Aminophylline and beta-adrenergic agonists are widely used in the treatment of obstructive lung diseases. It has been suggested that combined aminophylline and beta-agonist therapy may promote the development of atrial and ventricular arrhythmias. The effects of these agents in combination on myocardial conduction and tissue refractoriness have not been documented. We evaluated the electrophysiologic effects of intravenous aminophylline and inhaled metaproterenol on canine myocardium. Aminophylline produced significant decreases from baseline in the AH interval (85 ± 6.5 [SD] to 63 ± 4.1 ms [p<0.02]), Wenckebach cycle length (WCL) (226 ± 8.7 to 182 ± 5.8 ms [p<0.02]), and ventricular effective refractory period (VERP) (166 ± 6.0 to 145 ± 4.9 ms [p<0.01]). Metaproterenol produced similar results, except metaproterenol significantly decreased the atrial effective refractory period (AERP) from 152 ± 6.6 to 130 ± 3.2 ms (p<0.02), an effect not seen with aminophylline alone. Metaproterenol also produced significantly greater reductions in AH interval and WCL, as well as a greater increase in heart rate than aminophylline did. When compared with aminophylline alone, combined metaproterenol and aminophylline therapy produced significantly greater reductions in the AH interval (63 ± 4.1 versus 48 ± 1.3 ms for combined therapy [p<0.01]), HV interval (32 ± 1.2 versus 28 ± 2.0 ms for combined therapy [p<0.02]), WCL (182 ± 5.8 versus 150 ± 7.1 ms for combined therapy [p<0.02]), and VERP (145 ± 4.9 versus 132 ± 2.0 ms for combined therapy [p<0.02]). We conclude that both aminophylline and metaproterenol significantly enhance AV nodal and His-Purkinje conduction. Metaproterenol produced significant changes in both atrial and ventricular refractoriness, while aminophylline affected only ventricular tissue refractoriness. Metaproterenol produced significantly greater changes than aminophylline alone, and inhaled metaproterenol combined with intravenous aminophylline produced greater changes in AV nodal and His-Purkinje conduction and ventricular refractoriness than did aminophylline alone in a canine model.

(Chest 1992; 100:232-38)

AERP = atrial effective refractory period; AV = atrioventricular; AVERP = atrioventricular nodal effective refractory period; COPD = chronic obstructive pulmonary disease; MAP = mean arterial pressure; VERP = ventricular effective refractory period; WCL = Wenckebach cycle length

Theophylline and beta-adrenergic agonists, such as metaproterenol, are widely used in the treatment of chronic obstructive pulmonary disease (COPD) and asthma. Inhaled beta-adrenergic agonists are often regarded as first-line therapy in COPD and asthma, with aminophylline preparations added in selected patients. Although aminophylline preparations are regarded as second-line therapy in the treatment of asthma and COPD, they are widely used in the United States.1

Despite the widespread use of aminophylline and beta-adrenergic agonists, the safety of combined therapy has been questioned. Wilson et al2 suggested that combined therapy was responsible for an increased mortality among asthmatic patients in New Zealand. Aminophylline has a narrow therapeutic index, and atrial and ventricular arrhythmias are significant clinical problems associated with aminophylline therapy.3-5 Several clinical studies have attempted to evaluate the combined use of aminophylline and beta-adrenergic agonists in promoting arrhythmias with conflicting results.6-13 Although the cardiotoxicity of aminophylline is well established, there are few reports of the effects of aminophylline on intracardiac conduction.14-15 Bittar et al16 reported accelerated intracardiac conduction in dogs given a toxic dose of aminophylline, and were able to induce ventricular fibrillation in three of eight dogs so treated.

No study to date has evaluated the effects of an inhaled beta-adrenergic agonist on intracardiac conduction and tissue refractoriness, and we are unaware of any electrophysiologic study of the combined effects of intravenous aminophylline and an inhaled beta-
adrenergic agonist on intracardiac conduction time and atrial and ventricular refractoriness. Understanding the physiologic effects of aminophylline and beta-adrenergic agonists on the conducting system may provide important insight into the potential toxicities of these agents in patients.

In this study, we characterized the changes in intracardiac conduction and atrial and ventricular refractoriness in response to aminophylline, metaproterenol, and combined aminophylline and metaproterenol in healthy dogs. We hypothesized that combined intravenous aminophylline and inhaled metaproterenol would accelerate intracardiac conduction and alter tissue refractoriness to a greater extent than would either agent used alone. Esmolol was used in aminophylline-treated animals to evaluate the role of the beta-adrenergic system in mediating the electrophysiologic effects of aminophylline.

**METHODS**

**Subjects**

Five mongrel dogs, weighing 25 to 40 kg, were the subjects of this study. All animals were quarantined for two weeks and were disease free prior to study. All animals were prescreened for heartworm and had normal chest radiographs prior to right heart catheterization. Each dog underwent percutaneous right heart catheterization for electrophysiologic studies on two different study days separated by at least one week, to allow for a drug-washout period. The dogs were euthanized after day 2, and an autopsy was performed to exclude heartworm infection. This protocol was approved by our institutional animal use and care committee.

**Animal Preparation**

Anesthesia was induced with intravenous sodium pentothal (20 mg/kg of body weight). All dogs were intubated, and anesthesia was maintained with 1.5 percent isoflurane delivered via an Ohio anesthesia ventilator (Ohio). Oxygen at 3 L/min was delivered to all dogs to prevent hypoxia. A femoral arterial line was placed, and blood gases were monitored frequently to ensure adequate ventilation. A central venous line was placed via the femoral vein. The electrocardiogram was continuously monitored. Lactated Ringer's solution was given as a maintenance fluid, and the flow rate was adjusted according to the blood pressure, central venous pressure, and urine output. Core temperature was monitored with an esophageal probe and was maintained with an external warming blanket.

Three 5-F introducer sheaths were percutaneously placed into the femoral veins. Three 5-F quadripolar pacing catheters (USCI, Billerica, Mass) were advanced through these sheaths and, under fluoroscopic guidance, were placed at the high right atrium, right ventricular apex, and low right atrial septum for measurement of a His-bundle electrogram.

**Electrophysiologic Pacing Protocol**

Baseline cycle lengths were first obtained and included the PA, AH, and HV intervals. Wenckebach cycle length (WCL) was determined by atrial pacing. The atrial effective refractory period (AERP) and atrioventricular (AV) nodal effective refractory period (AVERP) were then determined with single atrial extrastimuli at a driving cycle length of 240 ms. Our ability to determine the actual AVERP was limited by atrial tissue refractoriness; therefore, the WCL became an indirect reflection of AV nodal refractoriness. The ventricular effective refractory period (VERP) was then measured by using single ventricular extrastimuli at a driving cycle length of 240 ms. This protocol was used for baseline studies on each day and after each experimental manipulation.

**Day 1 Studies:** Before baseline electrophysiologic data were obtained, all animals were stabilized hemodynamically, and serum electrolytes and arterial blood gases were measured. A baseline electrophysiologic pacing study (B) was performed. A loading dose of aminophylline (10 mg/kg) was administered to each dog over 30 minutes, followed by a maintenance infusion of 1 mg/kg/h. Prior to obtaining the postaminophylline pacing study (AM), serum electrolytes, arterial blood gases, and an aminophylline level were measured. After the AM, pacing study, each dog was given esmolol by infusion to return the heart rate to baseline while being maintained on an aminophylline drip. Serum electrolytes, arterial blood gases, and aminophylline level were measured, and a postesmolol pacing study (ESM,) was performed.

**Day 2 Studies:** All animals were stabilized, and baseline laboratory studies were obtained as on day 1. A baseline electrophysiologic pacing study (B) was performed. Thirty minutes after the B, study, each dog received 5 percent metaproterenol solution, 0.3 ml in 3 ml of sterile saline, nebulized into the endotracheal tube over 15 min. Fifteen minutes after the nebulization was complete, electrolytes, arterial blood gases, and plasma catecholamines were measured again, and the postmetaproterenol pacing study (MET) was performed. A bolus infusion of aminophylline was followed by a maintenance drip, as on day 1. Electrolytes, arterial blood gases, and an aminophylline level were measured. A repeat pacing study (MET/AM,) was performed during aminophylline administration and within 90 min of metaproterenol administration. At the end of day 2, the dogs were euthanized with potassium cardioplegia, and the heart was inspected to exclude heartworm infection.

Serum for electrolyte evaluation was analyzed with use of an electrolyte analyzer (Nova 4 + 4, Nova Biomedical, Waltham, Mass). Arterial blood for blood gas evaluation was analyzed on a pH and blood gas analyzer (model 1300; Instrumentation Laboratory, Lexington, Mass). Aminophylline levels were determined by homogeneous enzyme immunoassay (EMIT; Syra, Palo Alto, Calif).

**Statistics**

Conduction intervals and refractory periods are reported for each day's studies as the mean ± SEM. The difference between mean values was determined by using the paired t test or by using analysis of covariance when appropriate.

**RESULTS**

**Monitoring of Physiologic Parameters**

Serum electrolytes and arterial blood gases were measured throughout all experiments. There were no significant differences in serum potassium, PaO2, or pH during any experimental condition. Heart rate increased in response to aminophylline and metaproterenol, alone and in combination (Table 1). Mean arterial pressure (MAP) was significantly lower than at baseline after inhaled metaproterenol and after inhaled metaproterenol plus intravenous aminophylline. The MAP was not significantly different between the metaproterenol group and the aminophylline group or between the metaproterenol group and the metaproterenol plus aminophylline group. Core temperature and central venous pressure were held constant throughout all experimental conditions.
Table 1—Heart Rate and Blood Pressure Response*

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>AM1</th>
<th>ESM1</th>
<th>B1</th>
<th>MET1</th>
<th>MET/AM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>113±5.3</td>
<td>152±18.7†</td>
<td>126±12.9</td>
<td>126±8.8</td>
<td>220±2.8†</td>
<td>214±5.6†</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>102±10.1</td>
<td>114±10.3</td>
<td>118±12.1†</td>
<td>118±12.3</td>
<td>91.8±12.2†</td>
<td>86.2±10.7†</td>
</tr>
</tbody>
</table>

*Values are expressed as mean ± SEM. MAP = mean arterial pressure. See Methods section for explanation of other abbreviations.
†Differs from baseline, p<0.05.
‡Differs from AM1, p<0.01.

Electrophysiologic Data

Baseline: Baseline intracardiac conduction times were obtained on day 1 and day 2 of the protocol (Table 2). There were no significant differences between any parameters.

Intravenous Aminophylline Alone: Aminophylline infusion alone significantly enhanced intracardiac conduction (Table 2). The mean aminophylline level for this group of animals was 12.9±0.74 µg/ml. The AH interval, WCL, and VERP all decreased significantly after aminophylline infusion. In response to aminophylline infusion, the heart rate increased from 113.2±5.3 beats per minute at baseline to 152.8±18.7 beats per minute (p<0.05).

The effects of esmolol infusion on aminophylline-induced changes in intracardiac conduction are shown in Table 3. The mean serum aminophylline level during esmolol infusion was 11.9±0.94 µg/ml. Esmolol administration resulted in normalization of aminophylline-induced decreases in WCL and VERP. Esmolol infusion significantly increased the AH interval, but it was still significantly below the baseline value.

Inhaled Metaproterenol Alone: Like aminophylline, metaproterenol significantly enhanced intracardiac conduction and decreased myocardial tissue refractoriness (Table 2). The AH interval, WCL, and VERP all decreased significantly after inhaled metaproterenol administration. Unlike aminophylline, inhaled metaproterenol caused a significant decrease in AERP.

In response to inhaled metaproterenol, heart rate increased from 126.4±5.3 beats per minute at baseline to 220.4±2.8 beats per minute (p<0.001). Interestingly, MAP decreased from 118.4±12.3 at baseline to 91.8±12.2 mm Hg after inhaled metaproterenol (p<0.04). After using analysis of covariance and statistically controlling for the reduction in MAP, only the reductions in AH interval (p<0.02) and WCL (p<0.001) and the increase in heart rate (p<0.01) remained significant. The decreases in AERP and VERP were no longer significant after statistically controlling for MAP in metaproterenol-treated dogs.

Inhaled Metaproterenol versus Intravenous Aminophylline: Inhaled metaproterenol and intravenous aminophylline alone both produced significant changes in intracardiac conduction (Table 2). However, metaproterenol produced significantly greater decreases in AH interval and WCL than those seen with aminophylline treatment. Metaproterenol also produced a significantly higher heart rate than that seen with aminophylline treatment. No significant difference in MAP was noted between dogs treated with aminophylline alone and those treated with metaproterenol alone.

Inhaled Metaproterenol and Intravenous Aminophylline in Combination: Combined metaproterenol and aminophylline treatment produced significant changes in intracardiac conduction times (Table 2). The mean aminophylline level during combined treatment was 11.5±0.88 µg/ml. The AH interval significantly decreased after combined therapy. The HV interval also significantly decreased after combined therapy, an effect not seen with either agent alone. The AERP, WCL, and VERP all decreased significantly after metaproterenol and aminophylline in combination. In response to combined treatment, the heart rate increased from 126.4±8.8 beats per minute at baseline to 214.4±5.6 beats per minute (p<0.001). As with metaproterenol treatment alone, combined

Table 2—Electrophysiologic Effects of Bronchodilator Medications*

<table>
<thead>
<tr>
<th></th>
<th>B1</th>
<th>AM1</th>
<th>B1</th>
<th>MET1</th>
<th>MET/AM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>6.0±2.4</td>
<td>2.0±2.0</td>
<td>0.0±2.7</td>
<td>-2.0±2.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>AH</td>
<td>85.0±6.5</td>
<td>63.0±4.1†</td>
<td>68.0±2.6</td>
<td>51.0±1.9§</td>
<td>45.0±1.2§</td>
</tr>
<tr>
<td>HV</td>
<td>35.0±1.2</td>
<td>32.0±1.2</td>
<td>33.0±2.0</td>
<td>30.0±3.2</td>
<td>28.0±2.0</td>
</tr>
<tr>
<td>AERP</td>
<td>154.0±10.3</td>
<td>132.0±5.8</td>
<td>152.0±6.6</td>
<td>130.0±3.2†</td>
<td>122.0±4.9†</td>
</tr>
<tr>
<td>WCL</td>
<td>228.0±8.7</td>
<td>182.0±5.8†</td>
<td>204.0±7.5</td>
<td>180.0±4.9§</td>
<td>150.0±7.1§</td>
</tr>
<tr>
<td>VERP</td>
<td>166.0±6.0</td>
<td>146.0±4.9†</td>
<td>160.0±4.5</td>
<td>136.0±2.4†</td>
<td>132.0±2.0†</td>
</tr>
</tbody>
</table>

*Values are expressed in milliseconds as mean ± SEM. See Methods section for explanation of abbreviations.
†Differs from baseline, p<0.02.
‡Differs from AM1, p<0.03.
§Differs from baseline, p<0.001.
|Differs from AM1, p<0.02.

Effects of Aminophylline and Metaproterenol on Canine Myocardium (Komadina et al)
metaproterenol and aminophylline caused a significant decrease in MAP from $118.4 \pm 12.3$ mm Hg at baseline to $86.2 \pm 10.7$ mm Hg ($p<0.01$). With the exception of the AERP, all decreases in conduction time and refractory periods remained significant after statistically controlling for MAP by analysis of covariance.

When compared with metaproterenol alone, combined metaproterenol and aminophylline produced no further decreases in conduction times. Additionally, heart rate and MAP were not statistically different between the metaproterenol group and the combined metaproterenol and aminophylline group (Table 1).

Aminophylline Alone versus Combined Metaproterenol and Aminophylline: When compared with aminophylline, metaproterenol alone produced significantly greater decreases in AH interval and WCL and a significantly greater increase in heart rate (Table 2). Analogous changes in the AH interval, WCL, and heart rate were seen with metaproterenol in combination with aminophylline. However, when compared with aminophylline alone, inhaled metaproterenol and intravenous aminophylline in combination produced additional significant decreases in the HV interval and VERP.

In contrast to aminophylline alone, combined aminophylline and metaproterenol was associated with a significantly lower MAP ($114.8 \pm 10.3$ mm Hg for aminophylline vs $86.2 \pm 10.7$ mm Hg for combined aminophylline and metaproterenol [p<0.02]). After statistically controlling for MAP by analysis of covariance, there was no significant difference between aminophylline and combined aminophylline and metaproterenol for any parameter.

### Discussion

Mortality due to obstructive lung disease has been increasing in the United States and other countries. Wilson et al noted that an increase in asthma mortality in New Zealand coincided with the introduction of over-the-counter inhaled beta-adrenergic agonists. They suggested that combined use of theophylline and beta-adrenergic agonists was responsible for the increase in asthma mortality. One possible explanation for this observation could be enhanced cardiac toxicity. In the COPD population, frequent ventricular premature beats have been noted in 35 percent of patients; nonsustained ventricular tachycardia, in 22 percent; and repetitive ventricular premature beats, in 64 percent. The COPD patient may therefore be at even greater risk for cardiac mortality related to beta-adrenergic agonist or theophylline therapy.

The cardiac toxicity of aminophylline is well known and includes sinus tachycardia, supraventricular tachycardia, multifocal atrial tachycardia, ventricular premature beats, ventricular tachycardia, and ventricular fibrillation. The most common cardiac effect of beta-adrenergic agonist therapy is sinus tachycardia. This effect may be mediated by chronotropic $\beta_2$ myocardial receptors and reflexly in response to $\beta_1$-mediated vasodilatation. In animal studies, combined therapy with aminophylline and beta-adrenergic agonists has resulted in significant cardiac toxicity, both as a result of arrhythmia and secondary to direct myocardial injury. These studies have usually been performed in animals with supratherapeutic aminophylline levels and with beta-adrenergic agonist doses far in excess of the human dose. In contrast to these studies, we chose therapeutic doses of aminophylline and metaproterenol for our studies. This study is the first to evaluate intracardiac conduction and myocardial tissue refractoriness in animals treated with a beta-adrenergic agonist and aminophylline in combination.

Although the cardiotoxicity of theophylline is well established, very little work has been done to examine the intracardiac conduction effects of theophylline. Eriksson et al reported significant decreases in AH and HV intervals, sinoatrial conduction time, sinus node recovery time, AERP and AVERP in ten COPD patients with therapeutic theophylline levels. The VERP was unchanged by theophylline. These authors also noted an increase in catecholamine levels after theophylline loading. Bidd et al reported similar findings in ten young patients being evaluated for transient bradycardias who were being treated with oral theophylline. Significant decreases in sinoatrial conduction time, sinus node recovery time, and AVERP were noted after theophylline administration. In neither study was the effect of a simultaneously administered beta-adrenergic agonist studied. Bittar et al reported significant decreases in AERP and VERP in a dog model of aminophylline toxicity. Ventricular fibrillation was induced in three of eight dogs given a toxic dose of theophylline. In both human and animal studies, aminophylline significantly enhanced conduction in atrial and ventricular tissue. This may play a role in the cardiac toxicity of theophylline. The electrophysiologic effects of inhaled metaproterenol have not been
studied, nor have its combined effects with aminophylline.

We selected a canine model to study the electrophysiologic effects of aminophylline and metaproterenol alone and in combination on normal myocardium. Body temperature, central venous pressure, oxygenation, pH, and serum potassium were all maintained at constant levels during the study to avoid confounding effects on intracardiac conduction. Each dog served as its own control on both days of the study. There were no significant differences between any baseline parameter on the two study days, indicating similar experimental conditions at the outset of each day (Table 2).

We found that a constant infusion of aminophylline produced significant decreases in the AH interval, WCL, and VERP and a significant increase in heart rate (Table 2). These findings are indicative of enhanced AV nodal conduction in response to aminophylline, as well as a decrease in AV nodal and ventricular tissue refractoriness. Eriksson et al.¹⁴ noted similar changes and suggested that these findings may be due to sympathetic nervous system activation by aminophylline, a hypothesis supported by elevated catecholamine levels in their aminophylline-treated patients. Our findings support a role for sympathetic nervous system activation by aminophylline. An esmolol infusion resulted in normalization of the WCL and the VERP. The AH interval increased after esmolol but still remained significantly below baseline levels (Table 3). The reversal of the aminophylline effect on intracardiac conduction by esmolol is consistent with the findings of Conrad and Prosnitz,²⁰ and suggests that the effects of aminophylline may be mediated by beta-adrenergic receptors. Our findings cannot be explained on the basis of changes in heart rate. All refractory periods were determined at the same pacing interval of 240 ms (250 beats per minute). The observed decreases in refractory periods are therefore independent of the underlying heart rate and are a reflection of drug effect. Furthermore, the AH interval normally increases with an increase in heart rate alone. The observed decrease in the AH interval is most likely due to drug effect.

Like aminophylline, metaproterenol significantly enhanced AV nodal conduction and decreased AV nodal and ventricular refractoriness. Metaproterenol significantly decreased the AH interval, WCL, and VERP (Table 2). These intervals were significantly shorter than those observed after aminophylline infusion. Furthermore, inhaled metaproterenol produced a significant decrease in atrial tissue refractoriness, an effect not seen with aminophylline. These findings suggest that aminophylline and metaproterenol may have differential effects on cardiac conducting tissue, and that metaproterenol produces greater enhancement of AV nodal conduction than aminophylline.

There was no difference in any physiologic parameter between animals treated with aminophylline and those treated with metaproterenol. However, the MAP after inhaled metaproterenol was significantly lower than the baseline value on day 2, but not lower than the values at baseline on day 1 or after aminophylline infusion (Table 2). Using analysis of covariance, and statistically controlling for the decrease in MAP only the reduction in AH interval, WCL and the increase in heart rate retained statistical significance. These data suggest that metaproterenol exerts its effects both directly and indirectly via a reduction in MAP in our dog model.

Inhaled metaproterenol in combination with intravenous aminophylline caused significant decreases in the AH interval, AERP, WCL, and VERP, as well as a significant increase in heart rate. The HV interval also decreased significantly with combined therapy, an effect not seen with aminophylline or metaproterenol alone (Table 2). The latter finding suggests that combined therapy has additive or synergistic effects on His-Purkinje conduction. The MAP decreased significantly from baseline after combined therapy. With the exception of the AERP, all decreases in conduction time with combined therapy remained significant after controlling for MAP by analysis of covariance. With the exception of the decrease in the HV interval, combined therapy resulted in no further enhancement of cardiac conduction than was seen with metaproterenol alone.

When compared with aminophylline alone, inhaled metaproterenol and intravenous aminophylline in combination produced analogous changes in the AH interval, WCL, and heart rate. In addition, combination therapy produced further significant decreases in the HV interval and VERP. However, MAP was significantly lower after combined therapy than after aminophylline alone. After controlling for MAP by using analysis of covariance, there was no significant difference between aminophylline and combined therapy for any parameter. These data suggest that the effects of combined therapy are mediated by both direct and indirect effects on the myocardium.

The large changes in heart rate and MAP observed in dogs treated with metaproterenol are potentially confounding variables. This is not the usual human response to metaproterenol. No data exist regarding the canine dose of metaproterenol that would be physiologically equivalent to the human dose. We therefore elected to use a normal human dose of metaproterenol as opposed to the supratherapeutic doses of beta-adrenergic agonists used in prior animal studies.²¹-²³ As noted previously, our findings were independent of drug-induced changes in heart rate.
Furthermore, after statistically controlling for the drop in MAP, significant drug effects persisted. Still, dogs seem more sensitive to the effects of metaprotenerol than humans, and a human study is needed to rule out a species-dependent effect of metaprotenerol on myocardial conduction and refractoriness.

Because of the significant drop in MAP in dogs treated with metaprotenerol, we used analysis of covariance to control for the fall in MAP. Differences in a variable of interest (such as conduction times and refractory periods) that may covary with a second, contaminating variable (such as MAP) can be statistically controlled for by entering the second variable as a covariate. After controlling for MAP statistically, we still found significant changes in conduction times and refractory periods. This suggests that some effects of metaprotenerol may be mediated by indirect mechanisms, such as sympathetic activation in response to the fall in MAP, while other effects are direct drug effects.

Although our sample size was small (n = 5), the multiple-measures design of the study increased the statistical power, to the equivalent of 10 or 15 animals per group. While the small sample size may allow subtle changes in measured variables to be missed, robust effects should be easily detected.

Anesthetic effects on cardiac conduction are another potential confounding variable. Isoflurane has been shown to have no effect on AV conduction and to minimally enhance epinephrine-induced arrhythmias in dogs.

In conclusion, aminophylline at therapeutic concentrations causes significant enhancement of intracardiac conduction in dogs. This is in keeping with the findings in human studies by Eiriksson et al and Benditt et al. In our canine model, metaprotenerol produced greater enhancement of intracardiac conduction than aminophylline did. These effects may be mediated by both direct and indirect mechanisms. Combined therapy produced greater enhancement of intracardiac conduction than was seen with aminophylline alone, an effect that may also be mediated by both direct and indirect mechanisms. The decreases in conduction time and tissue refractoriness observed may explain the increased incidence of arrhythmias in some patients treated with these agents. It must be borne in mind, however, that these changes are just two of many factors, including hypoxia, acidosis, catecholamine levels, and electrolyte abnormalities, that predispose patients to reentrant and triggered arrhythmias.

Care must be taken before extrapolating our findings to human subjects. We studied the effects of aminophylline and metaprotenerol on healthy canine myocardium. Patients with COPD have a high incidence of ventricular arrhythmias. Underlying coronary artery disease and concomitant hypoxia, as well as the independent effects of aminophylline and metaprotenerol on the conduction system noted in this study, may account for this observation. Our data suggest a need for a similar study in human subjects.

ACKNOWLEDGMENTS: The authors gratefully acknowledge Edith Torres for her technical assistance, Velma K. Grantham and Deborah Ybara for their secretarial assistance, Dr Cliff Butzin for his statistical support, and Dr David A. Schenk for his review of the manuscript.

REFERENCES
2 Wilson JD, Southerland DC, Thomas AC. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma? Lancet 1981; 1:1235-537
3 Sessler CN, Cohen M, Garnett AR. Cardiac arrhythmias during theophylline toxicity. Chest 1990; 98:672-78
8 Kemp JP, Orzel HA, Meltzer EO, Noyes JH, Mingo TS. Concomitant bolus and mesylate aerosol and theophylline for asthma therapy, with 24 hour electrocardiographic monitoring. J Allergy Clin Immunol 1984; 73:32-43
10 Coleman JJ, Vollmer WM, Barker AF, Schultze GE, Buist AS. Cardiac arrhythmias during the combined use of beta-adrenergic agonist drugs and theophylline. Chest 1986; 90:45-51
12 Patel AK, Sletatub JD, Thomsen JH. Cardiac arrhythmias due to oral aminophylline in patients with chronic obstructive pulmonary disease. Chest 1986; 80:661-65
16 Bittar G, Friedman HS, Nguyen T, Dominguez A. Theophylline ethylenediamine (aminophylline) promotes atrial and ventricular fibrillation [abstract]. Chest 1988; 94(suppl):105
238 Effects of Aminophylline and Metaproterenol on Canine Myocardium (Komadina et al)

29 Booth NH. Inhalant anesthetics. In: Booth NH, McDonald LE, eds. Veterinary pharmacology and therapeutics. 5th ed. Ames, Iowa: Iowa State University Press, 1982; 199-200