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Diaphragmatic fatigue during inspiratory muscle loading in normoxia and hypoxia

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ABSTRACT

Introduction: Diaphragmatic fatigue (DF) occurs during strenuous loading of respiratory muscles (e.g., heavy-intensity whole-body exercise, normocapnic hyperpnea, inspiratory resistive breathing). DF develops early on during normoxia, without further decline toward task failure; however, its progression during inspiratory muscle loading in during hypoxia remains unclear. Therefore, the present study used volume-corrected transdiaphragmatic pressures during supramaximal magnetic phrenic nerve stimulation (Pdi,twc) to investigate the effect of hypoxia on the progression of diaphragmatic fatigue during inspiratory muscle loading.
Methods: Seventeen subjects completed two standardized rounds of inspiratory muscle loading (blinded, randomized) under the following conditions: (i) normoxia, and (ii) normobaric hypoxia (SpO_2 80%), with Pdi,twc assessment every 45s.
Results: In fatiguers (i.e., Pdi,twc reduction >10%, $n = 10$), biometric approximation during normoxia is best represented by $Pdi,tw_c = 4.06 + 0.83 \exp(-0.19 \times x)$, in contrast to $Pdi,tw_c = 4.38 - (0.05 \times x)$ during hypoxia.
Conclusion: Progression of diaphragmatic fatigue during inspiratory muscle loading assessed by Pdi,tw differs between normoxia and normobaric hypoxia: in the former, Pdi,tw follows an exponential decay, whereas during hypoxia, Pdi,tw follows a linear decline.

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1. Introduction

The human diaphragm is known to be relatively resistant to fatigue (Jammes et al., 1997). However, diaphragmatic fatigue can occur when respiratory muscles are strenuously loaded under the following circumstances: (i) heavy-intensity whole-body exercise (Johnson et al., 1993; Walker et al., 2011), (ii) normocapnic hyperpnea (Kabitz et al., 2011; Renggli et al., 2008), and (iii) inspiratory resistive breathing (Bellemare and Grassino, 1982; Laghi et al., 1998). In these particular conditions, diaphragmatic fatigue develops early, without a further loss of diaphragmatic contractility in the lead-up to task failure (Kabitz et al., 2011; Laghi et al., 1998; Walker et al., 2011). The time course of diaphragmatic fatigue has been shown to follow an exponential decay according to best-fit biometric approximation (Kabitz et al., 2011). Hypoxic conditions have been reported to enhance diaphragmatic fatigue associated with strenuous respiratory muscle loading (Bark et al., 1988; Jardim et al., 1981; Verges et al., 2010).

What remains unclear is how diaphragmatic fatigue progresses within the time course of inspiratory muscle loading under hypoxic conditions. This is of interest to understanding the implications of hypoxia on exercise performance in healthy subjects and for patients who suffer from acute and chronic hypoxic respiratory failure, respectively. Therefore, the current study aimed to investigate the effect of hypoxia on the progression of diaphragmatic fatigue during inspiratory muscle loading. Here it was hypothesized that the time course of diaphragmatic fatigue, assessed by transdiaphragmatic pressures during supramaximal magnetic phrenic

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nerve stimulation (Pdi,tw), differs markedly from normoxic conditions.

2. Materials and methods

This study received approval from the Institutional Review Board for Human Studies at the University Hospital Freiburg, Germany. Written informed consent was provided by each subject before participation. All procedures conformed to the standards described in the latest version of the Declaration of Helsinki.

2.1. Subjects

Nineteen healthy, non-smoking subjects who were not under any medication participated in the study. Any pre-existing pulmonary/cardiac disease or pregnancy led to exclusion from the study. Prior to measurements, all subjects had to avoid food intake for two hours, caffeine-intake for six hours and stressful physical activity for at least 24 h.

The entire study was supervised by a medical doctor. Vital parameters were closely monitored in each subject.

2.2. Lung function tests, pressure recordings and vital parameters

In accordance with international guidelines, pulmonary function testing was assessed by body-plethysmography (Masterlab-Compact®, Jaeger, Hochberg, Germany) (Miller et al., 2005a,b; Wanger et al., 2005). All pressure signals were assessed by a multiple pressure transducer (Disposable BP Transducer, ADinstruments Pty Ltd., Sydney, Australia). Airflow was recorded by a pneumotachograph (Hans-Rudolph Inc., Heated Pneumotach 8001 with Heater Controller, Shawnee, USA). Maximal static inspiratory mouth occlusion pressure (PImax) was assessed from residual volume, based on previous recommendations (American Thoracic Society, 2002).

Transcutaneous partial pressure of carbon dioxide ($P_{tc}CO_2$), heart rate and arterial oxygen saturation were assessed throughout the protocol using a digital monitor (SenTec Digital Monitor, SenTec AG, Therwil, Switzerland). Following in vitro calibration and temperature adjustment to 42 °C, the $P_{tc}CO_2$ sensor was attached to the right ear lobe. Additionally, end-tidal carbon dioxide and inspired oxygen fraction (FiO_2) were measured by a gas analyzer (ADinstruments Pty Ltd., Sydney, Australia; Range: 5–100% for O_2 and 0–10% for CO_2) throughout the protocol.

Two magnetic stimulators (Magstim® 200, Magstim® Inc., Wales, United Kingdom) with two 45 mm figure-eight coils (Magstim® Inc., Wales, United Kingdom) were used for bilateral anterior magnetic phrenic nerve stimulation (BAMPS) (Mills et al., 1996). During BAMPS, twitch esophageal (Pes,tw) and gastric (Pga,tw) pressures were recorded while participants sat with their mouth closed on a standardized chair with a back rest. A double-balloon catheter (Bösch Feinmechanik und Medizintechnik GmbH, Gottenheim, Germany) inserted trans-nasally into the distal esophagus (balloon volume 1 ml of air) and stomach (balloon volume 2 ml of air) was used to measure gastric and esophageal pressures. Pdi,tw was calculated by point-to-point subtraction of Pes,tw from Pga,tw.

Initially, supramaximality of BAMPS was ensured by assessing Pdi,tw on both study days at different stimulator outputs: 60, 70, 80, 90 and 100%. The exact localization of coil position was marked. In order to assess lung volume at the point of magnetic stimulation, inspiratory capacity was measured immediately after each Pdi,tw assessment (V_{tw}).

To minimize the confounding effects of the enhanced contractile response due to twitch potentiation, five maximal static inspiratory efforts lasting five seconds were performed prior to each Pdi,tw assessment in unloaded conditions including pre- and post-loading Pdi,tw measurements. (Mador et al., 1994; Vandervoort et al., 1983; Wrag et al., 1994).

Prior to respiratory muscle loading, each subject completed a series of Pdi,tw measurements at different lung volumes; this enabled later correction of Pdi,tw for changes in end-expiratory lung volume for values obtained during inspiratory muscle loading. It has been shown that diaphragmatic contractility depends on diaphragmatic fiber length (Hamnegård et al., 1995; Smith and Bellemare, 1987). It has been previously established, that Pdi,tw and lung volume are linearly correlated (Hamnegård et al., 1995; Hubmayr et al., 1989; Mier et al., 1990). Mathematical lung volume correction for Pdi,tw (i.e., Pdi,tw_c) was recently introduced as a means of accounting for changes in lung volume during Pdi,tw assessment in strenuous exercise (Walker et al., 2011). Between total lung capacity and residual volume, two Pdi,tw measurements were performed for each 500 ml change in lung volume as described in more detail elsewhere (Walker et al., 2011). Pdi,tw_c calculation was based on the two initial Pdi,tw readings taken at the beginning of inspiratory muscle loading. In contrast pre- and post-loading Pdi,tw measurements were not corrected for lung volume.

2.3. Experimental protocol

A synopsis of the entire protocol is given in Fig. 1. All subjects underwent two single-blinded and randomized study conditions: (1) normoxia and (2) normobaric hypoxia. Inspiratory muscle loading was performed until the point of task failure. To enable inter-individual comparison among subjects, at least 21 min (i.e., 14 units lasting 90 s each) of inspiratory muscle loading had to be completed.

Diaphragmatic fatigue was defined as a reduction in Pdi,tw_c >10%, where the first and final loading (task failure) units were compared (Mador and Dahuja, 1996; Verges et al., 2007; Walker et al., 2011). This criterion had to be fulfilled for both normoxia and normobaric hypoxia.

Inspiratory muscle loading was performed with a commercially-available threshold loading device (POWERbreathe® Classic, Level 2, HaB International Ltd., Warwickshire, GB). The device was targeted at 70% of each subject's PImax using equal settings on both study days, since diaphragmatic fatigue has been shown to occur under these circumstances (Laghi et al., 1998; Rohrbach et al., 2003; Sheel et al., 2001). In addition, the device was connected to a commercially-available hypoxia generator (Altitrainer®, SMTEC, Nyon, Switzerland). The generator delivers gas mixtures with a minimal FiO_2 of 5% and an inspired carbon dioxide fraction ($FiCO_2$) ranging from 0 to 6%. Subjects were instructed to breathe deeply through the mouth piece of the loading device while wearing a nose clip. Breathing frequency was controlled and had to be mimicked in the second study condition. Immediately before and after inspiratory muscle loading, blood gas samples were drawn from the arterialized left ear lobe (Finalgon®, Boehringer Ingelheim Pharma, Ingelheim, Germany) and analyzed (Super GL®, Hitado Diagnostic Systems, Moehnensee, Germany).

During the protocol, FiO_2 and $FiCO_2$ were adapted to meet the following target values: a SpO_2 of 80% during the hypoxic study condition and an endtidal carbon dioxide pressure of 35–45 mmHg in both study conditions. FiO_2 was set to 21% during inspiratory muscle loading in normoxia.

Steady state was achieved by having the subjects breathe quietly for at least ten minutes through a pneumotachograph connected to the hypoxia device with a two-way valve. Hereafter, five pre-loading Pdi,tw values were assessed and inspiratory muscle loading was started thereafter.

For standardization and calculation purposes, the entire protocol was divided into 90 s units. Pdi,tw was assessed every 45 s throughout inspiratory muscle loading including a "priming" and

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