Sevoflurane–Nitrous Oxide Anesthesia Attenuates the Heart Rate Response to Intravenous Isoproterenol Infusion

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Summary

We studied the effects of sevoflurane-N₂O anesthesia on isoproterenol-induced heart rate (HR) changes. Twenty-six patients (ASA class I, 23–46 y) were assigned to two groups. The control group (n=13) received no sevoflurane and no N₂O. Patients in the sevoflurane-N₂O group (n=13) received 5% sevoflurane and 67% N₂O in oxygen. After tracheal intubation with rocuronium, anesthesia was maintained with an end-tidal sevoflurane concentration of 1.5%, together with 67% N₂O in oxygen. Mechanical ventilation was performed to maintain EtCO₂ at 35 mmHg. After 15 min, all patients in both groups received intravenous isoproterenol at incremental infusion rates (2.5, 5.0, 7.5, 10, 12.5, 15, 17.5, and 20 ng/kg/min for 2 min at each infusion rate), until HR increased by more than 20 beats/min from baseline values. At the end of each infusion period, hemodynamic data were collected.

Though there were no significant differences between the groups with respect to age and sex distribution, basal HR (before isoproterenol infusion) was significantly higher in the sevoflurane group than the control group. The HR responses to isoproterenol at 2.5, 5.0, and 7.5 ng/kg/min were attenuated in the sevoflurane-N₂O group as compared to the control group (0 ± 2 vs. 2 ± 3, 3 ± 4 vs. 9 ± 4, and 6 ± 5 vs. 14 ± 4 beats/min, respectively; mean ± SD, P<0.05 between groups). During isoproterenol infusion at 17.5 ng/kg/min, HR increased by more than 20 beats/min in all patients in the control group, but only in 7 (54%) patients in the sevoflurane group (P<0.0001). These results suggest that a higher isoproterenol infusion rate may be required for the treatment of bradycardia or heart block in patients under sevoflurane-N₂O anesthesia as compared to awake patients.

Key words: Anesthetics, sevoflurane, nitrous oxide, heart, heart rate, isoproterenol

Introduction

Bradycardia and complete atrioventricular block have been reported during sevoflurane anesthesia in patients with hypertension and impaired cardiac conduction1-4. A β-adrenergic agonist, such as isoproterenol, may be required in certain patients under sevoflurane-N₂O anesthesia for the treatment of mild or transient episodes of heart block that do not require pacemaker therapy. Although isoproterenol is one of the alternative drugs to be considered for the treatment of adult bradycardia according to the American Heart Association advanced cardiac life support protocol5, the situation in patients during general anesthesia is different from that during advanced cardiac life support.

Beta-adrenergic-mediated chronotropic responses to bolus epidural test dose injection of isoproterenol during sevoflurane anesthesia have been studied6,7. However, the different methods of isoproterenol administration, i.e., bolus injection versus continuous infusion, seem to cause variable hemodynamic responses, because vagal activity increases during continuous intravenous infusion of isoproterenol8-9. Also, no clinical investigations have systematically proved the rate-related hemodynamic interaction between continuous isoproterenol infusion and sevoflurane-N₂O anesthesia in humans.
Hence, we compared the heart rate (HR) response to intravenous (IV) isoproterenol infusion in awake patients with that in sevoflurane–N₂O anesthetized patients, and evaluated the hemodynamic interaction between sevoflurane–N₂O and IV isoproterenol according to its infusion rate.

Methods

Twenty-six adult patients aged between 23 and 46 years, American Society of Anesthesiologists physical class 1, undergoing a variety of general surgical procedures, were studied. The study protocol was approved by our local ethics committee and written informed consent was obtained from all patients. Patients with a history of cardiovascular disorders, diabetes, disorders known to affect autonomic function, and those taking medications known to affect cardiovascular function were excluded. All patients received 20 mg famotidine (H₂-blocker) orally as preanesthetic medication 90 min before arrival at the operating room.

On arrival at the operating room, a 20-gauge intravenous cannula was inserted and lactated Ringer’s solution was administered at a rate of 10 ml/kg/h throughout the study. A standard lead II electrocardiography (ECD) and automated blood pressure (BP) cuff (Dynoscope, DS-5300, Fukuda Denshi Co., Ltd., Tokyo, Japan) were applied on the contralateral arm. HR was determined as the average value over 4–sec intervals, as recorded on the ECG monitor, and mean BP was determined with oscillometric method.

The patients were randomly assigned to two groups. Patients in the control group (n=13) received no anesthetic medication and hence, remained awake during the study. On the other hand, patients in the sevoflurane–N₂O group received 1% sevoflurane after an initial inhalation of 67% N₂O in oxygen by mask. After 5 breaths, the patients received 3% and 5% sevoflurane during spontaneous ventilation. Tracheal intubation was facilitated with IV rocuronium 0.6 mg/kg, and anesthesia was maintained with an end-tidal sevoflurane concentration of 1.5% and 67% N₂O in oxygen. Patients were mechanically ventilated to maintain their end-tidal carbon dioxide concentration at approximately 35 mmHg.

After attainment of a stable hemodynamic state, obtained by lying quietly for 15 minutes on the operating table in the awake control group and 15 minutes after tracheal intubation in the sevoflurane group, all patients in both groups received IV isoproterenol (Nikkenkagaku Co., Ltd., Tokyo, Japan) at incremental infusion rates (2.5, 5, 7.5, 10, 12.5, 15, 17.5, and 20 ng/kg/min for 2 min at each infusion rate) with a controlled infusion pump (model TE-312, Terumo Co., Ltd., Tokyo, Japan), until HR increased by more than 20 beats/min (bpm) from baseline values obtained during stable conditions before isoproterenol injection. The isoproterenol chloride solution was diluted with normal saline in a concentration of 4 µg/ml. HR and BP were measured at 2-min intervals at the end of each infusion period, while ECG was monitored continuously. Values of HR and BP at the end of each infusion period were recorded and subjected to data analyses, since HR responses in all patients reached a plateau 1–2 min following the start of each isoproterenol infusion rate. According to the study protocol, if systolic BP was less than 80 mmHg, 5 mg of ephedrine was given, and 0.5 mg of atropine was given for rescue treatment when HR was less than 50 bpm. The patient was then excluded from subsequent data analysis. No surgical stimulation was allowed during the study period. Changes in HR were plotted for isoproterenol infusion rates of 2.5, 5.0, and 7.5 ng/kg/min. We estimated each patient’s chronotropic dose required to increase their HR by >20 bpm (CD₂₀) by logarithmic interpolation between the two neighboring isoproterenol infusion rates. The cumulative percentage of patients in whom the HR increased by more than 20 bpm was also plotted against the isoproterenol infusion rate. The data are expressed as mean±SD, whereas CD₂₀ values are expressed as mean (95% confidence interval). Student’s t-test was used for comparisons between the groups. Correlation coefficients between baseline HRs and the increase in HR at each isoproterenol infusion rate were calculated by the method of least squares. Differences in the mean CD₂₀ values between groups were analyzed using the unpaired Student’s t-test with logarithmic transformation. Testing for significance in the incidence of positive HR responses after isoproterenol infusion between the two groups was accomplished by chi-square analysis. Results were considered statistically significant if P values were <0.05.

Results

There were no significant differences between the groups with respect to age, weight, and height (Table 1). Systolic BP remained above 80 mmHg and HR above 50 bpm in all patients. There were no significant differences between the groups in HR
before anesthesia. HR values remained unchanged after induction of anesthesia in the sevoflurane group. Basal HR (before isoproterenol infusion) was significantly higher in the sevoflurane group than the control group. Systolic, diastolic, and mean BP values decreased significantly after induction of anesthesia in the sevoflurane group (Table 2).

The changes in HR after isoproterenol infusion were significantly less in sevoflurane-N₂O anesthetized patients than in awake control patients; the increases in HR at isoproterenol infusion rates of 2.5, 5.0, and 7.5 ng/kg/min were 0 ± 2 vs. 2 ± 3, 3 ± 4 vs. 9 ± 4, and 6 ± 5 vs. 14 ± 4 bpm in the sevoflurane and control awake groups, respectively (P < 0.05 between groups, Fig. 1). However, there was no significant relationship between baseline HR and increases in HR at each isoproterenol infusion rate.

The mean CD₂₀ was 12 (10-13) ng/kg/min in the awake patients and 16 (13-19) ng/kg/min in the sevoflurane-anesthetized patients (Fig. 2). When isoproterenol was infused at a rate of 17.5 ng/kg/min, HR increased by more than 20 bpm in all patients in the control group, but in only 7 of 13 patients (54%) in the sevoflurane group (P < 0.0001 vs. the control group, Fig. 3).

Although systolic, diastolic, and mean BPs remained unchanged at isoproterenol infusion rates of 2.5 ng/kg/min in the control group, diastolic and mean BPs decreased significantly in the sevoflurane group, as compared with baseline values. At an isoproterenol infusion rate of 5.0 ng/kg/min, there were significant decreases in diastolic BP from baseline in the control group, and significant decreases in systolic and diastolic BPs from baseline in the sevoflurane group. At an isoproterenol infusion rate of 7.5 ng/kg/min, significant decreases in diastolic and mean BPs from baseline were noted in both the control and sevoflurane groups. Systolic, diastolic, and mean BPs were lower in the sevoflurane group than the control group at each rate of isoproterenol infusion (Table 2).

Correlation coefficients between baseline HRs and the increase in HR at isoproterenol infusion rates of 2.5, 5.0, and 7.5 ng/kg/min were 0.298 (P = 0.323), 0.325 (P = 0.279), 0.033 (P = 0.914) in sevoflurane group, and 0.005 (P = 0.988), 0.276 (P = 0.361), 0.288 (P = 0.340) in control group. There were no significant relationships between baseline HR values and the increase in HR at each isoproterenol infusion rate.

None of the patients receiving sevoflurane developed any arrhythmia after isoproterenol infusion.

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<thead>
<tr>
<th>Table 1</th>
<th>Patient Characteristics</th>
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<tr>
<td></td>
<td>Control</td>
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<tr>
<td>Male/Female</td>
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<tr>
<td>Age (yr)</td>
<td>32 ± 7</td>
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<tr>
<td>Height (cm)</td>
<td>163 ± 10</td>
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<td>Weight (kg)</td>
<td>57 ± 9</td>
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Values are mean ± SD.

<table>
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<tr>
<th>Table 2</th>
<th>Heart Rate and Blood Pressure at Each Rate of Intravenous Isoproterenol Infusion</th>
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<td>Isoproterenol infusion rate (ng/kg/min)</td>
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<tr>
<td></td>
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<tr>
<td>sBP</td>
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Values are mean ± SD. Baseline = before isoproterenol infusion in the control group and after induction of anesthesia (before isoproterenol infusion) in the sevoflurane group; HR = heart rate (beats · min⁻¹); sBP = systolic blood pressure (mmHg); mBP = mean blood pressure (mmHg); dBP = diastolic blood pressure (mmHg). * p < 0.05 versus baseline; † p < 0.05 versus before anesthesia; § p < 0.05 versus control group.
Figure 1 Heart rate responses to intravenous isoproterenol infusion at rates of 2.5, 5.0, and 7.5 ng/kg/min in awake control patients (n=13) and patients anesthetized with an end-tidal sevoflurane concentration of 1.5% together with 67% N2O in oxygen (n=13). Values are expressed as mean ± SD. P<0.05 versus awake control patients.

Figure 2 The chronotropic dose of isoproterenol infusion required to increase heart rate by >20 bpm (CD20) in patients anesthetized with 1.5% sevoflurane and 67% N2O in oxygen (n=13) and awake control patients (n=13). Data are expressed as mean and 95% confidence interval. * P<0.05 between sevoflurane and control group.

There were no other adverse effects related to isoproterenol infusion or sevoflurane–isoproterenol interaction.

Discussion

Our main observation was that sevoflurane-N2O anesthesia attenuated the HR response to IV isoproterenol infusion compared with that in awake, nonventilated individuals. The mean CD20 of isoproterenol infusion was 12 ng/kg/min in awake patients, whereas it was 16 ng/kg/min in patients anesthetized with sevoflurane–N2O. No detrimental effects related to sevoflurane, no greater incidence of arrhythmia due to isoproterenol, and no serious sevoflurane-isoproterenol interactions were observed.

The mechanisms of the difference in the HR
response to isoproterenol infusion between sevoflurane–N₂O group and control group are complicated and remain unclear. However, the following factors might affect the difference. First, it may be concerned that the basal HR before isoproterenol infusion was higher in the sevoflurane group than in the control group. However, there were no significant relationships between baseline HR values and the increase in HR at each isoproterenol infusion rate. Therefore, the difference of basal HR before isoproterenol infusion between groups may have little effect on the increase in HR after isoproterenol infusion. Second, not only sevoflurane effect but also N₂O effect may be concerned. Third, the tracheal intubation may affect our results.

We previously reported that propofol–N₂O anesthesia enhances the HR response to IV isoproterenol infusion compared with that in awake individuals. The difference between our previous and current protocol is the administration of propofol and the inhalation of sevoflurane. Therefore, it can be considered that the attenuation of HR response to IV isoproterenol infusion in sevoflurane group is not caused by N₂O and tracheal intubation but affected by sevoflurane. One of the mechanisms of attenuation of HR response to isoproterenol infusion caused by sevoflurane may be depression of the β-adrenoceptor signal transduction system, as well as alteration in the action potential characteristics and cardiac impulse conduction velocity.

Isoproterenol provides relatively pure non-selective β-adrenergic stimulation with no significant effect on α-receptors. Since the development of other inotropes, its popularity has declined because of its adverse effects of tachycardia and arrhythmias. Isoproterenol was historically used for the treatment of bradycardia or heart block resistant to atropine, and is one of the alternative drugs for adult bradycardia, as recommended in the American Heart Association adult advanced cardiac life support protocol 2010. However, the situation in patients during general anesthesia is different from that during advanced cardiac life support.

In conclusion, sevoflurane–N₂O anesthesia attenuates the HR response to IV isoproterenol infusion. This finding suggests that a higher continuous infusion rate of isoproterenol for the treatment of bradycardia or heart block may be required in patients under sevoflurane–N₂O anesthesia compared with awake patients.

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Figure 3 The cumulative percentage of patients whose heart rate increased by more than 20 bpm from baseline values after intravenous isoproterenol infusion in awake control patients (n=13) and patients anesthetized with an end-tidal sevoflurane concentration of 1.5% with 67% N₂O in oxygen (n=13). At an isoproterenol infusion rate of 17.5 ng/kg/min, heart rate increased by more than 20 bpm in all patients in the control group, but in only 7 of 13 patients (54%) in the sevoflurane group (P< 0.0001).

References


induction with sevoflurane was associated with complete atrioventricular block in a child with hypertension, renal dysfunction, and impaired cardiac conduction. Paediatr Anaesth 1998; 8: 73–8.


