RESPIRATORY MECHANORECEPTOR ACTIVATION OF SOMATOSENSORY CORTEX IN HUMANS

By

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This dissertation is dedicated to my beautiful homeland, Taiwan, and to my dearest parents, Dr. I-Chang Jou and Pao-Chu Huang

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RESPIRATORY MECHANORECEPTOR ACTIVATION OF SOMATOSENSORY CORTEX IN HUMANS

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Humans can consciously perceive difficulty with their breathing. It is known that humans can sense external respiratory loads by peripheral mechanoreceptors and process the afferent information via several afferent pathways. However, neural pathways processing the conscious sensation of respiratory loads and how this respiratory afferent information projects to higher brain centers are still poorly understood.

The respiratory-related potential (RREP) elicited by inspiratory occlusion in humans recorded from the scalp provided a unique way to investigate the neural mechanisms mediating respiratory load information and the activation of mechanoreceptor related brain activity. The major goal of this dissertation was to investigate the activation of respiratory mechanoreceptor eliciting RREP responses to inspiratory loads and its relation to somatosensory cortical activation. Using somatosensory evoked potentials as a model of RREP processing, RREP responses to

inspiratory occlusion and during breathing against inspiratory resistive loads with increased background resistance were studied in this dissertation.

The short-latency RREP components were compared with the components of the somatosensory evoked potential (SEP) elicited by mechanical stimulation of the hand, chest, and mouth. Short-latency components of the RREP were also compared between no-background resistance and increased background resistance to determine the mechanism of respiratory baseline state on afferents projecting to the cortex.

Three studies were conducted and a total of 60 healthy adults participated. Results from the first two studies demonstrated that the RREP and SEP are both observed over the somatosensory cortex. Unlike the SEP, the RREP appeared to be elicited by afferents that project simultaneously to both sides of the somatosensory cortex. The RREP may have greater amplitude due to greater population of afferents activated with a global stimulus such as inspiratory occlusion. These results further demonstrated that the RREP Nf peak is a unique frontal cortical activation elicited by inspiratory occlusion. The results from the third study demonstrated the RREP can be changed by increasing the background load and shifting the detection threshold of the subject. If the resistive load is detectable, the RREP was present; if the load is not detectable or became undetectable with increased background load, the RREP was absent.

CHAPTER 1
REVIEW OF CORTICAL PROJECTION OF RESPIRATORY MECHANORECEPTORS ACTIVATION IN RESPONSE TO MECHANICAL LOAD

Cortical Projection of Respiratory Mechanoreceptors

Respiration is regulated by brainstem respiratory centers, which act as intrinsic controllers to generate the respiratory activity. This respiratory activity can be modified by the afferent feedback from both chemoreceptors and mechanoreceptors to meet the respiratory demands. The automatic regulation of breathing can also be overridden by the cognitive centers of forebrain and by conscious control of respiration. Thus, respiration is regulated not only by brainstem automatic controller but also by cortical voluntary motor systems (American Thoracic Society, 1999).

Regular breathing can be modified by consciously perceived sensory inputs from changes in ventilation, such as volume, airflow, pressure, or force. It is well documented in human studies that sensory afferents project to the somatosensory cortex (Kakigi and Shibasaki, 1984). Thus, respiratory sensation and perception may result from the cortical integration of respiratory afferent information. Previous studies have shown the projections of low-threshold afferents from intercostals muscles to the cerebral cortex (Gandevia and Macefield, 1989), and phrenic afferents to the somatosensory cortex in both cats (Balkowice et al., 1995) and humans (Zifko et al., 1995; 1996). Cortical evoked potentials elicited by inspiratory occlusion (Davenport et al., 1986; Revelette and Davenport, 1990), direct vagal stimulation (Tougas et al., 1993), and pressure pulse stimulation to the mouth (Daubenspeck et al., 2000) have been reported. These previous

works suggested that humans can consciously perceive external added mechanical loads and lung volume changes. This conscious awareness of mechanical load implies that there must be activation of neurons in cerebral cortex that is measurable by electrophysiological approaches.

Balzamo et al. (1995) demonstrated that the load estimation of mechanical stimuli applied to the middle finger was significantly lowered by the increased background respiratory resistance in healthy humans. Activation of respiratory afferents by resistive loads also modified the somatosensory evoked potentials elicited by median nerve stimulation in humans (Balzamo et al., 1999). Thus, respiratory afferents activated by mechanical loads may have similar pathways as other somatosensory modalities and may project to the somatosensory cortex. If respiratory mechanical afferents are processed in part by the somatosensory cortex, then neurons of the somatosensory cortex must be activated by respiratory mechanoreceptors. In animals, afferent information processed from both phrenic afferents and intercostals muscle afferents has been demonstrated to activate the thalamus (Zhang and Davenport, 2003) similar to mechanosensation in other sensory modalities (Yates et al., 1994). In addition, phrenic afferents and intercostals muscle mechanoreceptors have been demonstrated to activate neurons of the somatosensory cortex in cats (Davenport et al., 1985; Davenport et al., 1993). Thus, respiratory mechanical afferents may project to the somatosensory cortex via the pathway that is similar to other sensory modalities.

Respiratory Related Evoked Potential

Evoked potentials have been used to record the cortical neural activity elicited by a synchronous stimulation of afferents that project to specific regions of the cortex. The respiratory-related evoked potential (RREP) elicited by inspiratory occlusion in humans

was recorded over the somatosensory cortex (Davenport et al., 1986). The RREP was present bilaterally in normal healthy subjects (Revelette and Davenport, 1990). The latencies of the RREP were inversely related to the respiratory drive and the increases in RREP amplitude were related to the magnitude of the inspiratory load (Knafelc and Davenport, 1997). In addition, the RREP was identified bilaterally in all subjects and the greatest amplitude of the P1 peak of the RREP was found in somatosensory cortex (Davenport et al., 1986; Logie et al., 1998). The RREP was reported using negative pressure mechanical stimuli, expiratory occlusions (Strobel and Daubenspeck, 1993; Hammond and Davenport., 1999) and different timing of inspiratory stimuli (Davenport and Revelette, 1990). Measurement of the RREP also provided a unique way to investigate the cortical activities elicited by respiratory loaded breathing. Humans can consciously perceive changes of airway pressure (Younes and Sanii, 1989). RREPs' were recordings that reflected the cortical activities in response to inspiratory occlusion and inspiratory mechanical obstruction. Thus, it is reasonable to expect that physiological stimulation should produce a RREP with components reflective of the nature of afferent activation of respiratory mechanoreceptors distributed throughout the respiratory system. However, the sources of mechanoreceptors and afferent mechanisms mediating the RREP are unknown.

The RREP elicited by inspiratory occlusion has been reported in animals (Davenport et al., 1985; Davenport et al., 1991; Davenport et al., 2001), children (Davenport et al., 2000), and adult subjects (Davenport et al., 1986; Revelette and Davenport, 1990). A consistent pattern of three components of the RREP (Nf, P1, N1) has been identified in response to occlusions presented either at the onset of inspiration or

by the mid-inspiration (Davenport et al., 1986; Davenport et al., 2000; Davenport et al., 1996).

The greatest amplitude of the P1 peak of the RREP has been identified by using dipole source techniques demonstrates that the generator of the P1 was bilaterally located within primary somatosensory (Davenport et al., 1986; Logie et al., 1998). The P1 component of the evoked potential has been demonstrated to reflect the integrity of primary sensory pathway and varies in morphology with stimulus parameters such as intensity and frequency (Strautus et al., 1997). Results from RREP studies using different levels of resistive loads suggested that the P1 peak is a cortical marker of the arrival of the mechanical sensory signal to the sensory cortex (Campbell et al., 1961; Johnson, 1993; Davenport et al., 1986). These findings suggested that the somatosensory cortex is one part of neural circuitry sub-serving respiratory load perception. In addition, Franzén and Offenloch (1969) reported that the amplitude of SEP components was correlated with the magnitude estimation of the stimuli. Similar results have been demonstrated in the RREP study that the amplitude of RREP P1 peak increased as the increase of resistive load magnitude (Knafelc and Davenport, 1997).

The N1 peak was found in the electrodes over the vertex, Cz (Davenport et al., 1986). The N1 peak can be recorded from the vertical dipole source and is affected by attention (Webster and Colrain, 2000). Evidence for cortical neural processing of respiratory sensation has been identified by using the dipole modeling and concluded the generators of N1 peak were bilaterally located within supplementary motor cortex (Logie et al., 1998). Thus, the N1 peak may be related to the second-order afferent information

processing to the load (Davenport et al., 1996) and may be related to attention (Webster and Colrain, 2000).

A unique negative peak, Nf, has been found at the pre-central electrodes 25-40 ms after the occlusion (Davenport et al., 1996). This short latency frontal peak (Nf) of the RREP represents respiratory load information processing which may be parallel to the somatosensory P1 peak information. The Nf-P1 was hypothesized to represent parallel activation of somatosensory cortex and prefrontal cortex (Logie et al., 1998).The short latency Nf peak has only been found in the pre-central electrodes referenced to the joined earlobes and the P1 peak has not been recorded from frontal electrodes (Davenport et al., 1986), suggesting that dual cortical generators separate via thalamic pathways (Hamalaimen et al., 1990). However, the exact neural mechanism of the Nf peak remains unknown.

The long-latency components of the RREP reflect cognitive and psychological states of the subject. They are influenced primarily by factors extrinsic to the physical stimulus, such as arousal, attention, motivation, and task difficulty and are thought to be related to the cognitive processing of respiratory load information (Bloch-Salisbury et al., 1998; Colrain et al., 1996; Harver et al., 1995; Webster and Colrain, 2000). The RREP P300 peak was found to exhibit changes in amplitude and latency in response to cognitive processing of the stimulus information and perceptual factors (Bloch-Salisbury et al., 1998; Webster and Colrain, 2000).

The role of the short-latency components of the RREP and their relationship with other mechnosensory modalities remains unknown. Therefore, a series experiments has been designed in the current dissertation to investigate the latencies and amplitudes of

short-latency peaks of RREP that are indicators for cortical processing of respiratory load information.

Potential Sources and Afferent Mechanisms of RREP

Afferents in many structures of the respiratory system may contribute to the RREP and the RREP may be the summation of activation of several afferent populations. Respiration against mechanical loads can alter the afferent activity of mechanoreceptors in the mouth, pharynx, larynx, lung and respiratory muscles. The inspiratory occlusion elicits the RREP reflecting the activation of the mechanoreceptors distributed throughout the entire respiratory system (Davenport et al., 1986).The afferent information from these mechanoreceptors is mediated via the facial nerve, vagus nerve, superior laryngeal nerve, recurrent laryngeal nerve, phrenic nerve, and other respiratory muscle nerves. Activation of cortical neurons by these afferents has been reported (Davenport et al., 1986; Zifko et al., 1996; Togus et al., 1993; Gandevia and Macefield, 1989). However, the afferents mediating inspiratory load information and the neural process associated with loaded breath that elicits the RREP remain uncertain.

The activation of cortical neural activity by respiratory mechanical loads has been studied using evoked potential techniques similar to those used in recording the SEP. The fact that subjects are consciously aware of breathing against the mechanical loads suggests that there must be activation of neurons in the cerebral cortex.

Chou and Davenport (2004) have demonstrated that stimulation of phrenic afferents would elicit cord dorsum potential in the dorsal horn of the cat's spinal cord. In this study, the phrenic afferents activated by single pulse stimuli were primary group I and II, and to a lesser extent group III afferents. Electrical stimulation of phrenic afferents has been shown to elicit evoked potential in the area 3a and area 3b of the somatosensory

cortex (Davenport et al., 1985). In addition, cortical evoked potentials elicited by both electrical and mechanical stimuli have been reported (Davenport et al., 1993). This study reported that intercostal muscle afferents project to the area 3a of the somatosensory cortex.

Stimulation of phrenic afferents activates the neurons in the ventroposterior lateral nuclei (VPL) of the thalamus (Davenport and Reep, 1995). The stimulation of intercostals muscle afferents activated different neurons in the VPL of the thalamus (Davenport and Revelette, 1995). Cortical evoked potentials found in the somatosensory cortex were associated with C5 root stimulation (Yates et al, 1994). Retrograde fluorescent tracers in this study found in labeled cells in the oralis nuclei of the ventroposterior complex (VPO) of the thalamus of cats suggested that phrenic afferents project to the somatosensory cortex via thalamocortical pathway. Straus et al. (1997) reported cortical evoked potentials elicited by phrenic stimulation in humans. In addition, Gandevia and Macefield (1989) demonstrated cortical projections by stimulating intercostals muscle afferents in humans. Evidence of neural substrates mediating the afferent information from respiratory mechanoreceptors to the somatosensory cortex has thus been provided from both animal and human studies. Therefore, information related to respiratory mechanical activity may be transduced by respiratory mechanoreceptors and project to the somatosensory region of the cortical cortex via a dorsal column lemniscal pathway, which is relayed at the VPL and/or VPO of the thalamus.

Single pulse vagal nerve stimulation elicited activity in sensory cortex and thalamus in the monkey (Hallowitz and MacLean, 1977). A similar study in cats reported that cortical evoked potentials recorded in both the somatosensory cortex and motor

cortex elicited by vagal afferents (Korn and Massion, 1964). A positive peak of the evoked potential with a latency of about 21-22ms was elicited by natural cutaneous stimulation directed to the skin of the face (Schieppati and Ducati, 1984). Similarly, two subsequent studies also showed that both facial and trigeminal nerve afferents could elicit neural activity in the somatosensory cortex in human (Hashimoto, 1987; Seyal and Browne, 1989). Cortical activities elicited by superior laryngeal nerve stimulation have also been recorded in cruciate sulcus, anterior sylvian sulcus, suprasylvian sulcus and orbital cortex in cats (Aubert and Guilhen, 1971).

There are two potential afferent pathways for lung vagal afferents: one projects to the somatosensory and motor cortices and a second projects to the mesocortex. Although there is limited information concerning vagal afferent pathways to the somatosensory cortex and the neural activity elicited by vagal afferent activation in humans, mechanoreceptor information from the upper airway and lung has been demonstrated to elicit cortical activation in response to negative pressure (Daubenspeck et al., 2000). The presence of both early- and late- RREP peaks in double lung transplant recipients with and without tracheostomy suggested lung vagal afferents and upper airway mechanoreceptors elicit a RREP in response to inspiratory occlusion but are not essential sources of the RREP response (Davenport et al., 2004; Zhao et al., 2002; 2003). Thus, respiratory related afferents activated by inspiratory occlusion or negative pressure pulses elicited cortical neural activity. This information may arise from respiratory muscles, the lung and/or the upper airways.

Breathing against an external resistive load changes the pressure, volume, and airflow in the entire respiratory tract. These mechanical changes are mediated by

mechanoreceptors from the lung, upper airway and respiratory muscles. There are many potential afferent sources and pathways that contribute to respiratory perception of loaded breaths. However, it is difficult to determine the specific neural mechanism subserving load related afferent information processing because the load dependent mechanical events are transmitted throughout the entire respiratory tract.

Several sensory sources may contribute to respiratory sensation. Among them, respiratory muscle afferents probably play a primary role. However, the roles of receptors in the upper airway and lung remain equivocal. Application of external loads to the airway increases the transluminal pressure gradient across the extrathoracic airways. This changes the airway wall configuration and consequently modulates the sensory information arising from those upper airways. Both animals (Davenport et al., 1985; Davenport et al., 1993; Davenport and Hutchison, 2001) and humans (Davenport et al., 1986; Davenport et al., 1996; Knafelc and Davenport, 1997) have been studied to understand the afferent mechanism of the RREP. Animal studies of respiratory sensation have been developed in dogs with tracheal stoma. These dogs were behaviorally conditioned to detect inspiratory resistive loads and occlusions. The stoma in these dogs excluded afferent information from the upper airway mechanoreceptors. It was found that dogs with a tracheal stoma could reliably detect inspiratory resistive loads and occlusion (Davenport et al., 1991). Thus, it appears that afferents in the mouth, nose, pharynx, larynx and upper extrathoracic trachea are not mediating load detection in these dogs. The remaining intact sources diaphragm muscle mechanoreceptors and intercostal muscle mechanoreceptors were likely the afferents mediating the load information. Phrenic and intercostals muscle afferents have been reported to activate neurons in somatosensory

region of the cat brain (Davenport and Reep, 1995; Davenport and Revelette, 1995). Animal studies of the neural mechanism mediating respiratory sensations have demonstrated that respiratory muscle afferents may be, in part, mediating respiratory sensation (Davenport et al, 1985; Davenport et al., 1993; Davenport and Hutchison, 2001; Zhang et al., 2003). The occlusion-elicited evoked potential, which is analogous to the RREP in human studies, has been recorded in the somatosensory cortex of awake lambs (Davenport et al., 2001). The RREP was present when the lambs respired via their mouth and via an endotracheal tube.

Stimulation of intercostal muscles (Gandevia and Macefield, 1989), vagal afferents (Tougas et al., 1993), supraglottal afferents (Daubenspeck et al., 2000), and phrenic afferents (Straus et al., 1997; Zifko et al., 1996) activates the somatosensory cortex with short latency evoked potentials in humans. This somatosensory cortical projection is via the thalamus which is similar for mechanoreceptor sensation for other sensory systems. However, the neural mechanism and afferent pathway of the RREP elicited by inspiratory occlusion in humans remain unknown.

In summary, there may be two cortical pathways involved in respiratory central neural processing (Davenport et al., 1995). One is the pathway for respiratory muscle afferents. Neural information arising from respiratory mechanoreceptor enters the spinal cord, ascends in the dorsal column, relays in the brainstem, projects to the ventroposteral region in the thalamus via the medial lemniscal tract, and is projected through a thalamocortical pathway to the sensorimotor cortex (Zhang et al., 2003). The function of this pathway could relate to the mechanical events of respiratory muscles. The second pathway involves ascending afferent information from pulmonary stretch receptors via

the vagal nerve and its branches, and possibly the upper airways mediated by the RLN, SLN, trigeminal and facial nerves. They relay sensory information to the brainstem and then project to the mesocortex. This circuit may be related to the behavioral aspect of respiration.

Mechanical SEP and Somatosensory Pathway

There are receptors that inform the brain about mechanical stimuli from touch, pressure, and vibration (Mountcastle, 1980). Cortical evoked potentials can be elicited by different sensory modalities (Mima, 1997). Evoked potentials have been studied extensively in humans from somatosensory modalities and provide information regarding cutaneous potential fields generated by synchronous activation groups of neurons. In addition, evoked potentials generated in the cerebral cortex have an inversion of polarity as the electrode is lowered from the surface to underlying cortex; that is, a change of polarity is recorded as an electrode passes from the positive voltage region (source current) to the negative voltage region (sink current). An inversion of polarity of large amplitude focal potentials thus provides strong evidence for the presence of a local generator with dipolar properties (Wood and Allison, 1981). The activation of somatosensory neuronal activities has been studied and well defined for its onset latency by recording the sensory evoked potential (SEP) associated with electrical and mechanical stimulation. Onofrj et al. (1990) concluded that short-latency SEP components recorded following mechanical stimuli were of longer latency and smaller amplitude than evoked potentials recorded following electrical stimuli. This result was supported by the findings from Buchthal (1980) that more time was needed for skin indentation and the process of receptor transduction with mechanical stimuli as compared to electrical stimuli.

The SEP is the result of the summed activity in the somatosensory cortex in response to somatosensory afferent input. The SEP can be expected with physiological stimuli and can be used as a method for measuring electrophysiological and perceptual events. Cortical surface recordings show that the early peaks of SEP were evoked only by contralateral stimulation; ipsilateral stimulation did not produce detectable activities (Lüder et al., 1986; Wood et al, 1988; Allison et al., 1989). Studies of the SEP have focused on the sources and components of the SEP considered to reflect both cortical and subcortical activation of the brain (Desmedt et al., 1983, 1984; Kekoni et al., 1997). In fact, the early components of the SEP following mechanical stimulation have been found to correlate with stimulus magnitude and magnitude estimation and are a summation of spatially and temporally overlapping potentials that may have separate origins (Hashimoto et al., 1987). Since the SEP is the result of summed activity in the somatosensory cortex in response to afferent outputs, methods can be used to quantify both electrophysiological and perceptual events (Regan et al., 1984). The short-latency component of the SEP elicited by mechanical stimulation was correlated with the magnitude of the stimulus and the magnitude estimation of the subjects (Franzěn and Offenloch, 1969; Hashimoto et al., 1992). The spatiotemporal pattern of these recordings has been demonstrated in previous studies that a series of two early peaks recorded within 100 ms after stimulation were largest over the contralateral somatosensory cortex (Kakigi and Shibasaki, 1984; Hashimoto, 1987). Inputs from the somatosensory cortex were essential for activation of other cortical regions. This may explain why lesions or surgical removal of the hand area of the human somatosensory cortex appears to abolish all cortical SEP peaks (Stohr and Goldring, 1969; Williamson et al., 1970; Allison et al.,

1992). Patients with cerebral lesions producing abolition of contralateral short-latency SEP also exhibit bilateral loss of long latency SEP peaks (Williamson et al., 1970).

The short-latency peaks of the SEP originate from the somatosensory cortex located in the rostral bank of post central gyrus (Allison et al., 1989a; Allison et al., 1991; Wood et al., 1988) in humans and indicate that cutaneous mechanosensation is initially processed in somatosensory regions of the cortex (Geyer et al., 1999). Results from direct subdural strip recordings have shown that the occurrence of the early peaks in the somatosensory cortex appears to play a necessary but not sufficient role in conscious awareness of an afferent stimulus (Ray et al., 1999). Peterson et al. (1995) reported in monkeys that short-latency components of epidural SEP elicited by median nerve stimulation were the result of separate generators, which consisted of a number of dipole sources in precentral gyrus (frontal electrodes).

Information related to different sensory modalities is initially transmitted along parallel, modality-specific, multisynaptic pathways (Mountcastle, 1980). Information detected by external sensory receptors is relayed via the pathway stations in the brainstem to thalamus, then projected to specialized areas of the cortex. Studies of primates have demonstrated that the primary somatosensory cortex has not only a somatotopic but also modality-specific organization (Kaas, 1991). Area 3b and area 1 were mainly activated by cutaneous stimulation, while area 3a receives afferent input from deep sensory receptors and area 2 plays a somatosensory integrative function for all modalities. Previous studies have shown the projections of intercostal muscle afferents and of the phrenic afferents to the somatosensory cortex (Gandevia and Macefield, 1989; Davenport et al., 1993; Zifko et al., 1995; 1996). These results support the conclusion that cortical

activation was the summation of respiratory afferents projecting to the sensory region of the cortex.

Perception of Mechanical Loads

Mechanoreceptors activated by mechanical loads during respiration and the pathway mediating the afferent information to higher brain center play an important role for the perception of respiratory obstruction. Perception of respiratory mechanical events depends on cognitive processing of afferent information from peripheral mechanoreceptors. This is measured in conscious humans by determination of the threshold value of a stimulus required for detection and/or the estimation of load magnitudes over a range of stimuli above the detection threshold. Signal detection may only require activation of a set of parallel somatosensory pathways, but magnitude estimation involves cognitive evaluation.

Sensation of respiratory resistive loads, using psychophysical studies of load detection and magnitude estimation of respiratory resistive load, is similar to other mechanical load interventions to the respiratory system (Killian et al., 1980; Stubbing et al., 1981). Psychophysical methods have been used to quantify respiratory sensation (Wiley and Zechman, 1966). The perception of respiratory mechanical events, such as an applied resistive load, is dependent on two processes (Johnson, 1993). The first step is load detection, which has been studied by using difference threshold methods (Campbell et al., 1961; Davenport et al., 1986). The second perceptual process includes differentiation of the load type and estimation of the load magnitude. Experimentally, subjects were required to provide an estimate of the sensory magnitude of a load above the detection threshold using a numerical scale or cross-modality matching, such as handgrip tension sensation to match the magnitude of respiratory sensation (Davenport et

al., 1996; Revelette and Davenport, 1990; Davenport et al., 1991). These studies showed that the perceived magnitude of an increased extrinsic load is linearly related to the load magnitude when a log-log transformation is used. The slope of the line is a measure of the sensitivity of the subject to the stimulus.

Adult humans can perceive and scale respiratory mechanical loads (Bennett et al., 1962; Buki et al., 1983; Strobel et al., 1993; Fitzpatrick et al., 1995). The mechanical loads are added to the breathing pathway of human subjects. Resistive loads alter respiratory pressure-flow dynamics. Added resistive loads are constructed of porous material and are connected in series to a breathing circuit to provide linear increases in airflow resistance. Resistive loads serve to mimic the type of internal airflow limitation experienced by patients with obstructive lung disease such as asthma. Typically, a series of known resistive loads are added for one or several breaths and the subject indicates if the added load is sensed (Zechman et al., 1979). The detection of respiratory loads is dependent on the background resistance of the subject's airways and the breathing apparatus (Wiley and Zechman, 1966). The ability of a subject to detect an added load, ΔR_{50}, is a function of the ratio of the added load to the background load (R_0) resulting in the Weber-Fechner Ratio, $\Delta R_{50}/R_0$. The $\Delta R_{50}/R_0$ for normal subjects is 0.3, meaning that the ΔR_{50} must be 30% above the total R_0 for the load to be detected. This $\Delta R_{50}/R_0$ is also 0.3 for COPD patients with elevated background resistance. The detection threshold ΔR_{50} is higher as is the R_0 but the ratio remains constant.

Ventilation is a mechanical process with respiratory muscles generating the driving force to the respiratory pump. Breathing against an external mechanical load changes the breathing pattern in a load-specific manner. Inspiration against a suprathreshold load

results in a reduction of airflow for a resistive load (Zechman and Davenport, 1978). Inspiratory obstruction alters the mechanical breathing process and leads to a conscious perception of the mechanical loads. The pattern of airflow, volume and pressure changed by adding the resistive load and the perception of the added resistive load is also changed by adding a background load (Revelette et al., 1990). Perceiving a loaded breath is affected by the increased background resistance. The detection threshold of increased internal (Burdon et al., 1982) or external (Burki et al., 1978; Gottfreid et al., 1981; Wiley and Zechman, 1966) resistance depends on the change in the background resistance rather than the absolute value of the added load. Thus, the background resistance plays an important role in the perception of respiratory mechanical loads. These mechanical changes may be mediated by afferents from the mouth, airways and respiratory muscles. The detection threshold has been determined as the load that is detected 50% of the time (Bennet et al., 1962; Campbell et al., 1961; Wiley and Zechman, 1966). Different threshold values have been shown to be most reliable when they are expressed as a fraction of the background. The detection threshold has been shown to be constant in normal subjects with externally elevated background (Stubbing et al., 1981) and asthmatic patients with internally increased mechanical loads (Burki et al., 1978). Breathing against mechanical loads induces changes in respiratory mechanics and there are pathways to mediate afferent information from respiratory mechanoreceptors to the cortex. However, the effect of the background resistance to the cortical activation of a loaded breath is unknown.

Poor perception of respiratory effort in patients with chronic pulmonary disease may be due to a deficit in afferent information processing originating from respiratory

mechanoreceptors or the pathways to the somatosensory cortex. It has been reported that the perceived magnitude declines with a background resistive load of 14.2 cmH2O (Burdon et al., 1983). Decreased perception of inspiratory resistive loads occurred when a higher background load were present to the subjects (McCloskey, 1973). It is likely that load detection may only require the activation of the sensory pathway but the magnitude estimation may involve evaluation of information from multiple afferent pathways. Evidence for the somatosensory cortex involvement in the mediation of signal detection has been investigated with the use of the EEG (Hillyard et al., 1971; Wilkinson and Seales, 1978). They have demonstrated the relationship between evoked potentials and measures of signal detection in different sensory modalities. Measurement of the RREP provides a unique way to investigate cortical activity involved in the perceptual responses to external mechanical loads.

Asthma and other chronic obstructive pulmonary diseases are often associated with an increased airway resistance (like adding a background resistive load) and are known to decrease the perception of added resistive loads. Perception of inspiratory loads was blunted by the increased background airway resistance (Revelette et al., 1984). The short-latency component of evoked potentials reflects the integrity of the primary sensory pathways and varies in morphology with stimulus parameters such as intensity and frequency. The long-latency components of evoked potential reflect cognitive and psychological state of the subject. They are influenced primarily by factors extrinsic to the physical stimulus, such as arousal, attention, motivation, and task difficulty. Although it has been reported that the RREP can be elicited by different magnitudes of resistive loads, no study has addressed the relationship between the effect of increased background

resistance on the conscious sensation of resistive inspiratory loads and the RREP. It is unknown if the decreased perception of added loads in the presence of an increased background resistance is associated with a change of RREP peaks.

Summary of Experiments

Cortical activation by respiratory stimuli has been recorded in both human and animals. Animal studies have demonstrated that afferents in the respiratory system have projection pathways to the cerebral cortex. Respiratory mechanical changes associated with loaded breaths are mediated via those afferent pathways. Measurement of the RREP provides a unique method to study cortical responses to respiratory load stimuli. The afferent pathway, cortical distribution and neural mechanisms processing respiratory mechanoreceptors have been only implied in human studies. However, perceptual process related to RREP responses and the relationship between the RREP elicited by respiratory mechanical loads and the SEP from other mechanical stimuli remains unknown. The RREP and SEP elicited by different somatosensory modalities (negative pressure, air puff, cutaneous stimulation) were tested in the first two parts of this dissertation. The RREP response to resistive loads with increased background resistance was investigated in the last part of this dissertation. If the somatosensory system is processing respiratory perceptual information, then comparing the latencies and amplitudes of evoked potentials elicited by respiratory load stimuli with known somatosensory stimuli will determine if respiratory mechanosensation is processed, in part, through the somatosensory cortex.

The first two experiments were designed to determine the cortical localization and neural mechanism of the short-latency components (with peak latency < 100ms) of the RREP in healthy adults eliciting inspiration against mechanical loads. The short-latency peaks of the RREP were hypothesized as indicating the initial activation of the

somatosensory cortex by breathing against the respiratory resistive load and were similar to mechanically elicited sensory evoked potentials (Hamalaimen et al., 1990).

Rationale for Study 1

The activation of cortical neurons by respiratory mechanical loads has been studied using evoked potential techniques similar to those used in other somatosensory systems such as mechanical stimulation of the skin. The fact that subjects can sense the respiratory change against loads suggests that there must be activation of neurons in the cerebral cortex and this activation should be measurable. Therefore, the RREP provides unique neurophysiological evidence of cortical activation during mechanically loaded breathing. Revelette and Davenport (1990) found that the RREP was present bilaterally and can be elicited by occlusions either at the onset of inspiration or at mid-inspiration. They reported that the peak amplitude was greater and the peak latency shorter for the evoked potentials produced by the mid-inspiratory occlusions. The relationship of the RREP and mechanical load perception has been studied using graded resistive loads. Positive correlations were found between the peak amplitude of P1 and the magnitude of the added resistive load, and the magnitude estimation of the load (Knafelc and Davenport, 1997; 1999). A negative peak (Nf) occurred 25~40 msec after the loaded breath and was maximal at frontal electrode sites (Davenport et al., 1996). These topographical data provide evidence for dipole sources both pre (motor cortex) and post centrally (somatosensory cortex).

It is difficult to determine the specific afferent mechanism mediating the perception of inspiratory mechanical loads because load-dependent changes are transmitted throughout most of the respiratory tract and pump. It has been hypothesized that the somatosensory system is mediating respiratory perceptual information processing.

Comparing the neural markers for respiratory mechanical stimuli with known somatosensory stimuli (skin indentation) tests if respiratory mechanosensation is mediated, in part, by the same areas of the somatosensory cortex as mechanical stimulation of the skin. The results of this study will provide new information on the similarity between mechanical load neural activity related to the component peaks of the RREP and somatosensory mechanical skin stimulation. Although one report described the relationship between afferent activity in peripheral nerves and perception of the evoking mechanical stimulation of receptors in hand of human subject (Knibestol and Vallbo, 1979), it was unknown if or how the components of the SEP reflect the same processes as the RREP. Therefore, the present study investigated short-latency components in both the RREP and the SEP to identify the components showing a functionally similar distribution. The hypothesis tested in this part of the research:

The RREP response to inspiratory occlusion was similar to the SEP elicited by cutaneous mechanical stimulation on hand.

Rationale for Study 2

A cortical SEP can be recorded following air-puff stimulation of the hand (Schieppati and Ducati., 1984; Hashimoto, 1987; Hashimoto et al., 1990), face (Hashimoto et al., 1991) and foot (Hashimoto et al., 1992). These mechanical stimuli physiologically activate mechanoreceptors and are specific to mechanoreceptors unlike electrical stimulation usually employed to elicit SEPs (Gardner and Costanzo, 1980ab). Air-puff provides reproducible tap-like stimuli without steady pressure or direct contact to the skin. The air-puff stimulates a restricted area of skin in a spatial and temporal pattern and is known to activate cutaneous mechanoreceptors (Hashimoto et al., 1991b). Mouth mechanoreceptors have been proposed as one population of mechanoreceptors

mediating the RREP. If this is correct, then the air puff mouth stimulation will elicit an evoked potential similar to the RREP. The cortical response to air-puff stimuli has been reported in monkeys (Gardener et al, 1984) and humans (Gardner and Tast, 1981). Therefore, air puff seems to provide an excellent method for eliciting neurophysiological activity underlying the evoked potentials (Hashimoto et al., 1991b; Hashimoto et al., 1992; Hashimoto et al., 1987).

The SEP elicited by mechanical stimulation exhibited a gradual increase in amplitude and a decrease in latency with increasing stimulus intensity (Hashimoto et al., 1992). The SEP has been recorded in response to a variety of mechanical stimuli over the finger, palm, and face. The SEP elicited by mechanical stimuli were similar to those elicited by inspiratory occlusion. However, RREP studies with inspiratory occlusion have invariably documented latency delays and amplitude augmentation in early peaks relative to cutaneous mechanical counterparts. The latency delays and amplitude augmentation were ascribed to the global effect of mechanoreceptor activations and might be different sensory pathways processing the information.

The second study investigated the mechanics of latency delay, amplitude augmentation and patterns of peaks for inspiratory occlusion elicited RREP by comparing this potential to evoked SEP with different sensory modalities from two selected areas (chest and mouth). The chest and mouth are chosen because they have mechanoreceptors that have a similar neural path length as respiratory muscles (chest) and they may be activated by inspiratory occlusions to elicit the RREP (mouth). If the pattern of the RREP is similar to that of SEP's with activation of the chest skin and mouth, then the latency

and amplitude between the RREP and SEP should be similar. The hypothesis tested in this part of the research:

The RREP response to inspiratory occlusion is similar to the SEP elicited by activation of mechanoreceptors on the chest wall (the level of diaphragm location, 7^{th} ribcage) and the buccal surface of the mouth.

Rationale for Study 3

Perception of respiratory loads is dependent of the background conditions of the subjects' respiratory tract and is blunted by elevated background airway resistance (Wiley and Zechman, 1966). Asthma and chronic obstructive respiratory disease is often associated with an elevated background airway resistance and is known to decrease the perception of added resistive loads. It is unknown if RREP peaks will decrease their amplitude or will not be elicited in the presence of an increased background resistance. Therefore, the third experiment investigated the short-latency RREP components elicited by inspiratory resistive loads with and without increased background load. The aim of the third study was to determine the RREP responses to inspiratory resistive load when gating by the elevated background resistance, and the relationship between conscious perceptual process of respiratory mechanical loads and RREP components. Short-latency components of the RREP were measured in subjects under two conditions: with and without increased background resistance. Two hypotheses were tested in this part of the research:

Short-latency RREP components (P1, N1, and Nf) are involved in conscious perception of respiratory mechanical loads and are recorded only when the added resistive load is above the detection threshold, $\Delta R_{50}/R_0$ is greater than 0.3.

A resistive load detectable without increased background elicits an RREP but the RREP is not present when the background is increased to make the same load undetectable, $\Delta R_{50}/R_0$ is less than 0.3.

Summary of Hypotheses

The hypotheses are summarized below:

1. RREP response to inspiratory occlusion is similar to the SEP elicited by cutaneous mechanical stimulation on hand.

2. RREP response to inspiratory occlusion is similar to the SEP elicited by activation of mechanoreceptors on the chest wall (the level of diaphragm location, 7^{th} ribcage) and the buccal surface of the mouth.

3. Short-latency RREP components (P1, N1, and Nf) are involved in conscious perception of respiratory mechanical loads and are recorded only when the added resistive load is above the detection threshold, $\Delta R_{50}/R_0$ is greater than 0.3.

4. A resistive load detectable without increased background elicits an RREP but the RREP is not present when the background is increased to make the same load undetectable, $\Delta R_{50}/R_0$ is less than 0.3.

CHAPTER 2
THE CORTICAL RESPONSES TO INSPIRATORY LOADS AND TACTILE STIMULATION FOR HEALTHY ADULTS.

Introduction

The ability of the respiratory system to maintain normal ventilation when opposed by an external mechanical load is a motor process performed by the respiratory muscles acting as a pump to generate the driving force for air to flow and increase the lung volume. Application of extrinsic mechanical loads of sufficient magnitude alters this mechanical process and leads an activation of cortical neuron activities. The development of reliable objective neuronal methods for studying the sensory and motor mechanisms involved in respiratory load perception has resulted in a better understanding of the mechanisms of respiratory perception. Cortical activation by afferent stimulation is evidenced with event-related evoked potentials (ERP). The ERP elicited by visual, auditory and somatosensory stimuli have been well studied (Desmedt et al., 1987; Kekoni et al., 1992; 1997). The fact that subjects can sense a respiratory change against inspiratory loads suggests there must be activation of neurons in the cerebral cortex. The activation of cortical neurons by respiratory resistive loads has been studied using evoked potential techniques (Davenport et al., 1986). Davenport et al. (1986) applied inspiratory occlusions in healthy subjects and recorded the evoked potentials from the scalp. This study demonstrated that brief occlusion of the inspiratory airway in humans produces a series of respiratory related evoked potential (RREP) components. The RREP recorded over the somatosensory cortex provided a unique way to investigate higher cortical activities

associated with inspiration against mechanical loads. Revelette and Davenport (1990) also found that the RREP was present bilaterally and elicited by occlusions either at the onset of inspiration or at mid-inspiration. They reported that the peak amplitude was greater and the peak latency shorter for the evoked potentials produced by the midinspiratory occlusions. Thus, the RREP provides a unique measure of respiratory load neural processing.

A consistent pattern of three peaks of the RREP (Nf, P1, N1) has been identified (Davenport et al., 1986; Revelette and Davenport, 1990; Davenport et al., 1996; Knafelc and Davenport, 1997). The first peak of the RREP, P1, was a positive voltage that is elicited by the arrival of load activity from a population of afferents activated by the inspiratory occlusion stimulus depolarizing a column of neurons in the somatosensory cortex.

Both P1 and N1 peaks were found in the central and post-central electrodes which correlated with the somatosensory region of the cortex (Davenport et al., 1996). The amplitudes and location of P1 and N1 peak activity suggest that the somatosensory cortex is one part of the neural pathway sub-serving respiratory load information processing (Logie et al., 1998). Neither the P1 nor the N1 peak was recorded from frontal electrodes. A negative peak, Nf, was recorded from the pre-central electrodes 25-40 ms after the occlusion (Davenport et al., 1996). This short latency frontal peak of the RREP may be parallel to the processing of P1 peak information.

Human skin contains receptors that inform the brain about mechanical stimuli such as touch, pressure, and vibration (Mountcastle, 1980). The activation of somatosensory neuronal activity has been studied by recording the sensory evoked potentials (SEP) associated with mechanical or electrical stimuli (Onofrj et al., 1995; Desmedt et al., 1983;

1984; Deiber et a., 1986; Gardner et al., 1984; Gerber and Meinck, 2000). Onofrj et al. (1995) reported that short-latency SEP components recorded following mechanical stimuli were of longer latency and smaller amplitude than evoked potentials recorded following electrical stimuli. This result was supported by the findings from Buchthal (1980) that more time was needed for skin indentation and processes of receptor transduction with mechanical stimuli than electrical stimuli.

Studies of the SEP have focused on the issue of sources and components of SEP that reflect both cortical and subcortical activation of the brain (Larrson and Prevec, 1970; Desmedt et al., 1983, 1984; Kekoni et al., 1997). The SEP is the net result of activity in the somatosensory cortex in response to the afferent inputs. The SEP is correlated with physiological measures and used as method for measuring both electrophysiological and the perceptual events (Franzén and Offenloch, 1969; Gescheider and Wright, 1968; Hashimoto et al., 1988; 1992). The early components of the SEP following mechanical stimulation were reported to correlate with stimulus magnitude and magnitude estimation (Hashimoto et al., 1987; 1992). The activation of cortical neurons by respiratory mechanical loads has been studied using evoked potential techniques similar to those used in recording the SEP.

The afferents mediating load perception are primarily located in the respiratory muscle pump (Davenport et al., 1993). However, it is difficult to determine the specific afferent mechanism mediating the respiratory afferent information because load-dependent changes are transmitted throughout most of the respiratory tract and pump. The scalp was mapped for the distribution of the short latency peaks of the RREP using the earlobe reference. The P1 peak was found predominately over the somatosensory

region of the cortex in both animals (Davenport et al., 1985; Davenport and Hutchison, 2001) and humans (Davenport et al., 1986; Logie et al., 2000). The RREP associated with inspiratory occlusion was recorded bilaterally over the somatosensory cortex and was also elicited by occlusions either at the onset of inspiration or at mid-inspiration (Davenport et al., 1986; Revelette & Davenport, 1990). The P1 peak amplitude was greater and the peak latency shorter for the evoked potentials produced by the midinspiratory occlusions. These reports provide evidence for dipole sources both pre (motor cortex) and post centrally (somatosensory cortex). Thus, respiratory afferents project via somatosensory pathways to the cerebral cortex. This is similar to somatosensory cortical processing of cutaneous mechanical information.

Respiratory muscle afferents have transduction properties and cortical projection pathways consistent with their hypothesized role in respiratory load sensation. Logie et al. (1998) identified the dipole locations of the P1 peak bilaterally located within the primary somatosensory and the Nf peak bilaterally in the supplementary motor cortex. Activation of the contralateral sensorimotor cortex was reported following stimulation of the intercostal muscle afferents (Davenport et al., 1993; Gandevia and Macefield, 1989) and stimulation of phrenic afferents (Davenport et al., 1985). If this respiratory related cortical activity is similar to evoked potentials for other sensory system, then the early P1 potential represents the arrival of the sensory signal in the somatosensory region of the cerebral cortex.

The study of the RREP has focused on the short-latency components (P1, Nf and N1) because they were similar to the initial sensory components in the cortical processing of respiratory resistive load information (Davenport et al., 1986). The main function of

the somatosensory cortex is to integrate mechanical information from the skin, joint, and muscles afferents. Both RREP and SEP elicited by mechanical stimuli represent cortical neural activity with different scalp distributions. However, the correlation between RREP and the mechanical induced SEP is unknown. The purpose of the present study was to compare the inspiratory occlusion elicited RREP and the SEP elicited by cutaneous mechanical stimulation. The SEP and RREP were recorded in the same individuals. It was hypothesized that the P1 peak of the RREP and SEP are recorded over the somatosensory cortex. It was further hypothesized that the latency of the SEP elicited by mechanical stimulation is shorter than the RREP elicited by inspiratory occlusions.

Methods

Subjects

Adult subjects (9 male, 11 female; average age = 25.5) were recruited. The subjects were healthy and normal on the basis of no self-reported history of cardiorespiratory disease, no self-reported history of smoking and no evidence of current major or minor illness. They were informed of the nature of the study before starting the experiment and written consent was obtained. The institutional Review Board of the University of Florida reviewed and approved this study.

Pulmonary Function Testing

The subjects were asked to refrain from strenuous physical activity, large meals and caffeine for at least four hours prior to the test. Subjects were seated upright in a chair. Spirometry testing conformed to the American Thoracic Society Standards. Forced vital capacity (FVC), forced expiratory volume within 1 second (FEV1) and airway resistance by the forced oscillation method were measured in each subject. A FEV1 greater than 70 % predicted was required for the subjects to continue in the study.

RREP

The subject was seated in a sound insulated room, with the back, neck and head comfortably supported. An electrode cap with integral electrodes was used to record scalp EEG activity. The cap was placed on the subject's head, positioned and secured with a strap. Scalp and electrode contact was made by the application of electro-conducing paste administered through the center opening in the electrode. The impedance levels for each electrode was checked and maintained below 5 KΩ. The electrode cap was then connected to an electroencephalograph system (Model 12 Neurodata Acquisition System, Grass Instruments, Quincy, MA). The EEG activity was recorded from electrode positions; Fz, F4, F3, Cz, C4, C3, Cz', C4', C3', Pz, P4, and P3 according to the International 10/20 system with the joined earlobes as the reference. EEG activity was amplified and bandpass filtered (0.3Hz-1 kHz). Eye movements (EOG) were recorded with electrodes placed over the lateral edge of the eye. The EEG activities and mouth pressure (Pm) were recorded and led to a signal analysis system (Signal 2, Cambridge Electronics Ltd). The experimenter and recording equipment were in the adjacent room. The subject was monitored with a video camera during the experiment.

The subject respired through a non-rebreathing valve with the inspiratory port connected to a pneumotachograph and occlusion value. Mouth pressure was recorded at the center of the non-rebreathing valve, sensed with a differential pressure transducer and amplified with a signal conditioner. The inspiratory load was presented by silently inflating the occlusion valve at approximately the mid-inspiration point of the breath. Pm was used for timing of respiratory occlusion. There were 2 experimental trials for the RREP: control trial and load trial. Both trials were separated by a 5-minute rest period off the breathing apparatus. During the load trial, inspiration was occluded for about 300

msec every 2-5 breaths. A minimum of 100 occlusions were presented. The control trial consisted of 100 valve activations every 2-5 breaths. The subjects inspired through a side port on the occlusion manifold and the inspiration was not obstructed with the valve activations. The subject watched a video movie to mask the auditory cues. The RREP was obtained by averaging a minimum of 64 occlusions. An individual occlusion presentation was included in the average if it produced a minimum 3 cmH2O change in Pm and there was no eye blink. The early RREP components were defined as follows: P1 was the maximal positive deflection 40-60 milliseconds following the onset of the change in Pm. N1 was the negative deflection in the latency range of 80-120 milliseconds; Nf was the negative deflection in the latency range of 25-40 milliseconds. Baseline-to-peak amplitudes were determined for each peak. Latencies were determined as the time from the onset of the Pm change to the RREP peak. The control trial used the same procedures except there was no occluded breath.

SEP

Cutaneous mechanical stimulation consisted of a square wave indentation of the skin on the subject's non-dominant hand. The skin indentation was produced by a controlled linear induction motor attached to a blunt flexible tube placed 2mm above the surface of the skin. To obtain the SEP, subjects were asked to place their forearm on a handrest in a fixed position. The hand was placed in position with the hand and mechanical stimulator screened from the subject by a curtain. A series of 512 cutaneous stimulations were delivered. A strain gauge was used to calibrate mechanical pulses. Each skin indentation had a duration of about 400 msec and was delivered every 1 second. The subject watched a videotape movie. There were 2 cutaneous stimulation trials. The first trial was mechanical stimulation of the skin. The second trial was

activation of the stimulator but the skin was not indented. The order of the trials was counterbalanced across subjects.

The SEP was analyzed in the same manner as the RREP. EEG activity was recorded from scalp electrodes referenced to joined-earlobes. EOG was recorded and any presentation containing an eye-blink was rejected. A minimum of 256 cutaneous stimuli were averaged for each subject. Two SEP components elicited by cutaneous stimulation were defined as follow: P1 was the maximal positive deflection 20-30 milliseconds following the onset of skin indentation and N1was the negative deflection 50-70 milliseconds after the onset of skin indentation. Baseline-to-peak amplitudes were determined for each peak of the SEP. Latencies were obtained as the time from the onset of the indentation to the SEP peak. A total of 2 RREP and 2 SEP trials were presented in this study.

Statistical Analysis

One-way repeated measures analysis of variance (ANOVA) was used to determine differences between SEP and RREP components. When the ANOVA showed a significant group difference, a multiple comparison procedures was used to test for the differences between latencies and amplitudes for each RREP and SEP peak. The statistical significance was determined at $p < 0.05$ level in this study.

Result

The RREP elicited by inspiratory occlusion was observed bilaterally and was absent with unoccluded breaths. The P1 peak of the RREP was identified at C4' and C3' scalp sites (Fig. 2-3). The N1 peak of the RREP was found at C4' and C3' scalp sites (Fig. 2-3). Cutaneous stimulation applied to middle finger of the subject’s non-dominant hand

elicited the P1 peak at C4' scalp site (Fig. 2-2) in all subjects. The SEP N1 peak was obtained in the C3' and C4' scalp sites (Fig. 2-2).

The P1 and N1 peaks were observed bilaterally in the RREP (Fig. 2-3) but unilaterally in SEP (Fig 2-2). There was no significant difference in the RREP P1 peak latency and amplitude between right (C4') and left (C3') cortices. There was no significant difference in the RREP N1 peak latency and amplitude between right (C4') and left (C3') cortices. The SEP P1 peak amplitude was significantly greater in the C4' electrode site than the C3' electrode site (Fig. 2-6). The SEP N1 peak amplitude was significantly greater in the C4' electrode site than the C3' electrode site (Fig. 2-6).

The averaged latency and amplitude for the RREP and SEP peaks are presented in Table 2-1. The RREP peak latencies of the P1 and N1 were 63.22 $\pm$ 0.3 ms and 107.53 $\pm$ 0.3 ms, respectively. The SEP peak latencies of the P1 and N1 peaks were 27.41 $\pm$ 1.3 ms and 42.69 $\pm$ 0.9 ms, respectively. The peak latencies of the P1 and N1 RREP peaks were significantly longer than the corresponding peaks of the SEP ($p < 0.05$). The peak amplitudes of the P1 and N1 RREP peaks were 2.18 $\pm$ 1.49μV and -3.80 $\pm$ 2.11μV, respectively. The SEP peak amplitudes of P1 and N1 were 0.56 $\pm$ 0.30 μV and -0.48 $\pm$ 0.23 μV, respectively. The P1 and N1 peak amplitudes of the RREP were significantly greater than the corresponding peaks of the SEP ($p < 0.05$) (Fig. 2-5). The Nf peak was observed in the RREP but not observed in the SEP (Fig 2-4). The peak amplitude of the Nf peak was -2.51 $\pm$ 1.24μV. The peak latency of the Nf peak was 25.26 $\pm$ 5.1ms.

Discussion

The similarity of the RREP waveform to that observed in response to mechanically elicited SEP was demonstrated in the present study. The P1 peak of the RREP peaks was observed bilaterally, whereas, the analogous peak of the SEP was observed contralateral

to the stimulated hand. The scalp distributions of the RREP peaks were similar to the SEP at the electrode positions that are over the somatosensory cortex. The latencies of the P1 and N1 peaks of the RREP were significantly longer than those of the SEP ($p < 0.05$). The amplitudes of the P1 and N1 peaks of the RREP were significantly greater than those of the SEP. The Nf peak was only observed in the frontal scalp sites of the RREP.

Inspiratory occlusion is a mechanical load that alters the afferent activity of several populations of respiratory mechanoreceptors in the mouth, pharynx, larynx, lung and respiratory muscles. The inspiratory occlusion halts the normal changes in inspiratory airflow and lung volume. This change in breathing pattern results in a change in the afferent activities throughout the respiratory system. The RREP waveform elicited by inspiratory occlusion was similar to the SEP elicited by mechanically stimulating cutaneous afferents. The SEP from the present study is consistent with previous studies (Kakigi and Shibasaki, 1984; Mima et al., 1996). The latency for mechanical stimulation SEP is slower than electrical stimulation due to the time required for skin indentation and receptor transudation. In the present study, the RREP peaks elicited by inspiration against an occluded airway had significantly longer latencies and larger amplitudes than the SEP ($p < 0.05$). The difference between the RREP and SEP latencies may due to a longer transduction time required for respiratory mechanoreceptors to activate the respiratory afferents. The difference between the RREP and SEP amplitudes may be due to more respiratory afferents activated and respiratory mechanical change activating afferents from both sides of the respiratory tract.

The dorsal column-lemniscal system mediates the afferent pathway to the somatosensory cortex for the SEP (Williams, 1981). The SEP is elicited by activating

afferent fibers that travel through multiple relays via the thalamus to the somatosensory cortex (Horne and Tracey, 1979). Two ascending system may be involved to the relay of sensory information to the somatosensory cortex: (1) the lemniscal pathway and (2) the extra-lemniscal reticular pathway (Albe-Fessard and Bowsher, 1965). The lemniscal pathway includes the ventroposterolateral (VPL) nuclei and ventral basal nuclei in the thalamus. The extra-lemniscal pathway includes the brainstem reticular formation and ventral basal nuclei in the thalamus. Jasper (1949) reported that short-latency evoked potentials are produced by impulses traveling via the lemniscal pathway whereas; long-latency evoked potentials are produced by impulses traveling via extra-lemniscal pathway. The latency for the SEP in the present study is consistent with the lemniscal pathway.

The activation of a somatosensory modality projects to the contralateral somatosensory cortex (Kekoni et al., 1992; McLaughlin and Kelly, 1993; Nagamine et al., 1998). Recordings of cortical responses to afferent stimuli confirm that the electrical responses at 50 ms and 100 ms latencies are generated by activity in the SI and SII somatosensory cortices (Hari, 1980). The SEP evoked by electrical stimulation of median nerve at the wrist or the index finger has a similar cortical distribution (Onofrj et al., 1990; Grisolia and Wiederholt, 1980). The SEP has been recorded with electrical stimulation of the phrenic nerve (Zifko et al., 1995). The amplitudes of the phrenic SEP were greatest in the postcentral gyrus (somatosensory region), which lies just posterior to the diaphragmatic cortical representation reported by Colebatch et al. (1991). This is also supported by the recordings from the exposed cortex in human demonstrating that the short latency peaks of the SEP were generated in the primary somatosensory cortex

(Allison et al., 1980). The generation of short-latency SEP components reported by Deiber et al. (1986) and Desmedt et al. (1987) demonstrated that area 3b of the somatosensory cortex was activated by afferents from VPL via thalamocortical pathway. Several variables have been found to alter the hand mechanical SEP. Variation in the rise time of the stimulus alters the rate of mechanical indentation of the skin and thus the transduction process (Johansson et al., 1979b; Jarvilehto et al., 1981). The amplitude is dependent on the stiffness of the indentation probe, the surface area stimulated, the depth of the indentation and the indentation duration. In the present study, a square wave rapid onset indentation was used for focal stimulation with mild indentation depths to elicit a reproducible cutaneous SEP.

The P1 peak of the RREP was observed to be of greatest amplitude in the C3'and C4' electrode sites. These sites are caudal to the central sulcus (C3 and C4) and are over the post-central gyrus, the primary somatosensory region. This is consistent with the P1 peak of the SEP elicited by mechanical stimulation of the digits (Pratt and Starr, 1981). The P1 peak of the SEP in the present study had a latency of 20-25 milliseconds. The recording electrode sites were over the post-central gyrus lateral to the midline which is consistent with the somatotopical representation of the fingers in the primary somatosensory cortex. Thus, the mechanical SEP and the RREP P1 peaks are consistent with an activation of neurons in the primary somatosensory region of the cerebral cortex.

The N1 peak of the RREP was observed to be of greatest amplitude in the central electrode sites. These electrode sites were over the post-central gyrus of the cerebral cortex which is consistent with the somatotopical representation of the fingers in the sensorimotor cortex (Pratt and Starr, 1981). In addition, Webster and Colrain (2000)

reported that the N1 peak is recorded from the vertical dipole source and is affected by the attention. Thus, the N1 peak of RREP may be indicative of second order cortical processing of respiratory afferent information. The N1 peak of the SEP with a latency of 40-50 milliseconds was elicited by the cutaneous stimulation. The electrode sites were also over the post-central gyrus of the cerebral cortex (Pratt and Starr, 1981). Thus, the mechanical SEP and the RREP N1 peaks are consistent with an activation of neurons in the sensorimotor region of the cerebral cortex.

The Nf peak was observed 25-40 ms after the onset of inspiratory occlusion and was only found in the frontal electrode sites of the RREP. These electrode sites were over the pre-central gyrus, the prefrontal region of the cerebral cortex. Thus, the Nf peak is unique to the RREP and may be related to the feed-forward preparation of the respiratory behavioral motor response.

In the current study, the P1 and N1 peaks of the RREP and SEP were observed in the same subject. The difference between the RREP P1 and N1 amplitudes and the SEP amplitudes suggests that the magnitude of neural activity is correlated with the magnitude of stimulus. The smaller amplitude of the evoked potential recorded with cutaneous mechanical stimulation compared to the RREP suggest that inspiratory occlusion activates more afferents than focal mechanical stimulation of the skin.

Conclusion

Multi-channel evoked potential recordings have provided a measurement of cortical neural activity associated activation of respiratory and cutaneous mechanoreceptors. Mechanically stimulated cutaneous somatosensory evoked potentials has a maximal response over the cortex contralateral to the side of stimulation. The scalp distribution of RREP was bilateral but similar to the cortical regions of mechanically elicited SEP.

RREP P1 and N1peaks were found to correspond to those of the SEP. The results of the present study suggest that the P1 peak of the RREP and the analogous P1 peak of the SEP activated neurons in the somatosensory cortex. Thus, the P1 and N1 peaks of the RREP are analogous to the SEP P30 and N50 peaks. The RREP, however, has a unique activation of the pre-frontal cortex, Nf peak, which is not found in the SEP.

The exact sensory pathways mediating somatosensory processing of the respiratory afferent information remain unknown. The differences in amplitude suggest a greater population of respiratory afferents is activated by inspiratory occlusion than focal indentation of the skin. The longer latencies of the RREP peaks suggest a longer time is required for changes in airway mechanics to stimulate respiratory mechanoreceptors.

Table 2-1 Mean amplitude and latency data for the respiratory-related evoked potential and the somatosensory evoked potential

	P1 average at C3'	P1 average at C4'	N1 average at C3'	N1 average at C4'
Amplitude μV				
RREP	2.08 ± 1.53	2.18 ± 1.49*	-3.68 ± 2.02	-3.80 ± 2.11*
SEP	0.30 ± 0.16	0.56 ± 0.30#	-0.33 ± 0.17	-0.48 ± 0.23#
Latency msec				
RREP	63.22 ± 0.3*		107.53 ± 0.3*	
SEP	27.41 ±1.3		42.69 ± 0.9	

* indicates a significantly different between the RREP and SEP. # indicates a significantly different between C3' and C4'.

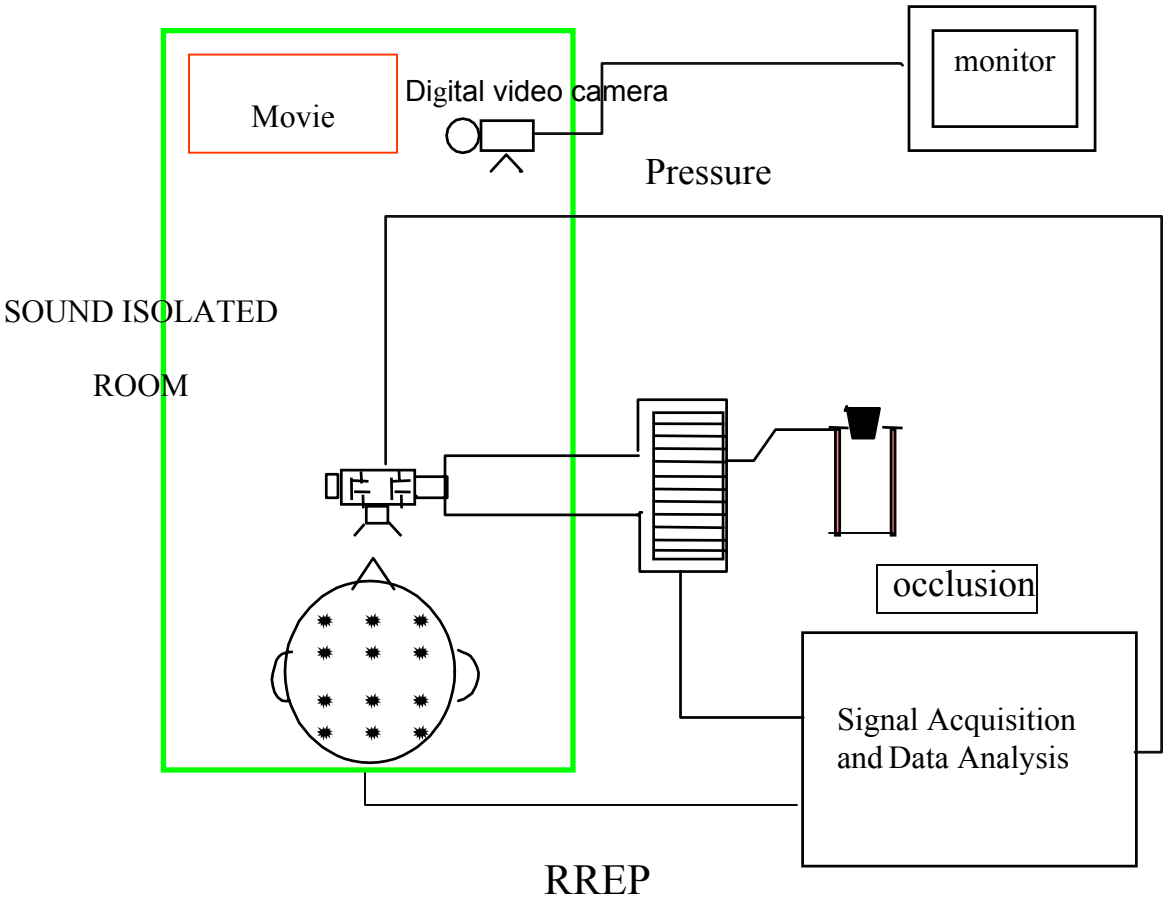

Figure 2-1. Respiratory-related evoked potential Schmidt

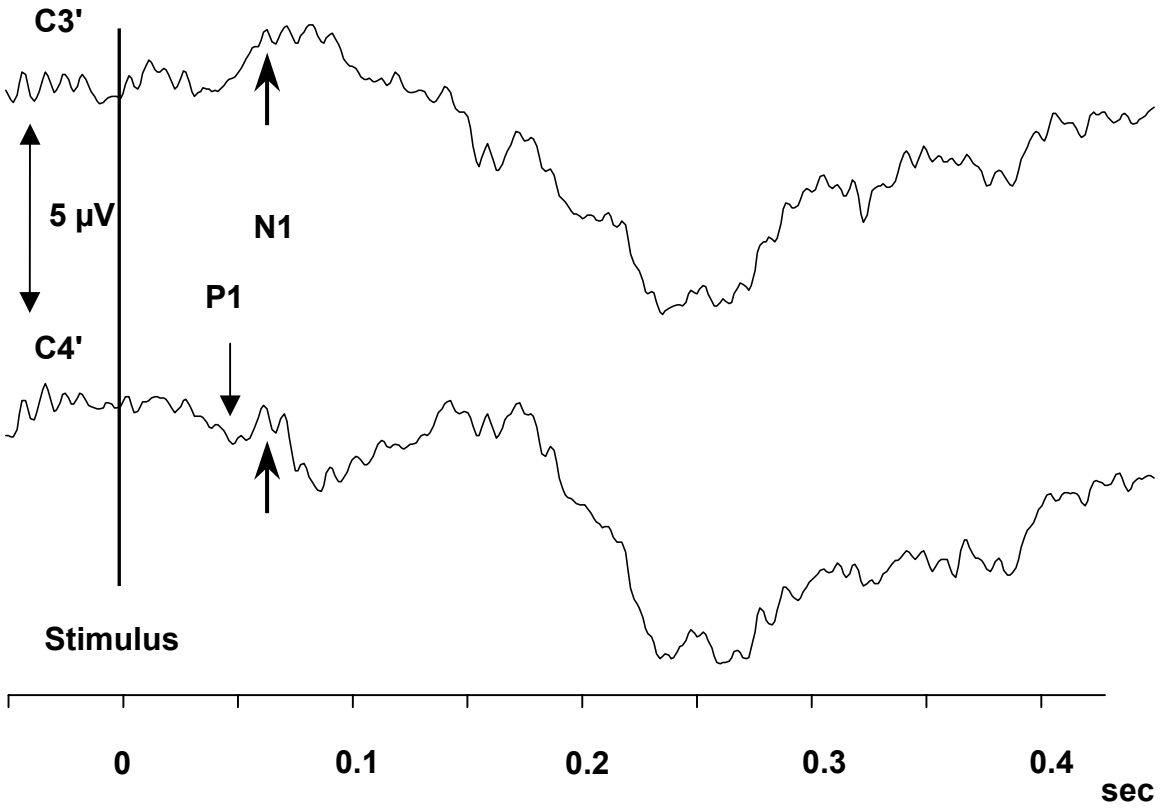

Figure 2-2. SEP at C4' and C3' electrode sites (C4'- Right hemisphere; C3'-Left hemisphere).

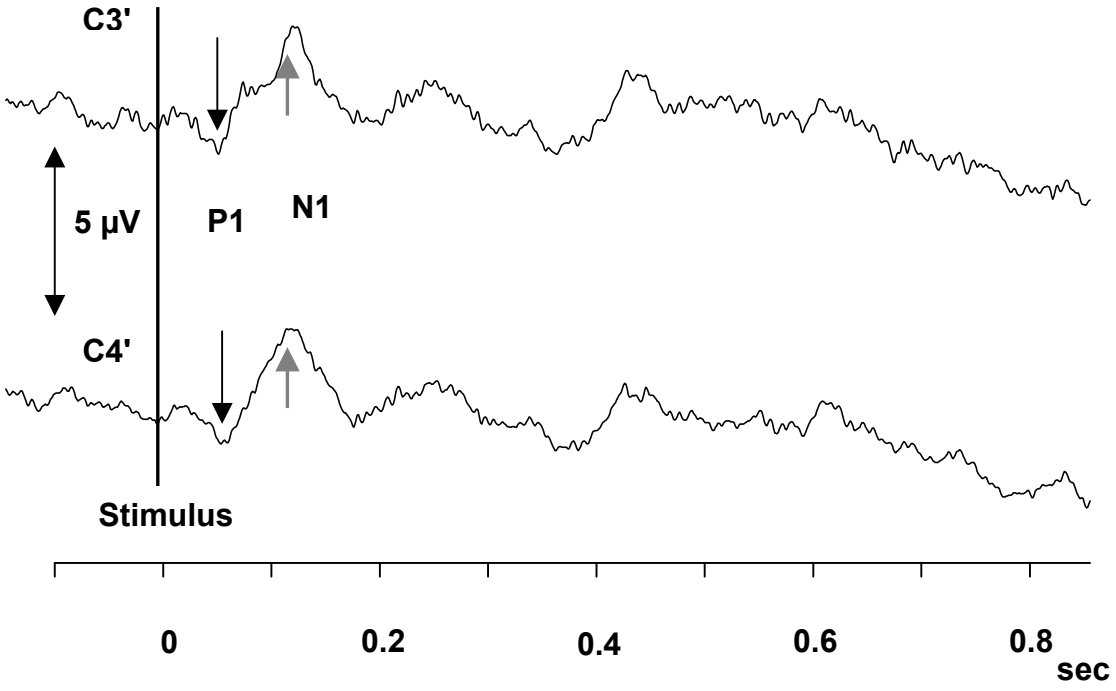

Figure 2-3. RREP at C4' and C3' electrode sites (C4'-Right hemisphere; C3'-Left hemisphere).

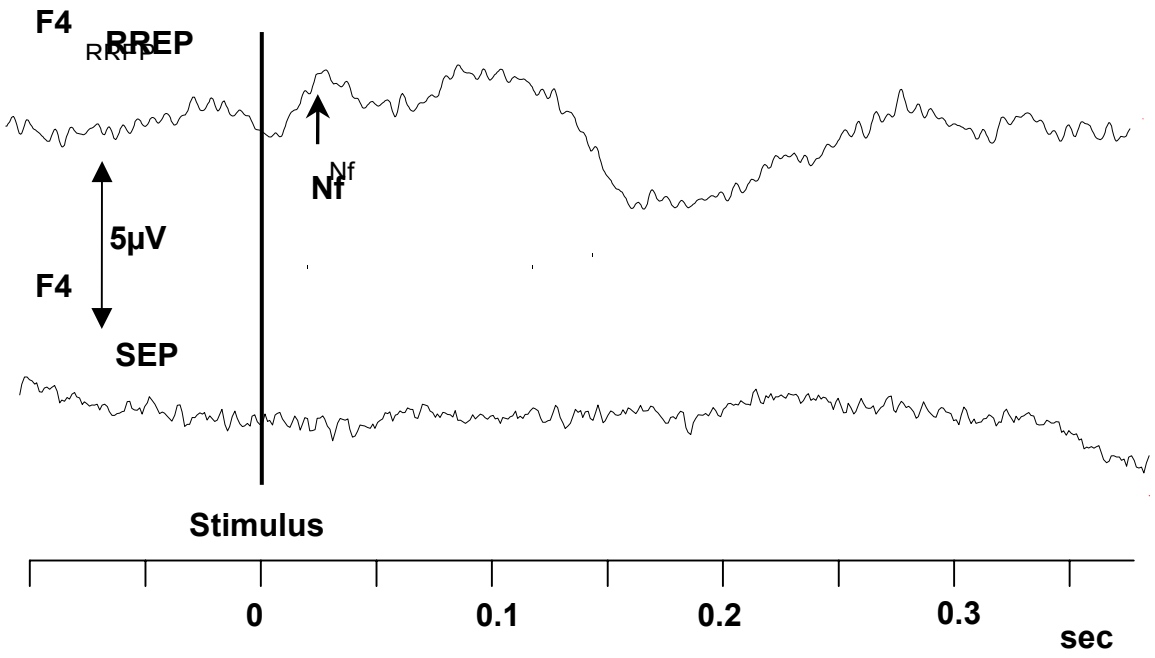

Figure 2-4. The RREP and SEP at F4 electrode site. The Nf peak was only observed in the RREP but not in the SEP.

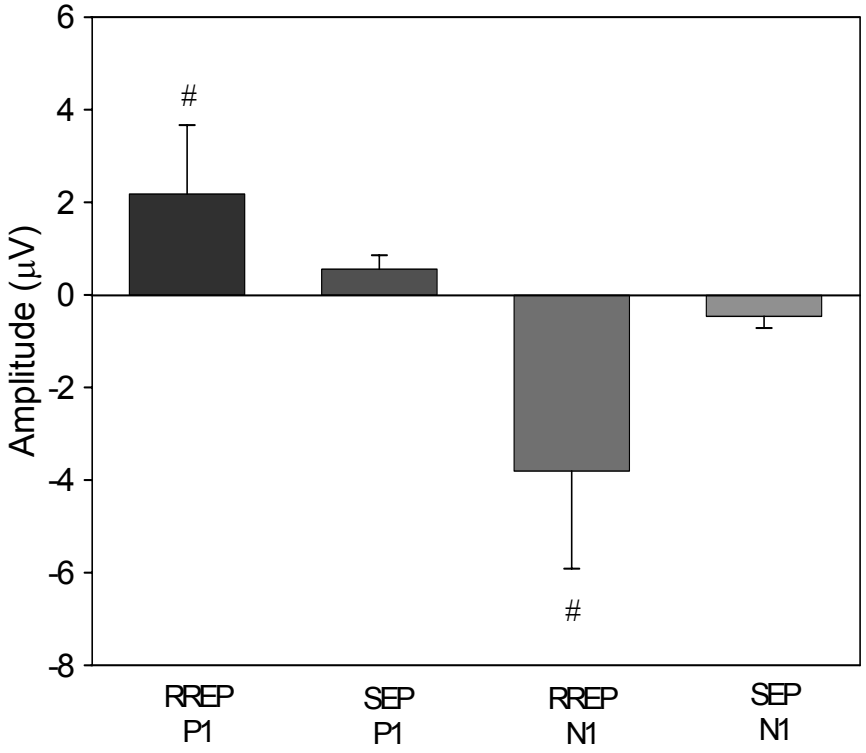

Figure 2-5. Comparison for the amplitudes of the P1 and N1 peaks of the RREP and the SEP. The amplitude of the P1 peak of the RREP was significantly greater than the SEP ($p < 0.05$). The amplitude of the N1 peak of the RREP was significantly greater than the SEP ($p < 0.05$). # indicates a significantly different between the RREP and the SEP.

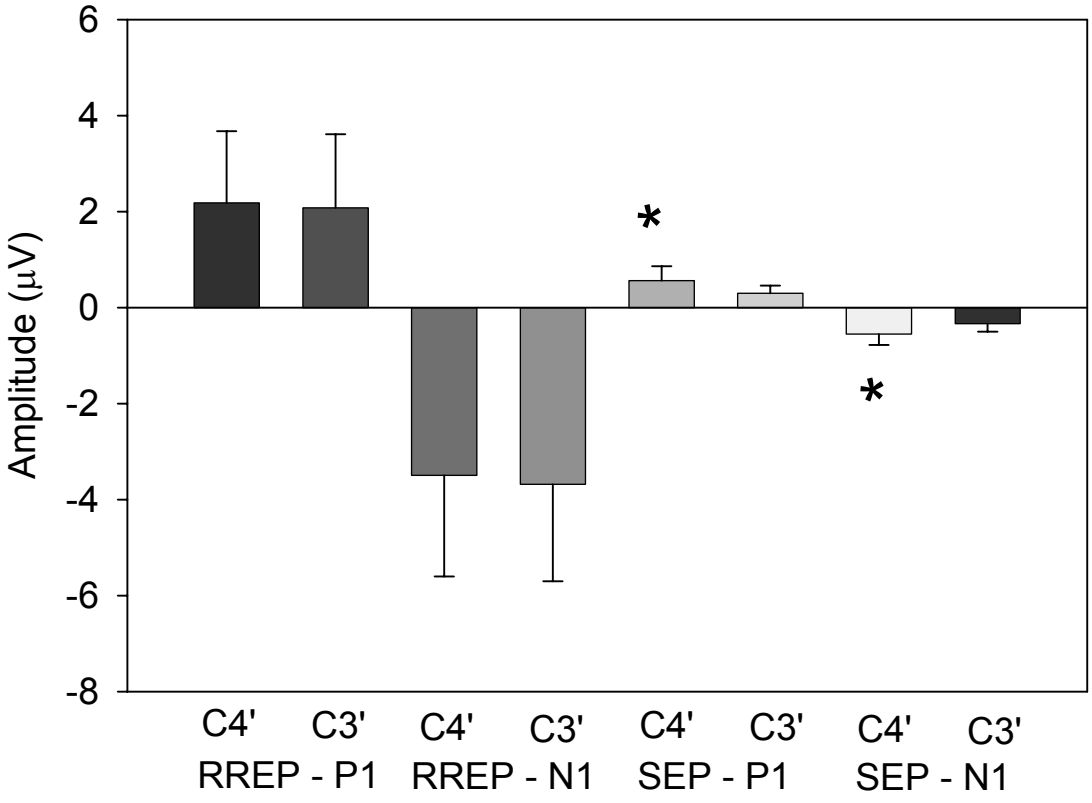

Figure 2-6. Comparison between the C3' and C4' electrode sites for the P1 and N1 peaks of the RREP and the SEP. The SEP P1 peak was significantly greater amplitude in the C4' electrode site ($p < 0.05$). The SEP N1 peak amplitude was significantly greater in the C4 electrode site ($p < 0.05$). There were no significant differences in the RREP P1 and N1 peak amplitudes between the C4' and C3' electrode sites.* indicates a significantly different between the C3' and C4' electrode sites.

CHAPTER 3
CORTICAL EVOKED POTENTIALS ELICITED BY INSPIRATORY OCCLUSION, AIR-PUFF, AND CUTANEOUS STIMULATION IN HEALTHY ADULTS

Introduction

Activation of mechanoreceptors by mid-inspiratory occlusion elicits the RREP (Revelette and Davenport, 1990). Activation of the intercostal muscles (Gandevia and Macefield, 1989), vagal afferents (Tougas et al., 1993), phrenic afferents (Straus et al., 1997; Zifko et al., 1995), and laryngeal afferents of the upper airway (Yin et al., 1997; Daubenspeck et al., 2000) are known to elicit cortical evoked potentials. These respiratory afferent sources may contribute to the RREP. The early peaks of RREP are an indicator of respiratory sensory information arriving to the cortex (Davenport et al., 1986; Logie et al., 1998; Colrain et al., 2000). The previous study indicated a similarity in cortical activation between the RREP and the SEP (Davenport et al., 1996; Logie et al., 1998). There were differences in the latency, amplitude and bilateral cortical activation. It remains unknown if these differences are due to the sources that generate the RREP, the neural path length and/or the cortical distribution of sensory activity.

In normal adult mammalian sensory systems information from specific sensory modalities is transmitted along parallel, modality-specific, multisynaptic pathways (Mountcastle, 1980). The cortical projection of human mechanoreceptors has been identified for skin mechanoreceptors. Information transduced by sensory receptors is relayed via the spinal cord to thalamus, then project to specific areas of the cortex. The primary somatosensory cortex has a somatotopic modality-specific organization (Kaas,

1991). Area 3b and 1 of the somatosensory cortex are mainly activated by cutaneous stimulation, while area 3a receives afferent input from deep sensory receptors and area 2 plays a somatosensory integrative function.

The SEP elicited by mechanical stimuli was similar to those induced by inspiratory occlusion. The SEP elicited by mechanical stimulation exhibited an increased of amplitude and decreased of latency with increasing stimulus intensity (Hashimoto et al., 1992). RREP studies with inspiratory occlusion have reported longer latencies and greater amplitudes for the P1 and N1 peaks when compared with the SEP elicited by mechanical stimuli. The latency delays and amplitude difference may be due to the number of mechanoreceptor populations activated or may be due to different sensory pathway processing of respiratory information.

Intercostals muscle afferents and the phrenic afferents project to the somatosensory cortex (Gandevia and Macefield, 1989; Davenport et al., 1993; Zifko et al., 1995). In addition, cortical evoked potentials have been elicited by vagal stimulation (Tongus et al., 1993), inspiratory occlusion (Davenport et al., 1986; Davenport et al., 2000), and expiratory occlusion (Hammond et al., 1999). These findings suggest that respiratory sensation is the result, in part, of the cortical integration of multiple respiratory afferents projecting to the somatosensory cortex.

Mechanoreceptors of the respiratory tract that can be altered by an inspiratory occlusion are in the upper airways, the lung, the chest wall and the respiratory muscles. The present study was designed to investigate the mechanism of the latency, amplitude and patterns of RREP peaks. Inspiratory occlusion elicited RREP was compared to mechanically elicited SEP with different modalities of stimulation from two selected

areas, chest wall and mouth. Thus, the purpose of this study was to compare the early peaks of the RREP with the SEP activated by mechanical stimuli in the respiratory related areas. If the pattern of the RREP is similar to the SEP with specific mechanical activation, then it was reasoned that those mechanoreceptors may mediate the RREP. However, if differences in the latencies and amplitudes occur between the RREP and the SEP, then the mechanoreceptors in these selective areas of stimulation are not the primary source of the RREP. Therefore, it was hypothesized that the latencies and amplitudes of short-latency RREP components are similar to those of the mouth SEP and chest SEP.

Method

Subjects

Twenty normal subjects were recruited (11 male, 9 female; average age = 22.35 years) for this study. Subjects were classified as normal on the basis of self-reported habitual good health, no self-reported history of cardiorespiratory disease, history of smoking nor evidence of current major or minor illness. Forced vital capacity (FVC) and forced expiratory volume within 1 second (FEV1) and airway resistance were measured in each subject. The Institutional Review Board of the University of Florida reviewed and approved this study. The study was explained to the subject and written consent obtained.

Pulmonary Function Testing

Subjects were asked to refrain from large meals and caffeine for at least four hours prior to the experiment. Subjects were seated upright in a chair to perform the spirometry testing that conformed to American Thoracic Society Standards. FVC, FEV1 and airway resistance were collected by a computerized spirometer and impulse oscillometer system.

RREP Elicited by Inspiratory Load

Subjects were seated in a sound insulated room, with the back, neck and head comfortably supported. An electrode cap with integral electrodes was used to record scalp EEG activity. The electrode positions were based on the International 10-20 System. The cap was placed on the subject's head, positioned and secured with a strap. Scalp and electrode contact has been made by the application of electro-conducing paste administered through the center opening in the electrode. The impedance levels for each electrode were checked and maintained below 5 kΩ. The electrode cap was connected to an electroencephalograph system and EEG activity recorded. Two electrodes were placed over the lateral edge of the eye for recording EOG. Any load presentation that occurs with an eye-blink was discarded. The EEG activity was bandpass filtered, amplified and led into an on-line signal averaging computer system (CED 1401, Cambridge Electronics Ltd., Cambridge, England). The EEG activity for each presentation was stored on computer disk. The experimenter and recording equipment were in the adjacent room. The subject was monitored with a video camera.

The subject respired through a non-rebreathing valve with the inspiratory port connected to the loading manifold. Mouth pressure was sensed with a differential pressure transducer and signal conditioner. The inspiratory load was presented by silently inflating the occlusion valve at approximately the mid-inspiration point of the breath. Each loaded breath was separated by 2-6 unloaded breaths. A TTL pulse generated by the inspiratory occlusion valve controller triggered the collection of 50ms of pre-trigger and 950ms of post-trigger EEG and mouth pressure (Pm) data. The duration of each occlusion was about 200ms. There were two respiratory experimental trials for the RREP: control trial and load trial. Both trials were separated by a 5-minute rest period off the breathing

apparatus. During the load trial, the subject was watching a pre-recorded videotape cartoon movie with the sound masking experimental noises. One hundred loaded breaths were presented in each trial. The control trial used the same protocol, except that there were no occluded breaths presented.

The recorded data for each presentation were evaluated for inclusion in the averaged RREP. The baseline EEG traces were DC corrected if necessary. The inclusion and exclusion criteria were the same as the previous study. The presence, latency and amplitude of RREP peaks: Nf, P1 and N1 were determined for each scalp location from the averaged EEG traces. Peak latencies were measured as the time from the onset of the change in mouth pressure, to the EEG peak. The zero-to-peak amplitude was measured at the peak of each component. The RREP peaks were identified in the following manner: P1 was defined as the positive peak within a latency window of 40-70 ms, Nf was defined as the negative peak within a latency window of 25-40 msec, N1 was defined as the negative peak within a latency window of 80-120 msec. The site with the largest amplitude and shortest latency for each peak was determined.

Mechanical Stimulation of the Chest and the Mouth

Cutaneous mechanical stimulation was performed on the subject's chest wall between the 6^{th} and 7^{th} ribs. This site was chosen because the nerve path length to the cortex is approximately equal to the phrenic nerve and intercostals muscles. The skin indentation was produced by a controlled linear induction motor attached to a blunt flexible tube placed 2mm above the surface of the chest wall. The probe tube was in a plastic sleeve that was placed in contact with the skin of the chest wall and fixed in position with a harness. The mechanical stimulator was screened from the subject by a

curtain. A series of 512 cutaneous stimulations were applied by linear displacement of the probe tube. Each indentation had a duration of 400 ms and was presented every second.

The buccal surface of the cheek was mechanically stimulated with air pulses. Air puff stimulation has been used to elicit cutaneous SEP in humans. The air puff provides reproducible mechanical stimuli without direct contact to the skin and permits stimulation of a restricted area of the buccal surface. Air puff mechanical stimulation was delivered by a tube puffing air onto the cheek of the buccal surface of the mouth. Air puff stimulation was delivered through the tube with one end fixed in the mouthpiece, the tip extending 2-5 mm lateral to the molars. The other end of the tube was connected to the pressure source. The air puff had a rise time of 0.2ms and duration of 300 msec and was driven by oxygen gas at 20 cmH2O. The cross-sectional area covered by the air puff was about 3.6 mm^2. Each trial consisted of 256 stimuli delivered every second to the buccal surface of the mouth.

During the mechanical stimulation sessions the subject watched a videotape cartoon movie and did not attend to the stimulus. There were 2-paired sessions (4 trials) for chest wall and mouth mechanical stimulation. The first chest trial consisted of cutaneous mechanical stimulation. The second chest trial consisted of activation mechanical stimulator but the skin has not been indented. The first mouth trial consisted of positive pressure pulses applied to the buccal surface of the cheek. The second mouth trial consisted of the activation of the positive pressure solenoid but no air was delivered. The order of the trials was counterbalanced across subjects.

The SEP elicited by air puffs delivered to the mouth and the SEP elicited by mechanical stimulation of the chest was analyzed in the same manner as the RREP. EEG

activity was recorded from scalp electrodes referenced to the joined earlobes. EOG was recorded and any presentation containing an eye-blink was rejected. The SEP and RREP peaks were identified. Both the latency and amplitude of each peak were determined for each stimulus condition (respiration, mouth or chest).

Statistical Analysis

The descriptive statistics of all variables in the study were calculated and expressed as mean ± standard deviation (SD). One way analysis of variance (ANOVA) for repeated measurement was conducted to compare the latencies and amplitudes of evoked potentials. The repeated measures ANOVA was performed for each peak with different modalities of evoked potentials. When the ANOVA showed significant differences in peaks, a multiple comparison (Bonforoni correction) was used to test for pairwise differences. The significant difference level of the study is set at $p < 0.05$.

Result

The P1, N1 and Nf peaks of the RREP were identified in all subjects (Fig 3-1. and Fig 3-2.). The P1 and N1 peaks were identified in the mouth SEP and chest SEP (Fig 3-3. and Fig 3-4.). The RREP elicited by inspiratory occlusion was observed bilaterally and was absent with unoccluded breaths. The P1 peak of the RREP was identified at C4' and C3' electrode sites (Fig. 3-2). The N1 peak of the RREP was found at C4' and C3' electrode sites (Fig. 3-2). The P1 peak of the mouth SEP was found at C4' electrode site (Fig 3-3). The N1 peak of the mouth SEP was found at C4' and C3' electrode sites (Fig 3-3). The P1 peak of the chest SEP was found at C4' electrode site (Fig 3-4). The N1 peak of the chest SEP was found at C4' and C3' electrode sites (Fig 3-4). The Nf peak was only found in the F4 electrode site of the RREP but not I the F4 electrode site of the mouth SEP and chest SEP (Fig 3-1).

The latencies and amplitudes for the P1 and N1 peaks of the RREP, mouth SEP and chest SEP are presented in Table 3-1. The P1 peak latency of the RREP was 63.49 $\pm$ 6.5 ms. The N1 peak latency of the RREP was 107.30 $\pm$ 11.8 ms. The P1 peak latency of the mouth SEP was 39.91 $\pm$ 3.7 ms and significantly shorter than the RREP P1 peak. The N1 peak latency of the mouth SEP was 76.10 $\pm$ 6.1 ms and significantly shorter than the RREP N1 peak. The P1 peak latency of the chest SEP was 31.00 $\pm$ 4.6 ms and significantly shorter than the RREP P1 peak but not significantly different form the mouth P1 peak. The N1 peak latency of the chest SEP was 54.17 $\pm$ 2.8 ms and significantly shorter than the RREP P1 peak but not significantly different from the mouth P1 peak. The P1 peak amplitude of the RREP was 1.9 $\pm$ 1.2 μV. The N1 peak amplitude of the RREP was -4.15 $\pm$ 2.6 μV. The P1 peak amplitude of the mouth SEP was 1.53 $\pm$ 0.1 μV. The N1 peak amplitude of the mouth SEP was -2.02 $\pm$ 1.4 μV. The P1 peak amplitude of the chest SEP was 1.19 $\pm$ 1.1 μV. The N1 peak amplitude of the chest SEP was -1.58 $\pm$ 2.4 μV. The amplitudes of the P1 peak were significantly greater for the RREP than the chest SEP ($p < 0.05$). However, there was no significant difference for the P1 peak amplitude of the RREP and mouth SEP. The N1 peak amplitude of the RREP was significantly greater than the mouth SEP and the chest SEP ($p< 0.05$). There were no significant differences for the P1 and N1 peak amplitudes between the mouth SEP and chest SEP.

Discussion

The P1 and N1 peaks of the RREP elicited by inspiratory occlusion were analogous to those of the SEP elicited by either air-puff stimulation to the mouth or cutaneous stimulation to the chest. The P1 peak of the RREP was found bilaterally in the centroparietal scalp over the somatosensory cortex. The SEP P1 peaks were also found

over the somatosensory cortex but were unilateral, contralateral to the stimulated side. The latencies of the P1 and N1 peaks of the RREP were significantly longer than those of the SEPs from either mouth stimulation or chest stimulation. The P1 and N1 peak amplitudes of the RREP were significantly greater than the corresponding peaks of the chest SEP. Only the N1 peak amplitude of the RREP was significantly greater than the N1 peak of the mouth SEP.

Evoked potentials elicited by mechanical stimulation of the skin (Hari, 1980 Hashimoto et al., 1987) and respiratory system have been reported (Davenport et al., 1986). However, no study has compared the cortical evoked potentials from the skin and respiratory mechanical stimulation. The results from the present study showed that inspiratory occlusion activates cortical neurons in the somatosensory cortex which was also found for the SEP elicited by mouth air puff and cutaneous indentation.

The RREP P1 peak had a bilateral localization while both the mouth SEP and chest SEP were lateralized. The P1 peak of RREP was observed to be of greatest amplitude in the C3'and C4' electrode sites. These electrode sites are over the post-central gyrus, the primary somatosensory region. This is consistent with the reports that the P1 peak of the RREP reflects the arrival of the afferent projection to the primary sensory area (Davenport et al., 1986; Davenport et al., 1996). The electrode sites of the P1 peak of the mouth SEP and chest SEP were over the post-central gyrus lateral to the midline which is consistent with the somatotopical representation of the fingers and mouth in the primary somatosensory cortex (Pratt and Starr, 1981). Thus, the mechanical SEP and the RREP P1 peaks are consistent with an activation of neurons in the primary somatosensory region of the cerebral cortex. Knafelc and Davenport (1997) reported that the P1 peak

amplitude of the RREP was correlated to the magnitude of the added resistive load. This was similar to the relationship reported by Hashimoto et al. (1988) that the peak amplitude of the SEP elicited by air puff stimulation was correlated to the magnitude of the stimulus intensity. Thus, the mechanically elicited SEP and the RREP may have similar neural processing mechanism but different afferent origins.

The N1 peak of RREP was observed to be of greatest amplitude in the Cz and Cz' electrode sites. These electrode sites were over the central sulcus at the midline of the cerebral cortex (Pratt and Starr, 1981). The electrode sites of the N1 peak of the mouth SEP and chest SEP were over the central sulcus at the midline of the cerebral cortex which is also consistent with the representation in the sensorimotor cortex (Pratt and Starr, 1981). Thus, the mechanical SEP and the RREP N1 peaks are consistent with an activation of neurons in the sensorimotor region of the cerebral cortex. The N1 peak of the RREP was the negative peak associated with the P1 peak of the RREP (Davenport et al., 1986). Bloch-Salisbury et al. (1998) reported that N1 peak amplitude of the RREP decreases as the resistive load decreased, similar to P1 peak of the RREP. The N1 peak amplitude also increases with attention to the load. Thus, the N1 peak of the RREP may be the second order cortical processing of the respiratory afferent information that is based on perceiving the first-order somatosensory information and may affect subsequent cognitive processing.

The bilateral frontal Nf peak of the RREP was not present in chest or mouth SEP's. The Nf peak may reflect activity in prefrontal structures (Logie et al., 1998). Thalamocortical inputs to the somatosensory cortex project predominantly to deep cortical layers generate a surface positive initial potential (Wood and Allison, 1981;

Wood et al., 1985). The frontal Nf peak was not due to the activity in the somatosensory cortex. It has been reported that the prefrontal cortex gated the early stage of somatosensory input and that it exerts inhibitory modulation on sensory processing (Yamaguchi and Knight, 1990). This may be the reason that the Nf peak was only observed in the RREP. The Nf peak may reflect a feed-forward preparation for compensation by a behavioral motor response, simultaneous with respiratory sensory perception. In addition, the Nf peak generated in the prefrontal cortex may be part of the integration of information for motor cortical output as part of the behavioral motor response to loaded breathing (Davenport et al., 1996). The neural generators of the Nf peak, however remain unknown.

The cortical projection of skin mechanoreceptors has been identified. Information thansduced by sensory receptors is relayed via the spinal cord to thalamus, then project to specific areas of the cortex. The primary somatosensory cortex has a somatotopic modality-specific organization (Kaas and Pos, 1988).

The activation of cortical neurons by mechanical loads has been studied using evoked potential techniques similar to those routinely used in other somatosensory systems (Buchner et al., 1996; Rossini et al., 1996). The P1 peak followed by the N1 peak was identical in all evoked potentials with different latencies and amplitudes. Minor differences in the extent of negative and positive fields on the scalp could be observed in the same subject when changing the stimulus modality, but evoked potential components and localization followed the pattern suggested by Desmedt et al. (1987).

The fundamental difference in sensory nerve conduction measured by electrical stimulation and mechanical stimulation is that electrical stimulation activates the distal

axon and bypasses the transduction process of the receptors. Mechanical receptor potentials are graded and sustained depolarizations of the sensory terminals and nerve impulses are generated by this potential (Katz, 1950). Changes in receptor properties of skin mechanoreceptors in neuropathy have been characterized by high mechanical thresholds without significant change in receptor transduction time (Mizobichi et al., 2002). Inspiratory occlusion, air-puff pressure pulses and chest cutaneous stimulation used in the current study include the transduction time for the afferent mechanoreceptors, most likely large-diameter cutaneous afferents (Johansson and Vallbo, 1979b). The RREP and chest SEP may have similar afferent conduction distance, suggesting that time is required when breathing against the inspiratory occlusion to bring the respiratory mechanoreceptors to threshold. Thus, the latency differences in normal subjects between the RREP and mechanically evoked potentials in the current study may be due to the rise time of the mechanical stimulus (inspiratory occlusion), force transfer process within the respiratory system, the receptor transduction time and the conduction in the terminal axon. The transduction time for respiratory mechanoreceptor activation during inspiratory occlusion is unknown. In addition, the SEP elicited by air puff stimulation to the mouth had a longer latency than the SEP elicited by cutaneous stimulation to the chest wall. This difference may be due to the variations in the rise time of the stimulus that alters the rate of mechanical indentation and the transduction process (Pratt and Starr, 1981).

The RREP and mouth SEP may have similar afferent sources (upper airway) and sensory modality (pressure), suggesting that time is required when breathing against the inspiratory occlusion to bring the respiratory mechanoreceptors to threshold. Thus, the amplitude differences in normal subjects between the RREP and mechanically evoked

potentials in the current study may be due more mechanoreceptor populations activated or different neural processing for the respiratory afferent information.

The SEP following mechanically air puff stimuli to the mouth had a greater amplitude than the SEP recorded following mechanical stimulation on the chest wall. The difference of the amplitude between the air puff stimulation and the cutaneous stimulation may be due to a wider surface area stimulated with air pressure, greater receptor density and/or differences in sensory amplification by second order neural processing system. In addition, Hashimoto et al. (1992) reported that the SEP elicited by air puff stimulation exhibited an increased amplitude and decreased latency with increasing intensity. Thus, the amplitude differences between the air puff and cutaneous stimulation may be due to different stimulus intensity. However, it is difficult to compare the intensity between two different sensory modalities (pressure versus skin indentation).

Conclusion

In summary, the observation of the evoked potentials elicited by different types of mechanical stimulation demonstrated that: 1)The inspiratory occlusion may activate mechanoreceptors in the mouth, upper airway, lower airway, lung, and respiratory pump muscle; 2) These mechanoreceptors may activate cortical neurons in the somatosensory region of the cerebral cortex; 3) The P1 and N1 peaks of the RREP elicited by interrupting occlusion are analogous to the P1 and N1 peaks of the SEP elicited by air puff or cutaneous mechanical stimulation.; 4) a similar temporal activation sequence for the P1 and N1 peaks was observed for the RREP and the SEPs; 5) The Nf peak was only elicited by inspiratory occlusion; 6) The RREP P1 and N1 peak latencies were longer than the corresponding peaks of the mouth SEP and chest SEP; 7) The P1 and N1 peak amplitudes of the RREP were significantly greater than those of Chest SEP; 8) The N1

peak amplitude of the RREP was significantly greater than the mouth SEP; 9) There were no significant difference between the chest SEP and mouth SEP for the P1 and N1 peaks; 10) The P1 dipole sources were located in the contralateral somatosensory area for the mouth and chest SEPs and bilaterally in the same somatosensory cortical region for the RREP. Thus, it is concluded that the RREP elicited by inspiratory occlusion processes respiratory mechanical information from multiple, bilateral afferent sources. Mechanically elicited SEPs project to similar regions of the somatosensory cortex. Cortical activation elicited by respiratory mechanical loads is evidenced by RREP recordings. The cortical neurons activated by respiratory mechanical loads elicit the RREP similar to the SEP for other somatosensory systems. This suggests that respiratory mechanoreceptor-activated cortical neurons are in the somatosensory cortex and the information is mediated through somatosensory pathways. The location of the mechanoreceptors and neural mechanism involving the respiratory sensation remain uncertain.

Table 3-1 Group mean amplitudes and latencies for P1 and N1 peaks of the RREP, mouth SEP, and chest SEP.

	P1 - C3'	P1 - C4'	N1 - C3'	N1 - C4'
Amplitude (μV)				
RREP	1.89 ± 1.40*	1.90 ± 1.23*	-3.90 ± 2.01*$	-4.15 ± 2.55*$
Mouth-SEP	0.94 ± 0.76	1.53 ± 0.91†	-1.58 ± 1.45	-2.02 ± 1.39
Chest-SEP	0.56 ± 0.62	1.19 ± 1.1†	-1.25 ± 2.05	-1.58 ± 2.41
Latency (msec)				
RREP	63.49 ± 6.53*$		107.30 ± 11.82*$	
Mouth-SEP	39.91 ± 3.71		76.10 ± 6.08	
Chest-SEP	31.00 ± 4.55		54.17 ± 2.76	

* indicates a significant difference between RREP and chest SEP.
$ indicates a significant difference RREP and mouth SEP.
† indicates a significant difference between right and left cortices.

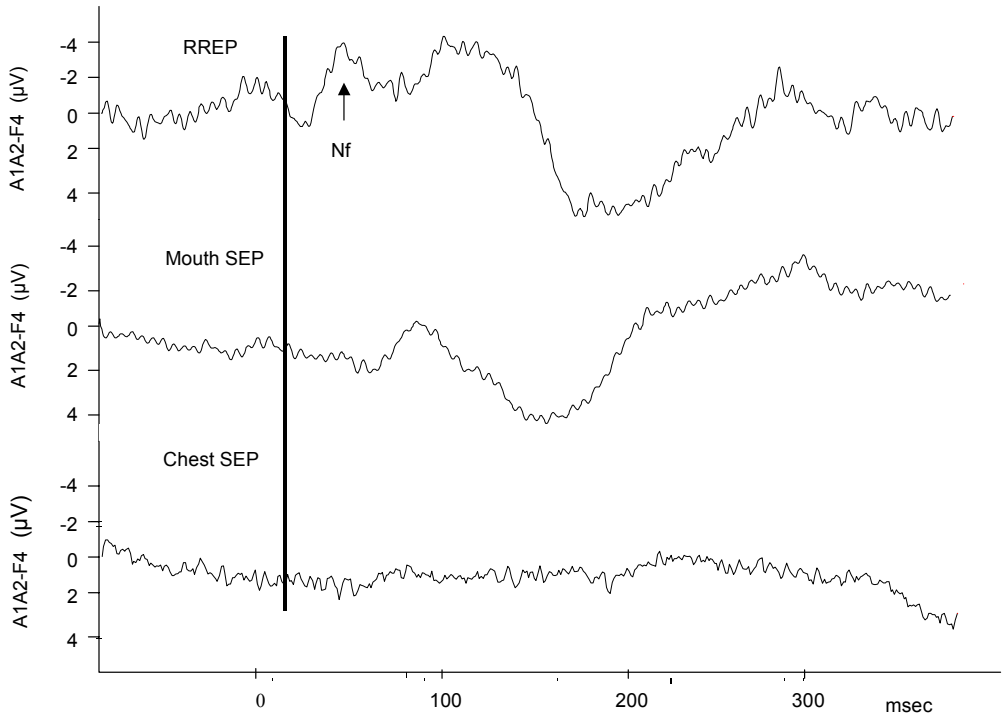

Figure 3-1. Comparison of the RREP, Mouth SEP, and Chest SEP from frontal electrode (F4). The black line represents the stimulus. The Nf peak was only observed in the RREP elicited by inspiratory occlusion.

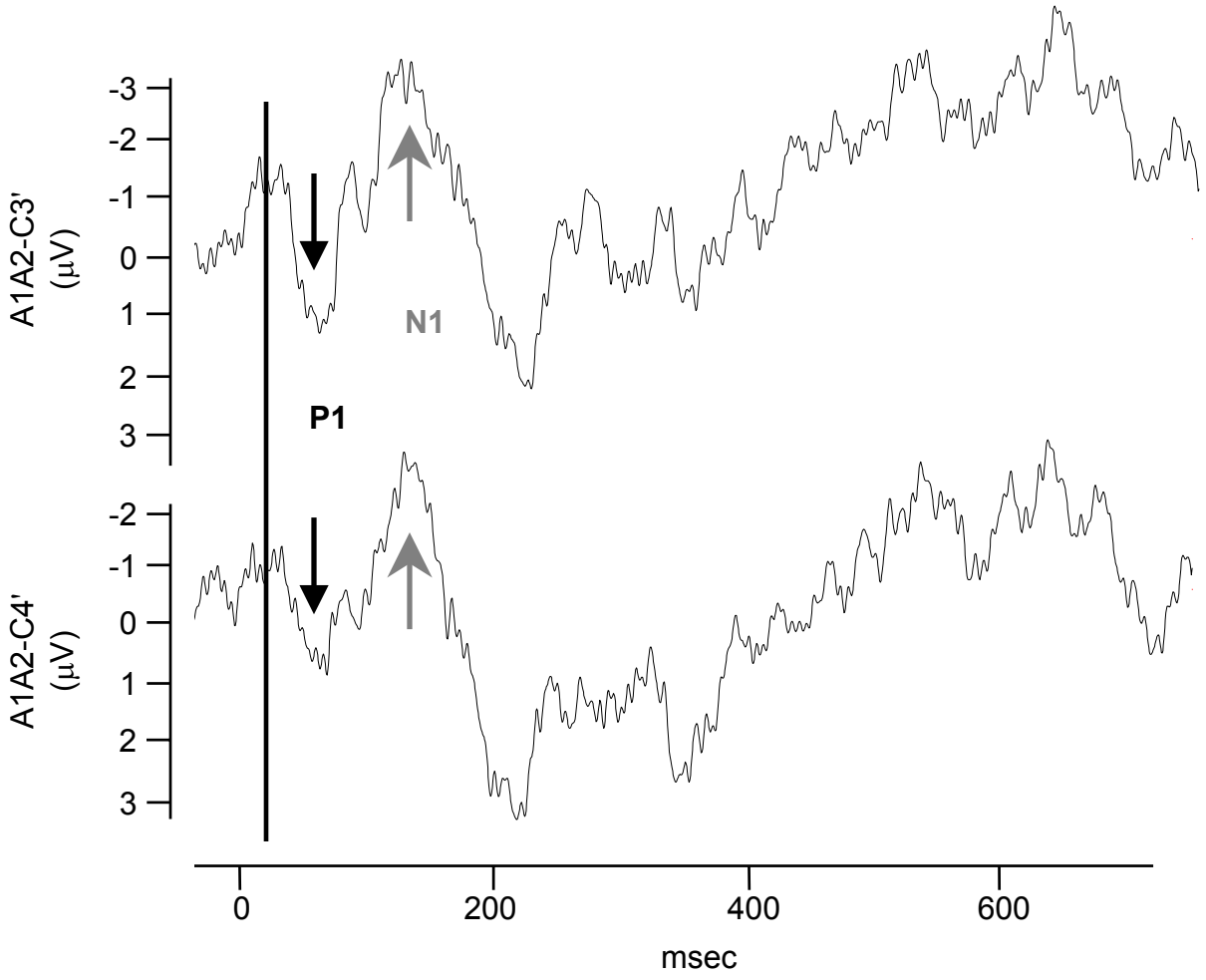

Figure 3-2. Comparison of the RREP from right (C3') and left (C4') electrodes. The black line represents the inspiratory occlusion. P1, which is the positive peak of RREP, represented by black arrow; N1, which is the negative peak of RREP, represented by gray arrow.

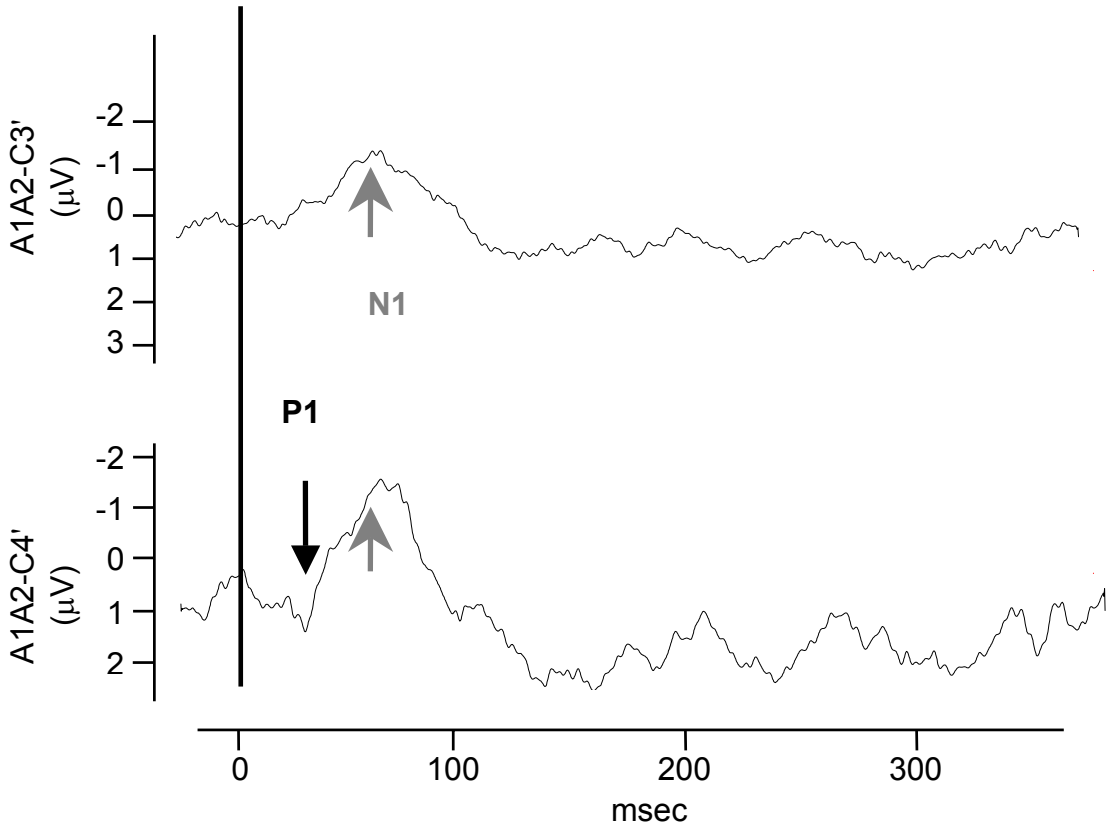

Figure 3-3. Comparison of the mouth SEP from right (C3') and left (C4') electrodes. The black line represents air-puff stimulus. P1 is the positive peak of the mouth SEP (black arrow). N1is the negative peak of the mouth SEP (gray arrow).

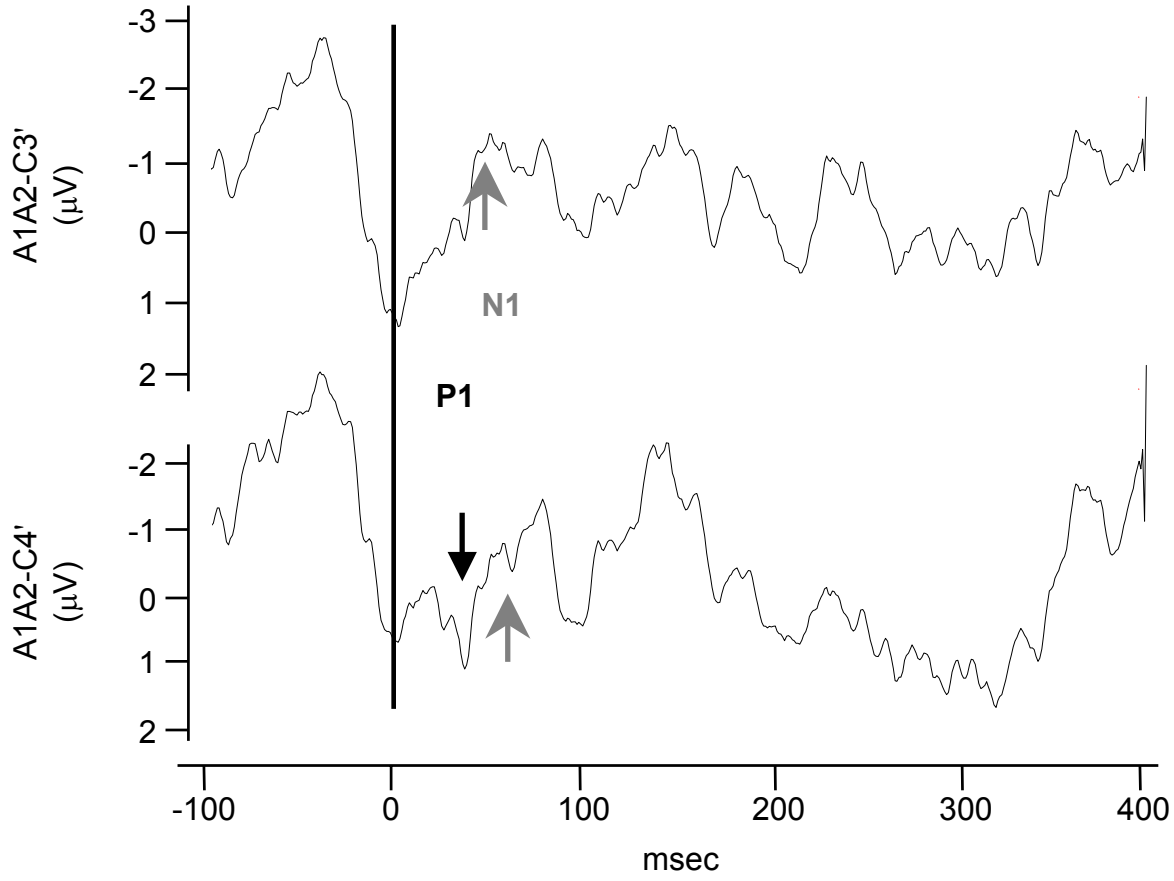

Figure 3-4. Comparison of the chest SEP from right (C3') and left (C4') electrodes. The black line represents the cutaneous stimulus. P1 is the positive peak of the chest SEP (black arrow). N1 is the negative peak of the chest SEP (gray arrow).

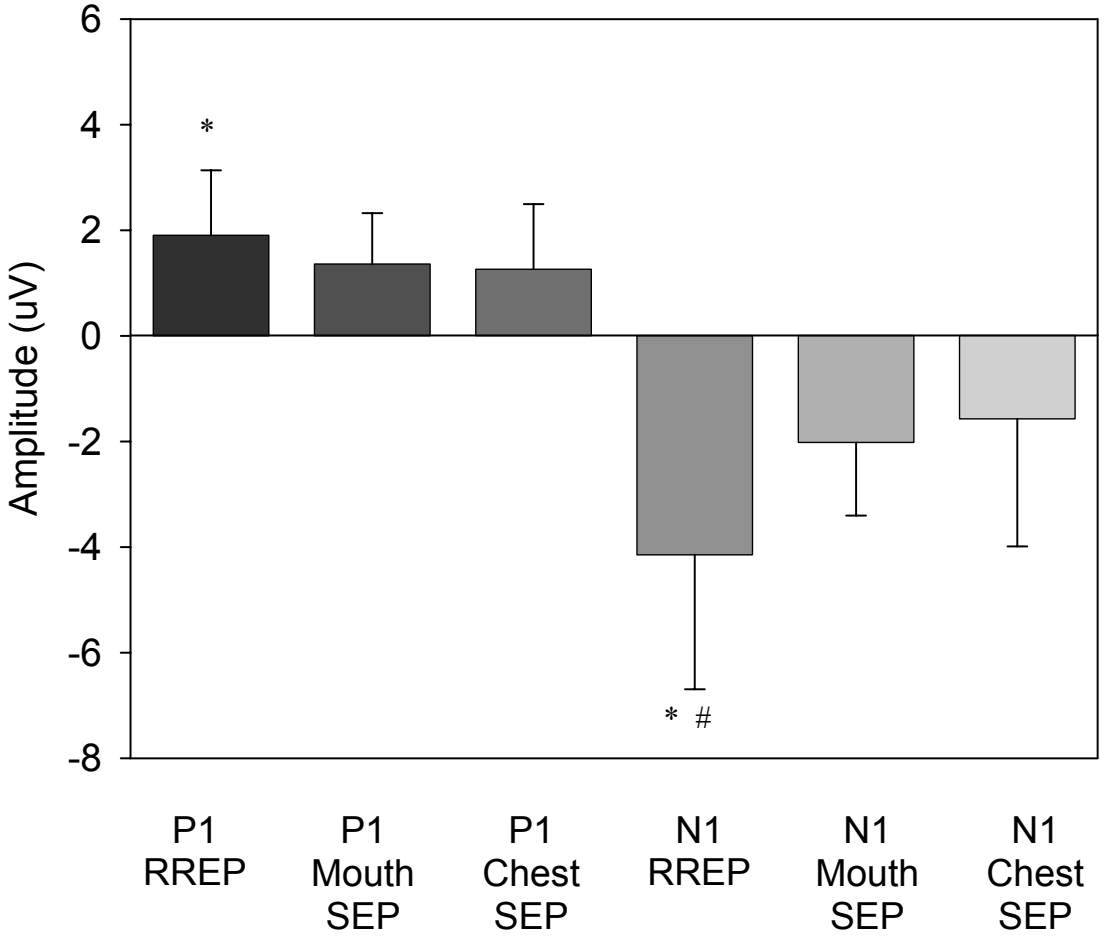

Figure 3-5. Comparison for the amplitudes of the P1 and N1 peaks of the RREP, mouth SEP and chest SEP. The amplitude of the P1 peak of the RREP was significantly greater than the mouth SEP ($p < 0.05$). The amplitude of the P1 peak of the RREP was significantly greater than the chest SEP ($p < 0.05$).The amplitude of the N1 peak of the RREP was significantly greater than the chest SEP ($p < 0.05$). There were no significant difference between the P1 peak of the mouth SEP and chest SEP. There were no significant difference between the N1 peak of the mouth SEP and chest SEP. * indicates a significant difference between the RREP and chest SEP amplitude. # indicates a significant difference between the RREP and mouth SEP.

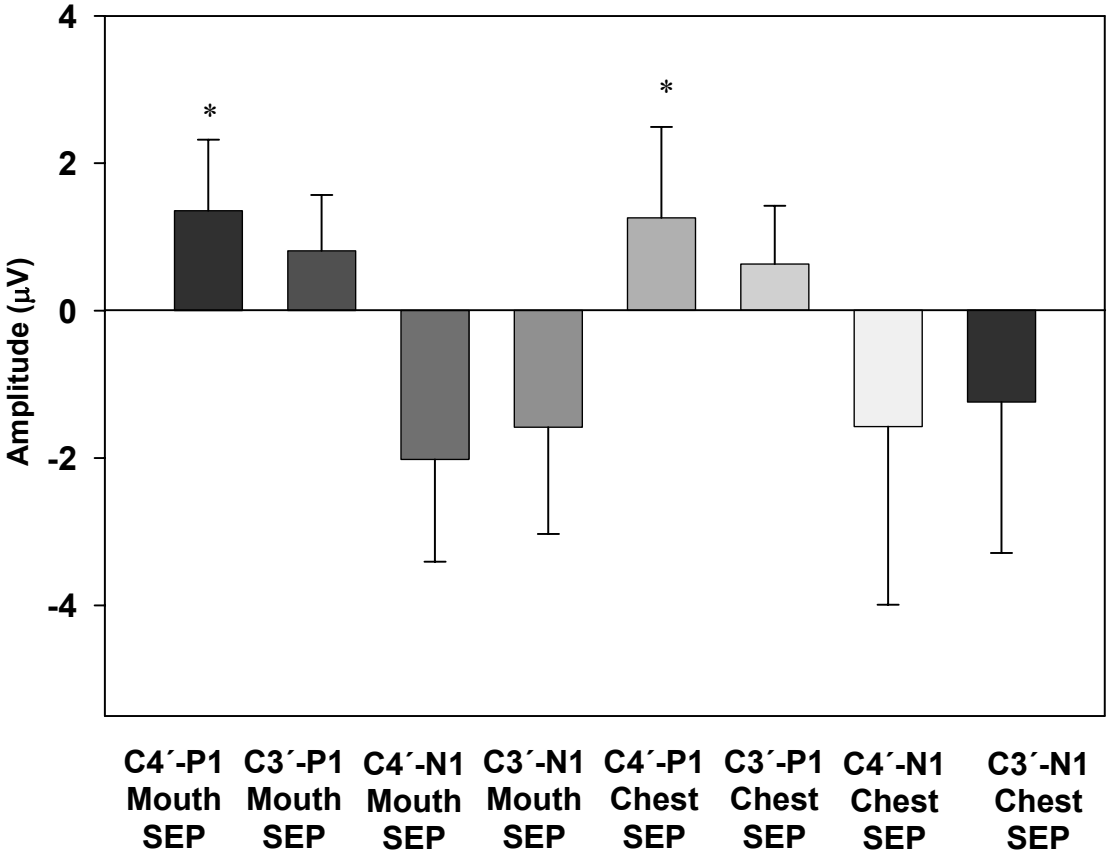

Figure 3-6. Comparisons between the C3' and C4' electrode sites for the P1 and N1 peaks of the mouth SEP and chest SEP. The mouth SEP P1 peak was significantly greater amplitude in the C4' electrode site ($p < 0.05$). The chest SEP P1 peak was significantly greater amplitude in the C4' electrode site ($p < 0.05$). * indicates a significantly different between the C3' and C4' electrode sites.

CHAPTER 4
RESPIRATORY LOAD PERCEPTION AND RREP WITH INCREASED BACKGROUND RESISTANCE.

Introduction

The inspiratory airflow is impeded by applying resistive loads during breathing. The breathing pattern during a resistive loaded breath decreases (more negative) mouth pressure as airflow increases, both parameters peak at mid-inspiration. When the magnitude of the resistive load increased, airflow decreases further due to the impedance imposed by the resistive load (Noble et al., 1972). As the resistive load magnitude increases, more negative pressure is needed to overcome the resistance. When the resistive load magnitude reaches a sufficient level, cognitive awareness (detection) of the load occurs. Load detection (LD is studied using techniques to measure the ability of subjects to signal detection of added loads to breathing. The ability of a subject to detect an added load, ΔR, is a function of the ratio of added load to the initial background load (R_0), called the Weber-Fechner fraction, $\Delta R/ R_0$. The detection of resistive loads is dependent of the background resistance of the subjects' airways and the breathing apparatus. The detection threshold is defined as the ΔR that is signaled as detected for 50 % of the load presentation, ΔR_{50}. The threshold for detection of resistive loads has been reported to be a constant fraction $\Delta R_{50}/ R_0$ of about 0.3 for normal subjects and patients with respiratory disease. The perception of respiratory mechanical events depends on cognitive processing of afferent information from mechanoreceptors in the respiratory system. Bennett et al. (1962) reported a variable detection threshold ΔR_{50} for resistive

loads in healthy adults of 2-4 cmH2O/ℓ/sec. Wiley and Zechman (1966) reported that the relationship between the background resistance and the detection threshold for a various background load conditions was 0.25-0.3 despite a large variability in the ΔR detection threshold values. The variability in the detection threshold value among these studies was thus due to the variation in the background resistance, which includes both the subject's intrinsic respiratory resistance and the resistance of the apparatus.

Killian et al. (1980) compared the detection threshold when the resistive loads were applied at different inspiratory flows with different background resistances. They suggested that the resistive load was modulated by the relationship between pressure and airflow over the early part of inspiration, rather than changes of pressure alone. Zechman et al. (1985) reported that transdiaphragmatic pressure (Pdi) increased significantly just before detection of added loads without change in airflow or volume. They concluded that load detection occurred when the change in Pdi reached a critical level. This study demonstrated that there was a transdiaphragmatic threshold for load detection and implicated that the respiratory pump may be a source for the afferent signals of load detection (Zechman et al., 1985).

The pattern of airflow, volume and pressure changed by adding resistive loads and the perception of the added resistive load was also changed by adding the background load (Revelette et al., 1990). These mechanical changes may be mediated by afferents from the mouth, airways and respiratory muscles. Multiple respiratory sensory mechanisms may contribute to the respiratory sensation when breathing against a mechanical load. Breathing against mechanical loads may induce changes in respiratory

mechanics and there must be pathways to mediate afferent information projection from respiratory mechanoreceptors to reach the cortex.

Poor perception of respiratory loads in patients with chronic pulmonary disease may be due to altered processing of afferent information from respiratory mechanoreceptors. It has been reported that the perceived load magnitude declines with a background resistive load of 14.2 cmH2O (Burdon et al., 1983). Decreased magnitude perception of inspiratory resistive loads occurred when a higher background load was present (McCloskey, 1973). Thus, it is likely that load detection may only require the activation of the sensory pathway while magnitude estimation may involve evaluation of information from multiple afferent inputs.

The short-latency components of evoked potentials reflect the integrity of the primary sensory pathways and vary with stimulus parameters such as intensity and frequency (Nagamine et al., 1998). The long-latency components of evoked potentials reflect cognitive and psychological state of the subjects (Webster and Colrain, 2000). Inspiratory occlusion produces a series of short-latency RREP peaks, P1 and N1 peaks recorded from electrodes overlying the somatosensory cortex and Nf identified over the frontal region of the cortex (Davenport et al., 1996; Webster and Colrain, 2000). Inspiratory occlusion of the respiratory system elicited the RREP reflecting the activation of respiratory mechanoreceptors (Davenport et al., 1986). Dipole sources for the P1 and Nf peaks were bilaterally located within primary somatosensory and supplementary motor cortices, respectively (Logie et al., 1998). However, the pathway of respiratory loaded information to the cortex is unknown .

Knafelc and Davenport (1997) demonstrated a relationship between the amplitude of the P1 peak of the RREP and the perceived magnitude of inspiratory resistive loads. They reported that the P1 peak amplitude of the RREP was a function of the perceived load and proportional to the magnitude of the resistive load. However, the relationship between the effects of increased background resistance on the RREP is known. If the RREP is associated with perception of added loads then the addition of an increased background resistance should affect the RREP. Therefore, the purpose of the present study is to determine the effects of background load on RREP responses to inspiratory resistive loads. It was hypothesized that short-latency components (P1, N1, and Nf) of the RREP are involved in conscious perception of respiratory mechanical loads and are recorded only when the added resistive load is above the detection threshold of the subject. It was further hypothesized that a resistive load detectable without increased background resistance may have an RREP but the RREP may not be present when the background is increased to make the same load undetectable.

Method

Subject

Subjects (10 men, 10 women, averaged age= 25.8 yr) with no history of cardiovascular disease, neurological disease, no history of smoking and no evidence of current major illness participated in the study. The Institutional Review Board of University of Florida reviewed and approved the protocols used in this study. All subjects were informed of the nature of the study before starting the experiment and written consent was obtained.

Pulmonary Function Testing

All subjects were seated upright in a chair to perform a pulmonary functional test that conformed to American Thoracic Society Standards. The subjects must have an FEV1 greater than 70% predicted to continue in the study.

Procedures

The subject was seated comfortably in a lounge chair in a sound-isolated chamber, separated from the experimenter and experimental apparatus. A standard set of instructions was presented to the subjects to inform them of their task. The subject respired through a mouthpiece and nonrebreathing valve (Hans Rudolph, 2600 series, Kansas City, MO) connected to a loading manifold. The loading manifold was hidden from the subject's view and connected to a pneumotachograph (Hans Rudolph, Model 4813) attached by reinforced tubing to the inspiratory port of the nonrebreathing valve. The resistive loads were sintered bronze disks placed in series in the loading manifold and separated by stoppered ports. Mouth pressure (P_m) was recorded from a port in the center of the nonrebreathing valve. The P_m was displayed on an oscilloscope for timing the load applications and stored on a computer (Model 1401, Cambridge Electronic Design).

An electrode cap with integral electrodes was used to record scalp EEG activity. The electrode positions were based on the International 10-20 System. The cap was placed on the subject's head, positioned and secured with a strap. Scalp and electrode contact was made by the application of electro-conducing paste administered through the center opening in the electrode. The impedance levels for each electrode was checked and maintained below 5 KΩ. The electrode cap was then connected to an EEG system (Model 12, Grass instruments, Quincy, MA). EEG activity was monitored with an oscilloscope

monitor. The EEG activities were recorded and referenced to the joined earlobes. Two electrodes were placed over the lateral edge of the eye for recording vertical electrooculograms (EOG). Any load presentation that occurred with an eye-blink was discarded. The EEG signals were band-pass filtered (0.3 – 1 KHz), amplified and sampled (2 kHz) for computer analysis. The EEG activities were led into signal averaging computer system (Model 1401, Cambridge Electronics Design).

All subjects were instructed to relax all postural and facial muscles and to breathe as normally as possible. The subject wore a nose clip and breathed through a mouthpiece connected to the non-rebreathing valve and loading apparatus. The subject inspired through the minimum resistance port of the loading manifold. The occlusion valve was connected to the opening of this minimum resistance port. The inspiratory load was presented by silently inflating the occlusion valve at approximately the mid-inspiratory point of the breath. Activation of the occlusion valve closed this port and channeled the inspired air through one of three manifold resistance ports. When a resistance was presented, the stopper for that port was removed. Activation of the occlusion valve on the minimal resistance port was then closed and the subject inspired through the increased resistance. The inspiratory resistive load was presented as an interruption of inspiration. The balloon pressure was used to trigger the computer for data sample collection. Each load was separated by 2-6 unloaded breaths. The load was applied for a duration of 500 ms. Previous results from this laboratory have shown that the averaged detection threshold value for resistive loads in healthy subjects with no background load is 1-2 $cmH_2O/\ell/s$. One resistive load that was below the detection threshold and two resistive loads that exceed the

detection threshold were used for eliciting the evoked potentials (R1=0.2, R2=3.8, and R3= 23.3 cmH2O/ℓ/s).

Two trials were presented: 1) without elevated background resistance and 2) with an elevated background resistance of 13.3 cmH2O/ℓ/s. Each trial was separated into two sets of load presentations. Each set was separated by a rest period off the breathing apparatus. The order of the presentation of the three resistive loads was randomized to minimize temporal, order and sequence effects. Each set consisted of 120 presentations. Within each set of 120 load presentations were tested by using 24 blocks of five presentations of each load. Ordering of the different presentation blocks was randomized, with the restriction that each successive set of 3 blocks contained only one block of each resistive load level. Thus, over the set of 120 presentations each block of five trials of a given load was presented 8 times (40 total presentation of each load magnitude). The randomization was independently drawn for each set of 120 trials and for each subject with the 2 sets of presentations. Thus, each load magnitude was presented 80 times. The time required to present the entire study was ~3 hours, including subject preparation time. For 5 of the 20 subjects, an additional experiment was performed with inspiratory occlusion replacing R3.

Data Analysis

The Pm and EEG activity for each load presentation were digitized and stored on the computer for subsequent signal averaging (Signal 2, Cambridge Electronics Design). Each resistive load magnitude was averaged separately. The data analysis was performed for each load magnitude including the loads from the two trials.

Individual subject files were used for RREP peak component identification, amplitude and latency analysis. Baseline-to-peak amplitude values were determined separately for each peak. Peak amplitudes were correlated with the resistive load

magnitudes. The P1 peak is the positive potential occurring within a 40-70 ms time window. The N1 peak is the negative potential occurring between 80-120 ms. The Nf peak is the negative peak in the frontal electrodes occurring at 25-40 ms. The latency and amplitude of each RREP peaks (P1, N1 and Nf) were compared using one-way, repeated-measures analysis of variance (ANOVA). A $p < 0.05$ was considered as statistically significant.

Results

P1, N1, and Nf peaks were present in all subjects with no-background resistance for R2 and R3 loads (Fig 4-1a and Fig 4-1b). With increased background resistance, P1, N1 and Nf peaks were present in all subjects with the increased background load only for the R3 load and inspiratory occlusion (Fig 4-2a and Fig 4-2b). There was no significant effect of background resistance for the latencies of the P1, N1, and Nf peaks of the RREP for each inspiratory resistive load, and occlusion when present (Table 4-1).

Mean amplitudes of the P1, N1 and Nf peaks for each inspiratory resistive load and occlusion are presented in Table 4-1. P1 and Nf peaks showed a significant main effect of resistive load magnitudes with no-background resistance. The P1 peak amplitude showed a significant difference between no-background resistance condition and increased background resistance condition (Fig 4-3).

The ΔR_{50} remained the same but R_0 changed to R_0' when increasing the background resistance. Thus, the baseline background resistance was R_0= 4.8 cmH2O/ℓ/s, averaged resistance of the subject and apparatus with no-background load. The background resistance was increased to R_0'= 16.4 cmH2O/ℓ/s, the resistance consisted of the subject and 13.3 cmH2O/ℓ/s increased background resistance. The ratio ($\Delta R_{50}/R_0$) is 0.3 for normal subjects. $R2/R_0$ is changed with the increased background

resistance increased to 0.1 and becomes undetectable. There was no P1 peak present with R2. $R3/R_0$ was not changed with the background resistance increased and was detectable as it was above 0.3. Thus, P1 peak amplitude of the RREP is the function of the detection threshold (Fig 4-4).

Discussion

The RREP peaks, P1, N1, and Nf were present with detectable resistive load magnitudes (R2 and R3) and were not present with the load (R1) below the detection threshold for the no-background resistance trials. In contrast, P1, N1, and Nf peaks were absent with R1 and R2 loads below the detection threshold with increased background. All the peaks of the RREP were present with R3 load, which was above the detection threshold with increased background resistance. These results demonstrated that the P1, N1 and Nf peaks are related to load perception and changes in perception changes the RREP peaks.

Inspiratory resistive loads require the inspiratory muscles to overcome the load to generate airflow (Wiley and Zechman, 1966). The increased tension developed by the inspiratory muscles may be the stimulus mediating the perceived magnitude of added loads (Killian et al., 1980; Killian et al., 1984). Resistive loads are airflow-dependent loads and a decrease in the inspiratory airflow reduces the pressure changes associated with the increased load. The decrease in these load-related mechanical parameters with a decreased inspiratory effort can result in a reduced sensory stimulation and underestimation of the load magnitude. The ventilatory response to external mechanical loads depends on the type of load (Younes et al., 1994). It has been reported that both minute ventilation and mean inspiratory flow rate decreased when breathing against a resistive load in conscious man (Dressendorfer et al., 1977). The changes in the breathing

pattern compensate for the increased work of breathing (Zechman et al., 1985). However, the afferent mechanisms involved in the behavioral load compensation responses remain unclear.

When a stimulus of constant intensity is applied, the sensation it produces has two stages. The first stage consists of an increased sensory magnitude; during the second stage the sensation diminishes in magnitude over time as accommodation produces adaptation to the load. The afferent pathway mediating the load detection has not been identified; however, the receptors within the lung, chest wall, and upper airways may be involved in respiratory sensation (Davenport et al., 1991; Knafelc and Davenport, 1997; Harver, 1987). The detection of an inspiratory load is a complex chain of events involving cortical sensory processing of respiratory mechanoreceptor activity (Kifle et al., 1997; Fritz et al., 1999). Burdon et al. (1983) reported that perceptual performance was not altered by increased background resistance. It is likely they failed to demonstrate an effect of increased background load in scaling performance because their protocols resulted in decreased airflow and loss of stimuli with increased background resistance. Revelette et al. (1984) reported that the shift in the exponent for magnitude estimation with increased background resistance is associated with an increase in the load detection threshold. This is consistent with our findings in the present study that the resistive load, below the detection threshold with the increased background load will not elicit RREP.

The activation of cortical neural activity by resistive loads has been studied using evoked potential techniques (Knafelc and Davenport, 1997). The RREP elicited by inspiratory occlusion applied at mid-inspiration was recorded from the somatosensory region of the cortex in healthy adults (Davenport and Revelette, 1990; Davenport et al.,

1986). Early peaks of the RREP were identified in healthy adults, asthmatics and double lung transplant recipients (Davenport et al., 1996; Kifle et al., 2000; Zhao et al., 2003). The P1 peak reflects the depolarization of cortical neurons by the arrival of afferent activity stimulated by the occluded breath.

Franzén and Offenloch (1969) reported that the magnitude of the early positive peak of the touch elicited somatosensory evoked potential (SEP) was correlated with mechanical stimulus amplitude and magnitude estimation of the touch. If the RREP is analogous to the SEP, then the amplitude of the P1 peak of the RREP should correlate with the load magnitude. This is consistent with the result from Knafelc and Davenport (1997) reporting a relationship between the RREP P1 peak amplitude and resistive load magnitude. They reported that there was a log-log relationship between the magnitude of the resistive load and P1 peak amplitude when a series of resistive loads were applied (Knafelc and Davenport, 1997, 1999). However, it remained unknown if the threshold for eliciting the RREP corresponded to the detection threshold. The relationship between the RREP P1 peak amplitude and the resistive load magnitude was found in the present study that the relative afferent signal strength would be changed by increasing the background resistance. Thus, the RREP peaks were present or absent depending on the detectability of the load. If the load was above the detection threshold, the RREP was present. However, if the load was below the detection threshold, the RREP was absent. Moreover, changing the detection threshold by adding the background resistance decreased the amplitude of the load that remained detectable and the RREP was not present for the load forced below the detection threshold by the elevated R_0. This further supports the conclusion that the amplitudes of RREP peaks are directly related to the detectability and

magnitude of the load. RREP elicited by inspiratory occlusion was found unaffected by increased background resistance in the present study. This result was consistent with previous finding that the RREP elicited by the inspiratory occlusion remains unchanged with different type of loads and different background environments (Davenport et al., 1981).

Variations in RREP latencies and amplitudes in the current study provided evidence that cortical processes to mechanical loads were affected not only by the magnitude of load but also by the detection of the loaded information, suggesting a gated respiratory afferent feedback system. In the present study, the P1 peak amplitude of the RREP is not present with the increased background resistance because the applied resistive load is below the detection threshold ratio. The fact that the RREP is not present with increased background resistance suggests that the respiratory resistive load information was gated out by changing the background ventilatory state, such as increased background resistance. Thus, the respiratory afferent information will be gated in if above the detection threshold or will be gated out if the threshold was unregulated by other systems, such as increased background resistance.

Although the interaction between the conscious and the automatic control of breathing is uncertain, failure to have sufficient respiratory motor drive to meet the ventilatory demands will result in a conscious awareness of breathing and behavioral motor response. Thus, there must be a subcortical threshold to gate-in or gate-out the respiratory afferent input and feedback motor output. However, neural indicator and the possible mechanisms that subserve the respiratory sensory gating system are unknown.

Conclusion

In summary, the present study demonstrated that activation of cortical neural activity was associated with the perceptual processing of resistive load information. The detection threshold of inspiratory loads was increased by the increased background resistance but the relative threshold $\Delta R_{50}/R_0$ is unchanged. If the resistive load was detectable, the RREP was present. If the load was not detectable or becomes undetectable with increased background load, the RREP was not present, supporting the hypothesis that the RREP response could be changed by increasing the background load which shifts the detection threshold. Therefore, perceptual processing of respiratory load information may be gated-in subcortical centers as part of the central afferent pathway. Future studies are necessary to investigate the respiratory patterns and the cognitive component of the RREP P300 peak to extend these studies to the gating effects of the cognitive measures of respiratory mechanoreceptor processing.

Table 4-1 Group-averaged P1, N1, and Nf latencies and amplitudes of RREP for inspiratory resistive load and inspiratory occlusion.

	P1 - C3'	P1 - C4'	N1 - C3'	N1 - C4'	Nf – F3	Nf - F4
Amplitude (μV)						
R2 - No Background	1.40 ± 0.69	1.21 ± 0.53	-2.30 ± 0.85	-2.38 ± 0.90	-1.77 ± 0.98	-1.71 ± 0.62
R3 - No Background	2.20 ± 0.73 #	2.29 ± 0.57 # *	-2.85 ± 1.04	-3.14 ± 1.41	-2.27 ± 0.78 # *	-2.32 ± 0.85 # *
Occlusion - No Background	2.31 ± 0.93	2.38 ± 0.97	-2.02 ± 0.39	-2.31 ± 0.65	-2.09 ± 0.80	-2.11 ± 0.20
R3 - With Background	1.79 ± 0.75	1.79 ± 0.74	-2.45 ± 0.88	-2.54 ± 0.95	-1.66 ± 0.97	-1.70 ± 0.81
Occlusion - With Background	1.85 ± 0.22	2.12 ± 0.67	-3.01 ± 0.93	-3.13 ± 1.00	-1.69 ± 0.40	-1.72 ± 0.32
Latency (msec)						
R2 - No Background	65.73 ± 7.19		104.74 ± 8.99		34.88 ± 5.64	
R3 - No Background	63.57 ± 6.70		100.54 ± 10.05		36.75 ± 5.84	
Occlusion - No Background	64.53 ± 4.61		104.61 ± 7.50		34.05 ± 5.61	
R3 - With Background	72.20 ± 8.40		109.60 ± 13.52		35.30 ± 3.76	
Occlusion - With Background	69.98 ± 9.02		105.09 ± 10.24		31.28 ± 6.37	

Values were means ± SD. Occlusion was an infinitive load (maximal load) for the respiratory system.
indicated the significant difference between R2 and R3 resistive loads.
* indicated the significant difference between no-background resistance and increased background resistance.

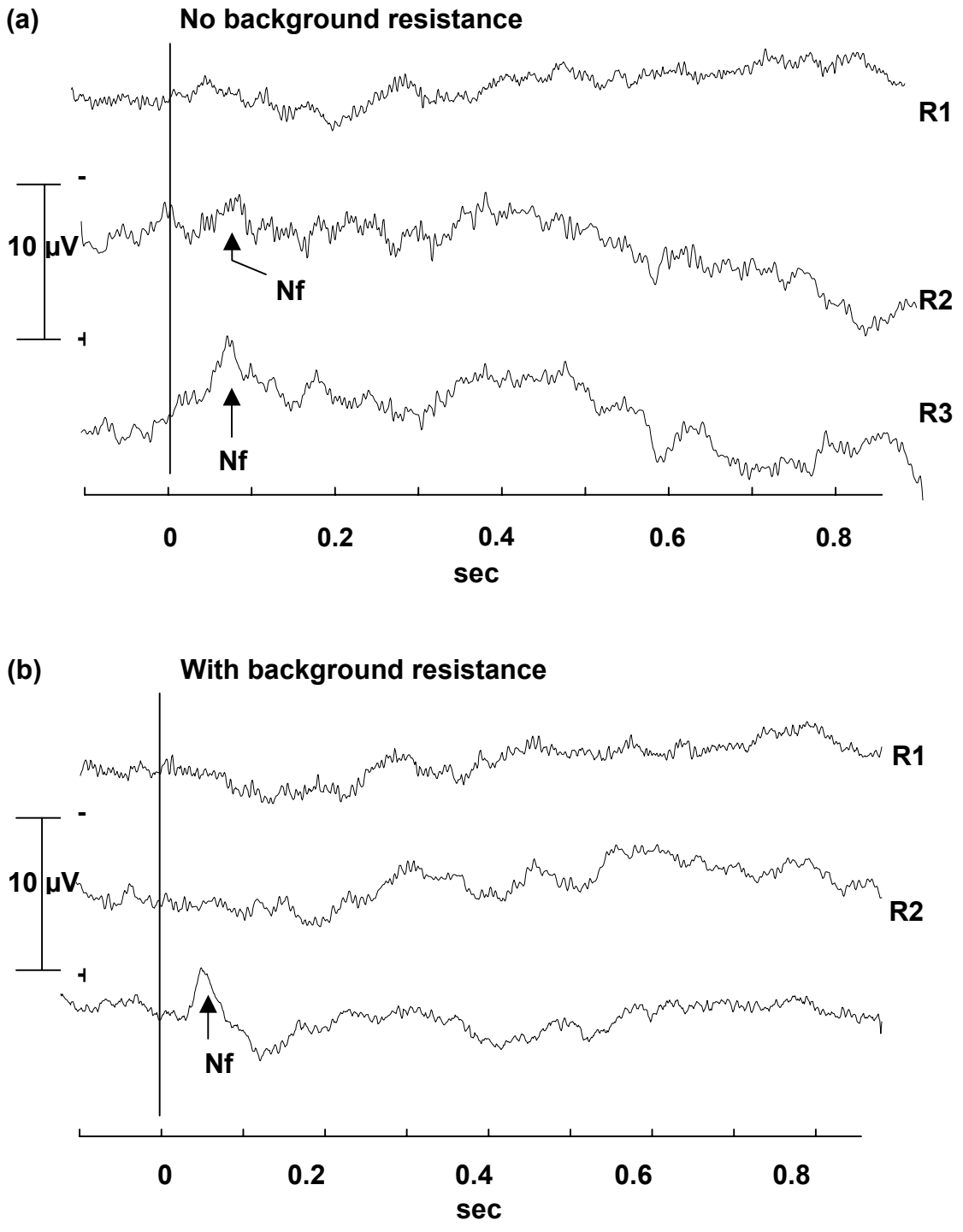

Figure 4-1. Nf peaks recorded from F4 electrode with different resistive loads in both no-background resistance (a) and increased background resistance (b).

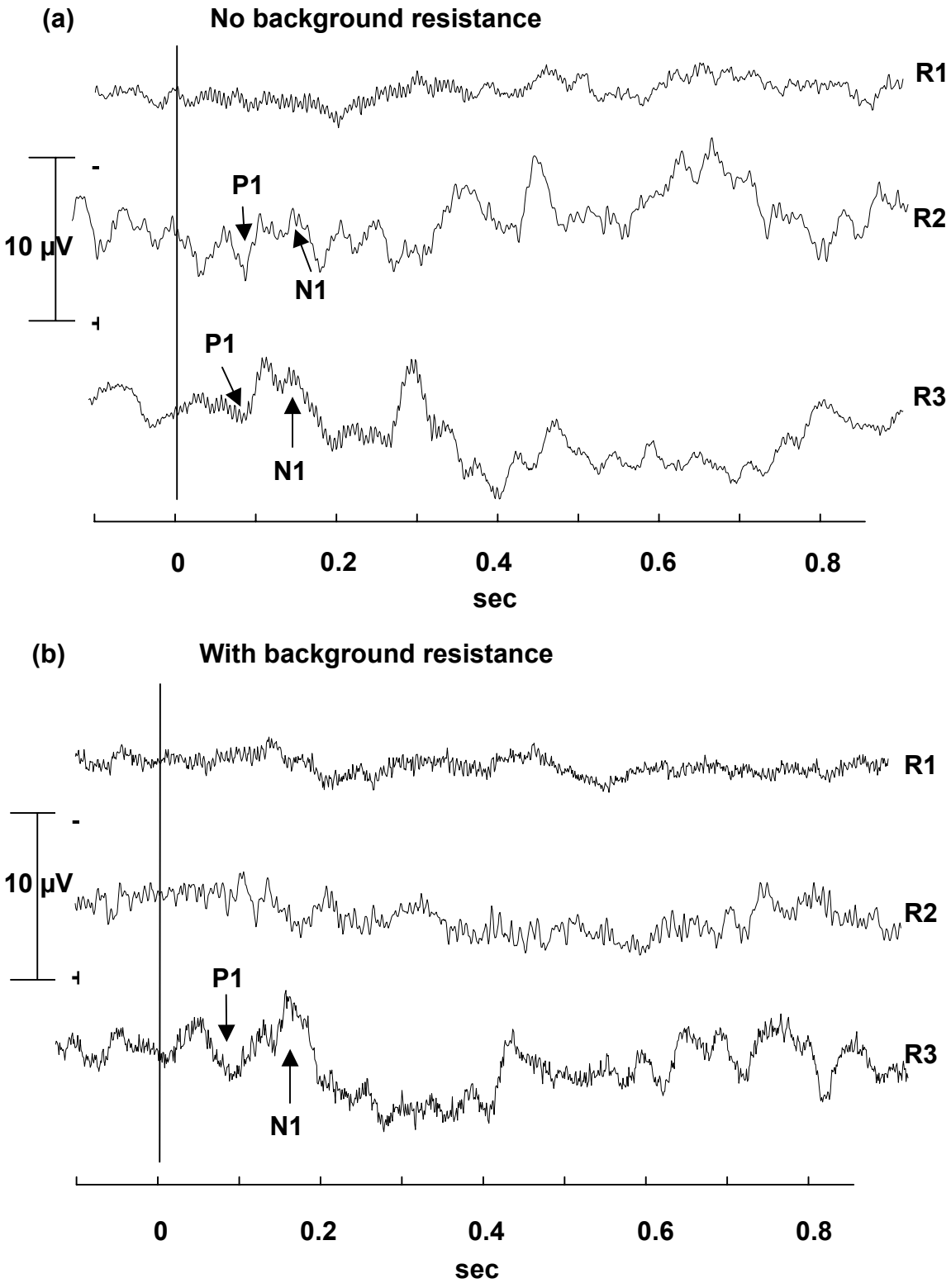

Figure 4-2. P1 and N1 peaks recorded from C4' electrode with different resistive load in both no-background resistance (a) and increased background resistance (b).

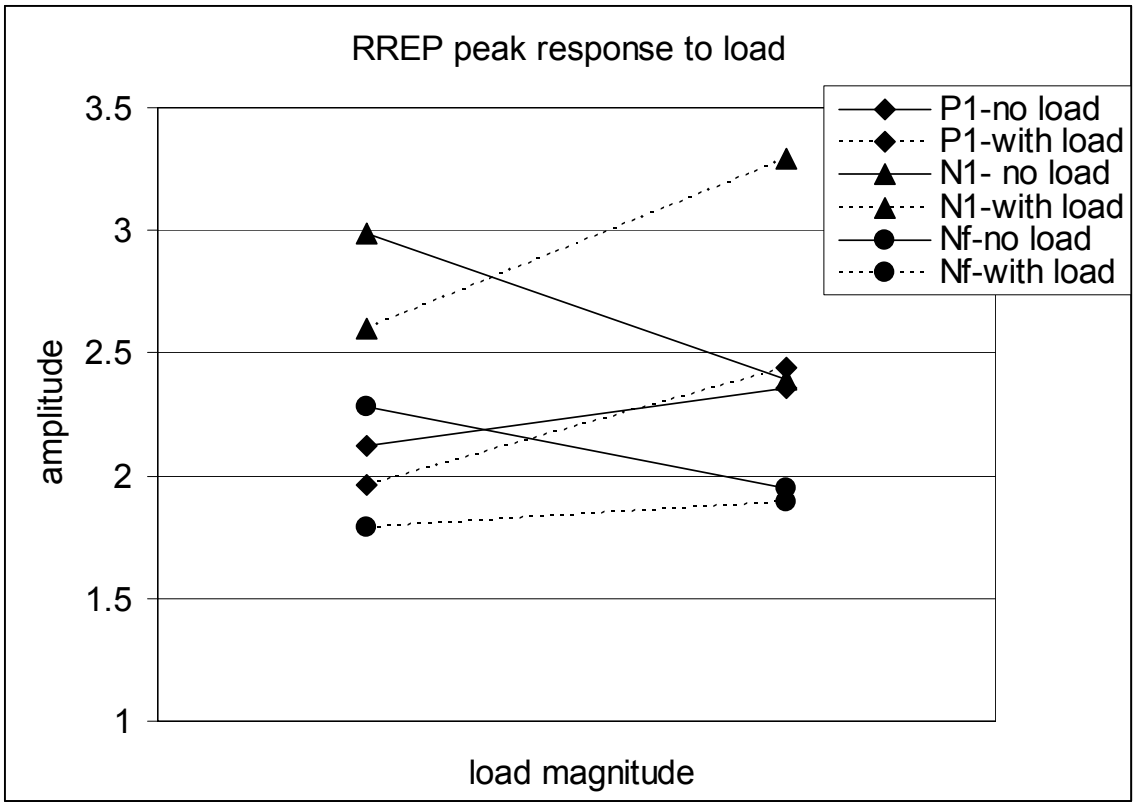

Figure 4-3. P1, N1 and Nf peaks recorded from C4' and F4 electrode sites, respectively with inspiratory occlusion (maximal resistive load) in both no-background resistance and increased background resistance conditions.

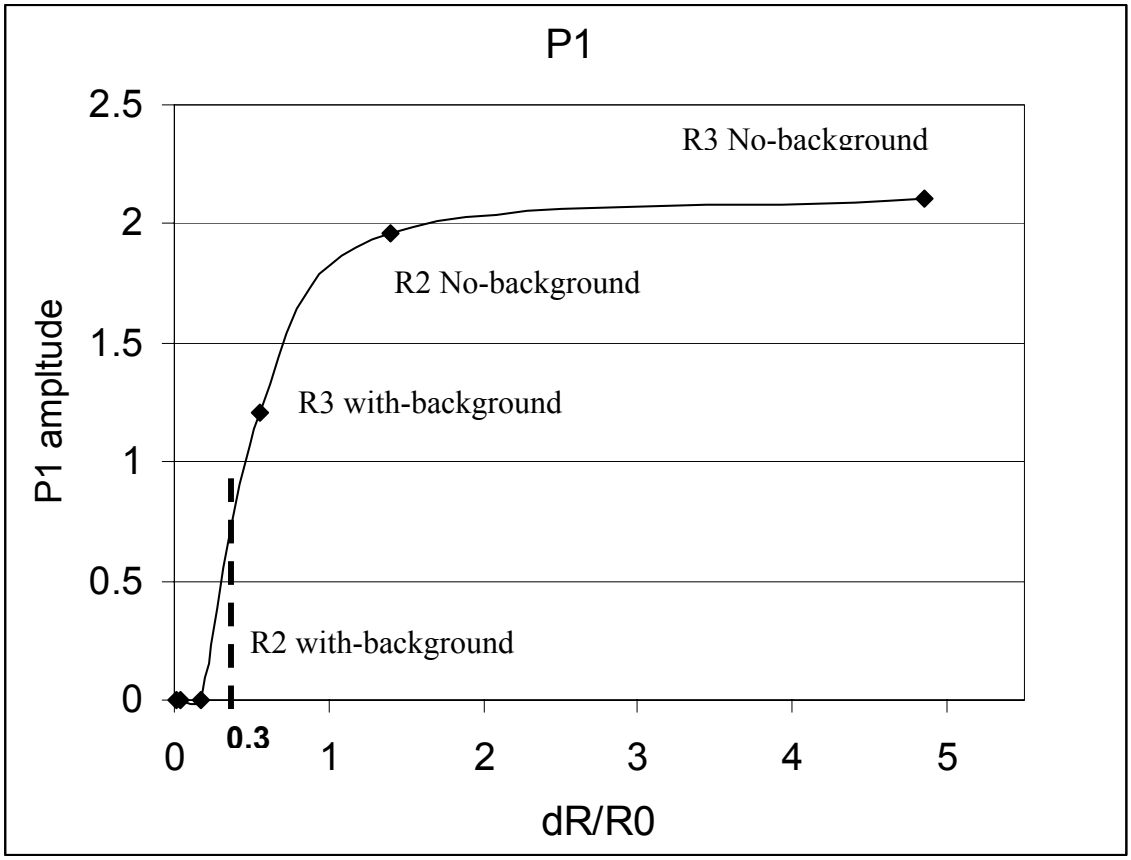

Figure 4-4. Relationship between amplitude of P1 peak and changes of resistive load magnitude with different background resistance. The change in resistive load magnitude was determined by resistive load magnitude divided by baseline resistance ($\Delta R_{50}/R_0$). R_0= 4.8 cmH2O/ℓ/s was the baseline resistance measured from both subject and apparatus with no-background load. R_0'= 16.4 cmH2O/ℓ/s is the baseline resistance measured from both subject and apparatus with increased background load. The ratio ($\Delta R_{50}/R_0$) is 0.3 for normal subject. R2 became undetectable as it was below 0.3 after increasing the background resistance. Therefore, there was no P1 peak present when R2 load was applied with increased background resistance.

CHAPTER 5
GENERAL DISCUSSION

Summary of Results

1. The results of the evoked potentials elicited by inspiratory occlusion and cutaneous stimulation demonstrated that short-latency components of the RREP and SEP project to the same scalp locations. The RREP components were observed bilaterally whereas the SEP was observed contralateral to the stimulated hand. The scalp distributions of the RREP and SEP P1 peaks were found at the centroparietal (C4') electrode position. The latencies of the P1 and N1 peaks of the RREP were significantly longer than the SEP. The amplitudes of the P1 and N1 peaks of the RREP were significantly greater than the SEP. The Nf peak was only observed in the frontal region of RREP.

2. The P1 and N1 peaks of the RREP elicited by inspiratory occlusion were similar to the peaks of the SEP elicited either by air puff stimulation to the mouth or cutaneous mechanical stimulation to the chest. The Nf peak was only observed in the frontal sites of RREP. The latencies of the RREP peaks were longer than the mouth SEP and chest SEP. The P1 and N1 peak amplitudes of the RREP were significantly greater than the chest SEP. The N1 peak amplitude of the RREP was significantly greater than the N1 peak of the mouth SEP. There was no significant difference between chest SEP and mouth SEP for P1 and N1 peaks.

3. The RREP response to resistive load magnitude was correlated with the presence of the RREP P1, N1, and Nf peaks with detectable resistive loads. The RREP was not

present with loads that were below the detection threshold. When an increased background resistance was applied, the RREP peaks were present with the load that was above the detection threshold but were absent with the load that was below the detection threshold.

Distribution of Evoked Potentials

RREP with Inspiratory Occlusion

RREP peaks, P1, N1 and Nf were identified in response to inspiratory occlusion, consistent with previous studies (Davenport et al., 1996; Davenport et al., 2000; Davenport et al., 1986). The amplitude of the P1 peak of the RREP increased with the magnitude estimation of the corresponding load and the inspiratory load magnitude (Knafelc and Davenport, 1997; 1999). In the present study, these RREP peaks were recorded in all three experiments. The RREP was not present however, if a load was below the load detection threshold. The P1, Nf and N1 peaks of the RREP were found bilaterally. The P1 peak location is consistent with the dipole in the somatosenory cortex. The Nf peak location is consistent with the dipole in the supplementary motor cortex. The N1 peak location is consistent with the midline of the cortex, greatest at the vertex.

SEP with Mechanical Stimulation

The P1 and N1 peaks of the limb SEP, mouth SEP and chest SEP were identified in scalp locations that were contralateral to the side stimulated. These peaks were not bilaterally symmetrical, a difference from the RREP. The electrode sites of the P1 peak of the limb SEP, mouth SEP and chest SEP were over the post-central gyrus lateral to the midline which is consistent with the somatotopical representation of the fingers in the primary somatosensory cortex (Pratt and Starr, 1981). Thus, the mechanical SEP and the RREP P1 peaks are consistent with an activation of neurons in the primary

somatosensory region of the cerebral cortex. The electrode sites of the N1 peak of the limb SEP, mouth SEP and chest SEP were over the central sulcus at the midline of the cerebral cortex which is also consistent with the somatotopical representation of the fingers in the sensorimotor cortex (Pratt and Starr, 1981). Thus, the mechanical SEP and the RREP N1 peaks are consistent with an activation of neurons in the sensorimotor region of the cerebral cortex.

Mechanical stimulation activates mechanoreceptors in a defined focal location in the hand, chest or buccal surface of the mouth. The mechanoreceptors are myelinated afferents with a rapid conduction velocity. The latency for mechanical cutaneous stimulation included mechanical transduction time and pathway conduction time. The latency for skin (limb and chest) mechanoreceptors to the cortex is less than either the mouth or RREP. However, the cutaneous peak amplitudes were smaller, most likely due to fewer mechanoreceptors activated by the focal stimulation compared to the widely distributed stimulation with inspiratory occlusion.

Latency and Amplitude of Short-Latency Peaks of Evoked Potential RREP

The P1 peak of the RREP has been reported to reflect the arrival of respiratory mechanoreceptor activity in the primary sensory area of the cortex (Logie et al., 1998). The P1 peak is determined mainly by the physical characteristics of the stimulus. The RREP P1 peak amplitude was correlated to the resistive load magnitude (Knafelc and Davenport, 1997; Webster and Colrain, 2000), suggesting that this peak is the indicator of the stimulus dependent activation of somatosensory cortical columns. The amplitude of RREP N1 peak was reported to decrease with a decrease of the load magnitude (Bloch-Salisbury et al., 1998). The P1 and Nf peak amplitudes were unaffected by attention

while attention increased the N1 amplitude (Harver et al., 1995). Zhao et al. (2002) also reported that there were no significant difference in either latency or amplitude of the P1 and Nf peaks of the RREP peaks between attend trials and ignore trials for both double lung transplant recipients and matched healthy subjects. Thus, the P1 and Nf peaks are dipoles in the cerebral cortex indicating the arrival and magnitude of respiratory afferent activation.

It is unlikely that the frontal Nf peak of the RREP reflects myogenic activity. The neural generators of the Nf peak are consistent with a pre-motor cortical location. The bilateral distribution of the Nf peak and the latency suggest that it reflects a parallel (to P1) input to activity in prefrontal structures. It is generally recognized that thalamocortical inputs to the somatosensory cortex project predominantly to deep cortical layers and that they generate a surface (P1) positive potential (Wood and Allison, 1981; Wood et al., 1985). The frontal Nf peak was not preceded by the P1 peak and can not be explained as voltage spread from the somatosensory cortex. The negative peak suggest a dipole generator in the more superficial layers of the prefrontal cortex

The prefrontal cortex gated the early stage of somatosensory processing and can exert an inhibitory modulation on sensory processing (Yamaguchi and Knight, 1990). The prefrontal cortex mediates cortical motor reflexes suggesting that the generation of the frontal Nf potential is a pre-motor respiratory cortical response to the respiratory load. The Nf peak generated in the prefrontal cortex may therefore function as the integration of load information related to the behavioral motor response to the mechanical stimulus produced by loaded breathing (Davenport et al., 1996). However, the exactly source of the Nf peak is unknown.

The N1 peak of the RREP was the negative peak associated with the P1 peak of the RREP (Davenport et al., 1986). The N1 peak of the RREP was observed to be of greatest amplitude in the central electrode sites. These electrode sites were over the central sulcus at the midline of the cerebral cortex which is consistent with the somatotopical representation of the fingers in the sensorimotor cortex (Pratt and Starr, 1981). In addition, Webster and Colrain (2000) reported N1 peak is recorded from the vertical dipole source and is affected by the attention. Thus, the N1 peak of RREP may be the second order cortical processing of respiratory afferent information. Bloch-Salisbury et al. (1998) reported that N1 peak amplitude of the RREP decreases as the resistive load decreased, similar to P1 peak of the RREP. Thus, the N1 peak of the RREP may be the second order cortical processing of the respiratory afferent information that is based on perceiving the first-order somatosensory information and may affect the cognitive processing.

SEP on Hand

The P1 peak was elicited by mechanical cutaneous stimulation of the load in the C3' and C4' electrode sites in the present study. This is consistent with the reports of SEP elicited by mechanical stimulation of the digits (Onofrj et al, 1990; Pratt and Starr, 1981), suggesting that the generation of this early positive peak was in the primary somatosensory region of the cortex (Hamalainen et al., 1990). In the current study, the latency of the SEP P1 peak elicited by cutaneous stimulation of the hand was about 25 msec. This is consistent with the report of Schieppati and Ducati (1984) that the P1 peak of the SEP is elicited by the cutaneous stimulation. Thus, the results of the present study are consistent with the P1 peak of the SEP generated in the somatosensory region of the cortex.

The P1 peak of the SEP generated by mechanical stimulation have been found in area 3b (somatosensory cortex) mediated by thalamocortical afferents from ventroposterolateral nuclei in the thalamus and in area 3a activated by afferents from ventroposterior nuclei in the thalamus (Dieter et al., 1986). Neurophysiological studies (Hashimoto et al., 1991; Johansson et al., 1980) that utilize the EEG as indices of sensory processing showed increased evoked potential P1 peak amplitudes were generally produced by an increase in the stimulus intensity. The P1 peak of the evoked potential in response to mechanical stimulation has been identified in the somatosensory regions of the cortex (Hamalainen, 1990). Thus, the P1 peak amplitudes of both the RREP and SEP are a function of the magnitude of neural activity directly correlated with the magnitude of stimulus.

SEP on Chest and Mouth

The activation of cortical neurons by mechanical loads has been studied using evoked potential techniques similar to those routinely used in other somatosensory systems (Buchner et al., 1996; Rossini et al., 1996). In the present study, minor differences in the extent of negative and positive fields on the scalp could be observed in the same subject when changing the stimulus modality, but the sequence of evoked potential peaks and scalp distributions followed the same pattern regardless of the stimulus modality.

Air-puff stimulation selectively activated cutaneous mechanoreceptors (Schieppati and Ducati, 1984). Variations in the rise time of the stimulus can alter the rate of mechanical indentation of the chest wall and the transduction process of the afferent information. The onset of the first SEP peak elicited by mechanical stimulation has been delayed 2-4 ms from that of the SEP elicited by electrical stimulation (Pratt and Starr,

1981). The latency difference was mainly the result of receptor transduction time and mechanical threshold differences from varies receptor locations (Mizobuchi et al., 2000).

The SEP following mechanical air puff stimuli to the mouth had a greater amplitude than the SEP recorded following mechanical stimulation on the chest wall. The difference of the amplitude between the air puff stimulation and the cutaneous stimulation may be due to a wide surface area stimulated with air pressure, greater receptor density and/or differences in sensory amplification by second order neural processing system.

The RREP and mouth SEP may have similar afferent sources (upper airway) and sensory modality (pressure), suggesting that time is required when breathing against the inspiratory occlusion to bring the respiratory mechanoreceptors to threshold. Thus, the amplitude differences in normal subjects between the RREP and mechanically evoked potentials in the current study may be due huge number of mechanoreceptor populations activated or different neural processing for the respiratory afferent information.

Afferent Mechanisms of Evoked Potentials

Sources of RREP

The P1 peak of the RREP is believed to reflect the arrival of respiratory afferent information in the primary somatosensory region of the cortex. Therefore, the application of inspiratory occlusion, which puts an infinite resistive load on the entire respiratory system, will bilaterally stimulate multiple respiratory mechanoreceptors mediating the neural activity in the cortex. Although the stimulated afferents are unknown, it is likely that mechanoreceptors in the respiratory pump and airways are the primary source of load related somatosensory activity. It has been reported that RREP peaks are present in subjects with denervation of lung vagal afferents (Zhao et al., 2002; 2003). This

laboratory has also reported the presence of the P1, Nf , N1 and P300 RREP peaks in double lung transplant recipients respiring through their tracheal stoma, which dennervates both lung vagal afferent and upper airway afferent inputs (Davenport et al, abstract, 2004). Thus, respiratory pump afferents can elicit the RREP with inspiratory occlusion. However, inclusion of mouth, pharyngeal and laryngeal afferents increases the amplitude of the RREP peaks, suggesting the RREP in intact subjects is the result of multiple respiratory mechanoreceptor modalities.

Afferent Pathways of RREP and SEP

The waveform of the RREP is similar to cutaneous SEP's in the present study. Inspiratory occlusion can alter the afferent activity of several populations of mechanoreceptors in the mouth, pharynx, larynx, lung and respiratory muscles. Inspiratory occlusion halts the normal changes in inspiratory airflow and lung volume. Animal studies have demonstrated that inspiratory resistive loads activate the proprioceptors of respiratory muscles (Jammes et al., 1986).

Recordings of cortical responses to afferent stimuli confirm that the electrical responses at 50 ms and 100 ms latencies are generated by activity in SI and SII somatosensory cortex (Hari, 1980). The SEP evoked by electrical stimulation of the median nerve at the wrist or the index finger also showed a similar SEP distribution (Onofrj et al., 1990; Grisolia and Wiederholt, 1980). The results of recordings from the exposed cortex in humans suggest that the short latency peaks of the SEP were generated from the primary somatosensory cortex (Allison et al., 1989a). The results from current SEP study with cutaneous stimulation of hand were constant with previous studies (Johansson et al., 1980; Gardner et la., 1984; Hashimoto et al., 1990), in which the latency delays for mechanical stimulation were accounted for by two peripheral

mechanisms: skin indentation and receptor transudation and lower conduction velocity of cutaneous afferents.

Comparisons between RREP and SEP

Evoked potentials elicited by mechanical stimulation of skin is affected by respiratory phase (Balzamo et al., 1995; 1999) however, no study has compared the cortical processing of skin and respiratory mechanical stimulation. In the present study, the latencies and amplitudes of the SEP elicited by mechanical air puff stimulation of the mouth and cutaneous stimulation of the hand and the chest wall were compared to the RREP components elicited by inspiratory occlusion. Results from this study showed that the mechanically loaded inspiratory occlusion activates cortical neurons in the somatosensory cortex eliciting peaks analogous to the SEP P1 and N1 peaks. The P1 and N1 RREP peaks had longer latencies and greater amplitudes than the corresponding SEP peaks. The difference in amplitude may be due to the greater activation of mechanoreceptors in the respiratory system. The difference in latency may be due to longer time required to recruit respiratory mechanoreceptors and bring them to threshold. The Nf peak was only elicited by inspiratory occlusion and is a unique feature of the RREP.

Knafelc and Davenport (1997) demonstrated a relationship between P1 peak amplitude and the magnitude of resistive loads. They reported that the amplitude of the P1 peak of the RREP significantly increased with increased resistive load magnitude. If the RREP is analogous to the SEP, then the amplitude of the P1 peak of the RREP should be correlated with the load magnitude. This is consistent with the report from Franzẽn and Offenloch (1969) that the magnitude of the touch elicited P1 peak of the SEP was correlated with mechanical stimulus amplitude and magnitude estimation of the touch.

Thus, the location, origin and amplitude of the RREP peaks correlate with the analogous peaks of the SEP.

The Relationship between RREP and Load Perceptual Process

Relationship between RREP and Load Perception

The detection threshold for resistive loads reported by Bennett et al. (1962) and Wiley and Zechman (1966) resulted in a Weber ratio of approximately 0.3. The detection threshold is a fraction of the background resistance. Variability between subjects when presenting the R2 (3.8cmH2O/l/s) load is likely due to the variability of their intrinsic resistance. Burdon et al. (1983) reported that magnitude estimation is not altered by increased background load. It is likely that they failed to demonstrate an effect of increased background load in their scaling task because their protocols resulted in the loss of lower stimuli with increased background resistance. The finding in the present study that resistive loads below the detection threshold do not elicit the RREP is consistent with the relationship between cortical activation and load detection. If a load does not elicit somatosensory cortical activity then detection of the load does not occur. Thus, the load must be above the Weber ratio detection threshold for the RREP to be elicited.

Knafelc and Davenport (1997) demonstrated a close relationship between the RREP P1 peak amplitude and magnitude estimation. They reported that there was a linear relationship between magnitude estimation of the resistive load and P1 amplitude. Similarly, there was a relationship between changes of RREP P1 peak amplitude and the load magnitude in the present study that is relative to the afferent signal strength above the increased background resistance. The RREP peaks were present or absent depending on the detection threshold. If the load was above the detection threshold, then the RREP was present and the P1 peak amplitude was a function of the load magnitude. The

detection threshold can be changed by adding background resistance (Revelette et al., 1984). The RREP was not elicited with increased background resistance that made the resistive load below the detection threshold. The RREP was elicited without the background resistance because the ΔR_{50} was above the detection threshold. Thus, a load that elicited the RREP was made undetectable with increased background resistance and the RREP could no longer be observed.

RREP Responses to Different Load Magnitude

Inspiratory airflow is impeded by applying a resistive load during breathing and the breathing pattern is changed during a loaded breath (Davenport et al., 1992). Thus, when the magnitude of the resistive load increased, airflow tended to decrease due to the impedance imposed by the resistive load. As the load increased, more negative pressure was needed to overcome the resistance. The peak negative pressure occurred at about mid-inspiration when airflow was highest. The pressure and airflow relationship was changed by increased background resistance. Variations in RREP latencies and amplitudes found in current study suggest that cortical responses to mechanical loads are affected not only by the magnitude of load but also by the detection of the load and may be mediated by a gated feedback afferent system.

Short-Latency RREP Peak in Response to Increased Background Resistance

Wiley and Zechman (1966) studied the relationship between the detection threshold and the background resistance. They have reported variable detection thresholds but a constant Weber's Ratio (0.3) with different background resistances. Burdon et al. (1983) reported that increased background resistance was associated with a change in the exponent for magnitude estimation of the resistive load. In contrast, Revelette et al. (1984) reported a significant increase in the power function for load magnitude

estimation with increased background resistance. In the present study, the RREP was present only if the applied resistive load was greater enough to be perceived. Many studies have examined the relationship between the perceived magnitude of loads and the intensity of the loads (Burki et al., 1983; Gottfried et al., 1981; Killian et al., 1981; Wolkove et al., 1981). The present study was the first to compare the RREP response to load perception with increased background resistance. The result from the present study showed that the P1 peak of the RREP was present if the load could be perceived and the amplitude of the P1 peak was larger if the perceived load magnitude was increased. This finding is consistent with the report of Knafelc and Davenport (1997). They demonstrated the relationship between the P1 peak amplitude of the RREP and the perceived magnitude of loads, the amplitudes of the RREP P1 peak was a function of perceived load magnitude and proportional to the intensity of resistive load.

With prolonged increases in background resistance, the perceptual sensitivity in healthy subjects is unlikely to be changed from normal and any adjustment in ventilation made on the basis of sensory perception would be expected to be maintained if the load is detected (Killian et al., 1984). This is important clinically to those patients with chronic pulmonary disease. These patients have the greatest need for optimizing their breathing strategy of respiratory muscle force production to maintain stable ventilation. The findings of the present study suggest that the neural activity of the cortex can be changed on the basis of sensory perception and afferents information may be gated into the cerebral cortex. Therefore, a sensory gated model (Fig 5-1) is proposed to explain the cortical processing of respiratory afferents.

Automatic breathing is regulated by brainstem respiratory center, which acts as an intrinsic controller to generate the respiratory motor activity. This respiratory motor activity is modified by the feedback from the chemoreceptors and mechanoreceptors to meet the respiratory demands. Afferent information from chemoreceptors increases or decreases the motor output until the arterial CO2 and O2 have returned to their set-points. On the other hand, afferents from respiratory mechanoreceptors modulate the central command of respiratory muscles to generate the optimal breathing pattern (Poon et al., 1992). Thus, respiratory afferent information modulates brainstem respiratory function but is normally gated-out of higher brain centers resulting in automatic ventilation with no cognitive awareness of breathing.

If there is an error signal from chemoreceptors and/or mechanoreceptors in responding the disruption of the automatic breathing, such as inspiratory occlusion, the RREP will be elicited and the respiratory information will be perceived. This suggests that respiratory perception is normally gated-out in regular breathing and inspiratory occlusion may change the cortical neuronal activity resulting in gating-in of respiratory information to cognitive awareness. Thus, the automatic regulation of breathing can be overridden by a gate which modulates the conscious perception of respiration. This conscious awareness of breathing consists of the modulation in breathing pattern which involves the changes in arousal levels, emotions and cognitive activities (Ley, 1999). Thus, the gating modulation may also correlate to the association cortex (attention, thoughts and experiences) and limbic system (emotion).

In the present study, the P1 peak amplitude of the RREP is not present with the increased background resistance because the applied resistive load is below the detection

threshold. The fact that the RREP is not present with increased background resistance suggests that the respiratory resistive load information was gated-out by changing the background ventilatory state, such as increased background resistance. Although the interaction between the conscious and the automatic control of breathing is uncertain, a mismatch between respiratory afferent feedback on ventilatory status and the ventilatory demand will result in a cortical response and conscious awareness of breathing. Thus, a subcortical threshold must exist to gate-in or gate-out the respiratory afferent input and motor drive. However, neural indicators and mechanisms of the respiratory gating are unknown. Future study may explore the hypothetical construct of respiratory gating and the possible mechanisms that subserve the respiratory sensory gating system.

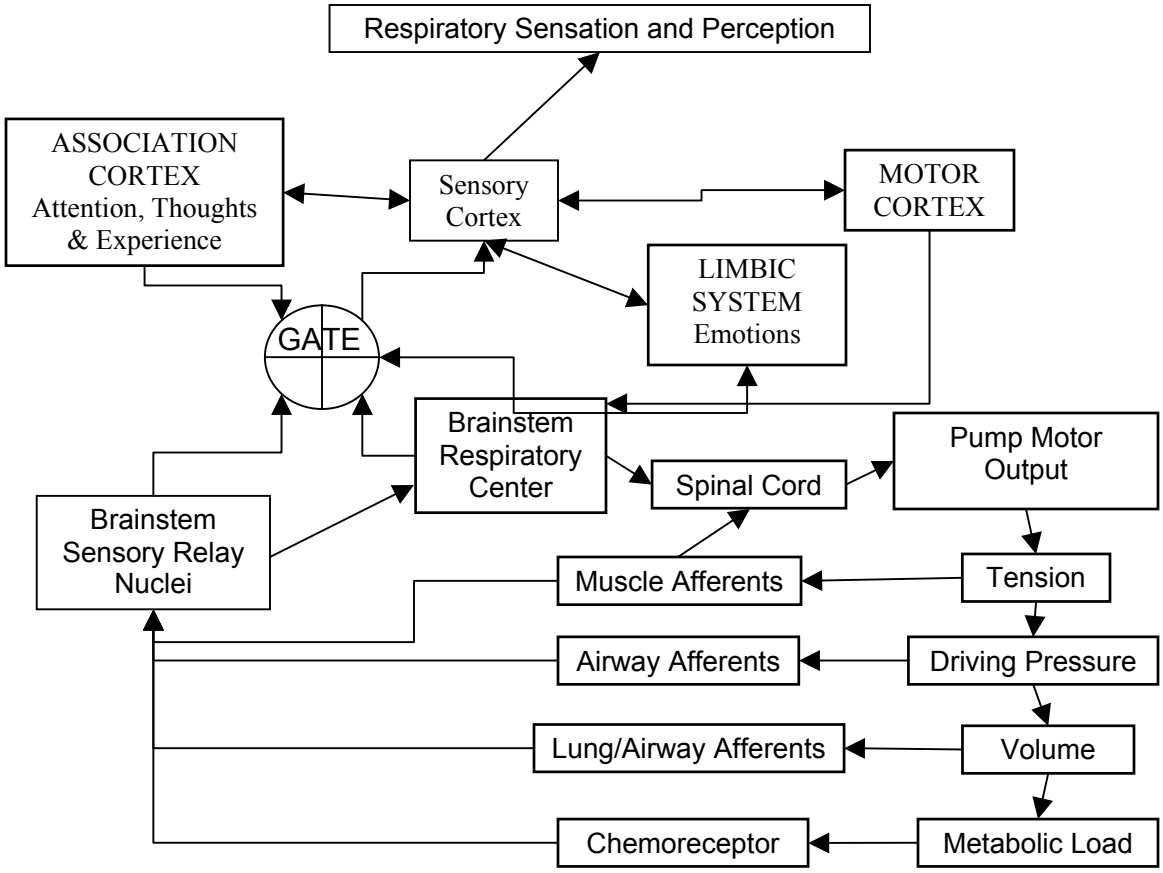

Figure 5-1. Proposed respiratory gating model.

CHAPTER 6
CONCLUSION

The scalp distribution of RREP was similar to the mechanical stimulation elicited SEP. The RREP had features that were unique. The RREP P1 and N1 peaks corresponded to analogous peaks of the SEP and were recorded in the same location. However, the SEP P1 peak was unilateral while the RREP was bilateral. Although the recording techniques used in the current studies have limitations in dipole localization, the results of this study demonstrated the presence of the P1 peak of the RREP and SEP had the greatest amplitude in the electrodes overlying the somatosensory cortex which means these electrodes were in closest proximity to the dipole generator. These results are consistent with the P1 peak dipole located in the somatosensory cortex. Thus, the cortical distribution, neural mechanism and afferent pathways for cortical processing of respiratory mechanical load activation of the somatosensory cortex are supported by these RREP results. The inspiratory occlusion may have activated mechanoreceptors located in the respiratory system which may include the mouth, larynx, pharynx, lung, and respiratory pump muscles. Some or all of these mechanoreceptors may be mediating the activation of cortical neurons in the somatosensory region of the cerebral cortex. The P1 and N1 peaks of the RREP elicited by inspiratory occlusion were analogous to the corresponding peaks of the SEP elicited either by air puff or cutaneous mechanical stimulation. A similar cortical activation sequence was observed between the RREP and SEP except the Nf peak was only present in the frontal regions of the RREP. Cortical neurons activated by mechanical loads elicit a RREP similar to the SEP in the

somatosensory system suggesting that these mechanoreceptor-activated neurons are in the somatosensory cortex and the information is mediated through the somatosensory pathway.

Finally, the presence and loss of the RREP peaks without and then with increased background load, respectively, support the correlation of the RREP with the detection threshold for inspiratory resistive loads. The P1 peak was only present for those loads that exceeded the detection threshold. This was true even when background resistance was applied to change the detection threshold. The similarity of the latencies and amplitudes also suggested that perception of inspiratory loads is associated with the neural activation of the cortex and evoked potential is an objective measurement for perceptual information processing.

In summary, the results from this dissertation suggested that inspiratory loads recruit multiple populations of respiratory mechanoreceptors. These afferents activate the somatosensory cortex. Cortical processing of respiratory loaded stimuli is a gated process with a threshold for cortical activation. Changing the respiratory status, such as the background resistance, changes the gate threshold requiring a greater stimulus to activate the cortex and elicit load detection.

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BIOGRAPHICAL SKETCH

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