A foundational concept in cardiac electrophysiology is that understanding the cellular mechanism of an arrhythmia provides essential insight for developing targeted therapeutic options. However, current clinical understanding of arrhythmogenic mechanisms other than re-entry is rudimentary, and the means by which to diagnose and differentiate these mechanisms are poorly defined. Grouping these mechanistic subtypes into broad and nonspecific categories, for example, non–re-entry or focal, further underscores our incomplete understanding of these arrhythmias. As the field of cardiac electrophysiology, like the rest of medicine, evolves toward the delivery of cell-based therapies, the need for a deeper understanding of clinical arrhythmia mechanisms and their arrhythmogenic cell lineages is apparent.

One major difference between re-entrant and non–re-entrant ventricular tachycardia (VT) is that the electrophysiological substrate for re-entry is acquired during postnatal development and is due to anatomic insult (eg, ischemic heart disease or viral myocarditis), whereas the substrate for triggered activity is likely often acquired during embryological development, occurring independent of anatomic injury or structural heart disease.1,2 These dichotomous electrophysiological substrates, re-entry and non–re-entry, require tailored approaches to confirm diagnosis. In this review, we will elaborate on the development of a methodological approach for diagnosing non–re-entrant VT, which centers on the unique mechanism-specific properties of adenosine. This approach differs substantively from standard laboratory pacing methodologies used to validate the diagnosis of re-entrant arrhythmias and which are founded on the principles of entrainment.3

Adenosine

Adenosine is an endogenous nucleoside that exercises multiple regulatory functions that affect impulse generation and conduction, autonomic function, contractility, coronary vaso-dilation, and O2 supply–demand balance.4 Adenosine is rapidly inactivated as it is taken up by the cell through simple diffusion or a nucleoside transport system and is then deaminated to inosine or phosphorylated to adenosine monophosphate.5 The plasma half-life of adenosine is <1.5 s.6

Four-myocardial adenosine receptor subtypes mediate adenosine’s effects. Receptors A1, A2a, A2b, and A3 are structurally related G-protein–coupled receptors, consisting of 7 transmembrane helices.7 A1 and A3 subtypes inhibit adenylyl cyclase, whereas A2 subtypes activate it. In the heart, the A1R subtype has the highest level of expression and is the receptor that mediates adenosine’s electrophysiologic effects through its activation of heterotrimeric G proteins.8

Drury and Szent-Gyorgyi8 made the seminal observation in 1929 that adenosine had a negative chronotropic effect on the heart, causing profound slowing of the sinus rate in dogs.8 Although research on the cardiac electrophysiological effects of adenosine followed in fits and starts over the next 50 years, the field took flight beginning in the 1980s.9 Parenthetically, Szent-Gyorgyi’s observations on adenosine were just one of many pivotal contributions made in a celebrated scientific career. He was granted the Nobel Prize in 1937 for his discovery of vitamin C and work on the catalysis of key intermediates in the tricarboxylic acid cycle.

Signal Transduction and Electrophysiological Effects

In supraventricular tissue, adenosine-mediated activation of G<sub>i</sub> results in release of G<sub>pr</sub> subunits, which activate G-protein–coupled inward rectifying K<sup>+</sup> channels and the current I<sub>KAdo</sub>, thus hyperpolarizing sinoatrial cells and abbreviating action potential duration in atrioventricular nodal tissue. These effects account for adenosine’s negative chronotropy at the level of the sinoatrial node and slowing of conduction (negative dromotropy) in the atrioventricular node. Also contributing in part to adenosine’s suppressive effects on the sinoatrial node is its attenuation of the hyperpolarization-activated cyclic nucleotide-gated channel, which carries the current I<sub>p</sub>. This current is enhanced by cAMP stimulation, and unlike most voltage-sensitive currents, it is activated by hyperpolarization (not depolarization). In atrial tissue, adenosine shortens action potential duration and refractoriness, thus decreasing the wavelength of activation, which facilitates the induction of atrial fibrillation. In addition, in supraventricular...
tissue, adenosine attenuates cAMP-stimulated increases of the L-type calcium current $I_{\text{CaL}}$ through activation of $\text{G}_{\alpha} \cdot \text{G}_{\text{o}}$.10

In contrast to its effects on supraventricular tissue, adenosine has little or no direct effect on ventricular resting membrane potential, amplitude, or action potential duration (Figure 1A). This is due to the absence of G-protein–coupled inward rectifying $\text{K}^+$ channel expression in ventricular tissue. Although adenosine has no direct effect on basal $I_{\text{CaL}}$ in ventricular myocardium, it has a potent indirect effect because it antagonizes the stimulatory effects of cAMP on the calcium current (Figure 1A and 1B).11–13 Adenosine also decreases other currents that are augmented by $\beta$-adrenergic stimulation, including the delayed rectifier potassium current ($I_{\text{K}^+}$), chloride current ($I_{\text{Cl}}$), and the transient inward current ($I_{\text{Wi}}$).

In canine His-Purkinje tissue (associated with normal resting membrane potential), adenosine directly diminishes intrinsic automaticity by transiently suppressing $I_{\text{f}}$.14,15 In contrast, adenosine has minimal effect on His-Purkinje automaticity in humans (Figure 2A).16 These putative, if trivial, direct effects of adenosine are abolished when intravenous propranolol is given before adenosine, suggesting that adenosine’s direct effects are actually mediated through its antagonism of endogenous catecholamines. Catecholamine-mediated increases in the automatic firing rate of the His-Purkinje system and accentuation of $I_{\text{f}}$ are also transiently abolished by adenosine, confirming its antiadrenergic effect (primary effect) on His-Purkinje automaticity (Figure 2A).

The electrophysiological effects of adenosine are mediated primarily at the level of the cardiomyocyte but also potentially through the autonomic nervous system where it has contrasting effects. It inhibits norepinephrine release from presynaptic postganglionic sympathetic nerve fibers17,18 but also triggers sympathetic neural activation, mediated through $A_2$-chemoreceptor stimulation and by baroreceptor unloading secondary to vasodilation. These sympathoexcitatory effects do not, however, override adenosine’s antiadrenergic/antiarrhythmic effects at the cellular level.19–22

### Junctional Tachycardia

Abnormal automaticity refers to arrhythmias that develop in His-Purkinje tissue (or ventricular myocardium) at partially depolarized membrane potentials, ie, $<-70$ mV. These rhythms are catecholamine responsive, are relatively more dependent on $I_{\text{CaL}}$ for depolarization than normally polarized tissue, and in general, do not respond to overdrive suppression. The reduced resting membrane potential inactivates the inward sodium current and the electrogenic sodium pump. In addition, arrhythmias caused by abnormal automaticity are not initiated or terminated with programmed stimulation and are unresponsive to adenosine. As shown in Figure 2B–2G, in canine Purkinje fibers with normal resting membrane potentials, the depolarization rate is accelerated with catecholamine stimulation (ie, normal or enhanced automaticity), which is reversed with adenosine. However, these antiadrenergic effects of adenosine on the depolarization rate are abolished when the resting membrane potential is reduced.14 Therefore, adenosine’s antiadrenergic effects on the His-Purkinje system are not absolute, but are dependent on the relative level of resting membrane potential.

Clinical junctional ectopic tachycardia is an arrhythmia whose mechanism has remained obscure. Adenosine has been instrumental in verifying that junctional ectopic tachycardia can be caused by either of 2 mechanisms: abnormal automaticity or triggered activity. In the abnormal automaticity subtype, junctional
Ventricular Tachycardia

Triggered Activity

Although the demonstration of entrainment (resetting with fusion) is the signature hallmark for identifying re-entry, no such pacing response is pathognomonic for clinical triggered activity. Despite previous reports of specific responses of triggered activity to programmed stimulation in multicellular preparations, these responses are not extrapolatable to the clinical setting. Similar to re-entry, triggered activity is initiated and terminated with rapid overdrive pacing or with programmed extrastimuli, but the nonspecificity of these responses renders them inconsequential for differentiating between the 2 mechanisms. In contradistinction to the findings with pacing, collective experimental and clinical data support the thesis that termination of tachycardia in response to adenosine is as fundamental to the diagnosis of triggered activity as the demonstration of entrainment is to re-entry, such that termination of VT with adenosine is mechanistically synonymous with cAMP-mediated delayed afterdepolarizations (DADs) and triggered activity. The sensitivity and specificity of adenosine’s effects in triggered activity have proven instrumental in identifying this mechanism as the basis for most forms of outflow tract tachycardia. To substantiate this claim, the available evidence will be considered.

The cellular basis for triggered activity due to DADs is abnormal calcium cycling. Underlying this process is an increase in sarcoplasmic reticulum (SR) calcium. This can lead to a spontaneous calcium release event because of random openings of the ryanodine receptor channel, which occurs independently of voltage-gated sarcolemmal calcium influx. Alternatively, the process can be initiated by increasing the open state of the L-type calcium channel and enhancing the slow-inward calcium current, leading to calcium-induced calcium release from the SR (ie, calcium sparks). Calcium sparks may lead to calcium-induced calcium release in neighboring SR and propagation of subcellular calcium waves within the cell, activating the electrogenic sodium-calcium exchanger and I_{Ca,L} to generate DADs. The genesis of calcium waves responsible for triggered activity may therefore be spontaneous or induced (dependent on I_{Ca,L}).

On a cellular level, the prototypical forms of DAD-mediated triggered activity are those related to either inhibition of Na+/K+-ATPase (digitalis derivatives) or catecholamine-cAMP stimulation. Although the common denominator for both mediators is intracellular calcium overload and an increased open probability of the SR, divergent paths lead to this outcome. In the case of digitalis derivatives, increased intracellular calcium is achieved through inhibition of Na+/K+-ATPase, whereas catecholamines activate the β-adrenergic receptor and stimulatory G protein, which sets in motion a concatenation of events that increase intracellular Ca. These include the activation of adenylyl cyclase, cAMP, and protein kinase A, leading to phosphorylation of the L-type Ca channel, ryanodine receptor, and phospholamban.

Data from cardiomyocytes provide crucial support for the adenosine-sensitive triggered activity hypothesis. Guinea pig myocytes that are paced at rapid rates and exposed to isoproterenol consistently generate DADs (which are not
Adenosine abolishes isoproterenol-induced DADs and associated triggered activity coincident with its elimination of \( I_{\text{Ti}} \) (Figure 5). Adenosine’s effects on \( I_{\text{Ti}} \), on an equimolar basis, are more potent than its inhibitory effects on catecholamine-induced action potential duration prolongation, elevation of action potential duration plateau, increases in \( I_{\text{CaL}} \), or contractility. Adenosine’s suppressive effects on \( I_{\text{Ti}} \) are reproduced by N6-cyclopentyladenosine, a selective \( A_1 \) receptor analogue, confirming that its action is mediated at the level of the \( A_1 \) receptor. Adenosine abolishes DADs and \( I_{\text{Ti}} \) through its effects at several levels. By reducing the activation of protein kinase A, adenosine diminishes the influx of \( I_{\text{CaL}} \) and calcium-induced calcium release. It also reverses the phosphorylation of ryanodine receptor and phospholamban, restoring the latter’s tonic inhibition of SR Ca ATPase, thus reducing SR Ca stores.

Central to adenosine’s antiarrhythmic effects on triggered activity is its inhibition of adenylyl cyclase, which is confirmed by adenosine’s abolition of isoproterenol and forskolin-induced DADs but not those induced by dibutyryl cAMP (Figure 6). Forskolin is a direct adenylyl cyclase activator, whereas cAMP analogues act independently of adenylyl cyclase activation, confirming that adenosine does not directly inhibit cAMP but indirectly turns off its production through its inhibitory action on adenylyl cyclase.

These effects are mediated in turn through an inhibitory G protein since the antiarrhythmic effects of adenosine on catecholamine-mediated DADs and \( I_{\text{Ti}} \) are eliminated in cardiomyocytes from guinea pigs pretreated with pertussis toxin (Figure 6). Pertussis toxin catalyzes ADP ribosylation of the \( \alpha_i \)-subunit of \( G_i \), inactivating the protein, thus preventing it and adenosine from inhibiting adenylyl cyclase. Therefore, adenosine’s effects on triggered activity are mediated by a series of events that begin with its activation of the \( A_1 \) receptor, which then activates \( G_i \) to inhibit adenylyl cyclase and the phosphorylation of critical downstream proteins that increase intracellular Ca and \( I_{\text{Ti}} \).

A fundamental issue is whether adenosine abolition of DADs is a generic effect on any form of triggered activity or one that is cAMP specific. To this end, we examined the effects of adenosine on DADs that are elicited independently of adenylyl cyclase activation. In support of the specificity argument, ouabain, which induces DADs and triggered activity by elevating intracellular Ca through inhibition of Na+/K+-ATPase, is insensitive to adenosine, as is triggered activity induced by elevated [Ca] (Figure 7). In addition, spontaneous triggered activity that develops under basal conditions in isolated myocytes is also unresponsive to adenosine. Therefore, the only form of DAD that is responsive to adenosine is that which is dependent on activation of adenylyl cyclase and cAMP.
Another subtype of triggered activity is due to early afterdepolarizations (EADs) that are related to a net inward depolarizing current during phase 2 or phase 3 of the action potential. Clinically, EADs are often related to channelopathies, for example, long QT syndrome, or to drugs that block the rapidly activating delayed rectifier potassium current ($I_{K1}$), for example, class IA and class III antiarrhythmic drugs. Therefore, another important part of the adenosine story is that it has no effect on EAD-mediated triggered activity. For example, EADs induced by quinidine are unresponsive to adenosine but are abolished by magnesium (Figure 8).33 Similarly, EADs induced by the $I_{CaL}$ channel activator Bay K8644 are insensitive to adenosine. Therefore, adenosine’s antiarrhythmic effects on triggered activity are consistent with its narrow spectrum of action, which is defined by its antiadrenergic effect on cAMP-mediated DADs.

On the basis of the effects of adenosine enumerated above, we reasoned that it could serve as a mechanistic probe for identifying clinical VT due to adrenergically mediated triggered activity.35 Exercise-induced right ventricular outflow tract tachycardia has at least 2 essential features to suggest that it might serve as a clinical prototype of a triggered mechanism. It is adrenergically mediated and focal in origin. In addition, most patients with this arrhythmia have no evidence of structural heart disease,1,2 suggesting that a re-entrant substrate is unlikely. Therefore, it is informative that adenosine’s effects on focal ventricular outflow tract tachycardia are identical to its effects in cellular preparations of cAMP-mediated DADs and triggered activity, ie, abrupt termination of the arrhythmia.36–41 Adenosine also terminates left ventricular outflow tract tachycardia,42,43 as well as tricuspid and mitral annular VT, suggesting a common electrophysiological mechanism for right and left ventricular outflow tract tachycardia and annular VT (Figure 9).44,45

Focal VT

For the purpose of understanding adenosine’s electrophysiological effects within the broad context of all forms of VT, it is useful to categorize the arrhythmogenic circuit as being either focal or nonfocal (ie, macro–re-entrant). As shown above, the only form of focal VT that terminates in response to adenosine is $\beta$-adrenergic–mediated triggered activity. Other focal forms

![Figure 4](http://circ.epub.ahajournals.org/)

**Figure 4.** Effects of adenosine on junctional ectopic tachycardia (JET) caused by triggered activity. A, Triple ventricular extrastimuli introduced during sinus rhythm initiate a narrow-QRS tachycardia. B, Advancement of His-bundle activation during tachycardia with an early coupled atrial premature depolarization during junctional ectopic tachycardia advances immediate His bundle and ventricular activation (without terminating the tachycardia), findings consistent with JET. C, JET terminates with a bolus dose of adenosine of 6 mg. Surface ECG leads as labeled; aVF indicates augmented vector foot; CS, coronary sinus recording; d, distal bipoles; His, His bundle electrogram; p, proximal; and RV, right ventricular electrogram. Reprinted from Liu et al23 with permission of the publisher. Copyright © 2011, John Wiley & Sons, Inc.

![Figure 5](http://circ.epub.ahajournals.org/)

**Figure 5.** Effect of adenosine on catecholamine-induced delayed afterdepolarizations (DADs) and the transient inward current ($I_{Ti}$). The leftward tracings show a single action potential recorded at a basal rate of 0.25 Hz. The middle tracings show the last 3 action potentials of a 15-s drive train paced at a frequency of 2 Hz, and the tracings on the right show the last 3 beats of a 12-s long train of 300 ms depolarizing voltage clamp steps from −80 mV to +40 mV. A, Control recording. B, Isoproterenol (ISO; 10 nmol/L) elicited a triggered beat (closed triangle), followed by a DAD (straight arrows) and $I_{Ti}$ (curved arrows). C, Adenosine (ADO; 100 μmol/L) abolishes isoproterenol-induced DADs and the transient inward current. Reprinted from Song et al33 with permission of the publisher. Copyright © 1992, American Heart Association, Inc. Right, Mechanistic schema of cAMP-mediated triggered activity due to DADs. Adenosine abolishes DADs and triggered activity through inhibition (−) of adenylyl cyclase. SR indicates sarcoplasmic reticulum.
PTX inactivates the inhibitory G-protein (Gi), demonstrating that myocytes from guinea pigs treated with pertussis toxin (PTX).

Adenosine (<20 s) but never terminated. This important normal resting membrane potential, are transiently suppressed matic ventricular arrhythmias, which originate from cells with VT cycle length, is also insensitive to adenosine. Finally, auto-

on closely spaced bipolar recording electrodes that span the

induced DADs and transient inward current (I

\text{Ca})_\text{in}

inhibited adenylyl cyclase, one step proximal to the produc-

tion of cAMP. Data are expressed as mean±SEM; *P<0.05. Lack of effect of adenosine (ADO) on isoproterenol (ISO)-

B, Lack of effect of adenosine (ADO) on isoproterenol (ISO)-

uced DADs and transient inward current (I

\text{Ca})_\text{in}

inhibited adenylyl cyclase through activation of G. Each bar expresses mean±SEM; *P<0.05. Reprinted from Song et al\textsuperscript{33} with permission of the publisher.

of triggered activity due to DADs and EADs are unrespon-
sive to adenosine. Furthermore, focal re-entrant VT, albeit relatively uncommon and identified by the demonstration of entrainment\textsuperscript{46} by the presence of fractionated electrograms on closely spaced bipolar recording electrodes that span the VT cycle length, is also insensitive to adenosine. Finally, automatic ventricular arrhythmias, which originate from cells with normal resting membrane potential, are transiently suppressed by adenosine (<20 s) but never terminated. This important distinction is often a source of confusion and misinterpre-
tation in the literature.

**Macro–Re-entry**

Although the most informative mechanistic finding in outflow tract tachycardia is its termination with adenosine, this is based in part on the specificity of adenosine’s response, which was recently defined by examining its effects in a canine model of re-entrant VT and in clinical re-entrant VT. VT was mapped to the epicardial border zone in postinfarcted dogs. Complete activation maps were identified with high-density electrode arrays, and figure-of-eight re-entrant tachycardia circuits were confirmed. In this re-entrant model of VT, adenosine failed to alter VT cycle length or terminate the arrhythmia.\textsuperscript{46} In patients, substrate mapping or electroanatomic activation and entrainment mapping confirmed a re-entrant mechanism for VT. All patients had structural heart disease, including ischemic and nonischemic substrates, or arrhythmogenic right ventricular cardiomyopathy, and all had evidence for endocardial or epicardial VT circuits. Adenosine given at doses sufficient to cause either ventriculoatrial block or sinus slowing did not perturb VT cycle length or terminate the re-entrant arrhythmia in 31/31 patients (Figure I in the Data Supplement). Adenosine was also given to 50 consecutive patients with inducible sustained right and left ventricular outflow tract tachycardia. All these VTs were focal in origin, demonstrated centrifugal activation, could not be entrained, and were associated with normal myocardial substrates, confirmed by normal myocardial voltages and discrete ventricular electrograms. Adenosine terminated 45 of 50 outflow tract VTs. On the basis of these data, adenosine’s sensitivity for identifying presumed cAMP-mediated triggered activity is 90% (95% confidence interval, 0.78–0.97) and its specificity is 100% (95% confidence interval, 0.89–1.0).\textsuperscript{46,47}

Of clinical note, catecholamine-facilitated re-entrant VT is also unresponsive to adenosine (Figure II in the Data Supplement).\textsuperscript{46,48}

In this regard, it is germane that adenosine’s electrophysiologi-
cal effects are attenuated in infarcted or partially depolarized myocardium.\textsuperscript{14} However, regardless of the explanation for this outcome, the evidence suggests that adenosine has no effect in catecholamine-dependent re-entry, further highlighting the specificity of its effects and reinforcing the conclusion that the only
form of catecholamine-dependent VT that terminates in response to adenosine is that due to triggered activity.

Electropharmacologic Matrix

A simple binary response (termination/no effect) of monomorphic VT to adenosine provides pertinent evidence on whether the arrhythmia is focal and due to cAMP-mediated triggered activity or whether it is nonfocal and due to re-entry. When monomorphic VT is focal but insensitive to adenosine, the likely diagnosis is focal re-entry. To further enhance the ability to discriminate among mechanisms, we have developed an electropharmacologic schema that is based on the principles elaborated above (Figure 10). Although the cornerstone of this schema is the response of VT to adenosine, it also based on the response of tachycardia to pacing, the presence or absence of entrainment, electrogram characteristics, whether the arrhythmia is catecholamine dependent, and the response of tachycardia to calcium channel blockade (ie, verapamil). Collectively, the responses to these maneuvers reliably differentiate mechanism, although

![Figure 8](http://circp.ahajournals.org/)

**Figure 8.** Lack of adenosine (ADO) effect on early afterdepolarizations (EADs). Action potentials are recorded from a guinea pig myocyte stimulated at a rate of 0.25 Hz. A, Control recording from an isolated myocyte. B, Quinidine-induced EADs (arrows). C, Adenosine has no effect on quinidine-induced EADs. D, Quinidine-induced EADs are abolished by magnesium. Reprinted from Song et al with permission of the publisher. Copyright © 1992, American Heart Association, Inc.

![Figure 9](http://circp.ahajournals.org/)

**Figure 9.** Representative responses of outflow tract tachycardia to adenosine and calcium channel blockade. A, Termination of sustained right ventricular outflow tract (RVOT) tachycardia with adenosine. B, Termination of sustained left ventricular outflow tract (LVOT) tachycardia with adenosine (different patient from that shown in A). C, Verapamil administered to a patient with incessant repetitive monomorphic ventricular tachycardia (VT) originating from the RVOT. D, Termination of arrhythmia shown in C. Reprinted from Lerman et al and Iwai et al with permission of the publishers. Copyright © 1995, American Heart Association, Inc. Copyright © 2006, John Wiley & Sons, Inc.

![Figure 10](http://circp.ahajournals.org/)

**Figure 10.** Schema for identifying the mechanism of ventricular tachycardia based on its response to adenosine. The results from pacing maneuvers, the demonstration of entrainment, local electrogram properties, and the response of tachycardia to catecholamine administration and blockade of the slow-inward calcium current further refine the diagnosis. +cAMP-mediated triggered activity. PES indicates programmed electric stimulation. Reprinted from Markowitz et al with permission of the publisher. Copyright © 2007, American College of Cardiology Foundation.
verapamil’s antiarrhythmic effects need to be interpreted within the context of other associated findings because it also terminates re-entrant fascicular VT (which is unresponsive to adenosine). 46

Conclusions
Adenosine is a unique mechanistic probe. Its short half-life permits repeated administration without altering the electrophysiological milieu, thus allowing reproducible confirmation of a given response. More important, however, is that in contrast to adenosine’s diverse electrophysiological effects in supraventricular myocardium, it has a singular electrophysiological effect in ventricular myocardium, which is based solely on its inhibitory effects on adenylyl cyclase and cAMP. These effects are discriminant because only one type of cAMP-mediated VT is sensitive to adenosine. To this point, adenosine has no antiarrhythmic effect in catecholamine-dependent re-entry (or in catecholamine-independent re-entry). Furthermore, all other types of VT fail to terminate in response to adenosine, whether due to other forms of triggered activity or abnormal automaticity. Therefore, the collective experimental and clinical data provide pivotal support for the adenosine-triggered activity hypothesis. Accordingly, adenosine termination of VT is a mechanism-specific response that is diagnostic of cAMP-mediated triggered activity. This mechanism accounts for most forms of right and left ventricular outflow tract tachycardia.

Disclosures
None.

References


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