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Diaphragmatic neuromechanical coupling and mechanisms of hypercapnia during inspiratory loading

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ABSTRACT

We hypothesized that improved diaphragmatic neuromechanical coupling during inspiratory loading is not sufficient to prevent alveolar hypoventilation and task failure, and that the latter results primarily from central-output inhibition of the diaphragm and air hunger rather than contractile fatigue. Eighteen subjects underwent progressive inspiratory loading. By task failure all developed hypercapnia. Tidal transdiaphragmatic pressure (ΔPdi) and diaphragmatic electrical activity (ΔEAdi) increased during loading – the former more than the latter; thus, neuromechanical coupling (ΔPdi/ΔEAdi) increased during loading. Progressive increase in extra-diaphragmatic muscle contribution to tidal breathing, expiratory muscle recruitment, and decreased end-expiratory lung volume contributed to improved neuromechanical coupling. At task failure, subjects experienced intolerable breathing discomfort, at which point mean ΔEAdi was $74.9 \pm 4.9\%$ of maximum, indicating that the primary mechanism of hypercapnia was submaximal diaphragmatic recruitment. Contractile fatigue was an inconsistent finding. In conclusion, hypercapnia during acute loading primarily resulted from central-output inhibition of the diaphragm suggesting that acute loading responses are controlled by the cortex rather than bulbopontine centers.

1. Introduction

Alveolar hypoventilation is a common finding in patients with a multitude of respiratory disorders (Tobin et al., 2012). Despite decades of research, we have a poor understanding as to why some patients exhibit alveolar hypoventilation and others, with apparently equivalent physiological derangements, do not. Attempting to shed light on this problem, investigators have conducted studies in patients with respiratory disorders (Tobin et al., 1986; Laghi et al., 2003), healthy volunteers (Mador et al., 1996; Eastwood et al., 1994), and animal models (Sassoon et al., 1996; Kanter and Fordyce, 1993; Watchko et al., 1988). Findings in these studies raise the possibility that some central (Gandevia, 2001) or local (Parthasarathy et al., 2007) mechanism may inhibit the respiratory muscles in the face of increased mechanical loads, and thus protect them against fatigue and damage – although at the cost of carbon dioxide (CO_2) retention.

Experimental evidence supports the existence of local protective mechanisms (Laghi et al., 2003; Mador et al., 1996; Eastwood et al., 1994). In patients who developed hypercapnia during a failed trial of weaning from mechanical ventilation, we observed sequential recruitment of the extradiaphragmatic muscles (Parthasarathy et al., 2007). The sequence began with greater-than-normal activity of inspiratory muscles followed by expiratory muscle recruitment. It is known that expiratory muscle activity is not confined to exhalation, but can also occur during inhalation and thus limit inspiratory shortening of the diaphragm (Abe et al., 1999). As such, recruitment of extradiaphragmatic muscles may have a dual role during loading: to protect the diaphragm against contractile fatigue, and to improve diaphragmatic neuromechanical coupling by limiting diaphragmatic shortening.

Evidence also supports the existence of reflex mechanisms that inhibit central neural output under loaded conditions. Implicated mechanisms include group III and IV afferents and

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mechanoreceptors originating in the contracting respiratory muscles (Gandevia, 2001). Reflex inhibition of central neural output causes hypercapnia, a potent source of air hunger (Banzett et al., 1996). This consideration raises the possibility that reflex inhibition of central neural output during loading may also have a dual role: to protect the respiratory muscles against damage and contractile fatigue, and to trigger intolerable air hunger, leading to task failure.

The objective of the current study, conducted in healthy volunteers, was to elucidate the physiological mechanisms involved in the development of CO_2 retention during progressive inspiratory threshold loading. In subjects undergoing progressive inspiratory threshold loading, we hypothesized that improvements in diaphragmatic neuromechanical coupling secondary to extradiaphragmatic muscle recruitment are insufficient to prevent alveolar hypoventilation and task failure, and the latter will result primarily from reflex inhibition of central neural output to the diaphragm and air hunger rather than contractile fatigue.

2. Methods

Experiments were performed on 18 healthy subjects (4 female), mean (±SE) age 33 ± 2 years; all but one were naïve to the investigation's purpose. The study was approved by the Institutional Review Board of Edward Hines, Jr. Veterans Affairs Hospital, which conforms to the provisions of the *Declaration of Helsinki*. Informed consent was obtained in writing from all subjects.

Measurements. Methods of measurements and data analysis have been described previously (Druz and Sharp, 1981; Beck et al., 2009). Signals of flow, volume, pressure (Paw) and end-tidal partial pressure of carbon dioxide ($P_{ET}CO_2$) were recorded at the mouth. Esophageal (Pes) and gastric pressures (Pga) were measured with balloon-tipped catheters (Laghi et al., 1996). Crural diaphragm electrical activity (EAdi) was recorded with 9 stainless-steel electrodes mounted on a polyurethane tube positioned across the gastroesophageal junction and wired as 8 overlapping bipolar pairs (Beck et al., 2009). Bilateral surface electrodes recorded compound diaphragmatic action potentials (CDAPs) elicited by phrenic nerve stimulation (Laghi et al., 1996). Two pairs of surface electrodes (lower abdomen and rectus abdominis) recorded abdominal muscle recruitment (Fig. 1) (Strohl et al., 1981). Cross-sectional area of upper and lower abdomen was monitored with respiratory inductive plethysmography (RIP) bands placed 2–3 cm above and 2–3 cm below the umbilicus. All signals were recorded continuously.

2.1. Experiment 1: neuromechanical coupling and central fatigue during loading

The purpose of this experiment, conducted in 17 subjects, was threefold: to examine diaphragmatic neuromechanical coupling during threshold loading; to measure extent of diaphragmatic recruitment at task failure (central fatigue); and to explore whether changes in diaphragmatic neuromechanical coupling during loading resolve after task failure.

After placement of transducers, subjects performed at least three inspiratory capacity (IC) maneuvers (Hussain et al., 2011) to determine maximum voluntary diaphragmatic activation (maximum EAdi) (Fig. 2) (Sinderby et al., 1998; Juan et al., 1984). Thereafter, subjects sustained an incremental inspiratory threshold load until task failure (Eastwood et al., 1994; Laghi et al., 2005). At the start of loading, a 200-g weight was placed on a platform connected to a one-way plunger valve. Every minute, the inspiratory load was increased by 100 g (Laghi et al., 2005). Loading was terminated when a subject was unable to sustain the breathing task

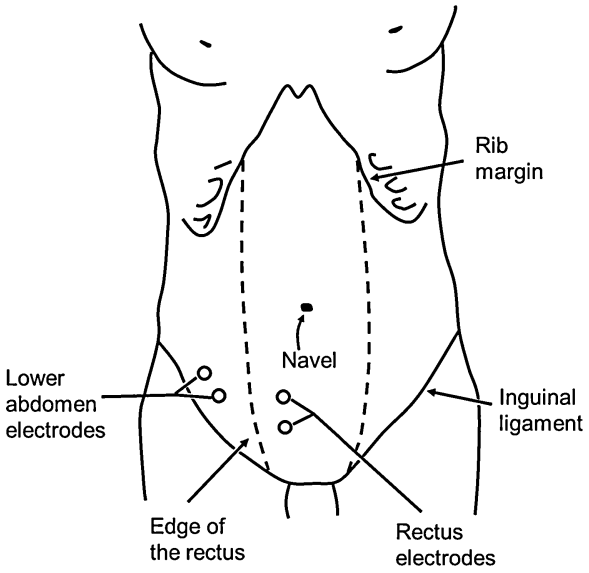

Fig. 1. Anterior abdominal-wall landmarks and position of two pairs of surface electrodes from which electromyographic activity was recorded. Ground electrodes (not shown) were placed as close as possible to the pairs of recording electrodes. Before placement of any electrode pair, the lateral border of the rectus abdominis muscle was identified using an ultrasound probe to enable proper positioning of the electrodes relative to the muscle.

despite strong encouragement (task failure). No instructions were given to the subjects regarding what breathing pattern to adopt (Laghi et al., 2005; Eastwood et al., 1994).

Immediately after task failure, subjects were asked whether they stopped because of unbearable breathing effort (defined as "*sensation of excessive respiratory muscle contraction to breathe in*"), unbearable air hunger (defined as "*the unbearable discomfort when asked to hold your breath longer than what you could*") or other reasons (Laghi et al., 1998).

Immediately before and immediately after task failure, and 5 and 15 mintes later, subjects breathed through a small, constant inspiratory threshold load set at −20 cm H_2O for at least 1 min (Fig. 2).

2.2. Experiment 2: end-expiratory lung volume and abdominal-wall muscles recruitment during loading

The purpose of this experiment was to determine whether changes in end-expiratory lung volume (EELV; 10 subjects) and abdominal muscle recruitment (5 subjects) accompanied changes in diaphragmatic neuromechanical coupling during loading.

Following instrumentation (same as *Experiment 1* plus abdominal electrodes and RIP bands), subjects undertook threshold loading. To track changes in EELV, subjects were required to perform one IC maneuver against no external load every minute during loading, and at task failure (Hussain et al., 2011).

2.3. Experiment 3: threshold loading and respiratory muscle fatigue

The purpose of this experiment, conducted in 8 subjects who sustained inspiratory threshold load to task failure, was: to determine whether contractile fatigue of respiratory muscles contributes to task failure and to identify determinants of contractile fatigue.

Contractile fatigue was assessed by measuring the transdiaphragmatic twitch pressures elicited by electrical stimulation (electrical-PdiTw) and magnetic stimulation of the phrenic nerves