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Isoflurane and Sevoflurane Augment Norepinephrine Responses to Surgical Noxious Stimulation in Humans

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Background: **Suppression of hypertensive response to noxious stimulation by volatile anesthetics may be a result of suppression of the stimulation-induced norepinephrine response or that of the cardiovascular response to catecholamines, or both. The suppression of the cardiovascular response is established, but that of norepinephrine response has not been confirmed. The authors hypothesized that the suppression of cardiovascular response but not that of norepinephrine response plays a major role in suppressing the noxious stimulation-induced hypertensive response by volatile anesthetics.**

Methods: **Forty healthy donors for living-related liver transplantation were allocated to four groups: receiving 1.2% (end-tidal) isoflurane in oxygen and nitrogen, 2.0% isoflurane, 1.7% sevoflurane, or 2.8% sevoflurane. The intraoperative plasma norepinephrine and epinephrine concentrations, arterial blood pressure and pulse rate were measured for the first 15 min of surgery and were compared with the preoperative values.**

Results: **Norepinephrine and epinephrine concentrations both increased intraoperatively in all four groups. The values of maximum increase and area under the concentration-*versus*-time curve of norepinephrine were greater in the high dose groups of both anesthetics. The intraoperative blood pressure did not differ by different doses of anesthetics, and the degree of increase of blood pressure was not proportional to the plasma catecholamine concentrations.**

Conclusion: **The effects of isoflurane and sevoflurane on the surgical noxious stimulation-induced norepinephrine response were inversely proportional to the dose. The suppression of noxious stimulation-induced blood pressure response by anesthetics that were studied may be the result of suppression of the responses of vascular smooth muscle and myocardium to catecholamines. (Key words: Human; stress response; sympathetic nervous system.)**

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INTRAOPERATIVE hypertension is treated commonly by an increase in the dose of volatile anesthetics. The suppression by volatile anesthetics of the surgical noxious stimulation-induced hypertension may be a result of a suppression of the sympathetic nervous system response to stimulation or the myocardial and the peripheral vascular response to the catecholamines, or both. The dose-related suppression of contraction of peripheral vascular smooth muscle and myocardium[1–6] and the membrane potential–operated calcium channel by halothane and other volatile anesthetics is well established.[7–10] Using a cross-circulation dog model, Wang *et al.*[11] observed that halothane produced significant hypotension and suppression of stimulation-produced hypertensive response when administered to the body, whereas it had less of an effect when administered to the brain, suggesting that the cardiovascular actions were exerted directly on the myocardium and peripheral vessels rather than through the central nervous system (*i.e.*, the sympathetic nervous system).[11] Their animal model was contaminated by collateral circulation, and a more conclusive study is necessary. Review of literature revealed that whether the volatile anesthetics suppress the noxious stimulation-induced release of catecholamines has not been established in animal models and a clinical setting. It is our hypothesis that the suppression by anesthetics of the hypertensive response to noxious stimulation is secondary to the suppression of the cardiovascular system re-

sponse to catecholamines, rather than suppression of the sympathetic nerve response *per se*. Because the sympathetic nerve activity is not impossible, but is extremely difficult, to record in clinical setting, plasma catecholamine concentrations were measured and correlated with arterial blood pressure and pulse rate. Because control response in an unanesthetized state can not be obtained, the effects of the two doses of isoflurane and sevoflurane were compared, and the dose-effect relationships are obtained by extrapolation.

Materials and Methods

Forty healthy donors undergoing left lobectomy of the liver for living-related transplantation were observed. The study protocol was approved by our institutional ethics committee, and informed written consent was obtained from each subject. The first 20 patients were allocated randomly to one of two groups receiving either 1.2% (1.0 minimum alveolar concentration [MAC], low-isoflurane group) or 2.0% (1.67 MAC, high-isoflurane group) end-tidal concentrations of isoflurane. The next 20 patients were allocated randomly to one of two groups receiving either 1.7% (1.0 MAC,[12] low-sevoflurane group) or 2.8% (1.67 MAC, high-sevoflurane group) end-tidal concentrations of sevoflurane.

Diazepam, 0.2 mg/kg *per os*, was administered 60 min before induction of anesthesia. In the operating room, an intravenous catheter was inserted into a forearm vein and lactated Ringer's solution was administered at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$ during the study period. Anesthesia was induced with 4–5 mg/kg intravenous thiopental, and tracheal intubation was facilitated by 0.2 mg/kg intravenous vecuronium. Intermittent doses of vecuronium were administered as necessary. The lungs were ventilated mechanically with a mixture of oxygen, air, and isoflurane or sevoflurane, and inspired oxygen concentration was adjusted to 30%. End-tidal concentrations of the anesthetics were monitored continuously using an anesthetic gas monitor (Type 1304, Brüel & Kjær, Nærum, Denmark) that was calibrated before each study with a commercial standard gas (oxygen: 47%, carbon dioxide: 5.6%, nitrous oxide: 47%, sulfur hexafluoride: 2.05%). The oxygen saturation (Sp_{O_2}) and the end-tidal carbon dioxide tension were monitored continuously and maintained between 99–100% and 30–35 mmHg, respectively, throughout the study period. Electrocardiogram and rectal temperature were monitored. An internal jugular vein was cannulated, and the catheter was advanced into the superior vena cava. A radial artery was cannulated for continuous monitoring of arterial pressure (Component Monitoring System; HP M1166A, Hewlett-Packard, Palo Alto, CA). Pulse rate and arterial blood pressure were automatically recorded every 10 s (Clinical Information System; HP YS99700, Hewlett-Packard) during the study period of 1 min before skin incision to 15 min after. This study period was chosen because the intraabdominal procedures were begun more than 15 min after the start of surgery in all patients.

After an equilibration period of 20 min or more of either anesthetic, the operation was started. All operations were performed by the same surgical team and the same procedures while the patient was in the supine position.

Blood samples were drawn 1 min before skin incision (−1 min) and 2.5, 5, 7.5, 10, 12.5, and 15 min after the start of skin incision. They were collected in prechilled plastic tubes that contained EDTA and were immediately placed on ice. They were centrifuged at 4°C, and the plasma was stored at −80°C until assay. Plasma catecholamine concentration was determined by high-performance liquid chromatography. The detection limit for epinephrine and norepinephrine both was 5 pg/ml. The coefficients of variation for measurement of epinephrine and norepinephrine were approximately 1.72% and 1.83%, respectively.

Data Analysis

All data are presented as median (25–75th percentile). Catecholamine values are presented by the maximum increase and the area under the concentration-*versus*-time curve of catecholamines during 15 min after skin incision. The area-under-the-curve of concentration reflects the amount of catecholamine secreted. The values at −1 min served as the baseline. Blood pressure and pulse rate are presented by the maximum and mean of all values of changes from the baseline measured every 10 s during the study period.

Statistical analyses were performed using the Kruskal-Wallis test followed by the Wilcoxon's rank sum test based on joint ranking for detection of significant differences from the baseline value. Wilcoxon's rank sum test was performed for detection of significant differences between the high and low groups, except for the ratio of gender, which was compared by chi-squared test. $P < 0.05$ was considered statistically significant.

Table 1. Demographic and Physiological Data of Subjects

Group	Anesthetic Concentration (%)	Age (yr)	Sex (male/female)	Body Height (cm)	Body Weight (kg)	Rectal Temperature before the Skin Incision (°C)
Low isoflurane	1.2 (n = 10)	38.0 (24–46)	4/6	158.7 (154–163)	58.6 (57–69)	36.2 (36.1–36.6)
High isoflurane	2.0 (n = 10)	31.0 (28–33)	5/5	164.7 (159–170)	54.2 (52–66)	35.8* (34.9–35.9)
Low sevoflurane	1.7 (n = 10)	33.0 (30–40)	4/6	161.5 (159–165)	59.8 (54–63)	36.0 (35.7–36.0)
High sevoflurane	2.8 (n = 10)	35.5 (28–39)	5/5	164.0 (161–168)	53.5 (50–66.5)	35.8 (35.5–35.9)

Values are median (25 percentile–75 percentile).

* Significant difference *versus* low isoflurane ($P < 0.05$).

Results

The study groups were comparable regarding age, gender, weight, and height (table 1). Rectal temperature immediately before skin incision was significantly lower by 0.4°C in the high-isoflurane group than in the low-isoflurane group. Blood loss during the study period was less than 10 ml in all patients. No arrhythmias were noted in all patients during the study period.

The baseline values of plasma catecholamine concentrations and the circulatory variables are summarized in table 2. The arterial blood pressure of the high-isoflurane group was significantly lower than that of the low-isoflurane group. Otherwise, there were no differences between the low and high groups regarding catecholamine concentrations, blood pressure, and pulse rate by the different doses of both anesthetics.

The norepinephrine concentrations during the study period are illustrated in figures 1 and 2. After skin incision, the norepinephrine concentrations significantly increased at all sampling times in the isoflurane and sevoflurane groups, except for the low-sevoflurane group, in which a significant increase was observed only at 12.5 min. The maximum increase and the area-under-the-curve of norepinephrine concentrations were significantly greater in the high groups than in the low groups of both anesthetics (fig. 3).

The epinephrine concentrations during the study period are illustrated in figures 1 and 2. After skin incision, the epinephrine concentrations increased significantly in all groups. The maximum increase and the area-under-the-curve of epinephrine concentration did not differ significantly by different doses of both anesthetics (fig. 3).

The maximum and mean of changes from the baseline value of blood pressure and pulse rate are illustrated in figure 4. The maximum increase and the mean of changes from the baseline value of blood pressure did not differ between the low and high groups of both anesthetics. The maximum and mean of changes of pulse rate were significantly greater in the high-isoflurane group than in the low-isoflurane group. The mean of changes of pulse rate in the high group was greater than that in low group of sevoflurane.

Discussion

Before incision, different doses of anesthetics did not result in different plasma norepinephrine concentrations or circulatory variables, except for arterial blood pressure in high-dose isoflurane. In contrast, these anesthetics affected the circulating norepinephrine response to surgical noxious stimulation in an inversely proportional manner: the greater concentration of both anesthetics induced the greater norepinephrine responses. Although the arterial blood pressure did not differ between the two different doses of

Table 2. Plasma Catecholamine Concentrations and Circulatory Variables before Surgery

Group (%)	Norepinephrine (pg/ml)	Epinephrine (pg/ml)	Mean Arterial Blood Pressure (mmHg)	Pulse Rate (beats/min)
Low isoflurane (1.2)	102.5 (87–114)	5.0 (5–5)	64.0 (57–71)	78.0 (63–80)
High isoflurane (2.0)	127.0 (117–186)	5.0 (5–5)	49.5* (44–52)	72.5 (63–77)
Low sevoflurane (1.7)	178.0 (133–189)	5.0 (5–6)	63.0 (58–75)	67.5 (64–73)
High sevoflurane (2.8)	128.0 (104–154)	5.0 (5–5)	62.5 (59–68)	87.0 (63–93)

Values are median (25 percentile–75 percentile).

* Significant difference *versus* low isoflurane ($P < 0.001$).

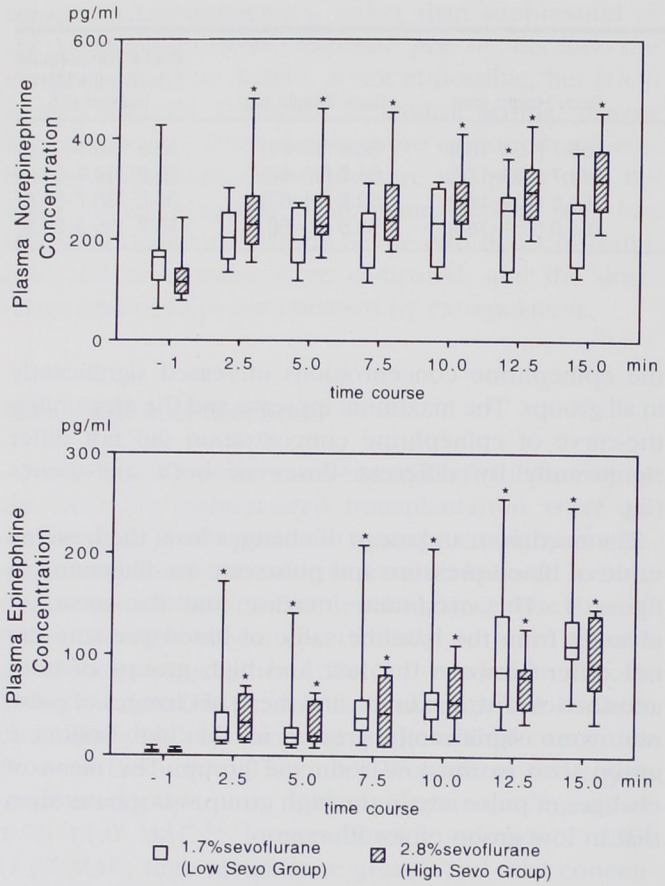

Fig. 1. Plasma norepinephrine (*upper*) and epinephrine (*lower*) concentrations during isoflurane anesthesia. Box-and-whisker plots represent the 10th, 25th, 50th (median), 75th, and 90th percentile of catecholamine concentrations at each sampling point. * Significant difference *versus* the values at −1 min ($P < 0.05$).

both anesthetics, the pulse rates were higher in the high groups of both anesthetics. The response in epinephrine did not differ significantly between different doses of both anesthetics.

The plasma catecholamine concentration was measured in the superior vena cava that represented venous blood returning from the head and upper extremities. Although the degree of activity of the sympathetic nervous system varies from organ to organ during a resting state, it discharges as a unit, especially during rage and fright, when sympathetically innervated structures over the entire body are affected simultaneously: heart rate is accelerated; blood pressure rises; and blood flow is shifted from the skin and splanchnic region to the skeletal muscles.[13] Because the states of rage and fright are best represented by the noxious stimulation-induced stress response, the norepinephrine response measured in the current study represents well the responses of sympathetic nervous system in the whole body.

Yamada *et al.*[14] reported modification by 1.25 and 2.0 MAC of sevoflurane, isoflurane, and halothane of the cardiovascular and norepinephrine and epinephrine responses to skin incision and concluded that halothane was the most potent with regard to suppressing the circulatory response to surgery.[14] However, perusal of their tables revealed that the responses in norepinephrine and epinephrine were greater in 2.0 MAC than 1.25 MAC of all three anesthetics at 5 min after the skin incision. They unfortunately discontinued observation at 5 min. Although no statistical analyses were performed, the findings of Yamada *et al.*[14] agree with our study.

The stress response, as measured by the plasma concentration of catecholamines, is not an all-or-none phenomenon. It is a graded response, and a greater intensity

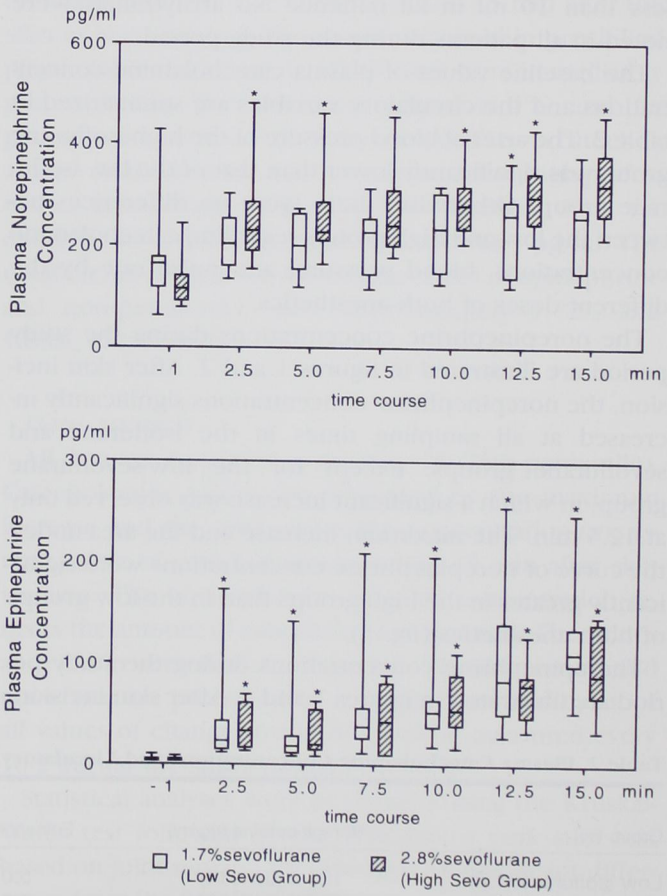

Fig. 2. Norepinephrine (*upper*) and epinephrine (*lower*) concentrations during sevoflurane anesthesia. Box-and-whisker plots represent the 10th, 25th, 50th (median), 75th, and 90th percentile of catecholamine concentrations at each sampling point. * Significant difference *versus* the values at −1 min ($P < 0.05$).

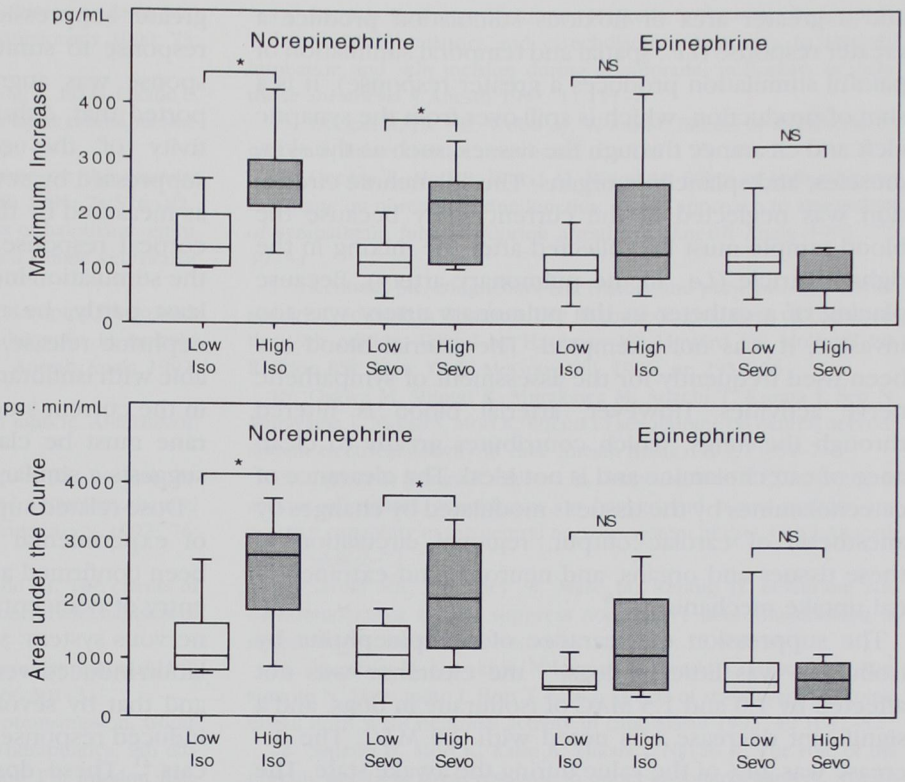

Fig. 3. Comparison of the maximum increase from baseline value (*upper*) and area-under-the-curve of plasma catecholamine concentrations (*lower*) between the low and high doses of isoflurane and sevoflurane. Box-and-whisker plots represent the 10th, 25th, 50th (median), 75th, and 90th percentile of the area-under-the-curve. * Significant difference with $P < 0.05$. Area-under-the-curve of norepinephrine was greater in the high-dose groups of both anesthetics than in the low-dose groups. No differences were observed in epinephrine.

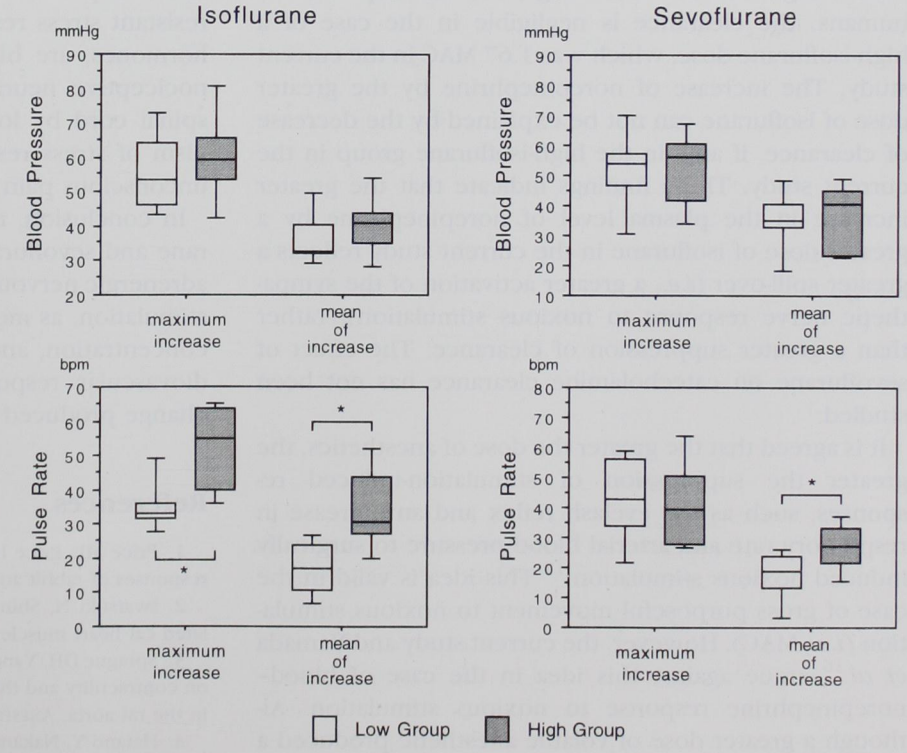

Fig. 4. Comparison of the maximum increase and mean of changes from the baseline value of mean arterial blood pressure and pulse rate. Box-and-whisker plots represent the 10th, 25th, 50th (median), 75th, and 90th percentile of the values. * Significant difference between low and high groups ($P < 0.05$).

and a greater area of noxious stimulation produce a greater response (*i.e.*, spatial and temporal summation of painful stimulation produces a greater response). It is a sum of production, which is spill-over from the synaptic cleft and clearance through the tissues, such as the skin, muscles, and splanchnic organs. The splanchnic circulation was neglected in the current study because the blood sample must be collected after the mixing in the right ventricle (*i.e.*, in the pulmonary artery). Because placing of a catheter in the pulmonary artery was too invasive, it was not attempted. The arterial blood has been used frequently for the assessment of sympathetic nerve activities. However, arterial blood is filtered through the lungs, which contributes greatly to clearance of catecholamine and is not ideal. The clearance of catecholamines by the tissue is modulated by changes by anesthesia of cardiac output, regional circulation to these tissues and organs, and neuronal and extraneuronal uptake mechanisms.[15]

The suppression of clearance of norepinephrine by isoflurane was little in dogs:[16] the clearance was not affected by 1.0 and 1.5 MAC of isoflurane in dogs, and a significant decrease was noted with 2.0 MAC. The decrease was 24% of the value during the awake state. The area-under-the-curve of norepinephrine in the 1.67 MAC was 270% of that of the 1.0 MAC in the current study. If the findings obtained in the dog study is extrapolated to humans, the clearance is negligible in the case of a high-isoflurane dose, which was 1.67 MAC in the current study. The increase of norepinephrine by the greater dose of isoflurane can not be explained by the decrease of clearance, if any, in the high-isoflurane group in the current study. These findings indicate that the greater increase in the plasma level of norepinephrine by a greater dose of isoflurane in the current study reflects a greater spill-over (*i.e.*, a greater activation of the sympathetic nerve response to noxious stimulation), rather than a greater suppression of clearance. The effect of sevoflurane on catecholamine clearance has not been studied.

It is agreed that the greater the dose of anesthetics, the greater the suppression of stimulation-induced responses, such as the eyelash reflex and an increase in respiratory rate and arterial blood pressure to surgically induced noxious stimulation.[17] This idea is valid in the case of gross purposeful movement to noxious stimulation (*i.e.*, MAC). However, the current study and Yamada *et al.*[16] argue against this idea in the case of blood-norepinephrine response to noxious stimulation. Although a greater dose of volatile anesthetic produced a greater suppression of the blood pressure or heart rate response to stimulation, the plasma catecholamine response was augmented by both anesthetics. We reported that, although the spontaneous background activity of the central nervous system neurons is suppressed by sevoflurane, the response to stimulation, as measured by the amplitude of somatosensory-evoked cortical response, is enhanced.[18,19] The facilitation of the stimulation-induced response by sevoflurane may, at least partly, be responsible for the enhanced norepinephrine release. However, such evidence is not available with isoflurane. Whether the augmentation revealed in the current study is specific to isoflurane and sevoflurane must be clarified. The study by Yamada *et al.*[14] suggests a similar facilitation by halothane.

Dose-related suppression by isoflurane and sevoflurane of experimental nociceptive neural information have been confirmed at the spinal cord dorsal horn cells, the entry of nociceptive neural information into the central nervous system: suppression by isoflurane of the stimulation-induced ventral root potential in neonatal rats,[20] and that by sevoflurane of the intraarterial bradykinin-induced response in the wide-dynamic-range neurons in cats.[21] These dose-related actions contradict the augmentation by these anesthetics of the surgical noxious stimulation-induced noradrenergic response in the current study. We confirmed that the general anesthesia-resistant stress responses, as measured by the pituitary hormones, are blocked completely by interruption of nociceptive neural information before it reaches the spinal cord by local anesthetics.[22] The neural mechanism of stress response to general anesthetic-resistant, unconscious pain remains to be clarified.

In conclusion, the current study revealed that isoflurane and sevoflurane do not suppress but augment the adrenergic nervous system responses to surgical noxious stimulation, as measured by the plasma norepinephrine concentration, and suggest that the suppression of cardiovascular response to catecholamine is the major change produced by these agents.

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