Heart Rhythm Disorders

Clinical and Electrophysiological Spectrum of Idiopathic Ventricular Outflow Tract Arrhythmias

Robert J. Kim, MD, Sei Iwai, MD, FACC, Steven M. Markowitz, MD, FACC,
Bindi K. Shah, MD, FACC, Kenneth M. Stein, MD, FACC, Bruce B. Lerman, MD, FACC

New York, New York

Objectives	This study sought to compare and contrast the clinical and electrophysiological characteristics of outflow tract arrhythmias.
Background	Idiopathic ventricular outflow tract arrhythmias manifest clinically in 3 forms: 1) paroxysmal sustained monomorphic ventricular tachycardia (SMVT), 2) repetitive nonsustained ventricular tachycardia (NSVT), or 3) premature ventricular contractions (PVCs). Although these arrhythmias have a similar site of origin, it is unknown whether they share a common mechanism or similar clinical features.
Methods	A total of 127 patients (63 female [50%], mean age 51 ± 15 years) were evaluated for outflow tract arrhythmias.
Results	A total of 36 (28%) presented with the index clinical arrhythmia of SMVT, 46 (36%) with NSVT, and 45 (35%) with PVCs. The sites of origin of the arrhythmias were similar among the 3 groups, occurring in the right ventricular outflow tract in 82%. Sustained ventricular tachycardia was more likely to be induced during exercise in the SMVT (10 of 15 patients [67%]) than NSVT or PVCs groups ($p < 0.01$). Sustained outflow tract ventricular tachycardia was induced at electrophysiology study in 78% of SMVT patients, 48% of NSVT patients, and 4% of PVCs patients. Adenosine was similarly effective in all 3 groups ($p = NS$).
Conclusions	Patients with outflow tract arrhythmias can be differentiated based on the subtype of arrhythmia. However, the observation that approximately 50% of patients with NSVT and ~5% of patients with PVCs have inducible sustained ventricular tachycardia that behaves in an identically unique manner to those who present with sustained ventricular tachycardia (e.g., adenosine-sensitive) suggests that rather than representing distinct entities, outflow arrhythmias may be considered a continuum of a single mechanism. (J Am Coll Cardiol 2007;49:2035–43) © 2007 by the American College of Cardiology Foundation

Idiopathic ventricular tachycardia (VT) most commonly arises from the right ventricular outflow tract, and less often from the left ventricular outflow tract. Two subtypes of outflow tract VT have been described: repetitive monomorphic ventricular tachycardia (RMVT) and paroxysmal, exercise-induced sustained VT. Gallavardin (1) first described RMVT in 1922 as repetitive salvos of monomorphic, nonsustained ventricular tachycardia (NSVT) occurring at rest, punctuated by single and double premature ventricular complexes and intervening periods of sinus rhythm. In some cases the repetitive salvos are incessant (2). In 1932, Wilson et al. (3) described the second subtype of idiopathic VT, in which there was an absence of ventricular

ectopy at rest, but paroxysms of sustained VT during exercise. Subsequent investigators have introduced classifications of these tachycardias based on VT morphology (4), response to exercise testing (5), and response to pharmacologic agents (6). As a result, comparing these studies and interpreting their results in the context of the original subtypes of idiopathic VT remains challenging. Moreover, a third form of ventricular arrhythmia, repetitive uniform premature ventricular contractions (PVCs), can be considered part of this spectrum encompassing 3 distinct subtypes of idiopathic ventricular outflow tract arrhythmias (7).

We have previously elucidated the mechanism underlying paroxysmal exercise-induced sustained VT (8,9). In general, these patients show a unique arrhythmogenic substrate and electropharmacologic profile, i.e., the VT is adrenergically mediated and sensitive to perturbations that lower intracellular calcium (e.g., adenosine and verapamil). These findings are consistent with triggered activity secondary to cyclic adenosine monophosphate-mediated delayed afterdepolar-

Abbreviations and Acronyms
ECG = electrocardiogram
MRI = magnetic resonance imaging
NSVT = nonsustained ventricular tachycardia
PVC = premature ventricular contraction
RMVT = repetitive monomorphic ventricular tachycardia
SMVT = sustained monomorphic ventricular tachycardia
TWA = T-wave alternans
VT = ventricular tachycardia

izations (9). It remains unclear, however, whether all patients with RMVT and those with repetitive PVCs also share this mechanism.

To date there has been no systematic study examining the clinical and electrophysiological characteristics of patients with idiopathic ventricular outflow tract arrhythmias classified according to these 3 distinct subtypes. The purpose of this study was to compare and contrast the clinical and electrophysiological characteristics of these 3 subtypes of arrhythmias in a large series of consecutive patients.

Methods

Study population. We evaluated 106 consecutive patients with outflow tract arrhythmias who presented to our laboratory for electrophysiological evaluation from February 1998 through September 2006. An additional 21 patients for whom complete records were available before that time also were included. Reasons for referral included arrhythmias noted on resting electrocardiogram (ECG), telemetry monitoring, or during exercise stress testing, as well as symptomatic ventricular arrhythmias refractory to medical therapy. This study was approved by our institutional review board.

Clinical classification. Patients were classified according to the index clinical arrhythmia on presentation: sustained VT, NSVT, or repetitive PVCs. Sustained VT was defined as lasting ≥30 s, and NSVT was defined as ≥3 beats and <30 s.

Noninvasive evaluation. Patients underwent evaluation of cardiac structure, function, and ectopy burden. This often included cardiac magnetic resonance imaging (MRI) as well as 24-h Holter monitoring and/or inpatient telemetry. The presence of coronary artery disease was assessed by stress testing and/or cardiac catheterization (≥70% stenosis of any major epicardial vessel). Left ventricular systolic function was quantified by MRI, echocardiography, radionuclide ventriculography, and/or ventricular cineangiography. Structural heart disease was defined as presence of coronary artery disease (as previously defined), left ventricular ejection fraction <40%, and/or moderate or severe valvular disease.

Electrophysiological testing. After giving informed consent, patients underwent electrophysiological testing after an overnight fast. Patients were locally anesthetized with 0.25% bupivacaine, and if necessary were minimally sedated with intravenous midazolam and/or fentanyl. Quadripolar 6-F catheters were advanced to the high right atrium, His bundle position, and right ventricular apex and/or outflow tract. Bipolar intracardiac electrograms were filtered at 30 to 500 Hz. If further mapping and/or ablation in the left ventricle or sinuses of Valsalva was required, a retrograde aortic approach was used.

The stimulation protocol included burst atrial and ventricular pacing, and the introduction of single atrial extrastimuli and up to triple ventricular extrastimuli from 1 or 2 right ventricular sites. Stimuli were delivered as rectangular pulses of 2-ms duration at 4× diastolic threshold. If necessary, to facilitate induction of sustained tachycardia, programmed stimulation was repeated during infusion of isoproterenol or dobutamine at a rate that decreased the sinus cycle length by approximately 20% to 30%.

Three-dimensional mapping was performed in 97 patients using 1 of 2 systems. The CARTO electroanatomic mapping system (Biosense-Webster, Diamond Bar, California) uses a reference locator pad for spatial reference and the QRS of an appropriate surface ECG lead as a temporal reference. Alternatively, the Endocardial Solutions noncontact mapping system (Endocardial Solutions, Inc., St. Paul, Minnsesota) was used in 4 patients.

Evaluation of microvolt level T-wave alternans (TWA) testing also was performed during atrial pacing at the time of the electrophysiological study according to standard techniques. The protocol (performed in 65 patients) involved recording at baseline and during right atrial pacing at 109 beats/min for 5 min. T-wave alternans was analyzed using either the Cambridge Heart CH2000 or HearTwave system (Cambridge Heart, Inc., Bedford, Massachusetts) according to standard criteria.

Pharmacologic testing. Adenosine was given when sustained VT was reproducibly induced during electrophysiological testing. Adenosine (Adenocard, Astellas Pharma US, Inc., Deerfield, Illinois) was administered as a bolus through a central venous catheter, followed by a 10-ml flush of normal saline. The usual initial dose of adenosine was 6 mg, with the dose titrated incrementally by 6 mg until tachycardia was terminated, was suppressed, or ventriculoatrial block occurred. Similarly, verapamil (5 to 20 mg intravenously) was also infused over 60 s when clinically appropriate and/or tolerated, to determine its effect on tachycardia.

Statistics. Continuous variables were expressed as a mean ± SD. Comparisons between groups were made using one-way analysis of variance after determining normality of distribution. Categorical variables, expressed as numbers and percentages, were compared using Fisher exact test or chi-square test, depending on the number of variables. All tests of significance were two-tailed, and p values of <0.05 were considered statistically significant for comparisons of all 3 groups, with adjustments using the Bonferroni correction for multiple comparisons among the 3 pairs of groups as well as the continuity correction when applicable (10).

Results

Clinical classification. One hundred twenty-seven patients were evaluated for idiopathic ventricular outflow tract arrhythmias. Thirty-six patients (28%) presented with sustained ventricular tachycardia, 10 of whom experienced sustained VT during an exercise stress test, including 1 who subsequently also had sustained VT detected on telemetry. In all 10 patients the sustained episode was self-limited and spontaneously terminated or became NSVT with cessation of exercise. Fifteen patients presented urgently, requiring an antiarrhythmic agent and/or cardioversion to terminate their index episode of sustained VT. Four of these patients reported stressors (e.g., exertion or an argument) immediately preceding their episode of sustained VT. The remaining 11 patients had their initial episode of sustained VT identified during continuous ECG monitoring (i.e., Holter, event recorder, or during inpatient telemetry).

Forty-six patients (36%) presented with NSVT, 37 of whom had repetitive salvos of NSVT consistent with RMVT. Six of these patients (all of whom presented with RMVT) also experienced 1 isolated episode of sustained VT during subsequent monitoring; 2 patients had self-terminating episodes noted during continuous ECG monitoring, whereas 4 required an antiarrhythmic agent and/or cardioversion to terminate their sustained episode. Of 16 patients with NSVT who underwent Holter monitoring, all had repetitive PVCs in addition to frequent runs of NSVT.

Forty-five patients (35%) presented with frequent repetitive PVCs; 15 had only isolated PVCs and/or couplets, whereas 30 also had short runs of NSVT (most commonly ≤5 beats). The majority of these patients (78%) were initially identified by ambulatory continuous ECG monitoring (i.e., Holter or event monitoring) during exploration of palpitations.

Age, gender, and clinical presentation. The baseline characteristics of the patient population are summarized in Table 1. The mean age was 51 ± 15 years (range 6 to 80 years), and half (50%) were female. There were no differences among the groups with respect to age, gender, site of arrhythmia origin, or left ventricular ejection fraction. Echocardiograms and cardiac catheterizations were performed in a similar proportion of patients in all 3 groups. Structural heart disease was uncommon and did not differ among the 3 groups. Baseline 12-lead ECG findings were similar among the 3 groups with respect to the presence of atrial fibrillation, ventricular conduction delay, bundle branch block, or T-wave inversion in ≥2 precordial leads.

Patients experienced palpitations, chest pain, and syncope in similar proportions among the 3 groups. Patients subjectively experienced palpitations in the setting of stressors (e.g., exercise or stressful situations) more frequently in the sustained monomorphic VT (SMVT) group compared with the NSVT group (53% vs. 30% respectively, p = 0.07) and compared with the PVCs group (53% vs. 18%, p < 0.01), overall p < 0.01.

Noninvasive evaluation. The findings from additional noninvasive cardiac tests performed are presented in Table 2. Forty-seven patients have undergone cardiac MRI imaging since implementation of our current imaging protocol, and a similarly high proportion of patients from all 3 groups had normal findings (87% in SMVT group, 93% in NSVT group, 100% in PVCs group, p = 0.29). Of the 3 patients with abnormal findings on MRI (2 from the SMVT group and 1 from the NSVT group), 1 had slight thinning of the right ventricular free wall, one had mild right ventricular

Table 1	Clinical Characteristics: Outflow Tract Arrhythmias			
Characteristics	**SMVT (n = 36)**	**NSVT (n = 46)**	**PVCs (n = 45)**	**p Value**
Women	15 (42%)	21 (46%)	27 (60%)	0.21
RVOT site of origin	27 (75%)	41 (89%)	36 (80%)	0.24
Mean age	51.9 ± 15.7	51.7 ± 15.8	50.0 ± 14.7	0.77
Mean EF	58.0 ± 12.0	57.8 ± 8.5	53.9 ± 11.4	0.13
Structural heart disease	8 (22%)	5 (11%)	7 (16%)	0.38
≥70% lesion in major epicardial vessel	4	0	4	
Stress perfusion defects without catheterization	0	2	0	
EF <40% or ≥3 + valvular regurgitation	4	3	3	
Resulting 12-lead ECG findings				
Atrial fibrillation	0 (0%)	2 (4%)	1 (2%)	0.44
Ventricular conduction delay/bundle branch block	6 (17%)	9 (20%)	6 (13%)	0.73
Precordial T-wave inversions in ≥2 leads	2 (6%)	3 (7%)	3 (7%)	0.98
Symptoms				
Palpitations	29 (81%)	36 (78%)	37 (82%)	0.89
Chest pain	6 (17%)	11 (24%)	16 (36%)	0.14
Syncope	6 (17%)	13 (28%)	12 (27%)	0.44
Stress-associated palpitations	19 (53%)	14 (30%)	8 (18%)	<0.01*

*p < 0.01 for SMVT versus PVCs only, other paired comparisons nonsignificant.

ECG = electrocardiogram; EF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular contraction; RVOT = right ventricular outflow tract; SMVT = sustained monomorphic ventricular tachycardia.

Table 2	Noninvasive Evaluation			
Characteristics	SMVT (n = 36)	NSVT (n = 46)	PVCs (n = 45)	p Value
Echocardiogram normal	29/33 (88%)	40/43 (93%)	37/40 (93%)	0.70
MRI normal	13/15 (87%)	13/14 (93%)	18/18 (100%)	0.29
TWA negative	9/14 (64%)	11/21 (52%)	17/30 (57%)	0.78
TWA indeterminate	5/14 (36%)	10/21 (48%)	11/30 (37%)	0.69
TWA positive	0/14 (0%)	0/21 (0%)	2/30 (7%)	0.30
Exercise stress test	15/34 (44%)	20/42 (48%)	20/41 (49%)	0.92
Sustained VT induced at exercise stress test	10/15 (67%)	2/20 (10%)	2/20 (10%)	<0.01*
NSVT on Holter	3/4 (75%)	16/16 (100%)	18/25 (72%)	0.06†
NSVT >5 beats on Holter	3/4 (75%)	13/16 (81%)	5/25 (20%)	<0.01†
Percent ectopy expressed as PVCs and couplets	80% ± 27%	81% ± 17%	98% ± 5%	<0.01†
Number of PVCs in 24 h	4,141 ± 5,988	8,641 ± 6,635	16,526 ± 12,962	0.07†

*p < 0.01 for overall comparison, SMVT versus NSVT, and SMVT versus PVCs (p value for NSVT versus PVCs was nonsignificant). †p values are for NSVT versus PVCs only because an insufficient number of Holter data were obtained for SMVT patients to allow appropriate quantitative assessment.
MRI = magnetic resonance imaging; TWA = T-wave alternans; VT = ventricular tachycardia; other abbreviations as in Table 1.

wall motion abnormalities, and one had a dilated right ventricle with reduced function and a focal aneurysmal apex; none fulfilled the Task Force criteria for arrhythmogenic right ventricular dysplasia/cardiomyopathy (11).

Fifty-five patients (43%) underwent exercise stress testing before the electrophysiology study, and sustained VT developed during the stress test in 14 (26%) of those patients (Table 2). Sustained VT during an exercise stress test developed in a higher proportion of patients in the SMVT group as compared with the other 2 groups (67% vs. 10% of the NSVT group [p < 0.01] and 10% of the PVCs group [p < 0.01]; overall p < 0.01).

Sixty-five patients underwent TWA testing. More than half of the patients were negative in each of the 3 groups (64% of the SMVT group, 52% of the NSVT group, and 57% of the PVC group), and a similar proportion from each group had indeterminate results because of either ectopy or AV nodal Wenckebach during pacing (36% of the SMVT group, 48% of the NSVT group, and 37% of the PVCs group). Overall, only 2 patients (both in the repetitive PVC subgroup) had a positive TWA test result. One had a nonischemic cardiomyopathy with a left ventricular ejection fraction of 30%, whereas the other had no known history of coronary artery disease, a normal nuclear perfusion stress test result, and a normal ejection fraction with only mild aortic stenosis by echocardiography.

Electropharmacologic characteristics. All patients underwent electrophysiological testing, the results of which are summarized in Table 3. Sustained ventricular tachycardia was more likely to be induced in patients in the SMVT group (78%) compared with patients in either the NSVT group (48%) or the repetitive PVCs group (4%), p < 0.01 for comparison of SMVT group to NSVT and PVCs groups combined. Induction of sustained VT was catecholamine dependent in a similar proportion of patients in all 3 groups (17 of 28, 61% in SMVT group; 16 of 22, 73% in NSVT group; 2 of 2, 100% in PVCs group; p = 0.27 for SMVT group vs. NSVT and PVCs groups).

Five of 10 SMVT patients and 1 of 2 NSVT patients who had exercise-induced sustained VT were subsequently inducible for sustained VT at electrophysiological study, whereas neither of the 2 patients from the repetitive PVCs

Table 3	Electrophysiological Study Findings		
Characteristics	SMVT (n = 36)	NSVT + PVCs* (n = 91)	p Value
Inducible SMVT at EP study	28 (78%)	24 (26%)	<0.01†
Induced with PS alone	11/28 (39%)	6/24 (25%)	0.43
Induced with catecholamine alone	7/28 (25%)	11/24 (46%)	0.20
Required catecholamine with PS	10/28 (36%)	7/24 (29%)	0.84
Catecholamine-dependent inducible SMVT	17/28 (61%)	18/24 (75%)	0.27
Mean sustained VT cycle length (ms)	329.6 ± 69.1	324.0 ± 64.7	0.76
Adenosine tested during induced SMVT	25/28 (89%)	18/24 (75%)	0.32
Adenosine terminated induced SMVT	19/25 (76%)	18/18 (100%)	0.07
Adenosine dose for termination (mg)	12.3 ± 7.3	12.4 ± 9.8	1.00
Verapamil terminated induced SMVT	4/4 (100%)	3/3 (100%)	N/A
Vagal maneuver (i.e., Valsalva or CSM) terminated induced SMVT	6/11 (55%)	4/8 (50%)	1.00

*NSVT and PVC patients combined because only 2 patients in the PVCs group were inducible for SMVT. †p < 0.01 for SMVT versus NSVT + PVCs combined.
CSM = carotid sinus massage; EP = electrophysiological; PS = programmed stimulation; VT = ventricular tachycardia; other abbreviations as in Table 1.

group in whom VT had developed during exercise testing were subsequently inducible for sustained VT.

Adenosine was effective at terminating induced sustained VT in all 3 groups (76% in SMVT group, 100% in NSVT group, 100% in PVCs group, p = 0.07 for SMVT group vs. NSVT and PVCs groups combined). Because adenosine sensitivity had to be unequivocally shown (i.e., reproducible), the number of patients in whom adenosine sensitivity was reliably assessed was less than the total number of patients with inducible sustained VT. The mean dose of adenosine required for termination was similar for all 3 groups.

Two patients with repetitive PVCs were inducible for sustained VT with a morphology identical to that of their monomorphic PVCs. Figures 1 through 3 show the identical pattern of one of these patient's spontaneous PVC to induced VT, the induction of VT with rapid ventricular pacing and concurrent catecholamine infusion, adenosine sensitivity of the VT, and its right ventricular outflow tract origin.

In several patients we were able to observe the transitional nature of outflow tract arrhythmias. As shown from a patient whose index arrhythmia was exercise-induced sustained VT, there was progressive evolution of repetitive monomorphic PVCs, NSVT, and sustained VT during infusion of isoproterenol (Fig. 4). The 12-lead ECG of all 3 subtypes was morphologically identical. Ablation targeted at the PVC origin from the left ventricular outflow tract eliminated any evidence for any of the 3 subtypes.

Vagal maneuvers (Valsalva or carotid sinus massage) were performed, and verapamil was administered at the discretion of the physician performing the study when induced sustained VT was both hemodynamically tolerated and was reproducibly induced. Both were effective at terminating induced sustained VT in similar proportions of patients in the SMVT and NSVT groups (Table 3); however, no patient in the repetitive PVC subgroup underwent testing with either verapamil or vagal maneuvers.

Acute success rates of radiofrequency ablation did not differ among the 3 groups (SMVT = 85%, NSVT = 94%, PVCs = 88%; overall success = 89%).

Holter monitoring. A formal analysis of Holter data could not be performed in patients who presented with sustained VT with respect to ventricular ectopy and heart rate because of an insufficient number of comprehensive quantitative Holter recordings. However, Holter monitoring data from 20 patients with repetitive monomorphic PVCs showed 3 different qualitative patterns: 9 (45%) showed a concordant relationship between heart rate and PVC frequency, 2 (10%) showed a discordant relationship (Fig. 5), and 9 (45%) showed no consistent relationship whatsoever. Similarly, of the 8 patients with NSVT in whom quantitative Holter
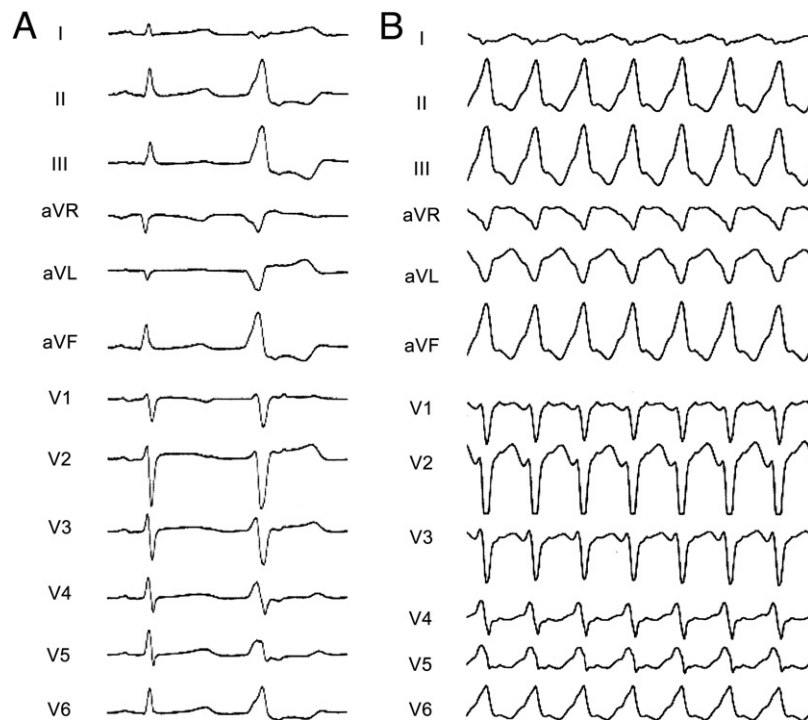
Figure 1   **Comparison of ECG Morphologies of Clinical PVC and Induced Sustained VT From a Patient Who Presented With Repetitive PVCs**

(A) 12-lead electrocardiogram (ECG) of a sinus beat followed by a premature ventricular contraction (PVC). **(B)** 12-lead ECG of induced sustained ventricular tachycardia (VT) from the same patient.
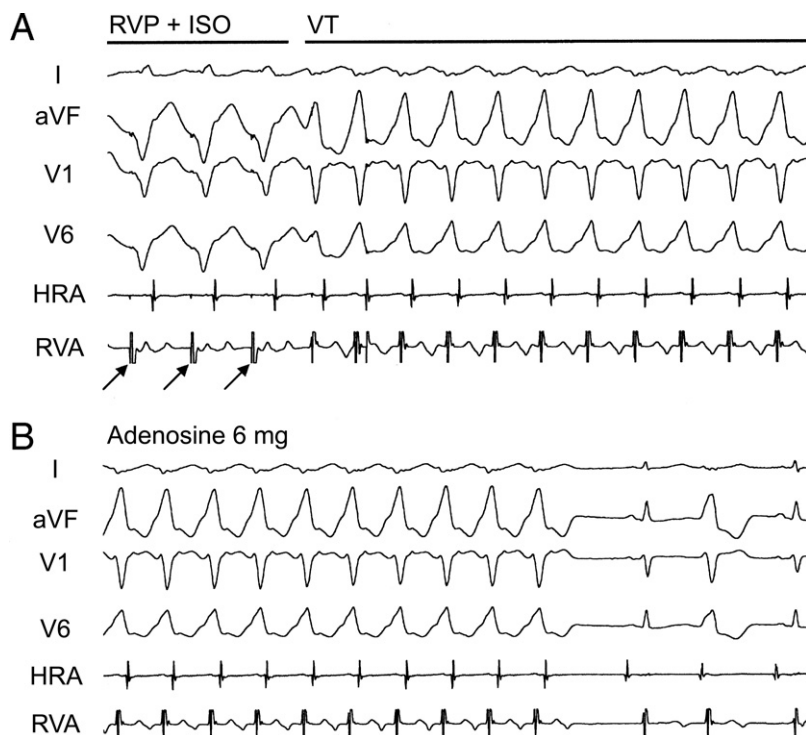
Figure 2   **Electrophysiologic Profile of Induced Sustained VT in a Patient Who Presented With Repetitive PVCs**

(A) Induction of sustained ventricular tachycardia (VT) with rapid ventricular pacing from the right ventricular apex **(black arrows)** during concomitant infusion of isoproterenol (ISO) (same patient as in Fig. 1). Note that the first beat of VT (fourth beat in the figure) represents pseudofusion between a ventricular pacing spike and the first beat of VT, and the fifth ventricular pacing spike (noncapture) occurs after the second beat of VT. **(B)** Termination of induced sustained VT with adenosine. HRA = high right atrium; PVC = premature ventricular contraction; RVA = right ventricular apex; RVP = right ventricualr pacing.

recordings were available, 2 (25%) showed a concordant relationship between heart rate and frequency of ectopy (both PVCs and runs of NSVT) (Fig. 5) whereas the others showed no consistent relationship.

Discussion

The principal finding of this study is that although patients with outflow tract arrhythmias present with clinically distinct grades of ventricular ectopy and VT, the electrophysiological findings in these patients suggest that these subtypes may represent a continuum of a similar mechanism with differential levels of arrhythmia expression.

In agreement with prior studies (12,13), we observed a higher rate of induction of sustained VT at electrophysiology study in those patients with clinical sustained VT as compared to those with NSVT. Nonetheless, approximately 50% of patients with NSVT were inducible for sustained VT, most of which was also catecholamine dependent. In addition, ~5% of those with PVCs were also inducible for sustained VT. Moreover, the induced VT in these patients (NSVT and PVC subtypes) was adenosine-sensitive as well as verapamil sensitive. This electrophysiological profile is identical to that associated with sustained outflow tract VT and is mechanistically consistent with triggered

activity caused by cyclic adenosine monophosphate-mediated calcium-dependent delayed afterdepolarizations (2,8,14). The effect of adenosine on VT is considered to be mechanism specific because it has no effect on re-entrant VT and only transiently suppresses (rather than terminates) VT caused by an automatic mechanism (9,15).

The concept of a threshold arrhythmic response with respect to adrenergic tone or its clinical surrogate, heart rate, has been previously introduced (16). Both isolated ventricular extrasystoles and repetitive NSVT in patients with RMVT were shown to be dependent on heart rate and the level of adrenergic tone. In the case of ventricular extrasystoles, heart rate dependence was associated with the disappearance of ectopy once the heart rate exceeded a critical upper threshold (i.e., during exercise) or fell below a lower threshold (i.e., during sleep). Similarly, repetitive ventricular beats were most often observed during periods of wakefulness and activity, and frequently disappeared entirely during sleep.

We made similar observations in the subset of our patients with NSVT who underwent quantitative Holter monitoring, most of whom had the repetitive form. In particular, all showed marked diminution of repetitive NSVT during periods of rest. In some, PVCs and ventric-
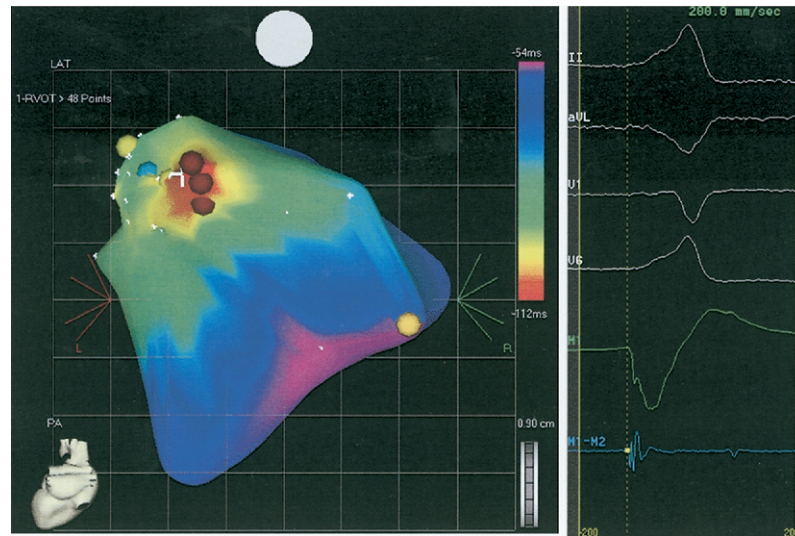
**Figure 3   Electroanatomic Map of Earliest Site of Activation
(Posterior Aspect of RVOT) of PVCs From the Same Patient Shown in Figures 1 and 2**

Surface electrocardiogram leads II, aVL, V$_1$, and V$_6$ and unipolar and bipolar electrograms (M1-M2) are shown on
the right. LAT = lateral; PA = postero-anterior; PVC = premature ventricular contraction; RVOT = right ventricular outflow tract.
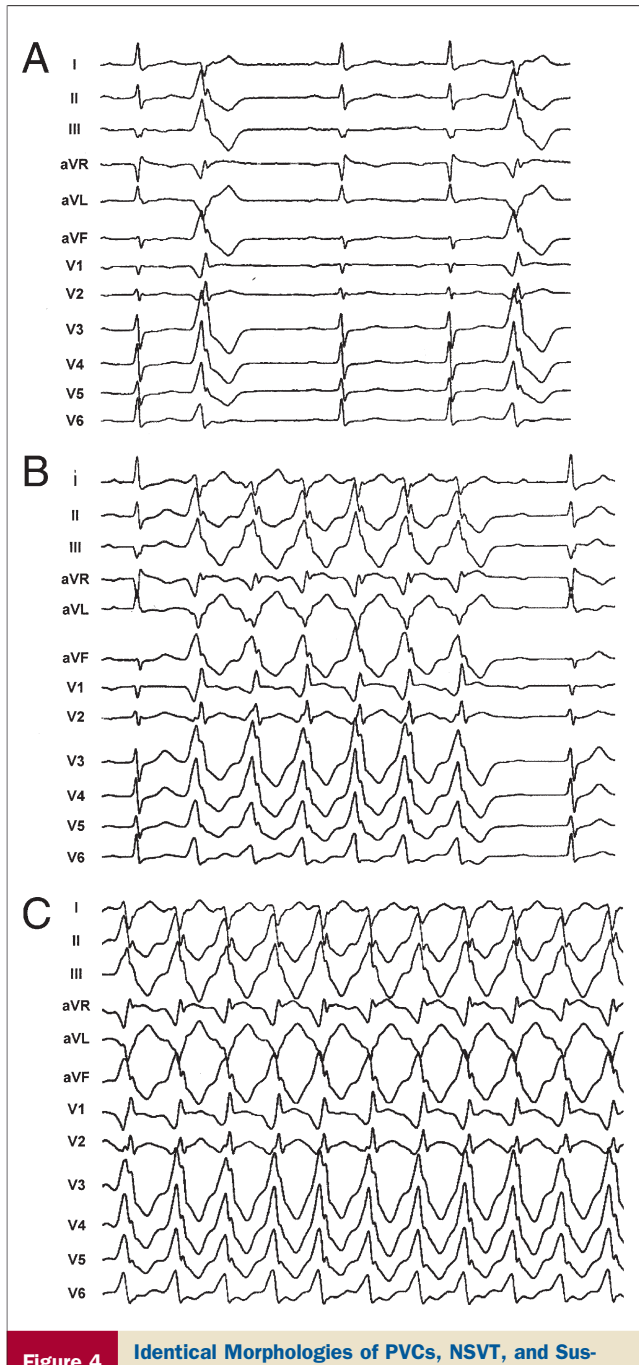
ular couplets were also reduced; however, in others this relationship was not observed. Interestingly, among some of the repetitive PVC subgroup, we also observed a similar dependence of overall ectopy (i.e., repetitive PVCs) on heart rate, as well as suppression of ectopy below a lower threshold and above an upper threshold. It should be noted, however, that in a substantial number of patients (9 of 20) with repetitive PVCs, no such rate-dependent relationship was appreciated, likely underscoring the imperfect correlation between heart rate and adrenergic tone, as well as dependence of arrhythmia expression on multiple factors.

An important observation is that subtype classification, although useful, is not necessarily precise. We categorized patients based on their index arrhythmia. However, prolonged telemetry as well as Holter recordings showed that patients often showed a spectrum of outflow tract ventricular arrhythmias. Nearly all patients with NSVT had high-density repetitive runs and frequent PVCs. In patients who presented with repetitive PVCs, NSVT was also observed in approximately 70%; however, only one-fifth of these patients had runs of more than 5 beats. Of note, despite the absence of spontaneous sustained VT in the PVC subgroup, 2 patients had exercise-induced sustained VT and 2 others had inducible adenosine-sensitive outflow tract tachycardia that was morphologically identical to their PVCs. This phenomenon underscores the point that a subset of patients who present with repetitive PVCs can have sustained VT caused by cyclic adenosine monophosphate-mediated triggered activity. This finding suggests the possibility that a similar electrophysiological substrate and mechanism may be responsible for repetitive PVCs in these patients as well. It would be highly improb-

able that 2 different mechanisms of focal arrhythmogenesis (such as triggered activity and automaticity, each of which is inherently rare) would occur in the same patient and only from a single focal source. A similar argument is applicable to patients with NSVT, in whom approximately 50% are inducible for sustained VT, all of which is adenosine-sensitive.

We draw several conclusions from these findings. First, there seems to be, with respect to induction of outflow tract VT, a graded response that depends on the complexity of the index arrhythmia, i.e., patients with repetitive PVCs are less likely to have inducible VT than patients who present with NSVT, who in turn are less likely to be inducible than those who present with sustained VT. Second, the identical morphologic relationship that exists between inducible sustained VT and the presenting or index arrhythmia, e.g., PVCs or NSVT, suggests a common site of origin for these arrhythmias in a given patient, as does the elimination of the other 2 subtypes when targeting the third during ablation (Fig. 4). Third, the observation that during either prolonged monitoring or electrophysiological study most patients with one subtype of outflow tract arrhythmia show evidence for at least 1 other subtype with an identical morphology (Fig. 4) supports the notion that these arrhythmias are interrelated and fundamentally linked, and suggests that the 3 subtypes represent a continuum of a common underlying etiology.
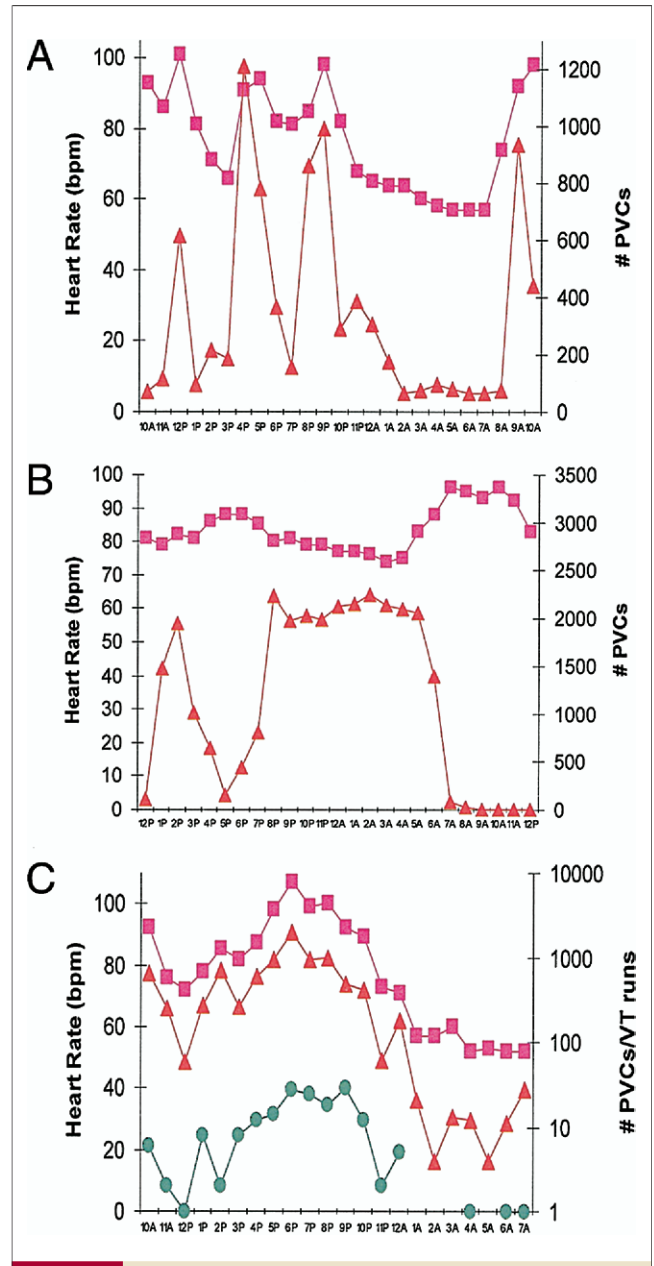
We therefore propose that the differences between VT induction rates between the 3 subtypes of outflow tract arrhythmias do not necessarily reflect a difference in cellular mechanism but rather are caused by an inherent difference in the ability to initiate an iterative response, i.e., VT. This

Figure 4   **Identical Morphologies of PVCs, NSVT, and Sustained VT From a Patient With Exercise-Induced VT**

The 12-lead surface ECG recordings show identical morphologies of repetitive monomorphic PVCs **(A)**, a 6-beat run of nonsustained ventricular tachycardia (NSVT) **(B)**, and sustained VT **(C)**, all of which occurred consecutively during infusion of isoproterenol. Ablation at the earliest site of activation of the PVC from the left ventricular outflow tract eliminated all 3 forms of arrhythmia. Abbreviations as in Figure 1.

Figure 5   **Relationship of Heart Rate to Frequency of Ectopy From 3 Representative Patients**

Data from Holter recordings obtained from **(A)** a patient who presented with frequent repetitive PVCs showing concordance between increased PVCs **(triangles)** to higher relative heart rate **(squares)**; **(B)** a patient who presented with frequent repetitive PVCs showing an inverse relationship between frequency of PVCs **(triangles)** and heart rate **(squares)**; and **(C)** a patient who presented with repetitive monomorphic VT showing concordance between increased frequency of PVCs **(triangles)**, runs of VT **(circles)**, and higher heart rate **(squares)**. Number of PVCs and VT runs expressed on log scale (for **C** only). Note that at hours 1 AM through 3 AM and at 5 AM there were no VT runs. Abbreviations as in Figure 1.

could be related to myriad factors, such as differences in adrenergic tone, beta-receptor sensitivity, sarcoplasmic reticulum calcium loading, or Na^+/Ca^{2+} exchanger activity, among many other yet-to-be-identified variables.

Study limitations. This study includes only those patients who were referred for electrophysiology testing, and there-

fore may reflect some selection bias for those patients who are more symptomatic from their ectopy and not the overall population of patients with outflow tract arrhythmias. As noted above, many patients with either repetitive PVCs or NSVT were not inducible for sustained VT and, therefore,

our conclusions regarding the mechanism of the observed arrhythmia are not definitive. However, the finding that some of these patients can be induced and shown to have adenosine-sensitive VT would suggest that a similar mechanism of arrhythmogenesis may be operative for repetitive PVCs and NSVT and the morphologically identical induced VT in a given patient.

Conclusions

Despite clinical differences among patients with the 3 subtypes of outflow tract arrhythmias, subsets of patients from each group show a similar electrophysiological profile, suggesting a common underlying cellular mechanism. Whether additional mechanisms are present in noninducible patients or whether they simply have higher thresholds for induction remains uncertain.

Reprint requests and correspondence: Dr. Bruce B. Lerman, Division of Cardiology, Cornell University Medical Center, 525 East 68th Street, Starr 409, New York, New York 10021. E-mail: blerman@med.cornell.edu.

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