LETTER TO THE EDITOR

Effects of Three Target-Controlled Concentrations of Sufentanil on MAC_{BAR} of SevofluraneZheng Liu,¹ Jia-Feng Wang,¹ Yan Meng,¹ Xiao-Hua Fan,¹ Xiao-Ming Deng,¹ Jin-Bao Li¹ & Guo-Jun Cai²¹Department of Anesthesiology and Intensive Care Medicine, Changhai Hospital, Second Military Medical University, Shanghai, China²Department of Pharmacology, Second Military Medical University, Shanghai, China**Correspondence**

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An acute increase in heart rate (HR) and blood pressure (BP) in response to surgical stimuli may increase the incidence of cardiovascular events such as acute pulmonary edema, cardiac ischemia, and stroke. Adequate depth of anesthesia is essential to inhibit such cardiovascular responses. A large dose is often required for single use of anesthetic agent, which may result in more severe adverse effects such as respiratory depression, postoperative nausea and vomiting, and cell death in the developing brain [1]. To reduce cardiovascular responses, inhalational anesthetics and opioids are often used in combination for balanced anesthesia, knowing that the synergetic effect between them is useful in reducing the adverse effects of a single agent.

The tenet of minimum alveolar concentration (MAC) is developed to evaluate the potency of inhalational anesthetics to prevent movement during skin incision. The potency of inhalational anesthetics in preventing cardiovascular responses is evaluated by MAC for blunting sympathetic responses (MAC_{BAR}). It was reported [2] that opioids decreased the MAC_{BAR} of volatile anesthetics after surgical incision. For example, 0.1 ng/mL and 0.5 ng/mL sufentanil reduced MAC of isoflurane by 44.2% and 77.8%, respectively. Sevoflurane is a safe and versatile inhalational anesthetic compared with the anesthetic agents currently available. Sevoflurane is useful in adults and children for both induction and maintenance of anesthesia in inpatient and outpatient surgery. In addition, sevoflurane is well known to exert a neuroprotective effect through anesthetic preconditioning or postconditioning [3]. Sufentanil is an opioid about 5–10 times as potent as fentanyl, and yet has a shorter duration of action. A recent study [4] reported that several opioid agents act on α_2 -adrenoceptors in the brain, including meperidine, remifentanyl, and tramadol, but

not sufentanil. The effect of sufentanil on MAC_{BAR} of sevoflurane remains undetermined. The aim of this study was to compare MAC_{BAR} of sevoflurane in the presence of three different target-controlled concentrations of sufentanil in an attempt to identify a relatively ideal dose of these anesthetics in balanced anesthesia.

This study was approved by the ethical committee of the Second Military Medical University, and written informed consent was obtained from every patient. Included in this study were 84 patients (American Society of Anesthesiologists physical status I) aged 20–55 years and weighing 45–75 kg who underwent abdominal surgery with an incision longer than 10 cm. The exclusive criteria included: (1) patients with systemic diseases in the cardiovascular system, lung, liver, or kidney; (2) patients with a BMI higher than 30 kg/m²; (3) patients who were alcohol or drug abusers; and (4) patients who were using medications that might affect cardiovascular responses to skin incision.

The patients fasted for 8–10 h and received no medication before surgery. Noninvasive BP, HR, electrocardiogram (ECG, lead II) and pulse oximetry were monitored with a Hewlett-Packard monitor after the patients were brought into the operating room. Bispectral index (BIS) was also monitored using a BIS lead (A2000 XPTM, Aspect, USA) in S/5TM anesthesia monitor (Datex Ohmeda, Madison, Wisconsin, USA). BIS is usually proposed as a measure of the effect of anesthetics on the brain, and BIS value between 40 and 60 is considered a sufficient anesthetic depth.

General anesthesia was induced by target-controlled infusion (TCI) of sufentanil (0.3 ng/mL) and propofol (3 μ g/mL). After loss of consciousness, BIS dropped to below 60, rocuronium

Figure 1 End-tidal concentrations and MAC_{BAR} of sevoflurane predetermined by patient responses to skin incision according to the up and down sequence. Patient responses were determined by measuring changes in blood pressure and heart rate. Open symbols represent positive responses (an increase of either heart rate or mean arterial pressure $\geq 15\%$ above the

mean of the values measured during the 2 min before skin incision) and filled symbols represent negative responses (neither heart rate nor mean arterial pressure increased $\geq 15\%$ above the mean of the values measured during the 2 min before skin incision). Differences in MAC_{BAR} between two of the three groups were statistically significant ($P < 0.01$).

(0.6 mg/kg) was administered intravenously, and tracheal intubation was performed. After intubation, the patients were ventilated with sevoflurane in oxygen. Propofol infusion was terminated once intubation was performed and anesthesia was maintained by inhaled sevoflurane and TCI of sufentanil at the designed concentration. According to different targeted concentrations of sufentanil, the patients were randomly assigned to three groups: 0.1 ng/mL group, 0.3 ng/mL group, and 0.5 ng/mL group. The targeted concentrations of sevoflurane and sufentanil were maintained for at least 15 min before skin incision. TCI was accomplished with a computer assisted syringe pump (Module DPS Orchestra IS3; Fresenius Vial, Le Grand Chemin, France) driven by a pharmacokinetic model described by Gepts E for sufentanil [5] and Marsh B for propofol [6]. End-tidal concentrations of oxygen, carbon dioxide, and sevoflurane were monitored in a multigas monitor (Dräger Primus; Dräger Medical, Lübeck, Germany). Ventilation was mechanically controlled by using a ventilator (Dräger Primus; Dräger Medical) to maintain an end tidal partial pressure of carbon dioxide between 30 and 40 mmHg. Fresh gas flow was set to 8 L/min.

HR, BP, and rate-pressure product (RPP, a product of systolic blood pressure [SBP] and HR) were determined before induction, 2 and 1 min before skin incision, at the time of skin incision, and at 1, 2, 3, 4, and 5 min after skin incision. Patients with se-

vere hypotension (mean arterial pressure [MAP] < 50 mmHg) before skin incision who required treatment with vasoactive medications such as atropine, ephedrine, and dopamine were excluded from the study. The person who was responsible for recording HR and BP and determining the response to skin incision was blind to patient grouping. All patients were followed-up the next day after surgery to assess any adverse event such as intraoperative awareness.

The MAC_{BAR} of sevoflurane was determined by using the up-and-down sequential-allocation technique described in the literature [7]. The concentration of sevoflurane was set at 3% in the first patient and then determined by the response of the previous patient to the stimulation of skin incision. If the response of a patient in that group was positive (an increase of either HR or MAP $\geq 15\%$ above the mean of the values measured during the 2 min before skin incision), the end-tidal concentration given to the next patient was increased by 0.5% (0.25 MAC). If the response was negative (neither HR nor MAP increased $\geq 15\%$ above the mean of the values measured during the 2 min before skin incision), the end-tidal concentration of sevoflurane given to the next patient was decreased by the same amount. After three changes of response type were observed, the test space was reduced to 0.2% (0.125 MAC) in the rest of the patients so as to increase the precision. The mean (with 95% confidence intervals) of MAC_{BAR} of

Figure 2 Comparison of mean arterial pressure (MAP) (A), bispectral index (BIS) (B), heart rate (HR) (C), and rate-pressure product (RPP) (D) between the three groups at different time points, * $P < 0.05$, 0.1 ng/mL versus 0.3 ng/mL; † $P < 0.05$, 0.1 ng/mL versus 0.5 ng/mL; # $P < 0.05$, 0.3 ng/mL versus 0.5 ng/mL.

sevoflurane was then calculated from the midpoints of pairs of concentrations from consecutive patients with different responses to skin incision after the initial test space was reduced [6,8].

Data are presented as mean $\pm$ SD and 95% confidence intervals. Comparisons of quantitative data including general data, cardiovascular data and MAC_{BAR} were performed using analysis of variance. Categorized data such as gender were compared using chi-square test. Statistical analysis was performed using SPSS 11.0.0 software (SPSS Inc., Chicago, Illinois, USA).

A total of 82 patients completed the study. One patient in 0.3 ng/mL group and another patient in 0.5 ng/mL group were excluded because their MAPs were lower than 50 mmHg during the study. Anthropometric data of the patients before anesthesia including gender, age, height, weight, SBP, diastolic blood pressure, HR, and BIS, were not significantly different between the three groups. BIS value was controlled at a level lower than 50 during surgery in all patients. All the patients recovered successfully after surgery, and no intraoperative awareness occurred in any patient according to the follow-up.

As shown in Figure 1, MAC_{BAR} value of sevoflurane was 4.4% (95% confidence interval: 4.3–4.5%) in 0.1 ng/mL group, 2.5% (2.4–2.6%) in 0.3 ng/mL group, and 2.0% (1.9–2.1%) in 0.5 ng/mL group. Differences in MAC_{BAR} between two of the three groups were statistically significant ($P < 0.01$). MAC_{BAR} reduced

by 43.2% when the sufentanil concentration was increased from 0.1 ng/mL to 0.3 ng/mL, and by 20.0% when it was increased from 0.3 ng/mL to 0.5 ng/mL.

Anesthesia induction resulted in a significant decrease in HR and MAP. However, HR and MAP were maintained at a constant level at all designated time points after induction. No significant difference was observed in MAP between the patients of the three groups. But a trend was observed that HR and RPP reduced with the sufentanil concentration increasing. HR and RPP were significantly lower in 0.5 ng/mL and 0.3 ng/mL groups than those in 0.1 ng/mL group after anesthesia induction, and the trend became more obvious after skin incision. At the last several time points after skin incision, HR and RPP decreased significantly in 0.5 ng/mL group compared with those in 0.3 ng/mL group ($P < 0.05$; Figure 2). BIS value was significantly higher in 0.5 ng/mL group than that in the other two groups at 1 and 2 min before skin incision ($P < 0.05$; Figure 2). Alterations in the mean value of MAP, HR, RPP, and BIS before and after skin incision were also analyzed. MAP, HR, and RPP increased significantly after skin incision compared with those before incision in 0.1 ng/mL group ($P < 0.05$); whereas in 0.3 ng/mL group, only MAP increased significantly after skin incision ($P < 0.05$); no significant change was observed before and after skin incision in 0.5 ng/mL group. BIS value was similar before and after incision in all three groups.

This study revealed that MAC_{BAR} of sevoflurane was reduced significantly by increasing the target concentration of sufentanil. In addition, HR and RPP were significantly higher in 0.1 ng/mL group than those in the other two groups. RPP is a parameter correlated closely with myocardial oxygen demand [9]. Lower RPP in the higher sufentanil dose group suggested that 0.3–0.5 ng/mL sufentanil might reduce myocardial oxygen demand significantly. Furthermore, MAP, HR, and RPP increased significantly after skin incision compared with those before incision in 0.1 ng/mL group. Although the changes in HR and BP were within 15% of the basic level, 0.1 ng/mL sufentanil might provide insufficient analgesia and a higher dose of sufentanil was protective for patients, especially for those with potential myocardial ischemia. It was found in our study that BIS value was higher in 0.5 ng/mL group than that in the other two groups at the two time points before skin incision, which might be attributed to the low concentration of sevoflurane. Although 0.5 ng/mL sufentanil blunted the sympathetic response induced by skin incision effectively, the low concentration of sevoflurane might not be enough to maintain sufficient anesthetic depth and increase the potential risk of intraoperative awareness.

A limitation of this study is that there was no control group free of sufentanil. However, it was found in our preliminary study that BIS was transiently higher than 60 during surgical incision even though the concentration of sevoflurane was as high as 8%.

Thus we terminated any attempt to maintain anesthesia without sufentanil to avoid intraoperative awareness. This is in accordance with the study of Ura et al. [10], who found that MAC_{BAR} of single sevoflurane was as high as 8%.

In summary, MAC_{BAR} of sevoflurane can be reduced by sufentanil. Increasing sufentanil from 0.1 ng/mL to 0.3 ng/mL reduced sevoflurane MAC_{BAR} to a larger extent as compared with that by increasing sufentanil from 0.3 ng/mL to 0.5 ng/mL. When the target concentration of sufentanil was 0.3 ng/mL and 0.5 ng/mL, myocardial oxygen consumption was reduced effectively. However, 0.5 ng/mL sufentanil combined with a low concentration of sevoflurane might increase the potential risk of intraoperative awareness. So, it might be more suitable to combine 0.3 ng/mL sufentanil and 2.5% (2.4–2.6%) sevoflurane for blunting skin incision-induced sympathetic responses effectively, and maintaining enough anesthetic depth to prevent intraoperative awareness.

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Conflict of Interest

The authors have no conflict of interest.

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