The effects of atropine and methotrimeprazine on the epinephrine-induced arrhythmias in halothane-anesthetized dogs

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Abstract

The effects of atropine and methotrimeprazine on epinephrine-induced ventricular arrhythmias were evaluated in halothane-anesthetized dogs. Ten mixed-breed dogs were assigned to 3 treatments (saline, atropine, and methotrimeprazine) in a randomized complete block design. Anesthesia was induced and maintained with halothane (1.5 minimum alveolar concentration) in oxygen. Controlled ventilation was used throughout to maintain eucapnia. Saline, atropine (0.05 mg/kg, IV) or methotrimeprazine (0.5 mg/kg, IV) were administered and, 5 minutes later the arrhythmogenic dose of epinephrine (ADE) was measured by IV infusion of progressively increasing infusion rates of epinephrine, until the ventricular arrhythmia criterion was met (at least 4 ectopic ventricular contractions (EVCs) during a 15-second period). Data were analyzed using a student’s t-test for ADE values and multivariate profile analysis for heart rate (HR), arterial blood pressure (ABP), and rate pressure product (RPP). The ADE increased in atropine- and methotrimeprazine-treated groups, whereas 1 and 4 animals from these groups did not develop any ventricular arrhythmia, respectively. Epinephrine induced multiformal premature ventricular contractions (PVCs) in the atropine group, whereas ventricular escape beats were observed in the control and methotrimeprazine groups. Heart rate and RPP decreased, and ABP increased at the time of ADE observation in the control group. Epinephrine infusion in the atropine group caused marked increases in HR, ABP, and RPP, which were associated with pulsus alternans in 2 animals. It was concluded that 1) the presence of cholinergic blockade influences the type of ventricular arrhythmia induced by epinephrine; 2) increased ADE values recorded following atropine administration must be cautiously interpreted, since in this situation the PVCs were associated with signs of increased myocardial work and ventricular failure; and 3) the use of a broader arrhythmia criterion (EVCs instead of PVCs) may not allow a direct comparison between ADE values, since it includes ventricular arrhythmias mediated by different mechanisms.

Résumé

Les effets de l’atropine et du methotrimeprazine sur l’arythmie ventriculaire causée par l’épinéphrine furent évalués chez des chiens anesthésiés avec de l’halothane. Dix chiens de race croisée furent répartis selon un modèle expérimental de randomisation complète par bloc à l’un des trois groupes de traitement (saline, atropine ou methotrimeprazine). L’induction et le maintien de l’anesthésie se fit avec de l’halothane (1,5 MAC) mélangé à de l’oxygène. Une ventilation contrôlée fut utilisée afin de maintenir l’eucapnie. Cinq minutes après l’administration par voie intraveineuse (iv) de saline, d’atropine (0,05 mg/kg) ou de methotrimeprazine (0,5 mg/kg), la dose arythmogène d’épinéphrine (DAE) fut déterminée par administration iv d’épinéphrine à des taux d’infusion augmentant de manière progressive, jusqu’à ce que le critère d’arythmie ventriculaire d’au moins quatre contractions ventriculaires ectopiques (CVE) durant un intervalle de 15 secondes fut atteint. Les valeurs de DAE furent analysées à l’aide du test de t de Student alors que les valeurs de rythme cardiaque (RC), de pression artérielle (PA) et du produit rythme pression (PRP) le furent à l’aide d’une analyse multivariée. Une augmentation de la DAE fut observée chez des animaux des groupes ayant reçu de l’atropine et du methotrimeprazine, où un et quatre animaux, respectivement, ne développent aucune arythmie. L’épinéphrine entraînait l’apparition de contractions ventriculaires prématurées (CVP) de formes multiples dans le groupe d’animaux recevant de l’atropine, alors que des battements ventriculaires échappés furent observés dans les groupes d’animaux témoins et ayant reçu du methotrimeprazine. Dans le groupe témoin, le RC et le PRP diminuèrent alors que la PA augmenta au moment où fut observée la DAE. Une infusion d’épinéphrine chez les animaux du groupe recevant de l’atropine entraînait une augmentation marquée du RC, de la PA et du PRP, associés au pulsus alternans chez deux animaux. Les conclusions sont : 1-la présence de bloqueurs cholinoergiques influence le type d’arythmie ventriculaire produite par l’épinéphrine; 2-l’augmentation des valeurs de DAE observées suite à l’administration d’atropine doit être interprétée avec précaution étant donné que les CVP étaient associées à des signes d’augmentation du travail du myocarde et d’une défaillance ventriculaire; 3-l’utilisation d’un critère plus large d’évaluation de l’arythmie (CVE plutôt que CVP) peut empêcher une comparaison directe des valeurs de DAE étant donné qu’il inclut des arythmies ventriculaires causées par différents mécanismes.

(Traduit par docteur Serge Messier)
Introduction

The occurrence of arrhythmias has been a major concern during the perioperative period. Even though retrospective studies about the incidence of arrhythmias during anesthesia are lacking in veterinary medicine, the incidence of cardiac arrhythmias during the transoperative period was reported to range between 20 to 50% in human patients (1). Among the currently used inhalant anesthetics, halothane is traditionally regarded as pro-arrhythmic, predisposing the heart to ventricular arrhythmias (2-4). Experimental studies have proposed that ventricular arrhythmias associated with halothane use are due to a reentrant mechanism even though this inhalant may suppress certain types of ventricular arrhythmias caused by increased automaticity (5-7).

The capacity of anesthetic drugs to induce ventricular arrhythmias can be assessed using the arrhythmogenic dose of epinephrine (ADE) model (3). According to this model, epinephrine is infused until obtaining a pre-defined criterion of ventricular arrhythmia. The arrhythmia criterion is particularly germane, since different criteria may prevent direct comparison between studies (8). In this regard, most studies have defined ADE as the total dose of epinephrine infused until the occurrence of at least 4 premature ventricular contractions (PVCs) over a 15-second period (4,8,9), whereas other reports have defined their arrhythmia end point as ectopic ventricular contractions (EVCs), a criterion which includes not only PVCs but also other types of ventricular arrhythmias (10,11,18). Because the total dose of epinephrine required to produce PVCs is much less for halothane than for isoflurane and other inhalation anesthetics, this drug is considered more arrhythmogenic (2-4).

Although the mechanism of myocardial sensitization to epinephrine by halothane remains unclear, there is evidence that the α1 adrenoceptors play an important role in the arrhythmogenesis during halothane anesthesia since the use of phenothiazines and other drugs that block this receptor subtype counteract ventricular arrhythmias (12-15). Apparent controversy exists regarding the influence of the parasympathetic tone on the arrhythmogenic activity of epinephrine (5,16-18). Studies have shown that vagotomy decreases ADE in dogs under thiamyl-halothane anesthesia (17), whereas other reports have shown that glycopyrrolate-induced vagal blockade increases the ADE during halothane and isoflurane anesthesia (18). Although the difference among these studies may be at least in part attributable to differences in methodology, the role of parasympathetic tone in the arrhythmogenesis during halothane anesthesia remains controversial. Therefore, this study aimed to evaluate the effect of cholinergic blockade produced by atropine sulphate on epinephrine-induced arrhythmias in dogs anesthetized with halothane. Additionally, the potential antiarrrhythmic effects of methotrimeprazine were investigated.

Methotrimeprazine is a phenothiazine derivative that has become popular as a premedication agent for small animals in Brazil (19). This phenothiazine produces dose-dependent sedation and has been sporadically used in Great Britain in association with the opioid, etorphine, to produce neuroleptanalgesia for small animals (20). Although the drugs of this class are not considered analgesics, methotrimeprazine has been occasionally used as an analgesic adjuvant in humans (21,22). Since the phenothiazine derivative, acepromazine, has been shown to protect the heart against epinephrine-induced ventricular arrhythmias (14,15), we hypothesized that methotrimeprazine would have a similar effect.

Materials and methods

This study was approved by the University Research Animal Committee. Ten healthy, adult mixed-breed dogs, 7 female and 3 male, weighing 12.1 ± 1.5 kg were assigned in a randomized complete block design to 3 treatments (saline, atropine, and methotrimeprazine), with a minimum interval of 15 d between each treatment.

Experimental protocol

The anesthetic procedures were carried out in the morning at a fixed time. Food, but not water, was withheld for 12 h prior to anesthesia. A complete physical examination, electrocardiogram, arterial blood gas analysis, packed cell volume, and total plasma protein measurements (Statprofile 5; Nova Biomedical, Waltham, Massachusetts, USA) were performed on each animal in order to certify that physiological parameters were within the normal range. Anesthesia was induced by a facemask attached to a semi-closed anesthetic system (Samurai III; K. Takaoka, São Paulo, São Paulo, Brazil). The vaporizer was adjusted to deliver 5% of halothane (Halotan; Hoechst, Suzano, São Paulo, Brazil) in oxygen (4 L/min). After the loss of laryngeal reflexes, each animal was intubated, the oxygen flow rate reduced to 1 L/min and end-tidal halothane concentrations were maintained at 1.5 minimum alveolar concentration (MAC) (1.3% end-tidal). End-tidal concentration was monitored with an infrared gas analyzer, calibrated before each experiment (Multigas Analyzer; Space Labs Medical, Redmond, Washington, USA). Gas samples for end-tidal measurements were collected near the carina through a polyethylene cannula inserted into the endotracheal tube. Controlled ventilation was used in order to maintain end-tidal CO2 (EtCO2) close to 35 mmHg. Blood gas samples were collected approximately 30 min after endotracheal intubation to certify that ventilation was adequate, with PaCO2 values close to 35 to 40 mmHg. Esophageal temperature was maintained above 36.5°C, using a radiant heater. The femoral artery was catheterized using an 18-gauge catheter (Insyte; Becton-Dickinson, Sandy, Utah, USA), which was connected to a pressure transducer (Model PX260; Baxter Healthcare Corp, Irvine, California, USA) for measurement of systolic, diastolic, and mean arterial blood pressures (SAP, DAP, and MAP). Lead II electrocardiogram (ECG) was monitored using needle electrodes. Expanded ECG and arterial blood pressure tracings were recorded throughout the procedure for ADE measurement (PC Scout Monitor; Space Labs Medical, Redmond, Washington, USA).

ADE measurement

Approximately 30 min after endotracheal intubation, placebo (5 mL of saline), atropine (Sulfato de Atropina, 0.5 mg; Ariston, São Paulo, São Paulo, Brazil) (0.05 mg/kg) or methotrimeprazine (Neozine, 25 mg; Roche, São Paulo, São Paulo, Brazil) (0.5 mg/kg) were administered through a 20-gauge intravenous catheter placed in the cephalic vein (Insyte; Becton-Dickinson). The dose of atropine...
used in this study is close to the clinically recommended dose for dogs (0.02 to 0.04 mg/kg), whereas the dose of methotrimeprazine was based on the recommended doses to produce sedation (0.5 to 1.0 mg/kg) (19). Five minutes after drug injection, ADE measurement was performed according to a modification of the method described by Pace et al (9). Epinephrine (Adrenalina, 1/1000; Ariston) was freshly diluted in saline solution (12 μg/mL) and administered through the cephalic vein catheter at progressively increasing infusion rates (1.25, 2.5, and 5.0 μg/kg/min) using a peristaltic infusion pump (FARS 600; Lifemed, São Paulo, São Paulo, Brazil) until the observation of the ADE criterion. The accuracy of the infusion pump was previously checked through an infusion device analyzer (IDA & PLUS; Bio-Tek Instruments, Vermont, USA). Each infusion rate was maintained for 3 min and 10-minute intervals were allowed between infusions. The ADE criterion was considered fulfilled when at least 4 ectopic ventricular contractions (EVCs) occurred during a 15-second period while epinephrine was infused or within 1 min after the end of each infusion rate. If the ADE criterion was met, the current infusion rate was maintained until its end-point (3 min) and the ECG and ABP recordings were kept until 1 min after the end of the infusion. The ADE was calculated according to the formula:

\[
\text{ADE (μg/kg)} = \text{infusion rate (μg/kg/min)} \times \text{time to first EVC that met the ADE criterion (min)}
\]

Table I. Incidence (number of animals) of supraventricular arrhythmias observed during epinephrine infusion for ADE measurement in the control, atropine and methotrimeprazine-treated groups

<table>
<thead>
<tr>
<th>Supraventricular arrhythmia</th>
<th>Control ((n = 10))</th>
<th>Atropine ((n = 10))</th>
<th>Methotrimeprazine ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinus bradycardia/bradyarrhythmia (HR &lt; 60 beats/min)</td>
<td>10</td>
<td>—</td>
<td>7</td>
</tr>
<tr>
<td>2nd degree AV heart block</td>
<td>5</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>AV dissociation</td>
<td>1</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Wandering pacemaker</td>
<td>—</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Junctional rhythm</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Sinus tachycardia (HR &gt; 160 beats/min)</td>
<td>—</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Supraventricular tachycardia (HR &gt; 160 beats/min)</td>
<td>—</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Atrial premature contraction</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Table II. Incidence (number of animals) of ventricular arrhythmias observed during epinephrine infusion for ADE measurement in the control, atropine and methotrimeprazine-treated groups

<table>
<thead>
<tr>
<th>Ventricular arrhythmia</th>
<th>Control ((n = 10))</th>
<th>Atropine ((n = 10))</th>
<th>Methotrimeprazine ((n = 10))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular escape beats</td>
<td>10</td>
<td>—</td>
<td>6</td>
</tr>
<tr>
<td>Ventricular escape rhythm (associated with 3rd degree AV heart block)</td>
<td>10</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Multiform ventricular premature complexes</td>
<td>—</td>
<td>6</td>
<td>—</td>
</tr>
<tr>
<td>Ventricular bigeminy</td>
<td>—</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Multiform ventricular tachycardia</td>
<td>—</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Heart rate (HR), SAP, DAP, MAP, and rate pressure product \((RPP = SAP \times HR)\) values were obtained before the infusion rate at which the ADE criterion was met and at the time of ADE observation. The ECG and arterial blood pressure recordings were subsequently analyzed for possible changes during epinephrine infusion.

**Statistical analysis**

Mean ADE values and mean infusion rate at which ADE was observed were compared using a student’s \(t\)-test considering unequal variances. Multivariate profile analysis was used for comparison of HR, arterial blood pressure and RPP values obtained within each group and between groups. A \(P\) value of < 0.05 was considered significant.

**Results**

**Electrocardiogram and blood pressure recordings**

Sinus bradycardia and/or bradyarrhythmia (HR < 60 bpm) were often associated with 2nd degree atrioventricular (AV) heart blocks in all control animals during epinephrine infusion (Table 1 and Figure 1A). One animal from this group also presented AV dissociation. The ADE criterion was met in all animals from this group.
and was characterized as ventricular escape complexes and ventricular escape rhythm associated with 3rd degree AV heart block (Table 2 and Figure 1B).

At the beginning of epinephrine infusion in the atropine-treated group, sinus tachycardia was observed, which in some cases developed into supraventricular tachycardia (Table 1). In 2 animals from this group, supraventricular tachycardia was associated with pulsus alternans (Figure 1C). During epinephrine infusion in the atropine-treated group, atrial premature contractions (Table 1 and Figure 1D), wandering pacemaker, junctional rhythm, and 2nd degree AV heart block were also observed (Table 1). Following atropine administration, 9 animals met the ADE criteria and 1 did not develop any ventricular arrhythmia at the highest infusion rate. The ventricular arrhythmias in this group were characterized as multiform PVCs, ventricular bigeminy (Figure 1E), and paroxysmal multiform ventricular tachycardia (Table 2 and Figure 1F).

In the methotrimeprazine-treated group a high incidence of bradycardia and other supraventricular arrhythmias was observed (Table 1 and Figure 1G). Ventricular escape beats and/or

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**Figure 1.** Simultaneous electrocardiographic and blood pressure recordings. A and B (control): A) Bradyarrhythmia and 2nd degree AV block (arrows), B) Ventricular escape rhythm (arrows) and 3rd degree AV block; C to F (atropine): C) Supraventricular tachycardia associated with pulsus alternans (arrows), D) Atrial premature contraction (arrow), E) Ventricular bigeminy (arrows), F) Multiform ventricular tachycardia (arrow); G and H (methotrimeprazine): G) Second degree AV block (arrow), H) Ventricular escape rhythm (arrows) and 3rd degree AV block.
ventricular escape rhythm were observed in 6 animals from this group (Table 2 and Figure 1H). Ventricular arrhythmias did not develop in 4 animals from this group even at epinephrine’s highest infusion rate.

**ADE measurement**

Only the dogs that reached the ADE criterion were included in the statistical analysis, yielding 10, 9, and 6 animals in the control, atropine, and methotrimeprazine groups, respectively. In the control group, ADE was 2.69 ± 0.81 μg/kg, significantly lower than the 4.43 ± 1.89 μg/kg and 6.45 ± 1.93 μg/kg in the atropine and methotrimeprazine groups, respectively (Figure 2). The infusion rate at which ADE was observed was 1.5 ± 0.52 μg/kg/min in the control and 2.2 ± 1.21 μg/kg/min in the atropine group, increasing only following the use of methotrimeprazine (3.5 ± 1.36 μg/kg/min) (Figure 2).

### Cardiovascular parameters

In the control group (n = 10), HR and RPP decreased, whereas SAP, DAP, and MAP increased at the time of ADE observation. In the atropine-treated animals (n = 9), HR, SAP, DAP, MAP, and RPP markedly increased during ADE observation. HR decreased and SAP increased at the time of ADE observation in the methotrimeprazine group (n = 6) (Table 3).

When comparisons were made between groups, HR, arterial blood pressure and RPP values were markedly higher in the atropine group at the time of ADE observation, whereas at the same time there was no difference between the methotrimeprazine and control groups, except for DAP, which was lower in the methotrimeprazine group.

### Discussion

ADE values may present considerable variability in the studies approaching epinephrine arrhythmogenicity during halothane anesthesia (4). Some of this variability may be attributed to differences in the protocols for ADE measurement: whereas some studies employ progressively increasing intravenous boluses in order to cause ventricular fibrillation (14,16), other reports administer epinephrine at progressively increasing infusions rates (4,8–12,15,

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Table III. Cardiovascular parameters observed before epinephrine infusion and at the time of ADE observation in the control (n = 10), atropine (n = 9), and methotrimeprazine-treated (n = 6) groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Atropine</th>
<th>Methotrimeprazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>73 ± 11&lt;sup&gt;A&lt;/sup&gt;</td>
<td>113 ± 23&lt;sup&gt;B&lt;/sup&gt;</td>
<td>93 ± 17&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>SAP (mmHg)</td>
<td>Control</td>
<td>93 ± 6&lt;sup&gt;A&lt;/sup&gt;</td>
<td>107 ± 9&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>DAP (mmHg)</td>
<td>Control</td>
<td>51 ± 5&lt;sup&gt;B&lt;/sup&gt;</td>
<td>68 ± 9&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>Control</td>
<td>64 ± 5&lt;sup&gt;B&lt;/sup&gt;</td>
<td>81 ± 9&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
<tr>
<td>RPP (units)</td>
<td>Control</td>
<td>6836 ± 1272&lt;sup&gt;B&lt;/sup&gt;</td>
<td>12 228 ± 2928&lt;sup&gt;A&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* Values are presented as mean ± SD
Rows: means followed by different capital letters are significantly different (P < 0.05)
Columns: means followed by different lowercase letters are significantly different (P < 0.05)
17,18,23). Regarding the latter method, the inter-infusion interval is particularly important, since it may result in different ADE values (23). Typically 10 min are allowed between each infusion and, even though this interval allows the return of arterial blood pressure to its pre-infusion values, it may not result in absolute equivalency of all hemodynamic parameters, since cardiac output, central venous pressure and heart rate may still be increased at the end of this period due to the residual effects epinephrine from the previous infusion (23). Since our study used 10-minute intervals between infusions, the hypothesis that background epinephrine plasma levels from the previous infusion may have influenced our ADE measurements cannot be discarded. According to our results, the mean ADE values observed for halothane alone (2.69 ± 0.81 μg/kg) were comparable to ADE values found by Woehlk et al (23), who reported ADE values of 2.54 ± 0.81 μg/kg (mean ± SD) infusing epi-

nephrine, with variable inter-infusion intervals (15 to 60 min), in order to allow hemodynamic equivalency before the start of each infusion rate. On the other hand, our ADE values tended to be lower than those reported by another laboratory (4,8,15). A possible explanation for this difference is the smaller inter-infusion interval used in our study (10 min versus 20 min), which may have influenced the pharmacokinetics of the epinephrine. However, it is more likely that this difference is related to the broader ADE criterion used in our study, which considered EVCs instead of PVCs as end point. This ADE criterion, differently from the definition used by other studies, encompasses all types of ventricular ectopy, including ventricular escape beats and premature ventricular con-

tractions. Therefore, the use of a broader ventricular arrhythmia criterion, coupled with the fact that the ventricular escape beats seem to antecede the PVCs during low epinephrine infusions rates in halothane-anesthetized dogs (8), may explain why our ADE values tended to be relatively lower (4,8,15). On the other hand, our results are comparable with other reports using a similar ADE criterion, which also resulted in a tendency for lower ADE values in the absence of cholinergic blockade (10,11,18). Even though we have chosen to use EVCs as our arrhythmia criterion, it should be considered that a more valid comparison between groups could be obtained if a more specific end-point (i.e. PVCs) had been selected.

The hemodynamic effects of epinephrine are complex and depend on the total dose and infusion rate (24). When given intravenously as a bolus, it increases arterial blood pressure due to a positive inotropic effect, increased heart rate, and peripheral vascular resistance. Heart rate may decrease at the time of peak rise in blood pressure, as a result of baroreceptor stimulation (24,25). In the control group, epinephrine administered by continuous infusion resulted in bradycardia, which was associated with increased arterial pressure, suggesting that in this case epinephrine resulted in reflex bradycardia.

It is well known that a baroreceptor-mediated increase in vagal tone decreases the rate of sinoatrial (SA) node depolarization and delays or completely blocks AV conduction, resulting in brady-

arrhythmias and AV heart blocks (24,25). Increased vagal activity decreases the automaticity of SA and AV nodal automaticity through the release of acetylcholine (ACH) from postganglionic fibers, which stimulates the myocardial muscarinic receptors (26,27). These receptors couple with the G protein complex, inducing increased outward K⁺ conductance and, possibly, decreased inward Ca⁺ current, and the net effect of ACh-induced changes in ionic transport across the myocardial membrane is hyperpolarization, which affects pacemaker activity by decreasing the rate of sponta-

neous SA node firing (26,27). Nonetheless, it must be considered also that halothane may directly decrease heart rate and depress AV con-

duction. In vitro studies have shown that halothane may reduce the rate of spontaneous discharge of SA node in guinea pigs (28), whereas in halothane or enflurane-anesthetized dogs, AV conduction time may be prolonged by 20% (29).

In the control group, depression of SA node automaticity was fol-

lowed by the emergence of ectopic pacemakers in the ventricles that were characterized as ventricular escape complexes. These ven-

tricular arrhythmias were probably induced by a baroreceptor-

mediated increase in vagal tone leading to bradycardia (24,30,31).

The findings of the present report are supported by the studies of Lemke et al (10,11,18), who stated that the ventricular complexes pro-

duced by continuous infusion of epinephrine during halothane and isoflurane anesthesia were probably ventricular escape complexes.

Normal automaticity is a primary property of the SA node, cer-

tain areas of the atrial tissue, the AV junctional region and the His-Purkinje system (30). The SA node suppresses the activity of other latent pacemakers through an override suppression mech-

anism (30). Even though studies have suggested that halothane induces ventricular arrhythmias through a reentry mechanism (5,6), our results suggest that the ventricular escape complexes were associated with abnormal automaticity. In this case, the bradycardia and AV blocks observed in the controls denoted sup-

pression of automaticity in the atrial tissue and AV junction, which probably allowed the emergence of an abnormal automaticity focus in the ventriculum (30). This phenomenon is analogous to cer-

tain pathological conditions, such as the sick sinus syndrome, where the primary pacemaker (SA node) and even the subsidiary atrial pacemakers and AV junction may present impaired capacity to generate the electrical impulses, leading to the emergence of an ectopic focus in the ventriculum (30).

Epinephrine infusion in atropine-treated animals resulted in tachycardia and severe hypertension. These findings reinforce the thesis of baroreceptor-mediated increase in vagal tone in the controls, since the cholinergic blockade inhibited the bradycardia and AV blocks and resulted in marked hypertension. In the atropine-treated group, vagal blockade evidenced the stimulating effect of epi-

nephrine on the SA node, resulting in marked tachycardia. Additionally, the high incidence of supraventricular arrhythmias in this group indicates the loss of dominance of the SA pacemaker and the emergence of subsidiary pacemakers within the atrial tissue. Since the vagal activity is important for suppressing spontaneous electrical activity in atrial myocardial cells, the use of an anti-

cholinergic drug may have allowed the emergence of atrial ectopic foci in this group.

Epinephrine infusion in the atropine-treated group resulted in ven-

tricular bigeminy, multiform ventricular premature complexes and multiform ventricular tachycardia. The etiologic factors of this type of ventricular arrhythmia are distinct from those involved in the genesis of ventricular escape beats observed in the control.
group (30,31). Myocardial hypoxia, resulting from a mismatch between tissue oxygen consumption and supply may cause arrhythmia during anesthesia (32). In the dog, heart rates above 200 beats/min may significantly reduce myocardial oxygen supply because of decreased diastolic filling time and reduced coronary artery perfusion (33,34). Additionally, increased myocardial oxygen consumption may develop as a result of excessively increased afterload (i.e., hypertension). It is likely that decreased myocardial oxygen supply associated with increased myocardial oxygen demand were induced by the marked tachycardia and hypertension. A marked increase in myocardial oxygen consumption was also suggested by the RPP values, which were substantially higher than those reported for anesthetized human patients with coronary artery disease, where a RPP greater than 12 000 resulted in the development of ischemic electrocardiographic changes (35). It was likely that myocardial hypoxia and excessive sympathetic stimulation may have contributed to the emergence of premature ventricular complexes in the atropine-treated group.

Atropine abolished the escape beats observed in the control group and increased ADE. This effect may be explained by the marked increase in SA node automaticity and other latent supraventricular pacemakers resulting in overdrive suppression of ventricular ectopic foci (30). However, the underlying cellular mechanism mediating arrhythmias in the atropine-treated group remains obscure. Assuming that the mechanism mediating the epinephrine-induced arrhythmias in the presence of vagal blockade is related to myocardial hypoxia, one may correlate our results with experimental studies inducing myocardial infarction by ligating the left anterior descending coronary artery in halothane-anesthetized dogs (7). According to these reports, depending on the stage of infarction, either abnormal automaticity or reentrant mechanisms may be responsible for the ventricular arrhythmias (7).

Pulsus alternans is an abnormal finding related to changes in the stroke volume induced by severe ventricular failure (36). This abnormality, characterized by a regular alternation of the amplitude of the blood pressure waveform associated with heart beats occurring at regular intervals, has been reported during halothane anesthesia in dogs and its substitution by isoflurane was effective in treating this condition (37). In the present study, the observation of pulsus alternans in 2 atropine-treated dogs was probably caused by increased myocardial work and decreased diastolic filling time, which may have resulted in left ventricular dysfunction (36). In the atropine-treated group, the analysis of blood pressure waveforms also revealed that the some PVCs did not result in a pressure waveform. This phenomenon is explained by the insufficient ventricular filling time caused by the premature beat. The same phenomenon occurred during the observation of atrial premature depolarizations in this group. On the other hand, ventricular escape complexes observed in the control group always resulted in effective ventricular systole (pressure waveform). In this case, prolonged periods of sinus arrest and marked bradycardia caused the ventricular escape beats, which is a protective mechanism to maintain cardiac output (31,33).

Increased parasympathetic tone may protect against ventricular arrhythmias (5,16,38,39). Studies have shown that vagal stimulation abolishes ventricular bigeminy and decreases the likelihood of epinephrine-induced ventricular fibrillation in halothane-anesthetized dogs (5,16). Additionally, the use of drugs that increase the vagal tone, such as morphine and the α1 agonist, dexmedetomidine, reduces the incidence of ventricular bigeminy and fibrillation (38,39). Even though other α1 agonist drugs, such as xylazine and medetomidine, also cause a similar increase in vagal tone, studies have been unable to show a significant change in ADE values following the use of these drugs during halothane and isoflurane anesthesia (8,10,11), whereas early studies reported that xylazine may increase the likelihood of ventricular fibrillation (14). The protective effect of increased vagal activity is also suggested by studies showing that epinephrine and other catecholamines have their arrhythmogenic effects enhanced by vagotomy in dogs anesthetized with thiamylal and halothane (17). In contrast, the results obtained in atropine-treated dogs would suggest that vagal blockade somehow protects the myocardium against ventricular arrhythmias because a higher ADE was recorded. This hypothesis is further supported because one animal from this group did not develop any ventricular arrhythmia. However, direct ADE comparison between groups is not appropriate since the ventricular arrhythmias observed in the controls (ventricular escape beats) and atropine-treated dogs (PVCs) were likely to be induced by different mechanisms. Additionally, it should be appreciated that the ventricular arrhythmias observed in atropine-treated dogs carries an increased risk of ventricular fibrillation, a terminal event that precedes asystole (31,33).

In the methotrimeprazine-treated group a high incidence of bradycardia and 2nd degree AV blocks occurred during epinephrine infusion. Similarly to the control group, the ADE criterion was met by the observation of ventricular escape beats rather than PVCs. The anti-arrhythmogenic action of methotrimeprazine was suggested by the increase in ADE values, as well as by the absence of ventricular arrhythmias at the maximum dose of epinephrine used in 4 animals. However, we were unable to show a protective effect against PVCs and it should be considered that, had the epinephrine infusion been indefinitely increased, PVCs were likely to occur (8).

Assuming that the ventricular escape beats observed in the controls and methotrimeprazine-treated dogs were induced by similar mechanisms, one may hypothesize that there may be a correlation between methotrimeprazine-induced ADE increase and its anti-hypertensive effects. Evidence for this correlation arises from the similarity of arterial pressure at the moment when the ADE criterion was met for both control and methotrimeprazine groups, even though epinephrine’s infusion rate was substantially higher in the phenothiazine-treated group. Nonetheless, studies have shown that ventricular bygeminism may be induced by the artificial elevation of arterial blood pressure during the infusion of a sub-arrhythmogenic dose of epinephrine and a sudden reduction of blood pressure results in the return to the sinus rhythm (5). This hypothesis is not supported by other studies, reporting that the anti-hypertensive effects of sodium nitroprusside did not block epinephrine-induced ventricular arrhythmias (12). More specifically, the anti-arrhythmogenic action of phenothiazines has been attributed to their capacity of blocking α1 adrenergic receptors (4). Even though there is a greater density of β adrenoreceptors in canine myocardial cell membranes (40), there is evidence that these
receptors do not play a primary role in the myocardial sensitization to catecholamines during halothane anesthesia (12). Evidence for the participation of α₁ adrenoceptors in the genesis of ventricular arrhythmias has been provided by studies using α₁ blocking agents, such as prazosin, which were shown to inhibit epinephrine-induced arrhythmias (12).

It is concluded from the results of this study that the presence or absence of cholinergic blockade influences the ventricular arrhythmia formation induced by epinephrine. The increased ADE value recorded following atropine administration in halothane-anesthetized dogs must be cautiously interpreted, since in this case, the ventricular arrhythmias resulted in pulse deficits and were more likely associated with myocardial hypoxia. Even though methotrimeprazine inhibited the ventricular escape beats, its protective effect against PVCs still remains to be shown. Finally, when evaluating ADE data it is important to appreciate that different mechanisms may originate the ventricular arrhythmias and a more specific ADE criterion should be favored in order to allow a direct comparison of ADE values obtained between groups.

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