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Effects of oral atenolol on volatile anesthetic induction with sevoflurane in adults

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Abstract
Purpose. To determine whether premedication with a β-blocker can bring about a more rapid and smooth induction of anesthesia, we investigated the effect of oral premedication with atenolol on volatile anesthetic induction with sevoflurane by monitoring the cardiac output (CO) and bispectral (BIS) index.
Methods. Twenty-four patients undergoing general anesthesia with endotracheal intubation were randomly divided into two groups: a control group ($n = 12$) and a β-blocker group ($n = 12$). Each patient in the β-blocker group was premedicated with oral atenolol 25 mg 1 h before the induction of anesthesia. Anesthesia was induced by the repeated vital capacity technique with 5% sevoflurane and 66% nitrous oxide. The trachea was intubated 5 min after sevoflurane exposure. The CO and BIS index, as well as the induction time and specific side effects of induction (e.g., movement of limbs), were recorded.
Results. There were no significant differences in induction time and specific side effects between the groups. The downward-sloping part of the BIS index curve in the β-blocker group (mean, 2.9 ± 0.2) was significantly sharper than that in the control group (2.5 ± 0.2), and the BIS index after induction of anesthesia was significantly lower in the β-blocker group (21.0 ± 2.2) than in the control group (24.2 ± 2.0). CO in the β-blocker group was significantly lower than in the control group during the study period. The hemodynamic changes caused by endotracheal intubation were inhibited in the β-blocker group but not in the control group.
Conclusion. Oral premedication with 25 mg of atenolol provides a more rapid decrease in BIS index and is recommended for use in stable volatile anesthetic induction with sevoflurane.

Key words Sevoflurane · Volatile induction and maintenance of anesthesia (VIMA) · β-Adrenergic blocker · Induction time

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Introduction

Induction of anesthesia can be achieved rapidly using single vital capacity [1] or repeated tidal breathing [2] techniques with sevoflurane and nitrous oxide, techniques that typically produce loss of consciousness in approximately 60–70 s. Although the technique using sevoflurane is associated with minimal complications compared with the techniques using halothane [3,4] and isoflurane [5], appropriate hypnotic premedication should be used for smoother induction of anesthesia and for the patient's comfort [6,7]. It has recently been reported that a β-adrenergic blocker (β-blocker) not only reduced the anesthetic requirement for skin incision during anesthesia [8,9], but also reduced the bispectral (BIS) index and promoted electroencephalographic burst suppression during anesthesia [10]. Since a β-blocker can also reduce cardiac output, leading to acceleration of the increase in partial pressure of volatile anesthetics in the blood and brain [11], we hypothesized that premedication with a β-blocker would bring about a more rapid and smooth induction of anesthesia by sevoflurane. To determine the validity of this hypothesis, we investigated the effect of oral premedication with the β-blocker atenolol on volatile anesthetic induction with sevoflurane in adults by monitoring the hemodynamic changes, cardiac output, and BIS index.

Patients and methods

After institutional approval and informed consent from each patient had been obtained, 24 ASA physical status I or II adult patients who were scheduled to undergo general anesthesia with endotracheal intubation for minor surgery were enrolled in this study. Patients with a history of, or evidence from laboratory or physical examination indicating, hepatic, renal, or significant respiratory or cardiovascular disease were excluded from the

study. The patients were randomly divided into two groups by the envelope technique: a control group (n = 12) and a β-blocker group (n = 12). Each patient in the β-blocker group was premedicated with oral atenolol 25 mg 1 h before the induction of anesthesia, whereas no premedication was given to the patients in the control group. In the operating room, each patient was requested to lie in a supine position in a quiet environment. Cardiac output and BIS index were monitored continuously by the use of a thoracic electrical impedance cardiac output monitor (NCCOM3, BoMED, Irvine, CA, USA) [12] and a BIS monitor (A-2000; Aspect Medical Systems, Newton, MA, USA) [13]; these values were recorded every 10 and 5 s, respectively.

While the patients were breathing room air before the induction of anesthesia, the anesthetic circuit was circulated with 3 l·min^{-1} oxygen, 6 l·min^{-1} nitrous oxide, and 5% sevoflurane for 1 min. The patients were instructed to breathe out to residual volume, and then the anesthetic mask was fitted tightly. They were then told to take repeated vital capacity breaths through the mouth. Loss of consciousness was defined by the loss of eyelash reflex. The eyelash reflex was checked at 5-s intervals. After loss of consciousness had been confirmed, the fresh gas flow rates of oxygen and nitrous oxide were decreased to 2 l·min^{-1} and 4 l·min,$^{-1}$ respectively, and the patient's breathing was assisted thereafter. After insertion of an intravenous catheter into the left cephalic vein, vecuronium was injected at a dose of 0.12 mg·kg^{-1}, and the trachea was intubated 5 min after sevoflurane exposure. In addition to the cardiac output and BIS index, the induction time and specific side effects of induction were recorded by an independent observer. The induction time was defined as the time from sevoflurane exposure to loss of consciousness. The definitions of induction side effects were those reported by Lamberty and Wilson [5] and Philip et al. [14]. Briefly, possible side effects were categorized in six groups: hypotension/bradycardia (more than 20% change from the preanesthetic mean blood pressure and heart rate), coughing, laryngospasm, breath holding, movement of limbs, and excessive secretions. The heart rate and mean blood pressure were also recorded every 10 and 30 s, respectively.

Data are expressed as numbers or as mean ± SD. The sample size was determined by power analysis on the basis of the results of a previous study by Beller et al. [15]. Considering an equivalence range within 20% and accepting a type 1 error of 0.05 and a type II error of 0.1, it was decided to enroll patients to obtain at least 12 complete data sets per group for this study. Changes in BIS index during the study were fitted to sigmoid curves (Boltzmann expression), and the slope factor and the index before and after anesthetic induction were calculated. Statistical analyses were performed using the unpaired t-test, χ^2-test, or one-way ANOVA with Fisher's test as a post hoc test. A P value less than 0.05 was considered to indicate statistical significance.

Table 1. Demographic characteristics and cardiac output before induction of anesthesia[a]

Characteristic	Control (n = 12)	β-Blocker (n = 12)
Sex (male/female)	8/4	7/5
Age (yr)	56.8 ± 7.2	58.9 ± 8.2
Height (cm)	161.2 ± 11.8	159.4 ± 13.1
Weight (kg)	61.3 ± 6.2	60.4 ± 5.2
ASA physical status (1/2)	8/4	9/3
Cardiac output (l·min^{-1}·m^{-2})	3.7 ± 0.4	3.1 ± 0.3*

[a] Values are numbers or means ± SD
* $P < 0.05$ vs control group

Table 2. Induction time and adverse side effects during the induction of anesthesia

Variable	Control (n = 12)	β-Blocker (n = 12)
Induction time (s)	66 ± 7	65 ± 7
Adverse induction side effects (n)	2	1
Hypotension/bradycardia	0	0
Coughing	0	0
Laryngospasm	0	0
Breath holding	0	0
Movement of limbs	2	1
Excessive secretions	0	0

[a] Values are numbers or means ± SD

Results

The two groups were comparable with respect to sex, age, height, weight, and ASA physical status (Table 1). The cardiac output before the induction of anesthesia was significantly lower in the β-blocker group (3.7 ± 0.4 l·min^{-1}·m^2) than in the control group (3.1 ± 0.3 l·min^{-1}·m^2). The induction time and details of the specific side effects during induction are shown in Table 2. There were no significant differences between the groups in induction time and incidence of side effects.

Changes in BIS index during the study period are shown in Fig. 1. Even though the induction times per se in the two groups were not different (Table 2), the downward-sloping part of the BIS index curve in the β-blocker group (slope, 2.9 ± 0.2) was significantly sharper than that in the control group (2.5 ± 0.2). Although the BIS indices before the induction of anesthesia in the two groups were not different, the index was significantly lower in the β-blocker group (21.0 ± 2.2)

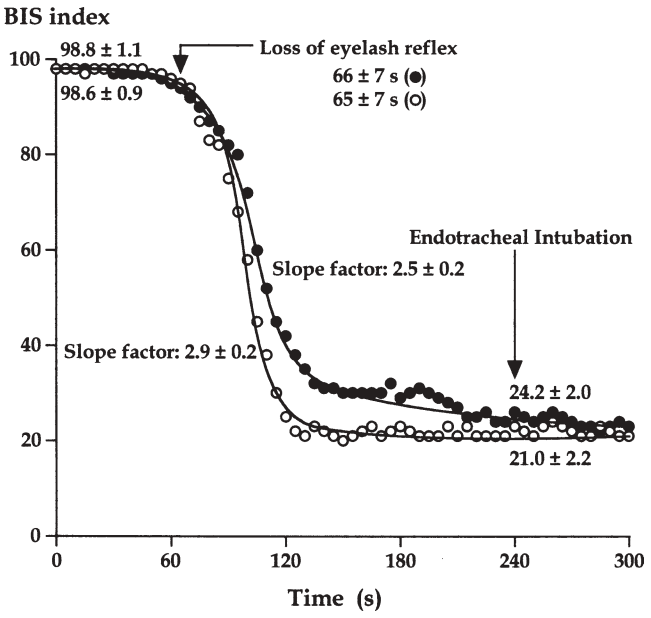

Fig. 1. Changes in bispectral (*BIS*) index during the induction of anesthesia with sevoflurane. Mean ± SD, $n = 12$ each. ● Control group, ○ β-blocker group. Slope: 2.9 ± 0.2 and 2.5 ± 0.2 in the β-blocker and the control groups, respectively ($P < 0.05$). BIS index after the induction of anesthesia: 21.0 ± 2.2 and 24.2 ± 2.0 in the β-blocker and the control groups, respectively ($P < 0.05$)

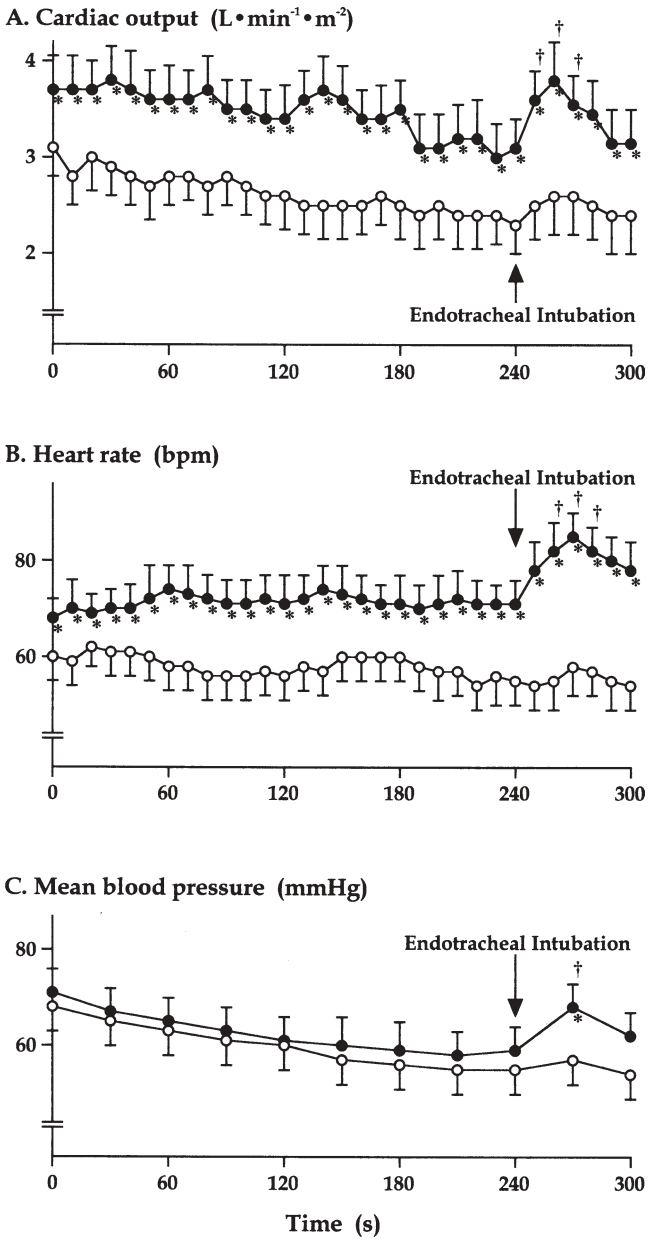

Fig. 2. Changes in cardiac output (**A**), heart rate (**B**), and mean blood pressure (**C**) during the induction of anesthesia with sevoflurane. Mean ± SD, $n = 12$ each. ● Control group, ○ β-blocker group. The mean cardiac output in the β-blocker group was significantly lower than that in the control group throughout the study period. Compared with the values just before endotracheal intubation, the procedure of endotracheal intubation significantly increased the cardiac output, heart rate, and mean blood pressure by 0.9 ± 0.3 l·min^{-1}·m^{-2}, 11 ± 4 bpm, and 8 ± 3 mmHg, respectively, in the control group, whereas these values did not change in the β-blocker group. *$P < 0.05$ vs β-blocker group, †$P < 0.05$ vs the values just before endotracheal intubation

than in the control group (24.2 ± 2.0) after induction of anesthesia.

Figure 2 shows the hemodynamic changes during the study period in both groups. There was no significant change in cardiac output per se in either group during the study period before endotracheal intubation; however, the mean cardiac output in the β-blocker group was significantly lower than that in the control group throughout the study period due to a significantly lower heart rate in the β-blocker group. Compared with the values just before endotracheal intubation, the procedure of endotracheal intubation significantly increased the cardiac output, heart rate, and mean blood pressure by 0.9 ± 0.3 l·min^{-1}·m^{-2}, 11 ± 4 bpm, and 8 ± 3 mmHg, respectively, in the control group, whereas these values did not change in the β-blocker group. The hemodynamic changes caused by endotracheal intubation were therefore significantly inhibited in the β-blocker group but not in the control group.

Discussion

Although neither the induction time nor the incidence of adverse effects was changed by premedication with the β-blocker, the BIS index decreased significantly more quickly and the index after induction of anesthesia

was significantly lower in the β-blocker group than in the control group (Fig. 1). Since it has been reported that a significant cortical depression and the onset of burst suppression during stable propofol/alfentanil anesthesia were associated with infusion of the β-blocker esmolol [10], it is reasonable to assume that atenolol used as a premedication in our study could have enhanced the anesthetic potency of sevoflurane/nitrous oxide. This assumption is supported by the fact that the BIS index after induction of anesthesia in the β-blocker group was significantly lower than that in the control group. The BIS index at the time of loss of eyelash reflex was approximately 96 to 97 in this study. However, it has been pointed out that BIS most accurately reflects the level of consciousness of the patient approximately 60 s previously [16]. This seems to be realistic, because the total update delay of BIS is approximately 30 s [17]. Thus, there seems to have been a discrepancy between the BIS index measured at the time of loss of the eyelash reflex and the real sedative level at the same time [18].

Decreased cardiac output can accelerate the increase in partial pressure of volatile anesthetics in the blood and brain [11], leading to a rapid onset of anesthetic induction. A change in cardiac output slightly affects the blood/alveolar concentration of a poorly soluble agent such as sevoflurane. However, the gradient of partial pressure of the agent would be much larger during induction of anesthesia with a high concentration (5%) of sevoflurane, and the changes in cardiac output would also have had some effect on the changes in the anesthetic partial pressure in the blood and brain in this study. The onsets of decrease in BIS index in the two groups in this study were not different. This is because the rather slow increase in volatile anesthetic concentration in pulmonary arterial blood in this study, compared with a rapid bolus injection of anesthetics such as intravenous anesthetics, could counteract the effect of cardiac output [19]. It is also possible that the circulatory time from the lung to the brain is too short for cardiac output to have any effect.

This study also revealed that the hemodynamic changes, cardiac output, blood pressure, and heart rate during endotracheal intubation were significantly more inhibited in the β-blocker group than in the control group. Stone et al. [20] reported that mild hypertension, when untreated prior to the induction of anesthesia, was associated with a high incidence of myocardial ischemia and that a single small oral dose of a β-blocker such as atenolol, given as premedication, significantly reduced this risk. Since the incidence of ischemic events has always been associated with tachycardia, not with hypertension, the smaller hemodynamic changes in the β-blocker group in this study could have a beneficial action with respect to cardiac ischemic events [21,22]. Contrary to the beneficial action of a β-blocker, a detrimental circulatory failure may occur by interaction with the anesthetic sevoflurane. However, cardiac output did not change significantly after the induction of anesthesia in the β-blocker group. Moreover, sevoflurane per se has the least inhibitory effect on hemodynamic changes among the volatile anesthetics available [23]. Therefore, oral premedication with 25 mg of atenolol can be used for more stable induction of anesthesia by sevoflurane without troublesome hemodynamic suppression. However, since this study was performed with healthy subjects, it does not apply to those with significant cardiovascular disorders.

In summary, even though the anesthetic induction times per se in the two groups were not different, the decrease in the BIS index curve in the β-blocker group was significantly faster than that in the control group, and the hemodynamic changes caused by endotracheal intubation were significantly inhibited in the β-blocker group. Oral premedication with 25 mg of atenolol is recommended for stable induction of anesthesia using sevoflurane without significant hemodynamic derangement.

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