The effect of dexmedetomidine on the oral mucosal blood flow
— Its effect on the absorption of lidocaine —

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デクスメデトミジンが口腔粘膜血流に及ぼす影響
— 特にリドカインの吸収に及ぼす影響 —

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Abstract

Dexmedetomidine (DEX) is a sedative and analgesic agent that acts via the alpha-2 adrenoceptor, which is associated with reduced anesthetic requirements and an attenuated blood pressure and heart rate in response to stressful events. One study reported that cat gingival blood flow was controlled by the sympathetic alpha-adrenergic fibers involved in vasoconstriction. Alpha adrenoceptors are obviously involved in vascular constriction in the gingiva of cats and rats. Experiment 1 in the present study focused on the relationship between the effects of DEX on alpha adrenoceptors and vasoconstriction in the tissues of the oral cavity and compared the palatal mucosal blood flow (PMBF) in rabbits between general anesthesia with sevoflurane and that with DEX. The PMBF decreased due to the vasoconstriction of vessels following alpha-2 adrenoceptor stimulation by DEX. However, ideally, the absorption should be delayed when using a local anesthetic like lidocaine without adrenaline during dental procedures or oral surgeries. Accordingly, Experiment 2 in the present study monitored the serum lidocaine concentration in rabbits to compare the absorption of lidocaine without adrenaline between general anesthesia with sevoflurane and that with DEX. The depression of the PMBF by DEX did not affect the absorption of lidocaine, likely because lidocaine dilates the blood vessels, as is commonly suggested. In conclusion, local anesthetics with vasoconstrictors should be used in implant surgery and oral surgery under sedation or general anesthesia with DEX.

Key words: dexmedetomidine, palatal mucosal blood flow, lidocaine, sedation, general anesthesia

抄　録

デクスメデトミジン（DEX）は，そのα2アドレナリン作動性受容体を介して効果を表す鎮静薬であり鎮痛薬でもある。このデクスメデトミジンの併用は，麻酔薬の必要量を減少させ，ストレスイベントへの反応において低下させる血圧と心拍数に関連する。ある研究報告は，猫の歯肉血流は，血管収縮と関連する交感神経性のαアドレナリン線維によって支配されていると報告している。αアドレナリン作動性受容体は，明らかに猫やネズミの歯肉における血管収縮に関与している。本研究の実験1では，αアドレナリン受容体におけるデクスメデトミジンの効果と口腔容積組織における血管収縮の関係に焦点をあて，セボフルランを用いた全身麻酔とDEXを用いた全身麻酔の間で，ウサギにおける口蓋粘膜血流量（PMBF）を比較した。その結果，PMBFはDEXによるα2アドレナリン受容体に引き続く血管収縮によって減少した。しかしながら，理想的には，歯科処置や口腔外科手術の間にアドレナリン無添加リドカインのような局所麻酔薬を使った時に，吸収が遅れるべきである。そこで，本研究の実験2は，セボフルランを用いた全身麻酔とDEXを用いた全身麻酔間におけるアドレナリン無添加のリドカイン血清濃度を計測した。DEXによるPMBFの減少はリドカインの吸収に影響を与えず，一般的にいわれているように，リドカインが血管を拡張させたからである。結論として，DEXを用いた静脈内鎮静や全身麻酔下のインプラント手術や口腔外科手術時には，血管収縮薬入りの局所麻酔薬が使われるべきである。

Introduction

Adrenoceptors are mainly divided into two types: alpha-1 adrenoceptor and alpha-2 adrenoceptor. The alpha-1 adrenoceptor mediates sympathetic vasoconstriction of the blood vessels[1], and the alpha-2 adrenoceptor induces a hypnotic-anesthetic effect in rats via the activation of central alpha-2 adrenoceptors[2]. Dexmedetomidine (DEX) is a sedative and analgesic agent that acts via the alpha-2 adrenoceptor, which is associated with reduced anesthetic requirements and an attenuated blood pressure and heart rate in response to stressful events[3~7]. DEX has a relatively high ratio of alpha-2/ alpha-1-activity (1620:1) in comparison to clonidine (220:1). Alpha-2 adrenoceptors within the spinal cord modulate the pain pathways, thereby providing some degree of analgesia[8~10]. In addition, DEX induces a sedative response that exhibits properties similar to natural sleep without significant respiratory depression, unlike other hypnotic anesthetics[11]. DEX is therefore frequently used in sedation for oral implant surgery[12].

However, oral surgery is performed in the oral cavity, where there is an abundance of blood vessels. Significant bleeding during surgery can disrupt the technique or procedure in oral surgeries. Several interesting reports[13~15] have been published regarding the vasoconstriction in the oral cavity. Izumi H *et al.* [13] reported that cat gingival blood flow was controlled by the sympathetic alpha-adrenergic fibers involved in vasoconstriction, and Michael[14] found that electrical stimulation of the cervical sympathetic nerve trunk uniformly induced vasoconstriction in tissues of the oral cavity in all species studied. Alpha adrenoceptors are obviously involved in vascular constriction in the gingiva of cats and rats. For precisely this reason, the oral mucosal blood flow was thought to be reduced due to the activation of DEX in alpha-2 adrenoceptors. The present study focused on the relationship between the effects of DEX on alpha-2 adrenoceptors and vasoconstriction in the tissues of the oral cavity in Experiment 1. If DEX was indeed found to reduce the oral mucosal blood flow in Experiment 1, we hypothesized that the absorption of lidocaine without adrenaline would be delayed due to the vasoconstriction by DEX. Accordingly, Experiment 2 in

the present study monitored the serum lidocaine concentration to compare the absorption of lidocaine without adrenaline.

Methods

Experiment 1: The effect of DEX on the palatal mucosal blood flow (Fig. 1)

Japanese white rabbits (n=22, male) anesthetized with 5% sevoflurane and 3 L/min oxygen underwent tracheotomy, after which they were maintained with 3% sevoflurane and 3 L/min oxygen. An intravenous line was placed in an ear vein, and the infusion was delivered at 30 mL/h. Catheters (3 Fr; Atom Medical, Tokyo, Japan) were inserted via the femoral vein and femoral artery under general anesthesia, and the tip of the catheter in the femoral vein was placed in the right atrium while that of the catheter in the femoral artery was placed in the thoracic aorta. A laser Doppler flowmeter probe (ALF21RTM; Advance, Tokyo, Japan) was fixed onto the palatal mucosal surface using a piece of sponge to monitor the palatal mucosal blood flow (PMBF) continuously. The rabbits were observed in a supine position for at least 5 minutes until the cardiovascular parameters had steadied (change in the vital signs less than 10%).

The rabbits were then randomly divided into two groups (n=11 each). One group was managed with sevoflurane, midazolam, and butorphanol (SMB group), and the other group was managed with DEX, midazolam, and butorphanol (DMB group). In the SMB group, a rabbit was induced with 0.2 mg/kg midazolam, 0.05 mg/kg butorphanol, and 2 mg/kg rocuronium in 5% sevoflurane after each control value was measured at baseline. Rocuronium (3 mg/kg) was additionally given 10 minutes after the above induction. Normal saline was given as the contrastive infusion for DEX at the same infusion speed as DEX in the DMB group. In the DMB group, a rabbit was induced as in the SMB group in a continuous DEX dose of 18 μg/kg/h after each parameter was measured at baseline. Rocuronium (3 mg/kg) was additionally given at 10 minutes after the above induction, and the continuous infusion dose of DEX was changed from 18 to 2.8 μg/kg/h at the same time. The mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), end tidal CO_2 (E_TCO_2), and palatal mucosal blood flow were measured at 0 (baseline), 12, 17, 22, 27, 32, and 42 minutes after the induction in sevoflurane or DEX (Fig. 2).

Experiment 1 was performed in accordance with the Animal Experiment Regulations of Ohu University (Permit No. 2013-42, 2015-9).

Experiment 2: The effect of DEX on the absorption of lidocaine (Fig. 3)

Japanese white rabbits (n=16, male) anesthetized with 5% sevoflurane and 3 L/min oxygen underwent tracheotomy, after which they were maintained with 3% sevoflurane and 3 L/min oxygen. An intravenous line was placed in an ear vein, and 3-Fr catheter was inserted via the femoral artery under general anesthesia with 3% sevoflurane and 3 L/min oxygen. The tip of the catheter in the femoral artery was placed in the thoracic aorta to take blood samples.

The rabbits were then randomly divided into two groups, as in Experiment 1. One group was managed with sevoflurane, midazolam, and butorphanol (SMB group), and the other group was managed with DEX, midazolam, and butorphanol (DMB group). In the SMB group, a rabbit was induced with 0.2 mg/kg midazolam, 0.05 mg/kg butorphanol and 2 mg/kg rocuronium in 5% sevoflurane. Rocuronium (3 mg/kg) was additionally given 10 minutes after the above induction. In the DMB group, a rabbit was induced as in the SMB group in a continuous DEX dose of 18 μg/kg/h. Rocuronium (3 mg/kg) was additionally given at 10 minutes after the above induction, and the continuous infusion dose of DEX was changed from 18 to 2.8 μg/kg/h at the same time (Fig. 4). In both groups, 0.5 mL each of 2% lidocaine without adrenaline was injected submucosally into the right and left palatal mucosa at 12 minutes after the induction. The total dosage of 2% lidocaine without adrenaline was 1.0mL. Blood samples (3 mL) were taken at 17, 22, 27, 32, and 42 minutes after the induction.

Serum was separated from the blood samples by centrifugation (3000rpm, KUBOTA 5910; Tokyo, Japan) for 10 minutes. After centrifugal separation, the lidocaine concentration in the serum sample was measured via high-speed liquid chromatography (Jasco PU-2080 Plus Intelligent HPLC Pump, Jasco AS-2050 Plus Intelligent Autosampler, Jasco UV-2075 Plus Intelligent UV/Vis Detector; Jasco Corporation, Ontario, Canada). The conditions for the HPLC analysis of lidocaine are shown in

Table 1.

Experiment 2 was performed in accordance with the Animal Experiment Regulations of Ohu University (Permit No. 2013-42, 2016-14).

Statistical analyses

The parameters in Experiment 1 were compared between the groups using Friedman's test followed by Wilcoxon's t-test with Bonferroni correction. The Mann-Whitney U-test was used between the groups. The serum lidocaine concentrations in Experiment 2 were compared between the groups using the Mann-Whitney U-test. A p value of < 0.05 was considered to indicate statistical significance in both experiments.

Results

Experiment 1

1) Animal's weight

The mean weight (± standard deviation) of the rabbits for both groups was 3.2±0.2 kg. There was no significant difference in the weight between the two groups.

2) MAP (Fig. 5)

The MAP was significantly lower than the control values in both groups ($p<0.05$). On comparing the two groups, the value in the DMB group was significantly lower than in the SMB group at 12 minutes after induction (SMB group: 70.7±9.3 mmHg vs. DMB group: 61.2±10.0 mmHg, $p<0.05$).

3) HR (Fig. 6)

The HR in the DMB group was significantly lower than the control values ($p<0.05$).On comparing the two groups, the value in the DMB group was significantly lower than that in the SMB group from 10 to 42 minutes after induction (DMB values at 12, 17, 22, 27, and 32 minutes decreased $p<0.05$, and the DMB values at 42 minutes decreased, $p<0.01$).

4) CVP (Fig. 7)

No significant differences in the CVP were noted in either group or between the groups.

5) E_TCO_2 (Fig. 8)

No significant differences in the E_TCO_2 were noted in either group or between the groups.

6) PMBF (Fig. 9)

The PMBF in the DMB group was significantly lower than the control values ($p<0.05$). On comparing the two groups, the PMBF in the DMB group was significantly lower than in the SMB group from 12 to 42 minutes after induction (DMB values decreased at 12, 17, 22, and 42 minutes, $p<0.05$, and the DMB values at 27 and 32 minutes, $p<0.01$).

Experiment 2

1) Animal's weight

The mean weight (± standard deviation) of the rabbits was 2.7 ± 0.4 kg in the SMB group and 2.8 ± 0.3 kg in the DMB group. There was no significant difference in the weight between the two groups.

2) Serum lidocaine concentration (Fig. 10)

There were no significant differences in the serum lidocaine concentration between the two groups from 17 (5) to 42 (30) minutes after induction.

Discussion

DEX is a sedative used for postoperative management in Intensive Care Units (ICUs) and provides a unique sedative effect akin to natural sleep[11]. Agitation and cognitive thought rarely occur in patients sedated with DEX[3, 11, 12]. DEX is used as a sedative during dental procedures or oral surgeries. However, oral surgery is accompanied by a risk of bleeding, as these procedures are performed in oral cavity, where there is an abundance of blood vessels. Significant bleeding during surgery can disrupt the technique or procedure during oral surgeries. Experiment 1 in the present study compared the oral mucosal blood flow between general anesthesia with sevoflurane and that with DEX to investigate the effect of DEX. Experiment 2 focused on the absorption of lidocaine (without adrenaline) due to vasoconstriction by DEX, and investigated the serum lidocaine concentration.

Regarding sevoflurane and DEX infusion in the present study, 5% sevoflurane was given to maintain the end-tidal sevoflurane at a maximum of 3.9%[16,17], because the flow volume (3 L/min oxygen) in the anesthetic circuit of the present study was lower than that for humans. The 5% sevoflurane used in the present study was almost 3 times the minimum alveolar concentration of humans. For this reason, we set the infusion dose of DEX at three times that in humans.

1) MAP

The MAP in both groups was significantly lower at each point assessed than at baseline; however, there were no significant differences in the values between the groups, except at 12 minutes after induction. MAP is determined by the cardiac output and peripheral vascular resistance, and the left ventricular afterload reflects the peripheral vascular resistance in MAP. Sevoflurane reduces the left ventricular afterload[18], and Ebert *et al.*[19] found that sevoflurane maintains a normal cardiac output because sevoflurane hardly inhibits the myocardial contractility and sevoflurane decreases the left ventricular afterload. This is suspected to be the reason underlying the decreased MAP in the SMB group.

Similarly, the MAP in the DMB group was also decreased; this is thought to be a result of the depression of the peripheral vascular resistance, which is mediated via central α2A adrenoceptor agonists[20]. When DEX is administered as a single dose, a loading dose of DEX is generally infused first, and then continuous infusion is used to maintain the sedation level. Transient hypertension tends to be observed during infusion of the loading dose of DEX, based on the effect of α2B adrenoceptor agonists. Kamibayashi *et al.*[21] found that the α2B adrenoceptor subtype mediates the short-term hypertensive response to α2 agonists[22], whereas the α2A adrenoceptor is responsible for the anesthetic and sympatholytic response. In the present study, we noted a decrease in the MAP in the DMB group after the infusion of the loading dose. This suggested that the peripheral vascular resistance was indeed reduced in response to the administration of a central α2A adrenoceptor agonist, results that concurred with those in Hall *et al.*[23]'s report.

2) HR

The HR in the DMB group was significantly lower than the control value ($p<0.05$) from 12 to 42 minutes, although the SMB group showed no significant change. In addition, the value in the DMB group was significantly lower than that in the SMB group at all time points examined. This bradycardia was thought to be due to stimulation by α2A adrenoceptor agonists like DEX. MacDonald *et al.*[20] found that the bradycardic effect induced by α2 adrenoceptor agonists is partly mediated by α2A adrenoceptors and partly by baroreflex. In addition, these finding suggest that DEX is suitable for sedation of patients with heart disease like angina because its bradycardic effect reduces the myocardial oxygen consumption by decreasing the HR. Tachycardia has been occasionally reported in patients undergoing dental treatment with local anesthetics[24] because local anesthesia (e.g. 2% lidocaine) includes adrenaline in Japan (1:80,000 ratio). Therefore, DEX seems suitable for sedation during oral surgeries or implant surgeries using of local anesthesia.

3) CVP and E_TCO_2

There were no significant differences in the CVP and E_TCO_2 in comparison between the two groups, indicating that both groups were examined under the same conditions. CVP is used as an indicator for adjusting the circulating blood volume and influences the MAP. Given that we noted no significant differences in the CVP between two groups, the fluid management was deemed to be adequate. We also concluded that our data were gathered under appropriate respiratory management because of the lack of any significant changes in the E_TCO_2. Given that a previous report[25] stated that changes in the E_TCO_2 during DEX infusion affected the oral tissue blood flow in rabbits, we monitored E_TCO_2 in the present study. However, we found no marked differences in this parameter between the groups, suggesting that the respiratory management in the present study had no effects on the oral tissue blood flow.

4) PMBF

The PMBF in the DMB group was significantly lower than at baseline. In addition, on comparing the two groups, the PMBF in DMB group was also significantly lower than in the SMB group. Oral mucosal blood vessels reportedly contract due to α adrenoreceptor stimulation[13]; we therefore surmised that the PMBF was reduced due to vasoconstriction in response to the α2 adrenoreceptor stimulation of DEX. Kawaai *et al.*[15] reported that the decreased in the cardiac output by HR depression due to DEX did not subsequently reduce the stroke volume. In the present study, we observed HR depression due to DEX suggesting that the PMBF may have been reduced due to cardiac output depression.

5) Serum concentration of lidocaine

The absorption of lidocaine in the DMB group was predicted to be delayed based on the results of Experiment 1. However, in Experiment 2, the serum concentration of lidocaine showed no significant difference between the two groups, indicating that the PMBF depression by DEX did not affect the absorption of lidocaine likely due to the dilating effect of lidocaine on blood vessels, as is most commonly suggested.

Burton *et al.*[26] reported that lidocaine exerted significant dose-dependent dilation of

the pial terminal arterioles in an experiment using rat cerebral spinal fluid. In their study, 0.1-20 mg/mL lidocaine in 0.1mL was injected into vessels in the pial terminal arterioles. Consequently the arterioles dilated with a percentage change of 15-45%. The concentration of lidocaine used in our study (20 mg/mL, 2% lidocaine) was the same as the maximum concentration in Burton's experiment. While we cannot conduct a simple comparison of the data in our and Burton's experiments, oral mucosal blood vessels in the two groups in the present study were likely dilated due to the 2% lidocaine.

Another studies[27,28] investigated the plasma concentration of lidocaine based on the absorption of lidocaine with and without adrenaline. Those authors found that the plasma concentration of lidocaine with adrenaline was lower than that without adrenaline. In the present study, the serum lidocaine concentration showed no significant difference between the SMB and DMB groups, indicating that the vasoconstriction effect of DEX was weaker than the vasodilation effect of lidocaine in the oral mucosal blood vessels. As such local anesthetic with a vasoconstrictor should be used even under sedation and general anesthesia with DEX.

Conclusion

DEX is an appropriate sedative for implant surgeries and oral surgeries because it significantly decreases the PMBF. However, our results indicate that the vasodilation effect of lidocaine is stronger than the vasoconstriction effect of DEX. Therefore, lidocaine with a vasoconstrictor should be used in implant surgery and oral surgery under sedation and general anesthesia with DEX in clinical situations, as we found that the vasodilation effect of lidocaine exceeds the vasoconstriction effect mediated via adrenoceptors of DEX.

Conflicts of Interest

The authors of this paper have no conflicts of interest to declare.

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Table 1. Conditions for the HPLC Analysis of Lidocaine

HPLC, high-performance liquid chromatography; AUFS, absorbance units full scale.

Fig. 1. Method of general anesthesia in *Experiment 1*

General anesthesia was induced by 5% sevoflurane and 3 L/min oxygen, after which tracheotomy was performed and general anesthesia maintained. A laser Doppler flowmeter probe (ALF21RTM; Advance, Tokyo, Japan) was fixed onto the palatal mucosal surface using a piece of sponge to monitor the palatal mucosal blood flow continuously.

Fig. 2. Time course of the investigation in *Experiment 1*

The mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), end tidal CO_2 (E_TCO_2) and palatal mucosal blood flow (PMBF) were measured at 0 (baseline), 12, 17, 22, 27, 32, and 42 minutes after induction with 0.2 mg/kg midazolam, 0.05 mg/kg butorphanol, and 2 mg/kg rocuronium in sevoflurane or DEX.

Fig. 3. Method of general anesthesia in *Experiment 2*

General anesthesia was induced by 5% sevoflurane and 3 L/min oxygen, after which tracheotomy was performed and general anesthesia maintained. An intravenous line was placed in an ear vein, and a 3-Fr catheter was inserted via the femoral artery under general anesthesia with 3% sevoflurane and 3 L/min oxygen. The tip of the catheter in the femoral artery was placed in the thoracic aorta to take blood samples.

Fig. 4. Time course of the investigation in *Experiment 2*

In both groups, 0.5 mL each of 2% lidocaine without adrenaline was injected submucosally into the right and left palatal mucosa at 12 minutes after induction with 0.2 mg/kg midazolam, 0.05 mg/kg butorphanol, and 2 mg/kg rocuronium. The total dosage of 2% lidocaine without adrenaline was 1.0 mL. Blood samples (3 mL) were taken at 17, 22, 27, 32, and 42 minutes after induction with 0.2 mg/kg midazolam, 0.05 mg/kg butorphanol, and 2 mg/kg rocuronium.

Fig. 5. Changes in the MAP

The MAP was significantly lower than the control values in both groups at 12, 17, 22, 27, 32, and 42 minutes ($p<0.05$). On comparing the two groups, the value in the DMB group was significantly lower than in the SMB group at 12 minutes after induction with 0.2 mg/kg midazolam, 0.05 mg/kg butorphanol, and 2 mg/kg rocuronium (SMB group: 70.7±9.3 mmHg vs. DMB group: 61.2±10.0 mmHg, $p<0.05$).

Fig. 6. Changes in the HR

The HR in the DMB group was significantly lower than the control value ($p<0.05$). On comparing the two groups, the value in the DMB group was significantly lower than that in the SMB group from 10 to 42 minutes ($p<0.05$).

Fig. 7. Changes in the CVP

There were no significant differences in the CVP between the two groups and in each group.

Fig. 8. Changes in the E_TCO_2

There were no significant differences in the E_TCO_2 between the two groups and in each group.

Fig. 9. Changes in the PMBF

The PMBF in the DMB group was significantly lower than in the SMB group from 12 to 42 minutes after induction (the PMBF at 12, 17, 22, and 42 minutes decreased with a significant difference of $p<0.01$, and that at 27 and 32 minutes decreased with a significant difference of $p<0.05$).

Fig. 10. Changes in the serum lidocaine concentration

There were no significant differences in the serum lidocaine concentration between the two groups and in each group. Numbers in parentheses indicate the time elapsed after the injection of 1.0 mL of 2% lidocaine without adrenaline.

Table 1 Conditions for HPLC Analysis of Lidocaine

Pump	PU-2080 Plus
Detector	Jasco UV-2075 Plus
Sensitivity	0.001 AUFS
Column SUPELCOSIL	LC-8-DB 150 × 4.6 mm
Column Temperature	40℃
Mobile phase	50mM KH2PO4 : CH3CN＝4:1
Flow rate	1.0ml/min
Wave length	205 nm
Degasser	GL Sciences DG660B

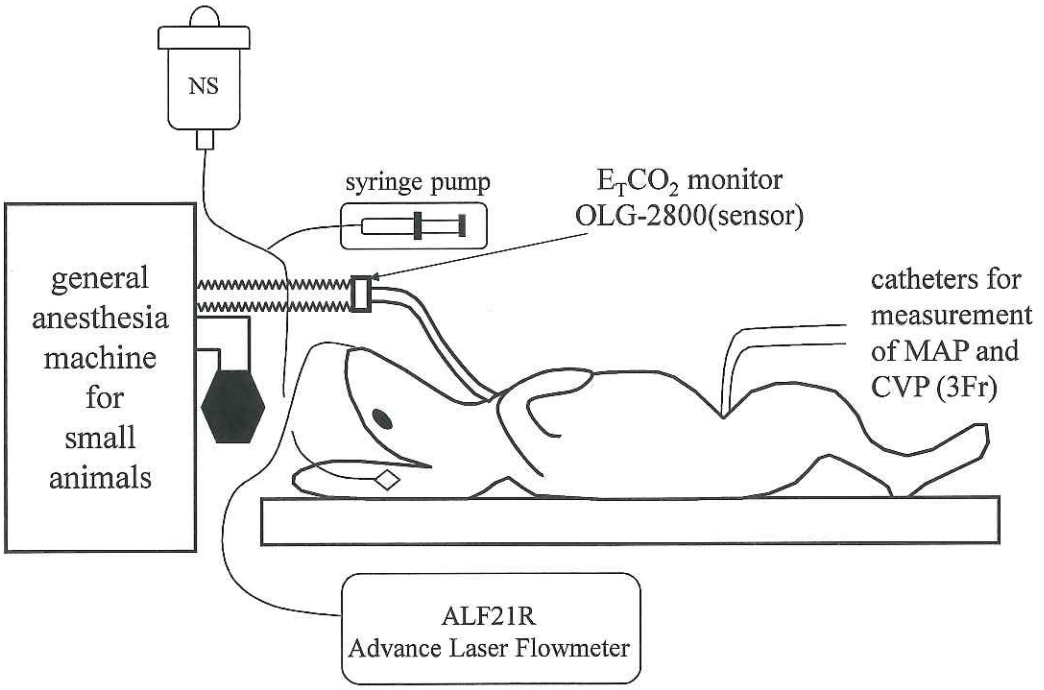

Fig. 1 Method of general anesthesia in *Experiment 1*

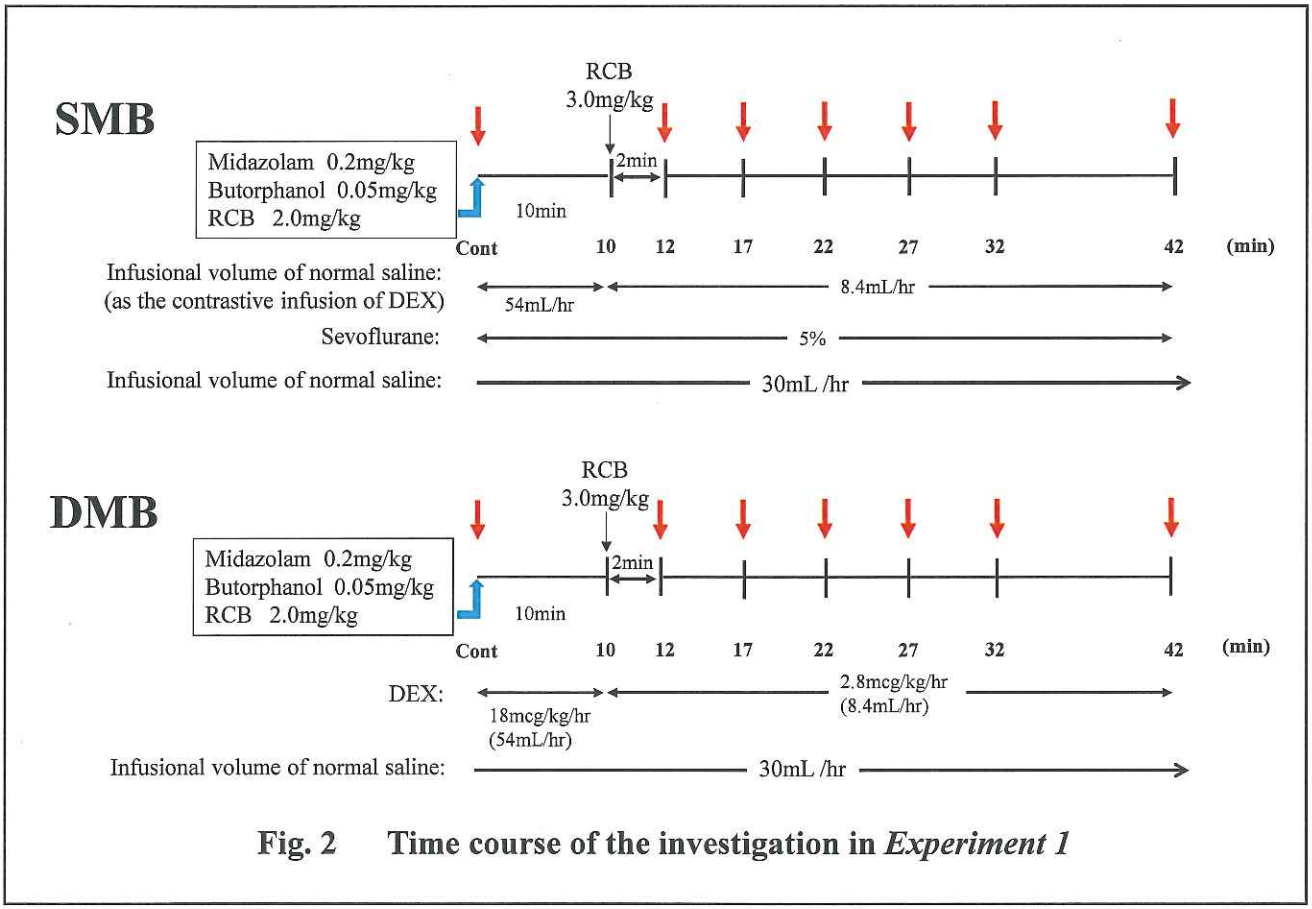

Fig. 2 Time course of the investigation in *Experiment 1*

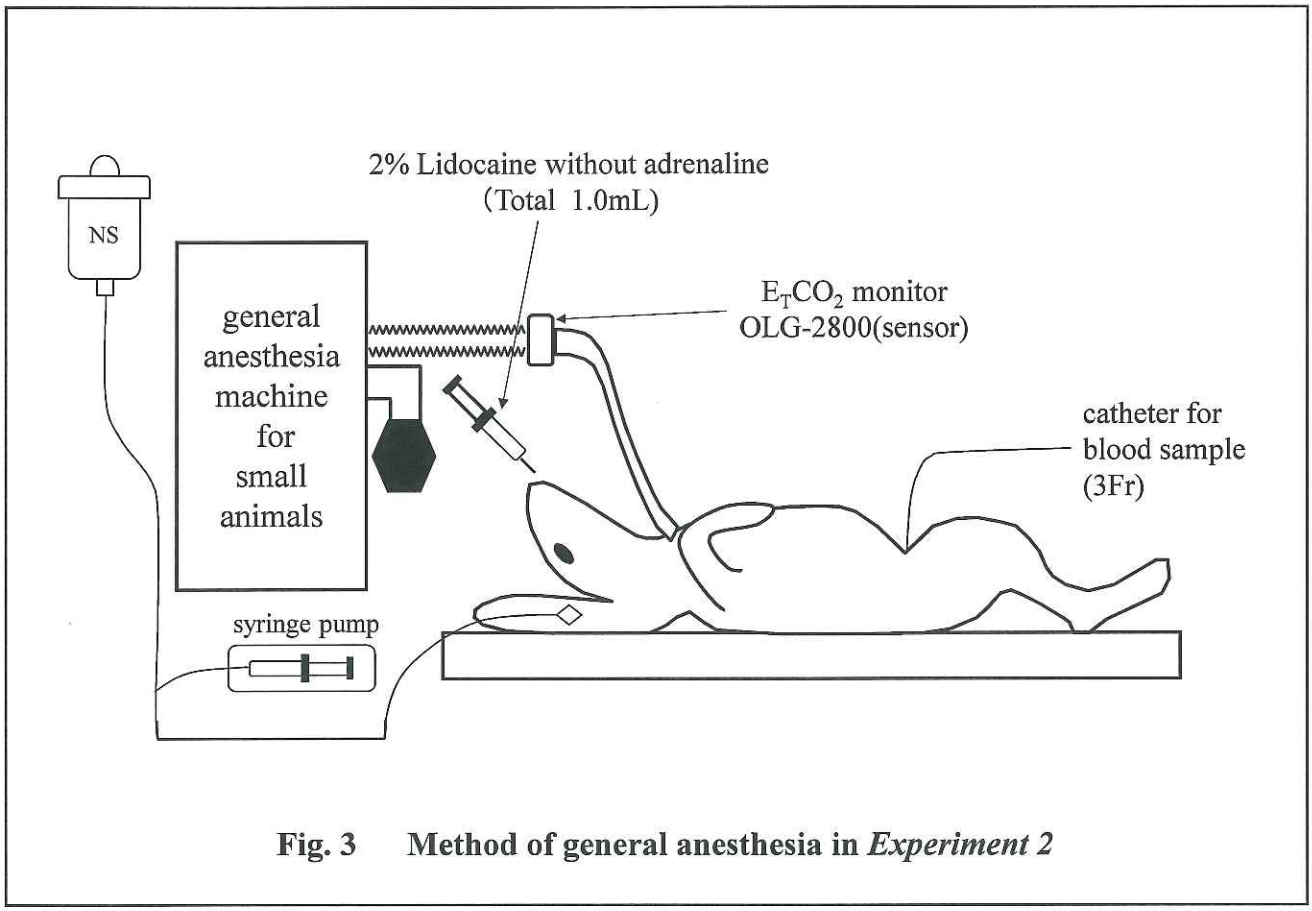

Fig. 3 Method of general anesthesia in *Experiment 2*

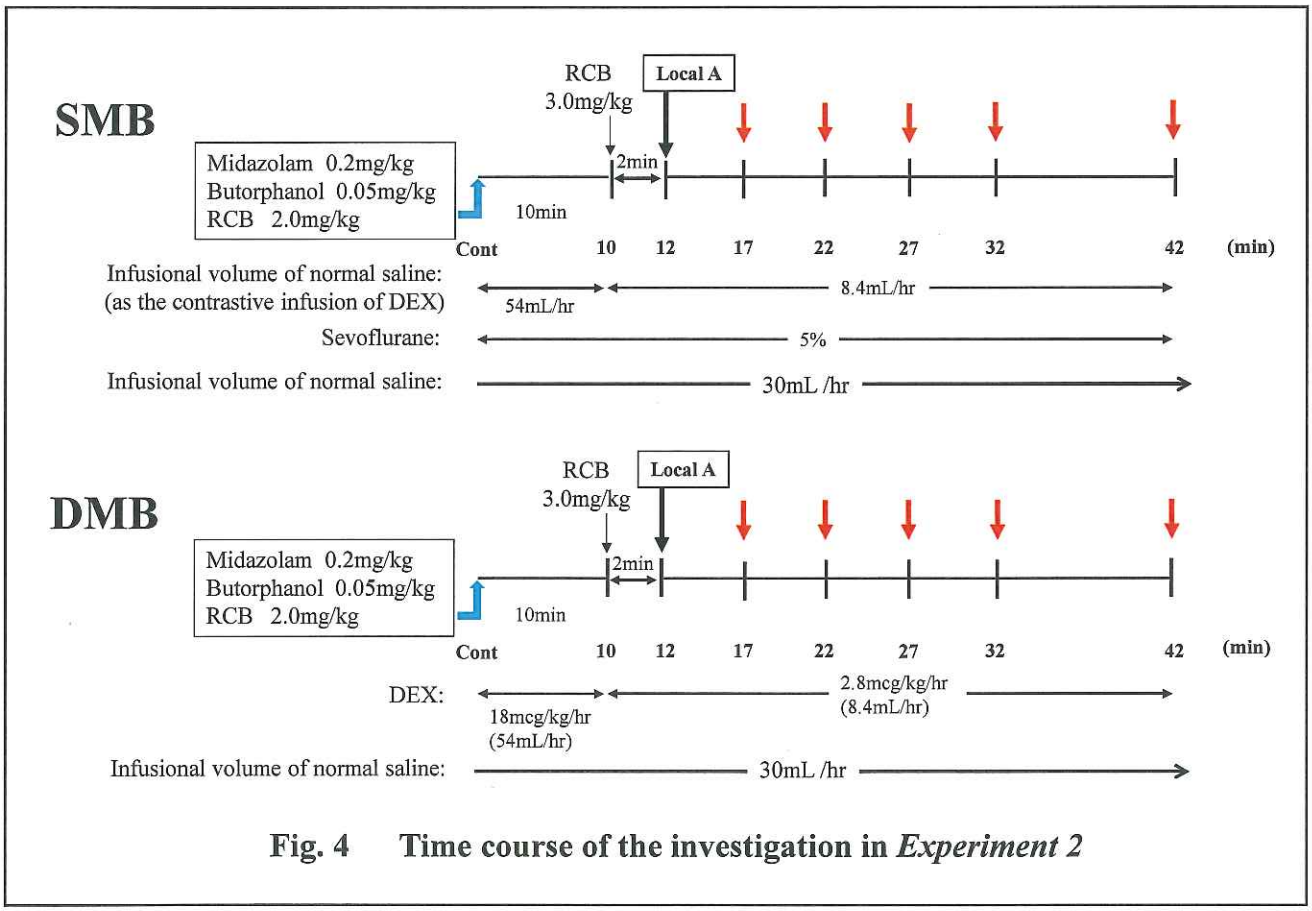

Fig. 4 Time course of the investigation in *Experiment 2*

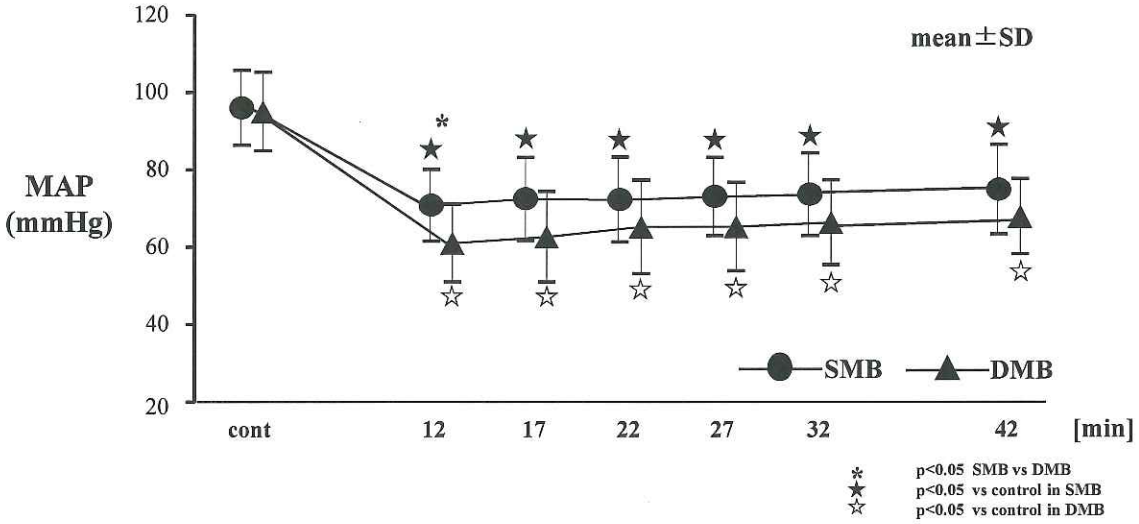

Fig. 5 Changes of the MAP

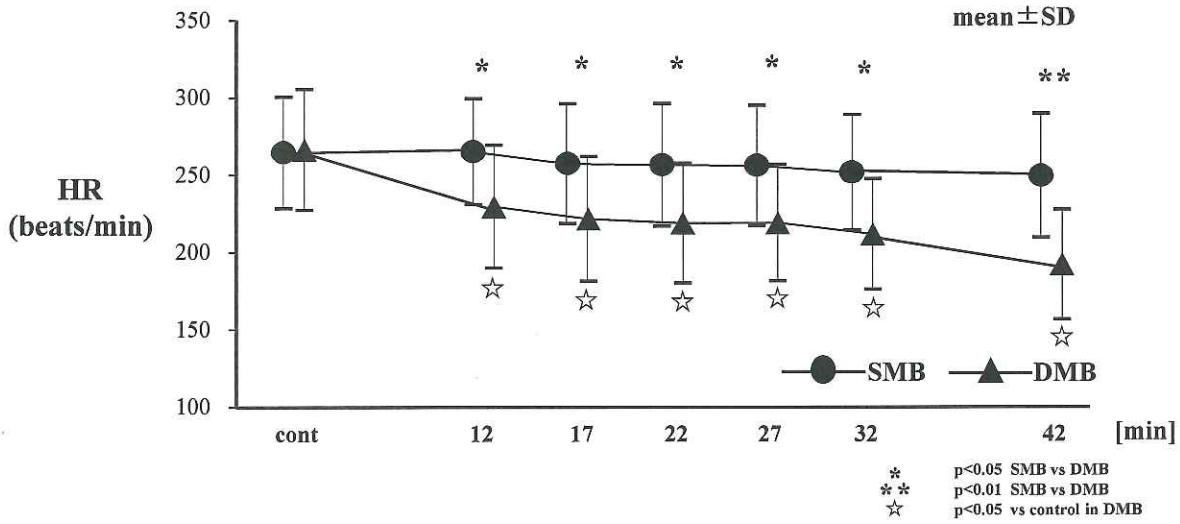

Fig. 6 Changes of the HR

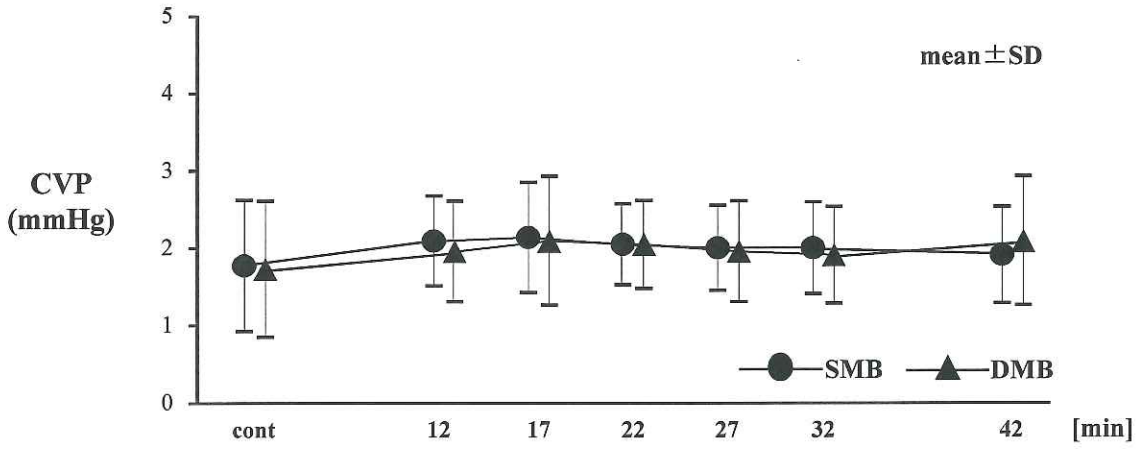

Fig. 7 Changes of the CVP

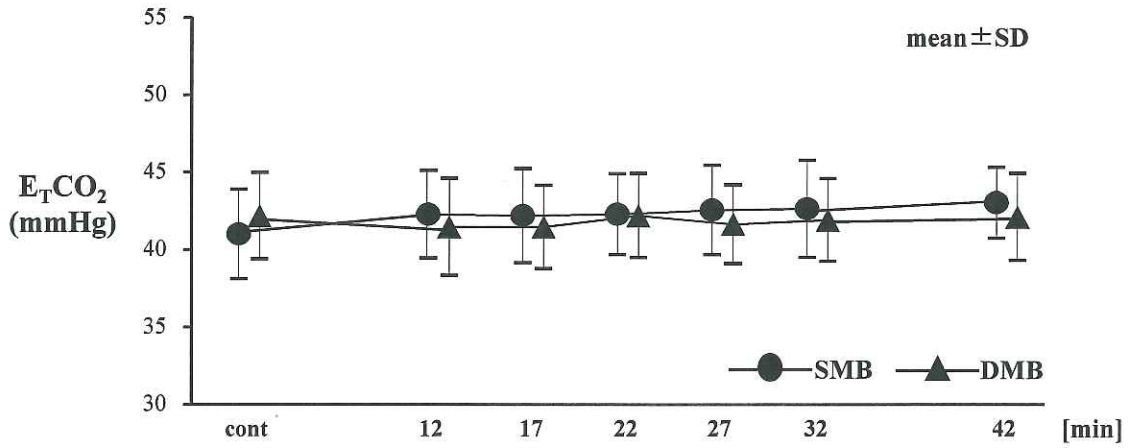

Fig. 8 Changes of the E_TCO_2

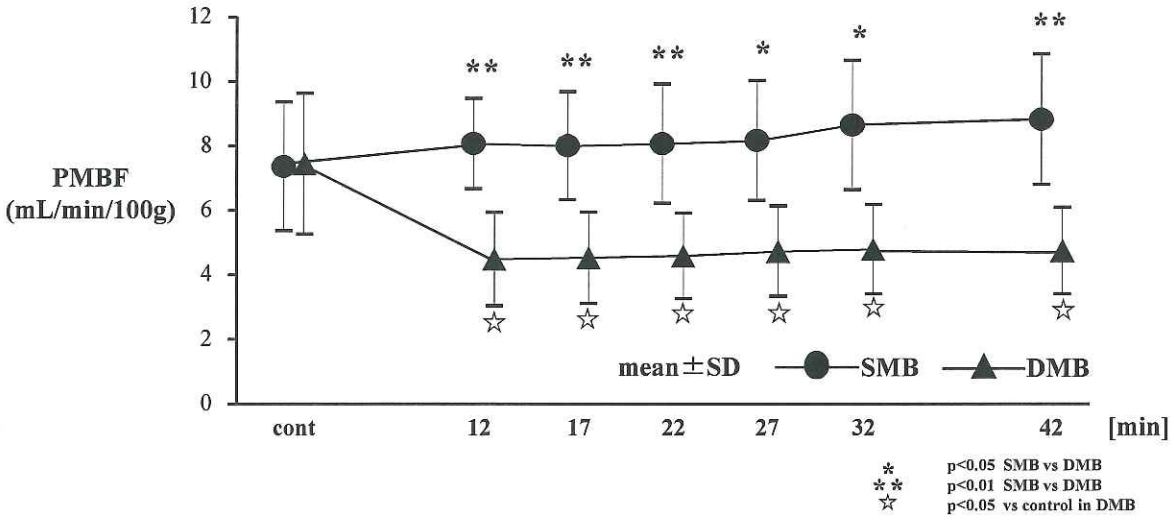

Fig. 9 Changes of the PMBF

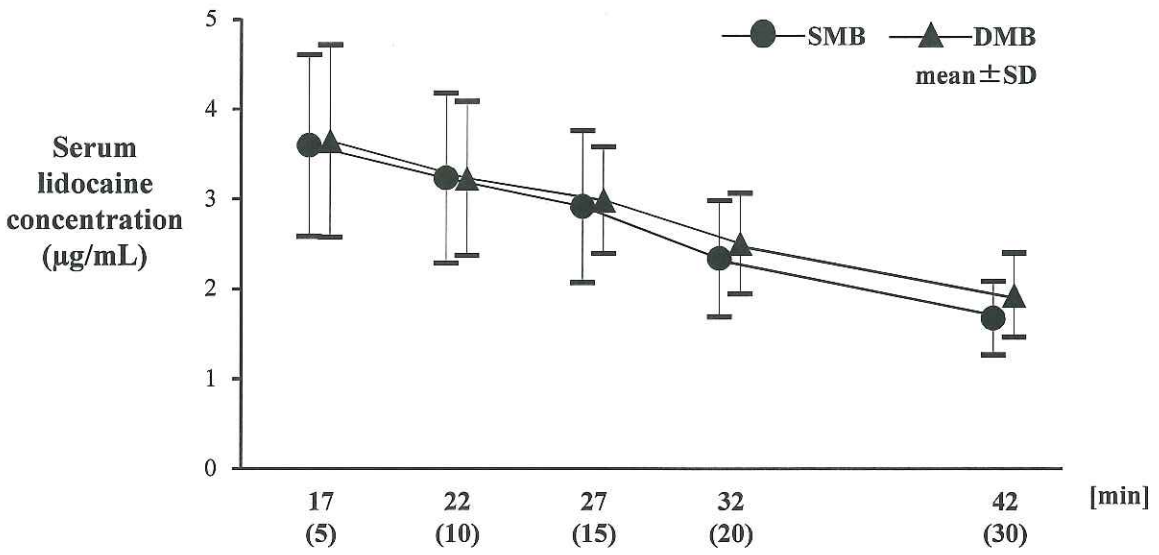

Fig. 10 Changes of the serum lidocaine concentration