Title: Changes in partial pressure of arterial carbon dioxide induces redistribution of oral tissue blood flow in the rabbit

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Changes in PaCO₂ induces redistribution of oral tissue blood flow in the rabbit

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Running title: PaCO₂ and blood flow redistribution

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Abstract

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Changes in PaCO₂ induced redistribution of oral tissue blood flow in the rabbit


The purpose of this study was to investigate the effect of PaCO₂ changes on oral tissue blood flow. Twenty male tracheotomized Japan White rabbits were anesthetized with isoflurane (ISO) or propofol (PROP) under mechanical ventilation. Observed variables included heart rate, blood pressure, common carotid artery blood flow (CBF), tissue blood flow of the mandibular bone marrow (BBF), of the masseter muscle (MBF), and of the mandibular periosteum (PBF). After completion of the experimental preparation, CO₂ was added to inspired gas to change inspired CO₂ tension. Measurements were performed when end-tidal CO₂ tension (ETCO₂) was maintained at 4, 5.3, 6.7 and 8 kPa. Heart rate in both groups gradually decreased as ETCO₂ increased. In contrast, both systolic and diastolic arterial pressures gradually increased as ETCO₂ increased. Both CBF and BBF increased, while MBF decreased as ETCO₂ increased. PBF showed no change throughout the experiment. Positive relationship was observed between CBF and BBF. In contrast, negative relationship was observed between CBF and MBF. These results suggested that changes in PaCO₂ may induce redistribution of oral tissue blood.
flow during both ISO and PROP anesthesia.

Key words: blood flow oral surgery $\text{ETCO}_2$ isoflurane propofol

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Introduction

Blood loss during surgery should be reduced for a good recovery after surgery and to avoid blood transfusion. In oral and maxillofacial surgery, bleeding in the surgical area increases the possibility of not only blood transfusion but also postoperative airway obstruction. Therefore, control of oral tissue blood flow is an important issue in anesthesia care for oral and maxillofacial surgery.

To minimize bleeding, deliberate hypotension using nitroglycerin (NTG), adenosine triphosphate (ATP), sodium nitroprusside (SNP), prostaglandin E$_1$ (PGE$_1$) and trimetaphan camsilate (TMP) have been widely used (1-6). Since ATP-induced deliberate hypotension produces stable control of blood pressure and dry surgical field, it is a good candidate for orthognathic surgery. However, deliberate hypotension was sometimes associated with critical complications (7). Therefore deliberate hypotension is not always safe, especially when it is applied to geriatric or medically compromised patients.

Another method to control oral tissue blood flow is to utilize the effects of anesthetic agents on blood vessels (8, 9). Changes in blood flow of the tongue mucosa in rabbits or gingiva in humans during isoflurane (ISO) administration was compared to propofol (PROP) and fentanyl administration (10-12). Blood flow of tongue mucosa or gingiva increased during ISO administration, did not change during PROP administration and decreased during fentanyl administration. These results propose a
new blood control method using pharmacological actions of anesthetic agents without hypotension. However, tissue blood flow in other regions such as bone marrow or muscles is still unknown.

Control of PaCO$_2$ is a possible technique to regulate tissue blood flow. Hypercapnia increased regional myocardial tissue oxygen tension (13, 14), whereas it decreased skeletal muscle tissue oxygen tension (15-17). In our previous study, tissue oxygen tension of the masseter muscle in rabbits decreased during hypercapnia (unpublished data). These results suggest that changes in PaCO$_2$ are associated with blood flow redistribution between vital and non-vital organs. However, those studies have not shown the effects of PaCO$_2$ on blood flow in bone marrows and skeletal muscles. So we investigated the effects of the changes in PaCO$_2$ on tissue blood flow of the masseter muscle (MBF), the mandibular bone marrow (BBF) and the mandibular periosteum (PBF) during isoflurane and propofol anesthesia in a rabbit model.

**Material and methods**

All animals received humane care in accordance with the Guideline for the treatment of Experimental Animals approved by Tokyo Dental College, Chiba, Japan. Twenty male Japan White rabbits weighing 2.3-2.9 kg were studied. Animals were housed in an air-conditioned room (24 ± 3 º and 65 ± 5 % humidity) regulated by light and dark cycle every 12 h and maintained on commercial laboratory chow and
water ad libitum for two weeks before the experiment.

Anesthesia was induced with oxygen and isoflurane with end-tidal concentration at 4 % delivered via a mask and then isoflurane concentration was reduced to 1-2 %. Each experimental preparation was performed with an appropriate dose of lidocaine. A #20 French non-cuffed pediatric endotracheal tube was inserted into the trachea via a tracheotomy. A 22 gauge Teflon catheter was inserted into the left posterior auricular vein for infusion. A 20 gauge Teflon catheter was inserted into the right femoral artery for blood pressure and heart rate (HR) monitoring using a pressure transducer (P23ID, Gould, Oxnard, California). HR was recorded by a tachograph triggered by the blood pressure wave. After muscle relaxation with an intravenous administration of alcuronium chloride, the rabbit was mechanically ventilated with an animal ventilator (Model 613, Harvard, South Natick, Massachusetts). Tidal volume and respiratory rate were kept at 30-50 ml and 30-40 times min⁻¹, respectively, to maintain end-tidal CO₂ tension (ETCO₂) at about 4 kPa.

After the skin incision along the left inferior border of the mandible without local anesthesia, the masseter muscle and the periosteum on the mandibular body were exposed. The mandibular periosteum was stripped off at a size of 5 mm in diameter at the front margin of the masseter muscle near the mandibular base. A hole perforating into the bone marrow was drilled with an electrical drilling device. MBF and BBF were monitored using a hydrogen clearance tissue blood flowmeter (MGH-D1, Unique
Medical, Tokyo). Two needle electrodes (UHE-100, Unique Medical, Tokyo) were inserted and fixed into the center of the masseter muscle and the mandiblar medulla through the bone hole. PBF was continuously monitored using a laser Doppler blood flowmeter (ALF21, Unique Medical, Tokyo). A contact-type probe (Type C, Unique Medical, Tokyo) was placed on the mandiblar periosteum at the front margin of the masseter muscle in the mandibular body. Common carotid artery blood flow (CBF) was continuously monitored using an ultrasonic blood flowmeter (T108, Transonic, Ithaca, New York). A flow probe (Type 3SB, Transonic, Ithaca, New York) was fixed to the left common carotid artery. Arterial blood gas was analyzed using a blood gases analyzer (Stat Profile 5, Nova Biomedical, Massachusetts).

ETCO$_2$ was continuously monitored using a capnograph (Capnomac, Datex, Helsinki). Acetated Ringer’s solution was infused at 10 ml$\cdot$kg$^{-1}$$\cdot$h$^{-1}$ throughout the experiment. Body temperature was kept at 39.0-39.5 $^\circ$C using a heat lamp.

After completion of the experimental preparation, animals were divided into two groups. Ten rabbits were anesthetized with ISO at 1.0 % of end-tidal concentration (Group I). The other 10 rabbits were anesthetized with continuous infusion of PROP at 12 ml$\cdot$kg$^{-1}$$\cdot$h$^{-1}$ (group P). Sixty minutes were elapsed for hemodynamic stabilization. Then, the control values were recorded (I4 or P4). After that, CO$_2$ was added to the inspired gas to maintain ETCO$_2$ at about 5.3, 6.7 and 8 kPa. More than 15 min was elapsed for hemodynamic stabilization at each ETCO$_2$ level. Measurements were
repeated at ETCO$_2$ levels of 5.3 kPa (I5.3 or P5.3), 6.7 kPa (I6.7 or P6.7) and 8 kPa (I8 or P8), respectively.

Observed variables included HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), MBF, BBF, PBF and CBF. All data except MBF and BBF were continuously recorded on a polygraph (Polygraph series 360, NEC Sanei, Tokyo, Japan).

Data are shown as mean ± standard error of the mean. One-way ANOVA for repeated measurements were used for intragroup comparisons. Student-Newman-Keuls test was used for multiple comparisons. Student t-test was used for intergroup comparisons. Linear regression and Pearson’s correlation coefficient were used to analyze the relationship of two variables. A $P$ value less than 0.05 was considered to be statistically significant.

Results

ETCO$_2$ in both groups at each observation period was shown in Table 1. There were no differences between respective ETCO$_2$ of the two groups. PaCO$_2$ was almost equal to the respective ETCO$_2$ throughout the experiment.

HR in both groups gradually decreased as ETCO$_2$ increased. In contrast, SAP and DAP gradually increased as ETCO$_2$ increased (Table 1).

1. Changes in CBF
CBF in both groups showed significant increase as ETCO$_2$ increased. In group I, CBF at I4, I5.3, I6.7 and I8 were 32.4 ± 5.8, 36.6 ± 6.2, 40.7 ± 7.1, and 45.9 ± 8.1 ml·min$^{-1}$, respectively. In group P, CBF at P4, P5.3, P6.7 and P8 were 28.4 ± 4.1, 32.9 ± 4.8, 38.0 ± 6.6, and 40.5 ± 6.7 ml·min$^{-1}$, respectively. There were no differences between respective CBF of the two groups, though CBFs in group I were a little higher than those in group P (Fig. 1).

2. Changes in BBF

BBF in both groups showed significant increase as ETCO$_2$ increased. In group I, BBF at I4, I5.3, I6.7 and I8 were 43.9 ± 4.6, 48.0 ± 4.7, 55.0 ± 5.1, and 59.8 ± 5.7 ml·min$^{-1}$·100g$^{-1}$, respectively. In group P, BBF at P4, P5.3, P6.7 and P8 were 40.9 ± 6.4, 49.6 ± 5.9, 55.6 ± 5.8, and 59.5 ± 7.3 ml·min$^{-1}$·100g$^{-1}$, respectively. There were no differences between respective BBF of the two groups (Fig. 2).

3. Changes in MBF

MBF in group I showed significant decrease as ETCO$_2$ increased. In group I, MBF at I4, I5.3, I6.7 and I8 were 33.3 ± 2.8, 27.4 ± 4.0, 21.9 ± 3.9, and 15.6 ± 2.5 ml·min$^{-1}$·100g$^{-1}$, respectively. In group P, MBF at P4, P5.3, P6.7 and P8 were 22.9 ± 3.7, 20.0 ± 3.8, 17.8 ± 4.5, and 19.0 ± 3.7 ml·min$^{-1}$·100g$^{-1}$, respectively. MBF at I4 was higher than that at P4 (Fig. 3).

4. Changes in PBF

PBF in both groups did not change throughout the experiment. In group I,
PBF at I4, I5.3, I6.7 and I8 were 19.4 ± 5.0, 18.4 ± 5.2, 20.5 ± 5.6, and 19.1 ± 4.8 ml•min⁻¹•100g⁻¹, respectively. In group P, PBF at P4, P5.3, P6.7 and P8 were 11.9 ± 1.5, 11.7 ± 1.4, 12.2 ± 1.6, and 12.3 ± 1.4 ml•min⁻¹•100g⁻¹, respectively. There were no differences between respective PBF of the two groups, though PBFs in group I were a little higher than those in group P (Fig. 4).

5. Relationship between CBF and other parameters

Positive correlation (r=0.99 in group I and r=0.99 in group P) was observed between CBF and BBF (Fig. 5). In contrast, negative correlation (r=-0.999 in group I and r=-0.89 in group P) was observed between CBF and MBF (Fig. 6). There was positive relationship between CBF and PBF in group P (r=0.80) (Fig. 7). However, no changes in PBF were observed as ETCO₂ increased in both groups.

Discussion

Our results indicate that CBF and BBF increased while MBF decreased and PBF remained unchanged as ETCO₂ increased during both ISO and PROP anesthesia. It is therefore suggested that changes in PaCO₂ are associated with blood flow redistribution in oral tissues.

In this experiment, anesthesia was maintained with 1% ISO or 12 ml•kg⁻¹•h⁻¹ propofol. Minimum alveolar concentration (MAC, anesthetic concentration at which 50% of patients or animals do not respond to surgical stimuli) of ISO in the New
Zealand White rabbit was 2.05 ± 0.18 % (18). Therefore, it was calculated that rabbits were anesthetized at 0.5 MAC level. This level might be well over minimum alveolar concentration for loss of consciousness (MAC-awake, anesthetic concentration at which 50% of patients do not respond to verbal commands) (19-22). Blood concentration of PROP for loss of consciousness (Cp50_{loss of consciousness}, blood concentration at which 50% of patients do not respond to verbal command) was about 3.3-4.4 μg·ml⁻¹ in humans (23, 24). Infusion rate of PROP to keep this blood concentration was about 9-12 ml·kg⁻¹·h⁻¹. Therefore, the depth of anesthesia of the rabbits receiving PROP in the present study was comparable with those receiving 1% ISO.

Hypercapnia increases sympathetic nervous activities which are followed by an increase in cardiac output and peripheral vasodilatation (25-28). Increases in CBF in both groups were proportional to those in ETCO₂ in the present study. These results suggest that the change in CBF is attributable to the change in cardiac output. CBF in group I was a little higher than that in group P, though not statistically significant. This might be attributable to stronger vasodilatation of ISO than that of PROP (29, 30).

The increase in CBF may induce an increase in total tissue blood flow in oral and maxillofacial region supplied by the external carotid artery because cerebral blood flow supplied by the internal carotid artery was maintained almost constant by the autoregulation mechanisms. Therefore, it was speculated that BBF, MBF and PBF showed increases propotional to the increase in CBF. However, this hypothesis was
rejected.

It was reported that changes in BBF was dependent on CBF changes which were proportional to cardiac output (31). Results of the present study agree with that study because BBF increases were proportional to CBF increases. Therefore, it is suggested that cardiac output is the main determinant of BBF. In contrast, MBF in both groups decreased as ETCO$_2$ increased. In our previous study, tissue oxygen tension of the masseter muscle showed a decrease during hypercapnia with the PaCO$_2$ level at 8 kPa in rabbits (unpublished data). Since measurement of the tissue oxygen tension was performed during muscle relaxation, muscular oxygen consumption could be minimal. Therefore, decreases in tissue oxygen tension of the masseter muscle might be proportional to those in MBF. Previous studies reported that hypercapnia decreased blood flow of skeletal muscles other than head and neck regions (15-17). These results suggest that changes in PaCO$_2$ inversely affect the blood flow of skeletal muscles. PBF was not affected by hypercapnia under both anesthetic conditions. PBF in group I was a little higher than that in group P, though not statistically significant. This might be attributable to stronger vasodilatation of ISO than that of PROP (29, 30).

Our findings indicate that changes in PaCO$_2$ are associated with blood flow redistribution in oral tissues. Although mechanisms for the redistribution is unclear, it is possible that vascular responses to carbon dioxide itself and secondary sympathetic acceleration or inhibition may be different among various tissues such as bone marrow,
skeletal muscles, periosteum, and mucosal membrane (13, 31-33). It is reported that
distributive ratio of adrenergic alpha and beta receptors are different between skeletal
muscles and skin / mucosal membrane (34). This diversity of distribution may
contribute to redistribution of tissue blood flow.

In the clinical situation, it is suggested that if the mandibular medulla is
involved in the surgical field such as orthognathic surgery, bleeding may be reduced
under hypocapnic condition. Anesthesia with PROP may be more preferable to that with
ISO. In contrast, if the skeletal muscles such as the masseter muscle are involved in the
surgical field, bleeding may be reduced under hypercapnic condition. Anesthesia with
PROP may be also more preferable to that with ISO. In addition, PROP is better than
ISO because PROP has strong anti-emetic effects along with clear emergence (35-37).
Therefore, it is suggested that PROP anesthesia with PaCO$_2$ level adjusted by the
planned surgery is a good candidate for oral and maxillofacial surgery. Profound
hypercapnic and hypocapnia may increase arrhythmogenic myocardial sensitivity to
epinephrine which will be used along with local anesthetics during surgery (38).
Therefore, excessive PaCO$_2$ increase or decrease should be avoided.

In the present study, SAP at I5.3 and I8 were higher than I4. However this
difference was only 0.8 kPa and should have minimal effect on tissue blood flows. An
elevation of SAP up to 20 kPa did not change oral mucosal blood flow (39). Since
fentanyl decreases tongue mucosal blood flow in rabbits (10), studies with a
combination of PROP and fentanyl on tissue blood flow deserve future investigation.

In conclusion, oral tissue blood flow was affected by the change in PaCO₂ during both ISO and PROP anesthesia. BBF increase and MBF decrease were both observed during hypercapnia and *vice versa*. Oral tissue blood flow during the PROP anesthesia was relatively less than that during the ISO anesthesia.

**Acknowledgements**

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Table and figure legend

Table 1. ETCO₂ and hemodynamic variables.

Data are expressed as mean ± standard error of the mean.

ETCO₂: End-tidal CO₂ tension, HR: heart rate, SAP: systolic arterial pressure, DAP: diastolic arterial blood pressure.

I4 and P4 show ETCO₂ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show ETCO₂ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show ETCO₂ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show ETCO₂ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 1. Changes in CBF. CBF in both groups increased as ETCO₂ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show ETCO₂ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show ETCO₂ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show ETCO₂ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show ETCO₂ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 2. Changes in BBF. BBF in both group increased as ETCO₂ increased.

Data are expressed as mean ± standard error of the mean.
I4 and P4 show ETCO₂ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show ETCO₂ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show ETCO₂ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show ETCO₂ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 3. Changes in MBF. MBF in both group decreased as ETCO₂ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show ETCO₂ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show ETCO₂ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show ETCO₂ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show ETCO₂ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 4. Changes in PBF. PBF in both group did not changed as ETCO₂ increased.

Data are expressed as mean ± standard error of the mean.

I4 and P4 show ETCO₂ at 4 kPa during isoflurane or propofol anesthesia.

I5.3 and P5.3 show ETCO₂ at 5.3 kPa during isoflurane or propofol anesthesia.

I6.7 and P6.7 show ETCO₂ at 6.7 kPa during isoflurane or propofol anesthesia.

I8 and P8 show ETCO₂ at 8 kPa during isoflurane or propofol anesthesia.

Fig. 5. Relationship between CBF and BBF. Positive correlation (r=0.99 in isoflurane
group and r=0.99 in propofol group) was observed between CBF and BBF.

Fig. 6. Relationship between CBF and MBF. Negative correlation (r=-0.999 in isoflurane group and r=-0.89 in propofol group) was observed between CBF and MBF.

Fig. 7. Relationship between CBF and PBF. No increases (r=0.14 in isoflurane group and r=0.80 in propofol group) in PBF were observed as ETCO₂ increased.
Fig. 1

- CBF (ml/min) for different conditions:
  - I4 P4: ISO
  - I5.3 P5.3: ISO
  - I6.7 P6.7: ISO
  - I8 P8: ISO

- Comparison labels:
  - * $ P < 0.05$ vs I4 or P4
  - # $ P < 0.05$ vs I5.3 or P5.3
  - $ $ P < 0.05$ vs I6.7
PBF
ml\cdot min^{-1}\cdot 100g^{-1}

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<th>ISO</th>
<th>PROP</th>
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<tr>
<td>I4 P4</td>
<td>19.0</td>
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<td>I5.3 P5.3</td>
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<td>I8 P8</td>
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Fig. 4
BBF (ml·min⁻¹·100g⁻¹)

\[ y = 1.49x - 0.62 \ (r = 0.99) \]

\[ y = 1.22x + 4.24 \ (r = 0.99) \]

Fig. 5
Fig. 7

- **PBF**: ml·min⁻¹·100g⁻¹

- **Equations**:
  - \(y = 0.02x + 18.58\) (with \(r = 0.14\))
  - \(y = 0.04x + 10.54\) (with \(r = 0.80\))
Figure 6

MBF
ml min$^{-1}$ 100g$^{-1}$

CBF
ml min$^{-1}$

r = 1.0

r = 0.89

ISO
PROP