Dependence of the gradient between arterial and end-tidal $P_{CO_2}$ on the fraction of inspired oxygen

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**End-tidal CO$_2$ concentrations usually reflect arterial CO$_2$ tensions.**

**Absolute values depend on the end-tidal to arterial CO$_2$ gradient and alveolar dead space, but were thought to be independent of $F_{IO_2}$.**

**Here, the arterial to end-tidal CO$_2$ gradient increased significantly with increased $F_{IO_2}$ in anaesthetized ventilated patients.**

**This may reflect changes in alveolar dead space, pulmonary shunt, or cardiac output.**

Anaesthetists use end-tidal $P_{CO_2}$ ($P_{ECO_2}$) values routinely to monitor the adequacy of ventilation. The clinical utility of $P_{ECO_2}$ as a surrogate for arterial $P_{CO_2}$ ($P_{ACO_2}$) depends on the gradient between them ($\Delta P_{A-CO_2}$). This gradient depends primarily on the degree of alveolar dead space ($V_{Dalv}$). Larson and Severinghaus 1 reported that the administration of O$_2$ to awake sitting subjects led to an increase in $\Delta P_{A-CO_2}$. They attributed this finding to the vasodilating effect of O$_2$ on blood vessels at the base of the lungs, which results in the expansion of the apical $V_{Dalv}$. However, Whitesell and colleagues 2 failed to demonstrate such a relationship in supine subjects under the influence of general anaesthesia. In that study, the fraction of inspired O$_2$ ($F_{IO_2}$) was not well controlled and the range examined was narrow. Therefore, in this study, we used a prolonged steady state over a wide range of $F_{IO_2}$ levels to determine whether hyperoxia increases $\Delta P_{A-CO_2}$ and $V_{Dalv}$ in supine subjects during general anaesthesia.

**Methods**

This study was approved by the ethics committee of Nagoya City University Graduate School of Medical Science, and informed written consent was obtained from each participant. The subjects were ASA I/II grade patients undergoing elective lower abdominal surgery; no patient received premedication. An epidural catheter was placed into the lower thoracic epidural space before induction of general anaesthesia. After preoxygenation of the lungs with 100% O$_2$, anaesthesia was induced with propofol (1.5–2.0 mg kg$^{-1}$), fentanyl (1.5–2.0 μg kg$^{-1}$), and rocuronium (0.6–1.0 mg kg$^{-1}$). Anaesthesia was maintained with air-and/or-oxygen–sevoflurane.
(1.5–2.5%) combined with a continuous epidural infusion of ropivacaine (0.375%) at a rate of 4–6 ml h\(^{-1}\). Sevoflurane concentration was kept constant and complete muscle relaxation was maintained during the measurement phase of our study. Standard anaesthesia monitors were used. End-tidal gas was sampled, and \(P_{\text{CO}_2}, P_{\text{O}_2}\), and sevoflurane concentrations were determined (GF-100; Nihon Kohden, Tokyo, Japan). The end-tidal values and \(F_{\text{IO}_2}\) were calculated by the standard anaesthetic monitors. A respiratory monitor (NICO\(^{14}\), Novametrix, CT, USA) which calculated \(V_{\text{O}_2}\) values by single-breath \(CO_2\) analysis\(^3\) was installed in the respiratory circuit. An indwelling radial arterial catheter allowed for continuous arterial pressure monitoring and intermittent arterial blood sampling. All the monitors were calibrated before use. The patients’ lungs were ventilated using a volume-controlled mode (Aestiva/5; Datex-Ohmeda, Buckinghamshire, UK), \(I:E\) (inspiratory-to-expiratory) ratio, 1:2 without PEEP. \(F_{\text{IO}_2}\) levels of 0.21, 0.33, 0.5, 0.75, and 0.97 were applied by altering the ratio of air to \(O_2\) (total inspiratory volume (\(V_{\text{I}}\)) and respiratory frequency (\(f\)) were both adjusted to maintain \(P_{\text{aCO}_2}\) at 4.00–4.65 kPa in the first \(F_{\text{IO}_2}\) level of each case. They were unchanged after the adjustment during the study. After establishing a steady haemodynamic and ventilatory state, only \(F_{\text{IO}_2}\) levels were changed whereas keeping both \(V_{\text{I}}\) and \(f\) constant. When the levels were ±1% the target \(F_{\text{IO}_2}\) level, each \(F_{\text{IO}_2}\) level was maintained for 15 min or more. At the end of each \(F_{\text{IO}_2}\) period, arterial blood was withdrawn for over 1 min and blood gas analysis was carried out immediately (ABL 725; Radiometer, Tokyo, Japan). \(\Delta Pa−\varepsilon_{\text{CO}_2}\) was obtained from the temperature-corrected \(P_{\text{ACO}_2}\), and \(P\varepsilon_{\text{CO}_2}\) values and \(V_{\text{O}_2}\) were calculated by the respiratory monitor.

**Statistical analysis**

Statistical analysis was performed using SigmaStat (HULINKS, Tokyo, Japan). The values of \(\Delta Pa−\varepsilon_{\text{CO}_2}\), \(V_{\text{O}_2}\), \(P_{\text{ACO}_2}\), and \(P\varepsilon_{\text{CO}_2}\) were analysed at different time intervals by one-way analysis of variance for repeated measures followed by Fisher’s least significant difference test. The values are expressed as mean [standard error of the mean (SEM)]. A value of \(P<0.05\) was considered to be statistically significant.

**Results**

**Study characteristics**

Twenty subjects (15 women) were studied. Their characteristics were as follows: [mean (range)]; age, 60.5 (36–78) yr; height, 159.4 (138–180) cm; and weight, 53.5 (35–79) kg. The settings of the artificial ventilators were as follows: [mean (range)]; \(V_{\text{I}}\), 453.8 (350–550) ml; \(f\), 10.2 (8–12) min\(^{-1}\). The types of surgeries performed are listed in Table 1. Three subjects had mild obstructive lung impairment (Table 1).

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics (n=20) expressed as mean (range), mean (SD) or number. RFT, respiratory function test</th>
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<tbody>
<tr>
<td><strong>Value</strong></td>
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<td>Age (yr)</td>
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<td>Sex (male-female)</td>
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<td>Height (cm)</td>
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<td>Weight (kg)</td>
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<td>Abnormal RFT (cases)</td>
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The mean (SEM) values of \(\Delta Pa−\varepsilon_{\text{CO}_2}\) at 0.21, 0.33, 0.5, 0.75, and 0.97 levels of \(F_{\text{IO}_2}\) were 0.13 (0.04), 0.28 (0.08), 0.29 (0.09), 0.44 (0.11), and 0.53 (0.09) kPa (n=20), respectively. \(\Delta Pa−\varepsilon_{\text{CO}_2}\) values differed significantly at all \(F_{\text{IO}_2}\) levels, except between the 0.33–0.5 and 0.75–0.97 levels. \(\Delta Pa−\varepsilon_{\text{CO}_2}\) increased consistently with an increase in \(F_{\text{IO}_2}\) (Fig. 1). The corresponding values of \(V_{\text{O}_2}\) were 25.5, 33.8, 35.8, 48.9, and 47.4 ml (mean), \(V_{\text{O}_2}\) increased by 86% at \(F_{\text{IO}_2}=0.97\) compared with the value at \(F_{\text{IO}_2}=0.21\) (Fig. 2). The mean \(P_{\text{ACO}_2}\) values at \(F_{\text{IO}_2}\) levels of 0.21, 0.33, 0.5, 0.75, and 0.97 were 4.55, 4.33, 4.52, 4.56, 4.54, and 4.76 kPa, respectively. The corresponding mean values of \(P\varepsilon_{\text{CO}_2}\) were 4.42, 4.24, 4.27, 4.10, and 4.23 kPa, respectively (Fig. 3). The value of \(P_{\text{ACO}_2}\) when the \(F_{\text{IO}_2}\) was 0.97 was statistically higher than the values at other \(F_{\text{IO}_2}\) levels (Fig. 3).

**Discussion**

The major finding of this study is the dependence of \(\Delta Pa−\varepsilon_{\text{CO}_2}\) on \(F_{\text{IO}_2}\), which is associated with \(V_{\text{O}_2}\). We found
The dependence of $\Delta P_a - \varepsilon CO_2$ on $FI_o$.

Intrapulmonary shunt can also influence $\Delta P_a - \varepsilon CO_2$. It leads to the increase in $\Delta P_a - \varepsilon CO_2$ as a consequence of the increase in $P_{ACO_2}$ with venous admixture. Although this gap with the shunt has nothing to do with real dead space, it is erroneously interpreted as $V_{Dav}$, which has been referred to as ‘shunt dead space’. Thus, the calculated $V_{Dav}$ includes the ‘shunt dead space’ and is overestimated. However, the influence of the shunt on the calculated $V_{Dav}$ is fairly small in low shunt values. According to Medicinski and colleagues, even if the shunt rate is 20%, ‘shunt dead space’ is only a small percentage of the $V_T$. Similarly, Suter and colleagues reported that ‘shunt dead space’ amounted to only 1–2% of the $V_T$. A major cause for intrapulmonary shunt during general anaesthesia is the development of atelectasis. Breathing pure $O_2$ also causes absorption atelectasis. Dantzker and colleagues reported that breathing pure $O_2$ induced absorption atelectasis within ~9 min and that pulmonary shunt increased abruptly when $FI_o$ increased above 0.8. Mantell and colleagues reported that intrapulmonary shunt created by $FI_o$ above 0.95 remained larger when $FI_o$ was returned to 0.21, indicating that absorption atelectasis produced during $O_2$-rich breathing persisted throughout anaesthesia in horses. Brismar and colleagues found that in chest computed tomography study, atelectasis rapidly developed in the dependent lung regions during the induction of general anaesthesia, probably with pure $O_2$ preoxygenation, but it did not progress with time or increased $FI_o$. General anaesthesia was induced after preoxygenation using 100% $O_2$, which is a standard clinical practice. Some absorption atelectasis must have persisted, even if $FI_o$ was changed. Thus, the atelectasis would have little impact on the phase increases in $\Delta P_a - \varepsilon CO_2$. However, it is assumed to be constant when $P_{ECO_2}$ is used to assess the adequacy of ventilation. Few studies have reported on the effect of the phase change in $FI_o$ on $\Delta P_a - \varepsilon CO_2$ and $V_{Dav}$.

The respiratory monitor used in our study utilizes the single breath test for CO$_2$ (SBT-CO$_2$) analysis to calculate $V_{Dav}$. This method was validated in animal experiments and the values thus calculated did not differ from those calculated using the Bohr–Enghoff equation in ventilated newborns.

$\Delta P_a - \varepsilon CO_2$ depends on factors that increase the fluctuation of alveolar $P_{CO_2}$ ($P_{ACO_2}$). $P_{ACO_2}$ usually fluctuates over the ventilatory cycle, whereas $P_{ECO_2}$ reflects the much dampened time-averaged $P_{ACO_2}$. At end-exhalation, $P_{ACO_2}$ is maximal and approaches the $P_{CO_2}$ of mixed venous blood. Thus, increases in the fluctuation of $P_{ACO_2}$, caused by changes in $V_T$, $f$, $P_{ACO_2}$, and $CO_2$ production ($V_{CO_2}$) increase $\Delta P_a - \varepsilon CO_2$. In this study, $V_T$ and $f$ were kept constant. $V_{CO_2}$ also likely remained constant, because the subjects were anaesthetized and maintained under normothermic conditions. The changes in $\Delta P_a - \varepsilon CO_2$ were due to the changes in $P_{ACO_2}$, because $P_{ACO_2}$ remained constant, except when $FI_o$ was 0.97. Hardman and Aitkenhead indicated a high correlation between $\Delta P_a - \varepsilon CO_2$ and $V_{Dav}$ and $V_{Dav}/alveolar tidal volume in the presence of intrapulmonary shunt or $V_{CO_2}$ in their model analysis. Thus, the changes in $\Delta P_a - \varepsilon CO_2$ were most likely due to the dilution effect of $P_{ACO_2}$ with gas from $V_{Dav}$. We presume that the mechanism of the increase in $V_{Dav}$ with the increase in $FI_o$ is that high $FI_o$ reduces vascular resistance in high perfusion alveolar areas, resulting in the redistribution of blood flow away from low perfusion alveolar areas as proposed by Larson and Severinghaus.
remains possible that an increment of the shunt effect due to the redistribution of pulmonary flow with the changes in $F_{IO_2}$ was associated with the increase in $\Delta P_a - \epsilon CO_2$. The increment of the shunt effect should cause the increase in $\Delta P_a - \epsilon CO_2$ with the increase in $P_{aCO_2}$. In this study, the increase in $\Delta P_a - \epsilon CO_2$ with the increase in $P_{aCO_2}$ seen just at $F_{IO_2}$ of 0.97 would reflect the reversible addition of the shunt effect.

A hyperoxia-induced reduction in cardiac output may contribute to an increase in $\Delta P_a - \epsilon CO_2$ and $V_{oalv}$. Anderson and colleagues reported that cardiac output decreased by 10.3% when $F_{IO_2}$ was changed from 0.21 to 1.0. Johann and colleagues reported that cardiac output decreased by 10.6% after a change in $F_{IO_2}$ from 0.6 to 1.0 in patients after coronary artery bypass surgery. The decrease in cardiac output increases $\Delta P_a - \epsilon CO_2$ and $V_{oalv}$ by causing the decrease in CO$_2$ elimination from alveoli and the redistribution of pulmonary blood flow. Isserles and Breen reported that during constant minute ventilation and tissue $V_{CO_2}$, there were reductions in $P_{ECO_2}$ of 7.4% and $P_{aCO_2}$ of 4.7% which resulted in the increase in $\Delta P_a - \epsilon CO_2$ when the reduction in cardiac output was $\sim 10\%$. If both $P_{ECO_2}$ and $P_{aCO_2}$ are 5.33 kPa, $\Delta P_a - \epsilon CO_2$ should increase by $\sim 0.13$ kPa. Although we did not detect any changes in heart rate and arterial pressure during this study or find any changes in cardiac output in another experiment changing $F_{IO_2}$ in the same manner as this study, it is likely that a small decrease in cardiac output contributed to the increases in $\Delta P_a - \epsilon CO_2$ and $V_{oalv}$ partially in high $F_{IO_2}$. However, in this study, we did not identify a decrease in $P_{aCO_2}$ with the decrease in cardiac output in high $F_{IO_2}$. We believe that was because the effect on $P_{aCO_2}$ of the increase in the shunt exceeded that of the reduction in cardiac output at $F_{IO_2}$ of 0.97.

Isoflurane increases $V_{oalv}$ more than propofol under positive pressure ventilation. Although sevoflurane we used may have the same mode of action as isoflurane, its concentration was kept constant throughout this study. Ventilation–perfusion relationships during epidural analgesia show no significant changes when compared with the control state. Therefore, neither sevoflurane nor epidural analgesia would have influenced our results. Although there is a gradual increase in $V_{oalv}$ with an increased duration of general anaesthesia, this effect is eliminated by varying the $F_{IO_2}$ levels in a random order.

In summary, we demonstrated that $\Delta P_a - \epsilon CO_2$ depends on $F_{IO_2}$ in anaesthetized ventilated patients. Not only the true $V_{oalv}$ but also intrapulmonary shunt and cardiac output may be associated with the magnitude of $\Delta P_a - \epsilon CO_2$ in the presence of variable $F_{IO_2}$. Although the effect of $F_{IO_2}$ on $\Delta P_a - \epsilon CO_2$ is small, it should be taken into account when using $P_{ECO_2}$ as a surrogate for $P_{aCO_2}$.

Conflict of interest
None declared.

References
The dependence of $\Delta P_{a-CO_2}$ on $F_{O_2}$


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