Orthostatic increase of respiratory gas exchange in hyperventilation syndrome

L Pekka Malmberg, Klaus Tamminen, Anssi R A Sovijärvi

Abstract

Background—Hyperventilation syndrome (HVS) is a common disorder which is difficult to diagnose because of somatic symptoms and its episodic nature. In previous studies respiratory alkalosis in arterial blood was often found during orthostatic tests in patients with HVS. The purpose of this study was to assess these orthostatic changes by non-invasive pulmonary gas exchange measurements and to evaluate whether these responses discriminate patients with HVS from healthy subjects.

Methods—Respiratory gases were collected with a face mask and pulmonary gas exchange was measured after 10 minutes at rest and after eight minutes standing upright in 16 patients with HVS and 13 healthy control subjects. In patients with HVS arterial blood samples were also drawn at rest and in the standing position.

Results—At rest the variables of respiratory gas exchange did not differ significantly between the groups. As a response to standing, minute ventilation increased in both study groups but significantly more in the patients with HVS (mean difference 5.4 l/min (95% CI 1.1 to 9.6)). The changes in end tidal CO2 fraction (FETCO2) and in ventilatory equivalents for oxygen (Ve/Vo2) and for CO2 (Ve/VcO2) during the orthostatic test were also significantly larger in patients with HVS than in healthy controls. During standing FETCO2 was significantly lower (mean difference –1.1 kPa; 95% CI –1.5 to –0.6) and Ve/Vo2 (mean difference 18.4; 95% CI 7.7 to 29.0) and Ve/VcO2 (mean difference 11.7; 95% CI 4.8 to 18.6) were significantly higher in HVS patients than in healthy controls. By using the cut off level of 4% for FETCO2, the sensitivity and specificity of the test to discriminate HVS were 87% and 77%, respectively, and by using the cut off level of 37 for Ve/Vo2 they were 93% and 100%, respectively. In the HVS patients arterial Pco2 and FETCO2 were closely correlated during the orthostatic test (r = 0.93, p<0.0001).

Conclusions—As a response to change in body position from supine to standing, patients with HVS have an accentuated increase in ventilation which distinguishes them from healthy subjects. These findings suggest that non-invasive measurements of pulmonary gas exchange during orthostatic tests are useful in the clinical evaluation of patients with hyperventilation disorders.

Keywords: hyperventilation syndrome; diagnosis; ventilatory gas exchange; orthostatic test; blood gas analysis

Hyperventilation is defined as a state of alveolar ventilation in excess of metabolic requirements resulting in decreased arterial partial pressure of carbon dioxide (PaCO2). When hyperventilation occurs chronically or in recurrent episodes and is associated with somatic (respiratory, neurological, intestinal) or psychological (anxiety) symptoms, the clinical entity is called hyperventilation syndrome (HVS).1 HVS and panic disorder are strongly associated; most patients show characteristics of both disorders, but they generally lack findings of any underlying organic disease.2 3

The correct diagnosis of HVS is of great clinical importance since at least 5–10% of general medical outpatients have been reported to suffer from this syndrome and, due to a variety of somatic symptoms, the risks of misdiagnosis are considered to be high.4 Several diagnostic tools have been described since only few patients with HVS are actually seen during a typical attack. The reproduction of the HVS symptoms during voluntary hyperventilation has been suggested as a basis for the diagnosis,5 but recent studies have shown that the test lacks both sensitivity and specificity.6 Even the validity of the test has been questioned, since the symptoms in HVS often precede events of hypocapnia rather than are a consequence of them.7

Symptoms and hyperventilation may also be provoked in susceptible patients by exercise,8-10 mental stress,9 and by pharmacological challenges.11 12 In our earlier studies respiratory alkalosis in arterial blood was frequently found during orthostatic tests in patients with HVS,8 suggesting that change in body posture provokes these patients to have abnormal ventilatory responses.

The aim of the present study was to assess the ventilatory responses of patients with HVS when changing the body position from supine to standing. We also compared these results with those of healthy subjects to evaluate whether the orthostatic changes in pulmonary gas exchange discriminate patients with HVS.

Methods

The anthropometric and lung function data of the patients and subjects are shown in table 1. Sixteen patients (eight women) with diagnosed HVS, but without signs of underlying cardio-
respiratory disease, were selected for the study. The basis for the HVS diagnosis was the history of recurrent or episodic dyspnoea, air hunger, dizziness, or paraesthesiae, and the detection of respiratory alkalosis (pH >7.45 and PaCO₂ <4.7 kPa) in arterial blood during symptoms of hyperventilation. Patients with a history of physician diagnosed asthma or ischaemic heart disease, with or without regular medication, were excluded from the study. None of the patients included used any anxiolytic medication. All patients underwent physical examination, chest radiography, spirometric tests.

Cardiopulmonary exercise tests with ECG to exclude any organic cardiorespiratory disease. Bronchial hyperreactivity with histamine provocation tests were performed in a quiet, dimly lit laboratory room during office hours. Before orthostatic testing the brachial artery of the patient was cannulated under local anaesthesia (1% lidocaine). Thereafter, two nurses conducted the test and recordings. After the patient had rested for 10 minutes in the supine position a face mask (Rudolf series 7910, Hans Rudolf Inc, Kansas City, USA) was tightly attached and connected to an automatic gas exchange analyser with a mixing chamber (Ergo-Oxy screening, Erich Jaeger, Würzburg, Germany). The mask and the valve system had a dead space of 185 ml.

The patients were allowed to breathe via the mask in the supine position for five minutes to adapt for the increased dead space; minute ventilation (Ve), breathing frequency (BF), oxygen consumption (Vo₂), and arterial blood samples were taken. During this phase the room was kept quiet and no conversation was allowed. Respiratory gas exchange and ECG (HR) were continuously monitored and, after standing for eight minutes, the blood pressure (BP) were also recorded at this stage.

After the orthostatic test the patients were asked to rise and to stand still and unsupported in the upright body position for eight minutes. During this phase the room was kept quiet and no conversation was allowed. Respiratory gas exchange and ECG (HR) were continuously monitored and, after standing for eight minutes, the blood pressure (BP) were also recorded at this stage.

In paired comparisons of test results between body positions the Wilcoxon signed rank test was used, and in comparisons between study groups the Mann-Whitney U test was applied. For correlation analysis the Pearson correlation coefficient was calculated.

Results

The orthostatic tolerance tests were performed in a quiet, dimly lit laboratory room during office hours. Before orthostatic testing the brachial artery of the patient was cannulated under local anaesthesia (1% lidocaine). Thereafter, two nurses conducted the test and recordings. After the patient had rested for 10 minutes in the supine position a face mask (Rudolf series 7910, Hans Rudolf Inc, Kansas City, USA) was tightly attached and connected to an automatic gas exchange analyser with a mixing chamber (Ergo-Oxy screening, Erich Jaeger, Würzburg, Germany). The mask and the valve system had a dead space of 185 ml.

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Results

The results of pulmonary gas exchange at rest and during the orthostatic test in healthy subjects and in patients with HVS are shown in table 2. The individual responses of Ve, Ve/Vo₂, Ve/VCO₂, and FETCO₂ during the orthostatic test are illustrated in figs 1, 2, 3 and 4, respectively. The resting values were not significantly different between the groups. In both groups the mean FETCO₂ was within the normal range but in individual patients and subjects the FETCO₂ at rest was slightly low. During the orthostatic test the controls did not show an increase in BF but their Ve increased significantly (p = 0.01). In the HVS patients both BF (p = 0.005) and Ve (p = 0.001) increased sig-
nificantly. RQ did not change markedly in either of the groups, but the patients with HVS had significantly higher values at the standing phase. $FETCO_2$ did not change significantly in healthy subjects but decreased in all the patients with HVS ($p = 0.0004$). While standing $FETCO_2$ was significantly lower in patients with HVS than in controls (mean difference $–1.1$ kPa; $95\%$ CI $–1.5$ to $–0.6$). As a response to standing up, $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ increased significantly in both groups. This change was, however, significantly larger in the patients with HVS than in the healthy subjects (mean difference $13.0$ (95\% CI $5.2$ to $20.8$) for $\dot{V}E/\dot{V}O_2$, and mean difference $9.0$ (95\% CI $2.8$ to $15.2$) for $\dot{V}E/\dot{V}CO_2$).

The sensitivity, specificity, and positive predictivity of respiratory gas exchange variables during the orthostatic tolerance test for discrimination of HVS were evaluated (table)

**Table 2 Respiratory gas exchange and circulatory responses during orthostatic tolerance test at rest and after 8 minutes standing in healthy controls and in patients with HVS**

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 13)</th>
<th>HVS patients (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At rest</td>
<td>Standing</td>
</tr>
<tr>
<td>BF (/min)</td>
<td>14.5 (0.8)</td>
<td>14.9 (0.9)</td>
</tr>
<tr>
<td>$\dot{V}E$ (/min)</td>
<td>8.1 (0.6)</td>
<td>9.3 (0.6)</td>
</tr>
<tr>
<td>RQ</td>
<td>0.79 (0.03)</td>
<td>0.77 (0.02)</td>
</tr>
<tr>
<td>$FETCO_2$ (%)</td>
<td>4.27 (0.12)</td>
<td>4.18 (0.08)</td>
</tr>
<tr>
<td>$\dot{V}E/\dot{V}O_2$</td>
<td>31.0 (1.2)</td>
<td>32.2 (1.0)</td>
</tr>
<tr>
<td>$\dot{V}E/\dot{V}CO_2$</td>
<td>39.2 (1.7)</td>
<td>41.8 (1.3)</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>65.0 (1.8)</td>
<td>77.1 (2.9)</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>122 (4.2)</td>
<td>125 (3.9)</td>
</tr>
</tbody>
</table>

*p<0.05; **p<0.01; ***p<0.001 compared with controls (Mann-Whitney U test).

The results within groups are expressed as mean (SE) and the changes as mean (95\% confidence intervals). BF = breathing frequency; $\dot{V}E$ = minute ventilation; RQ = respiratory exchange ratio; $FETCO_2$ = end expiratory tidal CO$_2$ fraction; $\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$ = ventilatory equivalents for O$_2$ and CO$_2$; HR = heart rate; BP = blood pressure.

Figure 1 Individual responses of minute ventilation ($\dot{V}E$) during the orthostatic test in (A) healthy controls (n = 13) and (B) patients with HVS (n = 16). The p value refers to the Wilcoxon signed rank test.

Figure 2 Individual responses of the ventilatory equivalent for oxygen ($\dot{V}E/\dot{V}O_2$) during the orthostatic test in (A) healthy controls (n = 13) and (B) patients with HVS (n = 16). The p value refers to the Wilcoxon signed rank test.
3). Depending on the variable chosen, the sensitivity ranged from 69% to 93% and the specificity from 77% to 100%.

**ARTERIAL BLOOD GAS RESPONSES**

Fourteen patients with HVS (87%) had hypocapnia (PaCO₂ < 4.7 kPa) with or without respiratory alkalosis (pH > 7.45) in the arterial blood while standing during the orthostatic test, indicating hyperventilation. As a response to the orthostatic test mean (SE) PaCO₂ decreased from 4.6 (0.1) kPa to 3.7 (0.2) kPa (p = 0.0006) and pH increased from 7.45 (0.01) to 7.50 (0.01) (p = 0.001).

In the patients with HVS the FETCO₂ during the standing phase correlated closely with the simultaneous PaCO₂ (r = 0.93, p<0.0001; fig 5); there was also a close relationship between arterial blood pH and VE/VCO₂ (r = 0.78, p = 0.0004).

**CIRCULATORY RESPONSES**

HR was significantly higher in the HVS group than in healthy controls both at rest (mean difference 7.9 bpm, 95% CI 1.6 to 14.2) and in the standing position (mean difference 16.4 bpm, 95% CI 4.8 to 27.9). The increase in HR as a response to standing up was also

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**Table 3** Sensitivity, specificity, and positive predictivity of respiratory gas exchange results (the values while standing and the change from supine to standing) during the orthostatic tolerance test for the diagnosis of HVS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cut off level</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FETCO₂ &lt; 4%</td>
<td></td>
<td>87</td>
<td>77</td>
<td>82</td>
</tr>
<tr>
<td>ΔFETCO₂ &lt; 0.5%</td>
<td></td>
<td>81</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>VE/VCO₂ &gt; 37</td>
<td></td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ΔVE/VCO₂ &gt; 5</td>
<td></td>
<td>75</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>VE/VCO₂ &gt; 47</td>
<td></td>
<td>69</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>ΔVE/VCO₂ &gt; 5</td>
<td></td>
<td>69</td>
<td>92</td>
<td>92</td>
</tr>
</tbody>
</table>

FETCO₂ = end expiratory tidal CO₂ fraction; VE/VCO₂ = ventilatory equivalents for O₂ and CO₂; sensitivity = true positives/(true positives + false negatives)%; specificity = true negatives/(true negatives + false positives)%; positive predictivity = true positives/(true positives + false positives)%.

Estimates are based on test result distributions of patients with HVS (n = 16) and healthy controls (n = 13).
significantly larger in patients with HVS (p = 0.04; table 2). The individual HR responses are illustrated in fig 6. At rest the systolic BP was slightly higher (mean difference 12.5 mm Hg; 95% CI 0.3 to 24.7 mm Hg) in the patients with HVS than in healthy controls, but the changes in BP from the supine to standing position did not differ between the groups (table 2).

SYMPTOMS DURING THE TEST
After the orthostatic tests the subjects and patients were asked for symptoms during the test. In the HVS group nine (56%) complained of dyspnoea, six (38%) of dizziness, three (19%) of numbness of the fingers or face, two (13%) of trembling, and one (6%) of sweating. In the healthy controls three (23%) reported dizziness but none complained of dyspnoea.

Discussion
This study shows that the change in body posture during the orthostatic test significantly increases pulmonary ventilation in excess of metabolic needs in many patients with HVS. Most of the patients with HVS showed an accentuated ventilatory response which distinguishes them from healthy controls. In HVS patients the consequent respiratory alkalosis or hypocapnia in arterial blood was closely associated with changes in non-invasive pulmonary gas exchange measurements.

In our patients with an established diagnosis of HVS organic cardiorespiratory diseases were excluded to assure that, when present, the hyperventilation was not secondary to any other disease. The gas exchange and circulatory responses were not modified by any medication since the patients were not receiving any drug treatment. The healthy controls were free of cardiorespiratory symptoms and diseases and their anthropometric data did not differ significantly from the HVS patients except for body mass index. The latter is unlikely to explain the different respiratory gas exchange patterns between the groups, since obesity is not known to induce hyperventilation. The study design was not completely identical between the groups as only patients with HVS had an arterial indwelling line placed under local anaesthesia before the test. However, the gas exchange variables at rest (after 15 minutes from arterial cannulation) did not differ between the groups, and therefore the significantly different responses during the orthostatic test are unlikely to result from this intervention.

At rest in both groups some subjects showed somewhat low \( F_{ETCO_2} \) values (fig 4) but the mean values were within normal limits (table 2). In patients with HVS the correlation between \( PaCO_2 \) and \( FETCO_2 \) was good and the calculated mean arterial end tidal difference in \( CO_2 \) at rest was 0.3 kPa which is close to the expected value \( 17 \); we therefore think that our end tidal measurements were reliable. Due to ethical reasons we did not sample arterial blood from the healthy controls but, based on the end tidal measurements, it is probable that in some of the subjects the test conditions induced slight hyperventilation. Since the control subjects were healthy and did not have any history of respiratory symptoms, we regard their results as a normal range of ventilation during the conditions of the present study. More importantly, the ventilatory responses during standing and not the baseline values were discriminatory between our study groups.

Figure 5 Relationship between arterial partial pressure of \( CO_2 \) and end expiratory tidal \( CO_2 \) fraction (\( FETCO_2 \)) in the patients with HVS (\( n = 16 \)) during the orthostatic test in the standing position.

\[
\begin{align*}
\text{PaCO}_2 (\text{kPa}) & \quad 2 \quad 3 \quad 4 \quad 5 \\
F_{ETCO_2} (\%) & \quad n = 16 \\
r & = 0.93 \\
p & < 0.001
\end{align*}
\]

Figure 6 Individual responses of heart rate (HR) during the orthostatic test in (A) healthy controls (\( n = 13 \)) and (B) patients with HVS (\( n = 16 \)). The \( p \) value refers to the Wilcoxon signed rank test.
The reproduction of the symptoms when the subject is instructed to hyperventilate voluntarily has been earlier considered as a cornerstone of the diagnosis of HVS. However, recent studies have shown that the test lacks both sensitivity and specificity. Gardner et al found in their series that six of 17 patients with HVS (35%) failed to satisfy the diagnostic criteria in the voluntary hyperventilation test. By using several criteria Vansteenkiste et al found concordances of 26–86% between a positive questionnaire score and the voluntary hyperventilation test. In the study by Hornsveld et al only 34% of the 85 patients thought by the hyperventilation test to have HVS were considered as true positives and 66% as false positives. In the latter study even the validity of the test was questioned, since the symptoms in HVS were often found to precede events of hypocapnia rather than being the consequence of them. It therefore seems that the voluntary hyperventilation test cannot serve as a gold standard in identifying patients with HVS.

Presenting symptoms in panic disorder and HVS share many similarities so questionnaires have been designed to identify these patients. We did not use standard questionnaires as earlier studies have suggested that the specificity and sensitivity of symptoms alone in diagnosing hyperventilation syndrome is poor. We agree with Cowley and Roy-Byrne and with Gardner that the hyperventilation syndrome probably has a more heterogeneous aetiology than panic disorder. This view is also in agreement with the history reported by our patients with HVS since not all reported symptoms suggestive of panic disorder.

Hyperventilation may also be provoked in susceptible patients by exercise, mental stress, and by pharmacological challenges. The orthostatic tolerance test as a provoking stimulus in HVS was originally described in 1981 by Sovijärvi et al who found respiratory alkalosis in arterial blood gas samples at the standing phase of the test in many patients with HVS. This suggested accentuated orthostatic ventilatory responses.

In the present study we cannot offer definite answers about the mechanisms of the observed orthostatic changes in pulmonary gas exchange in patients with HVS. In our method the added dead space due to the face mask probably also contributed to the increased ventilation. However, the dead space was small and the patients and subjects were allowed to adapt to the mask before resting values were recorded. We therefore believe that the changes in ventilation during the orthostatic test were due to the change in body posture alone. The patients with HVS were not chronically dyspnoeic, nor did they suffer from any cardiorespiratory diseases that would explain them becoming dyspnoeic while standing up. In most, but not all, patients the hyperventilation was associated with dyspnoea while standing. This suggests that other symptoms or mechanisms may also be responsible for the abnormal orthostatic ventilatory responses.

Change in posture from supine to standing has a stimulating effect on the respiratory drive, probably evoked by baroreceptor dis-
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