

Thoracic Epidural Anesthesia Attenuates Halothane-induced Myocardial Sensitization to Dysrhythmogenic Effect of Epinephrine in Dogs

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Background: The autonomic nervous system plays a critical role in the central modulation of cardiac dysrhythmias. Because sympathetic blockade by thoracic epidural anesthesia has been documented to protect patients from various stress responses, the authors speculate that epidural anesthesia can attenuate the dysrhythmogenic interaction between halothane and epinephrine.

Methods: In adult mongrel dogs anesthetized with halothane, the dysrhythmogenic dose (DD) of epinephrine, defined as the smallest dose producing four or more premature ventricular contractions within a 15-s period, was determined in the presence of thoracic epidural mepivacaine or saline. To address the effect of circulating mepivacaine after epidural administration, the authors examined the DD of epinephrine in the presence of intravenous mepivacaine. They also investigated the effect of thoracic epidural anesthesia in bilaterally vagotomized dogs.

Results: Epidural mepivacaine significantly increased the DD of epinephrine compared with epidural saline. However, intravenous mepivacaine did not affect the DD of epinephrine, even when the plasma concentration of mepivacaine during the dysrhythmias was twice that in the epidural mepivacaine group. The beneficial effect of epidural mepivacaine was not seen in bilaterally vagotomized dogs.

Conclusions: Thoracic epidural anesthesia attenuated the myocardial sensitization by halothane, and vagal activity had an essential role in this action. (Key words: Anesthetics, volatile; halothane. Anesthetic techniques: epidural. Heart: dysrhythmias. Sympathetic nervous system: catecholamine; epinephrine.)

ACTIVATION of the sympathetic nervous system may predispose ischemic myocardium to the development of dysrhythmias.¹ The myocardium is also sensitized to the dysrhythmogenic effect of epinephrine by halothane anesthesia.^{2,3} Thus far, several factors, including hemodynamic parameters and intravenous agents, have been shown to affect the halothane-induced myocardial sensitization to epinephrine.⁴⁻¹² Recently, the central nervous system has been reported to modulate the vulnerability to dysrhythmias, although the precise mechanisms underlying this action are not known.^{13,14} Clinically, sympathetic blockade by thoracic epidural anesthesia has been demonstrated to exert beneficial effects in patients exposed to stress associated with surgery and heart disease.¹⁵⁻¹⁷ Therefore, in the current study, we examined whether thoracic epidural anesthesia attenuates the interaction between catecholamines and halothane anesthesia in dogs.

Materials and Methods

The studies were conducted under guidelines approved by the Animal Care Committee of Osaka University Medical School.

Forty-four adult mongrel dogs of either sex weighing 8-12 kg were used in this study. Anesthesia was in-

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duced with halothane alone and maintained at an end-tidal concentration of 1.3%, which was monitored continuously by an anesthetic gas analyzer (Datex model AA 102-30-00; Datex, Helsinki, Finland). A different dog was used for each experiment; thus, only one dysrhythmogenic dose (DD) was determined in any individual dog. The trachea of each animal was intubated with a cuffed tracheal tube, and the lungs were mechanically ventilated (Aika R60; Aika, Tokyo, Japan). The end-tidal CO_2 concentration was continuously monitored with an expired gas monitor (Minato 1H 21 A; Minato, Osaka, Japan) and maintained at a level of 35–40 mmHg. A heating lamp and circulating water blanket were used to maintain the esophageal temperature at 37–38.5°C. A femoral artery catheter was inserted for both pressure monitoring and blood gas and serum electrolyte sampling. Lead II of the electrocardiogram was monitored continuously. A femoral vein was cannulated for administration both of drugs and of lactated Ringer's solution, which was infused at a rate of $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Serum K^+ was maintained between 3.5 and 4.5 mEq/l by infusing K^+ at a rate of 1–10 mEq/h. Arterial pH, oxygen tension (PaO_2), and serum Na^+ were maintained within the ranges of 7.35–7.45, 85–100 mmHg, and 135–150 mEq/l, respectively.

An epidural catheter was inserted in each animal under halothane anesthesia. The vertebral arches of T8 and 9 were surgically exposed and the catheter was introduced *via* the T8–9 interspace into the epidural space, which was identified by the loss-of-resistance technique. The catheter was advanced 5 cm into a cephalad direction and secured to the back. After this preparation, the experiment was performed and the position of the catheter was confirmed radiographically by injection of iopamidol (0.2 ml/kg) after each experiment.

The dysrhythmia threshold was achieved when four or more premature ventricular contractions occurred within 15 s. The DD of epinephrine was defined as the smallest dose that produced the dysrhythmias. According to our previous method,¹¹ the DD of epinephrine was determined with standardized logarithmically spaced infusions of epinephrine lasting 3 min with 10–30-min recovery periods between infusions. The infusion was started at the minimum dose of $0.67 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, and the dose was increased by $e^{0.4}$ until the dysrhythmia threshold was achieved. If dysrhythmias did occur at one of these doses, a smaller dose, divided by $e^{0.2}$, was tested.

At first, the animals were randomly assigned to two groups: the epidural group and the control group. Dogs in the epidural group received epidural anesthesia with 1% mepivacaine. Mepivacaine was administered in an initial dose of $0.2 \text{ ml} \cdot \text{kg}^{-1}$ and one-half of the mepivacaine dose was repeated at hourly intervals. The control group was treated with the same amount of epidural saline. Thirty minutes after the epidural injection, the epinephrine infusion was started. In separate animals, to examine the effect of intravenous mepivacaine on halothane-epinephrine dysrhythmias, mepivacaine was administered at two different doses; $2 \text{ mg} \cdot \text{kg}^{-1}$ intravenously followed by $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (high-dose intravenous group) or $1 \text{ mg} \cdot \text{kg}^{-1}$ intravenously followed by $1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (low-dose intravenous group). In these animals, an epidural catheter was inserted and epidural saline was injected. In addition, we investigated the effect of epidural mepivacaine on halothane-epinephrine dysrhythmias in vagotomized dogs with the same experimental design described above. After bilateral vagotomy performed by sectioning both vagus nerves at the C6 level, epidural catheterization was performed. The epinephrine infusion was started 30 min after the mepivacaine treatment and the dysrhythmogenic threshold was determined. In each experiment, a 5-ml blood sample was collected to allow measurement of plasma concentrations of epinephrine and mepivacaine, when the criterion for DD had been satisfied. We measured the plasma concentration of epinephrine with a fully automated high-performance liquid chromatography (HPLC)-fluorometric system (model HLC-8030 catecholamine analyzer; Tosoh, Tokyo, Japan), using a diphenylethylenediamine condensation method¹⁸; it was found to have a limit of sensitivity of 10 pg/ml for epinephrine and norepinephrine and an inter- and intraassay variation of less than 3%. Plasma concentrations of mepivacaine were measured by a modified version of the method described by Narang *et al.*¹⁹ using ether extraction and HPLC. Each 0.5-ml plasma sample was mixed with 0.5 ml of 0.5 N NaOH, 50 μl of $10 \mu\text{g} \cdot \text{ml}^{-1}$ propitocaine that was used as an internal standard for the correction of assay recovery, and 5 ml of diethyl ether. The mixture was shaken vigorously and then centrifuged at 4,000 rpm for 5 min. The ether layer was removed and evaporated to dryness under nitrogen, followed by reconstruction with 100 μl of 50 mM phosphate. Ten microliters of the sample were injected into a reversed phase ODS column (TSKgel ODS-80TM, 4.6 mm ID \times 150 mm, Tosoh), and the column was eluted with a

Table 1. Baseline Arterial Pressure and Heart Rate after Epidural or Intravenous Mepivacaine (MP) Treatment

| Treatment | N | SAP (mmHg) | DAP (mmHg) | HR (beats/min) |
|-----------------|---|------------|------------|----------------|
| Control | 8 | 124 ± 4.4 | 75 ± 3.1 | 107 ± 6.9 |
| Epidural MP | 8 | 81 ± 3.0* | 38 ± 1.7* | 98 ± 3.4 |
| Low dose iv MP | 7 | 111 ± 4.6 | 64 ± 3.1 | 98 ± 4.6 |
| High dose iv MP | 7 | 111 ± 5.5 | 66 ± 4.6 | 108 ± 5.9 |

Values are mean ± SEM.

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.

* $P < 0.01$ versus control value.

15:85 mixture of CH_3CN and 50 mM KH_2PO_4 , pH 3.0, at a rate of $1 \text{ ml} \cdot \text{min}^{-1}$. The absorbance at 210 nm of the column eluate was monitored with a UV detector (Model UV-8010, Tosoh) equipped with a data processor (Chromatocorder 12, Tosoh). The limit of sensitivity was 10 ng/ml and the inter- and intraassay variations were less than 5%.

Data were expressed as mean ± SEM. The results were analyzed by one-way ANOVA, and comparison between groups was assessed by Scheffe's test. A comparison of two groups was assessed by Student's t test. $P < 0.05$ was considered statistically significant.

Results

The baseline hemodynamic data after the various treatments are presented in table 1. Systolic and diastolic arterial pressures in the epidural mepivacaine group were significantly lower than those in the control group, while heart rate was not different between the treatment groups (table 1). Table 2 shows the basal plasma concentrations of endogenous catecholamines after each type of treatment. The norepinephrine concentration in the epidural group was much lower than

Table 2. Baseline Plasma Concentrations of Endogenous Epinephrine and Norepinephrine during Each Type of Mepivacaine (MP) Treatment

| Treatment | N | Norepinephrine (pg/ml) | Epinephrine (pg/ml) |
|-----------------|---|------------------------|---------------------|
| Control | 8 | 94 ± 19 | 373 ± 120 |
| Epidural MP | 8 | 24 ± 6* | 66 ± 22 |
| Low dose iv MP | 7 | 88 ± 12 | 341 ± 97 |
| High dose iv MP | 7 | 95 ± 16 | 300 ± 86 |

Values are mean ± SEM.

* $P < 0.01$ versus control value.

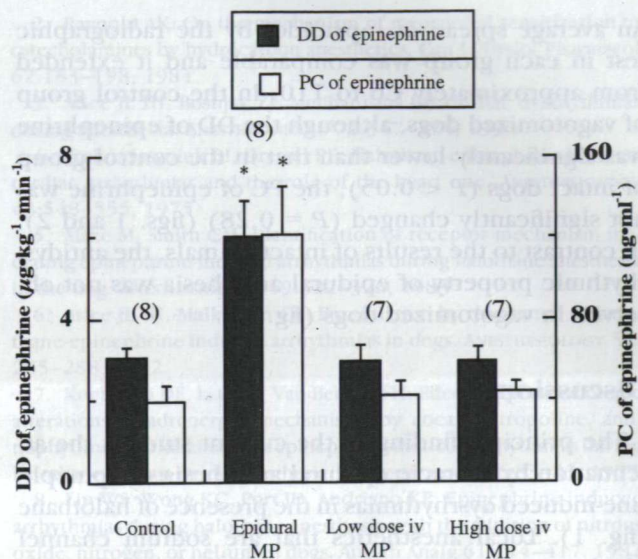


Fig. 1. Dysrhythmogenic doses (DDs) and plasma concentrations (PCs) of epinephrine in the presence of various kinds of mepivacaine treatment during halothane anesthesia in dogs (mean ± SEM; number of observations is shown in parentheses). * $P < 0.05$ compared with the control value.

that in control, while the epinephrine concentration was not significantly different between the groups. The DD and plasma concentration (PC) of epinephrine at the dysrhythmias at various mepivacaine treatments are shown in figure 1. Epidural mepivacaine significantly increased the dysrhythmogenic threshold (DD and PC) of epinephrine, whereas intravenous mepivacaine did not affect the threshold. The hemodynamic data obtained at the dysrhythmias are similar among the treatment groups (table 3). Plasma mepivacaine concentrations during the dysrhythmias in the epidural mepivacaine group, low-dose intravenous group, and high-dose intravenous group were 1.13 ± 0.1 , 1.07 ± 0.09 , and $1.98 \pm 0.22 \mu\text{g} \cdot \text{ml}^{-1}$ (mean ± SEM), respectively.

Table 3. Hemodynamic Data at the Time of Dysrhythmias Observed during Different Mepivacaine (MP) Treatments

| Treatment | N | SAP (mmHg) | DAP (mmHg) | HR (beats/min) |
|-----------------|---|------------|------------|----------------|
| Control | 8 | 236 ± 13.9 | 130 ± 8.4 | 136 ± 23.2 |
| Epidural MP | 8 | 233 ± 4.6 | 121 ± 4.5 | 102 ± 7.5 |
| Low dose iv MP | 7 | 238 ± 9.0 | 131 ± 6.4 | 114 ± 5.6 |
| High dose iv MP | 7 | 218 ± 18.9 | 118 ± 9.8 | 115 ± 12.4 |

Values are mean ± SEM.

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.

An average spread of iopamidol by the radiographic test in each group was comparable and it extended from approximately C6 to T10. In the control group of vagotomized dogs, although the DD of epinephrine was significantly lower than that in the control group of intact dogs ($P < 0.05$), the PC of epinephrine was not significantly changed ($P = 0.28$) (figs. 1 and 2). In contrast to the results of intact animals, the antidysrhythmic property of epidural anesthesia was not observed in vagotomized dogs (fig. 2).

Discussion

The principal finding of the current study is the attenuation by thoracic epidural anesthesia of epinephrine-induced dysrhythmias in the presence of halothane (fig. 1). Local anesthetics that are sodium channel blockers and belong to class I of antidysrhythmic agents may increase the dysrhythmogenic threshold.^{20,21} However, the antidysrhythmic action of mepivacaine in the intravenous group was slight, even when the plasma concentration of mepivacaine was twice that in the epidural group (fig. 1). Thus, circulating mepivacaine after epidural administration did not contribute to the antidysrhythmic benefit of epidural mepivacaine. Furthermore, the beneficial effect of epidural mepivacaine disappeared in vagotomized dogs (fig. 2).

Heretofore, numerous studies have investigated the mechanism involved in halothane-epinephrine dysrhythmias.^{2,3} The central nervous system has been demonstrated to play an important role in the genesis of several types of dysrhythmias^{22,23} and, recently, it has been reported to be the case with halothane-epinephrine dysrhythmias.^{13,14} The detailed mechanism whereby the central nervous system can contribute to the modulation of halothane-epinephrine dysrhythmias is not clear. Waxman *et al.*²⁴ indicated that vagal nerve stimulation increased the dysrhythmogenic threshold of epinephrine in the presence of halothane, and Zink *et al.*⁴ showed that vagal stimulation could abolish the dysrhythmias induced by epinephrine and halothane in the absence of vagal stimulation. Therefore, augmentation of parasympathetic nerve activity is likely to be involved in the central control of dysrhythmias. In comparison, when we compared the DD and PC of epinephrine in control dogs without vagotomy and vagotomized dogs, vagotomy definitely decreased the DD, whereas the PC was not significantly reduced (figs. 1 and 2). The reason for the dissociation between the DD and PC of epinephrine is obscure. One previous

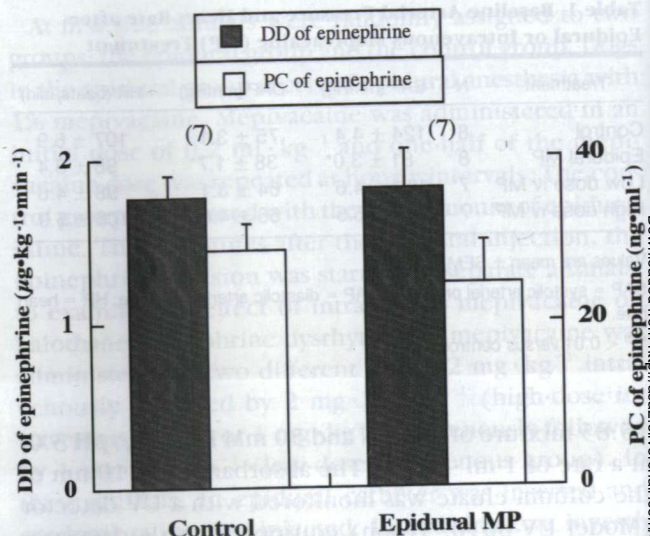


Fig. 2. The effect of epidural mepivacaine administration on the dysrhythmogenic threshold of epinephrine in vagotomized dogs (mean \pm SEM; number of observations is shown in parentheses). DD = dysrhythmogenic dose; PC = plasma concentration.

report documented that the PC is a more reliable indicator than the DD of epinephrine to evaluate the dysrhythmia threshold.²⁵ Thus, we may consider that restoring vagal tone with intact sympathetic activity does not significantly affect the vulnerability to epinephrine-induced dysrhythmias during halothane anesthesia. In the current study, iopamidol injected after the experimental spread epidurally from approximately the C6 level to the T10 level in the epidural group. Considering that the sympathetic nerves to the heart mainly come from ventral T1–T5, sympathetic activity to the heart in epidurally anesthetized animals was significantly attenuated, while parasympathetic activity was not affected. Therefore, the activity in the parasympathetic nerve may be relatively dominant to sympathetic tone after epidural treatment, and this situation is similar to vagal nerve stimulation, which was shown to prevent halothane-epinephrine dysrhythmias.^{4,24} Accordingly, as shown in figure 2, the antidysrhythmic action of epidural mepivacaine was not seen in vagotomized animals, because the vagal dominant condition after thoracic epidural anesthesia was abolished by bilateral vagotomy.

Arterial blood pressure has been suggested to be an important factor in the genesis of halothane-epinephrine dysrhythmias.^{2,3} Recently, Weiskopf *et al.*²⁶ demonstrated that epinephrine-induced dysrhythmias in

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swine developed at lesser blood pressures with halothane than with I-653 or isoflurane, which have little myocardial sensitizing effect, and indicated that anesthetics can alter the relationship between arterial blood pressure and development of dysrhythmias. Epidural anesthesia may induce vasodilation, leading to decreasing arterial blood pressure.²⁷ Actually, the current study showed that thoracic epidural anesthesia by mepivacaine decreased the baseline arterial blood pressure during halothane anesthesia (table 1). In addition, our data show that both systolic and diastolic arterial pressures during dysrhythmias in the epidural group were similar to those in the control group (table 3), although a higher epinephrine infusion was required to induce dysrhythmias in the epidural group (fig. 1). Provided that the relationship between arterial blood pressure and the development of dysrhythmias during halothane anesthesia is unchanged, one may speculate that the hypotensive effect of epidural anesthesia would contribute to its antidysrhythmic action. However, Maze and Smith⁵ demonstrated that blood pressure control by a potent vasodilator, nitroprusside, did not produce the prevention of halothane-epinephrine dysrhythmias. Therefore, it may remain a controversial issue that reducing blood pressure after epidural anesthesia is involved in its antidysrhythmic property.

Epidural anesthesia is widely accepted as a useful clinical technique. A previous clinical trial indicated that epidural anesthesia used in combination with light general anesthesia may lead to decreasing postoperative complications.¹⁵ The current data indicate that thoracic epidural anesthesia attenuates the tendency for intraoperative dysrhythmia induced by intraoperative stress and halogenated anesthetics, and, if applicable to clinical settings, provides further justification for the combined use of epidural anesthesia with general anesthesia.

We conclude that thoracic epidural anesthesia significantly attenuated the myocardial sensitization to the dysrhythmogenic effect of epinephrine by halothane, and bilateral vagotomy abolished this beneficial action.

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