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Surgery

Remifentanil decreases oral tissue blood flow while maintaining internal carotid artery blood flow during sevoflurane anesthesia in rabbits

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ABSTRACT. The aim of this study was to investigate the effect of remifentanil infusion on oral tissue blood flow including submandibular gland tissue blood flow (SBF) and internal carotid artery blood flow (ICBF) in rabbits during sevoflurane anesthesia. Twelve male Japan White rabbits were anesthetized with sevoflurane and remifentanil. Remifentanil was infused at 0.2 and 0.4 μg/kg/min. Measurements included circulatory variables, common and external carotid artery blood flow (CCBF, ECBF), ICBF, tongue mucosal blood flow (TMBF), masseter muscle tissue blood flow (MBF), mandibular bone marrow tissue blood flow (BBF), tongue muscle tissue blood flow (TBF) and SBF. Vascular resistances for each tissue, including the tongue mucosa, masseter muscle, mandibular bone marrow, tongue muscle and submandibular gland, were calculated by dividing the mean arterial pressure by the respective tissue blood flow. Remifentanil infusion decreased oral tissue blood flow and circulatory variables. CCBF, ECBF and ICBF did not change. The calculated vascular resistance in each oral tissue, except for the tongue mucosa, increased in an infusion-rate-dependent manner. These results showed that remifentanil infusion reduced TMBF, MBF, BBF, TBF and SBF in an infusion-rate-dependent manner without affecting ICBF under sevoflurane anesthesia.

KEY WORDS: internal carotid artery blood flow, oral tissue blood flow, remifentanil, sevoflurane

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Control of bleeding from the surgical field during oral and maxillofacial surgery, such as orthognathic surgery or oral cancer resection, is critical owing to the abundant microvasculature in the oral mucosa and bone marrow. Although several reports have recommended the use of deliberate hypotension to reduce perioperative blood loss [4, 6, 12, 30], other reports have examined the associated complications, including brain damage resulting from cerebral ischemia [3, 11]. Accordingly, anesthesiologists should prioritize decreasing oral tissue blood flow while maintaining cerebral blood flow during general anesthesia for oral and maxillofacial surgery.

Remifentanil is a μ-opioid receptor agonist like fentanyl. Because remifentanil is metabolized by esterases that are widespread throughout the plasma, red blood cells and interstitial tissues, it has a short context-sensitive half-time [1]. Thus, remifentanil can be administered via continuous intravenous infusion, which allows for the easy maintenance of stable blood concentrations even during prolonged general anesthesia, such as in orthognathic surgery or oral cancer resection.

Remifentanil has been reported to reduce blood flow to the mandibular bone marrow and tongue mucosa without a major decrease in mean arterial blood pressure (MAP) during propofol or sevoflurane anesthesia [16, 19]. In addition, a report has shown that the combined use of nitrous oxide and remifentanil during sevoflurane anesthesia reduces blood flow to the masseter muscle and mandibular bone marrow without lowering blood pressure [15]. Koshika *et al*. reported that the rate of decrease was less in the common carotid artery blood flow (CCBF) than in the tongue mucosal blood flow (TMBF), masseter muscle tissue blood flow (MBF), mandibular bone marrow tissue blood flow (BBF) and upper/lower alveolar tissue blood flow [19]. Based on these findings, it can be speculated that a redistribution of blood flow in the oral tissues occurs during remifentanil infusion. Therefore, the following two hypotheses were proposed. First, although remifentanil decreases TMBF, MBF and BBF, blood flow to other regions is likely to increase. One report has addressed increased salivary secretion during propofol/remifentanil anesthesia [13], while another report demonstrated a correlation between blood flow to the salivary glands and salivary secretion [9]. Accordingly,

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it is suggested that blood flow to the salivary glands may increase during this type of anesthesia. Second, CCBF is the sum of the external carotid artery blood flow (ECBF) and the internal carotid artery blood flow (ICBF). Decreases in blood flow to oral tissues in the absence of major changes in CCBF may be attributable to reduced ECBF in conjunction with a steady or increased ICBF.

To validate these two hypotheses, tongue muscle tissue blood flow (TBF), submandibular gland tissue blood flow (SBF), ICBF and ECBF were investigated in rabbits, in addition to TMBF, MBF and BBF, which were investigated in the previous research [19].

MATERIALS AND METHODS

Animals

The present study was approved by the Ethics Review Board of the Animal Experiments Committee at Tokyo Dental College (approval number: 272571). All animals received humane care in accordance with the guidelines for the treatment of experimental animals, as approved by Tokyo Dental College. Male Japan White rabbits (n=12; weight approximately 2.5 kg; Sankyo Labo, Tokyo, Japan) received rabbit chow and water *ad libitum* until the experiment.

Anesthesia and preparation of animals

Anesthesia was induced by inhalation of 3.0% isoflurane (Forane®; Abbott Japan, Tokyo, Japan). The animals were fixed in the supine position during the experiment. A tracheotomy was performed after subcutaneous injection of 0.5 m*l* 1% lidocaine hydrochloride solution (Xylocaine®; AstraZeneca, Osaka, Japan). A 20 French pediatric tracheal tube was then inserted and fixed in place. A 24-gauge indwelling catheter placed in the left auricular marginal vein was used as the drug delivery route, and Ringer's acetate solution was infused at a rate of 10 m*l*/kg/hr. Rocuronium bromide (Eslax®; Schering-Plough, Tokyo, Japan) was infused at a rate of 14 μg/kg/min [35] under controlled ventilation, and end-tidal carbon dioxide tension ($ETCO_2$) was maintained between 35–40 mmHg using an anesthetic gas monitor (Capnomac; Datex, Helsinki, Finland). After dissecting the right femoral artery and placing a 22-gauge catheter, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP and heart rate (HR) were continuously measured using a pressure transducer (model P231D; Gould, Oxnard, CA, U.S.A.); HR was calculated from pressure waveforms. CCBF and ICBF were continuously measured by attaching the probes (Type 3SB, Type 1.5PSB; Transonic Systems Inc., Ithaca, NY, U.S.A.) of an ultrasonic blood flowmeter (model TS420; Transonic Systems Inc.) to the left common carotid artery near the 5th or 6th cervical vertebra and the left internal carotid artery immediately after branching from the common carotid artery. ECBF was calculated as the difference between the CCBF and ICBF. The probe (type C; Unique Medical, Tokyo, Japan) of a laser Doppler blood flowmeter (model ALF21; Unique Medical) was placed in contact with the left dorsal surface of the tongue mucosa in order to measure TMBF. To eliminate the vasodilatory effect of lidocaine hydrochloride, an incision was made without local anesthesia on the left inferior margin of the mandible to expose the masseter muscle and mandibular periosteum. The periosteum was removed, and a small hole with an approximately 1-mm diameter was created to expose the mandibular bone marrow by using a round bar (ISO 008; Morita, Saitama, Japan). The probes of a hydrogen clearance blood flowmeter (UHE-100; Unique Medical) were inserted into the left masseter muscle, mandibular bone marrow, left anterior tongue muscle and left submandibular gland in order to measure the MBF, BBF, TBF and SBF, respectively. A heat lamp was used to keep the whole-body warm, and rectal temperature was maintained between 39.0 and 39.5°C during the study. To prevent the surgical field from drying, a few pieces of gauze wetted with physiological saline solution were placed there during the experiment.

After the experimental preparation was complete, inhalation of isoflurane was terminated and anesthesia was maintained using 1.8% sevoflurane (Sevofrane®; Maruishi Pharmaceuticals, Osaka, Japan) [16, 19, 32]. Control measurements were recorded when the respiratory and circulatory variables were stabilized after at least 1 hr of rest. SBP, DBP, MAP, HR, CCBF, ICBF and TMBF were continuously monitored using a polygraph device (Series 360; NEC Sanei, Tokyo, Japan). MBF, BBF, TBF and SBF were measured using the hydrogen clearance blood flowmeter, and analyzed using a data collection and analysis software system (model UCO; Unique Medical). Furthermore, tongue mucosal vascular resistance (TMVR), masseter muscle vascular resistance (MVR), mandibular bone marrow vascular resistance (BVR), tongue muscle vascular resistance (TVR) and submandibular glandular vascular resistance (SVR) were calculated by dividing the MAP by the respective tissue blood flow. Each resistance is expressed as a percentage of the respective baseline value.

Study protocol

After recording the baseline measurements, remifentanil (Ultiva®; Janssen Pharmaceutical, Tokyo, Japan) was infused at 0.2 and 0.4 μg/kg/min over 20 min in this order. Measurements were again taken 20 min after the infusion was completed.

Statistical analysis

Data are shown as the mean ± standard deviation. Repeated-measures analysis of variance and Dunnett's tests were used to compare the changes in circulatory variables against the respective control value. The Kruskal-Wallis H-test and Mann-Whitney *U*-test with Bonferroni correction were used to compare changes in blood flow and vascular resistance in each type of tissue. A P value less than 5% was considered statistically significant.

RESULTS

A continuous infusion of remifentanil reduced oral tissue blood flow and circulatory variables such as HR and SBP, while ICBF

Table 1. Hemodynamic variables and tissue blood flow

	Baseline	Remifentanil		20 min after the finish of infusion
		0.2 μg/kg/min	0.4 μg/kg/min	
Heart rate (beats per min)	293.5 ± 17.1	274.6 ± 23.0[a)]	261.8 ± 43.9[a)]	303 ± 30.5
Systolic blood pressure (mmHg)	113.0 ± 13.6	106.2 ± 12.8[a)]	106.8 ± 9.9[a)]	120.5 ± 13.1[a)]
Diastolic blood pressure (mmHg)	54.0 ± 7.1	52.6 ± 7.9	55.0 ± 6.8	61.4 ± 8.0[a)]
Mean arterial pressure (mmHg)	74.3 ± 7.4	71.5 ± 7.3	73.9 ± 6.8	82.2 ± 6.2[a)]
Common carotid artery blood flow (ml/min)	41.8 ± 8.8	38.0 ± 6.7	37.5 ± 8.1	41.4 ± 7.4
Internal carotid artery blood flow (ml/min)	16.6 ± 8.4	15.7 ± 7.6	15.9 ± 6.8	15.7 ± 7.3
External carotid artery blood flow (ml/min)	25.2 ± 6.4	22.3 ± 5.6	21.6 ± 8.6	25.4 ± 6.5
Tongue mucosal blood flow (ml/100 g/min)	31.5 ± 6.0	28.6 ± 5.9	27.6 ± 6.3[a)]	31.4 ± 5.6
Masseter muscle tissue blood flow (ml/100 g/min)	34.1 ± 9.2	29.6 ± 7.9[a)]	23.2 ± 7.5[a)]	31.7 ± 9.8
Mandibular bone marrow tissue blood flow (ml/100 g/min)	40.3 ± 18.2	34.4 ± 15.5[a)]	24.8 ± 8.9[a)]	28.5 ± 10.6[a)]
Tongue muscle tissue blood flow (ml/100 g/min)	60.3 ± 16.5	52.8 ± 13.6[a)]	47.7 ± 12.5[a)]	52.5 ± 13.6[a)]
Submandibular gland tissue blood flow (ml/100 g/min)	47.9 ± 11.4	40.7 ± 10.4[a)]	35.6 ± 9.1[a)]	41.8 ± 10.1[a)]

Data are presented as the mean ± standard deviation (n=12). a) indicate significant differences compared with baseline ($P<0.05$).

did not change. (Table 1, Figs. 1 and 2). TMBF, MBF, BBF, TBF and SBF decreased in an infusion-rate-dependent manner. In addition, 20 min after discontinuing the remifentanil infusion, SBP, DBP and MAP were higher and BBF, TBF and SBF were decreased compared to baseline.

The rate of the decrease in blood flow to each oral tissue was similar when the infusion rate was set at 0.2 μg/kg/min; however, at 0.4 μg/kg/min, the rates of decrease were greater in the MBF and BBF than in the TMBF (ECBF 11%, TMBF 9%, MBF 13%, BBF 14%, TBF 12% and SBF 15% at 0.2 μg/kg/min; ECBF 14%, TMBF 11%, MBF 31%, BBF 33%, TBF 20% and SBF 25% at 0.4 μg/kg/min) (Fig. 2).

Vascular resistance in each oral tissue except for TMVR increased in an infusion-rate-dependent manner. At 0.4 μg/kg/min, MVR increased by approximately 52%, BVR by 66%, TVR by 28% and SVR by 36%, respectively. The MVR and BVR increased more significantly than the TVR (Fig. 3).

DISCUSSION

The two main findings of the present study are as follows: a) remifentanil infused at 0.2 and 0.4 μg/kg/min caused no change in the ICBF in rabbits under sevoflurane anesthesia; and b) TMBF, MBF, BBF, TBF and SBF decreased in an infusion-rate-dependent manner, with a marked decrease in the blood flow to tissues at 0.4 μg/kg/min.

In the present study, isoflurane was used during the experimental preparation because the MAC (minimum alveolar concentration) of isoflurane is lower than that of sevoflurane, and therefore isoflurane has stronger anesthetic effects. Additionally, since Okamoto *et al*. [27] reported that blood flow increased in all oral tissues during isoflurane inhalation, sevoflurane was used for the maintenance of anesthesia during the observation period when at least 1 hr had elapsed following the discontinuation of isoflurane administration. Data collection was started after confirming that the inspiratory concentration of isoflurane was zero.

Koshika *et al*. [19] reported that CCBF decreased by up to 10%, and MBF and BBF decreased by approximately 30–40% during remifentanil infusion at 0.2 and 0.4 μg/kg/min; moreover, TMBF decreased by approximately 20% during those infusions under 1.8% sevoflurane anesthesia. In the present study, CCBF decreased by approximately 10% during remifentanil infusion at 0.2 and 0.4 μg/kg/min. At 0.4 μg/kg/min, the decreases in oral tissue blood flow were similar to those reported by Koshika *et al*. [19], with the exception of TMBF.

In the present study, the probe of an ultrasonic transit-time type of blood flow measuring equipment that is less affected by changes in vessel diameter was used to measure the absolute value of the blood flow. Since the control value of the CCBF in the present study was consistent with the data reported by Koshika *et al*. [19], it appears that the probe used in the present study had a minimal influence on the measurement of arterial blood flow. TMBF and TBF were also measured in the present study. TMBF was measured using a laser Doppler blood flowmeter as in the study by Koshika *et al*. [19], while the probe of a hydrogen clearance tissue blood flowmeter was inserted into the tongue muscle tissue for TBF measurement. Notably, the insertion of the probe into this tongue muscle has the potential to change blood flow distribution in the tongue tissue and thereby affect TMBF.

Compared to baseline, SBP, DBP and MAP were higher, and BBF, TBF and SBF were decreased at 20 min after the cessation of the remifentanil infusion. Slightly elevated blood pressures during this period were also observed in a previous study [15]. Prolonged decreases in tissue blood flow following the end of the remifentanil infusion suggest that these decreases require a long time to recover. BBF recovered about 1 hr after cessation of the 0.4 μg/kg/min remifentanil infusion (unpublished data).

The common carotid artery branches into the external and internal carotid arteries, and blood flow to the oral and maxillofacial region is supplied primarily by the external carotid artery. In humans, the internal carotid artery provides approximately 70% of the blood supply to the brain; the remainder is provided by the vertebral arteries [8, 31]. Although blood flow in the internal and external carotid arteries in rabbits has been investigated in one report [26], measurements were not collected under natural

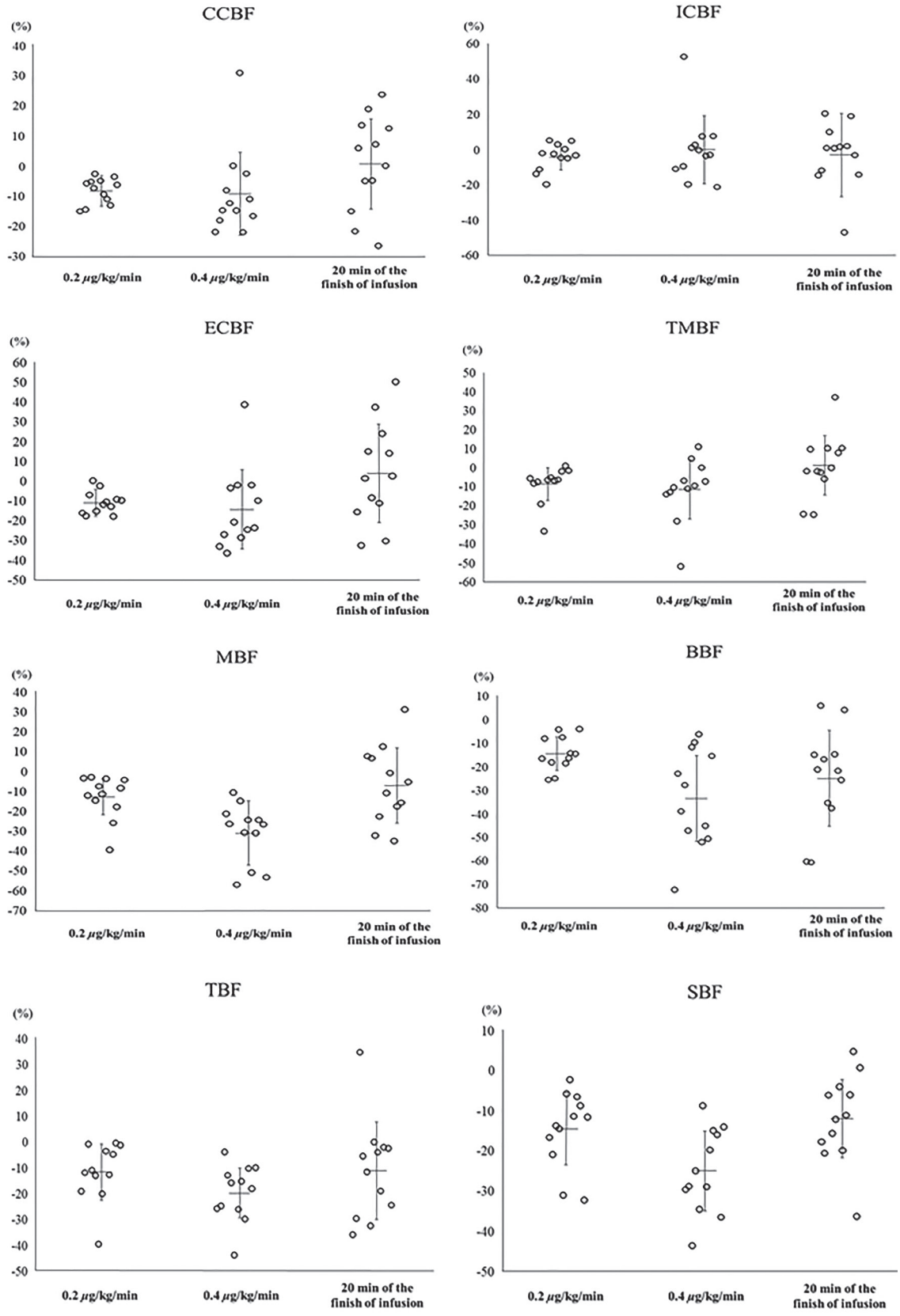

Fig. 1. Rates of decrease in the common, internal, and external carotid artery and oral tissue blood flow during remifentanil infusion. Abbreviations: CCBF, common carotid artery blood flow; ICBF, internal carotid artery blood flow; ECBF, external carotid artery blood flow; TMBF, tongue mucosal blood flow; MBF, masseter muscle tissue blood flow; BBF, mandibular bone marrow tissue blood flow; TBF, tongue muscle tissue blood flow; SBF, submandibular gland tissue blood flow. Bars indicate the mean ± SD.

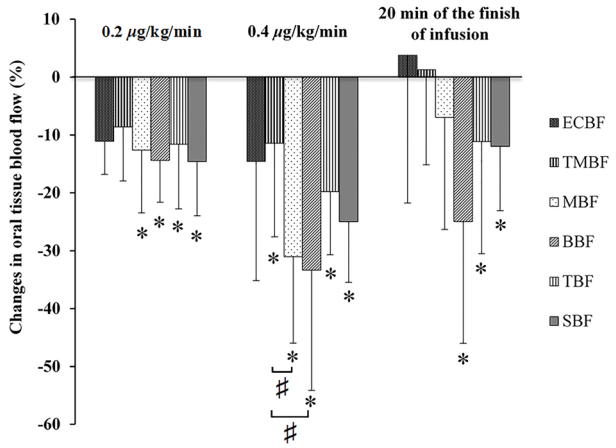

Fig. 2. Changes in external carotid artery blood flow and oral tissue blood flow during remifentanil infusion. Tongue mucosal blood flow, masseter muscle tissue blood flow, mandibular bone marrow tissue blood flow, tongue muscle tissue blood flow and submandibular gland tissue blood flow decreased in an infusion-rate-dependent manner. Bars indicate the mean ± SD. Asterisks indicate significant differences compared with baseline (P<0.05). Sharp signs indicate significant differences between two groups (P<0.05). Abbreviations: ECBF, external carotid artery blood flow; TMBF, tongue mucosal blood flow; MBF, masseter muscle tissue blood flow; BBF, mandibular bone marrow tissue blood flow; TBF, tongue muscle tissue blood flow; SBF, submandibular gland tissue blood flow.

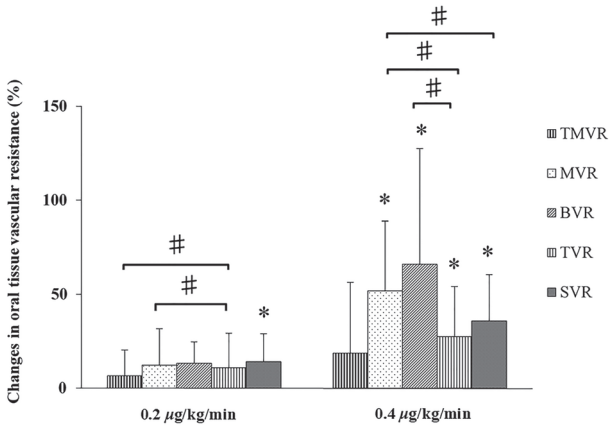

Fig. 3. Changes in the vascular resistance of the oral tissue during remifentanil infusion. Remifentanil infused at a rate of 0.4 μg/kg/min increased vascular resistance in all oral tissues except for the tongue mucosa. Bars indicate the mean ± SD. Asterisks indicate significant differences compared with baseline (P<0.05). Sharp signs indicate significant differences between two groups (P<0.05). Abbreviations: TMVR, tongue mucosal vascular resistance; MVR, masseter muscle vascular resistance; BVR, bone marrow vascular resistance; TVR, tongue muscle vascular resistance; SVR, submandibular glands vascular resistance.

conditions, because the measurement method for one carotid artery required the clipping of the other carotid artery. There have been several reports on blood flow in the middle cerebral artery in humans and laboratory animals during continuous remifentanil infusion using ultrasonic Doppler measurement equipment [10, 17, 18, 21, 37]. However, no previous report has addressed the changes in internal carotid artery blood flow during remifentanil infusion. In human studies using positron emission tomography, remifentanil infusion at 0.05 or 0.15 μg/kg/min resulted in increased cerebral blood flow to the prefrontal cortex, inferior parietal lobe, and supplementary motor area, and decreased blood flow to the cerebellum, superior temporal lobe, and midbrain gray matter [37]. Moreover, a study in adult subjects under sedation reported that remifentanil infusion between 0.05 and 0.2 μg/kg/min resulted in increased or decreased blood flow to the brain depending on the specific tissue, without changes in partial pressure of carbon dioxide in arterial blood ($PaCO_2$) [18, 21, 37]. High doses of remifentanil that are not used clinically (2.0 μg/kg/min and 4.0 μg/kg/min) have also been reported to decrease cerebral blood flow [17].

Remifentanil is known to cause hypotension and bradycardia [7, 39]. Ogoh *et al*. reported that cerebral blood flow is maintained by the redistribution of blood flow from the external to internal carotid arteries during periods of hypotension in healthy adults [25]. Furthermore, Lagace *et al*. reported that cerebral autoregulation was maintained in pediatric patients under remifentanil/propofol anesthesia and that cerebral blood flow did not change despite the decreased MAP and HR [20]. In the present study, decreased HR and SBP were observed during remifentanil infusion at 0.2 and 0.4 μg/kg/min, though ICBF was not affected by these changes. The above observations suggest that ICBF, and thus cerebral blood flow, is maintained by cerebral autoregulatory mechanisms during remifentanil infusion at 0.2 and 0.4 μg/kg/min. Although hypotension and bradycardia occur during remifentanil infusion at 0.4 μg/kg/min in humans, these changes were not observed in the present study. On the other hand, Koshika *et al*. [19] reported that remifentanil infusion at both 0.8 and 1.6 μg/kg/min caused significant hypotension and bradycardia in rabbits. Accordingly, the sensitivity of hemodynamic changes to remifentanil may be less in rabbits than in humans. Although Koshika *et al*. noted the possibility that blood flow between the oral tissues and the cerebral tissues is redistributed during remifentanil infusion [19], the results in the present study suggest that such a redistribution is unlikely.

In the present study, the rates of decreased TMBF, MBF, BBF, TBF and SBF did not exceed 15% during remifentanil infusion at 0.2 μg/kg/min. However, when the infusion rate was increased to 0.4 μg/kg/min, variations in the decreased rate of blood flow among the different types of oral tissue emerged, showing greater rates of decrease in the MBF and BBF than in the TMBF. Moreover, changes in the vascular resistance of each oral tissue except for TMVR increased during remifentanil infusion at 0.4 μg/kg/min, and the increases were greater in the MVR and BVR than in the TVR.

Volatile anesthetics have a vasodilatory effect and thereby decrease systemic vascular resistance [5, 28]. Okamoto *et al*. noted that vasodilation caused by volatile anesthetics increased oral tissue blood flow [27]; therefore, sevoflurane is believed not to increase the peripheral vascular resistance of the oral tissue. The present findings of increased vascular resistance in oral tissues

oppose the widely held view that remifentanil enhances parasympathetic nervous system activity, which leads to decreases in systemic vascular resistance [2]. In a study by Noseir *et al*., no hemodynamic changes were observed in human subjects during remifentanil infusion, though blood flow to the forearms increased [24]. Urination was increased in patients receiving remifentanil under general anesthesia; however, this was thought to be attributable to suppression of the stress response by remifentanil, which enabled blood flow to the kidneys to be maintained [22]. These observations suggest that remifentanil causes vasodilation in the organs and extremities, which may lead to the redistribution of blood flow from the head and neck area to these regions. However, no reports characterizing this mechanism have been published to date, and we leave this topic open for further study.

In the present study, the hypothesis that SBF would increase while TMBF, MBF, and BBF would decrease during remifentanil infusion was investigated. However, the present findings indicate that SBF decreases in an infusion-rate-dependent manner, which suggests that the redistribution of blood flow in the oral and maxillofacial region is not attributable to increased SBF. Salivary secretion is controlled mainly by the parasympathetic nervous system [29], and remifentanil enhances parasympathetic activity [2]. Salivary secretion has been shown to increase during general anesthesia using remifentanil in humans [13]. In addition, there is a correlation between blood flow to the salivary glands and salivary secretion in anaesthetized cats [9]. Therefore, it is possible that parotid or other salivary gland tissue blood flow, which was not observed in the present study, had increased.

The rate of decrease was less in the TMBF than in the MBF, BBF, TBF and SBF during remifentanil infusion. Koshika *et al*. also found a lower rate of decrease in the TMBF than in the other oral tissues [19]. Although oral tissue blood flow is supplied by the external carotid artery, there was a difference in the rate of decrease in the oral tissue blood flow in the present study. This result may be attributable to the difference in distribution density of the α-adrenoceptors in the blood vessels in the oral region. The distribution of α-adrenoceptors is greater in mucosal blood vessels than in the muscle and bone marrow blood vessels [23, 38]. It is reported that fentanyl has been shown to relax the aorta of rabbits and rats via an α-adrenoceptors-blocking action [14, 36] and to attenuate pulmonary artery contraction via $\alpha_{1\beta}$-adrenoceptors inhibition [33]. Therefore, it is suggested that remifentanil may contribute to the redistribution of blood flow among oral tissues through a similar mechanism. Moreover, given the finding of no significant decrease in the ECBF during remifentanil infusion, it is suggested that the redistribution of blood flow in oral and maxillofacial tissues may involve the deep tissue and skin/mucosa. To date, no reports have discussed the effects of remifentanil on blood flow to the skin, and this topic warrants investigation in the future.

In the present study, remifentanil reduced the TMBF, MBF, BBF, TBF and SBF in an infusion-rate-dependent manner. Decreased oral tissue blood flow should lessen bleeding from the surgical field during oral and maxillofacial surgery. However, the decreased tissue blood flow caused by remifentanil might lead to a concomitant reduction in tissue oxygen tension [34]. Since tissue hypoxia may aggravate wound healing, this issue should be examined in further studies.

Remifentanil suppresses stress hormone secretion caused by surgical invasion [22] and can be administered via continuous intravenous infusion, which facilitates the maintenance of stable blood concentrations even during prolonged general anesthesia. The present study showed that remifentanil reduced oral tissue blood flow without significant changes in cerebral blood flow when infused at 0.2 and 0.4 μg/kg/min. Therefore, remifentanil can be considered a suitable analgesic agent for oral surgery in human and animals.

In conclusion, remifentanil infusion reduced the blood flow of the tongue mucosa, masseter muscle tissue, mandibular bone marrow tissue, tongue muscle tissue and submandibular gland tissue without changing internal carotid artery blood flow under sevoflurane anesthesia in rabbits.

CONFLICTS OF INTEREST. The authors have no conflicts of interest to declare.

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