following chemoreceptor stimulation in awake, sleeping, and exercising humans (4). Furthermore, ongoing subthreshold oscillatory respiratory nervous activity has also been shown to persist, even in the absence of rhythmic respiration. This was nicely demonstrated by Horner et al. (5) in the continuing respiratory sinus arrhythmia in unanesthetized dogs. It has also been shown previously in more reduced preparations by continued oscillatory activity in laryngeal nerves, glossopharyngeal nerves, and in some inspiratory and expiratory premotor medullary neurons during phrenic silence (1).

Apnea in the study of Horner et al. (5) was induced by hypocapnia via mechanical ventilation, but memory effects of inhibitory influences may also cause and prolong apnea independently of, and even despite, chemical stimuli. For example, electrical stimulation of the central cut end of the vagus nerve or the superior laryngeal nerve in anesthetized animals caused phrenic apnea that persisted well beyond the period of electrical stimulation. The duration of the poststimulation phrenic inhibition was markedly influenced by the duration of the preceding stimulus (9). The apnea that followed augmented inspirations in dogs (7) and cats (12) may be another example of an inhibitory memory-like effect related to lung stretch. Similarly, short apneas also occur after brief periods of normocapnic hypoxic-induced hyperpnea in the awake intact dog, and these apneas were prevented by cervical vagal blockade (15). Apparently, in these studies involving one or more actively augmented inspirations or increased tidal volumes, both an excitatory STP and inhibitory mechano-receptor memory effect occurred simultaneously; however, when the vagi were intact, the inhibitory effect prevailed and ventilation was inhibited. Inhibitory memory effects have also been induced in humans by nonchemical mechanoreceptor influences. Over 40 years ago, Fowler (3) showed that brief interspersed periods of rebreathing would prolong breath-holding time. More recently, sleeping and waking subjects mechanically ventilated at high tidal volumes and frequencies for long periods with end-tidal pressure of CO, held at normocapnia (10) experienced prolonged apneas on cessation of the mechanical ventilation. Whether these inhibitory effects in humans are purely reflexive in nature, as they apparently are in dogs and cats, has not been shown conclusively; in fact, these effects have only been shown thus far to occur after very long durations of normocapnic mechanical ventilation.

These inhibitory memory effects may involve a central reorganization or habituation of central neural output (12). Apnea (i.e., phrenic silence) is often accompanied at its onset by tonic expiratory activity in late augmenting expiratory medullary cells following augmented inspirations in awake cats (12) and in early expiratory medullary cells after electrical stimulation of the superior laryngeal nerve or vagi in the anesthetized cat (13). Similarly, tonic activation of expiratory...
motorneuron activity has been evidenced in the periphery during hypocapnia-induced apnea in both the inter- nal intercostal neurogram of anesthetized cats (14) and in the laryngeal adductor muscle electromyogram (EMG) of awake lambs (8). Furthermore, during neurumechanically induced apneas, tonic expiratory EMG ac- tivities are observed in the transversus abdominus EMG of the awake dog (10) and in the triangularis sterni EMG activity in awake and sleeping dogs (7). This tonic expiratory muscle EMG activity has also been shown to be state dependent (6).

Theoretically, this tonic expiratory neural activity would continue until the persistent inhibitory memory effect had dissipated sufficiently to permit rising chemoreceptor input to “break through” and initiate inspira- tion and thus phasic respiration. Presumably, this tonic expiratory activity would coexist with the sub- threshold oscillatory respiratory-related activities as summarized above. In the study by Iorner et al. (5), the amplitude of the RSA decreased as the apnea pro- ceeded and then increased just before the reinitiation of breathing. These subthreshold time-dependent changes in amplitude might provide a window to the waning of the memory effect and the subsequent gathering in strength of the chemoreceptor input just prior to the breaking of the apnea. The tonic expiratory activity might serve [acting via reciprocal inhibition (14)] to maintain inspiratory neurons below the threshold activity level required for an inspiratory effort. Perhaps many types of apneas whether of chemical or mechani- cal origin are “actively” maintained in this manner. Of course, we do not know what mechanism might trigger the onset of this proposed tonic expiratory activity or how this tonic activity interacts with cells simultaneously experiencing subthreshold oscillatory activity. Neither do we understand exactly how the rising chemoreceptor input and declining memory influences inter- act to ensure the smooth transition into a breath. It is certain that apneas are highly active periods of neuronal activity, as manifested both at the level of the premotor neurons and in the periphery.

The concept of memory, excitation and inhibitory, has several implications for the control of breathing and breathing stability. First, these lingering influences make it difficult to identify primary excitatory or inhibitory influences to ventilation, because responses continue to occur or are modified after the identifiable stimulus is removed. That one breath can exert signifi- cant influences on the next is well established (2, 11). Second, the STP of respiratory motor output following stimulated breathing exerts an important stabilizing influence on ventilation. This is especially true in sleep during which variations in levels of consciousness will change the gain of the central controller, the magnitude of the sensory inputs, and even the mechanical imped- ance of the pump. On the other hand, when inhibitory chemoreceptor and mechanoreceptor influences are dominant (over excitatory STP) and apnea is initiated, these apneas are frequently of much longer duration, and the asphyxia developed is much greater than one would predict based solely on the magnitude of the thresholds that were surpassed to precipitate the ap- nea. In other words, once the apnea is initiated, it appears to be more difficult to reestablish rhythmic breathing, and this may be due in part to the strength of lingering inhibitory memory effects that keep inspira- tory motoneurons suppressed below threshold levels.

REFERENCES