Unifying Mechanism of Sustained Idiopathic Atrial and Ventricular Annular Tachycardia

Running title: Ip et al.; Peri-annular Tachycardia

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Abstract:

**Background** - Based on current understanding of cardiac conduction system development and the observation that arrhythmogenic foci can originate in areas near the atrioventricular annuli, we hypothesized that focal annular tachycardias, whether atrial or ventricular, share a common mechanism. We therefore prospectively evaluated this hypothesis in patients with sustained atrial and ventricular tachycardia originating from the peri-tricuspid and mitral annuli.

**Methods and Results** - Forty-nine consecutive patients with sustained, focal annular tachycardia comprise the study group. All underwent electrophysiologic evaluation and the mode of tachycardia initiation, termination, sensitivity to catecholamine infusion and response to adenosine/verapamil were evaluated. Electroanatomical activation maps identified the sites of arrhythmia origin. Tachycardias could be initiated and/or terminated with programmed stimulation in 46/46 patients and most (70%) were catecholamine facilitated. Of the 9 patients with sustained annular VT, 3 were localized to the tricuspid annulus, and 6 to the mitral annulus. All 9 VTs (100%) terminated with adenosine, 2/2 terminated with verapamil, and 2/2 terminated with Valsalva. Of the 40 patients with annular AT, 4 tachycardias were localized to the mitral annulus and 37 to the tricuspid annulus (including 9 para-Hisian), and all were adenosine-sensitive.

**Conclusions** - Peri-annular atrial and ventricular tissue correspond to a region enriched with arrhythmogenic foci, which may reflect to a common developmental origin. Furthermore, the sensitivity of these tachycardias to adenosine provides evidence for a shared arrhythmia mechanism, consistent with intracellular calcium overload and triggered activity.

**Key words:** atrial tachycardia, ventricular tachycardia, adenosine, mitral valve annulus, tricuspid

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Introduction

Idiopathic ventricular tachycardias (VTs) most often originate from the right ventricular outflow tract.\textsuperscript{1} Its mechanism has been shown to be due to cyclic AMP-mediated triggered activity.\textsuperscript{2} Another common area of origin for idiopathic ventricular arrhythmias is the ventricular aspect of the tricuspid and mitral annuli. The mechanism of these arrhythmias has not been studied systematically because most of these patients present with frequent premature ventricular contractions (PVCs) alone,\textsuperscript{3-6} precluding a comprehensive evaluation, which would include initiation and termination with programmed stimulation and/or isoproterenol infusion, termination with adenosine and/or vagal maneuvers, sensitivity to beta-blockade and verapamil.

The atrial aspect of the tricuspid and ventricular annuli are also frequent sites of focal atrial tachycardia (AT).\textsuperscript{7-10} We have previously demonstrated that tricuspid and mitral annular atrial tachycardias are due to cyclic AMP-dependent triggered activity.\textsuperscript{9-10} Based on current understanding of cardiac conduction system development and the observed propensity of arrhythmogenic foci to originate in areas near the atrioventricular annuli, which may reflect a common pathophysiological process, we hypothesized that idiopathic annular VT share a common mechanism with AT. We prospectively evaluated this hypothesis in patients with sustained atrial and ventricular annular tachycardia (peri-annular tachycardia).

Methods

Patient Characteristics

The study group consists of forty-nine consecutive patients with sustained, focal peri-annular tachycardia undergoing invasive electrophysiology study at our institution in whom the effects of adenosine on tachycardia could be reliably evaluated. None of the patients were reported in our previous studies.\textsuperscript{9-11} Baseline characteristics of the patients, including age, gender, cardiac
history and left ventricular ejection fraction were collected. Structural heart disease was defined as the presence of coronary artery disease (>60% occlusion), a left ventricular ejection fraction ≤45%, and/or moderate/severe valvular disease. This study was approved by the Weill Cornell Medical College Institutional Review Board.

**Baseline Electrophysiological Study**

After giving informed written consent, patients underwent electrophysiological testing after an overnight fast. Patients were locally anesthetized (with 0.25% bupivacaine) and sedated with intravenous midazolam and fentanyl. Quadripolar 6-Fr catheters were advanced to the His bundle position and right ventricular apex. Right atrial electrogram recordings were obtained with either a quadripolar catheter positioned in the high right atrium (RA) or a 7-Fr duodecapolar halo catheter positioned along the tricuspid annulus. A 6-Fr decapolar catheter was positioned in the coronary sinus to record left atrial activity along the mitral annulus. Tachycardia mechanism was evaluated by a previously published schema.11 The mode of tachycardia initiation, termination, sensitivity to catecholamine infusion and response to adenosine and verapamil were evaluated. The stimulation protocol included rapid atrial and ventricular pacing and introduction of atrial and ventricular extrastimuli at several basic drive cycle lengths. To facilitate induction of sustained tachycardia, when necessary, programmed stimulation was repeated during isoproterenol infusion at a dose sufficient to decrease the sinus cycle length by approximately 30%. All but two patients underwent electroanatomic mapping using the Biosense CARTO system (Biosense-Webster, Diamond Bar, CA) or the St. Jude Medical NAVX system (Saint Paul, MN).

**Focal Tachycardia Diagnosis**

Atrial tachycardia was distinguished from other supraventricular tachyarrhythmias, including
atrioventricular (AV) nodal reentry and AV reciprocating tachycardia, by standard electrophysiological criteria. Focal AT was defined based on the following characteristics: (1) centrifugal atrial activation pattern, (2) early local atrial activation relative to the surface P wave, and/or (3) atrial activation map encompassing <50% of TCL. Annular focal AT was identified when the above criteria were met, fluoroscopic and three-dimensional electroanatomic sites were consistent with an annular site, and an atrial and ventricular electrogram were present simultaneously at the site of successful ablation. A location was considered para-Hisian when either a His deflection was observed at the site of earliest atrial activation during tachycardia or the successful ablation site along the tricuspid annulus was within 1 cm of a site recording the His bundle potential.

**Pharmacological Evaluation**

Adenosine (Adenocard; Fujisawa, Deerfield, IL) was administered to all patients during tachycardia, as a rapid bolus through a central venous catheter, followed by a 10-mL flush of normal saline. Sensitivity (termination or transient suppression) or insensitivity was noted. The response to verapamil was also evaluated in two patients during VT, as was the response to Valsalva in two other patients.

**Catheter Ablation**

Catheter ablation was performed using either radiofrequency (RF) or cryoablation. RF energy was applied using a non-irrigated 7-Fr 4-mm-tip ablation catheter (Biosense-Webster) with a target temperature of 60°C and maximal allowed power output of 50 W or a 3.5 mm (Thermocool, Biosense Webster) or 4 mm (Safire BLU, St. Jude Medical) open-irrigation ablation catheter at power settings between 15 and 45 W for 30 – 60 seconds using a power-controlled mode with an irrigation rate of 17-30 ml per minute. Cryoablation was performed in
three patients with para-Hisian atrial tachycardia using a 4-mm-tip ablation catheter with a target temperature of -80°C. Energy was applied for up to 4 minutes at each location.

Statistics

Results are presented as mean ± SD where appropriate. Comparison of patients with AT and VT was performed using the two-tailed t test for continuous variables and the chi-squared test for categorical variables. P<0.05 was considered statistically significant.

Results

Patient Characteristics

The baseline characteristics of the patients are listed in Tables 1 and 2. The mean age was 58.0 ± 16.4 years and 45% of the patients were women. All patients were treated within one year of presentation. The mean left ventricular ejection fraction (LVEF) was 56.7 ± 11.8%; 7 pts had LVEF ≤ 45%. Only 1 of 9 patients with VT had an LVEF ≤ 45%. This patient also had frequent PVCs and her ejection fraction normalized post-ablation. Of the 40 AT patients, only 6 patients had LVEF ≤ 45% - 3 of whom had complete recovery of LVEF after ablation (presumably due to resolution of tachycardia-induced cardiomyopathy) and 2 others were lost to follow-up.

Twenty-one (43%) patients had hypertension and four (8.2%) had coronary artery disease, and three underwent previous cardiac surgery. One (patient # 14) was on an antiarrhythmic drug (sotalol) at the time of the procedure. Nine annular ventricular tachycardias and 41 annular atrial tachycardias (in 40 patients) were identified. A schematic of their various locations is shown in Figure 1. Eight of nine patients with ventricular tachycardia presented with sustained VT, one patient presented with a PVC-induced cardiomyopathy.

Comparison of Groups

There was no significant difference between patients with VT compared to patients with AT in
age (55.7 ± 20.0 versus 58.6 ± 15.7 years, respectively; P = NS) or sex (56% versus 48% female, respectively; P = NS), or ejection fraction (57.4 ± 9.8 versus 56.4 ± 12.5, respectively; P = NS).

All peri-annular tachycardias responded to adenosine and there was no significant difference in ablation success (89 versus 95%, respectively; P = NS).

**Electrophysiological Characteristics**

In three of the 9 patients with sustained annular VT, the arrhythmia originated from the tricuspid annulus (Figure 2), and in 6 patients, VT originated from the mitral annulus (Figure 3). Three of annular VTs were epicardial in origin (2 from the mitral annulus, 1 from the tricuspid annulus) (Figure 4). The mean ventricular tachycardia cycle length (TCL) was 450 ± 87 msec. In 6 of 9 patients, programmed stimulation initiated or terminated tachycardia (programmed stimulation was not evaluated in 3 VT patients who were in incessant tachycardia). Isoproterenol facilitated initiation of tachycardia in 7/9 (77.8%) of patients. All 9 VTs terminated with adenosine (mean dose 12.7 ± 5.6 mg). Verapamil terminated VT in the two patients in whom it was administered (Figure 3A). Valsalva terminated VT in two patients (Figure 4B).

Of the 41 cases of annular atrial tachycardia, four were localized to the mitral annulus (Figure 5), 37 to the tricuspid annulus (Figure 6) (including 9 para-Hisian). One patient had both an anterior mitral annular and a septal tricuspid annular atrial tachycardia. The mean TCL was 412 ± 77 msec. In all 41 atrial tachycardias, programmed stimulation initiated or terminated tachycardia. Isoproterenol was required to facilitate initiation of tachycardia in 28 of 41 (68.3%) of annular ATs. Adenosine terminated sustained AT in all cases with a mean dose of 8.9 ± 3.1 mg.

The mechanism of all tachycardias was consistent with triggered activity as demonstrated by reproducible initiation and termination with programmed stimulation (94%), and sensitivity to
adenosine (Figures 2A, 4B, 5A, 6A), verapamil (Figure 3A), and Valsalva maneuvers (Figure 4B). In addition, catecholamine infusion facilitated induction of tachycardia in 64% of patients. Features of enhanced automaticity (i.e. spontaneous initiation and/or termination, failure to initiate with programmed stimulation, and demonstration of “warm-up” and/or “cool-down” phenomena) and microreentry (i.e. entrainment and fractionated electrograms at the origin of tachycardia) were absent.

Of note, one patient in this study presented with a PVC-induced cardiomyopathy (43% PVC prevalence) [Patient #5; Table 1]. Although the patient had no evidence of clinical sustained VT, during electrophysiologic study, sustained VT was induced with programmed stimulation during concurrent isoproterenol infusion (Figure 7B). The induced VT and clinical PVCs had an identical QRS morphology (Figure 7C). The PVC was targeted for ablation, which also eliminated induction of VT.

Tachycardia Mapping and Catheter Ablation

Three-dimensional activation mapping was performed in all but two patients. Activation mapping demonstrated a centrifugal activation pattern, consistent with focal activation. Catheter ablation was successful in 38/40 (95%) patients with annular AT and 8/9 patients with annular VT. One case of atrial tachycardia along the posterolateral tricuspid annulus remained inducible despite attempted ablation, and another case was not targeted for ablation because the clinical arrhythmia was AV nodal reentrant tachycardia. In five patients, mapping and ablation were performed in the noncoronary cusp of the aortic valve for para-Hisian atrial tachycardia.

Discussion

The atrioventricular continuity is an area enriched with arrhythmogenic foci. This is the first study to systematically characterize the mechanism of sustained, peri-annular VT and comparing
the electrophysiologic properties of peri-annular VT and AT. The major finding of this study is that these arrhythmias share a common electrophysiologic mechanism, irrespective of atrial or ventricular annular origin. These arrhythmias are focal in origin, inducible with programmed stimulation, facilitated by catecholamines and sensitive to adenosine, verapamil and Valsalva maneuvers. These shared electrophysiological findings are mechanistically consistent with cyclic AMP-mediated triggered activity due to intracellular calcium overload. The contiguous location of these atrial and ventricular arrhythmias and identical mechanism suggest a common developmental origin. These arrhythmogenic cells may arise from a common source, located on either the atrial or ventricular aspect of the annulus, which ultimately determines the phenotype of tachycardia.

**Tachycardia Phenotype**

In our series, these tachycardias more often originated on the atrial aspect of the annuli, with the tricuspid annulus a more common site than the mitral annulus (Figure 1). All patients in our study had sustained tachycardia. Nearly all studies published to date on ventricular annular arrhythmias comprise patients with frequent PVCs, not sustained arrhythmias. This unique circumstance of our study offered an opportunity to formally investigate mechanism. Of the 9 patients with inducible sustained VT, 8 had clinically documented sustained VT (3 of which were exercise-induced). One patient had ambulatory monitoring prior to electrophysiologic evaluation that showed frequent PVCs (43% prevalence). In this patient, the PVCs were uniform in morphology and had a similar morphology to the sustained clinical and inducible VT in the laboratory, suggesting that the PVC may have had a similar electrophysiologic mechanism (Figure 7).
Proposed Embryonic Origin of Annular Tachycardia

The primary heart tube, derived from heart progenitor cells of the first heart field, gives rise to the left ventricle, a portion of the atria and the atrioventricular (AV) canal. The embryonic AV canal comprises precursors of the AV node and AV ring bundles, the latter of which encircle the orifices of the tricuspid and mitral valves and emerge from inferior extensions of the compact AV node.13 The AV ring, in contrast to working myocardium, expresses Tbx3, Hcn4 and Cx45 and is negative for Cx40, Cx43 and Nav1.5.14 Typically, during the latter phases of development, expression of markers like Tbx3 and mink-lacZ become limited to the AV node, whereas the remainder of the AV canal undergoes apoptosis or differentiation into working myocardium.15

However, vestiges of primitive myocardium from the AV canal, resembling nodal cells, persist circumferentially along the AV valves in the adult human heart.16 This may be due to incomplete regression of embryonic tissue, or re-expression of the embryonic gene program, and provides a possible substrate for the tachycardias described in our study. To this end, multiple studies have confirmed nodal-like action potentials along the AV valves.17,19 These cells histologically resemble atrial cells but lack Cx43, and respond to adenosine in a manner similar to AV nodal cells, with a decrease in action potential amplitude and duration. Furthermore, a zone of cells with action potential characteristics intermediate between atrial and AV nodal cells is interposed along a 1 cm rim around the annuli, which also respond to adenosine.19

Although speculative, some inferences can be drawn with regard to the mechanism of arrhythmia in our study. Nodal like cells in the peri-annular region can demonstrate spontaneous firing, suggesting the possibility of automaticity. However, we believe this mechanism is unlikely applicable to our study since the arrhythmias were reproducibly initiated and terminated with programmed stimulation. Furthermore, adenosine terminated the arrhythmias rather than
causing transient suppression. Both of these findings are inconsistent with an automatic mechanism.

Another possibility is that the arrhythmias are due to triggered activity. In support of this hypothesis, isolated preparations of muscle fibers from the mitral valve demonstrate sustained arrhythmias due to delayed afterdepolarizations and triggered activity.\textsuperscript{18,19} In these studies, the arrhythmias initiate with rapid pacing or catecholamines and terminate with single extrastimuli, verapamil or acetylcholine. Similarly, the arrhythmias in our study were focal in origin, initiated with programmed stimulation, and were responsive to adenosine and verapamil, findings consistent with a triggered mechanism.

It is notable that many atrial arrhythmias originate from corresponding regions in the developing heart that do not initially differentiate into working myocardium. These areas express Tbx2 and/or Tbx3, which inhibit differentiation of primary/embryonic myocytes, capable of nodal activity, into working myocardium. This is mediated by repression of chamber-specific gene programs. These regions include structures derived from the sinus venosus, including the crista terminalis and structures derived from the AV canal; i.e., the myocardium encircling the tricuspid and mitral valves. As identified above, triggered activity has been shown to occur in the latter structures,\textsuperscript{19} whereas the crista terminalis is also a common source of triggered activity in isolated preparations\textsuperscript{20} and clinically in humans.\textsuperscript{9,21} It has been proposed that these arrhythmias may owe their origin to a common primary myocardial lineage.\textsuperscript{15,19,22}

Mechanistically, there may be an important link between nodal-like cells capable of automaticity and triggered activity. This can be considered analogous to the behavior of nodal cells that populate the sinoatrial node. Normal automaticity in this structure is thought to be due to a membrane voltage clock as well as to a calcium clock. In the latter case, under normal
conditions, spontaneous release of local intracellular Ca$^{2+}$ from the sarcoplasmic reticulum activates the electrogenic sodium-calcium exchanger (I_{NCX}) to produce a net inward positive depolarizing diastolic current. However, under specific conditions that produce a critical degree of intracellular calcium overload, such as during catecholamine stimulation, this same cellular process is augmented, eliciting triggered activity within the sinoatrial node. A similar mechanism may be operative in dormant nodal-like remnant cells surrounding the tricuspid and mitral annuli. Therefore, although these tissues may support both automaticity and triggered activity, our data suggest that triggered activity is the more clinically prevalent.

Our findings also suggest that peri-annular tissue can give rise to not only atrial tachycardia but also to ventricular tachycardia. We surmise that this is related to an arrhythmogenic focus that originates from the inferior aspect of either annulus, and therefore activates ventricular rather than atrial myocardium.

**Limitations**

Although the preponderance of evidence suggests that the mechanism of arrhythmogenesis of annular tachycardia is triggered activity, it is possible that reentry could account for some of these arrhythmias. However, adenosine does not terminate macroreentrant atrial or ventricular tachycardia, or that due to microreentry. Nevertheless, it is important to acknowledge that, although the majority of the patients in this study did not have structural heart disease based on echocardiography, and the single VT patient with cardiomyopathy did not have myocardial scar detected with cardiac MRI (and LV function subsequently improved after ablation), we cannot exclude the possibility that some patients may have had an underlying subclinical substrate of non-ischemic cardiomyopathy with peri-annular scar since cardiac MRI imaging was performed in a minority of patients.
Because some of the tachycardias were difficult to induce despite provocative measures and the indication for the study was ablation of clinical VT, verapamil was not given to all patients. However, the administration and termination in 2 of 2 patients with VT provides data to support the proposed mechanism of triggered activity.

In three patients with VT (#2, #7 and #9) inducibility and/or termination of tachycardia was not systematically evaluated. Therefore, we cannot definitively conclude that these cases were due to triggered activity; however, based on their pharmacologic responses and location, we believe this is a reasonable, albeit speculative, conclusion.

Conclusions
The present study demonstrates that the tissue surrounding the tricuspid and mitral annuli is enriched with arrhythmogenic foci, which can manifest as focal atrial or ventricular tachycardia. The sensitivity of these tachycardias to adenosine provides insight into a shared arrhythmia mechanism, one that is due to intracellular calcium overload and triggered activity, findings consistent with a common myocardial lineage.

Conflict of Interest Disclosures: Dr. Liu receives research support from Biosense Webster, and speaker honoraria from St. Jude Medical. Dr. Thomas receives speaker honoraria from St. Jude Medical. Dr. Cheung receives speaker honoraria from St. Jude Medical and fellowship grant support from St. Jude Medical and Biosense Webster. All others have none.

References:


Table 1: Characteristics of study patients with ventricular tachycardia

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<th>Age</th>
<th>Sex</th>
<th>LVEF</th>
<th>Cardiac History</th>
<th>Presentation</th>
<th>CL (ms)</th>
<th>Initiation/Termination</th>
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<th>ADO; Verapamil (Dose/Effect)</th>
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ADO = adenosine, CL = cycle length, F = female, HTN = hypertension, ISO = isoproterenol facilitated, M = male, MA = mitral annulus, N = no, NICMP = non-ischemic cardiomyopathy, nl = normal, PES = programmed extrastimuli, PVCs = premature ventricular contractions, RVP = rapid ventricular pacing, SP = spontaneous, TA = tricuspid annulus, VT = ventricular tachycardia, Y = yes
Table 2: Characteristics of study patients with atrial tachycardia

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? = unknown, ADO = adenosine, AES = atrial extrastimuli, AS = aortic stenosis, ASD = atrial septal defect, AVR = aortic valve replacement, CABG = coronary artery bypass surgery, CAD = coronary artery disease, CL = cycle length, F = female, HTN = hypertension, ISO = isoproterenol facilitated, M = male, MA = mitral annulus, MI = myocardial infarction, MR = mitral regurgitation, MVP = mitral valve prolapse, N = no, NICMP = non-ischemic cardiomyopathy, nl = normal, PAD = peripheral arterial disease, palps = palpitations, PCI = percutaneous coronary intervention, PES = programmed extrastimuli, PFO = patent foramen ovale, PSVT = paroxysmal supraventricular tachycardia, RAP = rapid atrial pacing, SP = spontaneous, TA = tricuspid annulus, VVS = vasovagal syncope, WPW = Wolf Parkinson White, Y = yes
Figure Legends:

Figure 1. A. Location of annular ventricular tachycardias. Schematic showing location of tricuspid annulus (TA) and mitral annulus (MA) in the left anterior oblique projection with anterior position represented at top, posterior on bottom, septal in center and lateral along periphery. Epicardial locations denoted by marks external to circle. B. Location of annular atrial tachycardias using the same schema as identified in panel A.

Figure 2. Example of patient (# 9) with anterior tricuspid annular ventricular tachycardia. A. Tachycardia terminates with adenosine administration (12 mg) at the time of atrioventricular block. ABL = ablation, CS = coronary sinus, d = distal, RV = right ventricle, p = proximal, B. Electroanatomical mapping system in the left anterior oblique projection showing the site of origin along the superior (anterior) aspect of the tricuspid annulus (arrow). Gray outline of the right ventricular outflow tract (RVOT) is shown. Red circle denotes the relative position of the tricuspid annulus (TA).

Figure 3. Superior mitral annular ventricular tachycardia (Patient #7). A. Verapamil (10mg) administration results in termination of the tachycardia within 60 seconds. B. Ablation at the site of origin along the superior mitral annulus results in termination of ventricular tachycardia. Note the annular signal on the ablation catheter as shown by the atrial (A) and ventricular (V) electrograms. C. Electroanatomical mapping system in the left anterior oblique cranial projection showing site of successful ablation along superior MA. Note the annular signal of the site of successful ablation (top right).
Figure 4. Tricuspid annular ventricular tachycardia (Patient #6). A. Initiated by exercise. B. Valsalva maneuver terminates tachycardia. C. Fluoroscopy with coronary angiography showing presence location of successful epicardial ablation site along the posteroseptal tricuspid annulus.

Figure 5. Mitral annular atrial tachycardia (Patient #35). A. Adenosine terminates atrial tachycardia with earliest activation along the posterior mitral annulus. B. Electroanatomical map in the left anterior oblique projection showing the site of successful ablation (arrow) along the posterior mitral annulus. Red circle denotes where the relative position of the mitral annulus. Note the annular signal of the site of successful ablation. CS = coronary sinus, LA = left atrium.

Figure 6. Tricuspid annular atrial tachycardia (Patient # 41) A. Tachycardia terminates with adenosine 12 mg. B. Ablation at earliest site of activation along the superior tricuspid annulus terminates tachycardia (right panel). Annular signal demarcated by the atrial (A) and ventricular (V) electrograms. Left panel shows site of ablation during sinus rhythm. C. Electroanatomical map in the left anterior oblique projection showing the site of earliest activation along the superior tricuspid annulus that was successfully ablated. Red dots denotes the ablation lesions. His and coronary sinus (CS) catheters are shown. The yellow dot demarcates the location of the His bundle.

Figure 7. Relationship of premature ventricular contractions (PVCs) to sustained ventricular tachycardia (VT). A. Patient (#5) presented clinically with only frequent PVCs. B. During electrophysiologic study, sustained VT was induced with rapid ventricular pacing and isoproterenol infusion. C. Sustained VT matched (12/12 ECG leads) the clinical PVC morphology. D. Termination of VT with rapid ventricular pacing.
Verapamil 10 mg

Verapamil (cont'd)
Unifying Mechanism of Sustained Idiopathic Atrial and Ventricular Annular Tachycardia
James E. Ip, Christopher F. Liu, George Thomas, Jim W. Cheung, Steven M. Markowitz and Bruce B. Lerman

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