



# Remifentanil infusion during desflurane anesthesia reduces tissue blood flow while maintaining blood pressure and tissue oxygen tension in the masseter muscle and mandibular bone marrow

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**ABSTRACT.** The aim of this study was to compare changes in tissue blood flow and tissue oxygen tension in the masseter muscle and mandibular bone marrow induced by remifentanil under desflurane or sevoflurane anesthesia. Eleven male tracheotomized Japan White rabbits were anesthetized with desflurane or sevoflurane under mechanical ventilation. The order of the inhalation of desflurane or sevoflurane was randomized. Desflurane or sevoflurane was administered at 1.0 minimum alveolar concentration and remifentanil was infused at 0.4 µg/kg/min. Observed variables included heart rate (HR), blood pressure (BP), common carotid artery blood flow (CCBF), mandibular bone marrow tissue blood flow (BBF), masseter muscle tissue blood flow (MBF), mandibular bone marrow tissue oxygen tension (PbO<sub>2</sub>), and masseter muscle tissue oxygen tension (PmO<sub>2</sub>). Two way repeated measures ANOVA showed no interaction between volatile anesthetics and remifentanil infusion except for MBF. There were significant differences in HR, SBP, DBP, MAP and CCBF between desflurane and sevoflurane groups. There were also significant differences in HR, SBP, DBP, MAP, CCBF, BBF and PbO<sub>2</sub> before, during and after remifentanil infusion. Desflurane reduced tissue blood flow in the masseter muscle and mandibular bone marrow while better maintained HR and BP than sevoflurane. Under remifentanil infusion, although both anesthetics reduced tissue blood flow, tissue oxygen tension was maintained in masseter muscle and mandibular bone marrow.

**KEY WORDS:** desflurane, oral tissue blood flow, oral tissue oxygen tension, remifentanil, sevoflurane

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Because oral and maxillofacial surgery is performed in the region which has an abundant blood supply, controlling tissue blood flow makes a major contribution to improving the visibility of the surgical field and reducing blood loss. We have previously conducted a number of studies focusing on the effect of volatile anesthetics and opioids on oral tissue blood flow [10, 14, 15, 17].

Volatile anesthetics affect both hemodynamics and oral tissue blood flow [17]. Okamoto *et al.* reported that sevoflurane at 1.0 minimum alveolar concentration (MAC) reduces blood pressure and increases tissue blood flow in the masseter muscle in rabbits [17]. In contrast, desflurane at 1.0 MAC did not reduce blood pressure and maintain tissue blood flow in the masseter muscle and mandibular bone marrow in rabbits [17]. This is because desflurane has less vasodilatory effects than sevoflurane [1, 18], and this agent thus has less effects on blood pressure and tissue blood flow in the masseter muscle and mandibular bone marrow [17].

Desflurane has a low blood/gas partition coefficient, thus it can rapidly induce anesthesia. It also has the lowest metabolic rate of any of the volatile anesthetics [7, 26]. However, the anesthetic effect is weak because of high MAC value, and analgesic effects are minimal as with other volatile anesthetics. Therefore, in its clinical use in general anesthesia, opioids such as remifentanil are often employed for pain relief.

Remifentanil is a µ-receptor agonist [2]. With both a short duration of action [6], and a short context-sensitive half-time [13] remifentanil provides stable analgesia under continuous infusion. This makes the agent suitable for pain control during general anesthesia.

Remifentanil infusion during sevoflurane anesthesia reduces tissue blood flow in the masseter muscle and mandibular bone

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marrow in a dose-dependent manner [15]. Hirata *et al.* reported that the reduction in tissue blood flow in the masseter muscle and mandibular bone marrow during remifentanyl infusion under sevoflurane anesthesia without changes in internal carotid artery blood flow is greater than the reduction in tissue blood flow in oral mucosa, and suggested that blood flow might be redistributed from the masseter muscle and mandibular bone marrow to skin and oral mucosa [10]. The reduction in tissue blood flow in the masseter muscle and the mandibular bone marrow can be expected to reduce blood loss during oral surgery, while a reduction in blood flow may cause hypoxia. Terakawa *et al.* have reported that tissue blood flow and tissue oxygen tension in the masseter muscle and mandibular bone marrow increased on the ipsilateral side after stellate ganglion block, while decreased on the contralateral side in a rabbit model, indicating that oral tissue blood flow positively correlated with tissue oxygen tension [23].

Meanwhile, when remifentanyl was infused during sevoflurane anesthesia, tissue blood flow in the masseter muscle and mandibular bone marrow decreased, while tissue oxygen tension was maintained [14]. Kobayashi *et al.* showed that tissue oxygen consumption declined during continuous remifentanyl infusion by calculating the difference between arterial and venous blood oxygen contents [14]. Thus, the maintenance of tissue oxygen tension suggests that tissue oxygen demand/supply balance is well-maintained during remifentanyl infusion.

Although previous studies have addressed the effect of remifentanyl infusion during sevoflurane anesthesia on oral tissue blood flow and oral tissue oxygen tension [10, 14, 15], no other study has described the relationship of remifentanyl infusion to oral tissue blood flow and oral tissue oxygen tension during desflurane anesthesia. We therefore hypothesized that continuous infusion of remifentanyl during desflurane anesthesia would reduce tissue blood flow in the masseter muscle and mandibular bone marrow, while maintain the tissue oxygen tension under well-maintained hemodynamics. Specifically, we expected heart rate and blood pressure would be higher during remifentanyl infusion under desflurane anesthesia than under sevoflurane anesthesia. In contrast, tissue blood flows in the masseter muscle and mandibular bone marrow would decrease in a similar degree during remifentanyl infusion under desflurane and sevoflurane anesthesia, and tissue oxygen tension would be maintained.

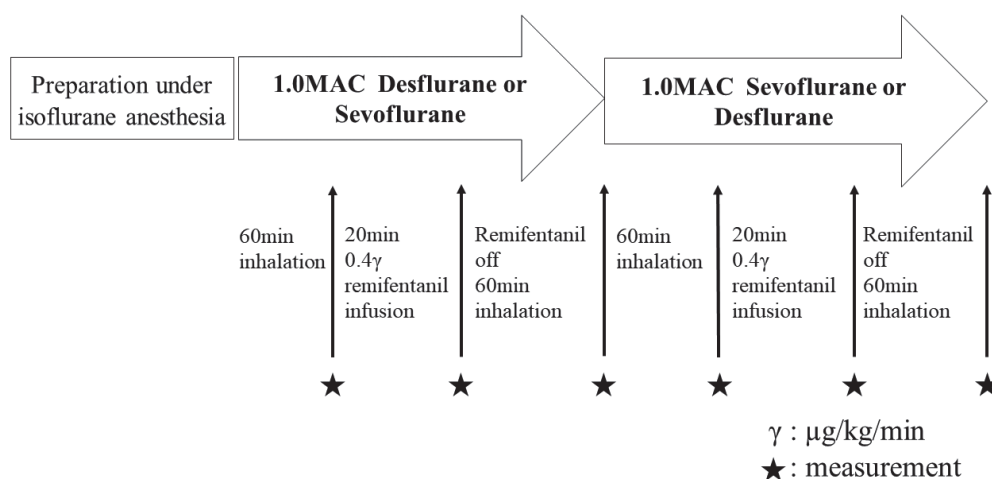
Our objective in this study was thus to investigate the effect of remifentanyl infusion during desflurane anesthesia on circulatory variables as well as on tissue blood flow and tissue oxygen tension in the masseter muscle and mandibular bone marrow, and to compare the results with the effects of remifentanyl during sevoflurane anesthesia.

## MATERIAL AND METHODS

This study was approved by the Animal Research Ethics Committee at Tokyo Dental College (approval number 192702). Eleven male Japanese White rabbits weighing about 2.5 kg (Sankyo Labo, Tokyo, Japan) were used in this study, and received humane care in accordance with the guidelines for experimental animals approved by Tokyo Dental College. All animals were given free access to water and food until the morning of the day of the experiment.

Anesthesia was induced by inhalation of 4.0% isoflurane (Forane<sup>®</sup>; Abbott, Japan, Tokyo, Japan) via a mask. After the rabbits were secured in the supine position and received infiltration anesthesia with 0.5 ml of 1% lidocaine hydrochloride solution (Xylocaine<sup>®</sup>; AstraZeneca, Osaka, Japan), tracheotomy was performed via cervical midline incision, and a 20 French pediatric tracheal tube was inserted into the trachea and secured. Two 22-gauge catheters were placed in the right femoral artery and the left posterior auricular vein for arterial pressure measurement and as a route of drug administration. Acetated Ringer's solution was administered at 10 ml/kg/hr until the end of the experiment. Muscle relaxation was achieved by an administration of rocuronium bromide (Eslax<sup>®</sup>; Schering-Plough, Tokyo, Japan) at 14 µg/kg/min [24]. Rabbits were ventilated with a tidal volume of 30 to 50 ml and a respiratory rate of 30 to 40 times per min. End-tidal carbon dioxide tension was measured using an anesthesia gas monitor (Capnomac<sup>®</sup>; Datex, Helsinki, Finland) and was maintained between 35 and 40 mmHg. Blood pressure was recorded continuously with a pressure transducer (model P231D; Gould Oxnard, CA, USA). Heart rate (HR) was calculated from the pressure waveform. The probe (type 3SB; Transonic, Ithaca, NY, USA) of an ultrasound blood flowmeter (T108; Transonic) was attached to the left common carotid artery. An incision was made from the left inferior margin of the mandible to expose the periosteum of the mandibular body. Local anesthesia was not used during this procedure to avoid effects on tissue blood flow by the vasodilatory effects of lidocaine. The periosteum was detached to expose the bone surface. A round bur with a diameter of 1.0 mm (ISO 008; Morita, Saitama, Japan) was used to make a hole in the cortical bone to provide access to the mandibular bone marrow. The probe of hydrogen clearance tissue blood flowmeter (UHE-100; Unique Medical, Tokyo, Japan) was inserted into the left mandibular bone marrow and left masseter muscle. The probe of tissue oxygen tension (UOE-04T; Unique Medical) was also inserted into the same sites [22]. The tips of probes were adjusted to be 2 mm apart from each other.

After experimental preparation was completed, isoflurane was replaced with desflurane (Suprane<sup>®</sup>; Baxter, Tokyo, Japan) or sevoflurane (Sevofrane<sup>®</sup>; Maruishi Pharmaceutical, Tokyo, Japan) for inhalational anesthesia. Each animal was observed during both desflurane and sevoflurane anesthesia, with the order of inhalation decided at random. Sixty min after the experimental preparations, and after confirming stable circulatory variables at end-tidal concentration of the volatile anesthetic at 1.0 MAC level, baseline measurements were performed. Desflurane was inhaled at a concentration of 8.9% and sevoflurane at 3.7% [4, 21]. Fraction of inspiratory oxygen was set at 0.4. The observed variables included HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), common carotid artery blood flow (CCBF), mandibular bone marrow tissue blood flow (BBF), masseter muscle tissue blood flow (MBF), mandibular bone marrow tissue oxygen tension (PbO<sub>2</sub>), and masseter muscle tissue oxygen tension (PmO<sub>2</sub>). All circulatory variables were continuously recorded on a tachometer (HRM-100; Unique Medical). BBF, MBF, PbO<sub>2</sub>, and PmO<sub>2</sub> were analyzed by a data collection analysis system (model UCO; Unique Medical). After baseline measurements, remifentanyl (Ultiva<sup>®</sup>; Janssen Pharmaceutical, Tokyo, Japan) was infused at a rate of 0.4 µg/kg/min for 20



**Fig. 1.** The experimental protocols. After confirming stable circulatory variables at end-tidal concentration of the desflurane or sevoflurane at 1.0 minimum alveolar concentration (MAC) level, baseline measurements were performed. After baseline measurements, remifentanil was infused at a rate of 0.4  $\mu\text{g}/\text{kg}/\text{min}$  for 20 min. Measurements were 20 min after the start of remifentanil infusion, and 60 min after the completion of remifentanil infusion.

min. Measurements were 20 min after the start of remifentanil infusion, and 60 min after the completion of remifentanil infusion (Fig. 1).

An investigation using mean MAP values measured in desflurane and sevoflurane anesthesia in a preliminary experiment found that at least 10 rabbits were needed for have enough statistical power ( $\alpha$  error=0.05,  $\beta$  error=0.2). We therefore used 11 rabbits in this study. All data are expressed as mean  $\pm$  standard deviation. Statistical analysis was conducted using two way repeated measures ANOVA. The SPSS ver. 27 was used for the statistical analyses. A *P* values less than 0.05 was considered statistically significant.

## RESULTS

Seven rabbits received sevoflurane at first and then received desflurane. Four rabbits received desflurane at first and then received sevoflurane.

Changes in HR, SBP, DBP, MAP and CCBF during desflurane or sevoflurane anesthesia are shown in Fig. 2. HR, SBP, DBP, MAP, and CCBF in the desflurane group were higher than those in the sevoflurane group. Two way repeated measures ANOVA showed no interaction between volatile anesthetics and remifentanil infusion except for MBF. Thus, MBF in the desflurane group was lower than that in the sevoflurane group before, during and after remifentanil infusion. In contrast, BBF,  $\text{PbO}_2$  and  $\text{PmO}_2$  were similar in both groups (Figs. 3 and 4).

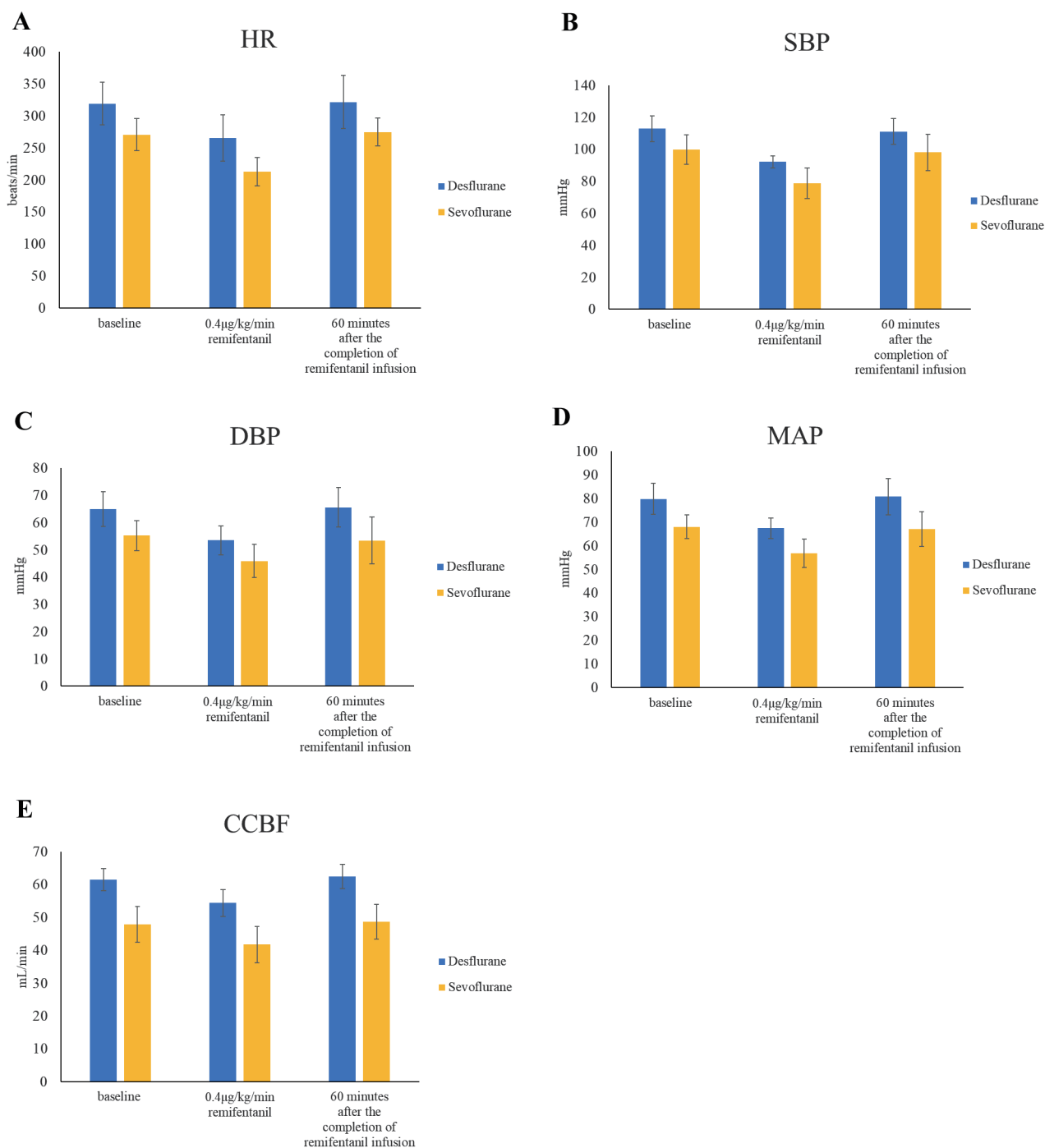
HR, SBP, DBP, MAP and CCBF in both groups were lower than their baseline values 20 min after starting remifentanil infusion (Fig. 2). MBF and BBF in both groups were reduced during remifentanil infusion (Fig. 3).  $\text{PbO}_2$  in both groups increased slightly during remifentanil infusion, while  $\text{PmO}_2$  remained unchanged (Fig. 4). Sixty min after discontinuation of remifentanil, all variables had returned to their baseline levels in both groups.

## DISCUSSION

HR, SBP, DBP and MAP were higher in the desflurane group than those in the sevoflurane group throughout the experiment. At 1.0 MAC level, HR is higher during desflurane anesthesia than during sevoflurane anesthesia in dogs [19]. This occurs through decreasing cardiac vagal activity [19]. Differences in vagal activity due to desflurane and sevoflurane are thought to cause a difference in HR [19]. Volatile anesthetics have a vasodilatory effect, reducing arterial pressure in a dose-dependent manner [12, 25]. Desflurane has a less vasodilatory effect than sevoflurane in rats [1]. Because of these mechanisms, desflurane might produce higher HR, SBP, DBP and MAP than sevoflurane in this study.

CCBF was also higher in the desflurane group than that in the sevoflurane group. Because both desflurane and sevoflurane reduce blood pressure by decreasing vascular resistance, cardiac output is relatively preserved [5, 7]. Although both desflurane and sevoflurane reduce stroke volume in dogs [16], cardiac output is higher in desflurane anesthesia than sevoflurane anesthesia because desflurane increases HR to a greater extent than sevoflurane [19]. Therefore, CCBF might be greater in desflurane anesthesia in this study.

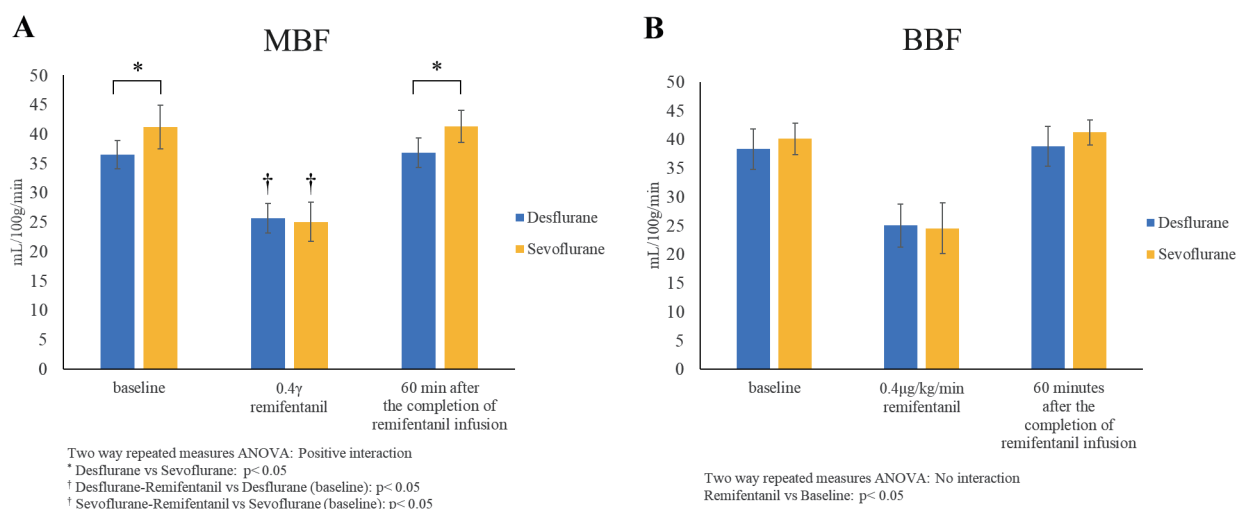
MBF was lower in the desflurane group than that in the sevoflurane group, whereas BBF was similar in both groups. In contrast, CCBF was higher in the desflurane group than that in the sevoflurane group. These results are similar with those in a previous



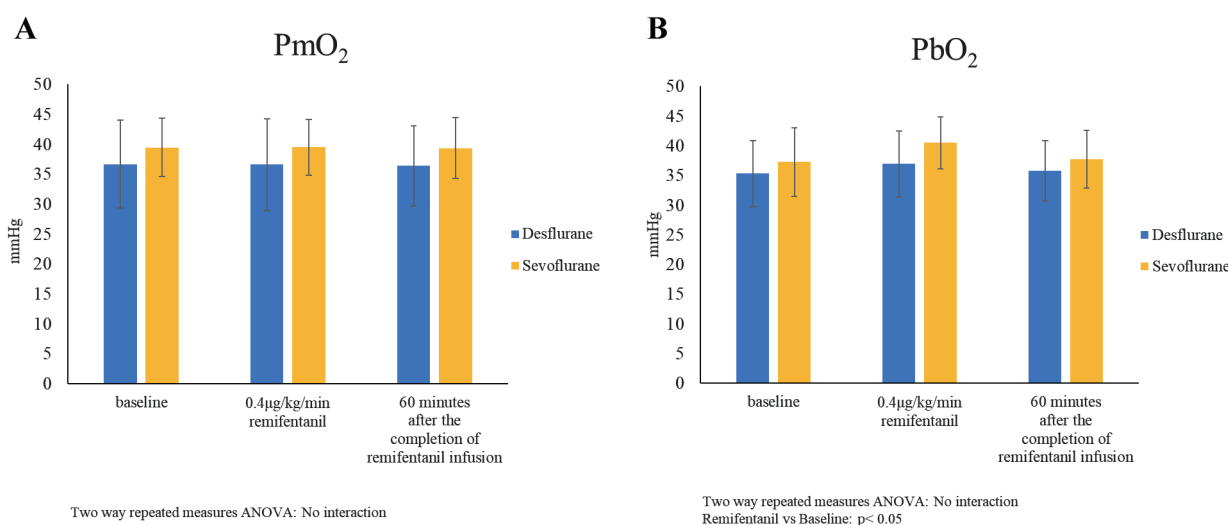
**Fig. 2.** Changes in heart rate (HR: A), systolic blood pressure (SBP: B), diastolic blood pressure (DBP: C), mean arterial pressure (MAP: D), and common carotid artery blood flow (CCBF: E) during and after remifentanyl infusion under desflurane or sevoflurane anesthesia. Two way repeated measures ANOVA showed no interaction between volatile anesthetics and remifentanyl infusion in each item. All items in the desflurane group were higher than those in the sevoflurane group. In addition, all items in both groups were lower than their baseline values during remifentanyl infusion. Data are shown as mean  $\pm$  SD (n=11). Desflurane vs. Sevoflurane  $P < 0.05$ . Remifentanyl vs. Baseline  $P < 0.05$ .

study [17]. The following reasons may explain these results.

Desflurane has been found to have no effect on blood flow in canine skeletal muscle [9], and also shows no effect on muscle tissue blood flow in the human calf [25]. Skeletal muscle blood vessels contain a large number of  $\beta_2$  receptors, and exhibit vasodilation in response to  $\beta_2$  receptor stimulation. However, it has been suggested that desflurane does not produce  $\beta_2$  sympathetic stimulation [25]. The smaller MBF seen in the desflurane group in this study may thus be due to the weaker stimulation of  $\beta_2$  receptors in muscle tissue blood vessels, resulting in a smaller vasodilatory effect. This also suggests that CCBF, which was higher in the desflurane group than that in the sevoflurane group, may redistribute blood to areas not measured in this study. In addition,



**Fig. 3.** Changes in masseter muscle tissue blood flow (MBF: A), and mandibular bone marrow tissue blood flow (BBF: B) during and after remifentanyl infusion under desflurane or sevoflurane anesthesia. Two way repeated measures ANOVA showed interaction between volatile anesthetics and remifentanyl infusion in MBF. MBF in the desflurane group was lower than that in the sevoflurane group at baseline and after remifentanyl infusion. BBF was similar in both groups throughout the experimental period. MBF and BBF in both groups were lower than their baseline values during remifentanyl infusion. Data are shown as mean  $\pm$  SD ( $n=11$ ). Interaction between volatile anesthetics and remifentanyl in MBF. Desflurane vs. Sevoflurane  $P < 0.05$ . Remifentanyl vs. Baseline  $P < 0.05$ .



**Fig. 4.** Changes in masseter muscle tissue oxygen tension (PmO<sub>2</sub>: A), and mandibular bone marrow tissue oxygen tension (PbO<sub>2</sub>: B) during and after remifentanyl infusion under desflurane or sevoflurane anesthesia. Two way repeated measures ANOVA showed no interaction between volatile anesthetics and remifentanyl infusion in PmO<sub>2</sub> and PbO<sub>2</sub>. PmO<sub>2</sub> and PbO<sub>2</sub> were similar in both groups. PbO<sub>2</sub> in both groups increased slightly during remifentanyl infusion, while PmO<sub>2</sub> remained unchanged. Data are shown as mean  $\pm$  SD ( $n=11$ ).

it is suggested that sevoflurane may induce an excessive increase in masseter muscle blood flow. It is reported that sevoflurane increased cerebral blood flow, while desflurane did not [26]. Similar phenomenon may explain the result of this study.

No difference in PmO<sub>2</sub> and PbO<sub>2</sub> was observed between desflurane and sevoflurane groups. In this study, MBF was smaller in the desflurane group than that in the sevoflurane group, while PmO<sub>2</sub> was comparable in both groups. Therefore, it is suggested that desflurane might reduce tissue oxygen consumption in the masseter muscle to more extent compared with sevoflurane. However, since we did not measure tissue oxygen consumption in the masseter muscle in this study, the details remain unknown. As both BBF and PbO<sub>2</sub> were similar in desflurane and sevoflurane groups, tissue oxygen consumption in the mandibular bone marrow was assumed to be similar in both groups.

During remifentanyl infusion, MBF and BBF reduced compared with baseline values in both groups, while PmO<sub>2</sub> and PbO<sub>2</sub> were maintained. In a previous study, remifentanyl infusion during sevoflurane anesthesia has been shown to reduce MBF and BBF, but not PmO<sub>2</sub> and PbO<sub>2</sub> [14]. Our results were consistent with those in that study [14]. Remifentanyl has been interacted with the

$\alpha$ 2-adrenoreceptor and might constrict peripheral vasoconstriction in the masseter muscle and mandibular bone marrow [8, 11, 14]. Hirata *et al.* reported that calculated peripheral vascular resistance in the masseter muscle and mandibular bone marrow increased during remifentanyl infusion [10]. Therefore, it is considered that the peripheral vascular resistance of the masseter muscle and the mandibular bone marrow might increase and the tissue blood flow decreased during remifentanyl infusion.

Calculated tissue oxygen consumption by the difference between the arterial oxygen content of the femoral artery and the venous oxygen content of the retromandibular vein decreased during remifentanyl infusion, which suggested that the tissue oxygen consumption might decrease during remifentanyl infusion [14]. It was reported that calf muscle oxygen consumption decreased during remifentanyl infusion under sevoflurane anesthesia in humans [3]. In this study, it is suggested that remifentanyl might reduce tissue oxygen consumption as well as tissue blood flow, and thus tissue oxygen tension was maintained.

Our results showed that although desflurane–remifentanyl anesthesia reduced tissue blood flow in the masseter muscle and mandibular bone marrow as with sevoflurane–remifentanyl anesthesia, the tissue oxygen tension in the masseter muscle and mandibular bone marrow was maintained. Both these anesthetics are thus useful in oral surgery from the standpoints of controlling blood loss and tissue protection. Of these, desflurane–remifentanyl anesthesia maintains blood pressure at a higher level than sevoflurane–remifentanyl anesthesia, and thus it may better preserve organ perfusions. One study has also reported that the amount of blood loss during oral and maxillofacial surgery was lower during desflurane–remifentanyl anesthesia than during sevoflurane–remifentanyl anesthesia [20]. Therefore, desflurane–remifentanyl anesthesia may offer more advantages than sevoflurane–remifentanyl anesthesia for oral and maxillofacial surgery.

This study was conducted in a non-invasive rabbit model, and we did not investigate oral tissue blood flow or oral tissue oxygen tension during surgical intervention. Further studies are therefore required to verify whether desflurane–remifentanyl anesthesia provides further advantages over sevoflurane–remifentanyl anesthesia in terms of controlling blood loss and tissue protection during surgical intervention.

In this study, infusion rate of remifentanyl was set at 0.4  $\mu$ g/kg/min. This is because this dosage produced marked decreases in tissue blood flow without substantial blood pressure changes in a previous study [15]. We focused to compare the changes in hemodynamics, oral tissue blood flow and oral tissue oxygen tension during remifentanyl infusion between desflurane and sevoflurane anesthesia in this study. Therefore, the desflurane group without receiving remifentanyl was not used.

In conclusion, remifentanyl infusion during desflurane anesthesia decreased tissue blood flow compared with during sevoflurane anesthesia, while maintaining blood pressure and tissue oxygen tension in the masseter muscle and mandibular bone marrow.

CONFLICT OF INTEREST. None of the authors have any relevant financial relationship(s) with a commercial interest.

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