Effects of hyperventilation on the inspiratory to end-tidal oxygen difference

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SUMMARY

We assessed the inspiratory to end-tidal oxygen difference \( (P_{\text{lo}} - P_{\text{ET}}) \) during voluntary hyperventilation in 10 healthy male volunteers. The oxygen difference was measured with a fast-response paramagnetic differential oxygen sensor. As simultaneous changes in metabolism and cardiac output also influence \( (P_{\text{lo}} - P_{\text{ET}}) \), oxygen uptake was measured with indirect calorimetry and non-invasive transthoracic electrical bioimpedance was used for measurement of cardiac output. After a rest period, subjects were instructed to double their minute ventilation volume \( (VE) \) and after 5 min triple their resting \( VE \) for another 5 min. \( (P_{\text{lo}} - P_{\text{ET}}) \) decreased from a zero value of 6.4 kPa to 3.9 kPa at 5 min \( (P < 0.01) \) and 2.9 kPa at 10 min \( (P < 0.01) \). At 15 min \( (i.e. 5 \text{ min after the end of hyperventilation}) \) there was an increase in \( (P_{\text{lo}} - P_{\text{ET}}) \) to 8.3 kPa \( (P < 0.05) \). Regression analysis between \( (P_{\text{lo}} - P_{\text{ET}}) \) and \( VE \) \( (\text{litr} \text{e} \text{m}^{-2} \text{min}^{-1}) \) gave the formula: \( (P_{\text{lo}} - P_{\text{ET}}) = 1/ \left( 0.053 + 0.034VE \right) \), \( r = -0.92 \), \( n = 158 \). Oxygen uptake and cardiac output did not change significantly during hyperventilation, but decreased in the post-hyperventilation period. An oxygen difference of more than 8 kPa was associated with significant arterial desaturation. (Br. J. Anaeth. 1994; 73: 140-144)

KEY WORDS

Oxygen uptake. Oxygen inspired concentration. Ventilation: hyperventilation

During the past few years, fast-response oximetry has been introduced into clinical practice in anaesthesia and intensive care. Breath-by-breath analysis of oxygen concentration is available with display of inspiratory oxygen concentration, end-tidal concentration and the inspiratory to end-tidal oxygen concentration difference \( (P_{\text{lo}} - P_{\text{ET}}) \) \([1, 2]\). Few studies have been designed specifically to evaluate changes in \( (P_{\text{lo}} - P_{\text{ET}}) \). In animal experiments, an increasing difference between inspiratory and end-tidal oxygen concentrations was the most sensitive indicator of hyperventilation and exceeded the sensitivity of end-tidal carbon dioxide concentration \([3]\). This finding has been confirmed in clinical anaesthesia \([4]\). However, little is known about the effects of hyperventilation or the quantitative implic-
carbon dioxide gas fractions in inspired and mixed expired gas [5]. All gas exchange results are expressed in STPD, except for $V_E$ which is expressed in BTPS. The expired carbon dioxide fraction was measured with an infrared carbon dioxide sensor. The difference between inspired and expired oxygen fractions was measured with a fast-response paramagnetic differential oxygen sensor [1]. As the expiratory volumes were not displayed by the Deltatrac, an Ohmeda 5420 volume monitor (Ohmeda, BOC Health Care Division) was used to guide the subjects during the hyperventilation period. This monitor has a turbine vane transducer sensor with a stated accuracy of ±8%.

Inspiratory oxygen, $(P_{1O_2} - P_{E'CO_2})$, end-tidal oxygen $(P_{E'CO_2})$, end-tidal carbon dioxide $(P_{E'CO_2})$ and ventilation frequency were measured at the mouth piece with a side stream analyser (Capnomac Ultima, Datex Instrumentarium OY, Helsinki, Finland). The Capnomac Ultima measures oxygen by a paramagnetic method. The 10–90% response time is 150 ms with a non-linearity error of less than ±1% [2]. $P_{E'CO_2}$ was measured by infrared absorption.

A Datex Cardiocap was used for measurement of oxygen saturation $(SPO_2)$ by pulse oximetry. Non-invasive transthoracic electrical bioimpedance cardiac output measurements were obtained using the NCCOM3-R7 (BoMed Medical Manufacturing Ltd, Irvine, CA, USA) [7, 8].

Transcutaneous oxygen tension $(P_{TCO_2})$ and carbon dioxide tension $(P_{TCO_2})$ were measured with a Radiometer TCM3 (Radiometer A/S, Copenhagen, Denmark), the probe set on the right side of the chest.

The Deltatrac and Capnomac Ultima analysers were calibrated with calibration gas containing 5.0% carbon dioxide and 95% oxygen, and 3.0% carbon dioxide and 31% oxygen, respectively. Both these analysers use autocalibration with room air.

A standardized sequence of measurements was used for all subjects who were in the supine position. After a rest period, indicated by stable $P_{E'CO_2}$, they were instructed to double their $V_E$ as displayed by the Ohmeda 5420 volume monitor. Five minutes after the start of this hyperventilation, the subject was instructed to triple the original $V_E$ value. This period lasted for another 5 min. Thereafter the subjects breathed as desired during another 5-min period.

Atmospheric pressure was 103.2–103.7 kPa during the study. Thus oxygen 10 kPa is equivalent to 9.7 vol%.

**Statistics**

Statistical significance was tested with repeated measures ANOVA and, where indicated, followed by the Wilcoxon signed rank test for comparisons between the zero value and the 5-, 10- and 15-min values. For comparison between subgroups of $(P_{1O_2} - P_{E'CO_2})$ and $SPO_2$, we used a one-way ANOVA and Bonferroni’s test for multiple comparisons. Simple regression analysis was used when appropriate. Statistical significance was assumed for values of $P < 0.05$.

**RESULTS**

From a mean value at rest of 3.3 litre m$^{-2}$ min$^{-1}$, $V_E$ increased to 6.4 litre m$^{-2}$ min$^{-1}$ at 5 min ($P < 0.01$) and to 8.4 litre m$^{-2}$ min$^{-1}$ at 10 min ($P < 0.01$) (table I, fig. 1). In the post-hyperventilation period, $V_E$ decreased to a minimum of 2.3 litre m$^{-2}$ min$^{-1}$ at 13 min to reach 2.5 litre m$^{-2}$ min$^{-1}$ at 15 min ($P < 0.01$) (i.e. 5 min after hyperventilation was discontinued). Ventilatory frequency increased from 7.8 b.p.m. at rest to 9.7 b.p.m. at 5 min ($P < 0.05$) and to 11.9 b.p.m. at 10 min ($P < 0.05$).

$(P_{1O_2} - P_{E'CO_2})$ decreased from a zero value of 6.4 kPa to 3.9 kPa at 5 min ($P < 0.01$) and to 2.9 kPa at 10 min ($P < 0.01$) (fig. 1). At 15 min, there was an increase in $(P_{1O_2} - P_{E'CO_2})$ to 8.3 kPa ($P < 0.05$). Regression analysis between $(P_{1O_2} - P_{E'CO_2})$ (kPa) and $V_E$ (litre m$^{-2}$ min$^{-1}$) gave the formula (fig. 2):

$$\left(P_{TCO_2} - P_{E'CO_2}\right) = \frac{1}{(0.059 + 0.034V_E)}$$

($r = -0.92, n = 158$).

$P_{E'CO_2}$ decreased from 6.0 to 4.5 kPa at 5 min ($P < 0.01$), to 3.6 kPa at 10 min ($P < 0.01$) and to 5.3 kPa at 15 min ($P < 0.01$).

Mean $V_O_2$ was 126 ml m$^{-2}$ min$^{-1}$ and cardiac index was 3.8 litre m$^{-2}$ min$^{-1}$ at rest. There were no statistically significant changes at 5 min or at 10 min in either of these variables (table I). At 15 min, $V_O_2$ had decreased to 108 ml m$^{-2}$ min$^{-1}$ ($P < 0.05$) and cardiac index to 3.2 litre m$^{-2}$ min$^{-1}$ ($P < 0.05$).

$SPO_2$, measured by pulse oximetry, increased from a resting value of 96.3% to 97.2% at 5 min ($P < 0.05$) and to 97.6% at 10 min ($P < 0.01$) (fig. 3). Three minutes after hyperventilation was discon-
Hyperventilation continued, $S_{\text{PO}_2}$ reached its lowest value of 92.9% ($P < 0.05$). There were significant decreases in $S_{\text{PO}_2}$ when comparing a $(P_{\text{O}_2} - P_{\text{E}_2})$ value of 6–8 kPa with 8–10 kPa ($P < 0.05$) and between 8–10 kPa and >10 kPa ($P < 0.001$) (fig. 4).

$P_{\text{TCO}_2}$ increased from 11.1 kPa at rest to 13.0 kPa at 5 min ($P < 0.01$) and to 13.3 kPa at 10 min ($P < 0.01$). At 15 min, $P_{\text{TCO}_2}$ had decreased to 8.5 kPa ($P < 0.01$). Linear regression analysis between $(P_{\text{O}_2} - P_{\text{E}_2})$ and $P_{\text{TCO}_2}$ gave the formula:

$$P_{\text{TCO}_2} (kPa) = -0.94 (P_{\text{O}_2} - P_{\text{E}_2}) (kPa) + 16.4,$$

$$r = -0.81, n = 160)$$

When calculating alveolar ventilation ($V_A$) (ml m$^{-2}$ min$^{-1}$), there was a close relation between $V_A$ calculated from carbon dioxide ($V_A = 0.863 V_{\text{CO}_2}/P_{\text{T}_2}$) and $V_A$ calculated from oxygen ($V_A = \ldots$)
0.863 \( \dot{V}O_2 / (F_iO_2 - P_{\text{E}O_2}) \). Linear regression gave the formula:

\[
\dot{V}A (\text{from } O_2) = -0.18 + 0.98 \dot{V}A (\text{from } CO_2),
\]

\( r = 0.88, n = 158 \)

The \( \dot{V}p/\dot{V}t \) quotient diminished from 0.28 at 0 min to 0.23 at 5 min \( (P < 0.05) \), to 0.20 at 10 min \( (P < 0.05) \) and then increased to 0.36 at 15 min \( (P < 0.01) \).

The respiratory exchange ratio changed from a resting value of 0.90 to 1.34 at 5 min \( (P < 0.01) \), to 1.47 at 10 min \( (P < 0.01) \) and then to 0.63 at 15 min \( (P < 0.01) \).

**DISCUSSION**

This investigation was designed to study the effects of ventilation on \( (P_{iO_2} - P_{\text{E}O_2}) \) (henceforth termed "oxygen difference"), without simultaneous changes in other variables of importance, such as metabolism or cardiac output. As hypventilation is difficult to study in unanesthetized volunteers, we chose to evaluate the effect of hypventilation and the effect of hypventilation during the post-hypventilation period. We found small effects on \( \dot{V}O_2 \) and cardiac output. These variables did not change significantly during hypventilation, but decreased in the post-hypventilation period. During hypventilation, we measured a slight increase in \( \dot{V}O_2 \), probably reflecting increased haemoglobin \( SpO_2 \), and increased \( P_{tcO_2} \) that is more of an increase in oxygen uptake than increased consumption. Part of the increase in \( \dot{V}O_2 \) could also be explained by oxygen consumption in respiratory work. The oxygen cost of breathing at rest is only 0.5-1 ml litre\(^{-1}\) ventilatory volume \[9\], but increases to about 4 ml litre\(^{-1}\) \( \dot{V}E \) during high levels of ventilation \[10\]. The measured decrease in \( \dot{V}O_2 \) after hypventilation is probably explained best by small ventilation volumes and represents decreased oxygen uptake but as we also found marked haemoglobin desaturation; oxygen uptake does not represent oxygen consumption in this case. During hyper- and hypventilation, the body stores of oxygen (i.e. in blood, body water and in FRC) are changed and measured \( \dot{V}O_2 \) represents oxygen uptake and not oxygen consumption until we reach a new steady state.

The oxygen difference was related inversely to \( \dot{V}E \). The relationship could be quantified in a simple formula. A 50 % decrease in \( \dot{V}E \) corresponded to about a 50 % increase in oxygen difference. Thus the smaller the \( \dot{V}E \) value, the larger the effect of a 1-litre change in ventilatory volumes on the oxygen difference.

The response in the oxygen difference during changes in ventilation was more prompt than that of \( P_{\text{E}CO_2} \). An advantage of the oxygen difference in monitoring compared with \( P_{\text{E}CO_2} \) is the greater response to increases or decreases in respiratory gas exchange. This is probably explained best by the large difference in body stores of the two gases. Approximately 120 litre of carbon dioxide is stored in the body under normal atmospheric pressure, to a great extent in bone as carbonate not immediately available to the body, but also dissolved in tissue and chemically bound as bicarbonate \[11\]. The easily accessible part of carbon dioxide accounts for about 15-20 litre compared with about 1 litre of oxygen. Thus a change in ventilation rapidly affects body oxygen status while it takes more time to achieve a new steady state for carbon dioxide. During hypventilation, the relative change in oxygen difference was also larger than that of \( P_{\text{E}CO_2} \). A steady state in oxygen homeostasis is reached after a short period of hypventilation. In contrast, increased carbon dioxide elimination during hypventilation only slowly decreases the body stores of carbon dioxide. Acute hypventilation is seen in the oxygen difference which increases earlier than does \( P_{\text{E}CO_2} \) \[3, 4\].

In the post-hypventilation period, there was "hypventilation", as assessed by \( \dot{V}E \) and oxygen difference. \( P_{\text{E}CO_2} \) on the other hand, displayed low values up to 3 min after hypventilation was discontinued. In normal individuals, the stimulus for ventilation from increasing arterial carbon dioxide concentration is more potent than that from hypoxia \[12, 13\]. Resting ventilation and chemosensitivity are blunted by alkalosis \[14\]. In the recovery period after general anaesthesia with controlled ventilation, ventilation is diminished to attain high enough \( P_{\text{E}CO_2} \) for spontaneous breathing to commence. In this situation, there is a risk of tissue oxygen desaturation while \( P_{\text{E}CO_2} \) is still on the low side. In other situations, when high \( F_iO_2 \) is used, \( SpO_2 \) is a poor measure of adequate ventilation and sudden changes in ventilation affect the oxygen difference very promptly, while \( P_{\text{E}CO_2} \) changes much more slowly and \( SpO_2 \) may still be normal. It seems reasonable that ventilation during anaesthesia, or in the ICU, should be guided not only by \( P_{\text{E}CO_2} \) but also by the oxygen difference and \( P_{\text{E}O_2} \). In spite of the limitations in this study, such as healthy subjects and air breathing, the oxygen difference did monitor body oxygen status. An oxygen difference of more than 8 kPa was associated with haemoglobin desaturation and there was a negative relation between the oxygen difference and \( P_{\text{E}CO_2} \). During anaesthesia with an \( F_iO_2 \) of 0.30 or 0.50, the relation between the oxygen difference and \( SpO_2 \) is probably more complex, as \( P_{\text{E}O_2} \) may be supranormal in spite of a high oxygen difference. During general anaesthesia, FRC is reduced and, using CT scan, atelectatic areas are found in dependent parts of the lung \[15\]. It has also been found, in healthy middle-aged patients, that shunting increases from about 1 % awake and supine to 8 % during anaesthesia with controlled ventilation \[16\]. The atelectatic areas correspond very well to the degree of shunt \[17\]. These changes result in an increased ventilation-perfusion mismatch and alveolar-arterial oxygen partial pressure difference \[18\], which make evaluation of the oxygen difference complex. A large inspiratory to end-tidal oxygen difference may still be an indication of inadequate ventilation. It is well known that lung disease may cause ventilation-perfusion mismatch and thus an alveolar-arterial oxygen partial pressure difference. This influences the oxygen difference which might still be a useful tool in monitoring and perhaps aid in quicker identification of acute lung affection before desaturation or other deleterious events occur.
Clinical studies have not yet been done and caution is required when evaluating the oxygen difference in patients with lung disease and during anaesthesia.

In a previous study during nitrous oxide anaesthesia, we found that the oxygen difference followed an asymptotically increasing curve because of decreasing uptake of nitrous oxide [19]. Several variables changed simultaneously in that study, precluding a definite examination of the influence of ventilatory changes on the oxygen difference and \( S_{O_2} \). However, during controlled ventilation, a change in \( V_{O_2} \) correlated with a change in the oxygen difference. In the present study, \( V_A \) could be calculated from the oxygen difference and \( V_{O_2} \), giving approximately the same values as if calculated from carbon dioxide. \( V_A \) is theoretically the ventilatory variable that influences the oxygen difference and is determined by \( V_T \) minus physiological deadspace (\( V_D \)). A constant anatomical deadspace and a \( V_T \)-dependent alveolar deadspace form the physiological deadspace. Knowing the \( V_D / V_T \) quotient through the Bohr equation gives: 

\[
V_A = V_E (1 - V_D / V_T).
\]

In this study there was significant change in the \( V_D / V_T \) quotient and \( V_E \) was not just a reflection of \( V_A \) but still corresponded very well to the oxygen difference without any need of correction for changing ventilatory frequency and \( V_T \). Respiratory gas exchange mirrors cellular metabolism in the body when steady-state conditions are present, that is when the respiratory exchange of oxygen and carbon dioxide is in equilibrium with the gas stores of the body [11, 20]. In this study respiratory exchange rate changed significantly, suggesting changing body gas stores.

In summary, we found that the oxygen difference was related to the expiratory minute ventilation volume during and after voluntary hyperventilation in healthy subjects. In our opinion the oxygen difference offers a fast and continuous measure of ventilation and is a valuable contribution to other variables in determining adequate ventilation during anaesthesia and intensive care.

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REFERENCES