

EXPERIMENTAL STUDIES

Effects of Adenosine and Adenosine 5'-Triphosphate on Ventricular Escape Rhythm in the Canine Heart

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The effects of adenosine and adenosine 5'-triphosphate (ATP) on ventricular escape rhythms were studied in 16 closed chest dogs after electroablation of the His bundle region. All dogs exhibited complete atrioventricular (AV) block and stable ventricular escape rhythm with a mean cycle length of $1,210 \pm 80$ ms and a QRS width of 91 ± 5 ms. Physiologic AV sequential pacing was operative during experiments and was interrupted for rapid (≤ 1 second) administration of either adenosine or ATP ($3 \mu\text{mol/kg}$) into the right atrium. Adenosine and ATP effectively depressed ventricular escape rhythms in a similar manner both qualitatively and quantitatively (cycle length from $1,210 \pm 80$ to $1,764 \pm 132$ ms and from $1,274 \pm 84$ to $2,000 \pm 150$ ms, respectively; each $p < 0.01$).

These effects were not significantly altered by either physostigmine (an acetylcholinesterase inhibitor) or atropine (a muscarinic cholinergic blocker), but were slightly attenuated by propranolol (a beta-adrenoceptor blocker). In the presence of autonomic blockade, the adenosine transport blocker dipyridamole markedly enhanced the depressant effects of adenosine and ATP. The adenosine competitive antagonist aminophylline reversed the action of dipyridamole. Thus, both adenosine and ATP depress ventricular escape rhythms in vivo, independent of the autonomic nervous system. Moreover, the effects of ATP can be accounted for in large part by its rapid breakdown to adenosine.

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Adenosine and adenosine 5'-triphosphate (ATP) exert pronounced effects on mammalian cardiac cellular electrophysiology (for a recent review see Ref. 1) which are manifest as depression of sinus node activity, as well as atrioventricular (AV) node conduction and automaticity (2,3). Very little is known regarding the effects of adenosine and ATP on ventricular electrophysiology. Previous in vitro studies investigated the effects of adenosine (4-7) and ATP (5) on the automaticity of guinea pig right ventricular strips (4) and canine Purkinje fibers (5,6). More recently, the negative chronotropic effects of adenosine and some of its analogs were studied in spontaneously beating, isolated, isovolumic rat ventricular preparations (7). The purpose of this study was to investigate the effects and mechanisms of action of

adenosine and ATP on ventricular escape rhythms using various pharmacologic interventions in the canine heart in vivo.

Methods

Experimental preparation. Sixteen mongrel dogs (15 to 25 kg; either sex) were anesthetized with sodium pentobarbital (30 mg/kg body weight, intravenously), intubated with a cuffed endotracheal tube and ventilated with room air, supplemented as necessary with oxygen, using a Harvard respirator. A large bore (1.5 mm) catheter cannula was introduced into the right atrium through the right femoral vein. A quadripolar electrode catheter was introduced through the left femoral vein and positioned in the right atrium for recording and pacing. A second quadripolar electrode catheter was introduced through the right jugular vein and placed in the right ventricle for recording and pacing. A tripolar electrode catheter was introduced into the left carotid artery and was positioned in the region of the noncoronary cusp of the aortic valve for recording His bundle activity and for ablation of the His bundle region. Systemic arterial pressure was recorded with a Millar catheter tip electrotransducer introduced through the left femoral artery.

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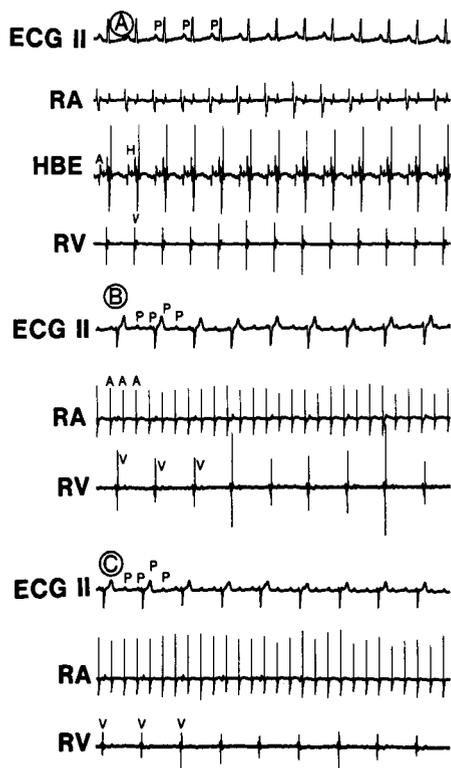
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His bundle ablation (8) was achieved by delivering a direct current electrical discharge (100 to 120 W·s) between that lead of the tripolar His catheter that yielded the maximal unipolar His bundle potential and a ground plate in contact with the dog's back using a standard direct current defibrillator (Narco Scientific Porta-Fib LPDII). To minimize the biochemical and electrophysiologic alterations associated with electrical shocks, only those dogs that exhibited ventricular escape rhythms after no more than two ablation attempts were included in this study. A ventricular escape rhythm was defined as: (1) a stable rhythm of infranodal origin with ventricular activation not preceded by His bundle activity, and (2) independence of atrial and ventricular activity (complete AV block). At the end of each experiment the heart was surgically exposed, the position of the His bundle catheter was confirmed and the gross morphologic location and size of the electrically induced lesion were examined.

Drug administration. Animals were left to stabilize for 1 hour after ablation. During that period AV sequential pacing (cycle length = 600 ms; AV interval = 100 ms)

Figure 1. Typical example of a stable ventricular escape rhythm after electroablation of the His bundle. Tracings are, from top to bottom, lead II electrocardiogram (ECG II), right atrial electrogram (RA), His bundle electrogram (HBE) and right ventricular electrogram (RV). A, Baseline conditions, before ablation. B, One minute after ablation. C, Sixty minutes after ablation. Paper speed was 100 mm/s in A and 25 mm/s in B and C. A, H, P and V = right atrial, His bundle, P wave and right ventricular activation, respectively.



was operative. Pacing was gradually interrupted for 90 seconds, including 30 seconds before and 60 seconds after the administration of either adenosine or ATP (3 μ mol/kg). These were administered as a very rapid (≤ 1 second) bolus injection into the right atrium in the absence of any other drug and in the presence of each of the following drugs, administered intravenously, sequentially in each animal: physostigmine (an acetylcholinesterase inhibitor, 50 μ g/kg), atropine (a muscarinic cholinergic blocker, 0.2 mg/kg), propranolol (a beta-adrenoceptor blocker, 1 mg/kg), dipyridamole (an adenosine transport blocker, 250 μ g/kg) and amiophylline (an adenosine competitive antagonist, 5 mg/kg). In the presence of dipyridamole, both adenosine and ATP produced prolonged cardiac asystole; therefore, cardiac pacing was instituted arbitrarily before the recovery of the ventricular pacemaker to avoid hemodynamic deterioration.

Recordings. Sequential AV pacing was performed with a programmed cardiac stimulator (Bloom Associates, Ltd.). Cardiac electrograms, standard electrocardiographic lead II and arterial blood pressure were continuously displayed on an HP 1308A monitor and recorded with a Hi-Fi instrumentation tape recorder (HP 3968A) as well as a chart recorder (Siemens Elema E183) at paper speeds of 25 to 100 mm/s. Arterial blood pH and gases were determined every 20 minutes using a blood gas analyzer (Corning 168).

Data analysis. The depressant effects of adenosine and ATP on ventricular escape rhythms were determined from the maximal prolongation (in milliseconds) of ventricular escape rhythm cycle lengths after the administration of these compounds. For this purpose the single largest RR interval during a regular rhythm was used in each case. These effects were also expressed as percent of the ventricular cycle length, where 100% represented the cycle length before the administration of either adenosine or ATP.

Data are presented as mean \pm SEM. Analysis of variance and corrected *t* tests for paired and unpaired samples were used to determine significance of results at the $p < 0.05$ level. Experiments conformed to the "Guide for the Care and Use of Laboratory Animals" of the American Physiological Society and the Lankenau Animal Care Policy.

Results

Electrical ablation of His bundle. In all dogs, gross morphologic examination performed at the end of experiments revealed extensive damage to the His bundle region. In addition, His bundle activation could not be detected in the His bundle electrogram in any dog after either one ($n = 11$) or two ($n = 5$) ablation attempts. All animals had a stable ventricular escape rhythm with a mean cycle length of $1,210 \pm 80$ ms (Fig. 1). In each case these rhythms exhibited overdrive suppression (9); namely, after abrupt termination of ventricular pacing at a rate greater than ventricular escape rhythm, there was a transient pause in au-

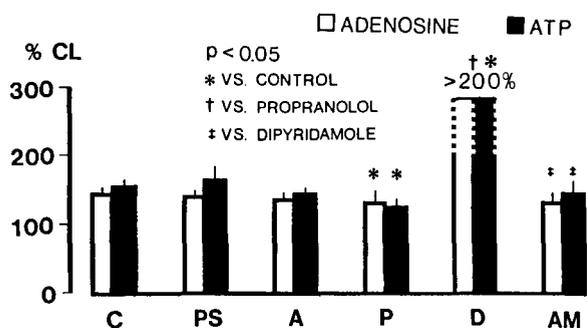


Figure 2. The percent maximal depressant effects of adenosine and adenosine 5'-triphosphate (ATP) on ventricular escape rhythm before and after sequential administration of various pharmacologic agents. The ventricular cycle length (CL) before administration of either adenosine or ATP was taken as 100%. A = atropine; AM = aminophylline; C = control; D = dipyridamole; P = propranolol; PS = physostigmine.

tomatic activity (that is, an escape interval longer than the baseline RR interval), subsequent resumption of the dominant ventricular escape rhythm at a rate slightly slower than baseline with gradual "warm-up" over several beats and return to the baseline RR interval. Electrocardiograms showed complete AV block and a QRS width of 91 ± 5 ms. Sinus rhythm cycle length was 385 ± 16 ms before and 366 ± 13 ms after ablation ($p = NS$).

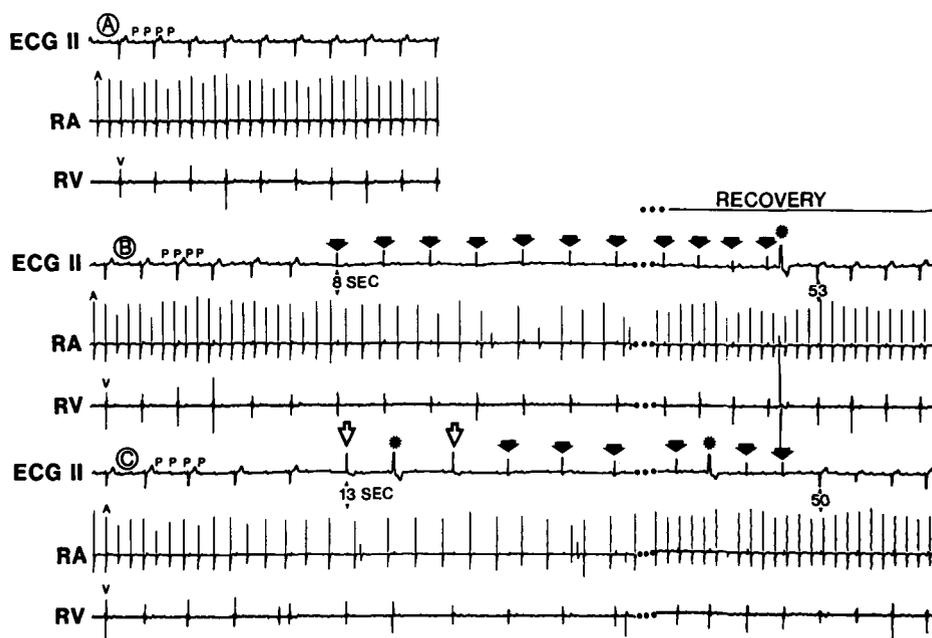
Effects of adenosine and ATP on ventricular escape rhythms. Both adenosine and ATP had similar transient depressant effects on ventricular escape rhythms (Fig. 2). Ventricular pacemaker cycle length was prolonged from

$1,210 \pm 80$ to $1,764 \pm 132$ ms by adenosine and from $1,274 \pm 89$ to $2,000 \pm 150$ ms by ATP (each $p < 0.01$). The time to peak effect was 23 ± 2 seconds after the administration of adenosine and 23 ± 1 seconds after ATP administration, and returned to baseline over the next 60 seconds. In many cases the maximal effects of adenosine and ATP coincided with abrupt changes in QRS configuration, suggesting the unmasking of a latent, subsidiary pacemaker, although an effect on intraventricular conduction cannot be excluded (Fig. 3).

Influence of vagoactive drugs. Neither the acetylcholinesterase inhibitor physostigmine nor the muscarinic cholinergic blocker atropine had a significant effect on the cycle length of the ventricular escape rhythms. Moreover, neither altered the depressant effects of either adenosine or ATP on ventricular escape rhythms (Fig. 2). In the presence of physostigmine, ventricular cycle length was prolonged from $1,284 \pm 91$ to $1,831 \pm 195$ ms by adenosine and from $1,261 \pm 72$ to $2,194 \pm 371$ ms by ATP. Subsequent administration of atropine did not alter this pattern significantly; ventricular pacemaker cycle length was prolonged from $1,319 \pm 95$ to $1,762 \pm 151$ ms by adenosine and from $1,312 \pm 114$ to $1,837 \pm 153$ ms by ATP.

Influence of beta-adrenoceptor blockade. In contrast to physostigmine and atropine, administration of propranolol significantly prolonged the ventricular pacemaker cycle length from $1,319 \pm 195$ to $1,870 \pm 170$ ms ($p < 0.05$), even before the administration of either adenosine or ATP. Characteristically, this was accompanied by alteration of the QRS configuration, suggesting either the emergence of

Figure 3. A typical example of the negative chronotropic effects of adenosine and adenosine 5'-triphosphate (ATP) on ventricular escape rhythms. Tracings are arranged as in Figure 1. **A**, Control, before administration of drugs. **B**, Transient effects of adenosine ($3 \mu\text{mol/kg}$) administered rapidly into the right atrium. Eight seconds after administration of adenosine, during which time the leading ventricular pacemaker was gradually prolonged, a latent pacemaker emerged or conduction alterations appeared (filled arrows), or both, and were manifest for 45 seconds. Note an "ectopic" beat (asterisk) just before the return of the leading pacemaker 53 seconds after administration of adenosine. **C**, Similar effects and their temporal pattern after administration of ATP ($3 \mu\text{mol/kg}$). Symbols as in **B**. An escape beat with a slightly different configuration is indicated by the open arrows. Paper speed is 25 mm/s. Abbreviations as in Figure 1.



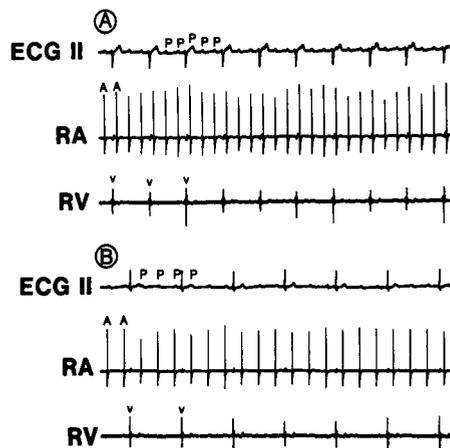


Figure 4. Typical example of the effects of propranolol (1 mg/kg) on ventricular escape rhythms. Tracings are arranged as in Figure 1. **A**, Ventricular escape rhythm before propranolol (in the presence of physostigmine [50 μ g/kg] and atropine [0.2 mg/kg]). **B**, Five minutes after propranolol the leading ventricular pacemaker is depressed and a stable latent pacemaker emerges. Note the similarity between the QRS configuration of this pacemaker and those transiently operative after either adenosine or ATP in Figure 2. Paper speed is 25 mm/s. Abbreviations as in Figure 1.

a previously latent pacemaker or pronounced intraventricular conduction alterations (Fig. 4). In the presence of propranolol the administration of adenosine resulted in further prolonged ventricular escape rhythm cycle length from $1,870 \pm 170$ to $2,370 \pm 258$ ms. ATP similarly increased the ventricular cycle length from $1,984 \pm 211$ to $2,304 \pm 203$ ms. Because the prolongation of ventricular cycle length caused by propranolol was not accompanied by proportional increases in the maximal prolongation caused by either adenosine or ATP, the relative effects of adenosine and ATP showed a small but significant attenuation (Fig. 2).

Influence of an adenosine transport inhibitor. In the presence of autonomic blockade the administration of the adenosine transport inhibitor dipyridamole had no significant effect on ventricular cycle length, but it markedly enhanced the depressant effects of both adenosine and ATP on ventricular escape rhythm (Fig. 2). Ventricular cycle length increased from $1,772 \pm 182$ to $4,499 \pm 674$ ms after adenosine and from $1,531 \pm 160$ to $6,046 \pm 1268$ ms after ATP (each $p < 0.01$). The difference in the absolute or percent increase in cycle length for ATP versus adenosine was not statistically significant.

Influence of a competitive antagonist of adenosine. Subsequent administration of aminophylline, a competitive antagonist of adenosine, had no significant effect on ventricular cycle length but resulted in pronounced attenuation ($p < 0.05$) of the effects of both adenosine and ATP recorded previously in the presence of dipyridamole (Fig. 2). In the presence of aminophylline, ventricular cycle length was increased from $1,533 \pm 133$ to only $2,004 \pm 200$ ms

by adenosine and from $1,730 \pm 146$ to only $2,466 \pm 345$ ms by ATP.

Discussion

The major findings of the present study are: 1) Both adenosine and ATP have pronounced depressant effects on ventricular escape rhythms in vivo; 2) these actions of adenosine and ATP are similar both qualitatively and quantitatively; 3) there is no significant involvement of the vagus in the effects of either adenosine or ATP; 4) beta-adrenoceptor blockade has only negligible influence on the actions of adenosine and ATP; 5) the adenosine transport blocker dipyridamole causes marked enhancement of the depressant effects of adenosine and ATP on ventricular escape rhythms; and 6) the competitive adenosine antagonist aminophylline reverses these effects of dipyridamole.

Effects of adenosine and ATP on infranodal pacemakers. Only five reports (4-7, 10) on the effects of adenosine on automatic activity of the mammalian ventricle are available, each an in vitro study. No comparable information is available on the effects of ATP. In earlier studies, the effects of adenosine on the automaticity of guinea pig right ventricular strips (4) and canine (5,6) Purkinje fibers were evaluated. In these preparations adenosine caused pronounced reduction in the spontaneous firing rate by reducing the rate of phase 4 depolarization (4,5), and in paced canine Purkinje fibers, adenosine also caused prolongation of the escape interval (6). In the latter study (6), the action of adenosine was abolished by propranolol, suggesting that the effects of adenosine were mainly due to antiadrenergic actions. West et al. (10) reported that adenosine had a negative chronotropic effect on ventricular escape rhythms in the isolated guinea pig heart. More recently Heller and Olsson (7) demonstrated that adenosine and some of its analogs exerted negative chronotropic effects on the spontaneous beating rate of an isolated, isovolumic rat ventricular preparation.

Thus, the present study shows for the first time that adenosine and ATP can suppress ventricular escape rhythms in vivo. These results are in congruence with those of previous studies (7,10) mentioned earlier. In addition, in the present study propranolol caused only a small attenuation in the relative negative chronotropic action of adenosine and ATP on ventricular escape rhythms. This argues against a major indirect, antiadrenergic component in the mechanism of action of adenosine and ATP. Although adenosine-catecholamine antagonism has been shown in ventricular myocardium in vitro (11), recent studies in vivo (12) indicated, in agreement with the present findings, that adenosine did not have any antagonistic effects on isoproterenol-induced inotropy and chronotropy in the intact dog heart. This also agrees with the lack of effect of propranolol on the action of adenosine in vitro (7).

Role of adenosine in the action of ATP. The time to peak effect of adenosine and ATP on ventricular escape rhythm was similar (23 seconds). This is longer than the time to peak effect (<15 seconds) on the sinus and AV nodes when adenosine and ATP are administered in the same manner, also in the right atrium (13). In view of the rapid degradation of ATP to adenosine by ectoenzymes (14), the relatively long time to peak effect of ATP suggests that the action of ATP is mainly due to its breakdown to adenosine. Thus, the fact that dipyridamole enhanced the effects of both adenosine and ATP, whereas these were reversed by aminophylline, indicates further that the major action of ATP on ventricular escape rhythms is through its degradation to adenosine. It has been previously shown that this pattern of modulation by dipyridamole and aminophylline is indicative of mediation by an extracellular R type purinoceptor (15). Dipyridamole was recently shown (16) to have direct electrophysiologic effects on guinea pig papillary muscle as well as canine Purkinje fibers. These include increase in action potential amplitude and duration as well as hyperpolarization of resting potential. The threshold for these effects was $5 \times 10^{-7} M$. Suppression of canine Purkinje fiber automaticity was observed with $10^{-5} M$ dipyridamole (16). The dose used in the present study could have resulted in initial blood levels of approximately $5 \times 10^{-6} M$. Therefore, although some effect on ventricular pacemakers in our model cannot be excluded, a direct action of dipyridamole cannot explain the pronounced enhancement of the negative chronotropic action of both adenosine and ATP.

Although the potential of methylxanthines to inhibit cyclic AMP phosphodiesterase activity is well known (17), relatively high concentrations ($\geq 2 \times 10^{-4} M$) of these agents are required for this action (18,19). The dose used in the present experiments would have resulted in much lower initial concentrations ($\sim 1 \times 10^{-4} M$). Therefore, it is assumed that inhibition of cyclic AMP phosphodiesterase is not involved in the effects of aminophylline. Furthermore, in a recent study (7), $10^{-4} M$ theophylline in the presence of propranolol inhibited the negative chronotropic action of adenosine on ventricular rhythm as did its nonpermeating analog 8-(4-sulfophenyl) theophylline. In further support of the hypothesis that ATP is essentially devoid of depressant effect on ventricular escape rhythms is the demonstration by Rosen et al. (5) that a stable analog of ATP, β - γ -methylene-ATP, had no effect on the automaticity of Purkinje fibers in vitro, whereas adenosine had significant depressant effects.

Role of the vagus in the actions of adenosine and ATP. The present study also shows that the vagus does not play a major role in the action of ATP on ventricular escape rhythms. This is in contrast to the previously established role of the vagus in mediating the negative chronotropic and dromotropic actions of ATP on the sinus and AV nodes in

a similar model (13,20). The lack of significant vagal involvement in the negative chronotropic action of ATP on ventricular escape rhythms is in agreement with the findings of Spear and Moore (21). They showed, in a similar model, that vagal stimulation had only a small depressant effect (cycle length prolongation of about 7%) on ventricular escape rhythms. The presence of such a small vagal effect cannot be excluded by our data. Moreover, it is tempting to speculate that a similarly small vagal input to the ventricle was indeed triggered by ATP because the control negative chronotropic effect of ATP on ventricular escape rhythms was greater than that of adenosine and the difference was of the same order of magnitude as the effect observed by Spear and Moore (21). This speculation is supported by the fact that physostigmine enhanced this difference and atropine attenuated it. However, even in the presence of physostigmine the difference between the depressant effects of ATP and adenosine was not statistically significant, thus negating the importance of a possible ATP-triggered vagal reflex component in the mechanism of action of ATP on ventricular escape rhythms.

Previous studies (13,20) showed that, although adenosine does not trigger vagal reflexes to the same extent as ATP, vagal tone appears to modulate its actions on the sinus and AV nodes. Indeed, physostigmine enhanced the negative chronotropic action of adenosine (20). In addition, the negative dromotropic action of adenosine was relatively more pronounced in animals anesthetized with chloralose, a vagal sparing agent, than in those anesthetized with pentobarbital, a vagolytic agent (22). No such vagal modulation was found with respect to the negative chronotropic action of adenosine on ventricular escape rhythms. Indeed, neither physostigmine nor atropine altered this effect of adenosine.

Experimental model and limitations. Electroablation of the His bundle resulted in stable ventricular rhythms with a mean rate of approximately 50 beats/min that were not affected by either physostigmine or atropine but were slowed by propranolol. These results are characteristic of ventricular escape rhythms comparable with those previously reported in similar models (21,23-26). The exact sites of the ventricular pacemakers that were operative in the present study were not determined. However, previous and present data can support certain assumptions in this regard. Under normal conditions ventricular pacemaker activity originates in the His-Purkinje system. This seems to be the case in the present study, because all ventricular escape rhythms exhibited overdrive suppression, characteristic of normal automatic mechanisms. This observation is in agreement with previous studies (27,28) that demonstrated overdrive suppression of ventricular pacemakers. The rate of the ventricular pacemaker in our study is similar to rates of normal ventricular pacemakers observed in two previous canine models (29,30). Moreover, faster rates, presumably resulting from abnormal automatic activity (or triggered activity)

such as those reported in these canine models (29,30) were not observed. It seems, therefore, that the different techniques used in these two earlier studies (29,30) created conditions that facilitated abnormal pacemaker activity.

In the present study various drugs were given sequentially and it could be argued that this protocol affected the results based on pharmacodynamic considerations. However, the extremely short half-lives of adenosine and ATP (<7 seconds) enabled the rapid successive administration of these compounds. Thus, the experimental protocol did not exceed the shortest half-life of all the drugs (that is, that of atropine) in this model. Indeed, we successfully used a similar protocol of pharmacologic interventions in previous studies employing a similar canine model (13,20).

Clinical implications. It is tempting to speculate that the negative chronotropic effects of adenosine and ATP on ventricular automaticity in vivo could have potential clinical relevance. This speculation is supported by a most recent provocative clinical report of ventricular tachycardia responsive to adenosine (31). Thus, it could turn out that the naturally occurring biologic compounds adenosine and ATP can be used as antiarrhythmic drugs in the ventricles, in addition to exerting their recognized antiarrhythmic effects on paroxysmal supraventricular tachycardia incorporating the AV node. Moreover, it is also tempting to speculate that under conditions of ventricular ischemia in which release of adenosine and ATP from myocardial cells is increased, regional electrophysiologic properties are deranged and autonomic tone is altered, adenosine and ATP may exert either antiarrhythmic or arrhythmogenic effects of potential clinical importance. However, the electrophysiologic effects of adenosine and ATP in the setting of abnormal ventricular rhythms have undergone only limited evaluation (32-35), and further experimental as well as clinical studies are required to evaluate these hypotheses.

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