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ORIGINAL ARTICLE

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Task failure from inspiratory resistive loaded breathing: a role for inspiratory muscle fatigue?

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Abstract The use of non-invasive resistive breathing to task failure to assess inspiratory muscle performance remains a matter of debate. CO_2 retention rather than diaphragmatic fatigue was suggested to limit endurance during inspiratory resistive breathing. Cervical magnetic stimulation (CMS) allows discrimination between diaphragmatic and rib cage muscle fatigue. We tested a new protocol with respect to the extent and the partitioning of inspiratory muscle fatigue at task failure. Nine healthy subjects performed two runs of inspiratory resistive breathing at 67 (12)% of their maximal inspiratory mouth pressure, respiratory rate (f_R), paced at 18 min^{-1}, with a 15-min pause between runs. Diaphragm and rib cage muscle contractility were assessed from CMS-induced esophageal ($P_{es,tw}$), gastric ($P_{ga,tw}$), and transdiaphragmatic ($P_{di,tw}$) twitch pressures. Average endurance times of the first and second runs were similar [9.1 (6.7) and 8.4 (3.5) min]. $P_{di,tw}$ significantly decreased from 33.1 to 25.9 cmH_2O in the first run, partially recovered (27.6 cmH_2O), and decreased further in the second run (23.4 cmH_2O). $P_{es,tw}$ also decreased significantly (–5.1 and –2.4 cmH_2O), while $P_{ga,tw}$ did not change significantly (–2.0 and –1.9 cmH_2O), indicating more pronounced rib cage rather than diaphragmatic fatigue. End-tidal partial pressure of CO_2 ($P_{ET}CO_2$) rose from 37.2 to 44.0 and 45.3 mmHg, and arterial oxygen saturation (S_aO_2) decreased in both runs from 98% to 94%. Thus, task failure in mouth-pressure-targeted, inspiratory resistive breathing is associated with both diaphragmatic and rib cage muscle fatigue. Similar endurance times despite different degrees of muscle fatigue at the start of the runs indicate that other factors, e.g. increases in $P_{ET}CO_2$, and/or decreases in S_aO_2, probably contributed to task-failure.

Keywords Inspiratory muscle endurance · Respiratory muscle fatigue · Task failure · Breathing pattern

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Introduction

The assessment of respiratory muscle performance and the role of respiratory muscle fatigue in task failure from inspiratory loading remain a matter of debate. The gold standards for measuring diaphragmatic fatigue are electrical phrenic nerve stimulation (National Heart, Lung, and Blood Institute 1990) and magnetic cervical stimulation; the latter co-stimulates the diaphragm and the rib cage muscles and thus allows discrimination between diaphragmatic and rib cage muscle fatigue (Similowski et al. 1998). Although both methods adequately detect and quantify respiratory muscle fatigue, they are invasive, with balloon catheters in the esophagus and stomach, and require extensive technical equipment as well as skilled experimenters. Thus, for daily routine these tests are less suitable.

Non-invasive assessment of global inspiratory muscle performance, as an indirect indicator of respiratory muscle fatigability, is performed with loading of the inspiratory muscles. This is carried out either by progressively increasing the inspiratory load and measuring the highest load achieved (Eastwood et al. 1994) or by holding an inspiratory load constant and measuring the time for which this load can be sustained (Zocchi et al. 1993; Mador et al. 1996; McKenzie et al. 1997; Travaline et al. 1997; Eastwood et al. 1998; Laghi et al. 1998). In recent years, however, several studies questioned the assumption that these methods do indeed indirectly measure inspiratory muscle — and in

particular diaphragmatic—fatigability. While diaphragmatic fatigue was shown to develop early during resistive loading when transdiaphragmatic pressure was targeted (Travaline et al. 1997; Laghi et al. 1998), little (Eastwood et al. 1998) or no (McKenzie et al. 1997; Gorman et al. 1999) diaphragmatic fatigue was detected at the point of task failure when subjects were targeting mouth pressure. McKenzie et al. (1997) and Gorman et al. (1999), suggested that CO_2-retention rather than diaphragm muscle fatigue causes task-failure (McKenzie et al. 1997; Gorman et al. 1999). Alternatively, Hershenson and coworkers (1989) found that the rib cage muscles fatigued more than the diaphragm during resistive breathing and argued that rib cage muscle fatigue may play a role in task failure from resistive breathing. This finding was corroborated by Laghi et al. (1998) who observed progressive recruitment of rib cage muscles during resistive diaphragmatic loading, and by Mador et al. (1996) who found that the rib cage muscles might fatigue preferentially during an inspiratory loading challenge.

In the search for good respiratory muscle performance tests the question also arises of what type of experimental load best reflects the loads imposed on the respiratory muscles in 'daily life'. To assess global inspiratory muscle endurance, constant loading of the respiratory muscles seems more appropriate since pathologies such as airway narrowing or obstruction, chest wall restriction, or muscle weakness are constant rather than quickly progressing 'loads'. Also, for repetitive respiratory muscle endurance testing, the degrees of freedom should be minimized, i.e. by imposing breathing frequency and duty cycle similar to keeping pedaling frequency constant for cycling tests. Targeting mouth rather than transdiaphragmatic or pleural/esophageal pressure is more practical because this procedure does not require balloon catheters. Taking into account these points the question still remains of whether task failure, under these conditions, is a good measure for inspiratory muscle fatigue. We previously found that subjects breathing at a constant load (~80% maximal inspiratory pressure; MIP) with paced respiratory frequency (f_R) and duty cycle until task failure can breathe for the same duration with only a 15-min break after the first run (Perret et al. 1999).

The aims of the present study were therefore to test a new standardized respiratory muscle performance test and:

1. To assess the extent of inspiratory muscle fatigue induced by resistive breathing to task failure with imposed breathing pattern and targeted mouth pressure;
2. To assess the partitioning between rib cage and diaphragmatic muscle fatigue when targeting mouth pressure without instructions for specific inspiratory muscle use;
3. To determine the reproducibility of the test with respect to specific muscle fatigue, after a 15-min rest.

Methods

Subjects

Nine healthy, non-smoking and regularly exercising male subjects participated in the study. Their average age [mean (SD)] was 29 (4) years, their height was 187 (8) cm, and their body mass was 77 (10) kg. They all had normal lung function: forced vital capacity was 5.95 (1.04) l, forced expiratory volume in 1 s averaged 4.75 (0.85) l, maximal voluntary ventilation was 208.9 (35.4) l min^{-1}, and MIP at residual volume (MIP_{RV}) was –184.3 (22.7) cmH_2O. Written, informed consent was obtained from all subjects and the study was approved by the local ethics committee. The experiments comply with the current laws of Switzerland.

Equipment

Spirometric variables as well as CO_2 partial pressure (PCO_2) were measured with an ergo-spirometric device (Quark b^2, COSMED, Rome, Italy). Volumes were determined with a turbine, PCO_2 by means of an infrared gas analyzer. MIP_{RV} and constant-load resistive breathing were performed with a special device (Tecuria, Chur, Switzerland). The mouthpiece was connected to a non-rebreathing valve (Y-Shape, NRBV 1420 Series, Hans Rudolph, Kansas City, Mich.) that was connected to two electronically controlled valves (inspiratory and expiratory) by a tube system. Flow was measured by a flow sensor (163PC01D75, Honeywell, Phoenix, Ariz.). Mouth pressure was measured by a pressure sensor (143C05PCB, Sensym, Milpitas, Calif.) close to the mouthpiece. Breathing resistance increased proportionally to the voltage applied to the valves. Feedback on the generated mouth pressure was displayed on an oscilloscope with which breathing frequency and duty cycle were paced as well. Air-filled balloon catheters (Jaeger, Hoechberg, Germany) were positioned in the middle third of the esophagus (0.5 ml) and the stomach (1.5 ml) in a standard manner. Catheter tubes were connected to two Validyne MP45 pressure transducers (Validyne, Northridge, Calif.) and the signals were amplified (CD19A, Validyne). CO_2 and pressure signals were ADD converted (MacLab, ADInstruments, Castle Hill, Australia), and recorded on a Macintosh computer (Chart Software 3.6/s, ADInstruments).

Blood lactate concentrations were determined using an enzymatic analyzer ESAT 6661 (Eppendorf, Hamburg, Germany) and arterial oxygen saturation (S_aO_2) was measured with an infrared finger clip sensor (Nellcor, Pleasanton, Calif.) respectively. Subjects were asked to rate their respiratory exertion as well as their perception of air hunger during resistive breathing using a modified Borg scale (Wilson and Jones 1991).

Cervical magnetic stimulation

Cervical magnetic stimulation (CMS), co-stimulating the phrenic nerves as well as the innervation of rib cage muscles, was performed with a circular 90-mm coil powered by a Magstim 200 (Magstim, Whitland, UK) using the standard technique described by Similowski et al. (1989). Twitch esophageal ($P_{es,tw}$), gastric ($P_{ga,tw}$), and transdiaphragmatic ($P_{di,tw}$) pressures were defined as the difference between baseline pressure immediately before stimulation and the peak pressure following CMS. All twitches showing changes in baseline–P_{es} or thoraco–abdominal configuration, as determined by circumference measurement using two pneumotrace bands (ADInstruments), were rejected from further analysis.

Study protocol

During preliminary testing sessions all subjects were familiarized with the different testing devices and procedures, particularly with

Table 1 Breathing endurance times ($Time_1$, $Time_2$), average minute ventilation ($V_{E,1}$, $V_{E,2}$) and blood lactate concentrations (Lac_1, Lac_2). None of the variables were significantly different between the two consecutive constant-load resistive breathing tests

Subject no.	$Time_1$ (min)	$Time_2$ (min)	$\dot{V}_{E,1}$ (l min^{-1})	$\dot{V}_{E,2}$ (l min^{-1})	Lac_1 (mmol l^{-1})	Lac_2 (mmol l^{-1})
1	5.1	5.4	14.5	15.3	1.91	2.05
2	7.2	14.4	15.6	15.9	1.97	1.50
3	10.5	9.9	12.6	12.9	1.07	0.91
4	10.5	8.7	23.0	23.4	2.93	3.42
5	3.9	4.9	23.5	23.1	2.48	2.10
6	23.9	11.4	19.9	19.1	1.99	1.96
7	5.2	5.1	15.8	14.9	1.94	1.83
8	2.9	5.1	14.9	15.0	3.30	3.14
9	13.2	10.7	13.6	12.7	1.38	1.41
Mean (SD)	9.1 (6.5)	8.4 (3.5)	17.0 (4.1)	16.9 (4.0)	2.11 (0.70)	2.04 (0.80)

resistive breathing. Spirometric measurements as well as MIP_{RV} maneuvers were performed until values were within ±5%. To determine the target for the constant-load resistive breathing tests, an incremental resistive breathing test was performed where the load for the first step was set at 60% MIP_{RV} and subsequently increased by 5% MIP_{RV} every 3 min. Breathing frequency for all tests was paced at 18 breaths min^{-1} with a duty cycle of 0.5. When subjects were no longer able to reach the target load, tests were terminated and the pressure of the last step that the subject had been able to sustain for 3 min was selected as the target pressure for constant-load resistive breathing.

At least 2 days later, all subjects performed two consecutive resistive breathing tests at the predetermined constant load. The two tests were separated by a 15 min rest period. During each test, subjects matched a mouth pressure square-wave-like waveform displayed on an oscilloscope. The shape of the waveform was recorded on a previous day in a trial during which subjects were asked to comfortably achieve the given target pressure for as long as possible during the inspiration. Target pressure averaged 66.9 (11.6)% of MIP_{RV}. During resistive breathing, end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) was measured breath by breath. Also, every minute, S_aO_2 was noted and subjects were asked for their sensation of respiratory exertion and air hunger. Before resistive breathing and at task failure, a 20-µl sample of blood was withdrawn from an ear lobe for blood lactate analysis. Task failure was defined as the time when the subjects were no longer able to follow the target waveform and the maximal breathing endurance time was noted.

To assess inspiratory muscle fatigue, CMS was performed immediately before (pre_1 and pre_2) and after ($post_1$ and $post_2$) the two breathing tests. To avoid the confounding effect of twitch potentiation, i.e. increased twitch amplitude after inspiratory efforts compared to measurements after 10–20 min of relaxed breathing (Vandervoort et al. 1983; Mador et al. 1994), we paid attention to record potentiated twitches not only after, but also prior to resistive breathing by having the subjects perform three maximal inspiratory maneuvers lasting 5 s. Immediately following this procedure, nine single twitches were obtained with the subjects performing another maximal inspiratory maneuver between the 3rd and 4th as well as between the 6th and 7th stimulation. For data analysis, the average amplitude of nine twitches was calculated unless one of the twitches was rejected post-hoc according the exclusion criteria (see above).

To assure supramaximal stimulation, series of CMS with increasing stimulator output (70, 90, 94, 98, 100%) were performed prior to pre_1- as well as immediately after $post_2$-measurements.

Statistical analysis

An analysis of variance (ANOVA) with repeated measures was used to assess changes in twitch pressures, S_aO_2, $P_{ET}CO_2$ as well as perception of respiratory exertion and air hunger. If significance was found, Fisher's PLSD post hoc analysis was applied to locate the significant differences. Breathing endurance times, average minute ventilation and blood lactate concentrations at the end of the resistive breathing task were compared between test series using a paired t-test. Results are given as mean (SD). Values were considered to be significantly different if $P < 0.05$.

Results

Times to task failure were not significantly different between the first and the second resistive breathing test (Table 1). Also, average minute ventilation ($\dot{V}_E$), being 1.9 times the resting value, and blood lactate levels at time of task failure did not differ significantly between test series.

Phrenic nerve stimulations were supramaximal before as well as after resistive breathing as assured by plateaus reached in $P_{di,tw}$ with increasing stimulator power output (pre: 70%: 15.6 (3.8) cmH_2O; 90%: 23.7 (5.1) cmH_2O; 94%: 25.8 (5.4) cmH_2O; 98%: 27.2 (5.3) cmH_2O; 100%: 27.2 (5.4) cmH_2O; post: 70%: 12.5 (3.3) cmH_2O; 90%: 19.7 (5.0) cmH_2O; 94%: 20.9 (4.8) cmH_2O; 98%: 21.8 (4.7) cmH_2O; 100%: 22.7 (5.3) cmH_2O).

As depicted in Fig. 1, significant reductions were observed in $P_{es,tw}$ as well as $P_{di,tw}$ at both $post_1$ and $post_2$ compared with pre_1, while no significant changes occurred in $P_{ga,tw}$. Mean $P_{es,tw}$ and $P_{di,tw}$ tended to be smaller at pre_2 compared with pre_1 ($P_{es,tw}$, $P = 0.0721$; $P_{di,tw}$, $P = 0.0556$). However, when performing the same statistical analysis using individual percent decrements in pre_2-twitch-pressures relative to baseline pre_1-values, pre_2-$P_{es,tw}$ and pre_2-$P_{di,tw}$ also proved to be significantly lower ($P_{es,tw}$, $P < 0.05$; $P_{di,tw}$, $P < 0.01$). Absolute and relative $P_{es,tw}$ and $P_{di,tw}$ tended to be slightly lower at $post_2$ compared with the $post_1$ resistive breathing test; however, they did not differ significantly. We did not observe significant changes in $P_{es,tw}/P_{ga,tw}$, although the ratio tended to decrease [pre_1: –1.84 (0.59) $post_1$: –1.73 (0.65); pre_2: –1.58 (0.54), $post_2$: –1.59 (0.47)].

As shown in Fig. 2, levels of perceived respiratory exertion and air hunger rose from zero at the beginning of the resistive breathing test to near maximal levels at the times of task failure. Neither values at the very end of the tests, nor values averaged over the entire test duration differed significantly between the two test sessions. $P_{ET}CO_2$ levels were significantly lower at the beginning of the two resistive breathing tests compared

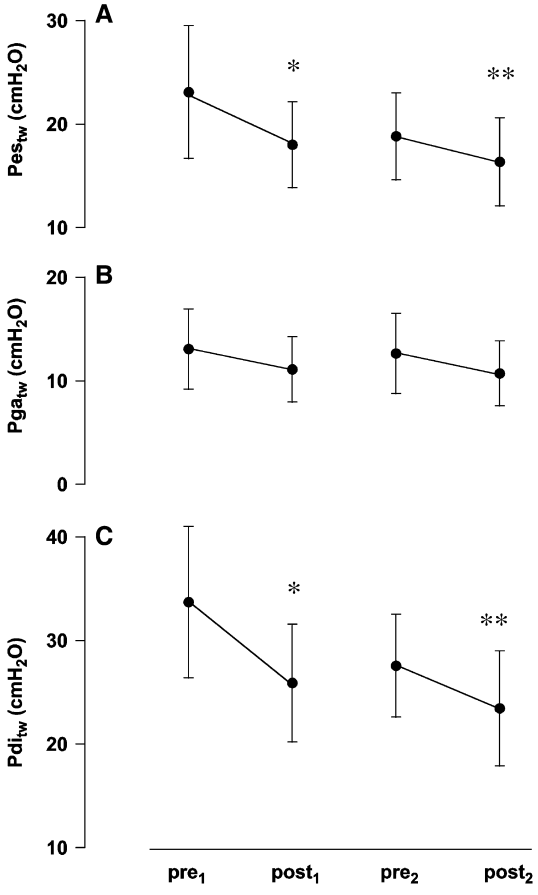

Fig. 1A–C Twitch pressures before (pre_1, pre_2) and after ($post_1$, $post_2$) the two consecutive constant-load resistive breathing tests. Twitch esophageal pressures ($P_{es,tw}$, **A**) and twitch transdiaphragmatic pressures ($P_{di,tw}$, **C**) were significantly (*$P < 0.05$; **$P < 0.01$) smaller $post_1$ and $post_2$ compared with pre_1. Values of twitch gastric pressures ($P_{ga,tw}$, **B**) were not significantly different

with resting values and rose to significantly higher levels after 80% of the test duration. S_aO_2 decreased slightly in the course of both tests and was significantly reduced at all times after 50% of the test duration.

Discussion

We found similar endurance times for the two subsequent resistive breathing tests with imposed breathing pattern (f_R and duty cycle) and targeted mouth pressure. Inspiratory muscle fatigue (–20% $P_{di,tw}$) developed during the first test. This fatigue did not fully recover during the 15 min rest (–16% $P_{di,tw}$ before the second of the two tests), and tended to be even more pronounced at the end of the second test (–28% $P_{di,tw}$). The ratio $P_{es,tw}/P_{ga,tw}$ [an indicator of rib cage muscle fatigue; (Similowski et al. 1998)] tended to decrease particularly during the first of the two resistive breathing tests. However, $P_{di,tw}$ or $P_{es,tw}$ at the end of the two breathing tests were not different and the time courses of subjective perception of respiratory effort as well as air hunger, $P_{ET}CO_2$ and S_aO_2 did not differ between the two resistive

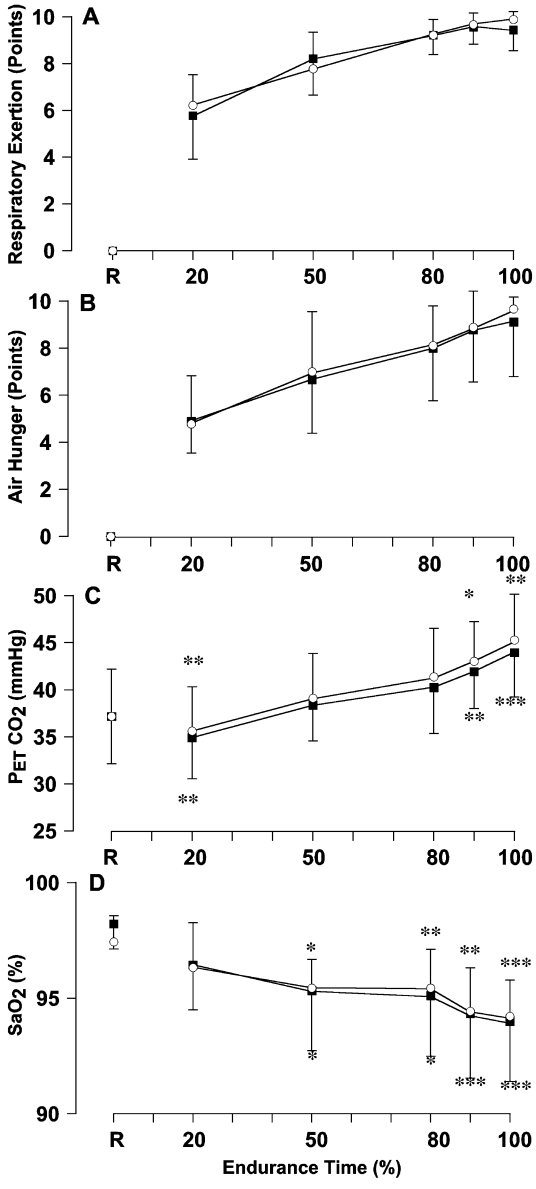

Fig. 2A–D Time course of respiratory exertion (**A**), air hunger (**B**), end-tidal partial pressure of CO_2 ($P_{ET}CO_2$, **C**), and arterial oxygen saturation (S_aO_2, **D**) during the two consecutive constant-load resistive breathing tests (○ test1; ■ test2). Values are given as means (SD) of nine subjects at distinctive time points. For all variables a separate value at rest (R) was obtained prior to the first breathing test. Compared with rest, respiratory exertion and air hunger were significantly higher ($P < 0.001$) than resting values (asterisks for clarity not shown), $P_{ET}CO_2$ was significantly increased at 90 and 100% endurance time, whereas S_aO_2 fell continuously during the constant-load breathing test and was significantly lower from 50% endurance time onwards. Significant differences are indicated with asterisks (*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$)

breathing tests either. What were the reasons causing the task failure– It is indeed striking that the subjects were able to breathe twice for the same duration despite prefatigued inspiratory muscles at the start of the second test. One potential confounding factor could be an inaccurate measurement of respiratory muscle fatigue by CMS. Since we performed series of CMS with increasing

stimulation intensity demonstrating supramaximal stimulation before and after resistive breathing, it is unlikely that submaximal stimulation after resistive breathing was the cause for the lower twitch pressures. It follows that the hypothesis of respiratory muscle fatigue leading to task failure may be too simplistic and other reasons should be taken into account to explain task failure in our experimental set-up.

Among these other variables are an increase in $P_{ET}CO_2$, as suggested by McKenzie et al. (1997) and Gorman et al. (1999), or a decrease in S_aO_2, both of which may have led to increases in strong respiratory sensations and therefore to task failure. With regard to $P_{ET}CO_2$, our subjects stopped the task at a $P_{ET}CO_2$ that was significantly higher than their resting values. Due to the imposed breathing pattern and the mouth pressure that subjects were tracking on the oscilloscope, their effective $\dot{V}_E$ was almost double that obtained at rest. Consequently the subjects first hyperventilated, while, in the course of the test, O_2-consumption most likely increased, increasing CO_2-output, and thereby eventually increasing $P_{ET}CO_2$. However, $P_{ET}CO_2$ rose only to 44.0 (4.7) mmHg ($post_1$) and 45.3 (4.9) mmHg ($post_2$) on average. Could our subjects have rated near maximal 'air hunger' due to the elevation of $P_{ET}CO_2$ only?

Banzett et al. (1996) tested the effect of increased $P_{ET}CO_2$ on the level of 'air hunger' in the absence of a change in $\dot{V}_E$ by mechanically ventilating healthy subjects and modifying inspired CO_2 concentration. At an average $P_{ET}CO_2$ of 45.5 mmHg, their subjects rated an 'air hunger' intensity of SLIGHT+, i.e. between slight and moderate (SLIGHT = sure that one feels respiratory discomfort, not very strong, could be tolerated for a very long time; MODERATE = very unpleasant level of respiratory discomfort, but could be tolerated for several minutes). Our subjects' $P_{ET}CO_2$ at the end of the test would thus be rated as only SLIGHT to MODERATE. However, resting $P_{ET}CO_2$ was 39.1 mmHg in Banzett's study (Banzett et al. 1996) and 37.2 mmHg in ours, increasing the difference above resting by 2 mmHg in our study. Two of our subjects had resting $P_{ET}CO_2$ levels below 30 mmHg, indicating they were hyperventilating prior to the test and were not in a respiratory steady-state. When excluding those two subjects, our subjects' average resting $P_{ET}CO_2$ was 39.6 (1.9) mmHg (range 37–42 mmHg), similar to the level reported by Banzett et al. (1996). Second, it is known that the perception of 'air hunger' for a given $P_{ET}CO_2$ depends on $\dot{V}_E$, i.e. the higher $\dot{V}_E$, the smaller is the perception of 'air hunger' at the same level of $P_{ET}CO_2$ (e.g. Manning et al. 1992). Banzett et al. (1996) used ventilations of 0.16 l min^{-1} kg^{-1} in their study, while in the present study $\dot{V}_E$ was nearly 40% larger than this, implicating that 'air hunger' ratings associated with the increase in $P_{ET}CO_2$ would have been smaller in our study. This assumption also seems to hold when considering that spontaneously breathing subjects need slightly larger (+17%) $\dot{V}_E$ than mechanically ventilated subjects for similar sensations of 'air hunger' at similar $P_{ET}CO_2$ (Shea et al. 1996). On the other hand, resistive breathing might require even larger $\dot{V}_E$ since the proprioceptive input is certainly further increased compared with spontaneous breathing. Therefore—as the $P_{ET}CO_2$ levels that were reached at the time of task failure did not differ significantly between the two test runs—one could argue, that our subjects stopped the task due to an increased sensation of 'air hunger' resulting from an increase in $P_{ET}CO_2$. However, individual changes in $P_{ET}CO_2$ reached at the end of the two tests were not related to the individual changes in endurance time suggesting that $P_{ET}CO_2$ and the associated sensation of 'air hunger' were not the only reason for subjects to stop the task.

Potentially, hypercapnia by itself could have accentuated the development of diaphragmatic fatigue as two recent studies assessing diaphragmatic fatigue after 2 min maximum minute ventilation (Rafferty et al. 1999) or exercise (Jonville et al. 2002) suggest. On the other hand, Mador et al. (1997) did not observe a change in diaphragm contractility with hypercapnia following moderate hyperpnea and McKenzie et al. (1997) could not even detect diaphragmatic fatigue despite subjects performing resistive breathing to task failure in the presence of hypercapnia. Thus, an effect of the mild hypercapnia on diaphragmatic fatigue in the present study seems unlikely to us.

Could the slight decrease in S_aO_2 (from 98% to 94%) have contributed to the increase in the perception of air hunger at a given $P_{ET}CO_2$? It was recently demonstrated that hypoxia causes the same sensation of 'air hunger' as increased $P_{ET}CO_2$ at comparable respiratory drives (Moosavi et al. 2003). However, oxygen partial pressure had to be reduced to below 60 mmHg (below 90% S_aO_2) to induce air hunger, a threshold similar to that required for a ventilatory response to hypoxia (Mohan and Duffin 1997). Nevertheless, we cannot entirely negate that the small decrease of 4% S_aO_2 increased the sensitivity to CO_2-related perception of 'air hunger'. However, in piglets, Mayok et al. (1992) did not observe an accentuation of diaphragmatic fatigue with moderate hypoxia (40 mmHg) during resistive breathing. In human subjects, supplemental inspired oxygen preventing desaturation during resistive breathing did not significantly increase respiratory time to task failure (McKenzie et al. 1997). These latter findings both argue against the influence of the changes in S_aO_2 on time to task failure in the present study.

While increasing inspiratory muscle fatigue may also have contributed to the time-dependent increase in the perception of 'air hunger' and was most likely the reason for increasing perception of respiratory effort during resistive breathing (Ward et al. 1988), it is rather difficult to say to what degree diaphragmatic and extra-diaphragmatic fatigue per se may have contributed to task failure. After the first of the two tests, $P_{di,tw}$ was reduced by 20%, mainly due to a significant decrease in $P_{es,tw}$, while $P_{ga,tw}$ tended to decrease slightly but not significantly, indicating extra-diaphragmatic muscle fatigue.

However, as a result of the subtle changes in $P_{ga,tw}$, the $P_{es,tw}/P_{ga,tw}$ ratio (a drop indicating inspiratory rib cage muscle fatigue; Similowski et al. 1998) did not decrease significantly, a conflicting finding also reported by Mador et al. (1996). Interestingly, in the present study, where mouth pressure was targeted and subjects were not instructed as to which inspiratory muscle group they should use preferentially—in contrast to other studies (Zocchi et al. 1993; Similowski et al. 1998)—a similar degree of diaphragmatic fatigue was found as with targeting transdiaphragmatic pressure (Laghi et al. 1998) suggesting that targeting transdiaphragmatic pressure is not a requirement to induce diaphragmatic fatigue in this kind of performance test.

It thus remains uncertain what led to the task failure in our experimental setup. Blood gas changes from hypoventilation probably played a role, but the role of respiratory muscle fatigue remains less clear. With regard to the design of respiratory performance tests we conclude that for the achievement of reproducible results, a large enough $\dot{V}_E$ must be ensured to avoid hypoventilation with concomitant increase in $P_{ET}CO_2$ and decrease in S_aO_2. For this purpose, threshold rather than resistive loads need to be applied, since with flow-independent threshold loads, pressure as well as volume can independently be targeted; this is in contrast to resistive loading where flow and pressure generation are linked. For loads of 60–80% MIP_{RV}, $\dot{V}_E$ must be more than double resting ventilation. To avoid hyperventilation at the beginning of the resistive breathing task, normocapnia needs to be assured by adding inspired CO_2 at least at the beginning of the test. Breathing frequency and duty cycle should be fixed to achieve most similar loadings between different test days. However, for the diaphragm to fatigue, there is no requirement to target transdiaphragmatic pressure since targeting mouth pressure seems to be sufficient.

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