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# Epinephrine-Induced Arrhythmias: Effects of Thoracic Epidural Anesthesia and Vagotomy during Enflurane Anesthesia in Rabbits

For evaluating the effects of thoracic epidural anesthesia, with or without bilateral vagotomy, epinephrine-induced arrhythmias were studied in 31 rabbits anesthetized with 1 minimum alveolar concentration of enflurane. We divided the rabbits into 5 groups: Group I (epidural saline as control group; n=6), Group II (epidural lidocaine without vagotomy; n=6), Group III (intravenous lidocaine; n=7), Group IV (epidural saline with vagotomy; n=6), and Group V (epidural lidocaine with vagotomy; n=6). Using logdose protocol, epinephrine was infused at an initial rate of 0.67 μg/kg/min and increased by Exp[0.4] until arrhythmias occurred; if arrhythmias occurred at any of these doses, a smaller dose, divided by Exp[0.2], was tested. Arrhythmic dose of epinephrine was defined as the smallest infusion rate needed to produce four or more arrhythmias within 15 sec during epinephrine infusion. Arrhythmic dose of epinephrine and its plasma concentration in epidural lidocaine group were significantly higher than control ($p<0.05$). Similarity of results was also noted amongst the intravenous lidocaine group, vagotomy only group, and vagotomized epidural lidocaine group with respect to the control. These results suggest that thoracic epidural anesthesia raises the threshold for enflurane-epinephrine induced arrhythmias in rabbits and that this effect is eliminated by bilateral vagotomy.

Key Words : *Arrhythmia; Epinephrine; Anesthesia, epidural; Lidocaine; Vagotomy; Rabbits*

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## INTRODUCTION

A previous study in dogs showed that halothane-epinephrine induced arrhythmias were significantly reduced by use of thoracic epidural anesthesia (TEA), but not after bilateral vagotomy (1). Despite the common use of enflurane in clinical settings, no studies have demonstrated the effect of TEA on enflurane-epinephrine induced arrhythmias. Johnston et al. (2) studied the comparative interaction of epinephrine with enflurane, halothane, and isoflurane in humans; they pointed out that the dose-response curves of halothane and isoflurane roughly paralleled each other. But enflurane did not fit this pattern and epinephrine $ED_{50}$ of arrhythmias for enflurane was higher than that of halothane and isoflurane, and showed a much larger standard deviation than either of these. It may thus be assumed that under TEA, different volatile anesthetics may affect the arrhythmic threshold in different ways.

We studied the effects of TEA on enflurane-epinephrine induced arrhythmias and determined the arrhythmic dose of epi-nephrine (ADE) and its plasma concentration (PCE) during arrhythmia. Indirect stimulatory effect of vagus nerve following TEA was also examined via bilateral vagotomy. The effect of intravenous lidocaine on ADE was also examined, in order to compare this with the effect of circulating lidocaine absorbed from epidural space.

## MATERIALS AND METHODS

### Experimental Preparation

This study was approved by the Committee on Animal Research at the Seoul National University School of Medicine. It involved 31 crossbred New Zealand white rabbits of either sex, weighing 1.50-2.45 kg, which were then divided into five groups (Fig. 1).

Thirty min prior to the subsequent procedures, all rabbits were intramuscularly injected with 2 mg/kg of diazepam. Anesthesia was induced by the inhalation of incremental concentrations of enflurane in 1.5 L/min of medical air and 1.5 L/min of oxygen, via a face mask. The ECG (Spacelabs

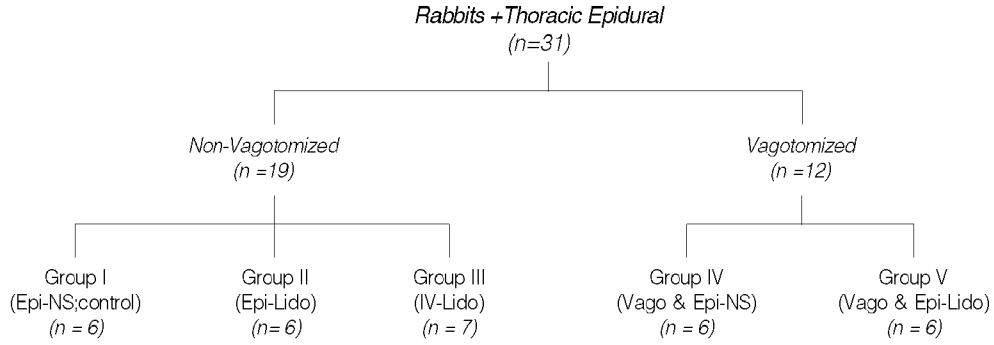


Fig. 1. Schematic representation of groupings. Epi, epidural; NS, 0.9% normal saline; IV, intravenous; Lido, lidocaine; Vago, vagotomy.

90603 A, WA) was monitored continuously via lead II. The trachea was intubated by tracheostomy with an uncuffed endotracheal tube (3.0-4.0 mm inner diameter, 10 cm in length), and the lungs were mechanically ventilated (Ohmeda 7000 electric anesthesia ventilator pediatric bellows assembly, BOC group Inc, WI). Anesthesia was maintained at 1 minimum alveolar concentration (MAC) (=2.86 Vol%) (3) of end-tidal enflurane (Ohmeda 5250, BOC group Inc, WI). End-tidal $CO_2$ (from the same supplier) was maintained at 35-40 mmHg. Rectal temperature was maintained at 37.0-39.4℃ by a heating lamp and a water blanket. Blood pressure at the common carotid artery was continuously monitored (Spacelabs 90603A, WA). Drugs and fluid were administered through an external jugular vein catheter. Lactate Ringer's solution was administered at a rate of 10 mL/kg/hr and for mechanical ventilation, vecuronium 0.3 mg/kg was administered intravenously. Arterial blood gas and pH analysis were performed to ensure normal ventilation and acid-base balance. When the base deficit was 5 mEq or greater, sodium bicarbonate (1/6 base deficit × body weight in kgs) was administered intravenously until the deficit fell to less than 5 mEq; this avoided metabolic acidosis resulting from the repeated infusion of epinephrine (4). Initial hemodynamic data were measured when end-tidal enflurane was steadily maintained to 1 MAC after induction of anesthesia.

In Groups IV and V (vagotomy without or with epidural lidocaine, respectively), bilateral vagotomy was performed at C6 level. An epidural catheter was placed in all rabbits; the vertebral arches of T8 and T9 were surgically exposed and the spinous process of T9 was removed. After gentle elevation of the spinous process of T8 with forceps, the midline of the ligamentum flavum just beneath the spinous process was carefully punctured with a round-tipped blunt hook (FD 397, Aesculap, Germany) as horizontally as possible to the inner table of the lamina. An epidural catheter (0.9 mm outer diamener, 0.19 mL priming volume; Portex, U.K.) was introduced and advanced about 5 cm in a cephalad direction (5). After an injection of 0.19 mL Isovist® 240 contrast media (Schering, Germany) to prime the epidural catheter after each experiment, the location of the catheter tip was radiologically confirmed, using a mobile C-arm X-ray system 9600 series with X-ray equipment accessories (OEC Medical System, UT). Catheter tips were located at the vertebral body of T3 or T4.

Rabbits in Groups II and V (epidural lidocaine without or with vagotomy, respectively) were injected with 1% epidural lidocaine. This was administered at an initial dose of 0.3 mL/kg along with a priming volume, and 0.1 mL/kg was repeated at hourly intervals. The remaining groups were epidurally treated with the same volume of 0.9% normal saline. Rabbits in Group III (intravenous lidocaine) were intravenously injected with 2 mg/kg lidocaine, followed by 2 mL/kg/hr after epidural saline treatment. Baseline hemodynamic data and the concentration of endogenous catecholamines were measured 10 min after the various treatments, and after a further 20 min, ADE was determined.

## Intervention

Using logdose protocol (6), epinephrine was infused for 3 min, at an initial rate of 0.67 μg/kg/min, with a recovery period of 10 min between infusions. The rate was increased by Exp[0.4] until arrhythmias occurred; if arrhythmias occurred at any of these doses, a smaller dose, divided by Exp[0.2], was tested. ADE was defined as the smallest infusion rate needed to produce four or more arrhythmias within 15 sec during epinephrine infusion (1). Arrhythmias were categorized as wandering atrial pacemaker, premature atrial and ventricular contraction, and atrioventricular dissociation. If arrhythmias did not occur, ADE was alternatively defined as the infusion rate which caused tachycardia associated with an inter-infusion end-tidal $CO_2$ level of less than 10 mmHg, a life-threatening decrease (7). In such circumstances, a smaller dose of epinephrine was not tried. The

arrhythmic threshold was defined as the value of either ADE or PCE.

### Measurements

In each experiment, hemodynamic data, PCE, and serum concentration of lidocaine (SCL) were measured when ADE was reached. SCL was analyzed by fluorescence polarization immunoassay method, using TDX (Abbott, IL). Plasma concentrations of catecholamine were analyzed by HPLC with electrochemical detector procedures (Model ICI, Australia) (8). This assay has a sensitivity limit of 20 pg/mL for each catecholamine. The interassay and intraassay variations are less than 5%.

### Statistical Analysis

Data is expressed as either mean±SD (normal distribution) or geometric mean · geometric SD (logarithmic distribution) after test of goodness. ADE and PCE were analyzed by Kruskal-Wallis test, and if statistical differences emerged ($p<0.05$), Mann-Whitney U test was used. Hemodynamic data, endogenous catecholamines, and SCL were analyzed by one-way ANOVA, and if statistical differences emerged ($p<0.05$), Student-Newman-Keul multiple comparison test was used. For statistical comparisons of means within a group, repeated-measure ANOVA was used. If the results were significant ($p<0.05$), paired t-test with Bonferroni correction was used.

## RESULTS

Initial hemodynamic data showed no significant differences among the groups (Table 1). Only in Groups II and V (epidural lidocaine without or with vagotomy, respectively), baseline mean arterial pressure and heart rate values were lower than their initial values. The former results were different from the values seen in Group I (control), and the latter were different from those seen in other groups (Table 1). Among the various groups, differences in endogenous catecholamines were not seen (Table 2). Mean arterial pressures at the arrhythmic threshold were higher than both initial and baseline mean arterial values in all groups, but did not differ among the groups. Heart rates at the arrhythmic threshold were not higher than either initial or baseline values in Groups I, III, and IV (groups without epidural lidocaine), but were higher than baseline in Group V (vagotomy with epidural lidocaine) and higher than both initial and baseline values in Group II (epidural lidocaine). Heart rate values at arrhythmic threshold of Group II and of other groups were different (Table 1).

All rabbits, except four in Group II (epidural lidocaine), showed arrhythmias during epinephrine infusion. We includ-

Table 1. Hemodynamic data at initial, baseline, and arrhythmic threshold in rabbits anesthetized with enflurane

| Groups | No. | MAP (mmHg) | | | HR (bpm) | | |
|---|---|---|---|---|---|---|---|
| | | Initial | Baseline | AT | Initial | Baseline | AT |
| I (Control) | 6 | 58 ± 6 | 53 ± 11 | 131 ± 24*§ | 272 ± 21 | 262 ± 19 | 267 ± 50 |
| II (Epi-Lido) | 6 | 57 ± 10 | 25 ± 4*‡ | 121 ± 17*§ | 257 ± 23 | 206 ± 30*# | 333 ± 8*§† |
| III (IV-Lido) | 7 | 50 ± 10 | 42 ± 19 | 105 ± 35*§ | 272 ± 22 | 250 ± 23 | 253 ± 37 |
| IV (Vago & Epi-NS) | 6 | 56 ± 6 | 40 ± 11 | 110 ± 19*§ | 274 ± 25 | 273 ± 27 | 282 ± 19 |
| V (Vago & Epi-Lido) | 6 | 52 ± 14 | 27 ± 5*‡ | 130 ± 23*§ | 245 ± 18 | 192 ± 20*# | 279 ± 25§ |

Values are mean ± SD. Initial, end-tidal enflurane was steadily maintained to 1 MAC after induction of anesthesia; Baseline, at 10 min after the various treatments; AT, arrhythmic threshold; MAP, mean arterial pressure; HR, heart rate; Epi, epidural; IV, intravenous; Lido, lidocaine; NS, 0.9% normal saline; Vago, vagotomy. *$p<0.05$ vs. Initial. §$p<0.05$ vs. Baseline. ‡$p<0.05$ vs. Group I. #$p<0.05$ vs. Groups I, III, & IV. †$p<0.05$ vs. other groups.

Table 2. Plasma concentrations of endogenous catecholamine after different treatments during enflurane anesthesia in rabbits

| Groups | No. | Norepinehrine (pg/mL) | | Epinehrine (pg/mL) | |
|---|---|---|---|---|---|
| | | GM | GSD | GM | GSD |
| I (Control) | 6 | 1660.71 | 3.54 | 665.47 | 1.84 |
| II (Epi-Lido) | 6 | 993.86 | 2.89 | 698.41 | 1.70 |
| III (IV-Lido) | 7 | 1723.13 | 1.76 | 670.75 | 1.43 |
| IV (Vago & Epi-NS) | 6 | 1147.34 | 2.29 | 729.53 | 1.60 |
| V (Vago & Epi-Lido) | 6 | 1420.83 | 2.32 | 708.18 | 2.07 |

Values are geometric mean (GM) · geometric SD (GSD). Epi, epidural; IV, intravenous; Lido, lidocaine; NS, 0.9% normal saline; Vago, vagotomy. There were no significant differences between the groups.

Table 3. The arrhythmic dose (ADE) and the plasma concentration (PCE) of epinephrine at arrhythmic threshold after different treatments during enflurane anesthesia in rabbits

| Groups | No. | ADE ($\mu$g/kg/min) | | PCE (ng/mL) | |
|---|---|---|---|---|---|
| | | GM | GSD | GM | GSD |
| I (Control) | 6 | 10.21 | 3.72 | 83.16 | 5.32 |
| II (Epi-Lido) | 6 | 118.90* | 2.05 | 677.76* | 1.54 |
| III (IV-Lido) | 7 | 6.34 | 2.93 | 96.42 | 3.09 |
| IV (Vago & Epi-NS) | 6 | 8.65 | 2.86 | 44.64 | 5.88 |
| V (Vago & Epi-Lido) | 6 | 12.03 | 1.98 | 95.35 | 3.22 |

Values are geometric mean (GM) · geometric SD (GSD). Epi, epidural; IV, intravenous; Lido, lidocaine; NS, 0.9% normal saline; Vago, vagotomy. *$p<0.05$ vs. other groups.

ed the data of those four into the data of Group II because their content has an alternative definition of ADE. ADE and PCE values in Group II were significantly higher than in the remaining groups (Table 3).

SCL in Groups II, III, and V (groups without epidural saline) was similar; the respective levels were $2.04\pm0.71$, $1.46\pm0.51$, and $1.44\pm0.58$ $\mu$g/mL.

## DISCUSSION

In our study, TEA significantly raised the ADE and PCE defined as the arrhythmic threshold of exogenous epinephrine infusion in enflurane anesthetized rabbits (Table 3). This agreed in general with the results of a previous study with halothane in dogs (1). Overall ADE and PCE values in Group II (epidural lidocaine) were, however, approximately 20 and 5 times higher, respectively, in our enflurane study in rabbits than in the corresponding group of dogs of that study (1).

The possible causes of these significant differences between the two anesthetics in thoracic sympathectomized animals are as follows: First, the ADE might differ according to species. Several previous reports have described the effects of volatile anesthetics on epinephrine induced arrhythmias in different animal species (2, 9, 10). Additional confirmation will thus be required with directly comparing the effect of TEA on halothane- and enflurane-epinephrine induced arrhythmias in the same species. Second, the myocardial sensitizing effect of halothane and of enflurane might be different (2). Third, there might be a difference in the number of epinephrine infusions required to establish ADE. The same logdose infusion was used in both studies, but in our Group II, the establishment of ADE required more epinephrine infusions (12-17 infusions) than in the corresponding group of dogs in the halothane study (<8 infusions) (1). Repeated challenges with epinephrine leads to tolerance and either an inability to produce arrhythmias or a need for much higher doses of epinephrine for these to occur (11). Such tolerance might have led to the higher ADE and PCE values in our enflurane study. Finally, differences in the way that mean values were determined (geometric mean vs. arithmetic mean) might also attribute to the differences. Vecuronium, however, did not affect the arrhythmic threshold because it appears to be essentially devoid of cardiovascular effects (12).

In our study, vagotomy nullified the protective action of TEA. It thus appears that the antiarrhythmic effect of TEA requires the indirect stimulatory effect of the vagus nerve following sympathetic blockage of the heart. There are conflicting data on the possible role of this nerve in volatile anesthetic-epinephrine arrhythmias. Some experiments, such as ours, have shown that direct or indirect vagal stimulation can terminate ventricular arrhythmias (1, 13, 14). Others did not adequately demonstrate that stimulation of this nerve can convert these arrhythmias (15, 16). This difference may have been caused either by differences in anesthetics or differences in the dosage of epinephrine required to induce arrhythmia. It is possible that very high doses of epinephrine inadvertently conceal a protective effect of vagal stimulation (13).

We have shown that vagotomy with intact sympathetic activity did not affect the arrhythmic threshold (Table 3), a result which can also be seen in halothane-epinephrine induced arrhythmias in dogs (1, 13).

SCL after the epidural administration of lidocaine rises as fast as during its intravenous administration in rabbits (17). We therefore anticipated that when administered epidurally, lidocaine, a class IB antiarrhythmic drug, may exhibit the same effects as when administered intravenously; the ADE, PCE, and SCL of Group III (intravenous lidocaine) were not different from those of Group I (control), however (Table 3). In our study, circulating lidocaine absorbed from epidural space did not, therefore, contribute to the antiarrhythmic effects on exogenous epinephrine infusion under enflurane anesthesia, despite the fact that a lower therapeutic plasma level of lidocaine was achieved. We speculate that very high doses of exogenous epinephrine might conceal the protective effect of circulating lidocaine.

Several studies (18, 19) have suggested that blood pres-

sure and heart rate are important factors in the genesis of volatile anesthetics-epinephrine arrhythmias. Kamibayashi et al. (1) assumed that hypotension following TEA may affect the arrhythmic threshold. They reported, moreover, that despite the fact that a relatively high epinephrine infusion rate was required to induce arrhythmias in the TEA group, blood pressure at the time of arrhythmia was similar. In most cases of our study, however, mean arterial pressure reached its maximal value before arrhythmia occurred (Table 3). In addition, four of six rabbits in Group II (epidural lidocaine) did not show arrhythmia during epinephrine infusion, regardless of the fact that their heart rate was significantly higher than that of the remaining groups (Table 1). In our study, hypotension and bradycardia following TEA might not, therefore, play a significant role in increasing the arrhythmic threshold. This disparity with halothane in dogs (1) may be caused by differences in their myocardial sensitizing activity between anesthetics (2). Weiskopf et al. (20) previously indicated that when halothane was used, epinephrine-induced arrhythmias developed at lower blood pressures than when enflurane or isoflurane was used.

We concluded that TEA raised the threshold for enflurane-epinephrine arrhythmias in rabbits and that this effect is nullified by bilateral vagotomy.

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