

# Respiratory Sensation and Control of Breathing

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**Abstract:** The observation that non-chemically mediated respiratory load compensation is dependent on a state of wakefulness suggested that the perception of the load or the conscious appreciation of the ventilatory consequences of the loading is required for respiratory motor output to increase. This led to studies of respiratory sensation using a variety of psychophysical approaches. These psychophysical studies revealed that respiratory-related physical changes are consciously appreciated and indicated that sensory information from the ventilatory apparatus does reach the cerebral cortex. This was further supported by physiological studies that demonstrated respiratory-related cortical-evoked potentials over somatosensory regions of the brain. Studies utilizing chest wall vibration support an important role for chest wall muscle spindles in mediating respiratory sensation. Our studies have also shown that voluntarily reducing the level of ventilation at a constant level of chemical drive results in a progressive proportional increase in the intensity of the unpleasant sensation of respiratory discomfort and the increase in respiratory sensation is predominantly a function of the degree to which tidal volume is reduced suggesting that limiting chest expansion or thoracic displacement is the proximate cause of the unpleasant sensation. Our observations that the sensation of dyspnea intensifies with increases in ventilation as well as when ventilation is reduced below the spontaneously adopted free breathing level can be simulated by mathematical models that suggest that respiratory drive integration depends not only on the direct effects of chemical and mechanical feedback but also on the perceptual consequences of these stimuli.

In the course of daily living, the body is challenged to maintain homeostasis by changes in metabolic, mechanical, and environmental conditions. Challenges posed to the respiratory system are greatest by diseases of the ventilatory apparatus that affect the mechanical properties of the lung and chest wall and the mechanical advantage of the respiratory muscles. In the face of all of these perturbations, the respiratory system manages to make appropriate adjustments so as to maintain ventilation at appropriate levels and preserve blood gas and acid-base homeostasis. The initial focus of our research was to identify the mechanisms of the respiratory adjustments to mechanical derangements and the interaction of chemical, neuromechanical, and behavioral systems in the regulation of breathing.

## OCCLUSION PRESSURE AS A MEASURE OF RESPIRATORY MOTOR OUTPUT

Traditional approaches to the study of respiratory regulation have focused on the automatic and involuntary control of breathing with an emphasis on chemical and neuromechanical reflex pathways. Key to the study of the respiratory adjustments to changes in the mechanical properties of the ventilatory apparatus is an accurate and reliable measure of respiratory motor output. For studies in human subjects, the airway occlusion pressure, a measure of the forces generated by the respiratory muscles contracting isometrically against a closed airway, served this purpose reasonably well [1]. In a series of studies we and others showed that respiratory motor output as measured by the occlusion pressure increased with

ventilatory loading in conscious but not in anesthetized animals and humans and the increase occurs even though chemical drive is held constant [2,3]. The dependence of this non-chemically mediated load compensation response on a state of wakefulness suggested that the mechanism was not simply an automatic reflex but rather involved conscious behavioral processing by higher brain centers. This raised the question of whether the perception of the load or the conscious appreciation of the ventilatory consequences of the loading is required in order that respiratory motor output be increased.

## Mechanisms of Respiratory Sensation

It has been long known that there are somatic sensations of position, movement and muscle tension. So it was not unreasonable to presume that there may also be a conscious appreciation of respiratory forces and displacements. Sensation originates with the stimulation of receptors and receptor stimulation is transduced into neural electrical impulses that are transmitted along afferent pathways to the central nervous system. Central processing by higher brain centers involving recapitulation, abstraction, and interpretation results in some evoked expression. With respect to the respiratory system, receptors that may subservise respiratory sensation include mechanoreceptors in airways, lungs, respiratory muscles, tendons, joints [4].

## Psychophysical Studies

Psychophysics is the study of the functional relations between stimulus variables on a physical continuum and the corresponding conscious sensation [5]. We and others have used the technique of psychophysics to examine the subjective perceptual responses to physical changes in the respiratory system.

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Experimental approaches include threshold detection that measure the smallest stimulus or smallest change in stimulus intensity that can be perceived and magnitude scaling that involve having subjects attempt to quantify the intensities of a range of stimuli. A popular approach involved the magnitude scaling of added external ventilatory loads. Loads over at least a 10-fold range are added to the breathing circuit for one or several consecutive breaths and with each presentation subjects respond by assigning a numerical value proportional to the perceived magnitude of the load. As the magnitude of the load increases, there is a proportional increase in the intensity of the response and the relationship between the physical magnitude of the load and the resulting sensation follows the psychophysical power law [6].

The conscious appreciation of these respiratory-related physical changes indicate that sensory information does reach the cerebral cortex, but because of the close linkages among changes in airflow, lung inflation, chest wall expansion and respiratory muscle force during the loaded breath it is not clear what are the specific receptors that mediate the respiratory sensations. Furthermore, the psychophysical responses to different kind of loads (elastic loads, a function of volume, as compared to resistive loads, a function of flow) are not the same. Subsequent studies by Killian *et al.* [7] showed that load sensation is preferentially shaped by the magnitude and duration of the forces generated by the respiratory muscles during the loaded breath. A role for rib cage muscle receptors is suggested by the impaired ventilatory load sensation in patients with low cervical spinal cord transection that blocks the central transmission of sensory information from rib cage receptors [8].

Other studies have also shown that subjects can separately quantitate respiratory force and respiratory displacement. We have assessed the sensations of thoracic displacement by magnitude scaling of breath volume and by the technique of matching the volume of control breaths with test breaths [9]. In matching studies, provided the mechanical conditions of both control and test breaths are the same, matching is highly accurate. However the error in matching increases when the mechanical conditions change between control and test breaths. The volume of a test breath taken against a load falls short of the unloaded control breath. Similarly, others have shown that the perceived magnitude of breath volume is greater during breathing against an added ventilatory load and less during passive mechanical ventilation [10]. These findings suggest that the sensations of displacement is shaped at least in part by the forces developed by the contracting respiratory muscles.

The sensation of respiratory force has been assessed by magnitude scaling of airway pressure during breathing maneuvers against a closed airway [11]. Respiratory force sensation appears to have two components: a sense of tension related to feedback of afferent signals from muscle receptors and a sense of effort based on central nervous system motor command signals [12]. Sensations of effort and tension are distinguishable and can be independently and separately perceived and depending on circumstances both may contribute to the sensations of respiratory force and displacement.

Our study involved matching of force sensation during inspiratory efforts against a closed airway starting from different lung volumes to change the resting length of the respi-

ratory muscles [11]. With lung volume increases to produce muscle shortening, forces perceived to be the same required greater drive as measured by the EMG; with decreases in lung volume to increase muscle resting length there was less drive for forces perceived to be the same. However, with changes in lung volume to alter resting muscle length, the perception of muscle force closely followed muscle tension.

## PHYSIOLOGICAL MECHANISMS

In addition to the psychophysical studies, there is convincing physiological evidence that afferent signals related to breathing are transmitted to higher brain centers. Respiratory-related sensory projections to the cerebral cortex and other forebrain structures have been identified through recordings of cortical-evoked potentials with electrodes over somato-sensory regions on the scalp or on the surface of the brain [13,14]. Brief early and mid-inspiratory airway ventilatory loads produce respiratory-related evoked potentials. Short latency components up to 100 msec appear to reflect the arrival of impulses to the primary somatosensory areas while longer latency components, from 200 to 400 msec represent cognitive processing by higher brain centers that are considerably influenced by alertness, experience and expectation. The close relationship between the amplitude of the short latency cortical-evoked potentials and the magnitude scaling of the load provides important physiological validation of the psychophysical studies and supports the idea of the respiratory-related evoked potentials as a neural measure of cortical activity related to respiratory load sensation [15].

It is still unclear which afferents mediate the respiratory-related evoked potentials. In patients following double-lung transplantation the early latency components in response to inspiratory occlusion are not significantly different from normal but the late latency respiratory-related evoked potential, P3, were delayed and of a smaller amplitude suggesting that vagal afferents are not essential to elicit the evoked response but may contribute to the cognitive processing of respiratory stimuli [16]. On the other hand, direct intramuscular microstimulation has demonstrated projections of low-threshold afferents from human intercostal muscles to the cerebral cortex [17].

A variety of other studies support an important role of chest wall receptors in mediating respiratory sensation. One approach involves chest wall vibration which is known to induce discharge from muscle spindles. Vibration of the chest wall to activate muscle spindles produces an illusion of chest movement. Chest wall vibration has also been shown to ameliorate the sensation of breathing difficulty during both hypercapnia and ventilatory loading and in-phase chest wall vibration also decreases the dyspnea experienced by patients with chronic lung disease [18].

We have also taken yet another approach in an attempt to define the mechanisms of respiratory sensation. Our approach was to assess the changes in respiratory sensation that accompany progressive voluntary reductions in the volume of ventilation below the spontaneously adopted breathing level while chemical drive is held constant [19]. Our studies showed that voluntarily reducing the level of ventilation at a constant level of chemical drive resulted in a progressive proportional increase in the intensity of the unpleasant sensation of respiratory discomfort. We further showed that when

breathing is constrained the increase in respiratory sensation is predominantly a function of the degree to which tidal volume is reduced suggesting that limiting chest expansion or thoracic displacement is the proximate cause of the unpleasant sensation and pointing to a key role for chest wall or possibly lung receptors. Additionally, we have observed that the uncomfortable sensation during constraining of ventilation is ameliorated by chest wall vibration, pointing to a specific role for respiratory muscle spindles.

We were interested in trying to determine the relative contributions of chemical drive on one hand and behavioral influences related to the sensations of respiratory force and/or displacement on the other hand in setting the spontaneous breathing level. We artificially hyperventilated our subjects with a positive pressure breathing machine down to a PCO<sub>2</sub> of about 30 mmHg at which time all spontaneous breathing efforts ceased and mechanical ventilation was fully controlled [20]. We then proceeded to raise the PCO<sub>2</sub> either by increasing the inspired CO<sub>2</sub> concentration, by progressively reducing the inspired ventilator volume, or by progressively reducing the ventilator frequency. There was no resumption of spontaneous breathing activity until the PCO<sub>2</sub> increased to near the spontaneous breathing level but the PCO<sub>2</sub> threshold for the resumption of spontaneous respiratory activity was significantly reduced when the tidal volume or frequency of mechanical ventilation was reduced [21]. These findings suggest that thoracic displacement even when produced by passive ventilation has an inhibitory effect on intrinsic respiratory activity and indicate the importance of non-chemical, neuromechanical feedback related to thoracic displacement presumably involving signals from lung and/or chest wall mechanoreceptors in setting the level of ventilation.

Our findings in awake subjects are in contrast to the finding of Levers *et al.* [22] who mechanically ventilated a group of sleeping subjects and even at eucapnic levels were able to cause a cessation of spontaneous respiratory activity. They further showed that after terminating controlled mechanical ventilation that stopped all thoracic movements apnea persisted for some time and spontaneous respiratory activity did not resume until there was a substantial rise in PCO<sub>2</sub>.

These two studies indicate that what we consider to be an imperative for thoracic movement or displacement at near eucapnic PCO<sub>2</sub> levels is manifest only during wakefulness but not during sleep and points to an important behavioral control mechanism that likely involves feedback from respiratory mechanoreceptors.

## CONTROL OF BREATHING BY HIGHER BRAIN CENTERS

Imaging studies using positron emission tomographic (PET) and functional magnetic resonance imaging (fMRI) have identified pathways for higher brain center control of volitional breathing, ventilatory load compensation, higher brain center contributions to the encoding of the respiratory response to exercise, and a possible behavioral component to the hypercapnic ventilatory response [23-26]. However, the actual sites of integration of automatic and behavioral control have not been well defined. One model outlines two distinct pathways from the motor cortex to the respiratory muscles: a corticospinal pathway from the cortex to spinal respi-

ratory motoneurons and a second cortico-bulbo-spinal pathway descending from the medulla in the ventro-lateral quadrant of the spinal cord to the respiratory motoneurons [27]. Thus, the integration may take place either at the level of the spinal respiratory motoneurons or alternatively at within the brainstem respiratory neurons.

## BEHAVIORAL CONTROL OF BREATHING

The observation that the sensation of dyspnea intensifies with increases in ventilation as well as when ventilation is reduced below the spontaneously adopted free breathing level suggests that breathing is controlled not only automatically but also behaviorally to minimize respiratory sensation [19,28]. This is also supported by mathematical models that include sensations of breathlessness and a dynamic CO<sub>2</sub> controller [29,30]. In these models, breathing sensations are assumed to depend on arterial PCO<sub>2</sub> level, automatic and willful motor commands and mechanoreceptor feedback. Automatic motor command arises from the bulbopontine controller, based on chemical and mechanical feedback. Willful control is assumed to arise from cortical centers. Simulations predict that respiratory sensation intensifies when ventilation is either voluntarily raised or lowered from the optimal level and suggest that respiratory drive integration depends not only on the direct effects of chemical and mechanical feedback but also on the perceptual consequences of these stimuli.

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