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Abnormal Heart Rate Turbulence Predicts the Initiation of Ventricular Arrhythmias

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IWASA, A., ET AL.: Abnormal Heart Rate Turbulence Predicts the Initiation of Ventricular Arrhythmias.

**Background:** Abnormal heart rate turbulence (HRT) reflects autonomic derangements predicting all-cause mortality, yet has not been shown to predict ventricular arrhythmias in at-risk patients. We hypothesized that HRT at programmed ventricular stimulation (PVS) would predict arrhythmia initiation in patients with left ventricular dysfunction.

**Methods:** We studied 27 patients with coronary disease, left ventricular ejection fraction (LVEF) 26.7 ± 9.1%, and plasma B-type natriuretic peptide (BNP) 461 ± 561 pg/mL. Prior to arrhythmia induction at PVS, we measured sinus cycles after spontaneous or paced premature ventricular contractions (PVCs) for turbulence onset (TO; % cycle length change following PVC) and slope (TS; greatest slope of return to baseline cycle). T-wave alternans (TWA) was also measured during atrial pacing.

**Results:** At PVS, abnormal TO (≥ 0%) predicted inducible ventricular tachycardia (VT; n = 10 patients; P < 0.05). TO was greater in inducible than in noninducible patients (2.3 ± 3.1% vs –0.02 ± 2.8%, P < 0.05) and correlated with LVEF (P < 0.05) but not with BNP. TS did not differ between groups. Conversely, ambulatory HRT differed significantly from HRT at PVS (TO –0.55 ± 1.08% vs 0.85 ± 3.02%, P < 0.05; TS 2.63 ± 2.09 ms/RR vs 8.70 ± 6.56 ms/RR, P < 0.01), and did not predict inducible VT but trended (P = 0.05) to predict sustained VT on 739 ± 179 days follow-up. TWA predicted inducible (P < 0.05) and spontaneous (P = 0.0001) VT but did not co-migrate with HRT.

**Conclusions:** Abnormal HRT measured at PVS predicted the induction of sustained ventricular arrhythmias in patients with ischemic cardiomyopathy. However, HRT at PVS did not correlate with ambulatory HRT, nor with TWA, both of which predicted spontaneous ventricular arrhythmias. Thus, HRT may reflect the influence of autonomic milieu on arrhythmic susceptibility and is likely complementary to traditional arrhythmic indices. (PACE 2005; 28:1189–1197)

ventricular arrhythmias, sudden cardiac death, T-wave alternans, premature ventricular contraction, electrophysiologic study, autonomic tone

**Introduction**

Sudden cardiac arrest (SCA) from ventricular tachycardia (VT) or fibrillation (VF) is a major cause of mortality, yet remains difficult to predict. Although reduced systolic function is the primary risk factor for SCA, the Multicenter Unsustained Tachycardia Trial suggested that inducible arrhythmias at programmed ventricular stimulation (PVS) modestly add to the predictive accuracy for SCA. Although other electrical risk factors have been suggested, studies suggest that autonomic derangements immediately preceding VT or VF may provide a novel index for arrhythmic susceptibility.

Heart rate turbulence (HRT) following a premature ventricular contraction (PVC) indicates heightened sympathetic tone that predicts all-cause mortality following myocardial infarction (MI). However, it is uncertain whether HRT identifies patients at risk for SCA. Confusion arises, in part, because studies have included patients with preserved systolic function whose sympathovagal tone differs from patients at risk for SCA. Moreover, diurnal fluctuations in autonomic tone suggest that HRT measured at one time may poorly reflect arrhythmias at a different time, under different autonomic conditions. Indeed, abnormal heart rate variability predicts imminent, but not remote, asynchronous events. Finally, although HRT has been measured during electrophysiologic study, it has not been related to arrhythmia initiation.

We hypothesized that abnormal HRT at the time of PVS may predict the induction of ventricular arrhythmias in patients with ischemic left ventricular (LV) dysfunction, yet may differ from HRT measured from remote ambulatory recordings. We tested this hypothesis in patients with coronary disease and moderate-to-severe systolic dysfunction undergoing PVS.
Methods

Patient Population

The protocol was approved by the joint Institutional Review Board of the University of California and Veterans Administration Medical Centers, San Diego, California, and all patients provided written informed consent. We enrolled 42 patients undergoing PVS for SCA risk stratification with LV ejection fraction (LVEF) ≤40% (from echocardiography within 3 months) attributed to coronary disease and recent Holter monitoring. Patients were not enrolled if they were too unstable to undertake the 30-minute protocol, were incompletely revascularized or had been revascularized within the past 30 days, or had a life expectancy ≤1 year. No patient had experienced prior sustained ventricular arrhythmias or SCA. Fifteen patients were excluded because of atrial fibrillation at the time of Holter or PVS or due to the absence during PVS of ≥2 PVCs separated from additional ectopy by ≥20 beats. The remaining 27 patients form the basis for this report.

Ambulatory Data Collection

Patients underwent digital 24-hour ambulatory ECG (Holter) monitoring while maintaining their routine medications, 47 ± 68 days prior to PVS. Recordings were performed with a GE Marquette SEER system digitizing at 125 samples per second (GE Marquette, Milwaukee, WI).

Programmed Ventricular Stimulation

Patients underwent PVS in the post-absorptive state. Sedation was kept to the minimum required to alleviate anxiety or discomfort, so that some patients received no sedation. Therapy with β-blockers, calcium antagonists, or digoxin was continued. Quadrupolar 6-Fr catheters were advanced transvenously to the right ventricle, right atrium, and His bundle position. All pacing was performed at twice the diastolic threshold. Intracardiac electrograms and 12-surface ECG leads were recorded continuously using a 16-channel analog amplifier (Bloom & Associates, Reading, PA) with bandpass 0.04–100 Hz, sampled at 1 kHz.

Delivery of Single PVCs

Before attempted arrhythmia induction, paced single PVCs were delivered during sinus rhythm from the right ventricular apex every 30 seconds. PVCs were initially coupled 50 ms shorter than the sinus cycle length (CL), then decremented successively by 50 ms until they failed to capture.

Recording Spontaneous PVCs

Sinus rhythm recordings with spontaneous PVCs prior to arrhythmia induction were also identified. In both cases, PVCs were acceptable for analysis if separated from ectopy by ≥20 sinus beats.

Atrial Pacing for TWA

Following single PVC analysis, and prior to arrhythmia induction, high right atrial pacing was delivered progressively at CLs of 650 ms (92 beats/min) to 550 ms (109 beats/min), for a total of 7–10 minutes. Surface ECG signals during pacing were analyzed continuously for T-wave alternans (TWA) using HeartWave™ (Cambridge Heart, Bedford, MA).

Computation of HRT and TWA

All analyses were performed blinded to clinical information and the results of PVS. HRT from ambulatory 24-hour Holter recordings was computed using software available from http://www.h-r-t.org7 applied to digital files exported from the Mars Holter system (GE Marquette).

HRT at PVS was computed by exporting digital ECG data at 16-bit digital resolution from our recording system (Labsystem Duo, Bard, MA). Data were analyzed on a PC using custom software written in Labview (National Instruments, Austin, TX) that applied validated algorithms7 to ECG segments spanning each PVC. Briefly, turbulence onset (TO) is the difference between the mean CL of the first two beats following the post-PVC pause (R_{+1}, R_{+2}) and the two beats preceding PVC (R_{-1}, R_{-2}) as a percentage of preceding CLs:

\[ TO = 100 \times \frac{(R_{+1} + R_{+2}) - (R_{-1} + R_{-2})}{R_{-1} + R_{-2}}, \]

where \( TO < 0\% \) is normal.

Turbulence slope (TS) is the steepest slope of linear regression lines for sequences of five consecutive post-PVC intervals for up to 20 beats. Normal TS is >2.5 mm/RR. We did not normalize post-ectopic intervals to the pre-PVC interval.

TWA was assessed using established criteria.13 TWA was positive if \( V_{alt} \geq 1.9 \mu V \) for ≥1 minute with onset heart rate ≤110 beats/min in one vector lead or two adjacent precordial leads. Negative TWA was defined as absence of the above criteria as long as maximum heart rate without TWA ≥105 beats/min. Other tests were indeterminate. We used the “A” rules, comparing negative-to-positive TWA, and also compared negative TWA with “abnormal” TWA (combining positive and indeterminate13).
Ventricular Arrhythmia Induction

Arrhythmia induction was performed in standard fashion by pacing first at the right ventricular apex. A drive train of eight stimuli at CL 600 ms was followed by single, double, or triple extrastimuli (coupled ≥ 200 ms) as required to induce sustained VT or VF. If necessary, pacing was repeated at CL 400 ms, then at the right ventricular outflow tract. Patients were considered inducible if they developed monomorphic VT (CL ≥ 240 ms for ≥ 30 seconds or causing hemodynamic compromise) or VF (CL < 240 ms or polymorphic, if induced with one to two extrastimuli). Noninducible patients were those in whom VT/VF were not induced or in whom VF required > 2 extrastimuli for induction (similar to prior criteria).  

Outcomes Analysis

Patients were followed prospectively for a mean of 739 ± 179 days, using six monthly interrogation of implantable defibrillators, telephone interviews, and review of records from our electronic medical records system (CPRS). Devices were programmed uniformly for all patients, and interrogations were reviewed for accuracy blinded to results of HRT or TWA. The primary endpoint was the incidence of appropriate device therapy or sustained arrhythmias; the secondary endpoint was all-cause mortality.

Statistical Analysis

Continuous data are presented as mean ± standard deviation. The two-tailed t-test was used to compare continuous variables including TO and TS. The χ² test was applied to contingency tables of, for example, HRT versus PVS. Kaplan-Meier analysis was used for analysis of arrhythmia-free survival for patients with normal and abnormal HRT, HRV, TWA, and PVS results. For all analyses, a probability < 5% was considered statistically significant.

Results

The population had LVEF 26.7 ± 9.1%. Ten were inducible into sustained ventricular arrhythmias and 17 were noninducible. Their characteristics are shown in Table I. Figure 1 shows data from one patient with abnormal TO, abnormal TWA, and VT at PVS.

HRT for Delivered versus Spontaneous PVC at PVS

At PVS, 7 ± 3 PVCs per patient were suitable for study (4 ± 2 delivered, 3 ± 2 spontaneous). This number is similar to prior invasive studies of HRT. HRT magnitudes did not differ between delivered versus spontaneous PVC for TO (1.00 ± 5.39% vs 0.41 ± 4.40%, P > 0.3), nor TS (9.16 ± 9.86 mm/RR vs 9.46 ± 7.58 ms/RR, P > 0.3). HRT was thus concordant between delivered and spontaneous PVCs for abnormal TO (TO ≥ 0%; P < 0.05, χ²) and abnormal TS (TS ≤ 2.5 ms/RR; P < 0.05, χ²). There was no relationship between the magnitude of TO or TS and elapsed time since prior MI (P = NS) or the presence of diabetes mellitus (P = NS).

HRT at PVS and Inducible Arrhythmias

Induced TO magnitude was significantly higher in patients with versus without inducible arrhythmias (Table II; P < 0.05; Fig. 2). For this reason, abnormal TO (≥ 0%) was more likely in inducible patients (P < 0.05). This difference was consistent for delivered and spontaneous PVCs. Conversely, abnormally induced TS (< 2.5 ms/RR) did not co-migrate with inducible arrhythmias (P > 0.4 for delivered or spontaneous PVC).

The relationship between TO and LVEF was linear for inducible patients (Fig. 3A; P < 0.001), surprisingly showing more abnormal TO for better preserved LVEF. The regression relationship was less steep in noninducible patients (P < 0.05). Again, TS correlated less strongly with LVEF for inducible and noninducible patients (Fig. 3B). The relationship between HRT and plasma B-type natriuretic peptide (BNP) was weak for TO (Fig. 4A) and TS (Fig. 4B).

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### Table I. Clinical Characteristics

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CABG = coronary artery bypass grafting; NYHA = New York Heart Association Heart failure class.

* Time since most recent documented myocardial infarction (MI).
Comparison of Ambulatory Versus PVS Measurements of HRT

From ambulatory ECGs, 266 ± 256 PVCs were analyzed per patient (vs 7 ± 3 at PVS, P < 0.001). HRT differed significantly for PVS versus ambulatory recordings for TO (PVS 0.85 ± 3.02% vs Holter −0.55 ± 1.08%, P < 0.05) and TS (PVS 8.70 ± 6.56 ms/RR vs Holter 2.63 ± 2.09 ms/RR, P < 0.01; Table II). Consequently, there was no concordance between HRTs measured at PVS versus ambulatory ECGs for abnormal TO (>0%, P > 0.4) or abnormal TS (<2.5 ms/RR, P > 0.4).

HRT from Holter and Inducible Arrhythmias

TO magnitude from Holter recordings did not differ between inducible and non-inducible patients. There was a nonsignificant trend for lower TS magnitude (more abnormal) in inducible patients (2.15 ± 1.50 ms/RR) compared to non-inducible patients (3.57 ± 2.41 ms/RR, P = 0.15; Table II).

TWA and Inducible Arrhythmias

Abnormal TWA tests (positive and indeterminate) predicted inducible VT, while negative TWA predicted noninducible patients (Table II; P = 0.02). The same separation was observed for positive versus negative tests (i.e., excluding indeterminate tests; P = 0.02). Notably, TWA did not co-migrate with TO or TS at PVS.

Measures of Heart Rate Variability from Ambulatory Recordings

HRV parameters (time and frequency domain) at the time of ambulatory ECGs did not separate inducible from noninducible patients (P = NS for each index; Table II) and did not differ significantly between patients with versus without diabetes mellitus (P = NS for each index).

Long-Term Follow-Up

All but one patient with inducible arrhythmias at PVS received an implantable cardioverter defibrillator (ICD). Follow-up was complete for all patients. Over a mean period of 739 ± 179 days,
there were six deaths (none were arrhythmic) and five episodes of sustained ventricular arrhythmias (one from hospital records and four from ICD interrogations). Only abnormal TWA testing predicted the primary endpoint of sustained ventricular arrhythmias (Fig. 5A; \( P = 0.00013 \)), while abnormal TS on ambulatory ECGs just failed to reach significance (Fig. 5B; \( P = 0.053 \)). Neither abnormal TO on ambulatory recordings, HRT indices at PVS, nor inducible arrhythmias at PVS predicted the primary endpoint. No index predicted all-cause mortality.

### Discussion

In patients with ischemic LV dysfunction, abnormal HRT just prior to PVS predicted induced arrhythmias, but not spontaneous arrhythmias on follow-up. Conversely, HRT from ambulatory ECGs trended to predict spontaneous rather than induced ventricular arrhythmias. Notably, HRT did not correlate with abnormal TWA, suggesting that these indices reflect distinct components of arrhythmic vulnerability. Therefore, this pilot study suggests that HRT reflects conditions favoring ventricular arrhythmias, yet are sensitive to the milieu at measurement. Future studies may enable HRT to better define autonomic contributions to SCA.

### HRT and Patients at Risk for Ventricular Arrhythmias

The present study links abnormal HRT with ventricular arrhythmias in patients with LV dysfunction post-MI. This observation is consistent with the fact that abnormal HRT reflects increased sympathetic tone \(^{18}\) and abnormal baroreflex sensitivity \(^{12}\), both facilitate ventricular arrhythmias.

The link between HRT and ventricular arrhythmias is far from clear. Abnormal TO and TS predicted fatal and nonfatal cardiac arrest in 1,212 post-MI patients from the ATRAMI database \(^9\), yet that population had well-preserved LVEF (49 \(\pm\) 12\%). Although the seminal study of HRT included post-MI patients with LVEF 29.9 \(\pm\) 9.3\%, abnormal HRT predicted total rather than arrhythmic mortality. \(^7\) In patients with nonischemic cardiomyopathy, HRT did not independently predict ventricular arrhythmias. \(^{19}\)

Autonomic lability may explain why HRT measured at one time (ambulatory recordings) may not reflect conditions prevailing during PVS. This concept may also explain why HRV falls in the minutes preceding ICD-detected spontaneous
ventricular arrhythmias, yet reduced HRV per se poorly predicts long-term arrhythmic mortality. In support of this notion, we found that abnormal TS averaged over 24 hours in ambulatory ECGs just failed to reach significance (P = 0.05) for predicting spontaneous arrhythmias, yet did not predict arrhythmia induction during the specific conditions occurring during PVS.

Figure 2. Summary tachograms. Beats are numbered relative to PVC (beat 0, labeled). For this figure, cycle lengths are normalized to the mean of five sinus intervals preceding PVC for each patient, and plotted as the mean ± SD at each beat for patients in each group. (A) In inducible patients, after a PVC of prematurity 40 ± 14%, RR lengthens (abnormal). (B) In noninducible patients, after a PVC of prematurity 37 ± 15%, RR shortens (P < 0.05 vs inducible; Table II).
HRT and Indices of Heart Failure

It is unclear why TO was less abnormal in patients with the lowest LVEF. This may reflect our small sample size. It is also possible that TO is less predictive in patients with severe structural disease, as shown for other indices,20 potentially because autonomic derangements attenuate PVC-related perturbations or because HRT is impaired at increased heart rates.12 The lack of relationship between HRT and BNP in this study hints that volume overload in heart failure, with its autonomic effects, does not affect HRT. Clearly, further studies should elaborate upon the relative influence of ventricular stretch (or neurohormonal activation) versus LVEF upon HRT.

HRT Differences at PVS versus Ambulatory Monitoring

Our observed differences in HRT between PVS and ambulatory ECGs are intriguing.18,21 It remains unclear how diurnal variations in autonomic directly influence arrhythmia initiation, contributing to our observation that HRT at PVS predicted inducible arrhythmias, while HRT on ambulatory ECGs trended to predict ambulatory arrhythmias. Autonomic lability supports the notion that short-term autonomic indices should have good short-term predictive value, while long-term indices inevitably “average” responses over 24 hours and may provide a more robust long-term measurement. It has been described that abnormal short-term measures of HRV predict SCA,22 while long-term measures are less predictive.11

Several mechanisms could explain differences in autonomic tone between PVS and ambulatory recordings. First, it is likely that the blood pressure response to PVCs, and hence the baroreceptor component of HRT,12 are blunted when patients lie supine even though EPS HRT has been validated.12,15,16 Other explanations for differences between PVS HRT and ambulatory HRT are less identifiable. Second, our patients were minimally sedated during PVS, although differences in arousal level may be contributory. Third, cardiac
medications did not differ from the time of ambulatory recordings to PVS. Fourth, HRT was measured prior to VT/VF induction, unlike some studies, and should not therefore reflect hemodynamic compromise from arrhythmias or the effects of defibrillation. Fifth, it is inevitable that fewer PVCs are analyzed at PVS than from ambulatory ECGs, yet analysis of similar PVC numbers has been validated in prior invasive studies. Finally, we confirmed concordance between induced and spontaneous HRTs in this population, as previously shown in normal individuals, validating clinical comparisons between HRT at PVS (from delivered PVCs) and ambulatory recordings (from spontaneous PVCs).

**PVS in the Present Study**

PVS is the prototypical method for inducing reentry and, in early studies, predicted the characteristics and incidence of spontaneous VT or VF. Its suboptimal predictive value for spontaneous VT in patients with ischemic cardiomyopathy may therefore reflect differences in milieu between the times of PVS and spontaneous arrhythmia onset. This could be due to MI scar maturation, although patients in this and prior studies were recruited months to years post-MI with relatively mature scars. Moreover, our results support a second possibility that measurable differences in sympathovagal tone between PVS and the time of spontaneous arrhythmia onset alter the arrhythmogenic milieu. Further studies should determine whether indices of sympathovagal tone may improve the utility of PVS.

**TWA, HRT, and Ventricular Arrhythmias**

Abnormal TWA predicted inducible and spontaneous ventricular arrhythmias in this study with a very high negative predictive accuracy, as shown in prior studies by reflecting temporal and spatial dispersion of repolarization. The fact that abnormal HRT and TWA did not co-migrate suggests that they indicate distinct substrates for arrhythmic vulnerability. Future studies may reveal whether these indices have additive value in predicting arrhythmia susceptibility.

**Limitations**

These preliminary findings require validation in a larger population. In particular, HRT interpretation is limited when using small numbers of PVCs, although this is common when measuring HRT at PVS. Future work could examine PVCs in patients with implanted devices, thus enabling wider scale studies in ambulatory patients. Studies should also compare HRT following atrial versus ventricular premature complexes that may result in comparable HRT TS parameters, yet may have differing predictive values for arrhythmic susceptibility.

**Conclusions**

Abnormal HRT measured at PVS predicted the induction of sustained ventricular arrhythmias in patients with ischemic cardiomyopathy. However, HRT at PVS did not correlate with ambulatory HRT, nor with TWA testing, both of which predicted spontaneous ventricular arrhythmias. Thus, HRT may reflect the influence of autonomic milieu on arrhythmic susceptibility and is likely complementary to traditional arrhythmic indices.

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