Cardiac Electrophysiology of Adenosine
Basic and Clinical Concepts

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Adenosine is an endogenous nucleoside that has potent electrophysiologic effects. As an antiarrhythmic agent, adenosine has several unique properties: 1) it is an intermediate metabolite (Figure 1), 2) it has a very short half-life (less than 1.5 seconds), 3) its effects are mediated by specific membrane receptors coupled to guanine nucleotide binding proteins (G proteins), and 4) it has site-specific actions in the myocardium with important differential effects in supraventricular and ventricular tissue.

Adenosine also has an important role in regulating the myocardial oxygen supply-demand balance. Adenosine achieves this by increasing oxygen supply through coronary vasodilation and by reducing oxygen demand by decreasing myocardial contractility, antagonizing the effects of catecholamines, and depressing automaticity and conduction within the sinus and atrioventricular (AV) nodes.

Recently, the United States Food and Drug Administration approved the use of adenosine for therapy of paroxysmal supraventricular tachycardia (PSVT), the first clinical application of adenosine. The purpose of this review is to present a rational approach for the therapeutic applications of adenosine for cardiac arrhythmias based on an understanding of its cellular and integrative mechanisms of action.

Adenosine System

The essential components of the adenosine system in the heart are 1) a mechanism for formation of adenosine, 2) a receptor-effector complex, and 3) a mechanism for the removal of adenosine and the attenuation of its actions (Figure 2).

Source of adenosine. Adenosine is formed by dephosphorylation of adenosine monophosphate (AMP) (ATP pathway, Figure 2, panel 1), catalyzed by the enzyme 5'-nucleotidase. This enzyme is mostly bound to cell membranes (ecto-5'-nucleotidase) in the heart but is also present in the cytosol (cytosolic 5'-nucleotidase). Therefore, adenosine can be formed either intracellularly or extracellularly by the degradation of AMP. Because all the enzymes required for the degradation of adenosine triphosphate (ATP) and AMP can be found extracellularly, adenine nucleotides released from platelets and endothelial cells are also potential sources of adenosine. Extracellular cyclic AMP (cAMP) can also lead to the formation of adenosine, which may be an important source of the nucleoside during β-adrenergic stimulation. In addition to the ATP pathway, adenosine can be formed intracellularly by the degradation of S-adenosylhomocysteine (SAH), catalyzed by the enzyme S-adenosylhomocysteine hydrolase (SAH pathway, Figure 2, panel 1). The relative contribution of each metabolic pathway to the formation of adenosine varies according to the experimental conditions. For example, in normoxic hearts a significant fraction of adenosine is derived from the SAH pathway, whereas during hypoxia the ATP pathway is the main source of adenosine.

Receptor-effector complex. Adenosine binds to specific cell surface receptors (intracellular adenosine is transported out of the cell), which in turn triggers a series of reactions that lead to activation of effector units such as membrane ionic channels (Figure 2, panel 2). The adenosine receptor-effector coupling system (Figure 3), its activation, and the associated cardiac responses are discussed in detail below.

Removal of adenosine. The actions of adenosine can be terminated by enzymatic metabolism and by adenosine receptor antagonists (e.g., alkylxanthines) (Figure 2, panel 3). The nucleoside can be either deaminated by adenosine deaminase to inosine, which is mostly inactive, or phosphorylated by adenosine kinase to AMP. Since both adenosine deaminase and adenosine kinase are cytosolic enzymes, adenosine must first be taken up by the cells, by either simple or facilitated diffusion via a nucleoside transport system. This nucleoside transport system is ubiquitous (e.g., present in endothelial cells, erythrocytes, and cardiomyocytes) and can be inhibited by
nucleoside transport inhibitors such as dipyridamole. Inhibition of this transport system leads to marked potentiation of the cardiac actions of adenosine. For example, in the heart a significant correlation exists between the degree of inhibition of adenosine uptake and adenosine-induced AV nodal conduction delay. An alternative way by which the cardiac actions of adenosine can be terminated (Figure 2, panel 3) is by adenosine receptor antagonists. Caffeine and theophylline (aminophylline) are the most widely known adenosine antagonists; however, neither is potent nor selective. That is, theophylline antagonizes both the A1 receptor–mediated actions of adenosine (e.g., AV block, bradycardia) as well as the A2 receptor effects (e.g., coronary vasodilation). In recent years, several newly developed alkylxanthines (e.g., 8-cyclopentyl-1,3-dipropylxanthine) have been shown to be significantly more potent than the methylxanthines and are relatively selective for the cardiac A1 receptor. These new adenosine antagonists, which are not yet available for clinical use, have already become valuable experimental tools, and their potential as therapeutic agents has also been proposed.

Cardiac Adenosine A1 Receptor

The existence of specific extracellular adenosine receptors is now well established. Two subtypes of adenosine receptors have been identified based on biochemical and radioligand binding studies in the heart and on pharmacologic responses to adenosine and adenosine derivatives. A1 receptors, present in endothelial and vascular smooth muscle cells, mediate coronary vasodilation, whereas A1 receptors, present in cardiomyocytes, mediate the negative chronotropic, dromotropic, and inotropic actions of adenosine (see Figure 3).

Characterization of the adenosine A1 receptor from bovine and chick heart membranes by photoaffinity labeling indicates that it is a polypeptide with a molecular weight of 35–37.6 kDa, which is similar to that (38–40 kDa) of the A1 receptor from membranes of rat and bovine brain tissue. Based on studies with various radioligands (agonists and antagonists) and competition studies with different adenosine analogues, the cardiac adenosine A1 receptor appears to exist in two affinity states (high and low); the nonhydrolyzable guanine nucleotide Gpp(NH)p converts the A1 receptor from the high to the low affinity state.

The number (Bmax) and affinity (Kd) of cardiac adenosine A1 receptors appear to vary with the tissue (i.e., atrium versus ventricle) and the species. For example, the density of A1 receptors in atrial membranes is significantly greater than that in ventricular membranes. In guinea pig atrial and ventricular membranes, Bmax estimated with the radioligand [3H]DPCPX is 33±4 and 18±2 fmol/mg protein, respectively (unpublished data). This difference between atrium and ventricle has been confirmed in the human heart (i.e., 26.9±2.33 fmol/mg protein in atrial and 16.2±2.30 fmol/mg in ventricular myocardium).

Like many other cell surface receptors, the number of cardiac adenosine A1 receptors undergoes upregulation and downregulation when cardiac tissues are chronically exposed to elevated concentrations of adenosine receptor antagonists and agonists, respectively. Recently, downregulation and upregulation of cardiac A1 receptors have been shown to be accompanied by desensitization and supersensitization of the responses to adenosine and the A1 analogue (R)-phenylisopropyladenosine, respectively. These findings have more recently been fully confirmed in chick atrial myocytes in culture.

Cardiac Actions of Adenosine

In the heart, in addition to causing coronary vasodilation, adenosine depresses sinoatrial (SA) node activity, AV nodal conduction, atrial contractility, and ventricular automaticity. Adenosine also attenuates the cardiac stimulatory actions of catecholamines and the release of norepinephrine from nerve terminals. Furthermore, adenosine inhibits oxygen metabolite generation by activated neutrophils and stimulates glycolysis. It is worth noting that the cardiac actions of adenosine are remarkably similar to those of the neurotransmitter acetylcholine (ACh). Both ACh and adenosine produce the same cardiac effects and share similar receptor–effector coupling systems (Figure 3). It appears, therefore, that a major role of ACh and adenosine, in addition to their direct effects (see below), is to function in parallel to oppose the cardiac stimulatory actions of the sympathetic neurotransmitters norepinephrine and epinephrine.

Electrophysiologic Effects

Adenosine A1 receptor–mediated actions in the heart are essentially of two types, those that are cAMP-independent (direct effects) and others that are cAMP-dependent (indirect or antiadrenergic effects).

Similar to other inhibitory receptors (e.g., the muscarinic receptor), the adenosine A1 receptor is coupled to its effector units (i.e., ionic channels and adenyl cyclase) via the guanine nucleotide binding inhibitory protein Gᵢ. Consistent with this coupling...
Mechanism for Formation

1. ATP pathway
2. SAH pathway

![Mechanism for Formation Diagram]

Receptor - Effector Complex

1. A1 receptor
2. Coupling protein (G̶)
3. K+/Ca++ channel

Mechanism for Removal

1. Transport
2. Enzymic Removal
3. Receptor Blockade

![Mechanism for Removal Diagram]

Mechanism for Formation

- ATP → ADP → AMP → 5'-nucleotidase
- SAH → Homocysteine + ADO → transport
- SAH Hydrodase

Adenine nucleotides

- AMP → 5'-nucleotidase
- ADO

Adenosine system comprises three components, that is, 1) a mechanism for its formation, 2) a receptor-effector complex (or coupling mechanism), and 3) a mechanism for its removal. Adenosine can be formed intracellularly or extracellularly. Adenosine receptor (A1 subtype) is coupled to ion channels via guanine nucleotide binding regulatory proteins (G proteins or G̶). Termination of adenosine's action occurs by cellular uptake and metabolism of the nucleoside. ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate; SAH, S-adenosylhomocysteine; ADO, adenosine; cAMP, cyclic AMP; R, receptor; GTP, guanosine triphosphate; Theo, theophylline.

As illustrated in Figure 3, activation of SA, atrial, and AV nodal adenosine A1 receptors results in activation of a specific outward potassium current, the ACh/adenosine-regulated potassium current (I_{KChA1}), which is cAMP-independent. Adenosine also causes a small (12–18%) inhibition of nonstimulated, basal inward calcium current (I_{Ca}) in atrial myocytes. This attenuation of the basal I_{Ca} in atrial cells by adenosine is not seen in either SA node cells or ventricular myocytes.

In ventricular myocytes, adenosine antagonizes the stimulatory actions of catecholamines on I_{Ca} and on the transient inward current (I_{IT}). This antagonism by adenosine or its A1 analogues of the actions of catecholamines and other agents known to increase the concentration of cellular cAMP (e.g., forskolin) is due to inhibition of adenylyl cyclase. However, a recent report suggests that adenosine may also reduce high-affinity binding of isoproterenol to the β-adrenergic receptor.

**Basis for Adenosine's Antiarrhythmic Properties**

Stimulation by adenosine of I_{KChA1} in supraventricular tissues (e.g., atrial myocardium and SA
ADENOSINE - MEDIATED EFFECTS

A. cAMP - Dependent
   (Antiadrenergic)

1. Antagonizes Positive Chronotropy
2. Antagonizes Positive Dromotropy
3. Antagonizes Positive Inotropy (Atria and Ventricles)
4. Suppresses Afterpotentials (Triggered Activity)

B. cAMP - Independent
   (Direct)

1. Negative Chronotropy
2. Negative Dromotropy
3. Negative Inotropy (Atria)

node) explains 1) shortening of the action potential in atrial cells, 2) sinus slowing and hyperpolarization of SA nodal cells to the potassium equilibrium potential, and 3) depression of the action potential in AV nodal cells. These electrophysiological effects of adenosine account for its termination of AV nodal reentrant tachycardia, its slowing of the sinus rate, and its potential for initiating atrial flutter. Whether the small decrease of basal ICa by adenosine in atrial cells contributes to the above effects remains to be determined. Regardless, the large increase in IK,Ch,Ado alone can explain the electrophysiological effects of adenosine in supraventricular tissue.

In ventricular myocardium, antagonism of catecholamine-stimulated ICa and ITI by adenosine accounts for the observation that adenosine decreases the amplitude of delayed afterdepolarizations and suppresses triggered activity induced by agents known to increase the concentration of cellular cAMP. This antagonism explains adenosine’s ability to terminate ventricular tachycardia induced by isoproterenol and to slow ventricular (His bundle) escape rhythms previously accelerated by isoproterenol.

Clinical Effects of Adenosine

Hemodynamics

The hemodynamic response to adenosine is dependent on its route and method of administration. Intravenous bolus injections (100 μg/kg) have a dose-dependent biphasic pressure effect. That is, an initial 10–15 mm Hg pressor response is followed by a slightly smaller depressor response. Other investigators, however, have failed to detect any change in systemic pressure.

Continuous infusion of adenosine (150–300 μg/kg/min) in anesthetized patients maintains controlled hypotension and is associated with a decrease in systemic vascular resistance, an increase in cardiac output, and a moderate increase in heart rate. Since venous tone is relatively unaffected, right atrial and pulmonary capillary wedge pressures are unchanged. In contrast to its effects in anesthetized patients, infusion of adenosine (140 μg/kg/min) in conscious subjects has no effect on mean arterial pressure since systolic pressure increases by 10% and diastolic pressure decreases by 6%. The sympathoadrenal system appears to be activated by adenosine since heart rate and plasma norepinephrine and epinephrine levels increase in a dose-dependent manner. These effects are not observed in patients with dysautonomia, suggesting that adenosine’s hemodynamic effects are not mediated by direct vascular effects but rather by autonomic reflex activation (e.g., carotid body chemoreceptors). For instance, adenosine has a pressor effect when infused proximal to the carotid arteries but lowers pressure when
infused into the descending aorta. Activation of carotid body chemoreceptors by adenosine is also thought to stimulate respiration and produce respiratory alkalosis. It is noteworthy that carotid body chemoreceptor reflexes are attenuated during anesthesia, perhaps accounting for the absence of a pressor response as previously noted.

Cardiac Electrophysiology

Sinus node. Bolus doses of adenosine have a biphasic effect on heart rate. An initial period of sinus bradycardia, observed within 20 seconds after injection and lasting less than 10 seconds, is followed by sinus tachycardia. The latter response is likely due to adenosine’s stimulation of carotid body chemoreceptors, resulting in respiratory stimulation and secondary activation of pulmonary stretch receptors. Adenosine has been proposed as a putative mediator of the sick sinus syndrome due to its direct negative chronotropic effect on the sinus node, reversal of symptomatic bradycardia by the adenosine receptor antagonist theophylline, and depression of sinus node automaticity by purinergic compounds in patients with sick sinus syndrome. Although this is a provocative hypothesis, it lacks experimental support.

Atrium. Limited data are available regarding the effects of adenosine in human atria. Consistent with experimental findings, adenosine shortens action potential duration and refractoriness. These effects may precipitate atrial flutter or fibrillation and is the mechanism by which nucleoside transport blockers like dipyridamole induce atrial flutter that is reversed by aminophylline.

AV node. Adenosine slows conduction within the AV node (negative dromotropy), which can result in transient AV block. Intracardiac recordings demonstrate that heart block is preceded by prolongation of the A–H interval, effects that are unaltered by atropine. Reversal of adenosine-induced slowing of AV nodal conduction by aminophylline is not affected by propranolol, suggesting that competitive antagonism of adenosine by aminophylline rather than aminophylline-induced release of catecholamines from adrenergic nerve terminals or the adrenal medulla is the operative mechanism. These findings are clinically relevant since aminophylline has been shown to restore AV conduction in patients with AV block complicating an inferior myocardial infarction. This observation raises the possibility that endogenous adenosine may mediate some clinical electrophysiologic effects (negative dromotropy) under conditions of oxygen supply–demand imbalance. Recently, dipyridamole, which elevates endogenous adenosine levels, was shown to significantly slow conduction across the AV node. This finding suggests that endogenous adenosine can also have electrophysiologic effects under normoxic conditions in the presence of specific pharmacologic perturbations.

His-Purkinje system. Adenosine has little, if any, direct effect on the His-Purkinje system. Conduction from the His bundle to the ventricular myocardium (H–V interval) is unaltered by adenosine. Furthermore, unlike observations in guinea pig and canine hearts, adenosine does not diminish His-Purkinje automaticity in humans under basal conditions. However, adenosine does have potent antidromic effects (i.e., it attenuates the effects of catecholamine stimulation). For example, in patients with complete heart block, adenosine reverses isoproterenol-induced acceleration of the ventricular escape rate.

Accessory pathway. Most anterograde and retrograde accessory pathways are insensitive to adenosine. However, pathways that demonstrate unusual conduction properties, that is, decremental conduction, respond to adenosine. The likely explanation is that most accessory pathways comprise normal atrial fibers with resting membrane potentials near the potassium equilibrium potential $E_K$ (−90 mV). Therefore, the membrane-stabilizing effects of adenosine have little effect in these tissues. In contrast, decremental conduction pathways may comprise partially depolarized atrial tissue with a resting membrane potential of less than −70 mV. These tissues would therefore be expected to respond to adenosine-induced hyperpolarization.

Therapeutic Effects

Sinus node. Adenosine causes transient slowing of sinus tachycardia due to its hyperpolarizing membrane effect and antagonism of the catecholamine effects on the pacemaker current ($I_p$). Adenosine-induced hyperpolarization likely accounts for the termination of tachycardia due to sinus node reentry in a recent case report.

Atrium. Adenosine has been reported in general to have no effect on atrial cycle length in atrial fibrillation, atrial flutter, and intra-atrial reentry, although rare exceptions are known. Automatic atrial tachycardia and multifocal atrial tachycardia have not been systematically studied with adenosine. Preliminary data suggest that adenosine may transiently suppress automatic atrial tachycardia but more often has no effect. The one reported patient with multifocal atrial tachycardia did not respond to adenosine.

AV node. Adenosine is nearly always effective in terminating supraventricular tachycardia in which the AV node forms part of the reentrant circuit. These arrhythmias include AV nodal reentry and orthodromic AV reciprocating tachycardia. In the latter case, the anterograde limb consists of the atrium, AV node, and His-Purkinje system and the retrograde limb consists of an accessory pathway. A mean adenosine dose of 6 mg terminates the usual form of AV nodal reentry within 20 seconds after injection. The site of termination can occur in either limb of the AV node. Tachycardia due to AV reciprocating tachycardia also terminates in the AV node in response to adenosine. The retrograde accessory pathway is not usually sensitive to adenosine except, as noted above, in those pathways that demonstrate decremental conduction properties similar to that of the AV node (e.g., accessory pathways...
associated with the permanent form of junctional reciprocating tachycardia.58

His-Purkinje system and ventricle. Junctional ectopic tachycardia, an automatic rhythm in children that originates from the region of the His bundle, has been reported to be transiently suppressed by adenosine in two of five patients.73,74 Nearly all types of ventricular tachycardia are insensitive to adenosine. For example, adenosine appears to have no effect on ventricular tachycardia due to either microreentry, macroreentry (bundle branch reentry), or enhanced automaticity.51,71,76 There is one type of tachycardia, however, in which adenosine is highly effective: that thought to be due to cAMP-mediated triggered activity.51 This type of tachycardia is often induced by exercise or catecholamine stimulation, originates from the right ventricular outflow tract, and is usually associated with a structurally normal heart. The mechanism of tachycardia in these patients is postulated to be due to catecholamine-induced delayed afterdepolarizations. Afterdepolarizations arise during phase 4 of the action potential and are dependent on intracellular calcium overload. Adenosine is thought to terminate these tachycardias by inhibiting adenyl cyclase through an inhibitory G protein (antiadrenergic effect) (Figure 3). This transduction process results in decreased intracellular production of cAMP, protein phosphorylation, and entry of calcium into the cell. Other perturbations that directly or indirectly decrease intracellular calcium (i.e., calcium channel blockers, β-blockers, and vagal maneuvers51,77) usually also terminate the arrhythmia. Several points are worth emphasizing. Catecholamine facilitation of ventricular tachycardia due to reentry does not appear to respond to adenosine. This may be because adenosine has little or no effect on isoproterenol-induced action potential changes in K+-depolarized ischemic guinea pig ventricles or in infarcted Purkinje fibers.77,78 Finally, adenosine appears to be effective only in triggered activity due to stimulation of cAMP. For example, adenosine is ineffective in ouabain-induced triggered activity, in which calcium overload is mediated by inhibition of Na,K-ATPase and not stimulation of cAMP.66 Based on these observations, adenosine may prove to be an important probe for differentiating ventricular tachycardia due to cAMP-mediated triggered activity from reentry, automaticity, and other forms of triggered activity.

Diagnostic Uses

In addition to its therapeutic benefit, adenosine has considerable diagnostic utility for distinguishing the mechanism of narrow and wide complex tachycardias (Figures 4 and 5). This is due to its relatively site-specific effects, short half-life, and minimal hemodynamic consequences. In narrow complex tachycardia, for instance, adenosine is useful in distinguishing between atrial tachycardias and those that require the AV node as part of the reentrant circuit. For example, in cases in which atrial flutter waves are difficult to discern on a surface electrocardiogram, an incorrect diagnosis of AV nodal reentry may result. In these patients adenosine-induced transient AV block with perpetuation of the atrial arrhythmia can facilitate the correct diagnosis and thus guide appropriate therapy. It is important to recognize that, although adenosine-induced termination of PSVT nearly always occurs within the AV node, there are notable exceptions (e.g., retrograde accessory pathways with decremental conduction properties68 and
possibly reentrant rhythms confined to the sinus node) (Figure 4).

In patients with wide complex tachycardia (Figure 5), adenosine, unlike verapamil,79 does not usually cause hypotension or acceleration of the tachycardia.71,76 Adenosine either terminates aberrant PSVT (due to AV nodal reentry or AV reciprocating tachycardia) or results in transient AV block (supraventricular tachycardia due to atrial tachycardia).

Unlike verapamil, adenosine causes no hemodynamic deterioration when given to patients with atrial flutter/fibrillation that conducts anterogradely over an accessory pathway. The mean R–R interval is unaltered, although the shortest R–R decreases by approximately 10%.76 This finding is consistent with the recent observation that adenosine may shorten refractoriness in the accessory pathway by at least 20 msec,80 an effect that may be related to an increase in sympathetic tone.

Preliminary findings in a single patient suggest that Mahaim fibers that give rise to decremental AV or atriofascicular pathways (and wide complex tachycardia), an uncommon etiology for preexcitation, are also sensitive to adenosine.81

Purinergic compounds including adenosine also have a role in identifying patients with intermittent or latent preexcitation. By slowing conduction or producing block in the AV node, preexcitation may become manifest.82–85 Seldom, however, patients with prolonged80 or even normal anterograde refractory periods of the accessory pathway87 show sensitivity to purinergic compounds.

Finally, caution should be exercised in patients with preexcitation who have AV reciprocating tachycardia. Precipitation of atrial fibrillation by adenosine could potentially result in rapid AV conduction over the accessory pathway.

**Adenosine Versus Verapamil**

Two retrospective studies have analyzed the relative efficacies of adenosine and verapamil in terminating PSVT. Adenosine had a slightly higher success rate and was associated with milder symptoms.88,89 A nonblinded prospective protocol comparing the two agents in the same patients with inducible supraventricular tachycardia showed similar efficacy rates.81 Termination of the arrhythmia with adenosine was often followed by atrial or ventricular premature complexes, although no sustained arrhythmias occurred. The largest study comparing the two agents to date was a randomized, prospective study involving 125 patients.90 Patients initially received either adenosine (6 mg) or verapamil (5 mg), followed by 12 mg or 7.5 mg, respectively, if the initial dose was unsuccessful in terminating the tachycardia. Cumulative efficacy rates were approximately 90% with either drug. Postconversion arrhythmias were equal in both groups. Spontaneous reinitiation of supraventricular tachycardia was more frequent with adenosine, although this difference did not achieve statistical significance. Similar efficacy results were also observed in studies comparing ATP and verapamil.91,92

The advantages of adenosine with respect to verapamil include faster onset of action (less than 30 seconds versus 1–2 minutes), absence of adverse hemodynamic effects, short half-life, and transient duration of side effects and bradyarrhythmias. The relative disadvantages of adenosine may include frequent recurrence of arrhythmia (which may be initiated by premature complexes triggered by adenosine) and a higher incidence of side effects, albeit well tolerated.

**Adenosine Versus ATP**

It was originally proposed that the electrophysiologic effects of ATP were in part due to its vagomimetic activity since in dogs, atropine and vagotomy attenuate the chronotropic and dromotropic effects of ATP.93 However, more recent data indicate that the electrophysiologic effects of ATP in the human heart are not attenuated by atropine.64 The observation that the effects of ATP are blocked by methylxanthines and potentiated by dipyridamole suggest that such actions are those of adenosine, generated by the degradation of ATP.64,94

There is one double-blind, randomized study comparing adenosine and ATP.95 Clinical efficacy for the diagnosis and termination of supraventricular tachycardia, onset and offset of action, molar potency, and the incidence and severity of side effects were similar for both compounds. The effective dose range for both compounds was 2.5–20 mg. The major advantage of adenosine over ATP is the former’s stability at room temperature. Fifty percent of ATP is degraded by 2 months when it is stored at room temperature, whereas adenosine is stable at 2 months.95

**Dosage and Interactions**

Adenosine is available in sterile saline for intravenous administration. For optimal therapeutic results, it is obligatory that adenosine be delivered as a rapid bolus followed by a saline flush. If administered as a slow bolus, adenosine’s electrophysiologic effects may not be manifest. Adenosine’s half-life in the blood pool is less than 1.5 seconds,96 and it is rapidly metabolized by endothelial cells and erythrocytes. Its myocardial actions are therefore due to first-pass effects. Factors such as site of injection, circulation time, and central volume determine the amount of adenosine that will reach its target site.

Myocardial effects from a peripheral route are manifest within 30 seconds,90 whereas adenosine’s effects from central access are usually apparent in 10–20 seconds.98,70 Due to its rapid metabolism and resolution of side effects, intervals between boluses can be 60 seconds. A 6 mg i.v. bolus is the recommended initial dose and has an efficacy rate of 60% for PSVT. A 12 mg i.v. dose has an efficacy rate of approximately 90%.90

Due to differences in individual sensitivities to the drug, an alternative dose-ranging protocol can be based on body weight. For instance, one can start
with an initial dose of 50 μg/kg and increment it by 50 μg/kg until PSVT is terminated or side effects become intolerable. This method may reduce the incidence of side effects and would be the preferred approach in children, in whom the mean effective dose is approximately 100–150 μg/kg.⁷³

Precautions should be taken in patients who are taking dipyridamole. The adenosine dose should be reduced to one fourth of the usual dose since dipyridamole potentiates the effects and half-life of adenosine.⁶³ Patients who are taking competitive antagonists such as theophylline or caffeine may require larger than usual doses of adenosine, although doses as high as 19 mg have been ineffective in patients on theophylline.⁷⁰ In heart transplant patients who develop PSVT, the adenosine dose should be reduced to one third to one fifth of the usual dose due to denervation-induced supersensitivity to the drug.⁹⁷

Caution should be exercised in treating patients with high-grade AV block since the degree of block may be temporarily exacerbated by adenosine. Similarly, adenosine may also cause prolonged sinus pauses in patients with sick sinus syndrome.

Adverse Effects

Cumulative clinical side effects occur in about 30% of patients.⁹⁰ Due to adenosine’s rapid clearance from the blood, these symptoms last less than 60 seconds. The most common symptoms are facial flushing (due to cutaneous vasodilation), dyspnea, and chest pressure. Adenosine is thought to have an important role in producing anginal pain,⁹⁸ the mechanism having been attributed to direct stimulation of cardiac afferents.⁹⁹ Although nebulated adenosine may cause bronchoconstriction,¹⁰⁰ particularly in asthmatic patients, intravenous adenosine has not been reported to have such an effect in a limited number of patients. Until further data are available, caution should be used when administering adenosine to such patients. Other less common side effects include nausea, headache, and lightheadedness. In general, the side effects of adenosine are mild and do not require clinical intervention.

The relative advantage of adenosine’s short half-life with respect to its side effect profile is also a limitation when considering therapeutic efficacy. Up to 35% of tachycardias may recur within 2 minutes after termination with adenosine.⁷⁰ However, repeated bolus administrations can be given safely and may result in sustained sinus rhythm. Short runs of nonsustained ventricular tachycardia, sinus tachycardia, or atrial fibrillation may also be observed after termination of tachycardia. In addition, transient sinus bradycardia and AV block may also occur.⁷¹ Prolonged sinus arrest or AV block is uncommon but is dose-dependent and is seen in patients with underlying conduction disturbances.⁷¹,⁷³

Future Directions and Conclusions

In the last 10 years evidence has emerged that adenosine is an important endogenous modulator of cardiac electrophysiology.¹ As an antiarrhythmic agent, adenosine has several unusual properties in that it is an intermediate metabolite with potent negative chronotropic and dromotropic effects within the SA and AV nodes, actions that are rapid in onset and offset. It should be emphasized that the potential antiarrhythmic effects of adenosine in tachycardias that do not require the AV node as part of the arrhythmia circuit have been reported in a relative paucity of patients and should be considered preliminary data.

Areas of further clinical investigation will include assessing the role of endogenous adenosine in mediating sick sinus syndrome, bradyarrhythmias associated with sleep apnea,¹⁰¹ and its potential as a marker for acute rejection in cardiac transplant patients.¹⁰² Both site-specific adenosine analogues and nucleoside transport blockers are required before longer-acting preparations can be developed that will preclude undesired systemic effects and facilitate new therapeutic approaches for chronic and prophylactic therapy of PSVT.⁶³

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