Changes in the period of no respiratory sensation and total breath-holding time in successive breath-holding trials

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1. Immediately after breath-holding at end-expiratory level, there is a certain period of no particular respiratory sensation which is terminated by the onset of an unpleasant sensation and followed by progressive discomfort during breath-holding. This period, defined as the time from the start of voluntary breath-holding to the point where the onset of an unpleasant sensation occurs, is designated 'the period of no respiratory sensation'. Although it has been shown that the maximum breath-holding performance is improved with successive trials, it is not clear whether this training effect exerts a similar influence on the period of no respiratory sensation during breath-holding.

2. Since the training effect seems to be associated with the stresses of breath-holding, we hypothesized that the initial period of no respiratory sensation during breath-holding might be less influenced by the training effect.

3. We studied 13 normal subjects who performed repeated breath holds while continuously rating their respiratory discomfort using a visual analogue scale. In addition, we measured the hypercapnic ventilatory response of each individual and obtained the relationship between the slope of the hypercapnic response curve and breath-holding periods.

4. Our results showed that there was little training effect on the period of no respiratory sensation and that the period of no sensation during breath-holding is inversely related to the slope of the hypercapnic ventilatory response curve.

5. The period of no respiratory sensation was also measured in eight patients with chronic obstructive pulmonary disease. The values of the period of no respiratory sensation in patients with chronic obstructive pulmonary disease were apparently lower than those obtained in normal subjects.

6. These findings suggest that measurement of the period of no respiratory sensation can be a useful clinical test for the study of genesis of dyspnoea.

INTRODUCTION

When a normal subject voluntarily stops breathing at functional residual capacity, the subject has no particular sensation for the first 30 s or so [1]. Shortly thereafter, a sensation of hunger for air appears and the respiratory muscles begin to contract so that the subject must close the glottis to prolong the breath-holding time. Thus, there are two distinctly different periods during the course of voluntary breath-holding. In accordance with these changes in sensation during breath-holding, the results of electromyogram (EMG) studies [2, 3] showed that immediately after the start of breath-holding there is a period of EMG quiescence of respiratory muscles lasting 20–40 s, which is followed by a progressive increase in EMG activity until the breakpoint at which the subject can tolerate breath-holding no more.

It has been demonstrated in several studies [4–10] that breath-holding performance is greatly influenced not only by physiological factors including changes in lung volume, respiratory movements, contraction of respiratory muscles and ventilatory responses to hypercapnia and/or hypoxia, but also by non-physiological factors such as personal characteristics, past experience and level of anxiety. Also, an improvement in breath-holding performance with successive trials has been documented [10–12], indicating the existence of a training effect on breath-holding. In most of the previous studies, however, the emphasis was laid on maximum duration of breath-holding (total breath-holding time) and separate analysis of the periods of the two different parts has been somewhat neglected.

It has been suggested that the training effect is associated with the habituation to the stresses of breath-holding [11]. Assuming that there may be little stress in the absence of respiratory discomfort, it is possible that the period of no respiratory sensation was less influenced by training than that of maximum breath-holding time.

During the period of EMG quiescence there is no activity in respiratory muscles and therefore the contribution of afferent input from respiratory muscles to the development of unpleasant respiratory sensation can be eliminated.

Assuming that the onset of respiratory muscle activity corresponds to the onset of unpleasant sensation and is mainly determined by chemical...
ventilatory drive, it is also possible that the greater the ventilatory response to CO₂ the shorter the period of no sensation during breath-holding. In order to test these possibilities, in the present study we evaluated hypercapnic ventilatory response and the effects of training in association with the onset of unpleasant sensation during breath-holding.

METHODS

We studied 13 adult male volunteers ranging in age from 24 to 40 years. None had clinical evidence of cardiovascular, respiratory or neuromuscular disorders. Three of the 13 subjects were current smokers. The research was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association and the protocol was approved by the institutional ethics committee. Each subject gave informed consent. None was familiar with the hypothesis being tested.

Each subject was seated during the experiment and breathed through a nasal mask, a pneumotachograph (CP-100; Allied Health Care Product Inc, St. Louis, U.S.A.) and a large three-way stopcock. Ventilatory airflow was measured with the pneumotachograph while the subject was breathing through the nose only. Tidal volume (VT) was obtained by electrical integration of the inspired flow signal. End-tidal CO₂ (PETCO₂) was monitored at a sideport of the three-way stopcock with an infrared CO₂ analyser (Aika® MEL RAS-41, Aika, Tokyo, Japan). Skin-surface electrodes were placed over the eighth or ninth intercostal space lateral to the mid-clavicular line in order to record electrical activity of the underlying respiratory muscles.

During the experiment, the subjects were asked to rate the intensity of the sensation of 'desire to breathe' using a visual analogue scale (VAS). The analogue scale, ranging from 0 to 100, was displayed on an oscilloscope screen and the subjects measured the VAS score by adjusting continuously the knob of a potentiometer, thus altering the display on the oscilloscope anywhere along the scale from 0 to 100 arbitrary units. The numerical value of 0 was given for the sensation of 'not at all unpleasant' and 100 for the (most intense imaginable) sensation of 'intolerable urge to breathe'.

Respiratory muscle EMG, VT, PETCO₂ and VAS score were all recorded on a four-channel recorder (Graphtec WR-3701, Graphtec, Tokyo, Japan).

The usual experimental protocol is described below. The subject was seated in a comfortable chair and was given a short training period to accustom himself to the VAS. The subject was then asked to breathe 100% oxygen through the tightly fitting nasal mask while closing his mouth. After a period of pre-oxygenation lasting for at least 5 min under quiet breathing, and when the breathing pattern and PETCO₂ were stable, the command was given and the subject was asked to stop his breathing at end-expiration and hold his breath for as long as possible while rating the intensity of sensation of the desire to breathe. The pre-oxygenation technique was used in this study to exclude any possible interaction of carbon dioxide and oxygen on respiratory control and respiratory sensation.

The same procedures were repeated four times with rest periods of 5 min or more between trials. During the successive trials the command to hold the breath was given without warning after a period of quiet breathing so that the starting PETCO₂ was as close as possible to the value observed in the first trial. After completion of breath-holding trials, the CO₂ rebreathing test was performed using a modified Read's technique [13] to obtain the ventilatory CO₂ response curve. The subject was also asked whether he felt any anxiety and to describe the sensations experienced during the trials.

The period of no respiratory sensation was defined as the time from the command of breath-holding to the onset of unpleasant sensation, and the total breath-holding time was defined as the time from the command of breath-holding to the breaking point.

In order to test the reproducibility of the results, the same experiment was repeated in five of the 13 subjects on different days. Furthermore, in order to test whether the measurement of the period of no respiratory sensation can be applied to clinical situations, we performed a pilot study in eight patients with chronic obstructive pulmonary disease (COPD) (Table 1). These patients all reported dyspnoea with exertion for at least 5 years, but at the time of study they were clinically stable. In this series of experiments the patients were instructed to start breathing at any time when they felt the desire to breathe during their breath-holding, and therefore only the period of no respiratory sensation was measured. In each patient four successive trials were performed with an interval of 5 min.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of patients with COPD. Values are means ± SD. Blood gas data were obtained while breathing air. FEV₁₀, forced expiratory volume in 1.0 s; FVC, forced vital capacity.</th>
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<tbody>
<tr>
<td>No. of subjects</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Vital capacity</td>
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<td>(% of predicted value)</td>
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<td>Forced vital capacity</td>
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<td>Paco₂ (mmHg)</td>
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Statistical analysis was performed using a two-way analysis of variance, followed by Scheffe's test where appropriate.

RESULTS

The mean values of $V_T$, respiratory frequency ($f$) and $P_{ETCO_2}$ obtained before the start of breath-holding during successive trials are listed in Table 2. There was a tendency for $V_T$ to increase and $f$ to decrease with successive trials. Although there was no significant difference in the pre-breath-hold values of $V_T$ between the trials, the pre-breath-hold value of $f$ at the fourth breath-holding trial was significantly lower than that at the first trial. The changes in pre-breath-hold $P_{ETCO_2}$ in each subject were always within 1.5 mmHg (0.2 kPa) with successive trials and there was no significant difference in the values of $P_{ETCO_2}$ between the trials.

Figure 1 shows examples of experimental recordings of the first (Fig. 1a) and the third (Fig. 1b) breath-holding trial in a single subject. Immediately after the start of the first breath-holding trial, there was no EMG activity of respiratory muscles. The desire to breathe appeared some 30 s after the start of breath-holding and progressively increased until the breaking point. Coinciding with these changes in sensation, a tonic EMG activity appeared and progressively increased during breath-holding. The

<table>
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<th>Trial no.</th>
<th>1</th>
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<th>3</th>
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<tr>
<td>$V_T$ (ml)</td>
<td>700±114</td>
<td>737±138</td>
<td>730±126</td>
<td>765±109</td>
</tr>
<tr>
<td>$f$ (beats/min)</td>
<td>13.0±2.4</td>
<td>12.4±2.1</td>
<td>12.6±2.3</td>
<td>11.7±1.7*</td>
</tr>
<tr>
<td>$P_{ETCO_2}$ (mmHg)</td>
<td>39.8±2.5</td>
<td>39.9±2.6</td>
<td>39.7±2.6</td>
<td>39.9±2.2</td>
</tr>
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* $P<0.05$, compared with the values of the first trial.

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Fig. 1. Experimental records illustrating changes in the EMG activity of the respiratory muscles (EMGm) and the VAS scores. (a) The first trial of breath-holding; (b) the third trial of breath-holding. The arrows of three different shapes indicate the start of breath-holding, the onset of unpleasant sensation and the end of breath-holding, respectively.
period of no respiratory sensation in the third trial was similar to that observed in the first trial. However, the total breath-holding time was apparently longer in the third than in the first trial.

In nine of 13 subjects, the period of EMG quiescence corresponded approximately to the period of no respiratory sensation (Fig. 2). However, in four other subjects, the EMG activity of respiratory muscles was too noisy to determine the end of the EMG quiescent period accurately.

Figure 3 shows changes in the periods of no respiratory sensation and the total breath-holding times in successive trials. Although there was a large interindividual variation, in each subject the periods of no respiratory sensation were remarkably constant with successive trials whereas there was a progressive prolongation in the total breath-holding time with successive trials.

Figure 4 shows the relationship between the slope of the hypercapnic ventilatory response curve and the corresponding value of the period of no respiratory sensation and total breath-holding time obtained from all 13 subjects. There was no significant correlation between the slope of the hypercapnic ventilatory response curve and the total breath-holding time. In contrast, there was a significant correlation between the slope of the hypercapnic ventilatory response curve and the period of no respiratory sensation, indicating that the smaller the slope of hypercapnic ventilatory response, the longer the period of no respiratory sensation.

Figure 5 shows the results of the CO₂ rebreathing test and successive trials of breath-holding repeated on different days in five subjects. These results show that the observations on the first occasion are reproducible on the second occasion.

Figure 6 shows the period of no respiratory sensation obtained in eight patients with COPD. The shaded area represents the 95% confidence intervals of the period of no respiratory sensation obtained from 52 trials in 13 healthy volunteers. All patients with COPD had values for the period of no respiratory sensation below the confidence intervals.

DISCUSSION

In the present study we demonstrated that (i) there is little training effect on the period of no respiratory sensation whereas the 'training' effect plays an important role in prolongation of the total
breath-holding time, and that (ii) hypercapnic ventilatory response is inversely proportional to the period of no respiratory sensation during breath-holding.

Our observation that overall breath-holding performance was improved with successive trials is consistent with the findings of previous investigations [10–12]. In fact, Gaensler et al. [10] claimed that the 'training' effect on breath-holding time is so large that its use as a clinical test of pulmonary function should be abandoned. Although underlying mechanisms of the 'training' effect are unclear, some kind of habituation to the stresses of breath-holding has been proposed. It is conceivable that endogenous opioids may be elaborated with successive trials, most probably in response to the stress of prolonged dyspnoea. In this respect, there is some evidence to suggest that endogenous opioids are released within the central nervous system in response to stressful respiratory stimuli in awake subjects [14, 15]. However, previous studies measured opioids in different situations from those studied by us. Therefore, the simple extrapolation of those results to our observation may not be entirely valid.

The initial alveolar $PCO_2$ at the start of breath-holding is known to influence breath-holding time and the observed training effect may be attributed to a progressive decrease in the initial alveolar $PCO_2$ during successive trials. However, there was no progressive decrease in pre-breath-hold $PETCO_2$, rather it remained constant during successive trials in our study, and therefore it is unlikely that the
changes in initial alveolar $P_{CO_2}$ can account for the 'training' effect.

Mechanical factors are also known to influence breath-holding time. For example, for a given inspired gas mixture, breath-holding time is directly proportional to lung volume [16]. Although in our study breath-holding was started at end-expiration, it is possible that the later breath-holds might be made with larger lungs and thus be longer than the earlier ones. Although there might be a small difference in lung volume during breath-holding between the trials, such a small change in lung volume may be insufficient to account for the marked improvement of breath-holding performance observed during successive trials.

Breath-holding performance is also greatly influenced by non-physiological factors. The fact that the duration of the first trial of breath-holding was always shortest in each subject may be associated with the level of anxiety. Although we did not systematically evaluate the level of anxiety, most of the subjects commented after the experiment that they had felt more anxiety in the early part of the experiment.

Unlike the total breath-holding time, there is little or no prolongation of the period of no respiratory sensation with successive trials. This lack of the 'training' effect on the period of no respiratory sensation may be partly due to the absence of any stress during this period of breath-holding. Thus, it is possible that non-physiological factors may exert their influence less on the initial period of no respiratory sensation than on the later period of breath-holding with hunger for air.

Despite the known importance of $CO_2$ chemical ventilatory drive, the relationship between $CO_2$ ventilatory chemosensitivity and breath-holding performance has not been fully elucidated. Florio et al. [17] showed that $CO_2$ ventilatory chemosensitivity in professional divers is lower than that in non-divers. The studies of Schaefer [18] and Masuda et al. [19] also showed decreased ventilatory responses to hypercapnia in diving populations. However, the relationship between $CO_2$ ventilatory chemosensitivity and breath-holding time was not examined in these studies, and therefore the results of these studies cannot conclude that $CO_2$ ventilatory response determines breath-holding performance. Bjurstrom and Schoene [20] studied the relationship between breath-holding performance and ventilatory chemosensitivity to hypoxia and hypercapnia in elite synchronized swimmers and normal volunteers who served as controls. They showed that the hypoxic ventilatory response was lower in the synchronized swimmers than in the control subjects whereas the hypercapnic ventilatory response was not different between the two populations. They also showed that breath-holding time during normoxia was greater in the synchronized swimmers whereas there was no difference in hypoxic breath-holding times between the two groups, suggesting that there is an association only between hypoxic ventilatory response and breath-holding time. A similar observation has been reported recently by Feiner et al. [21] who concluded that hypoxic ventilatory response, but not hypercapnic ventilatory response, is a significant predictor of breath-holding performance.

In agreement with the results of Bjurstrom and Schoene [20] and Feiner et al. [21], in the present study we demonstrated that there is no significant correlation between breath-holding time and $CO_2$ ventilatory chemosensitivity. However, when the period of no sensation during breath-holding was analysed separately, we found that there was a significant correlation between the period of no respiratory sensation and $CO_2$ chemosensitivity.

It has been suggested that the sensation of dyspnoea is determined by the magnitude of the centrally generated respiratory motor command signal, which is dictated mainly by chemical ventilatory drive in the absence of afferent information from the lung or chest wall [22]. It seems reasonable to assume that there would be a progressive increase in the centrally generated respiratory motor command signal with a concomitant rise in chemical ventilatory drive during the period of EMG quiescence. Our finding that the period of no respiratory sensation was inversely related to hypercapnic ventilatory response suggests that the rate of rise in centrally generated respiratory command may play an important role in the genesis of unpleasant sensation during the period of EMG quiescence. A sudden onset of unpleasant sensation after a constant period of no respiratory sensation may suggest that there is a certain central threshold below which the subject feels no unpleasant sensation.

The period of no respiratory sensation during breath-holding may have some physiological and clinical implications. Normal subjects can usually talk or eat for 10–15 s without taking a breath while feeling no unpleasant sensation. This ability, we believe, is provided by the period of no respiratory sensation. Some patients with COPD experience dyspnoea with talking or eating. Our conjecture is that in these patients the period of no respiratory sensation may be remarkably shortened. In fact, the results of our pilot study in eight patients with COPD is compatible with this hypothesis. Our findings suggest that measurement of the period of no respiratory sensation may be a useful clinical test for the study of genesis of dyspnoea.

ACKNOWLEDGMENT

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No respiratory sensation during breath-holding

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