

## Epinephrine-induced Premature Ventricular Contractions and Changes in Arterial Blood Pressure and Heart Rate during I-653, Isoflurane, and Halothane Anesthesia in Swine

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I653 is a new inhalation anesthetic having especially desirable recovery characteristics because of its very low blood and tissue solubility. Investigations of its cardiovascular and electroencephalographic effects have revealed actions similar to those of isoflurane. However, these studies did not evaluate the potential of I653 to predispose the heart to epinephrine-induced arrhythmias. In this investigation, we studied eight domestic swine to compare the effects of I653 with those of other anesthetics on the cardiac arrhythmogenic actions of intravenously infused epinephrine. I653, isoflurane, and halothane each were given, on separate days, at 0.7-0.8 and at 1.1-1.2 MAC. The rate of infusion of epinephrine needed to produce premature ventricular contractions (PVCs) when the animals were anesthetized with I653 ( $6.9 \pm 0.7$  and  $6.6 \pm 0.9 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  at 0.8 and 1.2 MAC) did not differ from that during isoflurane anesthesia ( $5.7 \pm 1.1$  and  $6.0 \pm 1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  at 0.7 and 1.1 MAC), but was greater than that required during halothane anesthesia ( $1.3 \pm 0.2$  and  $1.1 \pm 0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  at 0.7 and 1.1 MAC). Similar mean arterial blood pressures and heart rates resulted from like infusions of epinephrine during I653 and isoflurane anesthesia. PVCs occurred at lesser infusion rates of epinephrine and at lower mean arterial blood pressures and heart rates with halothane than with I653 or isoflurane. Anesthetic concentration, over the range studied, did not alter the infusion rate of epinephrine required to produce arrhythmias with any anesthetic. The authors conclude that I-653 and isoflurane have similar properties with respect to epinephrine-induced arrhythmias and increases in heart rate and arterial blood pressure. (Key words: Anesthetics, volatile: halothane; I653; isoflurane. Heart: arrhythmias. Hemodynamics: blood pressure; heart rate. Sympathetic nervous system, catecholamines: epinephrine.)

I653 (DIFLUOROMETHYL 1-FLUORO 2,2,2-TRIFLUOROETHYL ETHER) is a new inhaled anesthetic with several

advantageous properties, including low solubility in blood<sup>1</sup> and tissues (Yasuda N, personal communication), rapid recovery,<sup>2</sup> stability in soda lime,<sup>3</sup> absence of toxicity,<sup>4</sup> and flammability,<sup>5</sup> little or no metabolism,<sup>5</sup> and electroencephalographic depression without seizure activity during normocapnia or hypocapnia.<sup>6</sup> The cardiovascular actions of I653 are comparable to those of isoflurane at clinically useful concentrations.<sup>7</sup> Some anesthetics decrease the threshold for ventricular arrhythmias induced by exogenously administered epinephrine. Halothane and enflurane alter the cardiac rhythmic response to epinephrine, while isoflurane does not.<sup>8-10</sup> The investigation of the cardiovascular effects of I653 did not evaluate its potential to predispose the heart to arrhythmias following administration of epinephrine. We report here the comparative effects of I653, isoflurane, and halothane on cardiac rhythm, arterial blood pressure, and heart rate during administration of epinephrine to chronically instrumented domestic swine.

### Materials and Methods

Chronically indwelling aortic arterial cannulae were inserted as previously described<sup>7</sup> in eight young (weight  $16.6 \pm 0.7$  kg, mean  $\pm$  SE) female domestic swine. Each animal was anesthetized with I653, isoflurane, and halothane on separate days, except that one animal was given only halothane, and one only I653 and isoflurane. Studies in each animal were separated by 3-8 days. Anesthesia was induced with inhaled anesthetic in oxygen *via* a mask. After induction of anesthesia, succinylcholine, 2 mg/kg, was administered intravenously to facilitate tracheal intubation. No drugs other than epinephrine were given. Body temperature was maintained within  $0.5^\circ\text{C}$  of the awake value by circulating-heated water pads. Animals' lungs were ventilated with tidal volumes of approximately 20 ml/kg, with frequency adjusted to maintain normocapnia ( $P_{\text{CO}_2}$   $42.7 \pm 0.9$  mmHg). Aortic blood pressure (transduced by a Statham<sup>®</sup> 23Db transducer), lead V<sub>5</sub> of the electrocardiogram, and partial pressure of carbon dioxide at the endotracheal tube orifice (measured by an infra-red analyzer, Beckman<sup>®</sup> LB-2, Beckman Instru-

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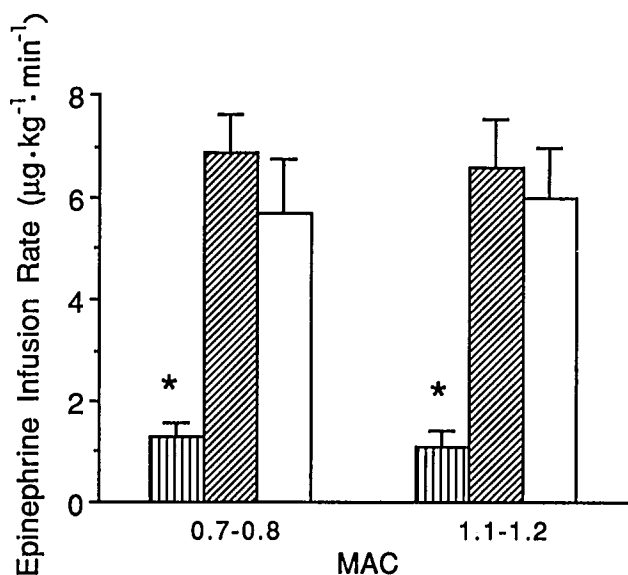


FIG. 1. Intravenous infusion rate (mean  $\pm$  SE) of epinephrine causing three or more PVCs within 1 min in swine anesthetized with I653 (▨), isoflurane (□), or halothane (▩). The rates for I653 and isoflurane do not differ at either anesthetic concentration. The rate for halothane is lower than that for I653 and isoflurane at both anesthetic concentrations. Concentration of any anesthetic did not alter arrhythmogenic rate.

ments, calibrated with a known concentration of  $\text{CO}_2^{11}$  were recorded on a multi-channel recorder (Gould Brush® 2800). End-tidal concentrations of anesthetics were measured by infra-red analyzers (Beckman® LB-2, Beckman Instruments; and Puritan-Bennett® Anesthetic Agent Monitor 222), calibrated with secondary (tank) standards, which had been calibrated against volumetrically produced standard flasks.

Each anesthetic was studied at two stable end-tidal concentrations, 0.7 and 1.1 MAC isoflurane and halothane and 0.8 and 1.2 MAC I653. We had intended to conduct this study at equipotent anesthetic concentrations (1.0 and 1.5 MAC, for all anesthetics). Our initial estimate of MAC for I653 and the published value of MAC for isoflurane in swine<sup>12,19</sup> were based on standard tail-clamp techniques. Subsequent to concluding the present study, we found the tail-clamp to be less than a supra-maximal stimulus.<sup>14</sup> Thus, this study was conducted at the lesser MAC values for I653 and isoflurane. Similarly, although these studies were conducted at 1.25% and 1.88% end-tidal halothane, which were thought to equal 1.0 and 1.5 MAC in swine,<sup>15</sup> the findings of Eger *et al.*<sup>14</sup> suggest that these concentrations approximate 0.7 and 1.1 MAC in the pig.

After maintaining a stable end-tidal anesthetic concentration for 15 min, control measurements were made and epinephrine was infused intravenously in progres-

sively increasing rates of 0.2, 0.4, 0.8, 2.0, and 4.0  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . The infusion was continuous, with each infusion rate continued for 5 min unless three PVCs occurred within 1 min. Although some pigs did not have PVCs at an infusion rate of 4.0  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , we did not exceed this rate because we observed extreme increases in blood pressure and heart rate (see figs. 2, 3) and thought that further increases might be injurious. After allowing hemodynamic parameters to return to values similar to those before infusion of epinephrine, the anesthetic concentration was changed to the second concentration (order randomly assigned) and the process repeated. One animal received epinephrine at only one concentration of isoflurane because she developed severe hypotension after the epinephrine infusion was terminated.

We compared the infusion rates of epinephrine at which arrhythmias occurred, and mean aortic blood pressure and heart rate for all anesthetics and between concentrations for each anesthetic by analysis of variance and the Newman-Kuels method of multiple comparisons.<sup>16</sup> When 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  epinephrine did not induce PVCs, we treated the data as if arrhythmias would have developed at the next higher infusion rate, 8  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ . Differences were accepted as statistically significant at  $P \leq 0.05$ .

## Results

Significantly greater infusion rates of epinephrine were required to produce PVCs during I653 or isoflurane anesthesia than during halothane anesthesia (fig. 1). Arrhythmias occurred in all animals anesthetized with halothane, but in only two of seven animals anesthetized with I653 and three of six animals anesthetized with isoflurane. This incidence of arrhythmias and the infusion rates of epinephrine required to produce these arrhythmias did not differ between I653 and isoflurane. Anesthetic concentration did not alter the epinephrine infusion rate that produced arrhythmias for any of the three anesthetics (fig. 1).

Epinephrine infusion produced similarly increased mean aortic blood pressure with all anesthetics (fig. 2), except that 0.2  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  epinephrine produced greater aortic blood pressure with the greater concentrations of halothane than with I653 or isoflurane, and 4  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  epinephrine produced greater aortic blood pressure with the greater concentration of isoflurane than with I653. Because less epinephrine was required to induce PVCs during halothane anesthesia, mean aortic blood pressure before the development of PVCs was less than the maximal pressures measured without development of PVCs during I653 anesthesia or isoflu-

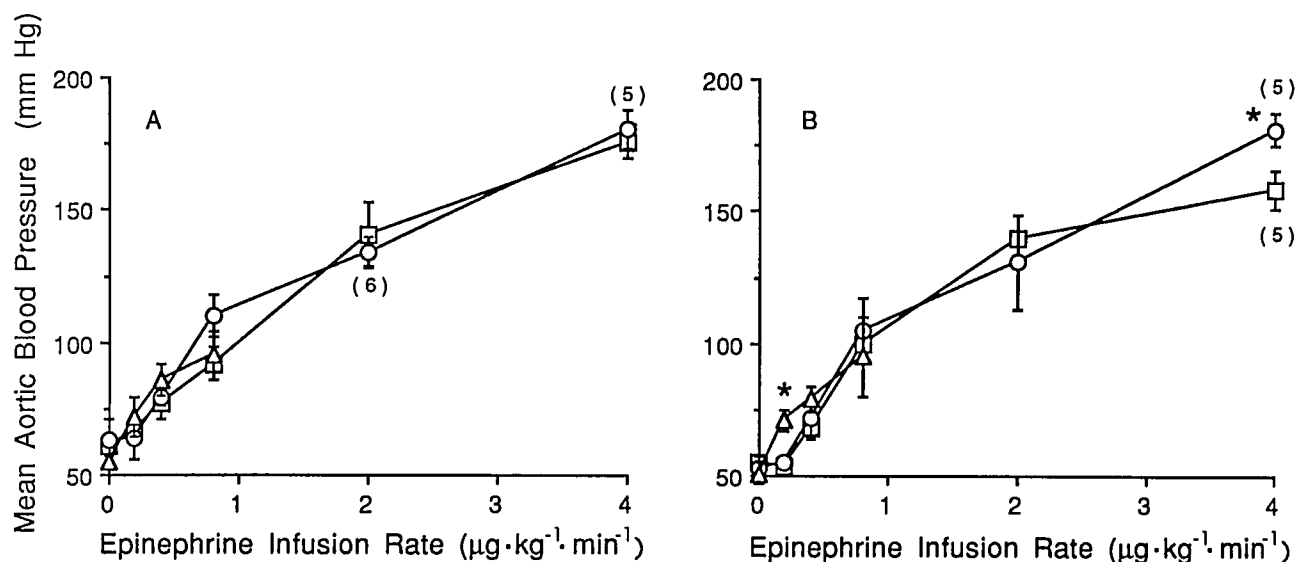


FIG. 2. Mean aortic blood pressure (mean  $\pm$  SE) during iv infusion of epinephrine in swine anesthetized with I653 ( $\square$ ; A. 0.8 MAC; B. 1.2 MAC), isoflurane ( $\circ$ ; A. 0.7 MAC; B. 1.1 MAC), or halothane ( $\Delta$ ; A. 0.7 MAC; B. 1.1 MAC). Responses among anesthetics are similar, and were not affected by anesthetic concentration. N = 7, except where indicated otherwise (parentheses). \*Indicates statistical difference from other anesthetic(s) at that epinephrine infusion rate.

rane anesthesia (table 1). Blood pressure during epinephrine infusion did not differ between the two concentrations of any anesthetic (fig. 2).

At all rates of epinephrine infusion, heart rate always was less during anesthesia with halothane than with I653 or isoflurane (fig. 3). Heart rate did not differ between I653 and isoflurane except that at  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  epinephrine heart rate was faster with the greater concentration of I653 than with the greater concentration of isoflurane. The response of heart rate to epinephrine was curvilinear. With all anesthetics, the increase in heart rate per increase in epinephrine infusion rate was greater with infusions less than  $1.0 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  than at higher infusion rates. Because heart rates were less at all epinephrine infusion rates during halothane anesthesia than during isoflurane or I653 anesthesia, and because PVCs developed at lower infusion rates of epinephrine during anesthesia with halothane, the maximum heart rate preceding the development of PVCs was slower during anesthesia with halothane than during anesthesia with I653 or isoflurane (table 2). For a given epinephrine infusion rate, heart rates did not differ between the two concentrations of isoflurane or halothane except for a greater heart rate with  $4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  epinephrine at the greater concentration of isoflurane, and a greater heart rate with  $0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  epinephrine at the greater concentration of halothane, compared to the lesser concentrations of each of these anesthetics. Heart rate with I653 was greater at 1.2 MAC than at 0.8 MAC for all epinephrine infusions greater than  $0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ .

### Discussion

Induction of PVCs required greater infusion rates of epinephrine during anesthesia with either I653 or isoflurane than during anesthesia with halothane. However, because we did not infuse sufficient epinephrine to produce arrhythmias in all swine anesthetized with I653 or isoflurane, we could not determine if these two anesthetics differ in their effect on cardiac rhythmic response to epinephrine. The anesthetics were administered at similar, but not exactly equipotent, concentrations. The minimal differences in anesthetic dose do not appear to have been a factor, because we did not find any difference in the rhythmic response to epinephrine between the two concentrations used for each anesthetic. We did not confirm the finding of Joas and Stevens that increasing anesthetic concentration increases the dose of epinephrine required to produce arrhythmias in dogs.<sup>8</sup> The difference between the two studies could be species-related, or a result of our

TABLE 1. Mean Aortic Blood Pressure at Highest Infusion Rate of Epinephrine Which Did Not Result in Development of Three PVCs in 1 Min

	I653	Isoflurane	Halothane
0.7-0.8 MAC	167 $\pm$ 7	154 $\pm$ 11	91 $\pm$ 8*
1.1-1.2 MAC	153 $\pm$ 11	146 $\pm$ 17	84 $\pm$ 9*

\* Indicates significant difference ( $P < 0.05$ ) from both other anesthetics. There were no significant differences between the two concentrations of any anesthetic.

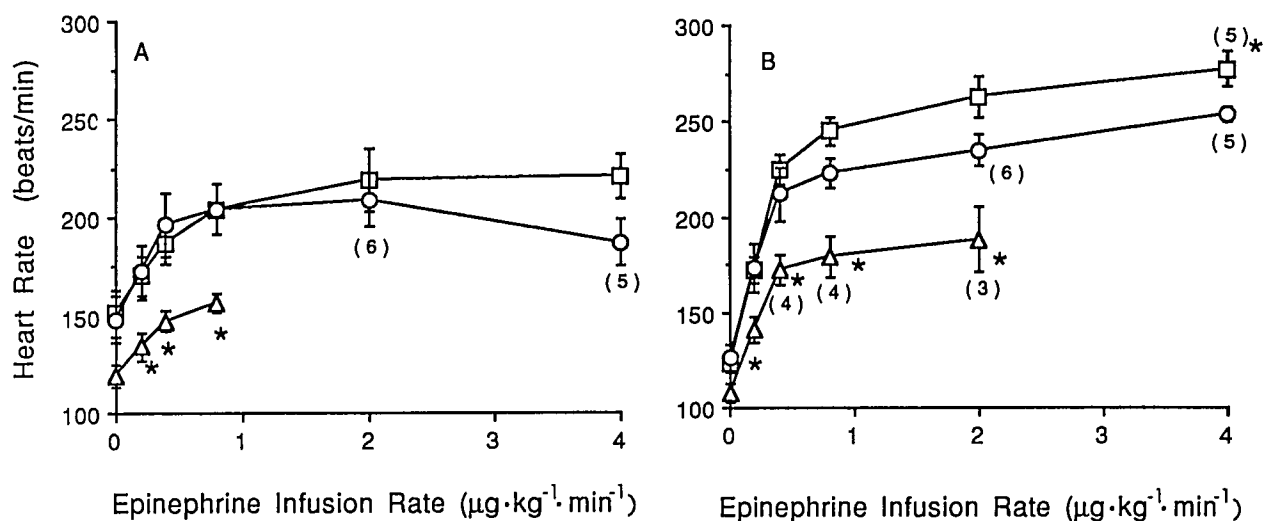


FIG. 3. Heart rate (mean  $\pm$  SE) during iv infusion of epinephrine in swine anesthetized with I653 ( $\square$ ; A. 0.8 MAC; B. 1.2 MAC), isoflurane ( $\circ$ ; A. 0.7 MAC; B. 1.1 MAC), or halothane ( $\Delta$ ; A. 0.7 MAC; B. 1.1 MAC). At a given infusion rate, heart rates were similar during anesthesia with I653 and isoflurane, and always lower during anesthesia with halothane. N = 7, except where indicated otherwise (parentheses). \*Indicates statistical difference from other anesthetic(s) at that epinephrine infusion rate.

animals not being anesthetized as deeply or over as wide a range of anesthetic concentrations (1.25 and 2.0 MAC) as were theirs. Difference in the ages of experimental animals is not likely to have caused this difference between our study and that of Joas and Stevens. Although 1–3-day-old piglets have an immature adrenergic system,<sup>17</sup> and are resistant to epinephrine-induced arrhythmias,<sup>18</sup> 55-day-old swine have mature  $\alpha$ - and  $\beta$ -adrenergic mechanisms,<sup>17</sup> and our data and those of Rao *et al.*<sup>18</sup> suggest that their rhythmic response to epinephrine is similar to adults of other species.

Like Joas and Stevens<sup>8</sup> and Imamura and Ikeda,<sup>19</sup> we found that arrhythmias occurred with lower epinephrine infusion rates in animals anesthetized with halothane than in animals anesthetized with isoflurane. Our infusion rates that produced PVCs in swine were similar to those found for halothane and isoflurane by the latter investigators, but half that found for halothane by Maze and Smith<sup>20</sup> and one-fifth to one-tenth those found for halothane and

isoflurane by the former investigators. Joas and Stevens may have needed a higher rate because they infused epinephrine for only 1 min, and, thus, the plasma levels of epinephrine they achieved are likely to have been substantially less than those we produced with similar concentrations of infusions of 3 min duration. The dogs studied by Maze and Smith may have required greater epinephrine infusion rates because the infusions were of shorter duration and separated by 10 min. They also infused epinephrine to a more severe end-point (four or more PVCs in 15 s) than did we; however, Imamura and Ikeda also used this more severe end-point and obtained results similar to ours. Others who have induced arrhythmias by epinephrine infusion in swine anesthetized with halothane have reported the cumulative infused dose of epinephrine, but not the rate of infusion required to induce PVCs.<sup>18,21</sup> Since epinephrine has a short plasma half-life, it would seem more appropriate to report infusion rate rather than cumulative dose administered over many minutes. Nevertheless, it appears likely that the arrhythmogenic infusion rate in at least one of these studies<sup>21</sup> was similar to ours. Our required infusion rates are remarkably similar to the ED50 arrhythmogenic dose of submucosally injected epinephrine in humans.<sup>10</sup>

Some investigators have correlated infusion rates, plasma concentrations of epinephrine, and the appearance of arrhythmias. Sumikawa *et al.* measured plasma epinephrine concentrations while infusing epinephrine to produce arrhythmias in dogs.<sup>22</sup> However, their results

TABLE 2. Heart Rate at Highest Infusion Rate of Epinephrine Which Did Not Result in Development of Three PVCs in 1 Min

	I653	Isoflurane	Halothane
0.7–0.8 MAC	218 $\pm$ 12	189 $\pm$ 8	150 $\pm$ 5*
1.1–1.2 MAC	272 $\pm$ 8	242 $\pm$ 8	158 $\pm$ 12*

\* Indicates significant difference ( $P < 0.05$ ) from both other anesthetics.

are confounded by their having induced anesthesia with thiopental, which decreases the arrhythmogenic threshold for at least 4 h.<sup>23,24</sup> Imamura and Ikeda found a good correlation between plasma epinephrine concentration at the time of development of ventricular arrhythmias and the 3-min intravenous infusion rate of epinephrine that produced those arrhythmias.<sup>19</sup> We did not measure plasma epinephrine concentrations during infusion of epinephrine; however, the correlation between the plasma concentration and the infusion rate of epinephrine appears to be independent of anesthetic.<sup>19,22</sup>

Arterial blood pressure has long been thought to be an important component in the development of arrhythmias. For example, using hemorrhage to reduce blood pressure, Moe *et al.*<sup>25</sup> were able to eliminate ventricular tachycardia in cyclopropane-anesthetized dogs during infusion of epinephrine. In addition, more epinephrine was required to produce ventricular tachycardia when blood pressure was controlled almost unchanged than when blood pressure was allowed to increase with epinephrine infusion. Similarly, Dresel *et al.*<sup>26</sup> infused epinephrine in cyclopropane-anesthetized dogs and were able to eliminate or produce bigeminy by decreasing or increasing arterial blood pressure by hemorrhage and reinfusion of blood. More recently, however, Maze and Smith<sup>20</sup> did not find a change in arrhythmogenic dose of epinephrine in halothane-anesthetized dogs when nitroprusside was used to control blood pressure during epinephrine administration. Our data indicate that anesthetics can alter the relationship between arterial blood pressure and development of arrhythmias. In our study, although the relationship of mean arterial blood pressure and epinephrine infusion rate was similar for all three anesthetics, arrhythmias developed at lesser blood pressures and infusion rates with halothane than with I653 or isoflurane at both anesthetic concentrations. Imamura and Ikeda also found that epinephrine-induced ventricular arrhythmias developed at a lesser arterial blood pressure in dogs anesthetized with halothane than in dogs anesthetized with isoflurane or sevoflurane.<sup>19</sup> When our animals were anesthetized with I653 or isoflurane, epinephrine infusion markedly elevated mean aortic blood pressure without causing arrhythmias in most animals.

Rapid heart rate also has been implicated as a factor predisposing to arrhythmogenicity,<sup>27</sup> and, as with blood pressure, our data show that anesthetics can alter the relationship between a specific heart rate and the development of arrhythmias: PVCs developed at lesser heart rates when the animals were anesthetized with halothane than with I653 or isoflurane.

Unlike Joas and Stevens,<sup>8</sup> we did not infuse epinephrine in our animals while they were conscious. Joas and

Stevens<sup>8</sup> found that isoflurane did not change the intravenous dose of epinephrine required to induce PVCs, while halothane significantly decreased this dose; a four- to fivefold greater rate of epinephrine infusion was required to produce PVCs in animals anesthetized with isoflurane than in animals anesthetized with halothane. We found a similar difference in the arrhythmogenic epinephrine infusion rates between these two anesthetics. Because we found no differences between I653 and isoflurane, and because of the similarity of our data for halothane and isoflurane to data in humans,<sup>10</sup> we predict that I653 is not likely to appreciably alter the dose of exogenously administered epinephrine required to induce ventricular arrhythmias in humans.

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