Tissue Blood Flow During Remifentanyl Infusion With Carbon Dioxide Loading

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The aim of this study was to investigate the effect of changes in end-tidal carbon dioxide tension (ETCO₂) during remifentanyl (Remi) infusion on oral tissue blood flow in rabbits. Eight male tracheotomized Japan White rabbits were anesthetized with sevoflurane under mechanical ventilation. The infusion rate of Remi was 0.4 µg/kg/min. Carbon dioxide was added to the inspired gas to change the inspired CO₂ tension to prevent changes in the ventilating condition. Observed variables were systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), common carotid artery blood flow (CCBF), tongue mucosal blood flow (TBF), mandibular bone marrow tissue blood flow (BBF), masseter muscle tissue blood flow (MBF), upper alveolar tissue blood flow (UBF), and lower alveolar tissue blood flow (LBF). The CCBF, TBF, BBF, UBF, and LBF values were increased, while MBF was decreased, under hypercapnia, and vice versa. The BBF, UBF, and LBF values were increased, while the MBF value was decreased, under hypercapnia during Remi infusion, and vice versa. The BBF, MBF, UBF, and LBF values, but not the CCBF and TBF values, changed along with ETCO₂ changes during Remi infusion.

Key Words: Remifentanyl; Oral tissue blood flow; Hypercapnia; Hypocapnia; End-tidal carbon dioxide

The oral region comprises mucosa and bone marrow, which include abundant vessels. Control of bleeding during oral and maxillofacial surgery is therefore important to establish a clear surgical field, to avoid blood transfusion, and to secure rapid postoperative recovery. Deliberate hypotension is a conventional method to reduce tissue blood flow during oral and maxillofacial surgery.¹⁻⁴ However, some reports pointed out that this technique may cause brain injury and other complications.^{5,6}

Accordingly, we have researched another approach to control tissue blood flow in the oral region during general anesthesia. Handa et al⁷ reported that hypercapnia increases common carotid artery blood flow (CCBF) and

mandibular bone marrow tissue blood flow (BBF), while it decreases masseter muscle tissue blood flow (MBF). Kemmochi et al⁸ reported that remifentanyl (Remi) decreases CCBF and BBF without a substantial reduction of blood pressure. Koshika et al⁹ reported that Remi decreases tongue mucosal blood flow (TBF), BBF, MBF, upper alveolar tissue blood flow (UBF), and lower alveolar tissue blood flow (LBF) in a dose-dependent manner and that a Remi infusion at a rate of 0.2 µg/kg/min decreases oral tissue blood flow without a substantial reduction of heart rate (HR) and blood pressure. Based on these findings, we suppose that changes in tissue blood flow may be modified by changes in arterial carbon dioxide level during Remi infusion. However, there has been no report that investigates the effect of a combination of Remi infusion and the change in arterial carbon dioxide level on oral tissue blood flow. In this study, therefore, we investigated the effect of changes in

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end-tidal carbon dioxide tension (ETCO₂) during Remi infusion on oral tissue blood flow in rabbits.

METHOD

Eight male Japan White rabbits weighing approximately 2.5 kg were used in this study. All animals received humane care in accordance with the Guideline for the Treatment of Experimental Animals approved by Tokyo Dental College, Chiba, Japan (approval no. 232501).

Anesthesia was induced with 3.0% isoflurane (Forane, Abbott Japan, Tokyo, Japan). Tracheostomy was performed using infiltration anesthesia with 0.5 mL of 1% lidocaine hydrochloride solution (Xylocaine, Astra-Zeneca, Osaka, Japan), and then a 20 Fr pediatric tracheal tube was inserted into the trachea and fixed. Animals were ventilated at a tidal volume of 30 to 50 mL and a respiratory rate of 30 to 40 breaths/min. The ETCO₂ was measured with an anesthetic gas monitor (Capnomac Ultima, Datex, Helsinki, Finland) and maintained at 30 mm Hg. Intravenous indwelling catheters were placed in the right femoral artery and the left posterior auricular marginal vein. These were used for arterial pressure measurement and as a route of fluid infusion and drug administration, respectively. Arterial pressure was continuously recorded with a pressure transducer (P231D, Gould, Oxnard, Calif), and HR was calculated from pressure waveforms. Acetated Ringer solution was infused at a rate of 10 mL/kg/h. Muscular relaxation was induced by an infusion of rocuronium bromide (Eslax, Schering-Plough, Tokyo, Japan) at a rate of 14 µg/kg/min.¹⁰ An incision was performed along the left inferior margin of the mandible without local anesthesia to expose the periosteum of the mandibular body. The periosteum was then detached to expose the surface of the mandibular body. A small hole penetrating into the bone marrow through the cortical bone was performed using a round bur with the diameter of 0.8 mm (ISO 008, Morita, Saitama, Japan). Needle probes of a hydrogen clearance tissue blood flowmeter (UHE-100, Unique Medical, Tokyo, Japan) were inserted into mandibular bone marrow, left masseter muscle, left upper alveolar tissue, and left lower alveolar tissue. The TBF was continuously monitored using a laser Doppler blood flowmeter (AFL21, Advance, Tokyo, Japan). A contact-type probe (type C, Advance) was placed in close contact with the lingual mucosa on the left side. The CCBF was continuously monitored using an ultrasonic blood flowmeter (T108, Transonic, Ithaca, NY). A flow probe (type 3SB, Transonic) was fixed to the left common carotid artery.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), HR, CCBF, and TBF were continuously recorded on a polygraph (Serise360, NEC San-ei, Tokyo, Japan). The BBF, MBF, UBF, and LBF values were analyzed by a data collection analysis system (UCO, Unique Medical, Tokyo, Japan). The rectal temperature was maintained between 39.0°C and 39.5°C throughout the experiment.

After experimental preparation had been completed, isoflurane inhalation was discontinued and inhalation of sevoflurane (Sevofrane, Maruishi Pharmaceutical, Osaka, Japan) was started. Sevoflurane was administered to maintain the end-tidal concentration at 1.8%, 0.5 minimum alveolar concentration for rabbits.¹¹ After the cardiorespiratory parameters had been stabilized for at least 1 hour, the control measurements were performed at an ETCO₂ level of 30 mm Hg. Carbon dioxide was then added to the inhaled air, and ETCO₂ was raised to 40 mm Hg and maintained for 15 minutes to prevent the changes in the ventilating condition. Thereafter, ETCO₂ was again raised to 60 mm Hg and maintained for 15 minutes. All parameters were measured at each time point. Inhalation of CO₂ was then stopped, and the animals were kept at rest for approximately 30 minutes. After recovery of blood pressure and HR to control values was confirmed, Remi (Ultiva: Janssen Pharmaceutical, Tokyo, Japan) infusion at a rate of 0.4 µg/kg/min was started. Each parameter was measured 15 minutes after the start of Remi infusion. Thereafter, CO₂ was again added to the inhaled air. ETCO₂ was raised to 40 and then 60 mm Hg at 15-minute intervals, and all parameters were observed at each time point. Finally, inhalation of CO₂ was stopped and animals were kept at rest for more than 30 minutes. Observations were concluded after the recovery of blood pressure and HR to control values during Remi infusion was confirmed.

Values are expressed as mean ± standard deviation. One-way repeated measurements analysis of variance followed by the Student-Neuman-Keuls test was used for statistical analyses. A *P* value less than .05 was considered statistically significant.

RESULTS

The SBP and MAP values were increased along with ETCO₂ elevation, although they did not change despite ETCO₂ elevation during Remi infusion. The DBP was increased along with ETCO₂ elevation, and it was also increased along with ETCO₂ elevation during Remi infusion. The HR was decreased along with ETCO₂ elevation, and it was also decreased along with ETCO₂

Mean ± SD (n = 8)

* $p < 0.05$ vs respective values at ETCO₂ 30 mmHg

$p < 0.05$ vs between two values at the same ETCO₂ level

Figure 1. Comparisons of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR) during remifentanyl (Remi) infusion with those during no Remi infusion. All variables were decreased during Remi infusion when compared under identical end-tidal carbon dioxide tension (ETCO₂) level. The DBP level was increased and HR was decreased along with ETCO₂ elevation during Remi infusion. Data are shown as mean ± SD (n = 8). * $P < .05$ versus respective values at ETCO₂ 30 mm Hg. # $P < .05$ between two values at the same ETCO₂ level.

elevation during Remi infusion. All of these variables were decreased during Remi infusion, when compared under identical ETCO₂ level (Figure 1).

The CCBF and TBF values were increased along with ETCO₂ elevation, although they did not change despite ETCO₂ elevation during Remi infusion. The BBF, UBF, and LBF values were increased along with ETCO₂ elevation, and they were also increased along with ETCO₂ elevation during Remi infusion. The MBF value was decreased along with ETCO₂ elevation, and it was also decreased along with ETCO₂ elevation during Remi

infusion. All of these variables were decreased during Remi infusion, when compared under identical ETCO₂ level (Figure 2).

The CCBF, BBF, UBF, and LBF values at an ETCO₂ level of 40 mm Hg without Remi infusion were comparable with those at an ETCO₂ level of 60 mm Hg with Remi infusion. In contrast, MBF at an ETCO₂ level of 40 mm Hg without Remi infusion was comparable with that at an ETCO₂ level of 30 mm Hg with Remi infusion.

Figure 2. Comparisons of common carotid artery blood flow (CCBF), tongue mucosal blood flow (TBF), mandibular bone marrow tissue blood flow (BBF), upper alveolar tissue blood flow (UBF), lower alveolar tissue blood flow (LBF), and masseter muscle tissue blood flow (MBF) during remifentanyl (Remi) infusion with those during no Remi infusion. All variables were decreased during Remi infusion when compared under identical end-tidal carbon dioxide tension (ETCO₂) level. The BBF, UBF, and LBF values were increased and MBF was decreased along with ETCO₂ elevation during Remi infusion. Data are shown as mean ± SD (n = 8). **P* < .05 versus respective values at ETCO₂ 30 mm Hg. #*P* < .05 between 2 values at the same ETCO₂ level.

DISCUSSION

In this study, MBF was decreased and other tissue blood flows were increased at a high ETCO₂ level. In contrast, MBF was increased and other tissue blood flows were decreased at a low ETCO₂ level. When Remi was infused, all tissue blood flows were decreased. The CCBF

and TBF values did not change despite ETCO₂ changes during Remi infusion. The CCBF, BBF, UBF, and LBF values at an ETCO₂ level of 60 mm Hg and MBF at an ETCO₂ level of 30 mm Hg during Remi infusion were comparable with those at an ETCO₂ level of 40 mm Hg without Remi infusion.

Handa et al.⁷ reported that deliberate elevation of ETCO_2 under isoflurane anesthesia induced increases in CCBF and BBF and a decrease in MBF, although there was no change in mandibular periosteal blood flow. In addition, HR was decreased while SBP and DBP were increased. Although the present study was performed under sevoflurane anesthesia, the results were similar to those by Handa et al.⁷ Meanwhile, Koshika et al.⁹ reported that SBP, MAP, HR, TBF, BBF, MBF, UBF, and LBF were decreased when Remi was infused at 0.4 $\mu\text{g/kg/min}$ under sevoflurane anesthesia at an ETCO_2 level of 35 to 40 mm Hg. In the present study, similar results were obtained at an ETCO_2 level of 40 mm Hg.

Hypercapnia activates the sympathetic nervous system and increases tissue blood flow.^{12–14} Meanwhile, other studies have reported that skeletal muscle blood flow decreased during hypercapnia¹⁵ or that tissue blood flow in the liver and kidneys increased while muscular blood flow decreased.¹⁶ In the present study, similar results were observed during hypercapnia. Despite apparent hypercapnia-induced activation of the sympathetic nervous system, HR was decreased in this study. Oikawa et al.¹⁷ reported that HR was decreased in healthy rats, although renal sympathetic nervous activity was increased, during hypercapnia. When rats with parasympathetic nervous blockade were exposed to hypercapnia, an elevation of blood pressure and an activation of the sympathetic nervous system similar to those in normal rats were observed.¹⁸ Interestingly, in these rats, the HR decrease observed in normal rats was canceled and it conversely increased. In other words, it is suggested that the decrease in HR in this study might be induced by the predominance of the parasympathetic nervous activities in the sinoatrial node. The HR further decreased when Remi was infused at a high ETCO_2 level. It is suggested that this result may be attributable to a negative chronotropic effect of Remi¹⁹ in addition to the predominance of parasympathetic nervous activities in the sinoatrial node.

In this study, continuous Remi infusion depressed hypercapnia-induced increases in CCBF and TBF. James et al.²⁰ reported that Remi decreased cardiac output. Accordingly, it is suggested that the Remi-induced decrease in cardiac output may cancel the CCBF increase during hypercapnia.

The tongue is a substantial muscle organ surrounded by a thin mucous membrane.²¹ Because the thickness of the lingual mucosa in rabbits is reported to be approximately 0.5 mm²² and the measurement depth of a laser Doppler flowmeter is approximately 0.5 mm to 1 mm,²³ it is suggested that no change in TBF may be attributable to combined measurements of tissue blood flow in both the lingual mucosa and the tongue muscle. In addition, there may be relatively greater distribution of

α -receptors in the vascular smooth muscle of mucosa including the lingual mucosa.^{8,24,25} Therefore, hypercapnia might produce enhanced vasoconstriction.

No change in CCBF during Remi infusion, even under hypercapnia, indicates minimal changes in total blood flow in the craniocervical area. In addition, responses of cerebral blood vessels to CO_2 is maintained during Remi infusion.^{26,27} It is therefore suggested that the changes in oral tissue blood flow other than TBF under hypercapnia may result from a redistribution of muscle blood flow.

The CCBF, BBF, UBF, and LBF values at an ETCO_2 level of 60 mm Hg and MBF at an ETCO_2 level of 30 mm Hg during Remi infusion were comparable with those at an ETCO_2 level of 40 mm Hg without Remi infusion. These results suggest that a combination of mild hyperventilation and Remi infusion could reduce BBF without a substantial increase in MBF. This outcome could be beneficial for oral and maxillofacial surgery, including surgical invasion to the jawbone.

In this study, the infusion rate of Remi was set at 0.4 $\mu\text{g/kg/min}$ based on the report of Koshika et al.,⁹ because this dosage clearly reduced oral tissue blood flow without a substantial decrease in blood pressure. To expose the masseter muscle and periosteum of the mandibular body, skin incisions were performed without local anesthesia to prevent lidocaine-induced changes in tissue blood flow. These surgical procedures per se might influence the tissue blood flow. However, these procedures were essential to place the needle electrodes precisely into the masseter muscle and mandibular bone marrow.

In this study, CCBF was observed as an index of total blood flow in the craniocervical region. However, because cerebral blood flow is supplied mainly by the internal carotid arteries while blood flow in the maxillofacial region is supplied by the external carotid arteries, separate observation of blood flows in the internal and external carotid arteries may allow a more detailed analysis of changes in the distribution of blood flow among tissues. Further study will be required in this respect.

In conclusion, CCBF and TBF did not change despite ETCO_2 changes during Remi infusion. The CCBF, BBF, UBF, and LBF values at an ETCO_2 level of 60 mm Hg and MBF at an ETCO_2 level of 30 mm Hg during Remi infusion were comparable with those at an ETCO_2 level of 40 mm Hg without Remi infusion.

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