Title

Dexmedetomidine dose dependently decreases oral tissue blood flow during sevoflurane and propofol anesthesia in rabbits

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Abstract

Purpose: The aim of this study was to investigate the effect of dexmedetomidine (DEX) continuous infusion on blood flow in rabbit oral tissues during sevoflurane or propofol anesthesia.

Methods: Twenty-four male tracheotomized Japan White rabbits were anesthetized with sevoflurane or propofol under mechanical ventilation. An initial loading dose of 6.0 μg·kg⁻¹·hr⁻¹ DEX was administered over 10 minutes. DEX was then maintained at 0.2, 0.4 and 0.6 μg·kg⁻¹·hr⁻¹ for one hour, respectively. Observed variables were systolic blood pressure (SBP), diastolic blood pressure, mean arterial pressure (MAP), heart rate (HR), common carotid artery blood flow (CCBF), tongue mucosal blood flow (TBF), mandibular bone marrow blood flow (BBF), masseter muscle blood flow (MBF), upper alveolar tissue blood flow (UBF), lower alveolar tissue blood flow (LBF) and vascular resistance for each tissue (TVR, BVR, MVR, UVR, LVR).

Results: HR, SBP, MAP, CCBF, TBF, BBF, MBF, UBF, and LBF showed dose-dependent decreases during DEX infusion during both sevoflurane and propofol anesthesia. The decreasing ratios in TBF, BBF, MBF, UBF and LBF were greater than
those in HR, SBP, MAP and CCBF. The vascular resistance of the oral tissues was increased in a dose-dependent manner during DEX infusion in both sevoflurane and propofol anesthesia.

Conclusion: Our findings suggest that infusion of DEX decreases TBF, BBF, MBF, UBF and LBF in a dose-dependent manner without significant changes in systemic hemodynamic variables during sevoflurane or propofol anesthesia.
Introduction

Bleeding during surgery should be minimized to avoid blood transfusion and to promote rapid recovery after surgery. In oral and maxillofacial surgery, control of bleeding is also important to establish a clear surgical field because oral mucosa and bone marrow consist of abundant vessels. Therefore, several studies have been conducted on the control of oral tissue blood flow during general anesthesia.

There have been a number of studies on the control of tissue blood flow using deliberate hypotension, and its usefulness is indicated. However, because complications of deliberate hypotension such as brain damage are also reported, safer strategies to control tissue blood flow has been investigated. We have studied the changes in oral tissue blood flow during general anesthesia and reported that remifentanil decreased tongue mucosal blood flow (TBF), mandibular bone marrow blood flow (BBF), masseter muscle blood flow (MBF) and alveolar tissue blood flow in a dose-dependent manner.

Recent studies report an infusion of dexmedetomidine (DEX), a highly selective α2 agonist, decreased bleeding during surgery. Durmus et al. and
Ayoglu et al.\textsuperscript{17} reported that DEX decreased bleeding during tympanoplasty and septorhinoplasty. Richa et al.\textsuperscript{18} reported that DEX decreased bleeding during maxillofacial surgery. These reports suggest that DEX may decrease tissue blood flow of the surgical field. Durmus et al.\textsuperscript{16} reported that the effect of DEX on systemic circulation was slight and thus bleeding might be reduced by the peripheral vasoconstrictive effect of DEX. It is reported that $\alpha_2B$ receptor-mediated vasoconstriction by DEX decreased blood flow in the brain\textsuperscript{19-21} and forearm.\textsuperscript{22} Meanwhile, Richa et al.\textsuperscript{18} reported that DEX decreased tissue blood flow through its hypotensive effects caused by an inhibition of sympathetic nervous activities. Another study reported that nutrient organ blood flow decreased through the reduction in oxygen consumption by the organs.\textsuperscript{23} Thus, the mechanism whereby DEX decreases tissue blood flow is still unclear. In addition, there are as yet no reports concerning the effect of DEX on the blood flow in oral tissues.

In this study, therefore, we investigated the effect of DEX on systemic circulation and blood flow in the oral tissues in rabbits. We discussed the mechanisms whereby DEX decreases blood flow in the oral tissues.
Methods

Twenty-four male Japan White rabbits weighing approximately 2.5 kg were used in this study. This study was approved by the Animal Research Ethics Committee at Tokyo Dental College (NO. 232502). All animals received humane care in accordance with the Guideline for the Treatment of Experimental Animals approved by Tokyo Dental College, Chiba, Japan.

Anesthesia was induced with 3.0% isoflurane (Forane, Abbott Japan, Tokyo, Japan). Tracheotomy was performed using infiltration anesthesia with 0.5 ml of 1% lidocaine hydrochloride solution (Xylocaine, AstraZeneca, Osaka, Japan), and then a 20 Fr pediatric tracheal tube was inserted into the trachea and fixed. Intravenous indwelling catheters were placed in the right femoral artery and the left posterior auricular marginal vein. They were used for measurement of arterial pressure and as a route of fluid infusion and drug administration, respectively. Arterial pressure was recorded continuously via a pressure transducer (P231D, Gould, Oxnard, CA) and heart rate (HR) was calculated from pressure waveforms. Acetated Ringer’s solution was infused at a rate of 10 ml·kg⁻¹·hr⁻¹. Muscular relaxation was obtained by
continuous infusion of 14 μg·kg⁻¹·min⁻¹ rocuronium bromide (Eslax, Schering-Plough, Tokyo, Japan) and animals were ventilated with a tidal volume of 30 to 50 ml and a respiratory rate of 30 to 40 times·min⁻¹. End-tidal carbon dioxide partial pressure was measured with an anesthetic gas monitor (Capnomac; Datex, Helsinki, Finland) and maintained between 35 and 40 mmHg. Incision was made 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 (approximately 1 mm in diameter) penetrating into the bone marrow through the cortical bone was made using a round bur (ISO. 008, Morita, Saitama, Japan). A needle probe of hydrogen clearance tissue blood flowmeter (UHE-100, Unique Medical, Tokyo, Japan) was inserted into the mandibular bone marrow, the left masseter muscle, the left upper alveolar tissue, and the left lower alveolar tissue. TBF was continuously monitored using a laser Doppler blood flowmeter (ALF21, Advance, Tokyo, Japan). A contact-type probe (Type C, Advance, Tokyo, Japan) was placed in close contact with the lingual mucosa on the left side. Common carotid blood flow (CCBF) was continuously monitored using an ultrasonic
blood flowmeter (T108, Transonic, Ithaca, NY). A flow probe (Type 3SB, Transonic, Ithaca, NY) was fixed to the left common carotid artery. After experimental preparation had been completed, isoflurane inhalation was discontinued and either infusion of propofol or inhalation of sevoflurane was started. In the sevoflurane group (S group, n=9), sevoflurane (SEVOFRANE, Maruishi Pharmaceutical, Osaka, Japan) was administered to maintain end-tidal concentration at 1.8%. In the propofol group (P group, n=9), propofol (Diprivan, AstraZeneca, Tokyo, Japan) was administered via continuous infusion at a rate of 12 mg\(\cdot\)kg\(^{-1}\)\(\cdot\)hr\(^{-1}\). Control values were measured after a resting period of 1 hour or longer to allow stabilization of respiration and circulation. An initial loading dose of 6.0 μg\(\cdot\)kg\(^{-1}\)\(\cdot\)hr\(^{-1}\) DEX was administered over 10 minutes. DEX was then maintained at 0.2, 0.4 and 0.6 μg\(\cdot\)kg\(^{-1}\)\(\cdot\)hr\(^{-1}\), respectively, in this order. Each infusion was maintained for 1 hour. Variables were observed at the end of each infusion.

To confirm the recovery of systemic hemodynamic variables and tissue blood flow after the completion of DEX administration, DEX was infused at 0.6 μg\(\cdot\)kg\(^{-1}\)\(\cdot\)hr\(^{-1}\) for 2 hours after the initial loading of 6 μg\(\cdot\)kg\(^{-1}\)\(\cdot\)hr\(^{-1}\) for 10 minutes in other rabbits in
both groups (n=3, each).

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), CCBF, and TBF were continuously recorded on a polygraph (Series360, NEC San-ei, Tokyo, Japan). BBF, MBF, upper alveolar tissue blood flow (UBF), and lower alveolar tissue blood flow (LBF) were analyzed by a data collection analysis system (UCO, Unique Medical, Tokyo, Japan). Vascular resistance for each tissue (TVR, BVR, MVR, UVR, LVR) was calculated as MAP divided by each tissue blood flow and expressed as a percent change of the respective control value. Rectal temperature was maintained at 39.0 to 39.5 throughout the experiment.

Values are expressed as the mean ± standard deviation. One-way ANOVA for repeated measurements followed by Dunnett test were used for intra-group comparisons. The Student t-test for unpaired samples was used for inter-group comparisons. A $p$ value less than 0.05 were considered statistically significant.
Results (Tables 1, 2, 3, 4, Figs. 1, 2)

HR, SBP and MAP were decreased in a dose-dependent manner during DEX infusion in both S and P groups. HR was decreased by 10-16%, SBP was decreased by 5-12% and MAP was decreased by 5-10% in both groups. DBP was decreased by 6% during DEX infusion at 0.6 μg·kg⁻¹·hr⁻¹ in P group.

CCBF was decreased in a dose-dependent manner during dexmedetomidine infusion in both groups. CCBF was decreased by 13-19% in S group and by 10-16% in P group. CCBF at 0.6 μg·kg⁻¹·hr⁻¹ of DEX infusion in S group was smaller than that in P group.

Oral tissue blood flows (TBF, BBF, MBF, UBF, LBF) were decreased in a dose-dependent manner during DEX infusion in both groups. TBF was decreased by 13-25% in S group and by 15-31% in P group. TBF at 0.2 μg·kg⁻¹·hr⁻¹ of DEX infusion in S group was smaller than that in P group. BBF was decreased by 12-25% in S group and by 14-31% in P group. MBF was decreased by 11-32% in S group and by 17-35% in P group. UBF was decreased by 15-36% in S group and by 21-39% in P group. LBF was decreased by 12-35% in S group and by 13-34% in P group.
The vascular resistances of the oral tissues were increased in a dose-dependent manner during DEX infusion in both groups. TVR was increased by 18-25% in S group and by 26-31% in P group. BVR was increased by 15-25% in S group and by 27-37% in P group. MVR was increased by 27-39% in S group and by 27-49% in P group. UVR was increased by 31-47% in S group and by 37-49% in P group. LVR was increased by 23-47% in S group and by 24-40% in P group.

Systemic hemodynamic variables and tissue blood flow recovered to the values before DEX infusion in both groups after the completion of DEX infusion. (Data not shown)
Discussion

This study showed that TBF, MBF, BBF, UBF, and LBF were decreased in a dose-dependent manner during DEX infusion in both S and P groups (30-40% at 0.6 μg/kg/hr). Although HR, SBP, MAP, and CCBF were also decreased, these changes were smaller than those in oral tissue blood flow. The decreases in systemic hemodynamic variables and tissue blood flows were comparable between S and P groups. It is therefore suggested that DEX shows similar effects during sevoflurane or propofol anesthesia.

In this study, the dose or concentration to maintain basal anesthesia was the same as that in the report of Kemmochi et al.\textsuperscript{11} These values are based on the blood concentration of propofol at Cp50\textsubscript{skin incision} (plasma concentration at which 50% of patients do not respond to skin incision) and 0.5 minimum alveolar concentration (MAC) for sevoflurane in rabbits.\textsuperscript{25-27} Terakawa et al.\textsuperscript{28} reported that the adequate infusion rate of rocuronium bromide which provide stable muscular relaxation was 14 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} during sevoflurane or propofol anesthesia. Therefore, this infusion rate was adopted in this study. To expose 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 tissue blood flow. However, these procedures were essential to precisely place the needle electrodes on the masseter muscle and periosteum of the mandibular body.

Putative mechanisms for decreased blood flow in oral tissues during DEX infusion are hypotension resulting from DEX-induced inhibition of sympathetic nervous activities or peripheral vasoconstriction by DEX. Richa et al. reported that bleeding during maxillofacial surgery was decreased by an initial loading dose of 0.1 μg·kg⁻¹·min⁻¹ followed by a continuous infusion at 0.4-0.7 μg·kg⁻¹·hr⁻¹, and they considered that this decrease was attributable to stable hypotensive condition (approximately 30% reduction in MAP). Meanwhile, during tympanoplasty and septorhinoplasty, Durmus et al. used an initial loading dose of 1 μg·kg⁻¹·hr⁻¹ followed by 0.5 μg·kg⁻¹·hr⁻¹, and Ayoglu et al. used an initial loading dose of 1 μg·kg⁻¹·hr⁻¹ followed by 0.7 μg·kg⁻¹·hr⁻¹. Although bleeding during surgery was decreased in these reports, MAP was decreased only by approximately 10% of the
control value.

In our study, SBP and MAP were decreased only by approximately 10% under 0.6 μg·kg⁻¹·hr⁻¹ DEX infusion. This result was similar to those reported by Durmus et al., Ayoglu et al., and Hall et al. In another report, MAP was decreased only by approximately 15% even during relatively high dose infusion of 2 μg·kg⁻¹ DEX. Thus, it is suggested that DEX-induced hypotension does not make a major contribution to the decreases in oral tissue blood flow.

Prielipp et al. administered an initial loading dose of DEX followed by an infusion at low flow rate (0.2 μg·kg⁻¹·hr⁻¹) or at high flow rate (0.6 μg·kg⁻¹·hr⁻¹) to volunteers, and measured cerebral blood flow at various sites. Their results showed that, at high flow rate, cardiac output, cerebral blood flow and MAP decreased by approximately 20%, 30% and 10%, respectively. These values were similar with the decrease in CCBF, an index of cardiac output, and in MAP in our study. Prielipp et al. reported that decreased cerebral blood flow might be attributable to sympathetic inhibition via α2A receptor-mediated mechanisms and peripheral vasoconstriction via α2B receptor-mediated mechanisms. In addition, they discussed another possible
mechanism that DEX might affect cerebral autoregulation. Zornow et al.\textsuperscript{20, 21} also reported that decreased cerebral blood flow was attributable to the cerebral vasoconstrictive effects of DEX.

Many \(\alpha_2B\) receptors are present in the smooth muscle, and their known action is related to vasoconstriction.\textsuperscript{15} DEX or another \(\alpha_2\) agonist clonidine constricts the middle cerebral artery, pial arteries, and microvessels.\textsuperscript{33-35} As described above, cerebral vessels are thought to contain many \(\alpha_2B\) receptors. Ogawa et al.\textsuperscript{24} administered DEX to volunteers either at low flow rate (3 \(\mu g \cdot kg^{-1} \cdot hr^{-1}\) for 10 min, followed by 0.2 \(\mu g \cdot kg^{-1} \cdot hr^{-1}\) for 60 min), or at high flow rate (6 \(\mu g \cdot kg^{-1} \cdot hr^{-1}\) for 10 min, followed by 0.4 \(\mu g \cdot kg^{-1} \cdot hr^{-1}\) for 60 min) and reported that cerebrovascular resistance increased significantly versus placebo controls. Chi et al.\textsuperscript{36} also administered DEX at 1 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) for 45-minute to normotensive rats and to arbitrarily hypotensive rats. In their results, cerebral blood flow decreased significantly in both groups, and cerebrovascular resistance increased approximately 2-fold in the normotensive group.

In our study, DEX at the rate of more than 0.4 \(\mu g \cdot kg^{-1} \cdot hr^{-1}\) increased vascular resistance in all oral tissues. The increase in the vascular resistance suggests that DEX
may induce peripheral vasoconstriction caused by \( \alpha_{2B} \) receptor-mediated mechanisms, as in cerebral vessels. However, the relative increase in vascular resistance in the oral tissues was smaller than that in cerebral vessels when compared to the report of Ogawa et al.\(^{24} \), even at the same administration rate. In addition, there is no report investigating the distribution of \( \alpha_{2B} \) receptors in oral tissues. Therefore, vasoconstrictive effect cannot fully explain the blood flow decrease in these tissues.

Another possibility based on the dose-dependent decrease in MAP and CCBF is that DEX may have decreased cardiac output, thereby decreasing blood flow in the oral tissues. Bloor et al.\(^{37} \) reported that cardiac output decreased in a dose-dependent manner when more than 0.5 \( \mu \text{g} \cdot \text{kg}^{-1} \) DEX was administered, and the decrease was by approximately 41\% at a dosage of 2 \( \mu \text{g} \cdot \text{kg}^{-1} \). Ebert et al.\(^{38} \) and Dutta et al.\(^{39} \) reported that DEX decreased cardiac output in a plasma concentration-dependent manner. Lawrence et al.\(^{23} \) also reported that DEX administered at 0.1, 1, or 10 \( \mu \text{g} \cdot \text{kg}^{-1} \) to dogs under general anesthesia decreased cardiac output, MAP and nutrient organ blood flow in a concentration-dependent manner. In our study, CCBF showed a decrease by approximately 10-20\% during DEX infusion. These findings suggest that \( \alpha_{2B} \)
receptor-mediated vasoconstriction and $\alpha_{2A}$ receptor-mediated sympathetic inhibition caused a decrease in cardiac output, and thus contributing to decreased tissue blood flow.

In our study, the effect of DEX on blood pressure was relatively small, and blood flow in oral tissues was found to decrease significantly. DEX has been used primarily in an ICU situation for sedation. However, DEX has many other useful actions, including an $\alpha_{2A}$ receptor-mediated analgesic effect even under general anesthesia, and a MAC-lowering effect due to sympathetic inhibition and a reduction of catecholamine release. These facts suggest that DEX may be a useful agent in general anesthesia for oral surgical procedures.

In conclusion, DEX decreased TBF, MBF, BBF, UBF, and LBF in a dose-dependent manner both under sevoflurane and propofol anesthesia. These decreases may be attributable to $\alpha_{2B}$ receptor-mediated peripheral vasoconstriction and cardiac output reduction through $\alpha_{2A}$ receptor-mediated sympathetic inhibition.
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<td>274.8±26*</td>
<td>265.6±27.2*</td>
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<td>SBP (mmHg)</td>
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Data are expressed as mean ± SD.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CCBF, common carotid artery blood flow; TBF, tongue mucosal blood flow; BBF, mandibular bone marrow blood flow; MBF, masseter muscle blood flow; UBF, upper alveolar tissue blood flow; LBF, lower alveolar tissue blood flow.

*p < 0.05 vs control.
Table 2. Hemodynamic variables and tissue blood flow in propofol group

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<td>HR (beats/min)</td>
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<td>DBP (mmHg)</td>
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<td>MAP (mmHg)</td>
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<td>CCBF (ml/min)</td>
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<td>BBF (ml/100g/min)</td>
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<td>33.3±4.1*</td>
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<tr>
<td>MBF (ml/100g/min)</td>
<td>44.5±6.0</td>
<td>36.5±3.6*</td>
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<td>UBF (ml/100g/min)</td>
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<td>39.9±5.5*</td>
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</table>

Data are expressed as mean ± SD.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CCBF, common carotid artery blood flow; TBF, tongue mucosal blood flow; BBF, mandibular bone marrow blood flow; MBF, masseter muscle blood flow; UBF, upper alveolar tissue blood flow; LBF, lower alveolar tissue blood flow.

*p < 0.05 vs control.
Table 3. Changes in oral tissue vascular resistance in sevoflurane group

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<th>Infusion rate of dexmedetomidine (μg·kg⁻¹·hr⁻¹)</th>
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<td>TVR (%)</td>
<td>110.4±11.9&lt;sup&gt;*&lt;/sup&gt;</td>
<td>118.4±10.9&lt;sup&gt;*&lt;/sup&gt;</td>
<td>124.8±18.0&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>BVR (%)</td>
<td>108.8±12.1</td>
<td>114.7±19.4&lt;sup&gt;*&lt;/sup&gt;</td>
<td>124.9±20.9&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>MVR (%)</td>
<td>108.4±10.3</td>
<td>126.7±32.7&lt;sup&gt;*&lt;/sup&gt;</td>
<td>138.9±29.3&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>UVR (%)</td>
<td>113.4±15.9</td>
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<td>147.0±25.3&lt;sup&gt;*&lt;/sup&gt;</td>
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<td>LVR (%)</td>
<td>109.1±9.1</td>
<td>122.9±18.9&lt;sup&gt;*&lt;/sup&gt;</td>
<td>146.5±32.2&lt;sup&gt;*&lt;/sup&gt;</td>
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</table>

Data are expressed as mean ± SD.

Abbreviations: TVR, tongue mucosal vascular resistance; BVR, mandibular bone marrow vascular resistance; MVR, masseter muscle vascular resistance; UVR, upper alveolar tissue vascular resistance; LVR, lower alveolar tissue vascular resistance.

<sup>*</sup>p < 0.05 vs control.
Table 4. Changes in oral tissue vascular resistance in propofol group

<table>
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<td></td>
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<tr>
<td>TVR (%)</td>
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<td>BVR (%)</td>
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<tr>
<td>LVR (%)</td>
<td>109.6±13.3*</td>
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</table>

Data are expressed as mean ± SD.

Abbreviations: TVR, tongue mucosal vascular resistance; BVR, mandibular bone marrow vascular resistance; MVR, masseter muscle vascular resistance; UVR, upper alveolar tissue vascular resistance; LVR, lower alveolar tissue vascular resistance.

*p < 0.05 vs control.
Figure legends

Fig. 1

Percent changes from control values in common carotid artery blood flow (CCBF), tongue mucosal blood flow (TBF), mandibular bone marrow blood flow (BBF), masseter muscle blood flow (MBF), upper alveolar tissue blood flow (UBF) and lower alveolar tissue blood flow (LBF) in sevoflurane group. Decrease in common carotid artery blood flow was less than those in the other tissues.

Data are expressed as mean ± SD, n=9.

Fig. 2

Percent changes from control values in common carotid artery blood flow (CCBF), tongue mucosal blood flow (TBF), mandibular bone marrow blood flow (BBF), masseter muscle blood flow (MBF), upper alveolar tissue blood flow (UBF) and lower alveolar tissue blood flow (LBF) in propofol group. Decrease in common carotid artery blood flow was less than those in the other tissues.

Data are expressed as mean ± SD, n=9.