Adenosine, which is an endogenous nucleoside produced in many tissues, acts locally to yield a number of specific effects. In 1929, Drury and Szent-Gyorgyi recognized that adenine compounds, such as adenosine, have important actions in the mammalian heart. These actions can influence virtually every aspect of cardiac function. Basically, adenosine affects the cardiac conduction system by depressing sinoatrial (SA) and atrioventricular (AV) node activity, as well as by reducing ventricular automaticity. Adenosine also regulates myocardial metabolic function through coronary vasodilation, depression of atrial contractility, and blunting of the stimulatory effects of catecholamines on the myocardium.

ADENOSINE FORMATION, TRANSPORT, AND DEGRADATION

Adenosine is formed by the dephosphorylation of adenosine monophosphate (AMP) both intracellularly and extracellularly. This is catalyzed by 5'-nucleotidase which may be found in both the cell membrane and the cytosol. This AMP may come from either an intracellular equilibrium with adenosine diphosphate (ADP) and adenosine triphosphate (ATP), a mitochondrial source, or may be formed from extracellular sources of adenine nucleotides such as platelets and endothelium. In addition, in the cell, S-adenosylhomocysteine (SAH) can be hydrolyzed to form adenosine. The relative contributions of these precursors to the available pool of adenosine is not known and may vary under different physiologic situations.

There are a variety of factors that influence adenosine production by the heart, but levels are primarily increased when the myocardial oxygen demand exceeds supply. Adenosine measurement is difficult in any given circumstance, as elements such as endothelial cell and blood uptake and release, interstitial concentration, intracellular binding with SAH-hydrolase, and flow all influence venous adenosine concentrations.

Adenosine is removed from tissues either by phosphorylation to AMP by adenosine kinase or by deamination by adenosine deaminase. Although extracellular adenosine deaminase exists, both of these enzymes are predominantly intracellular; therefore, adenosine must be transported into the cell for breakdown. This is achieved by simple and facilitated diffusion via a bidirectional nucleoside transport mechanism. Transport into cells is also necessary for the rapid removal of adenosine from its site of action on the cell surface. Conversely, adenosine formed inside the cell must be transported outside in order to activate extracellular receptors. Medications such as dipyridamole block the transport of adenosine resulting in a net accumulation of extracellular adenosine (Fig 1).

PHYSIOLOGIC EFFECTS OF ADENOSINE

The primary physiologic effects of adenosine depend on the different types of receptors present within the effector tissue. In the heart there are at least two different types of adenosine receptors, A₁ and A₂. Adenosine A₁ receptors are found in the cardiomyocytes that mediate the sinus slowing and AV-blocking actions of adenosine. Adenosine A₂ receptors are present in endothelial and vascular smooth muscle cells and cause coronary vasodilation when activated. Despite being a potent coronary vasodilator, thus improving coronary blood flow, the general effect of adenosine is to depress cardiac function. It slows heart rate, slows AV conduction, and antagonizes the inotropic effects of catecholamines. The sum of these effects is to increase oxygen supply and decrease myocardial oxygen consumption leading some to characterize adenosine as cardioprotective.

These cardiac effects of adenosine can be loosely classified as either direct or indirect (Table 1). When an adenosine effect does not depend on catecholamine...
stimulation, that effect is a direct effect. When cyclic AMP must be increased before the effect of adenosine is apparent, that effect is indirect.2

Electrophysiologic Effects?

Adenosine has several particular properties that make it unique among drugs with electrophysiologic effects. The two most important, from a practical standpoint, are its short half-life in humans and its specific actions in different cardiac tissues. Adenosine directly shortens the atrial action potential duration, and the automaticity of the SA node and other cardiac pacemakers are suppressed. Conduction through the AV node is depressed and refractoriness is prolonged by adenosine, thus transiently interrupting impulse propagation.7 There is little effect on ventricular myocytes in the absence of catecholamines. The indirect cardiac effects of adenosine are antiadrenergic.

Table 1—Cardiac Effects of Adenosine*

<table>
<thead>
<tr>
<th>Adenosine Receptor Effects</th>
<th>Effects</th>
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<tbody>
<tr>
<td>Direct</td>
<td>Decrease SA node automaticity</td>
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<tr>
<td></td>
<td>Decrease AV node conduction</td>
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<tr>
<td></td>
<td>Decrease atrial contractility</td>
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<tr>
<td></td>
<td>Decrease atrial action potential duration</td>
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<td></td>
<td>Suppress norepinephrine release</td>
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<tr>
<td>Indirect</td>
<td>Attenuate chronotropic, dromotropic, and isotropic effects of catecholamines</td>
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<tr>
<td></td>
<td>Suppress catecholamine-induced triggered ventricular afterpotentials</td>
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<tr>
<td>Aβ Receptor Effects</td>
<td>Vasodilation</td>
</tr>
<tr>
<td></td>
<td>Decrease blood pressure</td>
</tr>
<tr>
<td></td>
<td>Increase ventilation</td>
</tr>
<tr>
<td></td>
<td>Cause chest pain/discomfort</td>
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*SA = sinoatrial; AV = atrioventricular.

Adenosine antagonizes the positive chronotropy, dromotropy, and inotropy, and suppresses triggered ventricular afterpotentials induced by circulating catecholamines.8

Regulation of Coronary Blood Flow

Adenosine is a potent coronary vasodilator and is released by the myocardium in increased amounts during episodes of ischemia, probably as a result of myocyte adenine nucleotide degradation.2 Simply increasing myocardial oxygen consumption may cause increases in adenosine release, but this seems to be related to the mechanism by which oxygen consumption is increased and is controversial. For example, it appears that adenosine release is higher with catecholamine stimulation than with atrial pacing or increases in afterload.

There have been several studies in animal models that suggest that adenosine release by the heart is a sensitive marker of ischemia.3,9 However, the evidence for this in human hearts is mostly indirect, that is, the measurement of increased levels of adenosine breakdown products (ie, inosine and hypoxanthine) in coronary sinus blood during ischemia. Edlund and colleagues10 induced myocardial ischemia by atrial pacing and measured adenosine and its breakdown product hypoxanthine in the coronary sinus. During ischemia, they were unable to measure a change in adenosine, but levels of hypoxanthine increased significantly in coronary sinus blood. Remme et al11 similarly measured hypoxanthine in coronary sinus blood in patients with pacing-induced angina. They found a twofold increase in coronary sinus hypoxanthine after the onset of angina as compared with control. They also found that lactate extraction occurred earlier in the ischemia process than increased hypoxanthine.
Fox and colleagues evaluated the release of adenosine by the heart during pacing-induced angina in 15 patients undergoing cardiac catheterization. In 13 of these patients, a tenfold increase in adenosine levels appeared during ischemia compared with control. In 11 of the 13, adenosine had not been detectable during the control or recovery period. Fox et al also studied nine patients undergoing ischemic arrest during cardiac surgery. They measured adenosine, inosine, hypoxanthine, and lactate in the coronary sinus as indicators of ischemia during reperfusion both before and after the heart was beating. While the heart was still arrested, adenosine level was five times the control values. These levels were similar to those obtained in earlier animal experiments using an intermittent coronary occlusion model. While problems of technique exist with these studies, newer methods are being developed to provide more accurate measurements of coronary sinus adenosine. We have developed a dual-lumen catheter that allows in vivo adenosine sampling from the coronary sinus. Nine patients (four without significant coronary artery disease and five with severe coronary artery disease) underwent rapid atrial pacing during which the five patients with coronary artery disease developed evidence of ischemia. Significantly elevated adenosine levels were measured in the patients with ischemia as opposed to the patients without evidence of ischemia (Fig 2).

Adenosine release may also be associated with the sensation of angina-like chest pain. Adenosine administered as an intravenous bolus into healthy volunteers induces angina-like chest pain. The pain is independent of any change in coronary blood flow or obvious myocardial ischemia and the intensity of the pain experienced is dose dependent. The intensity of the pain can be worsened with administration of dipyridamole and lessened with aminophylline. Investigations in our laboratory demonstrate that this chest pain is cardiac in etiology and that intact cardiac afferent innervation is necessary for the transmission of the chest pain.

**Hemodynamic and Respiratory Effects of Exogenous Adenosine**

Biagioni et al studied the cardiovascular and respiratory effects of adenosine in healthy volunteers. Adenosine infusion (140 μg/kg/min) increased heart rate (+30 beats/min) and systolic blood pressure (+16 mm Hg), but decreased the diastolic pressure (-5 mm Hg) resulting in no change of the mean arterial pressure. Respiration was stimulated evidenced by a fall in PaCO2 of 10 mm Hg and rise in pH of 0.08. Ventilatory changes were not due to bronchoconstriction, hypoxia, or hypotension. Watt et al studied the heart rate and respiratory effects of adenosine bolus in both young and elderly patients. Using repeated boluses of increasing doses from 20 to 100 μg/kg, they found an increase in minute ventilation that was dose related but not age related. Likewise, the initial bradycardia that occurred as well as the tachycardia that followed was also dose related but not age related. Bush et al studied the hemodynamic effects of continuous infusions of adenosine on a group of healthy volunteers. Using doses of 70 μg/kg/min, they found a drop in estimated systemic resistance of 357 ± 44 dynes/cm² with no change in heart rate. This is
Table 2—Potential Applications of Adenosine

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<th>Therapeutic</th>
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<tr>
<td>Myocardial preconditioning</td>
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<td>Cardioplegia</td>
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<td>Substrate to replenish adenosine triphosphate</td>
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<tr>
<td>Preservative in organ transplantation</td>
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<td>Vasodilator in pulmonary hypertension</td>
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<td>Termination of supraventricular tachycardias</td>
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<td>Termination of catecholamine-induced ventricular tachycardias</td>
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Diagnostic

Coronary blood flow reserve assessment
Pharmacologic cardiac stress testing
Diagnosis of tachyarrhythmias

somewhat different from the clinical observations of Verani and colleagues in which 140 μg/kg/min infusions were used for cardiac imaging. They found a slight decrease in systolic and diastolic blood pressure (8.7 ± 19.3 mm Hg and 6.7 ± 9.4 mm Hg, respectively) and an increase in heart rate of 14.5 ± 11.0 beats/min. These findings are supported by Smits et al who describe an adenosine-induced vasodilation in the extremities. Blood flow to the forearm increased 572 percent as compared with placebo with an adenosine infusion into the brachial artery. In all studies, the hemodynamic changes induced by adenosine are resolved within several minutes of termination of infusion.

Diagnostic Uses of Adenosine

Despite only one FDA-approved indication, there are many other potential diagnostic and therapeutic applications for adenosine (Table 2).

Assessment of Coronary Flow Reserve

Because adenosine is such a potent coronary vasodilator, it has been used to assess coronary flow reserve (maximal compared with resting coronary flow). Although there are differences in maximal response noted and dose administered, several investigators have found intracoronary adenosine to be as effective as papaverine for assessing coronary flow reserve. Wilson and colleagues have shown that a 16-μg bolus into the left coronary artery causes a similar degree of coronary hyperemia as papaverine but with a shorter duration of effect. They also showed that 140 μg/kg/min intravenous infusion produces near maximal coronary hyperemia.

Pharmacologic Cardiac Stress Testing

Accumulation of adenosine in the extracellular space causes a relative augmentation of coronary blood flow in normally perfused areas as opposed to abnormally perfused areas. Cardiac imaging using thallium-201 takes advantage of this vasodilatory property. By causing a relative augmentation of coronary blood flow in normally compared with abnormally perfused areas, an imbalance in coronary perfusion can be demonstrated with thallium-201. When ischemia occurs as a result of this imbalance, mechanical consequences manifested initially by a decrease in left ventricular compliance and wall thickening, followed by focal wall motion abnormalities, may be demonstrated using wall motion imaging techniques.

Presently, dipyridamole is commonly used as a pharmacologic stressor to take advantage of these adenosine actions. Dipyridamole has several actions, but serves primarily as an adenosine transport blocking agent with the end result being an accumulation of extracellular adenosine. The most commonly used intravenous dose of dipyridamole for imaging is 0.56 mg/kg infused over 4 min. Oral dipyridamole may also be used in doses of 300 to 600 mg. This has some disadvantages, however, in that serum levels are inconsistent and a much longer period of medical supervision is necessary to perform the test safely. Subsequent imaging may be performed with either exercise or isometric handgrip in addition to dipyridamole in order to improve sensitivity.

Cardiac stress imaging with dipyridamole is fairly safe with serious cardiac side effects being rare. Minor noncardiac side effects are somewhat more common. If severe ischemia or side effects occur from dipyridamole administration, aminophylline, 75 to 250 mg, can be administered intravenously with prompt resolution of the symptoms. Aminophylline acts as a competitive adenosine receptor antagonist, thus limiting the effects of dipyridamole. Ranhosky et al reported the safety data on 3,911 patients who underwent dipyridamole-thallium cardiac imaging. Ten (0.3 percent) patients had major adverse effects (2 fatal myocardial infarctions [MIs], 2 nonfatal MIs, 6 acute bronchospasm). Minor side effects such as chest pain, headache, dizziness, nausea, and hypotension occurred in 1,820 patients (47 percent). Aminophylline was required in 454 (12 percent) patients to reverse dipyridamole-induced side effects. Lam and colleagues described a series of 337 patients undergoing intravenous dipyridamole imaging and found little difference in side effects between those older than 70 years of age and younger patients. Aminophylline was required to reverse side effects in 15 percent and severe ischemia was present in only 2.4 percent of patients. Because of the possibility of severe bronchospasm induced by dipyridamole, it should be given cautiously in patients with obstructive lung disease.

Because the mechanism of action of dipyridamole involves the blocking of adenosine uptake and the subsequent extracellular accumulation of adenosine, it is logical to use adenosine rather than dipyridamole. The half-life of the drug is very short in humans and thus the effects and side effects should be of shorter duration. Although not currently FDA approved for
this indication, some investigators have begun to use continuous infusions of adenosine for cardiac imaging. Verani and colleagues\(^{26}\) have reported on the use of adenosine with thallium-201 imaging in 89 patients unable to perform exercise. Adenosine was infused at a maximal rate of 140 \(\mu\)g/kg/min and the radioisotope was injected after 1 min of the maximum dose. Scanning was performed immediately and at 4 h. Although side effects occurred in 83 percent of patients, all resolved spontaneously within several minutes. The overall sensitivity was 83 percent and the specificity was 94 percent for detecting coronary artery disease. These data are similar to those reported for intravenous dipyridamole.

Adenosine thallium imaging has an excellent safety profile.\(^{26}\) In a series of 607 patients receiving 140 \(\mu\)g/kg/min of adenosine for 6 min, side effects were frequent but generally minor (flushing in 35 percent, chest pain in 34 percent, headache in 21 percent, and dyspnea in 19 percent). First and second-degree AV block occurred in 9.6 percent and 3.6 percent of the patients, respectively. Due to the ultrashort half-life of adenosine, simply stopping the intravenous infusion can resolve most untoward side effects of adenosine. Severe side effects without serious complication occurred in ten (1.6 percent) patients with only six (1 percent) requiring discontinuation of the adenosine infusion. Lee et al\(^{27}\) reported their experience with 858 patients who underwent adenosine thallium imaging. Fifty-four patients (6 percent) developed second and one (1 percent) developed third-degree heart block during intravenous infusion of adenosine at a rate of 140 \(\mu\)g/kg/min. Of these 55 patients with adenosine-induced AV block, only seven developed symptoms, and only one required premature discontinuation of the infusion. Chest pain developed in 384 of 858 patients (45 percent). There were no deaths or MIs reported.

Stress echocardiography has also been performed using adenosine to induce wall motion abnormalities. Zoghbi et al\(^{28}\) also performed adenosine echocardiography stress testing on 73 patients prior to planned cardiac catheterization. The sensitivity of adenosine echocardiography for the detection of \(\geq\)75 percent coronary artery diameter stenosis was 85 percent, with a specificity of 92 percent. Ischemic-type ECG changes were induced only in 15 percent.\(^{29}\) Martin et al\(^{30}\) compared the accuracy of adenosine, dobutamine, and dipyridamole stress echocardiography in detecting >50 percent coronary artery diameter stenosis in 40 patients. Dobutamine stress echocardiography had a higher sensitivity (76 percent) than that of adenosine (40 percent) or dipyridamole (56 percent); however, adenosine echocardiography had a higher specificity (93 percent) compared with dipyridamole (67 percent) or dobutamine (60 percent). Side effects were more commonly noted during the adenosine echocardiogram; yet, no patient required therapy for persistent symptoms as was necessary in 40 percent of the dipyridamole and 12 percent of the dobutamine tests.

Nguyen and colleagues\(^{31}\) evaluated the sensitivity and specificity of adenosine thallium, adenosine stress echocardiography, and exercise single photon emission computed tomographic thallium imaging compared with coronary arteriography. The predictive accuracy of adenosine thallium imaging was slightly better than that of exercise (90 vs 80 percent), although not statistically different. New wall motion abnormalities detected by echocardiography during adenosine infusion occurred in only 10 percent of their patients.

![Rhythm strip from a 39-year-old man with a rapid narrow complex tachycardia of unknown etiology. Adenosine, 6 mg, is administered as an intravenous bolus via the right antecubital vein 10 s prior to this ECG recording. When adenosine induces atrioventricular block, atrial flutter waves are then clearly recognized and the diagnosis made.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21678/)
with coronary artery disease. Therefore, adenosine echocardiography appears to be a useful tool in the detection and assessment of coronary artery disease, but more study is needed.

**Diagnosis of Tachyarrhythmias**

Adenosine may be very useful in the differential diagnosis of tachyarrhythmias. Because of its high degree of site of action specificity, bolus dosing can be used to distinguish the mechanism of both wide and narrow complex tachycardias (Fig 3). Also, its short half-life and minimal hemodynamic consequences make it fairly safe as a rapid diagnostic tool even in patients with somewhat unstable conditions. As with physiologic maneuvers that increase vagal tone, such as carotid sinus massage, adenosine can be used to temporarily slow AV conduction. This allows for the identification of the underlying atrial mechanism such as atrial flutter or may terminate AV nodal reentrant rhythms, thus both clarifying the diagnosis and treating the arrhythmia.

Several clinical studies have confirmed this concept. Rankin et al\(^3\) studied 64 patients with 92 episodes of sustained tachycardia. In the 40 patients with narrow complex tachycardia, adenosine restored normal sinus rhythm or produced AV block sufficient to reveal the diagnosis in all 40. In the other 24 patients with wide complex tachycardia, adenosine was useful in diagnosis in 92 percent. Of interest is that adenosine gave information supplemental to the surface ECG in 25 percent of patients. Griffith et al\(^3\) reported the use of adenosine in 26 patients with wide complex tachycardia. In these patients, adenosine had a sensitivity of 89 percent, a specificity of 94 percent, and a predictive accuracy of 92 percent for assessing the supraventricular origin of the tachycardia. Conti et al\(^3\) presented 12 ECG recordings of various tachycardias before and after adenosine administration to 20 internal medicine residents. The diagnostic accuracy of ventricular tachycardia rose from 45 percent to 72 percent following adenosine administration. No physician correctly identified tachycardia involving an accessory pathway. Following adenosine, the diagnostic accuracy increased to 45 percent. Likewise, the diagnostic accuracy following adenosine administration rose with AV nodal reentrant tachycardias by 22 percent and atrial fibrillation by 50 percent. No significant benefit was noted for the diagnosis of atrial flutter. Therefore, adenosine substantially improves even an inexperienced physician's ability to distinguish tachyarrhythmias.

In patients in whom an accessory pathway may not be apparent while in a sinus rhythm, temporary block in AV node conduction may cause preferential conduction through the accessory pathway, thus unmasking preexcitation.\(^3\) Conversely, adenosine infusion may also be used in this way as a diagnostic test to assess the completeness of accessory pathway ablation procedures.\(^3\)

**Therapeutic Uses of Adenosine**

### Acute Myocardial Ischemia

Intravenous adenosine infusion appears to be of little use in the treatment of acute myocardial ischemia. To the contrary, because adenosine may contribute to an imbalance in coronary blood flow between well-perfused and poorly perfused areas, it may potentially contribute to myocardial ischemia. In fact, adenosine antagonists may be useful. This concept has been exploited by the use of theophylline, an adenosine receptor antagonist, for angina. Picano and colleagues\(^3\) treated eight patients with either aminophylline infusion or placebo following a blinded protocol. After infusion, exercise testing was performed and there was an increase in both work tolerance and rate pressure product with aminophylline suggesting prevention of maldistribution of flow. Crea and colleagues\(^3\) found similar results using intravenous theophylline in a group of ten patients using exercise testing. These same investigators gave 9 patients oral theophylline and found that despite having an increased 24-hour heart rate compared with placebo, there was a lower total ischemia time as measured by ambulatory ECG monitoring.\(^3\) All of these data are somewhat contradictory to the notion that adenosine is cardioprotective. It is possible, however, that theophylline is working through some other mechanism to improve ischemia.

### Myocardial Preconditioning

This term describes the condition in which cardiomyocytes become tolerant to a prolonged ischemic insult through prior exposure to multiple brief episodes of ischemia. Murray et al\(^3\) found that they could reduce infarct size by 75 percent when the myocardial region at risk was previously exposed to several 5-min ischemic episodes prior to the prolonged ischemic event. Deutsch and colleagues\(^3\) report a similar tolerance to the ischemic insult that develops with repetitive coronary occlusions during angioplasty. A significant reduction in severity of angina, ST-segment deviation, and transmural myocardial lactate metabolism was noted following the second balloon inflation. Cribier et al\(^3\) confirmed these results in 17 patients. A significant reduction in severity of angina, ST-segment deviation, left ventricular filling pressure, and impairment of the left ventricular ejection fraction was noted with successive balloon inflations.

Adenosine seems to be associated with this myocardial protection afforded by preconditioning. Kerensky et al\(^3\) examined nine patients who had complete resolution of ischemic ST-segment changes that oc-
curred during angioplasty balloon inflation. Seven of the nine had much less ST-segment elevation with the second inflation, suggesting preconditioning had occurred. Eleven other patients received adenosine intracoronary prior to the first angioplasty balloon inflation. The amount of ischemia noted with the first inflation was reduced only in 1 of the 11 suggesting preconditioning had occurred prior to the first balloon inflation. Thereby, infusion of adenosine prior to ischemic episodes, such as angioplasty, may "precondition" the myocardium and prevent ischemic insults.

The role of adenosine in preconditioning the myocytes to resist injury during ischemia and reperfusion is multifaceted. Myocardial injury is due, in part, to activated leukocytes and platelets, ATP depletion and calcium overload of the myocardium, catecholamine release, and coronary vasospasm. Adenosine can attenuate each of these deleterious actions. Animal data support the fact that adenosine, when administered early in the course of a coronary occlusion with reperfusion, can reduce infarct size and improve subsequent ventricular function as compared with placebo. Olsson et al43 infused adenosine for 1 h into the left anterior descending artery of dogs following a 90-min occlusion of that vessel. After 24 h, the size of the infarct was 10 percent of the myocardial region at risk in the adenosine group compared with 41 percent in the control group. Additionally, regional and global left ventricular function was improved in the adenosine group compared with the control group. Babbitt et al44 demonstrated similar beneficial results of adenosine infusion following a 120-min occlusion of the left anterior descending artery in dogs; however, they found that the cardioprotective effects were lost with 180-min vessel occlusion.

Intravenous infusions of adenosine have also been shown to be effective in reducing infarct size. Pitarys et al45 infused adenosine intravenously at a rate of 150 μg/kg/min for 1 h following 90-min occlusion of the left anterior descending artery in dogs. Infarct size was 35 percent of the region of myocardium at risk in the control group compared with 17 percent in the adenosine-treated group. Again, improvement in regional ventricular function was noted in the adenosine-treated group. Toombs et al46 studied 4 groups of rabbits following 30 min of ischemia and 2 h of reperfusion. The infarct size in a group pretreated with adenosine, 140 μg/kg/min, for 5 min was 8 percent of the myocardial region at risk compared with 28 percent in the control group. A1/A2 blockade following adenosine pretreatment abolished the myocardial protection afforded by adenosine alone. A1/A2 blockade alone increased infarct size by 24 percent as compared with the control group, suggesting that endogenous adenosine release can confer some myocardial protection. Tadokoro et al47 infused adenosine (20 μg/kg/min) retrograde in the great cardiac vein for 30 min following a 60-min occlusion of the left anterior descending artery in pigs. Infarct size was reduced to 27 percent of the region at risk compared with 56 percent in controls. Therefore, animal data support the notion that when early reperfusion can be achieved, adenosine infusion by any route can significantly reduce infarct size and improve ventricular function.

Endogenous adenosine release in response to ischemia is also protective. Miura et al48 demonstrated that aminophylline could block the beneficial effects afforded with 2 min of ischemic preconditioning in rabbits. Dipyridamole potentiated the preconditioning effect by 60 percent over ischemic preconditioning alone. This suggests that through slowing adenosine degradation and thereby allowing increased stimulation of the adenosine receptors, endogenous adenosine mediates the increased ischemic tolerance.

The beneficial effects of adenosine seem to be mediated by the adenosine A1 receptor. Thornton and colleagues49 demonstrated this in rabbits. Myocardial preconditioning was accomplished by subjecting the animals to 5 min of ischemia and 10 min of reperfusion prior to 30 min of ischemia and 3 h of reperfusion. In the preconditioned group, infarct size was 8 percent of the myocardium at risk compared with 38 percent in the control group. Adenosine A1 agonists given 15 min prior to the 30 min of ischemia provided the same protection as the ischemic myocardial preconditioning. Infusion of the adenosine A1 agonist after ischemia and during reperfusion offered no benefit. Use of a pure adenosine A2 agonist failed to limit infarct size. These data have been substantiated by other investigations. These reports indicate that stimulation of the adenosine A1 receptor, from either endogenous or exogenous sources, is necessary for myocardial preconditioning to occur.

Open Heart Surgery

While the aorta is cross-clamped during open heart surgery, global myocardial ischemia occurs and adenosine is released.13 The effects of the ischemia are lessened with cardioplegia; however, tissue ATP levels still fall and are associated with diminished left ventricular power. It has been suggested that recovery of ATP during reperfusion is important for recovery of left ventricular power and that this ATP recovery is limited by a lack of nucleotide precursors. Animal studies with the isolated perfused rat heart model show that infusion of adenosine, an ATP precursor, during and following a prolonged ischemic insult can improve ATP levels and left ventricular power in the reperfused heart as compared with the control.50,51

This same concept of ATP depletion during ischemia has led many to use adenosine in cardioplegic solu-
tions. Hohlfeld et al.\textsuperscript{52} using an isolated heart model, found that the addition of adenosine at 15 to 30 \mu mol/L to cardioplegic solution would increase the ATP level, but would not improve ventricular function. Bolling et al.\textsuperscript{53-55} in a series of studies, demonstrated that higher doses of adenosine at 100 to 400 \mu mol/L would increase tissue ATP concentration and improve ventricular function as compared with controls. Therefore, animal data suggest that the addition of adenosine to cardioplegia will be helpful in the restoration of basal ATP tissue stores as well as the recovery of left ventricular contractility. Although adenosine has been added to some cardioplegia solutions, a definite beneficial effect has yet to be shown in humans.

\textit{Transplant Organ Preservation}

Present methods of tissue preservation for transplantation have limited the total ischemia time to approximately 4 h. Longer ischemic durations are associated with an increase in tissue edema and vascular endothelial injury. Two groups have reported that the addition of adenosine to the perfusion fluid in a continuous hypothermic perfusion system has allowed the successful storage and preservation of canine hearts for up to 24 h prior to transplantation.\textsuperscript{56,57} Human data are unavailable.

\textit{Vasodilator in Pulmonary Hypertension}

In patients with primary pulmonary hypertension, it is useful to identify those patients with reversible pulmonary vasoconstriction. Rich et al.\textsuperscript{58} found that those patients who responded to vasodilator agents had an average survival of 2 years, whereas those patients with fixed pulmonary hypertension had a life expectancy of 6 months. Adenosine, when infused centrally, is able to cause pulmonary vasodilation without any significant decrease in the systemic vascular resistance. Studies from our laboratory found that in normal patients, adenosine doses of 30 \mu g/kg/min infused into the right ventricle caused selective pulmonary vasodilation without significant systemic effect.\textsuperscript{59} Haywood et al.\textsuperscript{60} infused adenosine at 100 \mu g/kg/min via a peripheral intravenous line in 21 patients with biventricular failure. The pulmonary vascular resistance fell 41 percent with no change in the mean arterial pressure. Nitroprusside infusion provided a similar decline in the pulmonary vascular resistance; however, this was associated with a 16 mm Hg fall in the mean arterial pressure. These investigators concluded that adenosine is a potent selective pulmonary vasodilator agent in patients with biventricular failure. Morgan et al.\textsuperscript{61} reported results of adenosine infusion into the pulmonary artery of seven patients with primary pulmonary hypertension (Fig 4). At a dose of 50 \mu g/kg/min, they demonstrated a 39 percent decrease in pulmonary vascular resistance and 8 percent decrease in the mean pulmonary artery pressure. The systemic vascular resistance did decrease 31 percent at this dose. Schrader et al.\textsuperscript{62} describe use of adenosine as a continuous intravenous infusion to induce pulmonary vasodilation. The adenosine was infused via the left brachial vein at a mean dose of 236 \mu g/kg/min which decreased the pulmonary vascular resistance by 37 percent, and proved to be more effective than high-dose nifedipine. However, with the peripheral administration, the systemic vascular resistance also decreased by 40 percent. Therefore, adenosine, particularly when infused centrally, is a

![Figure 4. The effect of increasing doses of adenosine on the pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), cardiac output (CO), and mean pulmonary artery pressure (MPAP) in patients with pulmonary hypertension. A 10-min equilibrium period was allowed between increasing doses of adenosine. The percentage change from baseline is plotted for PVR, SVR, and CO on the Y1 axis. The change in mm Hg from baseline for the MPAP is plotted on the Y2 axis. Data from reference 61.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21678/ on 06/27/2017)
selective pulmonary vasodilator and may provide a safe and rapid determination of the reversibility of vascular resistance.

**Termination of Supraventricular and Ventricular Tachycardias**

Adenosine is usually effective for terminating supraventricular tachycardia when the AV node is part of the reentrant circuit (Fig 5). In patients with accessory pathways, which are generally insensitive to adenosine, it may still be effective depending on the role of the AV node in the reentrant circuit. DiMarco et al. studied a series of 46 patients with various rhythm disturbances given increasing doses of adenosine. In 16 of the patients with orthodromic reciprocating tachycardia, adenosine (mean dose, 91 ± 52 μg/kg; range, 2 to 23 mg) terminated the arrhythmia in every instance. In 13 patients with AV nodal reentrant tachycardia, adenosine (mean dose, 80 ± 47 μg/kg) also terminated the arrhythmia. The average time for termination in both groups was 19 ± 6 s. With the exception of one patient receiving sustained-release theophylline who did not respond to adenosine, there did not appear to be any significant drug interactions to either atropine or other antiarrhythmic drugs in the patients who received them.

Verapamil has become standard therapy for paroxysmal supraventricular tachycardia (PSVT) but may not always be effective and has potential disadvantages. Rankin and colleagues retrospectively reviewed their experience with verapamil and adenosine for termination of these arrhythmias and found that verapamil was successful in restoring sinus rhythm in 81 percent of episodes, whereas the adenosine was effective in 96 percent (diff, p<0.05). Recurrence of the arrhythmia was more common with adenosine (41 percent vs 1 percent); however, in those patients who received both agents at different times, adenosine seemed somewhat more effective for termination. DiMarco et al. also reported data from a multicenter study involving adenosine and verapamil compared with placebo for the termination of PSVT. Two specific trials were performed. The first protocol compared sequential doses of adenosine—3, 6, 9, and 12 mg—with equal volumes of saline solution. The second compared 6 mg and, if necessary, 12 mg of adenosine with 5 mg and, if necessary, 7.5 mg of verapamil. In protocol 1, there were 116 patients who were diagnosed as having PSVT and 42 more who were crossed over from placebo having not responded. Cumulative success rates with progressively higher doses for conversion to sinus rhythm were 35.2, 62.3, 80.2, and 91.4 percent with adenosine, whereas for saline solution infusion, the cumulative conversion rate was only 16.1 percent (p<0.001). In protocol 2, 64 patients received verapamil and 61 received adenosine. Of these, 93.4 percent converted with adenosine and 90.6 percent converted with verapamil (p = NS). In addition, in those who did not convert with verapamil, all converted with adenosine. Side effects were slightly more

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**Figure 5.** Rhythm strip from a 25-year-old woman with a rapid narrow complex tachycardia of unknown etiology. Adenosine, 6 mg, is administered as an intravenous bolus via the right antecubital vein 10 s prior to this ECG recording. When adenosine induces atrioventricular (AV) block, the patient's AV nodal reentrant circuit is broken and normal sinus rhythm is restored. In this example, not only the diagnosis of AV nodal reentrant tachycardia is made, but also a therapeutic benefit of adenosine is realized as the arrhythmia is terminated.
common with adenosine but these were generally mild and short lived.

Adenosine has also been shown to be effective for the termination of supraventricular tachycardia in children. Till and colleagues reported 117 episodes of supraventricular tachycardia in 50 children of which 90 (77 percent) were terminated with adenosine. The rhythm disturbances that were not terminated included atrial flutter, His bundle tachycardia, and ectopic atrial tachycardia. As in all of the reported series in adult patients, recurrence of the tachycardia was not prevented by adenosine and in this series, 13 episodes immediately recurred. Nevertheless, the authors concluded that adenosine was safe and effective and, as others have noted, often facilitated the diagnosis of the tachycardia.

Adenosine is generally ineffective for termination of ventricular tachycardia of a reentrant or enhanced automaticity origin. The major exception to this is catecholamine-related ventricular tachycardia, which often does respond to adenosine. Clinically, this is primarily manifested as exercise-induced ventricular tachycardia. In such circumstances, adenosine specifically attenuates catecholamine-induced afterdepolarizations and triggered activity through a reduction in the intracellular calcium and a decrease in the release of calcium from the sarcoplasmic reticulum.

Bradyarrhythmias and AV Block

Adenosine may play a role in the etiology of bradyarrhythmias and AV block noted with and without myocardial injury, and adenosine antagonism may improve these rhythms. Alboni et al. described 17 patients with symptomatic sick sinus syndrome. At baseline, the mean 24-h heart rate was 51 beats/min and the minimal 24-h heart rate was 36 beats/min. Four patients had sinus pauses >2.5 s. Theophylline, 700 mg, was given daily to achieve a mean level of 11 mg/L. The mean 24-h heart rate increased to 64 beats/min and the minimal 24-h heart rate was 48 beats/min. There were no sinus pauses >2.5 s. Twelve of the 17 patients (71 percent) had total resolution of symptoms. This study suggests that adenosine receptor blockade may be useful in the initial therapy of bradyarrhythmias.

Wesley et al. reported a case of acute inferior myocardial infarction complicated by second- and third-degree heart block. Atropine, 2 mg, intravenously failed to resolve the AV block. Aminophylline, 400 mg, was given as a bolus intravenously and led to complete resolution of the AV block. However, 10 h later, the AV block recurred. This case report suggests that adenosine antagonists may be useful for treating bradyarrhythmias and AV block noted with acute myocardial injury.

Conclusion

Adenosine is unique among cardiovascular drugs in that it has effects after endogenous release from the heart in response to various stimuli, and it can be administered as a drug with several well-defined physiologic effects. Because much of the human physiology of adenosine is well understood, its application as a diagnostic and therapeutic agent has been logical, well founded in basic research, and effective. As clinical experience with this drug increases, we can anticipate other potentially exciting applications of adenosine in various cardiac conditions.

References

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