J Anesth (2005) 19:213–217
DOI 10.1007/s00540-005-0318-0

Journal of
Anesthesia

Hemodynamic and catecholamine response to a rapid increase in isoflurane or sevoflurane concentration during a maintenance phase of anesthesia in humans

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Abstract
Purpose. The purpose of this study was to compare hemodynamic and catecholamine changes due to a sudden increase in inhalation anesthetic concentrations (isoflurane and sevoflurane) during surgery.
Methods. Thirty patients aged 40–70 years scheduled for lower abdominal surgery were anesthetized with either isoflurane or sevoflurane with nitrous oxide and epidural block. During surgery the isoflurane or sevoflurane concentration was kept at 0.5 minimum alveolar concentration (MAC) (end-tidal concentration) for 15 min. Then the isoflurane or sevoflurane concentration (inhalation concentration) was changed to 1.5 MAC and maintained at that level for 10 min. Thereafter, it was decreased to 0.5 MAC for 10 min. Blood pressure, heart rate, and plasma concentrations of epinephrine and norepinephrine were measured.
Results. The blood pressure decreased significantly in both groups after increasing the anesthetic concentration, and it increased after decreasing the concentration. The decrease in systolic blood pressure was significantly larger in the isoflurane group. The heart rate increased significantly after increasing the anesthetic concentration only in the isoflurane group. Plasma concentrations of epinephrine and norepinephrine increased significantly in the isoflurane group, whereas the epinephrine concentration (but not the norepinephrine concentration) decreased in the sevoflurane group.
Conclusion. During surgery a sudden increase in isoflurane concentration induced larger changes in hemodynamics and sympathetic nerve activity than sevoflurane.

Key words Isoflurane · Sevoflurane · Catecholamine · Anesthetic concentration

Introduction

During inhalation induction of anesthesia with a mask, stepwise increases in isoflurane concentration elicited hypertension and tachycardia as well as increments in plasma catecholamine concentration [1]. Sudden administration of 5% isoflurane caused immediate increases in blood pressure and heart rate [2]. In contrast, changes in sevoflurane concentration did not induce hyperdynamic responses [3]. The plasma norepinephrine concentration was significantly higher during isoflurane induction than that during sevoflurane induction [3].

During a maintenance phase of anesthesia, we sometimes increase the anesthetic concentration rapidly when surgical stimuli are expected to become stronger. Wajima et al. [4] reported a decrease in blood pressure and increases in heart rate and plasma norepinephrine concentration by a sudden increase in isoflurane or sevoflurane concentration after intubation but without any surgical stimuli. However, there have been no studies that compared the hemodynamic changes induced by a sudden increase in inhalation anesthetic concentration of isoflurane or sevoflurane during surgery. Therefore, we decided to study hemodynamic and catecholamine changes after a sudden increase in isoflurane and sevoflurane concentrations during surgery.

Materials and methods

After approval of the research committee of the hospital and obtaining informed consent from the patients, 30 patients aged 40–70 years scheduled for lower abdominal surgery were randomly divided into two groups using an envelope method (15 patients in each group). Those who had a history of liver or renal dysfunction, habituation of smoking or drugs affecting liver function

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Received: November 18, 2004 / Accepted: February 26, 2005

or autonomic nervous system, or endocrinological diseases such as diabetes mellitus were excluded from the study.

Atropine 0.01 mg·kg^{-1} (maximum 0.5 mg) and midazolam 0.04 mg·kg^{-1} were administered intramuscularly as premedication 15 min before entering the operating room. After epidural catheter insertion at L2–3, anesthesia was induced with midazolam 0.1 mg·kg^{-1} and thiopental 3 mg·kg^{-1}. Endotracheal intubation was facilitated with vecuronium 0.15 mg·kg^{-1}. The radial artery was cannulated to monitor arterial blood pressure and to obtain blood samples. Anesthesia was maintained with intermittent epidural block using 1% mepivacaine, isoflurane (Isoflurane group) or sevoflurane (Sevoflurane group), and nitrous oxide 4 L·min^{-1} in oxygen 2 L·min^{-1}. Pancuronium was used as a muscle relaxant during surgery. Pancuronium and epidural mepivacaine were not administered for 30 min before the start of and throughout the study. Ventilation was controlled to keep the arterial carbon dioxide tension between 30 and 35 mmHg. Lactated Ringer's solution was infused to keep the urine output at 1 ml·kg^{-1}·h^{-1}.

When blood pressure and heart rate were in the range of ±10% of the values of a recent 10 min, the end-tidal concentration of isoflurane or sevoflurane was kept at 0.5 minimum alveolar concentration (MAC) (1 MAC = 1.15% in isoflurane and 2.05% in sevoflurane) for 15 min. The isoflurane or sevoflurane concentration (inhalation concentration) was changed suddenly to 1.5 MAC and was kept there for 10 min. It was then decreased to 0.5 MAC and kept there for 10 min.

The blood pressure, heart rate, and end-tidal concentration of isoflurane or sevoflurane (Ultima; Datex, Helsinki, Finland) were measured at 0.5 MAC (0 min); again 1, 3, 5, 7, and 10 min after changing to 1.5 MAC; and finally 10 min after returning to 0.5 MAC. Plasma concentrations of epinephrine and norepinephrine were measured at 0.5 MAC; again 1, 5, and 10 min after changing to 1.5 MAC; and finally 10 min after returning to 0.5 MAC. Arterial blood was used for the measurements. Plasma concentrations of epinephrine (range of the measurement 0–10 ng·ml^{-1}) and norepinephrine (range of the measurement 0–10 ng·ml^{-1}) were measured by high performance liquid chromatography (HLC-8030; Toso, Tokyo, Japan) at the BML Laboratory (Tokyo, Japan).

Data are expressed as the mean ± standard deviation. Statistical analysis was performed with one-way factorial analysis of variance (ANOVA) and the chi-square test for demographic data and with the two-way repeated measures ANOVA followed by the Student-Newman-Keuls test, a multiple-comparisons correction as a post hoc test for measured variables. $P < 0.05$ was considered statistically significant.

Results

There were no significant differences between the two groups regarding the backgrounds of the patients, including the dose of mepivacaine used for epidural block (Table 1). Systolic and diastolic blood pressures decreased significantly in both groups after increasing the anesthetic concentration to 1.5 MAC, and they increased again after decreasing the concentration to 0.5 MAC (Fig. 1). The decrease in systolic blood pressure was significantly larger in the isoflurane group. The heart rate increased significantly after increasing the anesthetic concentration only in the isoflurane group (Fig. 1). The end-tidal concentration of inhalation anesthetics changed similarly in the two groups (Fig. 2).

Plasma concentrations of epinephrine and norepinephrine increased significantly in the isoflurane group, whereas the epinephrine concentration decreased with no change in the norepinephrine concentration in the sevoflurane group (Fig. 3).

Table 1. Background of the patients

Parameter	Sevoflurane group	Isoflurane group
Age (years)	58 ± 8	61 ± 7
Male/female	9/6	8/7
Body weight (kg)	57 ± 9	58 ± 8
Duration of anesthesia (min)	421 ± 85	389 ± 94
Interval between the start of surgery and the start of the study (min)	78 ± 14	85 ± 16
Fluid volume until the end of the study (ml)	1587 ± 248	1672 ± 295
Total dose of 1% mepivacaine administered before the study (ml)	14 ± 3	15 ± 3

Results are the mean ± SD

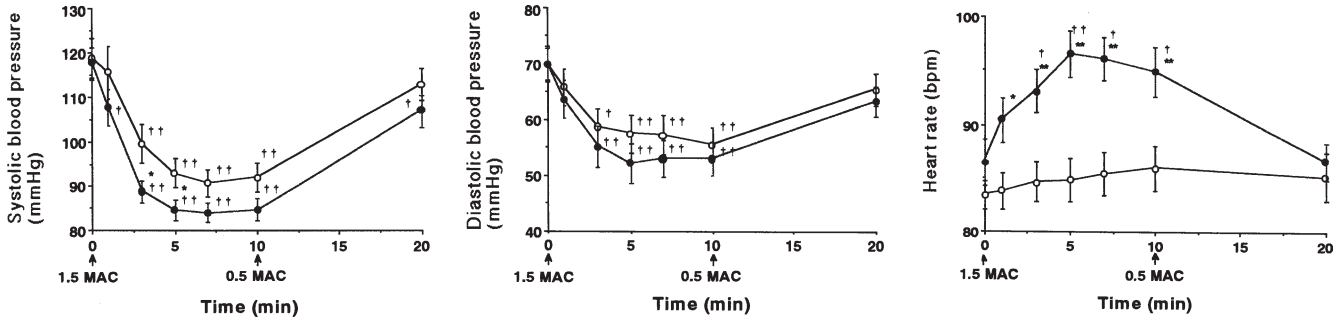

Fig. 1. Changes in blood pressure and heart rate (mean ± SD; $n = 15$ for each value). *MAC*, minimum alveolar concentration (1 MAC = 2.05% in sevoflurane and 1.15% in isoflurane); *bpm*, beats per minute. *Closed circles*, isoflurane group; *open circles*, sevoflurane group. $^{*}P < 0.05$ vs. sevoflurane group; $^{**}P < 0.01$ vs. sevoflurane group; $^{\dagger}P < 0.05$ vs. the value at time 0; $^{\dagger\dagger}P < 0.01$ vs. the value at time 0

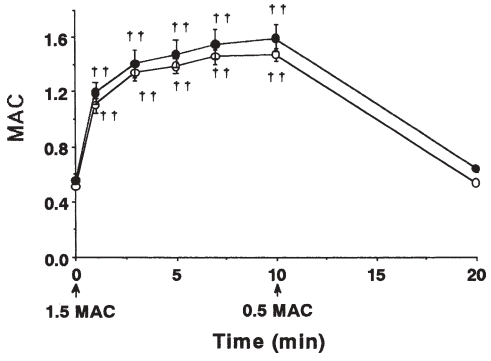

Fig. 2. Changes in end-tidal concentration of sevoflurane and isoflurane (mean ± SD; $n = 15$ for each value). *Closed circles*, isoflurane group; *open circles*, sevoflurane group. $^{\dagger\dagger}P < 0.01$ vs. the value at time 0

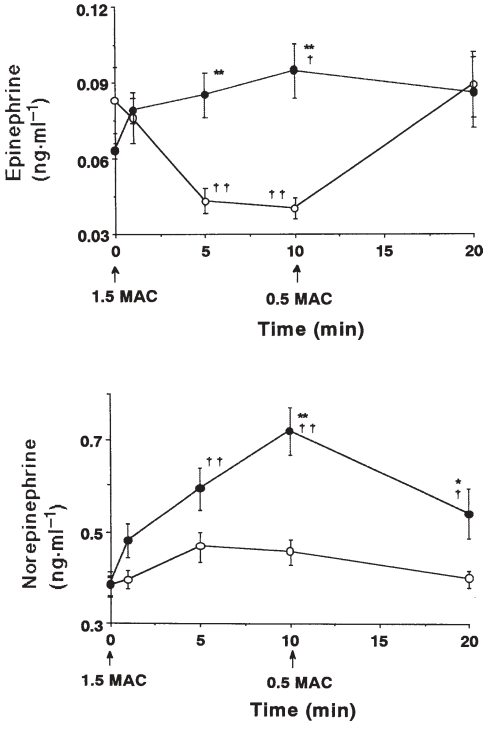

Fig. 3. Changes in plasma concentrations of epinephrine and norepinephrine (mean ± SD; $n = 15$ for each value). *Closed circles*, isoflurane group; *open circles*, sevoflurane group. $^{*}P < 0.05$ vs. sevoflurane group; $^{**}P < 0.01$ vs. sevoflurane group; $^{\dagger}P < 0.05$ vs. the value at time 0; $^{\dagger\dagger}P < 0.01$ vs. the value at time 0

Discussion

During surgery a sudden increase in the isoflurane concentration from 0.5 MAC to 1.5 MAC significantly decreased blood pressure and increased the heart rate and plasma concentrations of epinephrine and norepinephrine. A similar increase in sevoflurane induced significant decreases only in the blood pressure and plasma epinephrine concentration. These changes returned to the baseline after decreasing the inhalation anesthetic concentrations.

Clinically, when epidural block is not completely effective during abdominal surgery, a sudden increase in inhalation anesthetic is sometimes necessary to combat increasing surgical stimuli. However, it is difficult to quantitate the intensity of surgical stimuli and to simulate such a situation. Therefore, this study was performed during a stable surgical condition, as judged by hemodynamics. The study by Wajima et al. [4] was performed after intubation and before surgery. Thus, their results might have been due to the effects of intubation and not to surgical stimuli, whereas the present results reflect the effects of surgical stimuli. The different effects of sevoflurane in these two studies might be due to the different time course and interaction between sevoflurane anesthesia and the stimulus of intubation versus surgery.

In addition, the present study used epidural block, which might have some effect on the results because of the stable hemodynamics at the start of the study with low concentrations of the anesthetics. The anesthesia

level of the epidural block was not checked in the present study. However, the epidural block was not used for 30 min before the study, and hemodynamics were stable and were no different between the two groups at the start of the study. Therefore, even though the present results included the effects of epidural block, the groups might be comparable.

Isoflurane usually decreases the blood pressure mainly by reducing total peripheral resistance [5] and increasing the heart rate [6]. Although isoflurane directly depresses parasympathetic and sympathetic nervous activity dose-dependently [7], the depression is compensated for by reflex increases in sympathetic tone due to the hypotension [8]. Thus, isoflurane is thought to depress the parasympathetic nervous system more than the sympathetic nervous system [7], which then induces tachycardia. In the study by Weiskopf et al. [9], the rapid increase in isoflurane concentration from 0.55 MAC to 1.66 MAC increased the blood pressure, heart rate, and plasma epinephrine and norepinephrine concentrations, although the increased blood pressure returned to control levels in 4 min. Yli-Hankala et al. also reported that a rapid increase in isoflurane concentration induced a transient but clinically significant increase in heart rate, blood pressure, and norepinephrine concentration [10]. However, in the present study, the sudden increase in isoflurane concentration decreased the blood pressure, whereas the heart rate and catecholamine concentration increased, as in previous studies [9,10]. In those studies the changes were seen before surgery (i.e., without surgical stimuli), whereas in the present study they were seen in the presence of surgical stimuli. During surgery, increasing the anesthetic concentration could increase the balance of anesthetic depth against noxious stimuli, which might decrease sympathetic tone and then decrease the blood pressure.

Sevoflurane decreased the blood pressure [11] and catecholamine concentrations without changing the heart rate [12]. Murakawa et al. observed no changes in blood epinephrine or norepinephrine level in patients inhaling sevoflurane in doses higher than 1 MAC [13]. Rapid inhalation induction with 7% sevoflurane decreased the blood pressure and plasma epinephrine concentration, increased the norepinephrine concentration, but did not change heart rate [14,15]. The present results revealed changes compatible with those seen with rapid inhalation induction, except for the norepinephrine concentration. Rapid inhalation uses a much higher concentration of sevoflurane than the present study, which might induce a significant increase in the norepinephrine concentration.

The cardiovascular properties of sevoflurane are similar to those of isoflurane, except that the heart rate is lower with sevoflurane than with isoflurane [16,17]. The increased blood pressure and heart rate according to the increase in anesthetic concentration were significantly higher with isoflurane than with sevoflurane [18]. That study was performed just after intubation and application of intravenous anesthetics, which may have a significant effect on the parameters in question.

It has been suggested that isoflurane has an irritating effect on the airways that subsequently elicits tachycardia and hypertension [1,19]. In contrast, sevoflurane does not elicit these hyperdynamic responses, perhaps because it evokes less airway irritation [3]. In addition, sevoflurane had a tendency to inhibit the stress response to surgical stimuli more than did isoflurane [20]. Therefore, it seems reasonable that the heart rate and the catecholamine concentration were higher with isoflurane than with sevoflurane in the present study. However, the lower blood pressure with isoflurane (compared to that with sevoflurane) cannot be explained. Further studies are needed with a larger number of the patients to investigate whether this difference is clinically significant.

Conclusion

During surgery a sudden increase in the isoflurane concentration induced larger changes in hemodynamics and sympathetic nerve activity than did sevoflurane.

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