Adenosine-sensitive ventricular tachycardia: evidence suggesting cyclic AMP-mediated triggered activity

BRUCE B. Lerman, M.D., LUIZ BELARDINELLI, M.D., G. ALEXANDER WEST, PH.D., ROBERT M. BERNE, M.D., and JOHN P. DiMARCO, M.D., PH.D.

ABSTRACT Catecholamine-induced triggered activity is thought to be caused by intracellular calcium overload mediated by elevation of intracellular cyclic AMP (cAMP). Although shown to occur in isolated preparations, evidence supporting its clinical existence has been lacking. Electrophysiologic studies were performed in four patients with structurally normal hearts who had exertionally related sustained ventricular tachycardia (VT). Programmed stimulation reproducibly initiated and terminated VT in all patients. Induction of tachycardia was also facilitated by infusion of isoproterenol. Adenosine, an endogenous nucleoside, whose only known electrophysiologic effect on ventricular myocardium and Purkinje fibers is antagonism of catecholamine-induced stimulation of intracellular cAMP production, reproducibly terminated all episodes of VT. The tachycardia was also terminated by intravenous verapamil and by the Valsalva maneuver and/or carotid sinus massage. β-Adrenergic receptor blockade with propranolol either terminated or prevented induction of VT during programmed stimulation or catecholamine challenge. Adenosine was also administered during VT to 14 patients whose arrhythmias fulfilled standard criteria for reentry, two of whom also had exercise-induced VT. Adenosine, at a dose (112.5 to 225 μg/kg iv) sufficient to cause either sinus slowing/arrest or ventricular atrial block during ventricular pacing, failed to slow or terminate any episode of VT in these patients. Verapamil and autonomic modulation were also ineffective in this group of patients. Adenosine, verapamil, vagal maneuvers (acetylcholine), and β-adrenergic receptor blockade are all known to decrease the slow-inward calcium current either directly by modulating calcium channels or indirectly by inhibiting production of cellular cAMP. Therefore the observation in this study that interventions that lower intracellular cAMP either terminate or prevent induction of VT in patients with structurally normal hearts and exercise-induced VT suggests that the mechanism of tachycardia may be cAMP-mediated triggered activity.


VENTRICULAR TACHYCARDIA (VT) is usually attributed to one of two mechanisms, automaticity or reentry.1,2 A third mechanism of arrhythmia, triggered activity, has been demonstrated in studies of isolated tissues and single cells exposed to cardiac glycosides, high [Ca++], or catecholamines.3–8 This rhythm is initiated by afterdepolarizations triggered by the preceding action potential. The cellular mechanism responsible for catecholamine-induced triggered activity is thought to be overload of intracellular calcium and is mediated by elevation of intracellular cyclic AMP (cAMP).7

Recently, VT caused by triggered activity has been postulated to occur in man based on the response of arrhythmia to either programmed stimulation or to the slow-inward channel blocker verapamil.9–12 These conclusions may be premature, however, since both triggered activity and reentry can demonstrate similar responses to programmed stimulation12 and verapamil has been shown to terminate both types of arrhythmias in experimental preparations.13

We postulated that VT caused by cAMP-mediated triggered activity could be distinguished from reen-
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Traint rhythms by the response of the arrhythmia to pharmacologic and autonomic interventions that are known to lower intracellular cAMP. In particular, the response of VT to adenosine, an endogenous nucleoside whose only known electrophysiologic effect on ventricular myocardium and Purkinje fibers is inhibition of cAMP-mediated catecholamine effects, was evaluated.

This study describes the effects of adenosine in four patients with exercise-induced VT and in a control group of patients with reentrant VT.

Methods

Electrophysiologic study. All studies were performed with patients in the unsedated, postabsorptive state after informed consent had been obtained. All antiarrhythmic agents were discontinued for at least five half-lives before initial evaluation; however, results for adenosine reported in five of 14 control patients with reentrant VT (group II; see below) were obtained during follow-up study with the patients on antiarrhythmic drugs. Four quadrripolar electrode catheters were inserted percutaneously and advanced under fluoroscopic guidance to the high right atrium, coronary sinus, right ventricular apex, and atrioventricular junction for recording of the His bundle electrogram. Bipolar intracardiac recordings were filtered at 30 to 500 Hz and simultaneously displayed with three ECG leads on a multichannel oscilloscope (Electronics for Medicine, VR-16, White Plains, NY). Data were stored on magnetic tape (Honeywell model 101, Waltham, MA) and were later retrieved on photographic paper for illustrative purposes. Real-time recordings were made with an ink-jet recorder (Siemens Elema Minograph, Iselin, NJ). Stimulation was performed with a programmable stimulator and an isolated constant-current source (Bloom Associates, Narberth, PA). Stimuli were delivered as rectangular pulses of 2 msec duration at four times diastolic threshold.

Our stimulation protocol has been previously reported and includes the introduction of single, double, and triple extrastimuli during sinus rhythm and at several paced cycle lengths, and rapid burst pacing from multiple atrial and ventricular sites.

Pharmacologic assessment. Initiation of tachycardia in response to infusion of catecholamines was tested with isoproterenol. The infusion rate was started at 2 μg/min and was increased by 2 μg/min every 2 min until an infusion rate of 14 μg/min was achieved, 90% of age-predicted maximal heart rate was reached, VT occurred, or side effects developed.

The effects of intravenous adenosine on VT were evaluated. Crystalline adenosine (Sigma Chemical Co., St. Louis) was dissolved in normal saline at a concentration of 5 mg/ml and was prepared under sterile conditions. Adenosine concentrations were confirmed by high-pressure liquid chromatography. For patients with exercise-induced VT, adenosine was injected rapidly at a dose of 75 to 225 μg/kg into a central line and was flushed with 10 ml of saline. The elimination half-life of adenosine in the human circulation is less than 10 sec. By means of a nonblinded protocol, 2 ml of 0.9% saline was injected first; if the tachycardia did not terminate within 60 sec, adenosine was then injected. In alternate trials adenosine was injected first, at least 15 sec after initiation of tachycardia.

In patients in whom VT fulfilled the criteria for reentry (see below), adenosine was injected during VT at a dose (112.5 to 225 μg/kg) sufficient to cause either sinus slowing/cessation or ventriculoatrial block during ventricular pacing. Patients in this group were also evaluated for isoproterenol facilitation of VT. Catecholamine facilitation of VT was defined as (1) initiation of clinical VT during infusion of isoproterenol alone; (2) induction of VT during both programmed stimulation and simultaneous infusion of isoproterenol (4 μg/min) with a less vigorous induction protocol than with programmed stimulation alone, e.g., requiring a single ventricular extrastimulus rather than double extrastimuli; or (3) induction of sustained VT during simultaneous programmed stimulation and isoproterenol infusion when either one alone resulted in only nonsustained VT.

The response to slow-inward channel blockade was assessed by administration of 10 mg of intravenous verapamil during sustained tachycardia.

Autonomic assessment. During tachycardia, several vagal maneuvers were tested to assess autonomic effect on the rhythm. Right and left carotid sinus massage was performed sequentially and patients were instructed to perform theValsalva maneuver. The effect of β-adrenergic blockade on initiation or termination of VT was evaluated after intravenous infusion of propranolol (0.1 to 0.2 mg/kg).

The procedures described in this study were performed in accordance with a protocol approved by the Human Investigations Committee of the University of Virginia.

Results

Group I: Exercise-induced VT (no structural heart disease). Relevant patient characteristics are summarized in table 1. All patients were between 25 and 32 years old and had clinically documented recurrent, exertional (exercise) related sustained VT that lasted at least 1 hr and required medical intervention (table 1). No patient had apparent structural heart disease as evaluated by left ventriculography and coronary arteriography in patients 1 and 4 (patient 1 also had a normal right ventriculogram) or by exercise stress testing and two-dimensional echocardiographic/Doppler studies in patients 2 and 3. Results of thyroid function studies were normal in all patients.

Electrophysiologic findings. No patient demonstrated preexcitation during the introduction of atrial extrastimuli or decremental atrial pacing nor was there evidence for a Mahaim tract. Retrograde atrial activation was normal in all patients.

Sustained VT was reproducibly initiated with programmed atrial and/or ventricular stimulation in all patients (table 2). Initiation of tachycardia with ventricular extrastimuli always followed an 8 beat paced drive (figure 1). Rapid atrial pacing during simultaneous infusion of isoproterenol (see below) initiated VT in patients 2 and 3. The first beat of tachycardia occurred late in the cardiac cycle; however, there was no consistent relationship between the coupling interval of the initiating extrastimulus and the first beat of tachycardia. The tachycardia cycle length was nearly constant during each episode of VT, although small oscillations (<20 msec) were occasionally noted. No warm-up phenomenon was observed in any patient. VT showed a trend toward cycle length dependence in
patients 2, 3, and 4, i.e., the cycle length of tachycardia was dependent on the preceding sinus (isoproterenol-induced VT) or drive cycle length (figure 2). This finding was not always consistent, since patients 2 and 4 showed variability in this relationship in consecutive-day studies.

The diagnosis of VT was confirmed by standard electrophysiologic criteria. All episodes of induced VT longer than 10 beats were sustained, lasting at least several minutes before termination with programmed stimulation. VT was terminated with ventricular overdrive pacing in all patients (figure 1). In addition, coupled ventricular extrastimuli terminated VT in patients 2 and 4, whereas atrial pacing was able to terminate VT in patient 4.

The configuration of VT in the first two patients showed two discrete monomorphic morphologies during separate episodes, whereas patients 3 and 4 showed only one morphologic tachycardia (table 2). Right and left ventricular activation mapping performed in patient 1 during VT (left bundle branch block morphology) identified earliest ventricular activation in the region of the right ventricular outflow tract.

Response to isoproterenol. Isoproterenol alone did not initiate VT in patient 1; however, the infusion rate was limited to 4 µg/min because the patient developed headache and nausea (table 3). In patient 2, infusion of isoproterenol at rates from 8 to 12 µg/min repeatedly initiated sustained VT (figure 3). The sinus cycle lengths immediately preceding the onset of VT ranged from 420 to 550 msec. Atrial and ventricular stimulation alone in this patient induced only nonsustained VT; concomitant infusion of isoproterenol resulted in induction of sustained VT. In patient 3, rapid atrial pacing for 10 to 20 sec at cycle lengths between 240 to 320 msec during infusion of isoproterenol (4 µg/ml) reproducibly initiated sustained VT, whereas atrial pacing or isoproterenol alone failed to induce the ar-

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/sex</th>
<th>Cardiac diagnosis</th>
<th>ECG</th>
<th>No. of episodes of VT requiring intervention</th>
<th>Clinical morphology and rate</th>
<th>Duration of symptoms (yr)</th>
<th>Ambulatory monitoring (24 hr)</th>
<th>Exercise stress test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31/F</td>
<td>Normal</td>
<td>Normal</td>
<td>2</td>
<td>LBBB, 160/min</td>
<td>1.5</td>
<td>Frequent PVCs</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>25/M</td>
<td>Normal</td>
<td>Inverted T waves V1-V3a</td>
<td>5</td>
<td>LBBB, 160/min</td>
<td>3</td>
<td>Few PVCs, NSVT (≤5 beats)</td>
<td>Frequent NSVT (&lt;10 beats)</td>
</tr>
<tr>
<td>3</td>
<td>31/M</td>
<td>Normal</td>
<td>Normal</td>
<td>2</td>
<td>LBBB, 210/min</td>
<td>3</td>
<td>Few PVCs, NSVT (≤4 beats)</td>
<td>NSVT (6 to 12 beats)</td>
</tr>
<tr>
<td>4</td>
<td>32/M</td>
<td>Normal</td>
<td>Normal</td>
<td>9</td>
<td>LBBB, 150/min</td>
<td>6</td>
<td>Few PVCs</td>
<td>Normal (maximum heart rate 110/min)</td>
</tr>
</tbody>
</table>

LBBB = left bundle branch block; NSVT = nonsustained VT; PVCs = premature ventricular contractions.

aECG pattern believed to represent a persistent "juvenile pattern."

bNonsustained VT occurred 30 sec into the recovery phase.

**TABLE 2**

<table>
<thead>
<tr>
<th>VT initiation</th>
<th>VT CL (msec)</th>
<th>VT morphology</th>
<th>Termination</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>320-340</td>
<td>LBBB, L. inf. axis</td>
<td>RVP</td>
</tr>
<tr>
<td></td>
<td>320-340</td>
<td>RBBB, L. inf. axis</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>240-400</td>
<td>LBBB, L. inf. axis</td>
<td>DVPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBBB, R. inf. axis</td>
<td>RVP</td>
</tr>
<tr>
<td>3</td>
<td>240-320</td>
<td>LBBB, R. inf. axis</td>
<td>RVP</td>
</tr>
<tr>
<td>4</td>
<td>330-420</td>
<td>LBBB, L. inf. axis</td>
<td>AP, DVPD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RBBB, R. inf. axis</td>
<td>RVP</td>
</tr>
</tbody>
</table>

AP = atrial pacing; DVPD = double ventricular premature depolarizations; Iso. = isoproterenol; LBBB = left bundle branch block; RAP = rapid atrial pacing; RBBB = right bundle branch block; RVP = rapid ventricular pacing; SVPD = single ventricular depolarization; TVPD = triple ventricular depolarizations; VP = ventricular paced drive (8 beats).

aSimultaneous isoproterenol infusion.
rhythm. Rapid ventricular pacing during infusion of isoproterenol at cycle lengths identical to atrial pacing could not be evaluated in patient 3 because it resulted in hypotension and discomfort. Infusion of isoproterenol resulted in numerous nonsustained salvos of VT in patient 4. Isoproterenol facilitation could not be readily evaluated in this patient with programmed ventricular stimulation because sustained VT was readily initiated during both the ventricular drive and with single ventricular extrastimuli coupled to the drive.

Response to adenosine. Intravenous adenosine terminated VT in all trials with a mean time of 8 sec after injection (range 5 to 15 sec) (table 3). In patient 1, a dose of 8.8 or 13.3 mg (75 and 112.5 μg/kg, respectively) was given during 20 episodes of VT and in patient 2 a dose of 6 or 9 mg was administered during 10 episodes of VT (figure 3). In patient 3, 9.5 mg of adenosine was effective in five trials as was 15 mg (225 μg/kg) of adenosine in patient 4. Adenosine caused slight slowing of VT before termination in some trials in patients 2 and 3. All control trials tested with intravenous saline were ineffective.

Response to autonomic modulation. The Valsalva maneuver reproducibly terminated VT in all patients (figure 4, table 3). Right carotid sinus massage also terminated VT in patient 3. Intravenous propranolol was given to three patients; in patient 4, 7 mg of propranolol administered during tachycardia terminated the arrhythmia. In patients 1 and 2, 12 mg of propranolol infused during sinus rhythm prevented induction of sustained VT with programmed stimulation and/or infusion of isoproterenol. Tachycardia was also no longer inducible in patient 2 after oral loading with atenolol (50 mg daily). An exercise stress test in patient 3 during treatment with atenolol (50 mg daily) failed to induce any ventricular ectopy, whereas a control study demonstrated multiple 6 to 12 beat runs of VT (table 1).

Response to verapamil. In patient 1, 10 mg of intravenous verapamil terminated VT in 65 to 75 sec on two different days. After verapamil, VT was no longer inducible with programmed stimulation. Verapamil (10 mg iv) also successfully terminated tachycardia in patient 4.
Relevant patient characteristics are summarized in table 4. Patients ranged in age from 39 to 79 years. Twelve patients had coronary artery disease, of whom five had left ventricular aneurysm, one had a cardiomyopathy, and one had no structural heart disease. Two patients with left ventricular aneurysm had exercise-induced VT.

**Electrophysiologic results.** Adenosine had no effect on VT cycle length or termination in any patient in this group, including four of these patients who had isoproterenol facilitation of tachycardia (table 4). In two patients (patients 1 and 6), recurrent episodes of VT were related to exercise. Unlike patients in group I, however, these two patients had coronary artery disease and left ventricular aneurysm. An exercise test with thallium-201 myocardial scintigraphy in patient 1 failed to demonstrate delayed redistribution, suggesting that VT was not induced by ischemia. Similar to group I patients, this patient had both inducible VT and isoproterenol facilitation of tachycardia, but in contrast adenosine, vagal maneuvers, and intravenous propranolol had no effect on VT. Intraoperative mapping of VT demonstrated presystolic fractionated activity in the region of the apical septum. Subendocardial resection of this region and aneurysmectomy were performed. During a predischarge electrophysiologic study, VT was no longer inducible and the patient has remained free of VT on no antiarrhythmic agents during 6 months of follow-up.

Another patient (No. 2) with a structurally normal heart but without exercise-induced VT had isoproterenol facilitation of VT but no response to adenosine.
### TABLE 3
Response of VT to pharmacologic and autonomic modulation (group I)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Isoproterenol</th>
<th>Adenosine</th>
<th>Valsalva and/or carotid sinus massage</th>
<th>Propranolol</th>
<th>Verapamil</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No induction(^a)</td>
<td>Termination</td>
<td>Termination</td>
<td>Prevented VT induction during PS</td>
<td>Termination</td>
</tr>
<tr>
<td></td>
<td>(≤4 (\mu g/min))</td>
<td>(75–112.5 (\mu g/kg))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Sustained VT</td>
<td>Termination</td>
<td>Termination</td>
<td>Prevented VT induction during PS</td>
<td>Slowed VT</td>
</tr>
<tr>
<td></td>
<td>(8–12 (\mu g/min))</td>
<td>(75–112.5 (\mu g/kg))</td>
<td></td>
<td></td>
<td>(240 to 350 msec)</td>
</tr>
<tr>
<td>3</td>
<td>Facilitation of sustained VT(^b)</td>
<td>Termination</td>
<td>Termination</td>
<td>Prevented VT induction during PS</td>
<td>Not given(^c)</td>
</tr>
<tr>
<td></td>
<td>(4 (\mu g/min))</td>
<td>(112.5 (\mu g/kg))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NSVT</td>
<td>Termination</td>
<td>Termination</td>
<td>Termination</td>
<td>Termination</td>
</tr>
<tr>
<td></td>
<td>(4 (\mu g/min))</td>
<td>(225 (\mu g/kg))</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSVT = nonsustained VT; PS = programmed stimulation.

\(^a\)Infusion of isoproterenol limited by patient side effects. See text for details.

\(^b\)Induction only during simultaneous rapid atrial pacing; atrial pacing or isoproterenol infusion alone did not induce VT.

\(^c\)See text for details.

#### FIGURE 3
A. Initiation of VT during infusion of isoproterenol in patient 2 (group 1). B. Termination of the tachycardia initiated in A by adenosine in 7.5 sec. Note slight slowing of tachycardia before termination. At termination of VT there was temporary sinus slowing and AV nodal block caused by adenosine and an idioventricular escape rhythm that lasted 6 sec. Abbreviations as in figure 1.
### TABLE 4
Response to adenosine in patients with reentrant VT (group II)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)/Sex</th>
<th>Cardiac diagnosis</th>
<th>VT initiation</th>
<th>VT CL (msec)</th>
<th>VT morphology</th>
<th>Termination</th>
<th>Response to vagal maneuvers</th>
<th>Adenosine dose (mg, μg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>39/M</td>
<td>CAD, LV An</td>
<td>(1) VP-DVP</td>
<td>360</td>
<td>RBBB, R. sup. axis</td>
<td>AP, RVP</td>
<td>Neg. 14, 150</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Isoproterenol (4 μg/min) + AP, VP-SVPD</td>
<td>310–320</td>
<td>RBBB, R. sup. axis</td>
<td>AP</td>
<td>Neg. 14, 150</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>39/M</td>
<td>NL</td>
<td>(1) VP-TVPD</td>
<td>290</td>
<td>LBBB, L. inf. axis</td>
<td>Spontaneous (30 sec)</td>
<td></td>
<td>16, 187.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Isoproterenol (8 μg/min) + VP-TVPD</td>
<td>300</td>
<td>LBBB, L. inf. axis</td>
<td>RVP</td>
<td>ND 10.2, 150</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>67/M</td>
<td>CAD</td>
<td>(1) VP-TVPD</td>
<td>290</td>
<td>RBBB, R. inf. axis</td>
<td>RVP</td>
<td>ND 10.2, 150</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(2) Isoproterenol (4 μg/min) + VP-DVPD</td>
<td>310</td>
<td>RBBB, R. inf. axis</td>
<td>RVP</td>
<td>ND 10.2, 150</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>56/M</td>
<td>CAD, LV An</td>
<td>(1) Isoproterenol (12 μg/min)</td>
<td>335</td>
<td>RBBB, R. sup. axis</td>
<td>RVP</td>
<td>ND 8.7, 150</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>79/M</td>
<td>CAD, LV An, MR</td>
<td>VP-DVPD</td>
<td>400</td>
<td>RBBB, R. sup. axis</td>
<td>RVP</td>
<td>ND 13, 225</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>47/M</td>
<td>CAD, LV An, S/P CABG</td>
<td>VP-DVPD</td>
<td>570</td>
<td>RBBB, R. sup. axis</td>
<td>SVPD, DVPD</td>
<td>ND 12, 150</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>65/M</td>
<td>CAD</td>
<td>VP-SVPD</td>
<td>380</td>
<td>RBBB, R. sup. axis</td>
<td>RVP</td>
<td>Neg. 12.8, 150</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>53/M</td>
<td>CAD, LV An</td>
<td>VP-DVPD</td>
<td>450</td>
<td>RBBB, L. sup. axis</td>
<td>SVPD, DVPD</td>
<td>ND 7.5, 112.5</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>61/M</td>
<td>CAD</td>
<td>VP-SVPD</td>
<td>330</td>
<td>RBBB, L. sup. axis</td>
<td>RVP</td>
<td>ND 18, 225</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>65/M</td>
<td>CM</td>
<td>VP-SVPD</td>
<td>430</td>
<td>RBBB, L. sup. axis</td>
<td>RVP</td>
<td>ND 15, 225</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>57/M</td>
<td>CAD</td>
<td>AP, VP-DVPD</td>
<td>315</td>
<td>RBBB, L. sup. axis</td>
<td>RVP</td>
<td>Neg. 12, 225</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>72/F</td>
<td>CAD</td>
<td>VP-DVPD</td>
<td>360–410</td>
<td>RBBB, R. inf. axis</td>
<td>RVP</td>
<td>Neg. 15.1, 225</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>58/F</td>
<td>CAD, S/P CABG</td>
<td>VP-SVPD</td>
<td>430</td>
<td>RBBB, R. inf. axis</td>
<td>RVP</td>
<td>Neg. 9.1, 150</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>52/M</td>
<td>CAD, S/P CABG, MVR</td>
<td>VP-SVPD</td>
<td>340–360</td>
<td>LBBB, L. sup. axis</td>
<td>RVP</td>
<td>Neg. 16.4, 225</td>
<td></td>
</tr>
</tbody>
</table>

AP = atrial pacing; Amio. = amiodarone; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CL = cycle length; CM = cardiomyopathy; DVPD = double ventricular premature depolarizations; EPS = electrophysiologic study; LV An = left ventricular aneurysm; MR = mitral regurgitation; MVR = mitral valve replacement; ND = not done; Quin. = quinidine; RVP = rapid ventricular pacing; SER = subendocardial resection; SVPD = single ventricular premature depolarization; TVPD = triple ventricular premature depolarizations; VP = ventricular pacing.

**FIGURE 4.** Termination of VT by the Valsalva maneuver during the release in patient 4 (phase IV). Note oscillations in ECG lead I during Valsalva and release. Abbreviations as in figure 1.
Also worth noting, one patient (No. 11) with a macro-reentrant tachycardia involving the bundle branches did not respond to adenosine.

**Discussion**

This report demonstrates that adenosine, an endogenous nucleoside, terminates certain forms of clinical VT. Although the effects of adenosine on reentrant supraventricular tachyarrhythmias involving the AV node have been well characterized, its effects on VT have not been previously reported. In contrast to its direct effects on supraventricular tissue where it increases potassium conductance, adenosine has *no direct electrophysiologic effect* on ventricular myocardium or Purkinje fibers. Of key importance, however, is its indirect, antiadrenergic effect on ventricular myocardium and Purkinje fibers; that is, it antagonizes the inotropic and electrophysiologic effects of catecholamines that are mediated through stimulation of the adenylate cyclase–cAMP system.  

Based on the data presented in this study and from experimental work in our laboratory and from others, the tachycardia observed in this study is most consistent with cAMP-mediated triggered activity. For example, in experimentally produced triggered activity in isolated myocytes, adenosine has been shown to be effective in terminating only triggered activity that is mediated by cAMP. In contrast, adenosine is *ineffective* in terminating triggered activity caused by either elevated [Ca^{2+}]_{o} or ouabain inhibition of Na,K-ATPase (figure 5) (unpublished observations).

Experimental studies suggest that adenosine has little if any effect in infarcted myocardium and reentrant arrhythmias, a finding consistent with our observations in patients with coronary artery disease and reentrant VT. Rosen et al. showed that adenosine had no effect on depressed fast responses in infarcted Purkinje fibers. Furthermore, we have observed that adenosine has no effect on isoproterenol-induced action potential changes in ischemic guinea pig hearts (unpublished observations). It has also been demonstrated that adenosine antagonism of isoproterenol-induced electrophysiologic effects in both isolated ventricular myocytes and multicellular ventricular preparations are markedly blunted when the membrane potential is partially depolarized by increased [K^{+}]_{o}. These latter observations are consistent with the ineffective response to adenosine in patients with coronary artery disease and isoproterenol facilitated reentrant VT. Finally, we also have provided preliminary evidence to suggest that adenosine has no direct effect on human His-Purkinje system function, since adenosine was ineffective in the one patient studied with VT caused by bundle branch reentry.

The unusual observation that the tachycardia responded to the Valsalva maneuver (group I) provides additional evidence that the VT was mediated by cAMP. Episodes of VT were reproducibly terminated during phase IV of the Valsalva maneuver, a phase that is thought to be mediated by acetylcholine release. Acetylcholine exerts its predominant electrophysiologic effect on ventricular myocardium by antagonizing catecholamine-mediated increases in intracellular cAMP and has also been shown to terminate catecholamine-induced triggered activity in isolated preparations. The termination of tachycardia in response to carotid sinus massage in one patient in this study is also consistent with this mechanism of action.
Results of programmed stimulation also lend support to the diagnosis of triggered activity, i.e., initiation of VT after a decrease in sinus, atrial drive, or ventricular drive cycle length. Induction of VT with atrial pacing (patients 2 and 3) has also been suggested to be consistent with triggered activity. However, all these responses observed during programmed stimulation, although suggestive of triggered activity, may also be seen in reentry.

Verapamil has also been shown to suppress delayed afterdepolarizations and triggered activity but is mechanistically nondiscriminant, since it is effective in calcium-induced, ouabain-induced, and catecholamine-cAMP-mediated triggered activity. Furthermore, verapamil may also be effective in treating reentrant arrhythmias in chronically infarcted hearts. Thus termination of a VT with verapamil is not conclusive proof that the rhythm is triggered or cAMP dependent. Therefore, mechanistically, the single most important finding in this study was the consistent termination of the tachycardia by adenosine.

**Differentiation between triggered activity and automaticity.** Normal automaticity may be distinguished from triggered activity by the inability of programmed stimulation to initiate automatic rhythms. Automatic rhythms also show overdrive suppression, whereas triggered rhythms may be accelerated, terminated, or unaffected by overdrive pacing. Adenosine is useful in distinguishing between these rhythms because it only transiently depresses normal automaticity but terminates catecholamine-induced, cAMP-mediated triggered activity. The tachycardia described in this study was reproducibly initiated by programmed stimulation and was terminated by both programmed stimulation and adenosine, suggesting that an automatic mechanism of VT was unlikely.

Abnormal automaticity, in contrast to normal automaticity, is characterized by enhanced impulse formation in myocardial cells whose resting membrane potentials are reduced to less than −60 mV. Abnormal automaticity is terminated by blockade of the slow inward current; however, adenosine has no effect on this rhythm. Thus the ability of adenosine to terminate VT reproducibly in our study should exclude the possibility of abnormal automaticity.

**Receptor schema.** The following receptor schema can explain the pharmacologic and autonomic effects on VT observed in the group I patients with exercise-induced tachycardia (figure 6). Both acetylcholine and adenosine inhibit cAMP production via a common intracellular pathway, after binding to their respective extracellular inhibitory receptors (R), i.e., the muscarinic choliner gic and adenosine-A1 receptors. It is thought that coupling of the GTP-dependent regulatory protein (N) with R results in a high-affinity state of the receptor for its agonist. After the agonist binds to the cell receptor, intracellular GTP binds to N. This process results in dissociation of N from the receptor and inhibition of the catalytic subunit of adenylyl cyclase, thereby preventing cAMP formation. Intracellular calcium overload, afterdepolarizations, and triggered activity. Similarly, β-adrenergic blockade inhibits the cascade initiated by catecholamines to increase intracellular cAMP (mediated by the GTP-dependent regulatory protein N, figure 6). Verapamil, by blocking the slow inward calcium current, also prevents intracellular calcium overload and hence can terminate triggered activity without producing direct effects on intracellular cAMP.

**Conclusions.** The results from this study suggest that in addition to reentry and automaticity, a third clinical mechanism of VT exists, cAMP-mediated triggered activity. We propose that the criteria for diagnosis of this arrhythmia should include appropriate responses.
to programmed stimulation and that cAMP-mediated triggered activity may be distinguished by reentrant rhythms by the response of the arrhythmia to both pharmacologic agents and autonomic interventions that lower intracellular cAMP. In evaluating patients suspected of having this arrhythmia, it is essential to recognize that differentiation between triggered activity and reentry based on results of programmed stimulation alone can be misleading because their responses are often similar. Also, spontaneous changes in autonomic tone may result in the inconsistent induction of VT during catecholamine infusion and/or programmed stimulation and may alter the response of the arrhythmia to vagal maneuvers. It is important to emphasize that the conclusions of this study are preliminary and will require further clinical confirmation. Nevertheless, because of adenosine’s antiadrenergic effects on ventricular myocardium and Purkinje fibers, termination of VT with adenosine may prove to be a sensitive and specific method for identifying VT caused by cAMP-mediated triggered activity.

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FIGURE 6. Schema for inhibition of cAMP-mediated triggered activity. When the GTP-dependent regulatory protein (N1) is coupled with a stimulatory cell surface β-adrenergic receptor (R1), the receptor develops a high-affinity state for β-agonist. Upon binding of β-agonist with R1, intracellular GTP binds to and activates N1, which then dissociates from the receptor and stimulates the catalytic subunit of adenylate cyclase. β-Adrenergic blockade cannot prevent this cascade by competitively blocking the binding of a β-agonist to the β-receptor. Both the muscarinic cholinergic (MC) and the adenosine-A1 receptors are inhibitory (R1). Further details of the schema are discussed in the text. Ach = acetylcholine; A1 = extracellular inhibitory adenylate receptor; N1 = inhibitory guanine nucleotide-binding protein; C = catalytic subunit of adenylate cyclase; gCa = calcium conductance; EC = extracellular; IC = intracellular.

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