Respiratory Medicine (2006) **100**, 714–720

respiratoryMEDICINE

Tube breathing as a new potential method to perform respiratory muscle training: Safety in healthy volunteers

Ralph J.H. Koppers[a,*], Petra J.E. Vos[b], Hans Th.M. Folgering[b]

[a]*Department of Pulmonology, Medical Center Leeuwarden, Postbus 888, 8901 BR Leeuwarden, The Netherlands*
[b]*Dekkerswald, University of Nijmegen, The Netherlands*

Received 29 March 2005; accepted 20 July 2005

KEYWORDS
Normocapnic hyperpnea;
Respiratory muscle endurance training;
Tube breathing

Summary Normocapnic hyperpnea has been established as a method of respiratory muscle endurance training (RMET). This technique has not been applied on a large scale because complicated and expensive equipment is needed to maintain CO_2-homeostasis during hyperpnea. This CO_2-homeostasis can be preserved during hyperpnea by enlarging the dead space of the ventilatory system. One of the possibilities to enlarge dead space is breathing through a tube. If tube breathing is safe and feasible, it may be a new and inexpensive method for RMET, enabling its widespread use.

The aim of this study was to evaluate the safety of tube breathing and investigate the effect on CO_2-homeostasis in healthy subjects.

A total of 20 healthy volunteers performed 10 min of tube breathing (dead space 60% of vital capacity). Oxygen-saturation, $PaCO_2$, respiratory muscle function, hypercapnic ventilatory response and dyspnea (Borg-score) were measured. Tube breathing did not lead to severe complaints, adverse events or oxygen desaturations. A total of 14 out of 20 subjects became hypercapnic ($PaCO_2 > 6.0$ kPa) during tube breathing. There were no significant correlations between $PaCO_2$ and respiratory muscle function or hypercapnic ventilatory responses. The normocapnic versus hypercapnic subjects showed no significant differences between decrease in oxygen saturation (–0.7% versus –0.2%, respectively, $P = 0.6$), Borg score (4.3 versus 4.7, $P = 0.9$), respiratory muscle function nor hypercapnic ventilatory responses.

Our results show that tube breathing is well tolerated amongst healthy subjects. No complaints, nor desaturations occurred. Hypercapnia developed in a substantial number of subjects. When tube breathing will be applied as respiratory muscle training modality, this potential development of hypercapnia must be considered.

*Corresponding author. Tel.: +31 582866190; fax: +31 582866122.
E-mail address: R.J.H.Koppers@znb.nl (R.J.H. Koppers).

0954-6111/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.rmed.2005.07.013

Introduction

The function of respiratory muscles can improve in response to training. Normocapnic hyperpnea is probably the best technique for improving *endurance* respiratory muscle function, which is required during exercise.[1] During normocapnic hyperpnea the subject has to sustain a period of hyperpnea for about 10–15 min. Respiratory Muscle Endurance Training (RMET) is based on the principle of normocapnic hyperpnea. RMET, performed with a specially designed, expensive electromechanical device showed an improvement of 268% in breathing endurance in healthy sedentary subjects, and moreover, the endurance time of a sub-maximal exercise test increased with 50% in this study without placebo-training group.[2] RMET also led to improvements in respiratory muscle function and exercise performance in a study in trained athletes, also without a placebo group and in a randomized controlled trial in patients with Chronic Obstructive Pulmonary Disease (COPD).[3,4]

Despite these promising results, RMET is not applied on a large scale because of this complicated and expensive equipment that is needed to maintain O_2 and CO_2-homeostasis during hyperpnea. This CO_2-homeostasis can also be preserved during a period of hyperpnea by enlarging the dead space of the ventilatory system. One of the possibilities to do so is to breathe through a tube. Thus, RMET by means of tube breathing might be a new, inexpensive method to perform respiratory muscle training, possibly even in a home-based setting. However, the safety and the effects of this kind of tube breathing on CO_2-homeostasis have never been evaluated.

Therefore, we investigated whether tube breathing might be a safe and inexpensive technique to perform RMET, enabling widespread use.

The aim of this study was to study the safety and feasibility of tube breathing in healthy subjects. We therefore evaluated oxygenation, perception of dyspnea and CO_2-homeostasis in 20 healthy volunteers during tube breathing.

Subjects and methods

The study population consisted of 20 healthy subjects (13 females) (Table 1). Exclusion criteria were: a pulmonary medical history, pulmonary complaints and current smoking. Subjects were recruited by means of an advertisement in a free local paper. The subjects were informed about the purpose of this study and gave informed consent. The study was approved by the Ethics Committee of the University Hospital Nijmegen.

Pulmonary function test

Pulmonary function tests at rest were measured according to ERS-criteria[5] with a Sensorloop spirometer (Sensormedics corporation, Bilthoven, the Netherlands): forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) were recorded.

Hypercapnic ventilatory response

The steady-state ventilatory response to CO_2 was measured. Subjects breathed in a closed spirometer circuit (Godart, Bilthoven, the Netherlands) in which the soda lime absorber could be partially bypassed with a three-way valve. Oxygen was supplemented. End-tidal PCO_2 was monitored at the mouth (Drager, Type 8290000). After at least 5 min, when the end-tidal PCO_2 value was stabilized, the soda-lime absorber was partially bypassed. When the end-tidal PCO_2 increased by 1 kPa the bypass around the soda-lime absorber was readjusted to prevent the end-tidal PCO_2 from rising any further. After 5 min in this steady state, the test was ended. Tidal volume and breathing frequency were obtained from the spirometer and were converted to minute volume of ventilation (V_E). The ventilatory response (S) to carbon dioxide is the slope of the relationship of ventilation versus end-tidal PCO_2 (l/min/kPa).[6,7]

PI_{max}/PE_{max}

Maximal static inspiratory and expiratory mouth pressures (PI_{max} and PE_{max}) were measured using a flanged mouthpiece connected to a rigid, plastic tube with a small air leak. Pressure was measured with a pressure transducer (Validyne, Northridge, CA, USA) and recorded (Kipp and Zonen, Delft, the Netherlands). Plateau levels for PI_{max} were measured from residual volume, for PE_{max} from total lung capacity.[8]

Threshold loading

Inspiratory threshold loading was used to measure inspiratory muscle endurance.

Subjects, wearing a nose clip, were connected with a mouthpiece to a threshold loading device.[9] They inspired against a loaded valve, starting with a load equal to 10% of PI_{max}, and 25 g weights were added at 1.5 min intervals.[10] Pressure was

Table 1 Variables for normocapnic versus hypercapnic group.

Variable	Normocapnic mean (SD)	Hypercapnic mean (SD)	*P*-value (between groups)
Female/male	4/2	9/5	
Age (yr)	21 (2)	29 (13)	0.9
Height (cm)	176 (15)	177 (11)	0.7
Weight (kg)	73 (13)	74 (12)	0.3
FEV_1 (l)	4.0 (1.1)	3.9 (0.6)	0.9
FEV_1 (% predicted)	100 (12)	103 (10)	0.9
FVC (l)	4.6 (1.4)	4.4 (0.6)	0.7
FVC (%predicted)	97 (10)	97 (14)	0.9
$PaCO_2$ rest (kPa)	5.1 (0.3) (38 mmHg)	5.3 (0.4) (40 mmHg)	0.9
TB$PaCO_2$ (kPa)	5.2 (0.7) (39 mmHg)	6.6 (0.4) (50 mmHg)	0.01
Delta $PaCO_2$ (tube-rest (kPa))	0.09 (0.60) (1 mmHg)	1.29 (0.50) (10 mmHg)	0.01
SaO_2 rest	98.5 (0.5)	96.2 (2.0)	0.02
SaO_2 tube	97.8 (2.0)	95.9 (1.0)	0.02
Delta SaO_2 (tube-rest (%))	−0.7 (1.9)	−0.2 (1.9)	0.6
Heart beats/min rest	74 (6)	70 (11)	0.5
Heart beats/min tube	81 (10)	81 (12)	0.7
Borg	4.3 (2.9)	4.7 (1.9)	0.9
S (l/min/kPa)	6.7 (4.7)	10.8 (7.2)	0.7
SIP_{max} (kPa)	3.6 (1.6)	4.5 (1.9)	0.2
PI_{max} (kPa)	7.1 (2.7)	8.7 (2.4)	0.2
PI_{max} (% pred)	82 (32)	99 (28)	0.3
PE_{max} (kPa)	9.8 (3.9)	10.1 (3.1)	0.7
PE_{max} (% pred)	86.5 (29.1)	88.1 (26.3)	1.0

Data reported as mean (standard deviation).
FEV_1, forced expiratory volume in liters in 1 s; FVC, forced vital capacity in liters; $PaCO_2$, capillary blood pressure of carbon dioxide; $PaCO_2$ rest, $PaCO_2$ at rest/before tube breathing; TB$PaCO_2$, $PaCO_2$ at the end of 10 minutes tube breathing; Delta $PaCO_2$ tube-rest, difference between $PaCO_2$ value during tube breathing and resting value; SaO_2 rest, oxygen saturation at rest; SaO_2 tube, oxygen saturation at the end of 10 min tube breathing; Delta SaO_2 tube-rest, difference between SaO_2 value during tube breathing and resting value; Borg, Borg-score at the end of tube breathing; *S*, slope of ventilatory response to CO_2; SIP_{max}, maximal sustainable inspiratory pressure in kilopascal; PI_{max}, maximal inspiratory pressure in kilopascal; PI_{max} % pred, maximal inspiratory pressure as percentage from reference value; PE_{max}, maximal expiratory pressure in kilopascal; PE_{max} % pred, maximal expiratory pressure as percentage from reference value.

measured inside the mouthpiece with a pressure transducer (Validyne, Northridge, CA, USA). Breathing was continued until inspiration could no longer be sustained. The pressure achieved during the heaviest load tolerated for at least 45 s was defined as the maximal sustainable inspiratory pressure (SIP_{max}).

External dead space ventilation (tube breathing)

The external dead space consisted of a wide-bore spirometer-tube (internal diameter 3 cm, preliminary measured resistance of 1 m of tube: 0.03 kPa/l/s), connected to a mouthpiece. The length of the tube, representing the dead space, was adjusted to 60% of the FVC,[2] because during exercise, when minute ventilation rises, tidal volume increases to about 60% of the vital capacity and remains constant thereafter.[11] A capnograph (Drager, Type 8290000) was connected to the mouthpiece, to monitor the end-tidal PCO_2. The sampled gas was returned from the capnograph to the mouthpiece. The subjects breathed through the tube during 10 min, at an imposed frequency of 15 breaths/min, and at an inspiratory versus expiratory-time ratio of 1:2, using a metronome (Qwik Time QT5, quartz metronome). Before the experiment subjects were instructed to take deep breaths, to overcome the large dead space. They were seated and rested during 3 min. At 30 s before the start of tube breathing ($PaCO_2$ rest) and 30 s before ending tube breathing (TB$PaCO_2$), an arterialized capillary blood-gas sample was taken from a warmed fingertip. Arterial oxygen saturation and heart rate were measured noninvasively by oximetry (Nonin Medical Inc., USA Model 8500 MA). Perception of

dyspnea at the end of tube breathing was measured with a modified Borg-scale (BORG).[12]

Protocol

After the pulmonary function test, the hypercapnic ventilatory response was determined, followed by measurement of PI_{max} and PE_{max}. Next threshold loading was performed. The 3 h session ended with tube breathing. All experiments were performed in the late morning and early afternoon.

Subjects rested for 20 min between each test.

Statistics

Pearson correlations between different parameters were determined. Furthermore, subjects were divided into two groups: normocapnic versus hypercapnic, which was dependent on their TB$PaCO_2$. A $PaCO_2 \leqslant 6.0$ kPa was defined as normocapnia. Mean values between groups were compared. Data are reported as mean $\pm$ SD. The Mann–Whitney *U*-test was used to test significant differences between the two groups. Significance was set at $P < 0.05$. Statistics were performed using SPSS.

Results

Table 1 shows the characteristics and the results of the subjects.

Tube volumes ranged from 2.0 to 4.4 l (= 60% of FVC). During tube breathing, 14 out of 20 subjects became hypercapnic (TB$PaCO_2 > 6$ kPa). Besides of dyspnea, there were neither severe complaints, nor adverse events. There were no significant correlations between $PaCO_2$ and the ventilatory response to CO_2, PI_{max}, PE_{max} or SIP_{max}. Subsequently, the subjects were divided into two groups to compare mean values: normocapnic versus hypercapnic at the end of tube breathing. In the normocapnic group, $PaCO_2$ remained constant: 5.1 (0.3) kPa [mean ($\pm$ SD)] at rest, versus 5.2 (0.7) kPa at the end of 10 min tube breathing (range during tube breathing 4.2–6.0 kPa). In the hypercapnic group, $PaCO_2$ showed a rise from 5.3 (0.4) kPa at rest, to 6.6 (0.4) kPa, $P = 0.001$ (range during tube breathing 6.1–7.7 kPa). A significant difference was found for oxygen saturation at rest as well as at the end of tube breathing, $P = 0.02$ (Table 1). However, the change in oxygen saturation (tube breathing value minus resting value) did not differ significantly between the groups: normocapnic group –0.7% versus hypercapnic group −0.2%, $P = 0.6$. Clinically relevant desaturations did not occur in neither group. Lowest saturation in both groups was 94%.

No significant differences in heart rate at rest, heart rate during tube breathing, or perception of dyspnea (BORG) were recorded among the normocapnic and hypercapnic groups. Subjects had no complaints during tube breathing, besides of dyspnea.

Normocapnic and hypercapnic subjects showed no significant differences in the following characteristics: age, height, weight, FEV_1, FVC, $PaCO_2$ rest.

The ventilatory response to CO_2 (S) was not significantly different for the normocapnic (6.7 l/min/kPa (4.7)) versus the hypercapnic group (10.8 l/min/kPa (7.2)), $P = 0.2$.

The normocapnic and hypercapnic subjects did not differ significantly in maximal inspiratory pressure (PI_{max}) and maximal expiratory pressure (PE_{max}). PI_{max} was within a normal range in both groups: normocapnic: 82% (32%) predicted, versus hypercapnic 99% (28%) predicted, $P = 0.3$.[8]

Inspiratory muscle endurance measured with incremental threshold loading, showed no significant differences between the normocapnic and hypercapnic subjects: SIP_{max} 3.6 (1.6) kPa versus 4.5 (1.9) kPa, respectively, $P = 0.2$.

Discussion

The present study shows that tube breathing in healthy volunteers is well tolerated. No clinically significant desaturations, severe complaints or adverse events occurred. It leads to hypercapnia in several subjects. Thus tube breathing might be a feasible and inexpensive method to perform RMET, which suggests that it could become available to a large population. However, the potential development of hypercapnia must be considered when tube breathing will be applied as endurance training for the respiratory muscles.

To our knowledge this is the first study, evaluating tube breathing as a new method for RMET. Therefore, we investigated the safety of this method, first of all in healthy subjects. Tube breathing in our study did not lead to severe complaints, adverse events or relevant oxygen desaturations. A heart rate of 81 beats/min at the end of 10 min tube breathing does not reflect severe stress. Perception of dyspnea (Borg-score) was moderate to severe at the end of the tube breathing session.

We also looked at the effects of tube breathing on CO_2-homeostasis. Strikingly, ventilation was not

adapted to maintain a normal $PaCO_2$ during tube breathing in all healthy subjects and consequently alveolar hypoventilation occurred. One of the limitations of this study is the fact that we did not measure tidal volumes and minute ventilation during tube breathing in our subjects. Thus, the question remains whether tidal volumes or probably the fixed respiratory rate (15 breaths/min), or a combination of these two variables, were the limiting factors in achieving an adequate alveolar ventilation. On the other hand, the net effect of the alveolar ventilation was measured on end-tidal PCO_2. This partly obviates the necessity to measure minute ventilation as such. However, as a consequence, hypercapnia developed in this subset of subjects. Brief increases in $PaCO_2$ (lasting several minutes) produce a sensation of respiratory discomfort (air hunger), which is neither a harmful, nor a dangerous situation. Hypercapnia also leads to cerebral vasodilatation and it diminishes in- and expiratory upper airway resistance.[13,14] In several studies (in healthy subjects), the effect of induced acute hypercapnia on ventilation was evaluated.[15–17] However, the design of these studies was different from ours because, spontaneous breathing was compared to *mechanical ventilation*. It was shown that ventilation at the same level of hypercapnia, increased even more during spontaneous breathing, compared to mechanical ventilation. Furthermore, air hunger was much lower at the same level of hypercapnia during spontaneous breathing compared to mechanical ventilation. Mean levels of $PaCO_2$ ranged from 6.1 to 6.9 kPa. Thus, it can be speculated that a small rise in $PaCO_2$ during tube breathing might even lead to a more intense training stimulus. Moreover, even prolonged exposure (5 days) to elevated levels of CO_2 in healthy subjects, did not alter the ventilatory chemosensitivity to subsequent acute hypercapnia.[18]

However, *chronic* hypercapnia due to respiratory muscle failure is an important complication and a poor prognostic marker, especially in patients with COPD.[19] On the other hand, especially these patients are eligible for respiratory muscle training to attempt to prevent or postpone this respiratory muscle failure, which is, among other things, caused by impaired respiratory muscle function.[20] Nevertheless, before applying RMET by means of tube breathing to patients with COPD, the safety, applicability and the appropriate training scheme of this technique have to be investigated in these patients.

In Jederlinic's classical study on resistance stress-testing and training of respiratory muscles in COPD-patients, these authors found that all patients hypoventilated, and desaturated.[21] However, some of their patients were already hypoxemic at the start of the test (SaO_2, 84%). When performing this resistive stress test, Jederlinic's patients hypoventilated. The ''wisdom of their bodies'' had to make a choice between very strong exertion of their respiratory muscles versus accepting some degree of hypercapnia. Apparently, they chose the latter. The subjects in our study, and also possibly future patients, face similar choices. As the resistive load in our study was distinctly lower than in Jederlinic's study, one might expect that the urge/need to trade off a heavy respiratory load for some degree of hypercapnia, might be less.

Dead space breathing or tube breathing has been studied in the past; however, these studies are not comparable to our study design because our subjects were *instructed* to take deep breaths to overcome the large dead space (RMET modality), whereas in the other tube breathing studies the investigators looked at the spontaneous (physiological) effects of tube breathing on ventilation.[22–25]

In determining the safety of tube breathing, we looked, among other things, at oxygen saturation. The upper part of the oxygen saturation curve levels off, which means that the partial pressure of O_2 might fall while the oxygen saturation is still normal. However, the lowest saturation measured was 94%, which is not associated with (relevant) hypoxemia. This observation, along with dyspnea scores and heart rate during tube breathing, underlines that tube breathing is a safe method.

The striking observation that hypercapnia developed in a large number of subjects could be explained by several mechanisms, which will be discussed below.

A difference in the sensitivity of the chemoreceptors to a certain change in $PaCO_2$ might be responsible for the development of hypercapnia during tube breathing. This response to CO_2 is mediated centrally by brainstem chemoreceptors in the medulla and peripherally by the carotid and aortic bodies. A wide range of ventilatory responses to CO_2 has been reported in the literature.[26] Our subjects also showed a wide variance and the results of the hypercapnic ventilatory response could not explain the difference in $TBPaCO_2$ between the two groups.

Inspiratory muscle fatigue may lead to acute hypercapnic respiratory failure. One study investigated the effect of diaphragmatic fatigue on control of respiratory muscles and ventilation during CO_2 rebreathing in healthy volunteers. It was concluded that diaphragmatic fatigue induces proportionally greater contributions of inspiratory rib cage muscles, resulting in the preservation of

ventilatory response to CO_2, despite impaired diaphragmatic contractility.[27] Diaphragmatic fatigue measured by cervical magnetic stimulation occurs following voluntary hyperpnea (until task failure), and lasts for at least 1 h after hyperpnea.[28] The subjects in this study breathed at 60% MVV during 517 ± 58 s with a respiratory rate of 89 ± 5 breaths/min. Our subjects were healthy volunteers, breathing with a respiratory rate of 15 breaths/min. Furthermore PI_{max} was within a normal range in both groups. Therefore, respiratory muscle fatigue or weakness cannot explain the difference in TBP_aCO_2 between both groups.

There was a wider range of ages and there were more females in the hypercapnic group. It is difficult to establish whether this might have played a role in becoming hypercapnic. Despite this, they were all healthy subjects of whom it is difficult to estimate retrospectively whether these factors may have played a role in becoming hypercapnic. This would require another study. Furthermore, the sample size in our study could have contributed to the absence of statistically significant differences between the different parameters.

Based on the knowledge that tube breathing leads to a stimulation of ventilation because it increases the amplitude and leads to a change in the timing of the respiratory oscillations in arterial PCO_2, we would have expected our subjects to remain at least normocapnic, and possibly somewhat hypocapnic.[23–25] However, several subjects became hypercapnic. Neither respiratory muscle endurance, nor chemoreceptor sensitivity was significantly different between the groups, although the wide range in ventilatory responses to CO_2 makes it hard to detect significant differences. Especially when taken into account the small number of subjects that were studied, and therefore a type-II error cannot be excluded. Despite these statistical remarks, these subjects "accepted" a higher $PaCO_2$ value, rather than increase their minute ventilation and thus their work of breathing, in spite of the fact that there still was a breathing reserve. The perception of the work of breathing at the end of tube breathing was the same in both groups as shown by the Borg scores. Similar differences can be observed in patients with severe COPD. Some maintain a high ventilation in order to remain normocapnic (so called "pink puffers"), and others do not seem to be bothered by the hypercapnia (so called "blue bloaters"). This fits with the recently proposed theory of natural wisdom, that protects these patients from the detrimental consequences of their disease, but with the inevitable cost of hypercapnia.[29] It is, of course, extremely speculative to suggest that possibly these types of reactions may already be present in early life, before COPD ever develops. However, it is a known fact that there are great interindividual differences in ventilatory sensitivity to CO_2 and there are several reports suggesting that heredity plays a very important role.[25] Thus genetic set differences might determine the tendency to normocapnia or hypercapnia during tube breathing.

The observation that tube breathing is well tolerated in healthy subjects, might have important implications for the applicability of this training technique. Nevertheless, further studies are necessary before application of RMET by means of tube breathing can be recommended as safe in healthy subjects and these findings need to be confirmed in patients with COPD. The equipment for tube breathing is inexpensive and almost everywhere available. This means that RMET by means of tube breathing can be applied on a larger scale: in clinical research, and eventually in routine clinical use.

In summary, the results of this experiment show that tube breathing is well tolerated in healthy subjects. It does not lead to complaints, adverse events or desaturations. It results in hypercapnia in a substantial number of subjects. This response could not be related to any characteristics of the subjects. When tube breathing will be applied as a respiratory muscle training modality, this potential development of hypercapnia must be considered. Furthermore, the appropriate training scheme in healthy subjects and the safety and applicability of tube breathing in patients with COPD needs further investigations.

Acknowledgement

Grant: Netherlands Asthma Foundation project no. 3.4.99.40.

References

1. Reid WD, Samrai B. Respiratory muscle training for patients with chronic obstructive pulmonary disease. *Phys Ther* 1995;**75**(11):996–1005.
2. Boutellier U, Piwko P. The respiratory system as an exercise limiting factor in normal sedentary subjects. *Eur J Appl Physiol* 1992;**64**(2):145–52.
3. Boutellier U, Buchel R, Kundert A, Spengler C. The respiratory system as an exercise limiting factor in normal trained subjects. *Eur J Appl Physiol* 1992;**65**(4):347–53.
4. Scherer TA, Spengler CM, Owassapian D, Imhof E, Boutellier U. Respiratory muscle endurance training in chronic

obstructive pulmonary disease. Impact on exercise capacity, dyspnea, and quality of life. *Am J Respir Crit Care Med* 2000;**162**(5):1709–14.
5. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;**16**:5–40.
6. Smolders FD, Folgering HT, Bernards JA. Capnostat and oxystat. Electronic devices to automatically maintain the end-tidal PCO_2 and PO_2 of a subject connected to a closed respiratory circuit at adjustable levels. *Pflugers Arch* 1977;**372**(3):289–90.
7. Wagenaar M, Vos PJ, Heijdra YF, Teppema LJ, Folgering HT. Combined treatment with acetazolamide and medroxyprogesterone in chronic obstructive pulmonary disease patients. *Eur Respir J* 2002;**20**(5):1130–7.
8. Wilson SH, Cooke NT, Edwards RH, Spiro SG. Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax* 1984;**39**(7):535–8.
9. Nickerson BG, Keens TG. Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. *J Appl Physiol* 1982;**52**(3):768–72.
10. Martyn JB, Moreno RH, Pare PD, Pardy RL. Measurement of inspiratory muscle performance with incremental threshold loading. *Am Rev Respir Dis* 1987;**135**(4):919–23.
11. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. *Clin Chest Med* 1994;**15**(2):305–26.
12. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;**14**(5):377–81.
13. Ito H, Kanno I, Ibaraki M, Hatazawa J, Miura S. Changes in human cerebral blood flow and cerebral blood volume during hypercapnia and hypocapnia measured by positron emission tomography. *J Cereb Blood Flow Metab* 2003;**23**(6): 665–70.
14. Verin E, Tardif C, Marie JP, et al. Upper airway resistance during progressive hypercapnia and progressive hypoxia in normal awake subjects. *Respir Physiol* 2001;**124**(1): 35–42.
15. Bloch-Salisbury E, Shea SA, Brown R, Evans K, Banzett RB. Air hunger induced by acute increase in PCO_2 adapts to chronic elevation of PCO_2 in ventilated humans. *J Appl Physiol* 1996;**81**(2):949–56.
16. Shea SA, Harty HR, Banzett RB. Self-control of level of mechanical ventilation to minimize CO_2 induced air hunger. *Respir Physiol* 1996;**103**(2):113–25.
17. Banzett RB, Lansing RW, Evans KC, Shea SA. Stimulus–response characteristics of CO_2-induced air hunger in normal subjects. *Respir Physiol* 1996;**103**(1):19–31.
18. Crosby A, Talbot NP, Balanos GM, Donoghue S, Fatemian M, Robbins PA. Respiratory effects in humans of a 5-day elevation of end-tidal PCO_2 by 8 Torr. *J Appl Physiol* 2003; **95**(5):1947–54.
19. Calverley PM. Respiratory failure in chronic obstructive pulmonary disease. *Eur Respir J Suppl* 2003;**47**:26s–30s.
20. Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003;**168**(1):10–48.
21. Jederlinic P, Mussprat JA, Miller MJ. Inspiratory muscle training in clinical practice. *Chest* 1984;**86**:870–3.
22. Sackner JD, Nixon AJ, Davis B, Atkins N, Sackner MA. Effects of breathing through external dead space on ventilation at rest and during exercise. II. *Am Rev Respir Dis* 1980; **122**(6):933–40.
23. Fenner A, Jansson EH, Avery ME. Enhancement of the ventilatory response to carbon dioxide by tube breathing. *Respir Physiol* 1968;**4**(1):91–100.
24. Goode RC, Brown Jr EB, Howson MG, Cunningham DJ. Respiratory effects of breathing down a tube. *Respir Physiol* 1969;**6**(3):343–59.
25. Cunningham DJ, Pearson SB, Marsh RH, Kellogg RH. The effects of various time patterns of alveolar CO_2 and O_2 on breathing in man. *Acta Neurobiol Exp (Warsz)* 1973;**33**(1):123–38.
26. McGurk SP, Blanksby BA, Anderson MJ. The relationship of hypercapnic ventilatory responses to age, gender and athleticism. *Sports Med* 1995;**19**(3):173–83.
27. Yan S, Lichros I, Zakynthinos S, Macklem PT. Effect of diaphragmatic fatigue on control of respiratory muscles and ventilation during CO_2 rebreathing. *J Appl Physiol* 1993; **75**(3):1364–70.
28. Mador JM, Rodis A, Diaz J. Diaphragmatic fatigue following voluntary hyperpnea. *Am J Respir Crit Care Med* 1996; **154**(1):63–7.
29. Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl* 2003;**47**:3s–14s.