# The Changes in Brain Surface, Intracerebral Tissue, and Transconjunctival Oxygen Tension during Hypo- and Hyperventilation

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To evaluate the validity of organ surface oxygen tension monitoring for assessment of cerebral perfusion, the oxygen tension in brain surface ($Pbs_{O_2}$), intracerebral tissue ($Pic_{O_2}$), and conjunctiva ($Pcj_{O_2}$) were measured simultaneously during hypo- and hyperventilation in dogs, and the comparative study was done.

$Pbs_{O_2}$ and $Pic_{O_2}$ significantly increased during hypoventilation and decreased during hyperventilation. And the values of $Pbs_{O_2}$ and $Pic_{O_2}$ were correlated to the corresponding $Pa_{CO_2}$ values significantly ($P < 0.001$ in each case). On the contrary, $Pcj_{O_2}$ did not change significantly during hypo- and hyperventilation.

These findings indicate that $Pbs_{O_2}$ as well as $Pic_{O_2}$ could reflect the changes in cerebral perfusion caused by induced hyper- and hypocapnia but that $Pcj_{O_2}$ could not. (Key words: hypo- and hyperventilation, cerebral perfusion, organ surface oxygen tension, tissue oxygen tension, transconjunctival oxygen tension)

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A non-heated miniature $P_{O_2}$ sensor has made it possible to measure 'noninvasively' organ surface oxygen tension in experimental and clinical conditions[1], and served for assessment of organ perfusion in intestine and kidney[2]. As for brain surface oxygen tension ($Pbs_{O_2}$) monitoring, some preliminary reports were found during hemorrhagic and drug induced hypotension[3], and during the changes in inspired $CO_2$ concentration[4]. However, the changes in $Pbs_{O_2}$ related to physiologic alterations of cerebral perfusion caused by hypo- and hyperventilation which are routinely used in neurosurgeries[5], and the comparison of $Pbs_{O_2}$ with the 'invasive' intracerebral tissue oxygen tension ($Pic_{O_2}$) have not been reported.

In this study, simultaneous measurements of $Pbs_{O_2}$ and $Pic_{O_2}$ were performed during experimentally induced hyper- and hypocapnia which cause intense cerebral vasodilation and constriction, respectively[6]. The changes in these variables ($Pbs_{O_2}$ and $Pic_{O_2}$) related to the changes in blood gases ($Pa_{O_2}$ and $Pa_{CO_2}$) and to those in hemodynamics were investigated to evaluate the validity of the $Pbs_{O_2}$ monitoring for assessment of cerebral perfusion. The changes in the transconjunctival oxygen tension ($Pcj_{O_2}$) was also investigated as a comparative study.

## Materials and Methods

$Pbs_{O_2}$, $Pic_{O_2}$, and $Pcj_{O_2}$ sensors: The

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$Pbs_{O_2}$ sensor (Biomedical Sensors Inc., Kansas City, MO; size 10 × 6 × 2.5 mm) structurally same to the $Pcj_{O_2}$ sensor (Orange Medical Instruments, Costa Mesa, CA) consists of a Clark-type polarographic electrode with a platium cathode, silver-silver chloride anode was prepared. According to the manufacturer's recommendation, 2-point calibration, to room air and zero solution, was performed. The $Pic_{O_2}$ sensor consists of a bipolar polarographic electrode was an application of the intravascular $P_{O_2}$ sensor (model 636100, Kontron Instruments, Everett, MA; diameter 0.55 mm) to the cerebral tissue. Calibration was done in ambient air, and the temperature of this sensor was set at 37°C. The $Pcj_{O_2}$ sensor was prepared and calibrated in the same way to the $Pbs_{O_2}$ sensor.

Experimental preparation: Ten adult mongrel dogs of either sex weighing 12 to 25 kg were studied. The dog was anesthetized with pentobarbital (30 $mg \cdot kg^{-1}$, iv) and immobilized with pancuronium (0.1 $mg \cdot kg^{-1}$). These drugs were given for maintenance during the experiment if required. The trachea was intubated and ventilation was controlled with a Servo 900B ventilator. Minute volume (MV) and respiratory rate (RR) were initially adjusted to maintain normocapnia ($Pa_{CO_2}$ 35–45 torr) and fraction of inspired oxygen ($FI_{O_2}$) was set at 0.5 in nitrogen. Cannulae were inserted into a femoral artery for pressure measurement and blood sampling; into a femoral vein for saline infusion (5 $ml \cdot kg^{-1} \cdot hr^{-1}$); and into a pulmonaly artery via the other femoral vein for measurement of cardiac output by thermodilution. Core temperature measured by a thermister was maintained at 37°C with a heating pad and lamp. A transcutaneous $O_2$–$CO_2$ sensor (Kontron Instruments, Everett, MA) precalibrated at 44°C was placed on the anterior chest skin for the continuous monitoring of gas exchange. An electrocardiogram (ECG) was recorded continuously from limb leads.

The hemicranium was then exposed via an incision with lateral retraction of the frontal muscle. A burr hole approximately 1 cm in diameter was drilled to the level of the dure. After the atraumatic opening of the dure, the $Pic_{O_2}$ sensor was inserted vertically about 1 cm into the brain tissue. The $Pbs_{O_2}$ sensor was then inserted under the dure, and placed on the brain surface through the burr hole. Then, the burr hole was covered by the frontal muscle and head skin. Finally, the previously prepared $Pcj_{O_2}$ sensor was inserted into the left eye, and the eye lids were closed by an adhesive tape.

Physiologic measurements: When the dog's condition had stabilized, $Pbs_{O_2}$, $Pic_{O_2}$, and $Pcj_{O_2}$ were measured simultaneously. The corresponding blood gases ($Pa_{O_2}$ and $Pa_{CO_2}$) and following hemodynamic variables were also measured: heart rate (HR), mean arterial pressure (MAP), and cardiac output.

Protocol: Following the baseline measurements mentioned above, the dog was subjected to hypo-, hyper-, and normoventilation by changing the ventilator setting. Observing the changes in transcutaneous gases ($Ptc_{O_2}$ and $Ptc_{CO_2}$) as a guide to gas exchange[7], MV and RR was adjusted to induce the desired environments. Hyperventilation was conducted during first 30 min in an experiment, which was followed by hyper- and normoventilation during middle and last 30 min, respectively. Physiologic measurements were done every 15 min from the start to the end of an experiment. Therefore, including the data set for baseline, total 7 sets of data were collected per one dog per one experiment during 90 min. Addition to the intermittent data recordings, the signals of $Pic_{O_2}$, $Pbs_{O_2}$, $Pcj_{O_2}$, and $Ptc_{CO_2}$ were acquired directly to the personal computer (IBM PC-AT) via an analog-digital converter for the later analysis.

Statistical analysis: Data were expressed as mean ± SD. The statistical analysis of the changes in each variable during hypo-, hyper-, and normoventilation was done nonparametrically with the Friedman test followed by the Wilcoxon signed-rank test for the pairwise comparisons.

The relationships between $Pa_{CO_2}$ and the variables derived from the sensors ($Pbs_{O_2}$, $Pic_{O_2}$, and $Pcj_{O_2}$, such as $Pa_{CO_2}$ versus

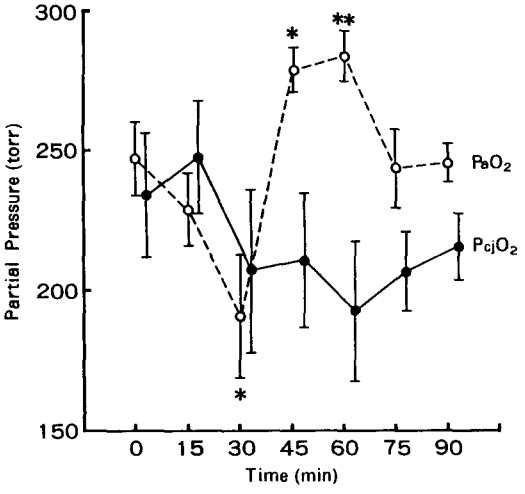



**Fig. 1.** The changes in $Pa_{O_2}$ and $Pcj_{O_2}$ during hypo- (0–30 min), hyper- (30–60 min), and normoventilation (60–90 min). Data were shown mean ± SEM with $n = 10$. $Pcj_{O_2}$; transconjunctival oxygen tension. * and **; $P < 0.05$ and $P < 0.01$, respectively, compared to control values.

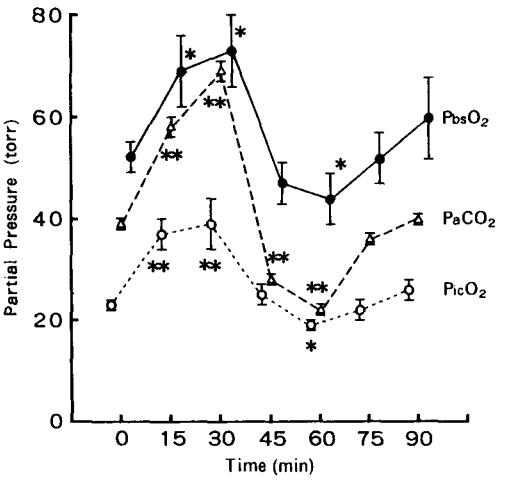



**Fig. 2.** The changes in $Pbs_{O_2}$, $Pic_{O_2}$, and $Pa_{CO_2}$ during hypo- (0–30 min), hyper- (30–60 min), and normoventilation (60–90 min). Data were shown mean ± SEM with $n = 10$. $Pbs_{O_2}$; brain surface oxygen tension. $Pic_{O_2}$; intracerebral oxygen tension. * and **; $P < 0.05$ and $P < 0.01$, respectively, compared to control values.

$Pbs_{O_2}$, were analyzed using the Pearson product-moment correlation coefficient after the certification of bivariate normal distribution calculated by standard procedures[8].

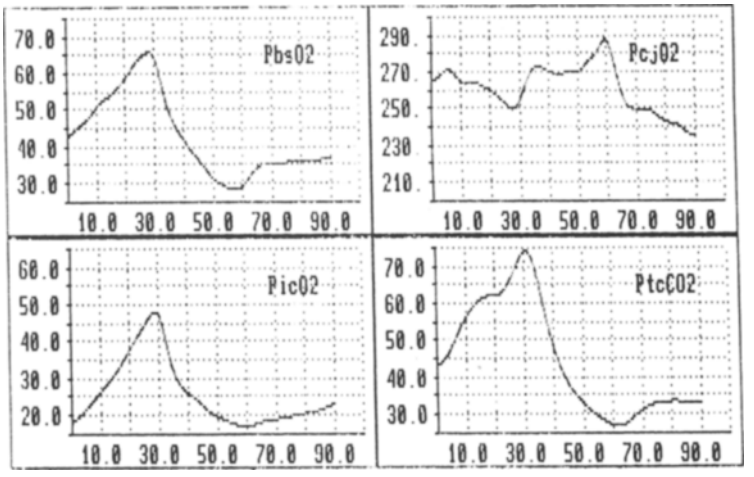
## Results

The intentional hyper- and hypocapnia were successfully induced by hypo- and hyperventilation, respectively, with a slight but significant changes in $Pa_{O_2}$ (fig. 1). Both $Pbs_{O_2}$ and $Pic_{O_2}$ increased significantly during hypoventilation and dereased during hyperventilation (fig. 2). The calculated correlation coefficients revealed that $Pbs_{O_2}$ and $Pic_{O_2}$ correlated significantly to $Pa_{CO_2}$ ($r = 0.52$, $P < 0.001$ and $r = 0.68$, $P < 0.001$, respectively), and that they did not correlate to $Pa_{O_2}$. On the contrary, $Pcj_{O_2}$ did not change significantly through the experiment, and did not correlate to either $Pa_{CO_2}$ or $Pa_{O_2}$. The continuous recordings of $Pbs_{O_2}$, $Pic_{O_2}$, $Pcj_{O_2}$, and $Ptc_{CO_2}$ in a typical case were shown in figure 3. The corresponding changes in blood gases were also shown. In this case, all of $Pbs_{O_2}$, $Pic_{O_2}$, and $Ptc_{CO_2}$ increased and decreased in response to the changes in $Pa_{CO_2}$. On the other hand, $Pcj_{O_2}$ deceased during hypoventilation and increased during hyperventilation, which were consistent with the changes in $Pa_{O_2}$.

The changes in hemodynamic variables were summarized in table 1. Cardiac output and HR were increased significantly during hypoventilation. MAP did not show any consistent changes through the experiment.

## Discussion

It is generally accepted that cerebral blood flow (CBF) is depend on MAP, $Pa_{CO_2}$, and $Pa_{O_2}$. Among these three determinants, the changes in $Pa_{CO_2}$ affect CBF most dominantly, and acute changes in $Pa_{CO_2}$ between 20 to 60 torr have been shown to change CBF 1 to 2 $ml \cdot min^{-1} \cdot 100\ gm^{-1}$ of brain per 1 torr change in $Pa_{CO_2}$[9]. In this study, to produce the changes in CBF, the intentional hyper- and hypocapnia were induced by hypo- and hyperventilation, respectively. As a result, although hyper- and hypocapnia were induced successfully, $Pa_{O_2}$ decreased and increased significantly during hyper- and hypocapnia, respectively. Nevertheless, both




| Time (min) | 0 | 15 | 30 | 45 | 60 | 75 | 90 |
|---|---|---|---|---|---|---|---|
| $PaO_2$ (torr) | 233 | 214 | 209 | 249 | 294 | 234 | 221 |
| $PaCO_2$ (torr) | 43 | 62 | 72 | 36 | 26 | 38 | 44 |

**Fig. 3.** The continuous recordings of $Pbs_{O_2}$, $Pic_{O_2}$, $Pcj_{O_2}$, and $Ptc_{CO_2}$ (top), and the changes in blood gases (bottom) in a typical case. In each graph, the vertical line shows gas tension (torr), and the horizontal line shows the progress time from the start of the experiment (min).

**Table 1.** The changes in mean arterial pressure (MAP), cardiac output (CO), and heart rate (HR) during hypo-, hyper-, and normoventilation

| Stage | control | hypoventilation | | hyperventilation | | normoventilation | |
|---|---|---|---|---|---|---|---|
| Time (min) | 0 | 15 | 30 | 45 | 60 | 75 | 90 |
| MAP (mmHg) | 113 ± 11 | 112 ± 14 | 120 ± 28 | 123 ± 18 | 123 ± 17 | 120 ± 12 | 121 ± 12 |
| CO ($l \cdot min^{-1}$) | 3.2 ± 0.6 | 4.6 ± 0.9 ** | 4.9 ± 1.0 ** | 3.7 ± 0.7 | 3.2 ± 0.5 | 3.0 ± 0.7 | 3.3 ± 0.8 |
| HR ($beat \cdot min^{-1}$) | 129 ± 36 | 149 ± 24 ** | 150 ± 25 * | 139 ± 37 | 130 ± 37 | 119 ± 44 | 124 ± 45 |

Data were shown as mean ± SD with $n = 10$.

Time means the progress time after the start of the experiment.

* and **; $P < 0.05$ and $P < 0.01$, respectively, compared to control values by the Wilcoxon signed-rank test following the Friedman test.

$Pbs_{O_2}$ and $Pic_{O_2}$ changed in response to the changes in $Pa_{CO_2}$ (fig. 2), and their changes were unrelated to the changes in $Pa_{O_2}$. This phenomenon was clearly observed in the continuous recordings of $Pbs_{O_2}$ and $Pic_{O_2}$ (fig. 3). In this case, during hypo- and hyperventilation, both $Pbs_{O_2}$ and $Pic_{O_2}$ increased and decreased, respectively, despite the corresponding blood gas data showed the reverse changes in $Pa_{O_2}$. These findings on $Pbs_{O_2}$ and $Pic_{O_2}$ are accordance with the view that hypercapnia causes increase of cerebral oxygen pressure more effectively than the changes in $Pa_{O_2}$[10]. On the other hand, $Pcj_{O_2}$ did not show any consistent changes during hypo- and hyperventilaltion, which is inconsistent with other reports that the changes in $Pa_{CO_2}$ affect those in $Pcj_{O_2}$[11,12]. However, in this study, $Pa_{O_2}$ also changed during the experiment, the effects of $Pa_{O_2}$ on $Pcj_{O_2}$ may have offset the changes in $Pcj_{O_2}$. The lack of correlation between $Pcj_{O_2}$ and cerebral per-

fusion has been already demonstrated in various situations[13–15]. Our results may further support the invalidity of $Pcj_{O_2}$ monitoring for cerebral perfusion because the changes $Pa_{CO_2}$ did not affect those in $Pcj_{O_2}$ more dominantly than $Pa_{O_2}$.

In this study, the baseline measurements (normoventilation with $F_{I_{O_2}}$ at 0.5) had a $Pic_{O_2}$ between 17 and 28 torr and a $Pbs_{O_2}$ between 42 to 77 torr. As the accuracy of the $Pic_{O_2}$ sensor in an intravascular use has been already reported[16], this $Pic_{O_2}$ value should have reflected the intracerebral tissue oxygen tension. These low values of $Pic_{O_2}$ compared to those of $Pbs_{O_2}$ may be due to the difference of measured sites in brain (inside vs superficial), or may be due to the tissue damage and impaired microcirculation caused by the needlelike 'invasive' electrode as the $Pic_{O_2}$ sensor[17]. The values of brain surface oxygen tension atraumatically measured with the multiwire oxygen electrode in human subjects have been reported between 17 ± 19 (mean ± SD) and 56 ± 20 torr from patient to patient with $F_{I_{O_2}}$ at 0.5[18]. The $Pbs_{O_2}$ values so far obtained in our study correspond well with these results, which would indicate atraumatic and successful measurements of brain surface oxygen tension were done with the $Pbs_{O_2}$ sensor.

There were no significant changes in MAP, but significant changes in cardiac output and HR were observed. The changes in MAP, if any, was not likely to affect cerebral perfusion due to the autoregulation of CBF[6]. The changes in cardiac output and HR observed only during hypercapnia and not during hypocapnia should be cardiovascular effects of carbon dioxide retention, and would not have affected the cerebral perfusion[19].

In summary, during hypo- and hyperventilation, there were no marked changes in $Pcj_{O_2}$ probably due to interactive effects of $Pa_{CO_2}$ and $Pa_{O_2}$ on $Pcj_{O_2}$, whereas there were dynamic changes in both $Pbs_{O_2}$ and $Pic_{O_2}$ related to the changes in $Pa_{CO_2}$ which should induce the changes in cerebral perfusion. These findings suggest that both $Pbs_{O_2}$ and $Pic_{O_2}$ could reflect the changes in cerebral perfusion. Further, because the measurement of $Pbs_{O_2}$ is less invasive than that of $Pic_{O_2}$, the $Pbs_{O_2}$ monitoring might be clinically available for assessment of cerebral perfusion in the case of such as neurosurgeries.

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