
The Mechanisms of Compensatory Responses of the Respiratory System to Simulated Central Hypervolemia in Normal Subjects

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Abstract

The compensatory responses of the respiratory system to simulated central hypervolemia (CHV) were investigated in 14 normal subjects. The central hypervolemia was caused by a short-time passive head-down tilt (HDT, -30° , 30 min). The results show that CHV increased the mechanical respiratory load and the airway resistance, slowed the inspiratory flow, increased the duration of the inspiratory phase, reduced the respiratory rate, but not changed the minute ventilation. CHV induced a significant rise in inspiratory swings of alveolar pressure (184 %), based on the inspiratory occlusion pressure measurement. These changes indicate a compensatory increase in the inspiratory muscle contraction force. A stable level of minute ventilation during CHV was an effect of increased EMG activity of parasternal muscles more than twice ($P < 0.01$). A contribution of the diaphragm and scalene muscles to ventilation during spontaneous breathing in HDT was reduced. An increase of genioglossus contractile activity during HDT contributed to the stabilization of airway patency. These results suggest that a coordinated modulation of inspiratory muscles activity allows preserving a constant level of minute ventilation during a short-time intrathoracic blood volume expansion. The mechanisms of respiratory load compensation seem to be mediated by afferent information from the lung and respiratory muscle receptors and from the segmentary reflexes and intrinsic properties of the muscle fibers.

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1 Introduction

When decreasing the effects of gravity in humans, such as by anti-orthostatic posture changes or immersion into the water, venous return is increased by some 25 % (Norsk 2005). A redistribution of blood from peripheral portions of the body to the intra-thoracic circulation leads to central blood volume expansion – central hypervolemia (CHV), which is accompanied by changes in pulmonary hemodynamics and may have an effect on the respiratory system (Bettinelli et al. 2002; West 2002). An increase in central venous pressure, a decrease of functional residual capacity and lung compliance at a postural change from supine to head-down tilt (HDT) of 30° has been shown in anesthetized cats (Aleksandrova et al. 2007; Donina et al. 2013). Increased blood supply to the lungs, which occurs under these conditions, reduces their elastic properties, causing narrowing of the airways and increasing the airway resistance (Estenne et al. 1992; Prisk 2000). The thoracic blood volume expansion changes the lung and diaphragm position and the chest configuration, which may lead to a decrease in lung volume and changes in breathing pattern (Prisk 2000; Prisk et al 2002; Estenne et al. 1992). The compensatory responses that keep the required level of ventilation and gas exchange under these conditions have not been sufficiently studied. Little is known about the inspiratory muscle function during CHV.

The purpose of this investigation was to examine the respiratory responses and compensatory capabilities of the respiratory system in normal subjects submitted to acute cardiopulmonary blood volume expansion by head-down tilt of 30°.

2 Methods**2.1 Subjects**

The study was approved by a local Ethics Committee and conducted in accordance with the ethical standards of the Helsinki Declaration for Human Experimentation. Fourteen healthy volunteers (F/M-4/10) participated in the study. All subjects were familiarized with the experimental procedures and gave informed consent. Their mean age was 22.4 ± 0.9 (19–25) years. Anthropometric data for men were as follows: height 178.1 ± 6.8 (167–186) cm, weight 77.6 ± 6.5 (65.2–84.5) kg, and vital capacity (VC) 4.3 ± 0.5 (3.6–5.1) l, and for women: height 163.2 ± 2.4 (160–171) cm, weight 57.1 ± 4.3 (51.9–65.9) kg, VC 3.3 ± 0.3 (2.9–3.6) l. All subjects had no pulmonary, cardiovascular, or neuromuscular disorders and had the ventilatory function within normal limits.

2.2 Ventilatory Parameters

Inspiratory flow (V_I) was measured with a pneumotachograph (Fleish No. 3), connected to the inspiratory port of a low-resistance valve (Hans Rudolph 2700, Shawnee, Kansas). The inspiratory flow signal was electronically integrated to obtain tidal volume (V_T) and was displayed on the multichannel recorder (Biograph, St. Petersburg, Russia). Inspiratory and expiratory time (T_I , T_E), total breath cycle (T_T), and breathing frequency (f) were measured from this tracing. Minute ventilation (V_E) was calculated as a product of V_T and f . Volume calibration was performed before each test using a 1 L syringe.

2.3 Mouth Pressure and Airway Resistance

An inspiratory mouth pressure (P_{mi}) was measured using a pressure tap at the mouthpiece connected to a differential pressure transducer (PDP 1000 MD, St. Petersburg, Russia). The occluding valve was actuated during quiet breathing in control (standing position) and at 1, 10, 20, and 30 min of HDT in order to obtain the alveolar pressure values (P_{occl}). The interrupter technique assumes that immediately after airflow interruption, mouth pressure equilibrates with alveolar pressure (Oswald-Mammosser et al. 2009). Airway resistance (R_{aw}) measurements were performed at the spontaneous breathing frequency of the subject. R_{aw} was calculated by the following formula: $R_{aw} = P_{occl}/V_I$; where P_{occl} , corresponding to alveolar pressure, is estimated during the 100 ms occlusion and V_I , corresponding to peak inspiratory flow, is taken at the mouth immediately before the occlusion.

2.4 Maximal Inspiratory Pressure and Peak Flow Measurements

Maximal inspiratory pressure (MIP), peak inspiratory flow (PIF), and peak expiratory flow (PEF) were measured in each subject before the start of experiment in standing position (control) and after 30 min of spontaneous breathing in the HDT position to evaluate the reserve capabilities of the respiratory system. The MIP was measured with a portable device (PowerBreath KH1, Southam, Warwickshire, UK) in accordance with the ATS/ERS Statement (ATS/ERS Statement 2002) and was recorded at the mouth during a quasi-state short maximal inspiration against occluded airways (Müller's maneuver). The maneuver was performed at residual volume (RV) (Troosters et al. 2005). Each participant was asked to perform a few maximal inspiratory efforts to adopt for the correct performance of this test during experiment. Maximal inspiratory efforts were maintained for 3–4 s separated by at least 1 min intervals. The subjects had a nose clip

in place during the maneuver. The subjects were verbally encouraged by the operators to achieve a maximal effort. For each body position, the subject performed a minimum of three maneuvers until two maximal pressure values were obtained which did not differ by more than 5 %; the higher of the two was chosen for analysis. For the sake of convenience, the MIP was expressed in positive values. The peak inspiratory flow was measured with the same portable device and the peak expiratory flow with a peak flow meter (MicroPeak, Micro-medical, Rhymney, Wales, UK).

2.5 EMG Recordings

The electromyograms of the diaphragm (EDI), parasternal (EPS), scalene (ESC), and genioglossus (EGG) were obtained with surface electrocardiographic electrodes (ARBO, TYCO Healthcare Deutschland GmbH, Neustadt/Donau, Germany). The skin was cleaned with alcohol. The surface EDI was recorded with electrodes applied to the skin over the seventh and eighth intercostal spaces close to the upper rib edge, while the EPS was recorded with electrodes placed in the second right intercostal space close to the sternum. The ESC was obtained from electrodes placed in the posterior triangle of the neck (right side) at the level of the cricoid cartilage. The place was located during sniff maneuvers through palpation of the neck in the lower third of a line drawn between the middle of the mastoid process and the sternal notch. Within each electrode pair, the inter-electrode distance was <2 cm. The EGG was obtained from two electrodes placed longitudinally on the underside of the chin at 5 and 10 mm from the inferior margin of the mandible after having checked that minimal inspiratory electrical activity was present during spontaneous breathing. All the EMGs were amplified and continuously recorded on a six-channel recorder (Biograph, St. Petersburg, Russia) and were displayed simultaneously. Data were stored on PC for future analysis. To quantify the EMG, the signals were filtered (10 Hz–1,000 kHz) and integrated on a

moving-time-average basis with a time constant of 150 ms. The peak amplitude of integrated EMG was measured for each inspiratory muscle during quite breathing and during Müller's maneuver throughout the study. The amplitude was measured in arbitrary units and then expressed as a percentage of the mean values reached during spontaneous breathing and maximum Müller's maneuver in the standing position.

2.6 Study Design

A head-down tilt of 30° that increases the central venous pressure due to fluid shifts within the entire body was used as a model for simulating central hypervolemia. After completing the MIP, PIF, and PEF measurements, the subject breathed quietly for several minutes to establish a stable pattern of breathing in the standing position. When the baseline parameters were collected, the subject was placed in the supine position using a tilting table and allowed resting in this position for 5 min. Then, the subject was exposed to 30-min tilt. After taking the measurements above outlined again, the subject was moved to the supine position for 5 min and then to the standing position. Ventilation, inspiratory swings of mouth pressure, and the EMGs were continuously monitored throughout the study.

2.7 Data Analysis

Baseline (control) respiratory variables and their values during the HDT were expressed as absolute values. Data were presented as means \pm SE. Control measurements were performed during spontaneous breathing in the standing position. Differences between respiratory variables and the peak integrated EMGs during quite breathing and Müller's maneuver in the HDT were compared with those of the standing position with a *t*-test. $P < 0.05$ was defined as the criterion of significant differences.

3 Results

3.1 Respiratory Pattern, Ventilation, and Time-Volume Parameters

The mean data for time-volume variables and minute ventilation in the upright posture and during the 30-min HDT are shown in Table 1. When compared with the control level, blood volume expansion significantly decreased the mean inspiratory flow (30 %). A longer T_I and T_T ($P < 0.05$), but no T_E resulted in a reduction in respiratory rate (15 %). Minute ventilation tended to decrease, but this change was insignificant. Central hypervolemia did not evoke significant changes in tidal volume.

3.2 Airway Resistance and Reserve Capacity of the Respiratory System

A significant increase in inspiratory occlusion pressure, which equals alveolar pressure, was observed immediately after the head-down-tilt (Fig. 1). All subjects demonstrated an approximately two-fold increase in P_{occl} and R_{aw} (Table 1). These changes were reversed on return to the standing position. The MIP ranged from 52 to 113 cm H₂O in the standing position. These values are approximately in the normal range as found by others (Sachs et al. 2009; Hautmann et al. 2000). The HDT lowered the MIP by 17.4 % ($P < 0.05$). After 30 min of head-down-tilting, PIF and PEF decreased significantly by 16.3 % and 20.0 %, respectively, compared with the standing position.

3.3 Electromyographic Responses

During quiet breathing while standing, phasic inspiratory activity was observed in the D and PS muscles of the subjects. In HDT, there are marked differences in the patterns of respiratory muscle activity during quiet breathing, compared

Table 1 Volume-time respiratory parameters, inspiratory occlusion pressure, airway resistance, peak respiratory flows, and maximal inspiratory pressure in control and during CHV

Variables	Control (Standing position)	HDT (-30°) (30 min)
V_I , l/s	0.53 ± 0.07 (0.39–0.64)	$0.37 \pm 0.05^*$ (0.26–0.47)
V_T , l	0.57 ± 0.10 (0.46–1.10)	0.56 ± 0.16 (0.37–1.20)
V_E , l/min	9.47 ± 0.71 (6.11–13.83)	8.20 ± 0.80 (5.08–13.10)
T_T , s	3.60 ± 0.41 (2.42–4.38)	$4.01 \pm 0.66^*$ (3.03–5.01)
T_I , s	1.34 ± 0.12 (1.11–1.66)	$1.78 \pm 0.63^*$ (1.40–2.92)
T_E , s	2.30 ± 0.39 (1.19–4.50)	2.39 ± 1.10 (1.72–3.48)
f_b , breaths/min	17.51 ± 1.80 (10.94–23.02)	$14.88 \pm 2.19^*$ (10.42–16.99)
P_{occl} , cm H ₂ O	2.50 ± 0.30 (1.80–2.90)	$4.60 \pm 0.40^*$ (4.10–5.30)
R_{aw} , cm H ₂ O/l·s ⁻¹	2.70 ± 0.30 (2.15–2.80)	$4.90 \pm 0.40^*$ (3.30–8.55)
PEF, l/min	559 ± 62 (370–800)	$448 \pm 41^*$ (320–590)
PIF, l/s	5.50 ± 0.60 (3.80–6.80)	$4.60 \pm 0.50^*$ (3.60–5.60)
MIP, cm H ₂ O	86 ± 11 (52–113)	$71 \pm 9^*$ (38–105)

Values are means \pm SE

V_I mean inspiratory flow, V_T tidal volume, V_E minute ventilation, T_T total breath cycle, T_I inspiratory cycle, T_E expiratory cycle, f_b breathing frequency, P_{occl} occlusion inspiratory pressure, R_{aw} airway resistance, PEF peak expiratory flow, PIF peak inspiratory flow, MIP maximal inspiratory pressure (range)

*P < 0.05 compared with control



Fig. 1 Typical inspiratory occlusion pressure swings: *Panel A* – control (standing position) and *Panel B* – after 30 min of head-down-tilting

with baseline, which may be related to CHV. Phasic PS activity increased more than twice ($P < 0.01$), which may contribute to the inspiratory rib cage expansion in this condition (Fig. 2A). Peak amplitude of the integrated EMG of the diaphragm decreased immediately the onset of HDT; the decrease was maintained (~40 %) throughout the 30-min tilt ($P < 0.01$).

In contrast, after shifting to supine and upright position, a reverse pattern of EMG-responses was observed; peak amplitude of D and PS EMG returned to the control levels (Fig. 2A). Furthermore, minimal electrical activity was present in the SC and GG muscles during quiet breathing in the upright position. This activity was phasic, occurring during inspiration

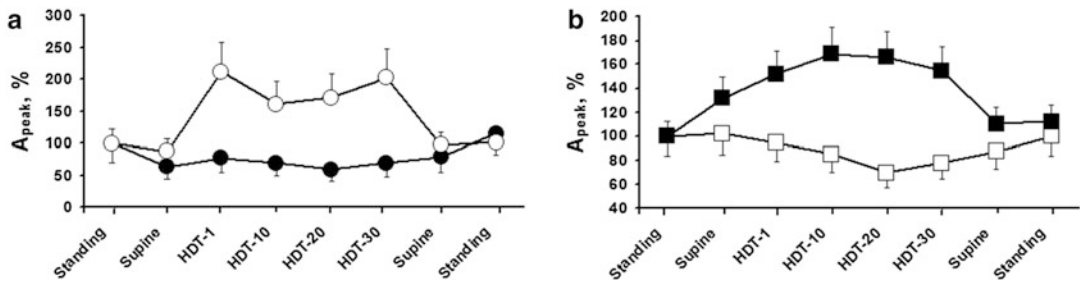


Fig. 2 Changes in peak amplitude (A_{peak}) of integrated EMG activity of the diaphragm (solid circles) and parasternal (open circles) (Panel A), genioglossus (solid squares) and scalene (open squares) (Panel B)

during spontaneous breathing in the supine position and the head-down-tilt after 1, 10, 20, and 30 min and then on return to the previous positions. A_{peak} was expressed as a percentage of control (standing position)



Fig. 3 Representative EMG recordings of the scalene (SC) and genioglossus (GG) muscles during spontaneous breathing in the standing (a) and HDT (b) positions

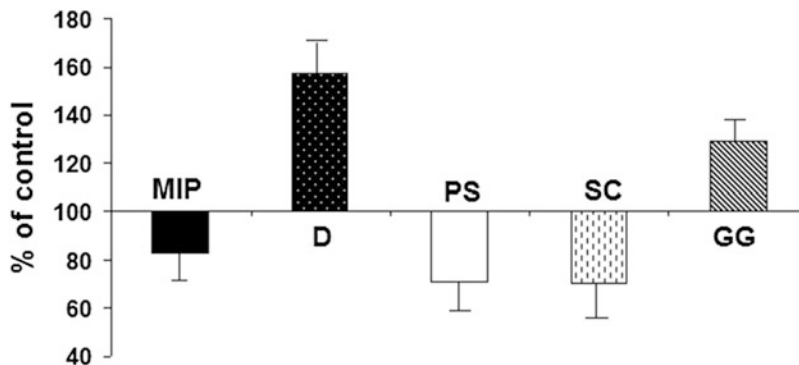


Fig. 4 Changes in maximal inspiratory pressure (MIP), peak amplitude (A_{peak}) of integrated EMG activity of diaphragm (D), parasternal (PS), genioglossus (GG) and

scalene (SC) during Muller's maneuver 30 min after assuming the head-down tilt. Each column represents the relative value as a percentage of control (standing position)

(Fig. 3). The transient EMG responses to shifting from the upright to HDT position consisted of a rapid increase in peak amplitude of GG EMG (~65%), whereas SC activity decreased during spontaneous breathing (~25%) (Figs. 2B and 3).

All subjects developed phasic inspiratory activity in the D, PS, SC and GG muscles during the voluntary maximal inspiration against closed airways (Müller's maneuver). Integrated EMG of each muscle was expressed as a percentage of its

value in the standing position, taken as 100%. We found differences in the inspiratory muscle activation during Müller's maneuver during the 30-min HDT compared with quiet breathing. The peak magnitude of D EMG increased by 57% during tilting ($P < 0.05$) (Fig. 4). As illustrated in Fig. 4, lower than control values for integrated EMG of PS and SC, by 29% and 30%, respectively, were achieved during Müller's maneuver in HDT ($P < 0.05$). The

amplitude of GG EMG was the greatest in the HDT positions during Müller's maneuver (130 % of control) ($P < 0.05$).

4 Discussion

During the head-down-tilt or head-out water immersion, intrathoracic blood volume increases due to central translocation of circulating blood and the central hypervolemia develops (Lin 1984; Norsk 2005). It is known that central hypervolemia induces changes in the cardiovascular system and in pulmonary mechanics. However, little is known about the compensatory responses of the respiratory system and about the inspiratory muscle function during the expansion of intrathoracic blood volume. Our present findings show that central hypervolemia increased airway resistance, but the compensatory responses provided the maintenance of the minute ventilation at the stable level. These responses were expressed in an increase of contractile activity and redistribution of the degree of participation of different groups of inspiratory muscles in the respiratory act. We found differences in the pattern of respiratory muscle use during quiet breathing in normal subjects submitted to acute cardiopulmonary blood volume expansion. The maintenance of adequate pulmonary ventilation was provided by a two-fold increase in the activity of the inspiratory muscles of the chest. This group of inspiratory muscles compensates for increased resistive load, ensuring the growth of alveolar pressure for adequate tidal volume during CHV. Electrical activity of the diaphragm was reduced compared with the usual conditions for human hemodynamics, so we can assume that the diaphragm's contribution to the compensation of respiratory effects of hypervolemia was reduced. The redistribution in the inspiratory muscle activity during CHV may be associated with the principle of energy optimization of respiratory movements underlying the patterning of breath (Otis et al. 1950; Segizbaeva 2010). In HDT an effective diaphragmatic contraction is energetically less profitable, since the

implementation of the inspiratory efforts are needed to offset the abdominal content, putting pressure on the diaphragm. It is likely that in such a condition an increase in inspiratory muscle contraction of the chest would be more favorable energetically. Accordingly, this group of muscles provides the required level of inspiratory oscillations of alveolar pressures during quiet breathing in HDT. A decrease in EMG activity of the SC muscle in the HDT position is explicable by the muscle's initial position (muscle length) and biomechanical conditions of respiratory movements. Possibly, a decrease in the length of the muscle's fibers, which occurs due to mechanical changes during antiorthostatic body position, does not allow increasing its activity. The genioglossus is a major dilator muscle of upper airways. GG does not participate in the generation of inspiratory pressure, but contributes to the stabilization of airway patency. Maximal activation of GG was obtained in the HDT position in all subjects. Upper airway dilator muscles are activated in phase with the respiratory cycle generated by the central nervous system. Studies have shown that non-physiological upper airway mechanoreceptive stimuli (e.g., rapidly imposed pulses of negative pressure) also activate these muscles. Such reflexes may become activated during conditions that alter airway resistance in order to stabilize airway patency (Akaoshi et al. 2001).

The mechanisms responsible for CHV-induced compensatory responses of the respiratory system seem complex. CHV reduced the inspiratory flow; therefore, stimulation of receptors sensitive to a dynamic component of lung tension was weaker. Decreased inhibitory afferentation from pulmonary stretch receptors could render higher EMG activity and power of inspiratory muscle contractions. The involvement of vagal afferents in the intensification of inspiratory efforts induced by CHV has been supported by studies on animal models. The CHV-induced esophageal pressure response is strongly suppressed by transection of the vagal nerves (Aleksandrova et al. 2007; Donina et al. 2013). The human upper respiratory tract has a rich sensory supply and the upper airway

receptors may play a significant role in the formation of adaptive reactions to increased resistive load (Winning et al. 1985). Furthermore, afferent information from intercostal muscle proprioceptors provides both the additional activation of the related spinal alpha-motoneurons (Corda et al. 1965) and the immediate information transmission to the bulbar respiratory structures, with the resultant changes in central inspiratory activity (Shannon et al. 1985). It is possible that the intrinsic properties of inspiratory muscles may also be essential for the respiratory load compensation during CHV, because the force of muscle contraction depends on the velocity of its shortening and the initial muscle length (Sharp 1980).

Analysis of changes in MIP, PIF, and PEF indicates that the intrathoracic blood volume expansion decreased the reserve capacity of the respiratory system and weakened the load compensatory responses. The HDT significantly decreased the indices outlined above compared with their control levels. Changes in muscle mechanics might influence MIP when moving from the standing position to HDT. Gravity pulls the abdominal content caudally, increasing the vertical diameter of the thorax in the standing position (Castile et al. 1982). In the HDT, the abdominal content pushes the diaphragm up into the thoracic cavity, raising the diaphragm length and decreasing functional residual capacity (FRC) relative to the standing condition. It is interesting that the maximal inspiratory efforts during HDT evoked the opposite EMG activity pattern; the contribution of inspiratory thoracic muscles decreased and diaphragm's EMG activity increased compared with spontaneous breathing.

In conclusion, the present study showed that in normal humans exposed to intrathoracic blood volume expansion there is an increase in respiratory loading and the development of compensatory responses. These responses are expressed by an increase in contractile activity and redistribution of the participation of different groups of the respiratory muscles. The mechanisms of respiratory load compensation seem to be underlain by the afferent information from the

lung and respiratory muscle receptors, the segmentary reflexes, and the intrinsic properties of muscle fibers. Respiratory effects of central hypervolemia are compensated during spontaneous breathing, but the maximal reserve capacity of the respiratory system decreases during intrathoracic blood volume expansion.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

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