Adenosine Causes Bradycardia in Pacing-Induced Cardiac Failure

Francis L. Belloni, PhD; Jie Wang, MD, PhD; and Thomas H. Hintze, PhD

Background. In normal, conscious dogs, systemic injection of adenosine causes arterial hypotension and a baroreceptor reflex tachycardia mediated in part by withdrawal of vagal tone to the sinoatrial node. After vagal section or muscarinic receptor blockade, however, adenosine injection causes bradycardia via a direct sinoatrial node inhibition. Because cardiac failure is marked by a loss of vagal tone, we hypothesized that adenosine injection in dogs with failing hearts would reduce heart rate.

Methods and Results. Mongrel dogs were instrumented with indwelling catheters, manometers, and ventricular pacing electrodes. After the dogs had recovered from the surgery, the ventricles were paced continuously at 210 beats per minute for 3 weeks, followed by pacing at 240 beats per minute for an additional week. This regimen caused mild ventricular and more striking atrial hypertrophy and a gradual onset of physiological and clinical signs of congestive heart failure. Adenosine injections that caused large tachycardias before the pacing regimen began caused progressively smaller increments in heart rate during the first 2 weeks of pacing. After 3 and 4 weeks, adenosine injections caused overt reductions in heart rate despite the concomitant arterial depressor response.

Conclusions. We conclude that the loss of vagal tone associated with the development of cardiac failure unmasks the direct negative chronotropic effect of exogenous adenosine on the sinoatrial node.

(Circulation 1992;85:1118–1124)

Key Words: sinoatrial node • hypertrophy • arrhythmias • baroreceptor reflex

Cardiac failure of various origins is marked by a reduced autonomic nervous control of cardiac function. For example, resting heart rate rises in failing hearts because of both increased sympathetic and reduced parasympathetic input to the sinoatrial (SA) node.1,2 Baroreceptor reflex control of heart rate is also impaired.1,2 Other anomalous rate responses in heart failure have been reported; for example, an unexplained, profound bradycardia has been observed in exercising heart failure dogs.3 These physiological changes reflect, in part, both the increased levels of circulating catecholamines4,5 and the loss of sympathetic and parasympathetic nerve terminals in the SA node.6 Adenosine is a potent inhibitor of atrioventricular (AV) node conduction in many species, which is the basis for adenosine’s therapeutic benefit in supraventricular tachycardia.7 In addition, adenosine exerts a powerful inhibitory effect on the SA node. When adenosine is administered systemically to an intact normal dog, however, its direct negative chronotropic effect is masked by the baroreceptor reflex tachycardia that is triggered by its concomitant arterial depressor effect.8 To a large extent, this baroreceptor reflex tachycardia results from a vagal withdrawal (i.e., a reduction in the firing rate of parasympathetic fibers innervating the SA node), although activation of sympathetic fibers also plays a role.1,2,8 We have previously found that pharmacological blockade of muscarinic receptors or bilateral vagotomies could unmask this negative chronotropic action of adenosine, presumably by eliminating the effective resting level of vagal “tone” that could subsequently be withdrawn.8–10 A similar pattern is seen in human subjects.11

The hypothesis we tested in the present study, therefore, was that the presence of cardiac failure associated with loss of cardiac parasympathetic control should enhance the susceptibility of the SA node to inhibition by adenosine. We examined this hypothesis using a model of pacing-induced cardiac failure in conscious dogs and a longitudinal study design.

Methods

Surgical Preparations and Instrumentation

Dogs instrumented with chronically implanted catheters and probes were used in this study. Each dog was sedated with acepromazine (1 mg/kg s.c.) and then anesthetized with sodium pentobarbital (25 mg/kg i.v. or to effect). A thoracotomy was performed in the fourth left intercostal space using sterile surgical technique. A Tygon catheter (Cardiovascular Instruments, Wakefield, Mass.) was placed in the descending thoracic...
aorta, and a solid-state manometer (Konigsberg P6.5, Pasadena, Calif.) was placed in the left ventricular lumen through the apical dimple. A corkscrew-style, unipolar electrode (Pacesetter, Los Angeles, Calif.) was implanted in the left ventricular free wall. All catheters and wires were channeled to a point on the back between the scapulae and were exteriorized there. The dogs were allowed to recover, and after 7–10 days, when they were afebrile and had been trained to lie quietly without restraint on the laboratory table, experiments were performed as described below.

On the day of each experiment, a catheter (I-Cath, Delmed, New Brunswick, N.J.) was placed percutaneously into a peripheral vein and attached to a longer infusion line for the administration of drugs. Adhesive cutaneous electrodes were placed on the upper segments of the four limbs to record the electrocardiogram (ECG).

The measured variables included arterial pressure (Statham P23-ID), left ventricular pressure, and lead II of the ECG. Heart rate was calculated electronically from either the arterial pressure or the ECG signal with a cardiotachometer (Beckman 9857B). Mean arterial pressure was derived on line from the phasic signals using a 2-Hz filter. The first derivative of left ventricular pressure, left ventricular dP/dt, was obtained on line using an analog differentiating circuit (National Semiconductor 324). Data were recorded on magnetic tape (Bell and Howell 3700B) and played back on an ink-writing oscillograph (Gould 2800-S).

**Chronic Cardiac Pacing Protocol**

After control responses were obtained, each dog began a regimen of continuous ventricular pacing with the implanted corkscrew electrode and a portable external pacemaker (Pace Medical EV3434, Waltham, Mass.). A pace rate of 210 beats per minute was sustained for 3 weeks; the pace rate was then increased to 240 beats per minute for an additional week. At the end of each week in this 4-week period, the dog was brought into the laboratory for the experiments described here. During these experimental sessions, each lasting 2–4 hours, the ventricular pacing was discontinued. All data reported here were obtained while the ventricular pacemaker was turned off.

**Injection of Agonists**

Adenosine (0.5–5 μmol/kg), isoproterenol (0.5 μg/kg), and nitroglycerin (25 μg/ml) were administered as rapid intravenous injections (in volumes of 1–5 ml) followed immediately by an injection of sterile, isotonic saline (5 ml) to flush the catheter. Volume-matched injections of saline had no noticeable effect on the measured variables. Sufficient time (generally 3–5 minutes) elapsed between injections to allow all measured variables to return to their baseline steady-state values. An adenosine challenge of 0.5 μmol/kg was administered each week. More complete dose–response relations were obtained before the pacing regimen and after 3 and 4 weeks of ventricular pacing.

**Statistical Analysis**

In total, 16 dogs were used in this study. The values for n indicated in the text, figures, and tables refer to the number of dogs. These values may be less than 16 because not all dogs were used for each experiment or received each drug dose. Values are reported as mean±1 SEM throughout the text, figures, and tables.

Data were assessed by ANOVA using a one-way classification (by dose or by time point within the longitudinal study design) with allowance for repeated measures in a single dog.12 Missing values were replaced by an iterative calculation of the least-squares estimate of the missing values.12 The degrees of freedom of the total and residual sums of squares were also reduced by one for each missing value. This method yields the least-squares estimate of every treatment mean and also the correct residual sum of squares. For cases where ANOVA indicated significant differences, individual group means were compared by the Student-Newman-Keuls test (within groups) or by the protected least significant difference test (between groups), as appropriate.12 A value of p<0.05 was taken as indicating statistical significance.

We also compared data obtained from 13 dogs used in the present study with data obtained from 13 historical controls from our earlier studies.13,14 Historical controls were also used in Table 1.

**Approval of Protocols**

All procedures used in this study that were related to the use and care of laboratory animals were approved in advance by the Institutional Animal Care and Use Committee of New York Medical College according to the guidelines set forth in the National Institutes of Health guide for the care and use of laboratory animals. Moreover, all experiments were conducted in accord with the guiding principles in the care and use of

### Table 1. Weights and Weight Ratios of Cardiac Sections in Normal and Chronically Paced Dogs

<table>
<thead>
<tr>
<th>Weight ratios (g/kg)</th>
<th>Normal (n=16)</th>
<th>After chronic pacing (n=6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart/body</td>
<td>6.07±0.22</td>
<td>6.82±0.15</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Left ventricle/body</td>
<td>3.13±0.11</td>
<td>3.64±0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right ventricle/body</td>
<td>1.66±0.07</td>
<td>1.89±0.11</td>
<td>NS</td>
</tr>
<tr>
<td>Weights of cardiac sections (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricle</td>
<td>75±3</td>
<td>90±4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>45±2</td>
<td>50±2</td>
<td>NS</td>
</tr>
<tr>
<td>Left atrium</td>
<td>2.43±0.27</td>
<td>4.95±0.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Right atrium</td>
<td>2.40±0.23</td>
<td>3.97±0.30</td>
<td>&lt;0.002</td>
</tr>
</tbody>
</table>
animals as approved by the Council of The American Physiological Society.

Results

Effect of Chronic Pacing on Cardiac Size

Four weeks of cardiac pacing according to the protocol used in this study led to cardiac hypertrophy. Table 1 shows the weights of various parts of the heart normalized to body weight. It can be seen that there was modest hypertrophy of the left ventricle (by about 16%) and more striking hypertrophy of the atria (increases of 65–104%). The wet-to-dry weight ratios of these hearts did not change over the 4-week course of the study. The weight changes, therefore, appear to have resulted from cardiac tissue growth rather than from intracellular or interstitial water accumulation.

Effect of Chronic Pacing on Cardiovascular Parameters

After 1 week of cardiac pacing, the mean arterial pressure fell slightly, as shown in Figure 1B, from a control value of 111±3 to 92±3 mm Hg. Baseline mean arterial pressure did not decline further during the next 3 weeks of chronic ventricular pacing. As shown in Figure 1A, spontaneous (i.e., unpaced) heart rate tended to increase over the time course of the study from an original (control) baseline value of 80±4 beats per minute to a baseline rate of 96±6 beats per minute after 1 week. Spontaneous heart rate rose further, to 120±6 beats per minute, after 4 weeks of chronic pacing.

Cardiac inotropic state tended to decrease over the time course of the pacing regimen. Table 2 reports data obtained from seven dogs in which left ventricular pressure and its derivative were measured. These dogs constituted a subset of the dogs used to determine adenosine responses. Resting left ventricular dP/dt\text{max} declined over the course of the study, suggesting a gradual reduction in inotropic state. The increments in heart rate and left ventricular dP/dt\text{max} observed in response to intravenous isoproterenol injections were also reduced as the chronic pacing regimen progressed. Peak values of left ventricular dP/dt\text{max} and heart rate after intravenous injection of 0.5 μmol/kg isoproterenol are reported in Table 2. The reduced basal contractile state and the diminished β-adrenergic reactivity suggest the gradual progression of cardiac failure in this model.

Responses to Adenosine Injections

Before ventricular pacing began, intravenous adenosine injections caused dose-dependent arterial hypertension and tachycardia, as previously observed. Heart rate and arterial pressure responses to a single dose of adenosine (0.5 μmol/kg) are shown in Figure 2. Heart rate and arterial pressure responses to a series of adenosine doses in this control state are shown in Figure 3.

After 1 week of ventricular pacing, the adenosine-induced tachycardia induced by 0.5 μmol/kg adenosine became smaller: For example, this dose of adenosine caused only a 22±6–beats per minute increment in heart rate after 1 week of cardiac pacing, which was significantly smaller than the prepping response of 66±7 beats per minute (Figure 2A). After 2 and 3 weeks of pacing, this adenosine dose caused no consistent change in heart rate on the average (7±11 and 2±9 beats per minute, respectively), and after 4 weeks, it caused a 7±2–beats per minute reduction in heart rate (Figure 2A). More dogs showed bradycardia in response to this dose of adenosine as the ventricular pacing regimen progressed. That is, whereas all 12 dogs showed

<table>
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<th>Table 2. Baseline Cardiac Performance and Responses to Isoproterenol in Normal and Chronically Paced Dogs</th>
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<tbody>
<tr>
<td>Week 0</td>
</tr>
<tr>
<td>Left ventricular dP/dt\text{max} (mm Hg/sec)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After isoproterenol</td>
</tr>
<tr>
<td>Heart rate (beats per minute)</td>
</tr>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>After isoproterenol</td>
</tr>
</tbody>
</table>

Week 0, before pacing regimen; Left ventricular dP/dt\text{max}, first derivative of left ventricular pressure; Baseline, unstressed left ventricular dP/dt\text{max} or heart rate with pacemaker turned off. Isoproterenol effects were statistically significant vs. baseline at all time points.

*p<0.05 vs. week 0 value.
tachycardia when challenged with this adenosine dose before the pacing regimen, bradycardia responses were exhibited by one of 11 dogs (9%) after 1 week of pacing, by five of 11 dogs (46%) after 2 and 3 weeks, and by six of nine dogs (67%) after 4 weeks. The remaining three of the nine dogs that were challenged with 0.5 μmol/kg adenosine after 4 weeks (those that did not display a sizable bradycardia) showed virtually no heart rate response to this dose; that is, the original tachycardia was eliminated.

Complete dose–response curves for adenosine obtained in the control state and after 3 and 4 weeks of cardiac pacing are shown in Figure 3. The larger doses of adenosine injected in this study caused substantial tachycardias in the control state (before pacing). After 3 weeks, adenosine injections of 3 and 5 μmol/kg caused overt bradycardias in seven of eight dogs challenged with these doses (Figure 3A). Similar data were obtained after 4 weeks of pacing. For all doses of adenosine studied, the absolute heart rates obtained in response to adenosine were significantly lower after 3 and 4 weeks of pacing than they had been before pacing. For example, 5 μmol/kg adenosine at week 0 caused heart rate to rise to 170±18 beats per minute (from a baseline of 81±3 beats per minute, n=8). At week 4, however, this adenosine dose caused heart rate to fall to 71±7 beats per minute (p<0.0001 vs. week 0 “peak” response, n=6, from a baseline heart rate of 118±6 beats per minute). Thus, the change in heart rate response shown in Figures 2A and 3A is not simply a mathematical effect of the changing baseline but rather represents a qualitatively different response.

The heart rate response to adenosine appeared to change in concert with the rise in baseline (unpaced) heart rate. That is, as baseline heart rate rose, the tachycardia response to adenosine became smaller and was eventually converted to a bradycardia response. Figure 4 displays this correlation for the responses to 0.5 μmol/kg adenosine.

Adenosine’s arterial depressor action was not significantly altered by chronic ventricular pacing. Figure 2B shows the reduction in mean arterial pressure elicited by 0.5 μmol/kg adenosine at the different time points of the study. The adenosine-induced reduction in arterial pressure of 16±4 mm Hg observed after 4 weeks of cardiac pacing was not significantly different from the prepping pressure reduction of 20±3 mm Hg. No statistical differences were found among the other weekly arterial pressure responses to this dose of adenosine. The arterial depressor responses to the other doses of adenosine used in this study were, in general, similar before and after chronic ventricular pacing, although some doses of adenosine caused slightly smaller falls in blood pressure after 4 weeks of ventricular pacing (Figure 3B).

**Apparent Sinoatrial Node Sensitivity to Adenosine**

The heart rate responses to various doses of adenosine obtained from 13 dogs studied after 4 weeks of ventricular pacing are depicted in Figure 5. Also shown
Responses to Nitroglycerin Injections

Before chronic pacing, nitroglycerin (25 μg/kg i.v., n=10 dogs) caused the expected transient arterial hypotension (−34±2 mm Hg from a baseline of 99±2 mm Hg) and baroreceptor reflex tachycardia (105±9 beats per minute from a baseline of 76±4 beats per minute). As the pacing regimen progressed, the heart rate response to nitroglycerin was still tachycardia, but the magnitude was reduced. For instance, after 4 weeks of pacing, nitroglycerin increased heart rate by only 26±10 beats per minute (p<0.05 versus week 0), from a baseline of 123±6 beats per minute (p<0.05 versus week 0) to a peak of 149±9 beats per minute (p<0.05 versus week 0 peak of 181±9 beats per minute). Similar but smaller changes were found during the first 3 weeks of pacing. The depressor response to nitroglycerin persisted throughout the pacing regimen, although it was slightly reduced after 3 and 4 weeks of pacing (−26±3 and −24±2 mm Hg, respectively, p<0.05 versus week 0). Baseline arterial pressure was not changed during the pacing regimen in this group of dogs.

Discussion

The major finding of the present study is that the development of pacing-induced heart failure was accompanied by a progressive conversion of the heart rate response to systemic adenosine injection from a tachycardia to a sinus bradycardia. The simplest explanation for this change in response is that the progressive loss of parasympathetic control of the SA node reduced the masking effect of the arterial baroreceptor reflex and allowed adenosine’s direct inhibitory action on the SA node to be expressed as an overt reduction in heart rate.5–10

Our model of pacing-induced cardiac failure displays many similarities to pacing-induced failure models used by other investigators. In particular, a rising baseline heart rate is a hallmark of cardiac failure with this2 and other1 failure models. The reduced β-adrenergic responsiveness we observed has also been reported in heart failure in humans12 and various animal models.4 The mild ventricular hypertrophy we observed is also consistent with the small changes in ventricular size found by other investigators.16,17 An interesting finding is the relatively large atrial hypertrophy that we and others16,19 have observed. The atrial hypertrophy may be a result of the asynchronous beating of the atria (at a rate determined by the SA node) and ventricles (at the exogenously driven rate), which would result in many atrial contractions against closed mitral and tricuspid valves.

One important difference between our pacing model and that used by others is the severity and time course of the failure that is induced. We have used a milder pacing regimen (210 beats per minute for 3 weeks plus 240 beats per minute for 1 week) than is generally used by others (usually ≥250 beats per minute for 4 weeks).2,4,16–18 In experiments reported elsewhere,20 we have determined the E_max from the slope of the left ventricular end-systolic pressure—volume relationship during successive contractions against a varying afterload.21 We have found that this index of myocardial inotropic state remains within normal limits for the first 3 weeks and then falls after the pacing rate is stepped up during...
the fourth week. The fall in $E_{\text{max}}$ corresponds to the appearance of clinical signs of congestive failure. Thus, our model may be generally characterized as displaying mild compensating hypertrophy for 3 weeks before the onset of acute congestive heart failure during the fourth week. Much of the change in responsiveness to adenosine occurs during the first 3 weeks, that is, before overt failure is manifest. Therefore, the changes we have described are not the result of cardiac failure per se but appear to occur in parallel with the hypertrophy/failure process. We have also observed a similarly enhanced susceptibility to adenosine-induced bradycardia in a dog with heart failure caused by chronic right ventricular pressure overload. This suggests that this change is found generally in cardiac hypertrophy and failure and is not specific to the pacing model used in the present study. It is also possible that the enhanced susceptibility to adenosine-induced bradycardia is more closely linked to the observed atrial hypertrophy rather than to the development of ventricular hypertrophy and failure. Our study does not allow us to choose conclusively between these possibilities.

It is possible that the fall in blood pressure caused by adenosine might have triggered the bradycardia in the paced dogs by upsetting a precarious oxygen supply-and-demand balance in the failing hearts. This seems unlikely, however, in light of the failure dogs' relatively normal, albeit attenuated, tachycardia response to nitroglycerin, despite a depressor response comparable to that caused by adenosine.

Adenosine may exert its negative chronotropic effect in part through a presynaptic inhibitory effect on sympathetic cardioacceleration. Basal sympathetic drive to the heart, including the SA node, may be increased in the model of failure used in this study, so it is possible that inhibition of sympathetic stimulation might be more important in explaining adenosine-induced bradycardia in failing hearts than in normal hearts. On the other hand, if sympathetic inhibition represented a major portion of adenosine's effect at the SA node, we might expect greater heart rate reductions for a given adenosine challenge in failing hearts than in normal hearts. The data shown in Figure 5 do not support this prediction. What seems more likely, therefore, is that the reduced vagal control of the cardiac pacemaker in the failing hearts allowed adenosine's direct inhibitory action on the SA node to be expressed, as our hypothesis had predicted.

In light of the known ability of cardiac adenosine receptors to display up- and downregulation, it is interesting to consider whether the cardiac sensitivity to adenosine may be altered by the chronic pacing regimen. Our comparison of the bradycardia responses of the chronically paced dogs in the present study with our previously reported data from normal dogs with combined $\beta$-adrenergic and muscarinic receptor blockade (Figure 5) suggests that there was no significant alteration in sensitivity of the SA node as a result of the 4-week pacing regimen. We did not quantify the extent to which vagal tone was eliminated by our chronic pacing protocol. Insofar as some vagal tone may have been present, the failure to find a significant vagal component in the paced dogs may have underestimated the importance of vagal tone in the paced dogs used in this comparison (122±7 beats per minute) was within the range of 120–140 beats per minute that would be expected in the dog in the complete absence of vagal tone, the extent of our possible underestimation of the SA node sensitivity to adenosine and any pacing-induced change in that sensitivity must have been slight.

**Clinical Implications**

Our findings may have relevance to understanding the control of heart rate in failing hearts. There is good evidence that arterial baroreceptor reflex control of heart rate is altered in heart failure. This altered control involves changes in the efferent pathways and in the sensitivity of the baroreceptor itself. Other factors may also contribute to altered heart rate control. It is possible that the altered cardiac wall stresses resulting from pacing-induced hypertrophy might affect reflex control of heart rate by the Bainbridge reflex or by other reflexes arising from cardiac, especially atrial, afferents. It has been suggested, for example, that such altered atrial stresses may affect the release of atrial natriuretic peptide. It is also known that the SA node is itself sensitive to physical distortion, and atrial remodeling might also affect this factor. Our work suggests that the chronotropic influence of adenosine and possibly of other endogenous paracrine or endocrine substances might be greater in cardiac failure, when the normal neural control of the SA node is altered.

In the case of adenosine, one would think particularly of situations involving hypoxia or ischemia. Basal cardiac production of adenosine has been found to be elevated in one model of volume-overload heart failure, perhaps because of the greater wall stress and the resultant reduction in oxygen supply-and-demand balance. Even greater adenosine production during hypoxia or ischemia would be expected. In heart failure, the normal neural control of the heart and its pacemaker might be reduced in importance compared with the influence of adenosine or other locally released or circulating humoral agents. For instance, cardiac arrest in human patients with advanced heart failure is often associated with bradycardia or bradycardias at the time of arrest. The anomalous bradycardia observed in exercising dogs with heart failure has already been noted. These patterns are not readily explained by neural mechanisms, because they are generally reduced in importance in heart failure. In light of our finding that adenosine's negative chronotropic actions are so readily manifest in at least one model of heart failure, it seems reasonable to include adenosine as one of the endogenous factors whose importance in the etiology of cardiac rhythm disturbances in heart failure needs to be investigated.

Adenosine has been established as the drug of choice in treating certain types of supraventricular tachycardia, specifically those involving a reentry conduction loop in the AV node. It is possible that the combination of sinus bradycardia, which would be present in failing but not in "normal" hearts, with the transient AV conduction block might elicit undesirable results, for example, by allowing ventricular ectopy or reentry to occur. In fact, we observed premature ventricular contractions or paroxysmal ventricular tachycardia after adenosine injection in five of 16 dogs studied after 3 or 4 weeks of pacing. Our study
also suggests, therefore, that it would be prudent to
evaluate the use of adenosine to treat supraventricular
tachycardia when it is accompanied by heart failure.

Acknowledgments

We thank the Pacesetter Co., Los Angeles, Calif., for their
generous donation of ventricular pacing electrodes. We are
grateful for the technical assistance of Francisca Y. Ochoa
and Manuel Ochoa.

References


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Circulation. 1992;85:1118-1124
doi: 10.1161/01.CIR.85.3.1118
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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