Breathing Patterns Associated with Trait Anxiety and Breathlessness in Humans

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Abstract: Idiopathic hyperventilation (IH) is a condition of uncertain aetiology characterized by sustained arterial and alveolar hypocapnia and a plethora of symptoms, the most commonly reported being shortness of breath, and breathlessness. We previously reported that anxiety increases respiratory frequency and minute ventilation with no change in metabolism in normal subjects. In this study, we compared the breathing frequency response to 5% and 7% of CO₂ gas mixtures in normal subjects (n = 13) and in subjects with IH (n = 9), taking into account anxiety and breathlessness in order to determine how breathing patterns may vary with changes in the degree of involvement of higher brain centers because of anxiety and the perception of breathlessness. CO₂ produced a significantly higher value in respiratory frequency (f) in subjects with IH. Subjects with IH also showed lower PETCO₂ than normal subjects. During the inhalation of room air, a significant correlation between f and trait anxiety scores was observed in normal subjects (r = 0.49) and IH subjects (r = 0.69). However, the IH group showed no significantly higher trait anxiety in comparison with normal subjects. There was a significant correlation between the level of perceived breathlessness and f during the inhalation of 5% and 7% CO₂, even during the inhalation of room air in IH subjects. This study suggests that an excessive increase in f in subjects with IH may be due to the interaction of two factors, trait anxiety and breathlessness. [The Japanese Journal of Physiology 54: 465–470, 2004]

Key words: idiopathic hyperventilation, breathing frequency, response to CO₂, trait anxiety, breathlessness.

It is generally agreed that a central pattern generator (CPG) for respiration exists in the lower brainstem; however, respiratory patterns in the awake state are also affected by the higher brain centers to varying degrees, dependent on the arousal level [1], the emotional state [2] and personality trait [3]. In the conscious state, carbon dioxide inhalation modifies the breathing pattern primarily by a stimulation of chemoreceptors. However, the final respiratory output results from a strong interaction between requirements from metabolism and behavior.

It is well known that the emotions of fear and anxiety generated in the limbic system cause physiological changes in heart rate, perspiration and respiration [4]. Anxiety increases respiratory frequency and minute ventilation with no change in metabolism [5].

During periods of increased anxiety there is an increase in respiratory frequency which correlates significantly with individual trait anxiety. These changes are observed especially in high trait individuals and occur with no change in V̇CO₂ or tidal volume, but with a resultant decrease in end tidal CO₂ (PETCO₂).

Recent work focusing on human brain activities has suggested that the temporal pole and the amygdala in the limbic system are activated during increased anxiety in high-trait individuals. The activation of these areas participates in the enhancement of respiratory frequency in normal subjects [6].

Idiopathic hyperventilation (IH) is a condition of uncertain aetiology that is characterized by sustained arterial and alveolar hypcapnia and a plethora of
symptoms, the most commonly reported being shortness of breath, dizziness and paraesthesia. Patients often visit chest clinics with unexplained dyspnoea but on investigation there is no evidence of organic disease. Physiological parameters measured at rest and during ramped incremental exercise testing show significantly lower \( P_{ET}CO_2 \) levels and increased respiratory frequency and minute ventilation when compared to healthy individuals [7]. Significant hypocapnia is present and studies have demonstrated increased levels of anxiety and depression.

Chemoreceptor sensitivities in subjects with IH have been tested by measuring the slope of ventilatory response to \( CO_2 \). This response has been shown to be within a normal range at rest by use of a \( CO_2 \) rebreathe test developed by Read [8]. However, the chemoreceptor threshold as assessed by the constant \( CO_2 \) inflow technique [9] was significantly lower during exercise than at rest [10]. Changes in ventilation as a result of \( CO_2 \) inhalation show various combinations of changes in tidal volume and respiratory frequency. It has been reported that the sensation of dyspnoea increases during hypercapnia [11]. Excessive cortical and subcortical involvement results in characteristic changes in these patterns of breathing which has led to studies into the relationships between anxiety levels, the sensation of breathlessness, and breathing patterns. However, these investigations have not been carried out in any detail in subjects with IH.

In this study, we compared the breathing frequency response to different \( CO_2 \) gas mixtures in normal subjects and in subjects with IH, taking into account anxiety and breathlessness in order to determine how breathing patterns may vary with changes in the degree of involvement of higher brain centers because of anxiety and the perception of breathlessness.

This study was performed in cooperation with the Department of Physiology at Showa University School of Medicine in Tokyo, Japan and the Aintree Chest Center at University Hospital Aintree in Liverpool, U.K. Hirshman and colleagues [12] have demonstrated that age is not a factor in determining hypercapnic responsiveness in normal subjects in a study population of 44 subjects (age range 21–51 years). We paid careful attention to using the same protocol and equipment; however, there might be criticism regarding the differences in race and, the distinction of sex and ages, all or any of which might affect the respiratory parameters.

In this study, we focused on comparable breathing parameters while observing \( f \) and \( P_{ET}CO_2 \), as well as psychological measurements of trait anxiety and breathlessness, and showed the breathing characteristic of subjects with IH.

**METHODS**

Thirteen normal subjects (all males; mean age 21.6 years, SD 1.13) recruited from a group of medical students from Showa University School of Medicine and nine subjects with IH (2 males, 7 females; mean age 55.6 years, SD 11) participated in this study.

The subjects with IH were recruited from respiratory clinics of the Chest Center at University Hospital Aintree with symptoms suggestive of hyperventilation. The criteria for symptoms suggestive of hyperventilation in this study included unexplained breathlessness, chest tightness with occasional tingling sensation in the fingers and toes, dizziness and dry mouth. All subjects with IH showed normal lung function tests, and cardiac and biochemical assessments. Hyperventilation was defined as \( P_{ET}CO_2 < 30 \text{mmHg} \) for > 1 min during an incremental ramp cardiopulmonary exercise test. There were no diseases of the respiratory organs in either subject.

**Procedure.** All subjects were assessed by Spielberger’s State Trait Anxiety Inventory (STAI) [13] to evaluate their state and their trait anxiety before the experiment. The STAI consists of two parts that separately measure two aspects of anxieties, the state and trait anxiety. The test comprises 20 questions and requires about 15 minutes to complete. The state anxiety scale evaluates how people feel “right now” in various situations. This scale is sometimes used to assess the level of anxiety for patients before operative procedures. The trait anxiety scale is used to evaluate how people generally feel, assessing their anxiety personality. This score is referred to as stable individual differences in trait. The state scores vary according to which situation the person is subjected to, but the trait scores are generally not influenced by specific situations.

After the STAI assessment, the subjects rested for 10 minutes to allow their adaptation to the laboratory situation. All subjects with IH provided written informed consent before participation, as approved by the Human Studies Committee of Showa University School of Medicine and South Sefton Research Ethics Committee and were informed of the two testing procedures.

**Respiratory measurement.** The subjects were seated with their eyes closed. After the adaptation period of 10 min, resting parameters were measured. The subjects breathed through a one-way valve connected to the mask/mouthpiece in order to prevent
rebreathing. They inhaled room air, 5% CO₂ and 7% CO₂ in random order on consecutive days. f and PETCO₂ were measured on a breath-by-breath basis with an aeromoniter (AE280, Minato Medical Science, Osaka, Japan) for normal subjects and with a breath-by-breath metabolic cart (Medgraphics CPX) for IH subjects. The aeromoniter consists of a microcomputer, a hot-wire flow meter, and O₂ and CO₂ analyzers. Gas was sampled by pumping through a filter into the analyzers at a rate of 220 ml/min. The system was calibrated for each study. For the breath-by-breath metabolic cart, flow was measured using bi-directional differential pressure Medgraphics pre Vent Pitot tube pneumotach [14]. Gas analyzers were a non-dispersive infrared carbon dioxide analyzer and a zirconia cell oxygen analyzer.

**CO₂ inhalation.** Steady state challenges were performed randomly in room air, 5% and 7% CO₂ to assess the response of f on consecutive days. All subjects’ f and PETCO₂ were measured during rest for three minutes and during steady state CO₂ challenges for two minutes.

On the first day, the subjects’ performed steady state CO₂ challenges on all gas concentrations in random order. On this occasion they were not informed of the contents of each bag. Before each CO₂ challenge on each gas concentration, state and trait anxiety were assessed by use of the STAI, and state anxiety was assessed post-CO₂ challenges. Perceived breathlessness levels were assessed during the inhalation of each gas by use of Visual analogue scales (VAS). On the second day, the subjects were tested under the same protocol; however, on this occasion they were informed of the gas concentration of each bag. These procedures were used to determine the effect of cognition and perception on anxiety, breathlessness and pattern of breathing.

**Psychological measurement.** During the inhalation of each bag, we asked the subjects about their breathlessness by use of a visual analogue scale (VAS). The VAS scale is a 10-cm horizontal line that indicates the maximum feeling of breathlessness on the very right side of the scale, and the feeling of no breathlessness on the very left side. The validity of measurements of dyspnea and breathlessness by use of the visual analogue scale has been confirmed by another study [15]. State anxiety levels were assessed with STAI after 2 min of inhalation in the bag; this procedure was repeated for all gas concentrations.

**Statistical analysis.** A software package (SPSS, SPSS Japan) was employed. Comparisons between normal subjects and IH during rest values in f and PETCO₂, and their trait anxiety and breathlessness were analyzed by non-parametric unpaired t-tests (Mann-Whitney Test). Data shown in Fig. 1 were analyzed with a two-way ANOVA to test for the effect of CO₂ and the effect of being a subject with IH. The slopes of the relation between f, and PETCO₂ for normal subjects and subjects with IH were compared by the analysis of covariance. A linear regression analysis was employed to calculate the correlation coefficient between f and trait anxiety (Fig. 2), between respiratory parameters and the level of breathlessness (Fig. 3), and between trait anxiety and the level of breathlessness (Fig. 4). If the calculated value of r is greater than 0.47 for normal subjects (n = 13) or 0.58 for subjects with IH (n = 9), it was considered significant (p < 0.05).

The data in Fig. 1 indicates the mean and SD for all normal subjects and those with IH. The data in Figs. 2–4 (open circles and closed circles) indicates mean values for each normal subject and IH respectively.

![Fig. 1. Comparison of respiratory frequency (f) and end tidal CO₂ (PETCO₂) responses to inspired room air, 5% CO₂ and 7% CO₂ in normal subjects (open circles) and in IH (closed circles). Significant main effect for inspired CO₂ (*p < 0.001); significant main effect of the factor that is hyperventilation (†p < 0.01).](image-url)
RESULTS

Resting State. Compared to normal subjects during the resting state, IH subjects showed high \( f \) (normal subjects, mean 14.1, SD 3.4; IH, mean 19.8, SD 6.2; \( p = 0.02 \)) and lower \( P_{\text{ET}}\text{CO}_2 \) (normal subjects, mean 39.0, SD 3.9; IH, mean 30.5, SD 5.0; \( p = 0.0008 \)).

Normal air and \( \text{CO}_2 \) inhalations with and without information of each bag. There were no differences during the two experiments (when subjects were informed or not informed about the content of the bags) in \( f \) and \( P_{\text{ET}}\text{CO}_2 \) (both variables \( p > 0.05 \)). State anxiety and VAS also showed no statistical differences between the two experiments (state anxiety and VAS; \( p > 0.05 \)).

Response to inspired room air and \( \text{CO}_2 \) in normal subjects and IH. Figure 1 shows the comparison of \( f \) and \( P_{\text{ET}}\text{CO}_2 \) responses to inspired room air, 5\% and 7\% \( \text{CO}_2 \) in normal subjects and IH subjects. \( \text{CO}_2 \) inhalation had no significant main effect on \( f \) (\( p = 0.548 \)). No interaction in \( f \) indicates that the lines for the two groups were parallel; \( \text{CO}_2 \) had a comparable effect on \( f \) in both groups. However, there were significantly higher values in \( f \) (\( p < 0.001 \)) in the IH group compared to normal subjects. \( P_{\text{ET}}\text{CO}_2 \) significantly increased with increased inhaled \( \text{CO}_2 \) in both groups (\( p < 0.001 \)), but the value of \( P_{\text{ET}}\text{CO}_2 \) in IH was significantly lower than normal subjects at all time points (\( p = 0.008 \)). The slopes of \( f \) and \( P_{\text{ET}}\text{CO}_2 \) in subjects with IH were significantly different from the normal subjects.

Correlation between \( f \) and trait anxiety scores during inhalation of room air. There was no significant difference of trait anxiety between normal subjects and the IH group (normal subjects, mean 38.2, SD 7.8; IH subjects, mean 35.5, SD 14.6; \( p = 0.24 \)).

Figure 2 shows the correlation between respiratory variables and trait anxiety scores during inhalation of room air. Each point indicates each subject’s mean (closed = subjects with IH, open = normal subjects); the two linear regression lines were superimposed. A significant correlation between \( f \) and trait anxiety scores during the inhalation of room air was observed in normal subjects (\( r = 0.49 \)) and IH subjects (\( r = 0.69 \)).

\[ r = 0.69^* \]
\[ r = 0.49^* \]
There was no significant difference of breathlessness during the inhalation of room air between normal subjects and subjects with IH (normal subjects, mean 2.2, SE 0.2, \( p = 0.55 \)), however, IH group had a significantly higher breathlessness during the inhalation of 5% and 7% CO\(_2\) compared with normal subjects (5% CO\(_2\); normal subjects, mean 3.7, SE 0.5, IH subjects, mean 4.5, SE 0.6; \( p = 0.05 \), 7% CO\(_2\); normal subjects, mean 3.9, SE 0.7, IH subjects, mean 5, SE 0.62; \( p < 0.05 \)). Figure 3 indicates a relationship between breathlessness (VAS) and \( f \) during the inhalation of room air, 5% and 7% CO\(_2\) in normal subjects (left panel) and IH subjects (right panel). In normal subjects, there was no relationship between \( f \) and breathlessness. In the IH group, there was a correlation between \( f \) and the level of breathlessness during the inhalation of room air (\( r = 0.61 \), 5% CO\(_2\) \( r = 0.59 \) and 7% CO\(_2\) \( r = 0.67 \)). There was also a correlation between trait anxiety score and breathlessness in the IH group (room air; \( r = 0.69 \), 5% CO\(_2\); 0.72, 7% CO\(_2\); 0.76). These correlations were not observed in normal subjects (room air; \( r = 0.01 \), 5% CO\(_2\); \( r = 0.46 \), 7% CO\(_2\); \( r = 0.12 \)).

**DISCUSSION**

The purpose of this study was to address the mechanism causing the excessive increase in ventilation and respiratory frequency in idiopathic hyperventilation by observing comparable respiratory parameters \( f \) and P\(_{ETCO_2}\), trait anxiety, and the perception of breathlessness.

Disregarding individual anxiety levels, the lines for \( f \) responding to different CO\(_2\) levels in both groups were parallel; these variables in the IH group were significantly high.

Previous studies have reported that high trait anxiety is observed in individuals who have a high respiratory frequency during stressful tasks [3, 5]. It was inferred from psychological symptoms of subjects with IH that the subjects would have high trait anxiety; that might increase their ventilation which may be mediated by frequency. As shown in Fig. 2, the IH group did not show significantly higher trait anxiety compared with normal subjects. Subjects with IH ranged from low to high scores, as did normal subjects. However, the subjects with IH showed a higher line for \( f \) at the same level of trait anxiety as the normal group. High trait anxiety might be one factor that contributes to an increase of \( f \) in subjects with IH; however, this increased \( f \) observed in the IH group is not only due to trait anxiety.

As seen in Fig. 3, there was a strong correlation between \( f \) and the level of breathlessness during inspired CO\(_2\) in IH subjects, even during the inhalation of room air. This suggests that a change in perception of breathlessness might be a contributory factor to a continuing increase in \( f \). Furthermore, a correlation between trait anxiety scores and levels of breathlessness were observed in IH subjects (Fig. 4), which was not observed in normal subjects.

Dyspnea/breathlessness is caused by multiple factors, such as inputs from chemoreceptors, from mechanoreceptors of the airway or respiratory muscles, and from central commands from voluntary or involuntary centers. Breathlessness and chest tightness are commonly reported in IH subjects as well as psychological symptoms such as anxiety and depression.

Homma et al. [16] showed that vibration applied to the intercostal muscle causes a tonic vibration reflex in the muscles and chest wall tightness. There is no direct evidence that the chest wall tightness commonly observed in subjects with IH is induced by the activation of muscle afferents or gamma motor activity. However, there is evidence to suggest that out-of-phase vibration induces breathlessness in normal subjects [17] and in patients with COPD. On the contrary, in-phase vibration decreases dyspnea [18].
Stress and anxiety have their effect on muscle tone by increased gamma-motor input on the muscle spindle and the increased intercostal muscle activity may be perceived as dyspnea [19].

Chest wall tightness might be one factor that causes breathlessness in subjects with IH. In our results, the mechanism of the increase of f in subjects with IH may involve multiple factors that include trait anxiety, breathlessness and chest wall tightness. These factors are interconnected and cannot be explained by single factor.

REFERENCES