Humans Anesthetized with Sevoflurane or Isoflurane Have Similar Arrhythmic Response to Epinephrine

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Background: Anesthetics can alter the dose of exogenously administered epinephrine that causes cardiac arrhythmias. The purpose of this study was to test the hypothesis that in humans anesthetized with sevoflurane, the arrhythmic response to epinephrine is not different from the response in humans anesthetized with isoflurane.

Methods: We determined the arrhythmogenicity of submuco- cosally administered epinephrine in 40 ASA physical status 1 or 2 patients who were to undergo transphenoidal surgery. Patients were assigned randomly to be given 1.0–1.3 minimum alveolar concentration sevoflurane or isoflurane. A surgeon, blinded to the anesthetic and the concentration of epinephrine, injected into the nasal submucosa epinephrine 10, 13.3, or 20 µg/ml in saline of volume sufficient for surgical need. We defined a “positive” response as three or more premature ventricular contractions within 5 min after initiation of injection. Responses between anesthetic groups within each dose range of epinephrine were compared by chi-squared analysis.

Results: No patient given either anesthetic developed pre- mature ventricular contractions with doses of epinephrine less than 5 µg/kg. At larger doses of epinephrine (5–9.9 and 10–14.9 µg/kg), the frequency of arrhythmias did not differ between patients given sevoflurane and patients given isoflurane. Patients anesthetized with 1.2 minimum alveolar concentration sevoflurane had blood pressure similar to and heart rate less than those of patients anesthetized with similar con- centrations of isoflurane. Blood pressure and heart rate were increased similarly in both groups after laryngoscopy and tracheal intubation and after epinephrine injection.

Conclusions: Sevoflurane and isoflurane do not differ in their sensitization of the human myocardium to the arrhythmogenic effect of exogenously administered epinephrine. (Key words: Anesthesia, mechanisms; cardiovascular. Anesthetics, volatile; isoflurane; sevoflurane. Complications: arrhythmias. Heart, arrhythmogenicity: epinephrine; isoflurane; sevoflurane. Sympathetic nervous system, catecholamines; epinephrine.)

ANESTHETICS can alter the dose of epinephrine that induces ventricular arrhythmias. Isoflurane1,2 does not change the sensitivity of the myocardium to exogenously administered epinephrine, but others, such as halothane,1,3 enflurane,3,4 thiopental,3,5 and propofol, do.6

The dose of intravenously administered epinephrine causing premature ventricular contractions (PVCs) in dogs anesthetized with sevoflurane does not differ from the dose in dogs similarly anesthetized with isoflurane.7 In the study reported here, we tested the hypothesis that in humans, the incidence of PVCs in response to submuco- cosally injected epinephrine during sevoflurane anesthesia does not differ from that during isoflurane anesthesia.

Materials and Methods

This study was approved by the University of California, San Francisco Committee on Human Research. We obtained informed consent from 40 ASA physical status 1 or 2 patients scheduled to undergo elective transphenoidal hypophysectomy. Patients were assigned randomly to receive either sevoflurane or isoflurane anesthesia. None had a history or physical findings of cardiovascular or pulmonary disease or were taking medications with cardiovascular actions. All had a normal preoperative electrocardiogram. Patients received premedication of up to 2 mg midazolam or 1.5

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μg/kg fentanyl intravenously. Anesthesia was induced with sevoflurane or isoflurane in 60–70% nitrous oxide in oxygen. Vecuronium 0.15 mg/kg was administered to facilitate tracheal intubation, after which ventilation was controlled to maintain normocapnia. Nitrous oxide administration was discontinued and anesthesia was maintained with sevoflurane or isoflurane, end-tidal concentrations equivalent to 1.0–1.3 minimum alveolar concentration (MAC) (sevoflurane 2.0–2.6% and isoflurane 1.3–1.7%) in 100% oxygen (flow rate 5–8 l/min), as measured by RAMAN spectroscopy (Rascal H, Ohmeda, Salt Lake City, UT). The spectrometer was calibrated with secondary (tank) standards, which, in turn, were calibrated by gas chromatography, against primary (volumetric) standards. The levels of 1.0–1.3 MAC and the elimination of nitrous oxide continued for at least 20 min before injection of epinephrine. The end-tidal concentration of nitrous oxide was always less than 2% at the time of epinephrine injection.

Lead II of the electrocardiogram was continuously monitored and recorded for 3 min before induction of anesthesia and for 3 min before and 5 min after initiating the injection of epinephrine. Approximately 30 min after induction of anesthesia, the surgeon, who was blinded to both the allocation of anesthetic and the concentration of epinephrine solution, injected into the nasal submucosa an epinephrine solution of 10, 13.3 or 20 μg/ml in saline of volume sufficient for surgical need. The initial patient in each group received the epinephrine concentration of 13.3 μg/kg. For subsequent patients, the response of the previous patient in that anesthetic group determined the epinephrine concentration. If the previous patient in that anesthetic group had ventricular arrhythmias (three or more PVCs) after epinephrine administration, the following patient received the next lower epinephrine concentration (or the lowest concentration if that had been used). If the previous patient did not have PVCs, the following patient received the next higher concentration of epinephrine (or the highest concentration if that had been used). We defined the appearance of three or more PVCs within 5 min of epinephrine injection as a “positive” response.

We tested the difference in arrhythmic response between the two anesthetic groups for each range of dose of epinephrine injected (0–4.9, 5.0–9.9, and 10.0–14.9 μg/kg) by Fisher’s exact test or chi-squared analysis. Correlations between blood pressure, or heart rate and epinephrine dose were performed by linear regression. We accepted a value of P < 0.05 as statistically significant. During this study, we also evaluated the response of blood pressure and heart rate to (1) 1–1.3 MAC sevoflurane or isoflurane, (2) tracheal intubation during 1–1.3 MAC sevoflurane or isoflurane, and (3) injection of epinephrine. Differences in heart rate and blood pressure between anesthetic groups were compared by unpaired t test. Data within a group, at different times, were compared by paired t test with Bonferroni correction. Statistical significance was accepted at P < 0.05.

Results

The two anesthetic groups did not differ in age, height, weight, estimated body surface area, sex distribution, premedication, anesthetic concentrations (sevoflurane 1.2 ± 0.0 and isoflurane 1.2 ± 0.0 MAC; mean ± standard error), or end-tidal carbon dioxide tension (sevoflurane 36 ± 0.7 and isoflurane 37 ± 0.7 mmHg) at the time of epinephrine injection (table 1).

No patient had PVCs before anesthesia or before epinephrine injection, nor did any patient develop PVCs during sevoflurane or isoflurane anesthesia with epinephrine doses less than 5 μg/kg. At larger doses of submucosally injected epinephrine, the incidence of PVCs was similar during sevoflurane and isoflurane anesthesia (fig. 1). Four of 12 patients given sevoflurane and 4 of 15 patients given isoflurane who received 5–9.9 μg/kg epinephrine developed three or more PVCs. One of the three patients given 10–14.0 μg/kg in each anesthetic group had a positive response. The one patient given more than 15 μg/kg epinephrine who was anesthetized with sevoflurane did not have PVCs but developed a rapid nodal rhythm. No patient who developed PVCs had associated hypotension, however, two patients in the isoflurane group were given 100

| Table 1. Demographic Data of 40 Patients Undergoing Transphenoidal Hypophysectomy |
|---------------------------------|------------|------------|
| N                              | Sevoflurane| Isoflurane |
| Age (yr)                       | 33.0 ± 1.8 | 33.1 ± 1.8 |
| Height (cm)                    | 66 ± 0.8   | 67.0 ± 0.9 |
| Weight (kg)                    | 75.0 ± 5   | 75 ± 4     |
| Body surface area (m²)         | 1.83 ± 0.06| 1.87 ± 0.05|
| Male/female                    | 4/16       | 4/16       |

Data are mean ± SE. There were no statistically significant differences between the groups.
mg intravenous lidocaine by the attending anesthesiologist.

Induction of anesthesia with sevoflurane and isoflurane decreased blood pressure equally before laryngoscopy and tracheal intubation ($P < 0.001$). Sevoflurane but not isoflurane decreased heart rate ($P < 0.005$), and as a result patients anesthetized with sevoflurane had a lower heart rate than did patients anesthetized with an equivalent concentration of isoflurane ($P < 0.01$; fig. 2). Tracheal intubation (before epinephrine injection) increased heart rate and blood pressure in both groups, to values that did not differ between groups. Similarly, injection of epinephrine increased heart rate and mean arterial pressure equally in both groups: peak heart rate and blood pressure after epinephrine injection did not differ between the groups (fig. 2). Heart rate and mean arterial blood pressure after epinephrine injection or changes in these variables did not correlate with the dose of epinephrine injected.

**Discussion**

Our results indicate that exogenously administered epinephrine has similar dose-related arrhythmogenic effects in humans anesthetized with sevoflurane as it does when they are anesthetized with isoflurane. Although the conscious human response to epinephrine has not been determined in the same patients in which it has been determined during anesthesia, in dogs, isoflurane does not sensitize the myocardium to exogenously administered epinephrine. Thus, presuming that isoflurane similarly does not sensitize the human myocardium, it appears likely that sevoflurane does not sensitize the human myocardium to epinephrine. Our findings for the arrhythmogenic threshold and relationship between epinephrine dose and incidence of PVCs during isoflurane anesthesia are similar to those reported by others.\(^5\,^8\)

![Fig. 1. Percentage of patients who developed three or more premature ventricular contractions (PVCs) in response to submucosal injection of epinephrine. There was no difference in incidence between the groups given sevoflurane (shaded bar) or isoflurane (hatched bar) at any dose range of epinephrine.](Image)

![Fig. 2. Mean arterial blood pressure (MAP) and heart rate (HR) in patients give sevoflurane (shaded bar) or isoflurane (hatched bar) while conscious (pre-ind); after induction of anesthesia and before laryngoscopy and tracheal intubation (pre-ett); after laryngoscopy and tracheal intubation (post-ett); before injection of epinephrine (pre-epi); and after injection of epinephrine (post-epi). There were no statistical differences between the groups for either variable, except for heart rate before laryngoscopy and tracheal intubation (*).](Image)
We avoided the use of thiopental and propofol and eliminated nitrous oxide before epinephrine injection because they influence the arrhythmogenic response to exogenously administered epinephrine. For similar reasons, we did not include lidocaine in the epinephrine solution, and maintained normocapnia throughout the study.

Although administration of epinephrine increased both heart rate and blood pressure, neither the absolute values nor the changes in these variables correlated with the dose of epinephrine administered. This finding is similar to that of Moore et al. The explanations they offered may apply equally to our results: (1) the doses of epinephrine may have approached those producing near-maximal effects; (2) the anesthetics may have limited the hemodynamic responses to epinephrine; or (3) the higher doses of epinephrine may have caused sufficient vasoconstriction to prevent its own absorption. In addition, our small population may have varied sufficiently to obscure any differences.

Patients responding positively to epinephrine injection did not differ from those responding negatively with respect to physical characteristics, premedication, temperature, end-tidal carbon dioxide tension at time of injection, concentration (MAC) of administered anesthetic, or blood pressure or heart rate at all times before epinephrine injection (including response to tracheal intubation). However, patients who had three or more PVCs after injection of epinephrine did develop higher blood pressures (mean arterial blood pressure 164 ± 7 mmHg) but not heart rates (100 ± 6 beats/min) after injection of epinephrine than did those who did not develop PVCs (mean arterial blood pressure 130 ± 5 mmHg, P < 0.001; heart rate 91 ± 3 beats/min, P > 0.1). Moore et al. noted a similar relationship for blood pressure and dysrhythmias, although their patients with a positive response also had higher heart rates than those who did not have a positive response. Others have postulated that an increased blood pressure or heart rate predisposes to or causes ventricular arrhythmias. However, our finding is only an association and no causality can be implied from our data because our study was not designed to address this issue.

Our finding that sevoflurane anesthesia decreases blood pressure is consistent with the reports of others. Similarly, the lower heart rate in patients anesthetized with sevoflurane than in those anesthetized with isoflurane supports the findings of Holaday and Smith and of Frink et al. Both of our groups responded similarly to the stimulation of tracheal intubation: neither heart rate nor blood pressure differed between the two groups. Frink et al. found that when these two anesthetics were titrated to a desired clinical effect, heart rate during sevoflurane anesthesia was generally lower than during isoflurane anesthesia, while systolic and diastolic blood pressures were similar. They, too, however, noted similar cardiovascular responses to tracheal intubation in patients anesthetized with these two anesthetics. In addition, in our study, in response to direct stimulation by epinephrine, there was no difference in response of blood pressure or heart rate between patients who received sevoflurane and those who received isoflurane. None of our patients developed clinical postoperative hepatic or renal dysfunction, and for none were laboratory findings abnormal.

In summary, exogenously administered epinephrine causes similar responses with respect to arrhythmogenicity, and increase in arterial blood pressure and heart rate in patients anesthetized with sevoflurane or isoflurane. In this study, no patient anesthetized with either anesthetic developed arrhythmias with epinephrine doses of less than 5 µg/kg.

References


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SEVOFLURANE AND EPINEPHRINE-INDUCED ARRHYTHMIAS


