Microvolt T-Wave Alternans with Exercise in Pediatrics and Congenital Heart Disease: Limitations and Predictive Value

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Background: *Microvolt t-wave alternans (TWA) in early exercise is a noninvasive marker of life-threatening ventricular arrhythmia in some adult cardiac populations. The incidence and potential significance of sustained TWA in pediatric and congenital heart disease (CHD) populations has not been well defined.*

Methods: *TWA treadmill exercise studies in pediatric patients with CHD, myopathy, potential myocardial ischemia, syncope, or history of cardiac arrest were analyzed. Tests were categorized as abnormal for sustained TWA with onset heart rate <130 beats/min with specific analyses for lower onset heart rates. Patient characteristics were analyzed as possible correlates of TWA.*

Results: *Over 2 years, 318 consecutive TWA exercise studies were performed in 304 patients (60% male, median 14 years, 6–41) for indications of syncope, cardiac arrest, possible ventricular arrhythmia, or evaluation of functional myocardial perfusion. Underlying conditions included apparently normal hearts (45%), CHD (16%), cardiomyopathy (11%), coronary anomalies (11%), electrical myopathy (9%), and transplant (8%). Abnormal TWA was seen in 24 (7%, onset HR 106 ± 18) and included 19 at high clinical risk for serious events including 3 with cardiac arrest. By multivariate analysis sustained TWA was associated with cardiac arrest, ventricular arrhythmias, and a clinical classification of high risk.*

Conclusions: *TWA is associated with pediatric and CHD diagnoses at high risk of serious events and may contribute, with other diagnostic tools, to management choices. While the absence of TWA has relatively high negative predictive value, it does not completely exclude the potential for serious sustained ventricular arrhythmias. A more robust noninvasive marker for risk stratification in these populations is required. (PACE 2006; 29:733–741)*

t-wave alternans, ventricular arrhythmias, congenital heart disease, pediatrics, exercise testing

Introduction

Evaluating risk for life-threatening ventricular arrhythmias represents a challenge. For the adult with recent myocardial infarction and depressed ventricular function, the 2-year risk of cardiac arrest approaches 20%. This is sufficiently high that ICD therapy is used as primary prevention in selected patients.[1] Further, with the high volume of patients and relatively concentrated risk, multiple tools have proven to be useful in predicting risk. The annual risks are notably lower in the heterogeneous patient populations cared for in pediatric cardiology practices. Therefore, precise tools are not readily available to accurately stratify patients with worrisome symptoms or arrhythmias in these groups.

Microvolt t-wave alternans (TWA) is a predictive tool in relatively high-risk adult populations. Specifically, the observation of significant TWA with an onset HR of ≤110 beats/min during bicycle exercise is associated with inducible VT on programmed stimulation, spontaneous VT during follow-up, and appropriate ICD discharge. Within a high-risk adult ischemic heart disease population, the absence of TWA is associated with a low incidence of appropriate ICD use.[2] Data in the pediatric and congenital heart disease (CHD) populations are limited. Using bicycle exercise in pediatric volunteers without apparent heart disease, 9% had significant TWA with a median onset heart rate of 138 beats/min and only 1% of subjects with an onset heart rate <130 beats/min.[3] In asymptomatic subjects with favorable repairs of tetralogy of Fallot, 14% had significant and sustained TWA at a lower onset HR and 42% of those with TWA had an onset HR of <120 beats/min. The presence of TWA did not correlate with any outcome variable or hemodynamic finding.[4]

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We hypothesized that in a larger, heterogeneous cohort of pediatric and CHD there would be sufficient outcomes to identify groups where further efforts to use TWA may be warranted. The purpose of this study is to describe the clinical use of TWA in pediatric and congenital heart patients undergoing treadmill exercise testing at a tertiary cardiovascular program. Specific goals were to identify (a) the incidence and onset HR of TWA overall and in specific subpopulations, (b) the frequency and sources of indeterminate studies, and (c) clinical correlates.

Methods

Patients

Data were collected in accordance with the policies and procedures of the hospital institutional review board. Consecutive patients with indications for TWA undergoing treadmill exercise testing as part of their scheduled clinical care underwent acquisition of TWA between August 2000 and August 2003. Potential indications included CHD, syncope, prior cardiac arrest, known or suspected ventricular arrhythmias, prior orthotopic heart transplant (OHT), syncope, cardiomyopathy (CM), and suspected or proven primary electrical disease. Exclusion criteria were TWA assessment in the previous 12 months, ventricular pacing, and exercise testing aimed primarily for the evaluation of supraventricular tachycardia. A standard Bruce protocol was modified by manually adjusting the treadmill speed early in exercise to hold the heart rate at 110 and then 120 beats/min for 3 minutes (and comparably lower rates in older patients) prior to initiating the standard increases in treadmill incline and speed and comparably lower rates in older patients. Recording was continued for 10 minutes following exercise, with the initial 3 minutes upright when possible, the remaining 7 minutes seated. Standard definitions of test classification were modified to reflect the younger population with specific analyses included for onset heart rates of 110 and 120 beats/min (Table I).

Microvolt TWAs were evaluated using a commercial integrated treadmill and TWA acquisition and analysis system with proprietary high-resolution electrodes (CH2000; Cambridge Heart, Bedford, MA, USA). Skin was prepared with abrasive tape (Red Dot, 3M; Minneapolis, MN, USA) and high-resolution silver-silver chloride electrodes were placed just inferior to the clavicles and at the left inferior rib margin just anterior to the anterior axillary line with standard electrodes used for 12-lead ECG acquisition. The tracings were then reviewed and read manually using the criteria noted in Table I to confirm and supplement the automated report.

Patient characteristics, procedural details, outcomes, and potential confounding diagnoses were extracted from the medical record. Follow-up clinical status in April 2003 was ascertained from a review of medical records. Patient classification, while including the results of the exercise test, was independent of the TWA results. Patients

Table I.

Definitions

		Adult	Pediatric
Positive	Significant	Onset HR $<$ 110 $>$1 min $\geq$1.9 μV $\geq$3.0 alternans ratio Single X, Y, Z, Vm lead Adjacent precordial leads Period of artifact-free data	Onset HR $<$ 130
	Sustained	Persists at resting HR or $>$110 Present at rest	Persists to HR $>$130
Negative	None	Noise $<$ 1.8 μV TWA $<$ 1.9 μV Artifactual alternans allowed*	Same
	Physiologic TWA	Onset HR $>$ 110	Onset HR $>$ 130
Indeterminate	Absence of artifact-free data	$<$110 bpm	$<$120 bpm
	Rapid heart rate rise	90–110	110–120

Pediatric criteria developed using data from Cheung et al.[3]

*Artifactual alternans was defined as transient alternans clearly associated with respiratory rates of 0.5 breaths/cycle or alternans resulting from ventricular bigeminy.

were classified as being normal (NL) if their clinical assessment suggested noncardiac chest pain or neurally mediated syncope and they were not viewed as having significant heart disease. CHD patients had defined structural heart disease. CM patients included all primary myocardial diseases, including hypertrophic and dilated CM. Electrical myopathies (EM) included long QT syndrome, Brugada syndrome, catecholaminergic VT, and idiopathic ventricular fibrillation without evidence of CM. Coronary artery anomalies (CA) included all patients with echocardiographic evidence of potentially important CA (e.g., left coronary from the right coronary commissure), prior surgery for those findings in the absence of CHD or prior coronary involvement in Kawasaki disease. Patients with heart transplant (OHT) were classified separately, regardless of their pretransplant diagnosis.

Outcomes identified included prior or subsequent cardiac arrest or appropriate ICD discharge for ventricular arrhythmia, sustained or recurrent ventricular arrhythmia (or syncope with a diagnosis of primary electrical disease), moderate or severe left ventricular dysfunction, hemodynamic intervention for CHD (e.g., conduit revision or pulmonary valve replacement), Grade III/IV rejection in transplant patients, or ischemia on stress nuclear perfusion studies. Taken together, patients with any of these predefined conditions were defined as "high risk."

Statistics

Continuous variables are summarized using means, medians, and standard deviations. The χ^2 and Fisher's exact tests were used to compare dichotomous variables. The Kruskal-Wallis test was used to compare variables that were not normally distributed. Patient characteristics, indications, and outcome results were coded and analyzed using univariate and multivariate logistic regression to identify predictors of outcome. Variables were included in the final multivariate model if their P value was less than 0.2. Within-group subtype analysis is reported when clinically interesting. For the patients with multiple tests the first test was used in all analyses. Confidence intervals at 95% are presented for odds ratios (OR) following logistic regression. Criterion for statistical significance was $P < 0.05$. All statistics were performed using Stata 8.1 software (Stata, College Station, TX, USA).

Results

The characteristics of the study population are characterized in Table II. There were 318 TWA studies in a heterogeneous cohort of 304 patients; 130 patients (43%) had apparently normal hearts with the remainder having CHD (16%); CM (13%); CA or prior Kawasaki's disease (11%); primary electrical diseases such as long QT syndrome (9%, EM), or a history of OHT (7%). The mean age was 14.7 (range 5.6–41) with the CHD cohort significantly older (18 ± 9, $P < 0.05$) than the remaining groups. In the NL group, 81% had echocardiograms confirming the clinical diagnosis of structurally and functionally normal heart. Of the 50 patients in the CHD group, 22 (45%) had tetralogy of Fallot, 11 (22%) had transposition of the great vessels with the remainder having a variety of lesions. The CM group included dilated CM in 14 (36%), hypertrophic CM in 10 (26%), and arrhythmogenic right ventricular dysplasia in 2. Table III documents the most significant ventricular arrhythmia observed with nearly 78% having no prior arrhythmia.

Significant TWA, defined as greater than 1 minute of TWA with any onset heart rate, was seen in 39 (13%) of the studies. Of these, 24 of 39 studies (62%) were defined as positive with significant and sustained TWA with an onset <130 beats/min (Fig. 1). In the remaining 15, the onset HR of TWA was >130 beats/min and the studies were classified as negative or indeterminate. Using more stringent definitions of positive, 18 (75% of positive studies) had an onset heart rate $\leq$120 beats/min and 12 (50% of positive studies) had onset heart rates of $\leq$110 beats/min. Positive studies were more frequent in CM or CHD patients.

Indeterminate studies are studies in which TWA cannot be evaluated between heart rates of 100 and 120 beats/min. By analogy to adult criteria, if there is artifact-free data at heart rates $\leq$120 beats/min, even if the noise level is excessive at higher rates, then a study can be judged as positive or negative. When the noise level exceeds 1.9 μV at rates <120 beats/min without significant TWA, then the presence of TWA cannot be excluded and the study is judged indeterminate. If there is TWA with a high V_{alt} and with a high ratio it may be possible to evaluate onset of TWA, even if noise levels are increased; however, low-amplitude TWA will be obscured. This was a significant limitation in this cohort, occurring in 89 (28%) of patients and 99 (31%) of the studies.

The potential sources of indeterminate studies were analyzed further. Noise levels were the primary challenge, accounting for over 50% of indeterminate studies. Noise generally increased with increasing exercise and heart rates. While fewer than 10% had excessive noise at heart rates <90, 61% exceeded noise levels of 1.9 μV at heart rates of 130 beats/min (Fig. 2). Multiple contributing factors, including high noise levels, were the second most common cause of indeterminate studies in 40% of indeterminate studies.

Table II.

Demographics and Results

		Overall	NL	CHD	CM	CA	EM	OHT
N		304	130	50	39	33	28	24
Age (mean ± SD)		14.7 ± 5.4, (5.6–41)	14 ± 4	18 ± 9*	15 ± 5	14 ± 5	12 ± 4	12 ± 3
High risk			3 (2%)*	22 (44%)	28 (72%)*	8 (24%)	22 (79%)*	0
T-wave alternans								
Significant		39 (13%)	10 (8%)	9 (18%)*	14 (36%)*	2 (6%)	3 (11%)	1 (4%)
Significant and sustained	Onset < 130	24 (8%)	1 (1%)	7 (14%)*	13 (33%)*	0	3 (11%)	0
Indeterminate		98 (32%)	43 (32%)	14 (28%)	14 (36%)	4 (12%)	13 (46%)	10 (41%)
If positive								
V_{alt} (μV)	XYZ	4.8 (±8, max 48)	4.5 ± 4.9	2.4 ± 2.3	7.5 ± 12.1	–	1.1 ± 0.47	–
	Precordial	8.2 (±12.4, max 72)	7.4 ± 5.6	4.6 ± 5.2	12.2 ± 17.7	–	2.5 ± 1.5	–
Ratio	XYZ	9.9 (±15, max 80)	13.7 ± 23.8	7.7 ± 9.4	11.7 ± 13.1	–	5.3 ± 6.1	–
	Precordial	11.8 (±27, max 141)	13 ± 27.8	4.3 ± 7.2	18.4 ± 35	–	1.4 ± 1.2	–
Onset HR (mean ± SD)	If onset <130	107 ± 19	102	115 ± 12	100 ± 22	–	116 ± 5	–
Onset HR (mean ± SD)		128 ± 34	159 ± 36	125 ± 24	110 ± 31	145 ± 7	116 ± 5	165

Patients first study analyzed.
*$P < 0.05$ compared with other subgroups.
NL = normal, apparently normal heart without either electrical myopathy, structural heart disease, hypertrophic, or dilated cardiomyopathy; CHD = congenital heart disease; CM = hypertrophic or dilated cardiomyopathy; EM = primary electrical disease/ion channel defect including long QT, arrhythmogenic right ventricular dysplasia, Brugada syndrome; OHT = orthotopic heart transplant; V_{alt} = maximal alternans amplitude in microvolts in either the XYZ or precordial leads; Ratio = maximal alternans ratio.

Table III.

Most Significant Identified Ventricular Arrhythmias

Arrhythmia	NL		CHD		CM		CA		EM		OHT		Total	
No arrhythmia	106	82%	35	70%	24	62%	32	97%	20	71%	23	96%	240	79%
Accelerated ventricular rhythm	2	2%	0	0%	0	0%	0	0%	0	0%	0	0%	2	1%
Isolated ventricular ectopy and couplets	8	6%	9	18%	4	10%	0	0%	3	11%	0	0%	24	8%
Nonsustained ventricular tachycardia	10	8%	2	4%	5	13%	1	3%	0	0%	1	4%	19	6%
Sustained VT without arrest	4	3%	4	8%	4	10%	0	0%	3	11%	0	0%	15	5%
Sustained VT/VF with cardiac arrest	0	0%	0	0%	2	5%	0	0%	2	7%	0	0%	4	1%
Total	130		50		39		33		28		24		304	

NL = normal, apparently normal heart without either electrical myopathy, structural heart disease, hypertrophic, or dilated cardiomyopathy; CHD = congenital heart disease; CM = hypertrophic or dilated cardiomyopathy; EM = primary electrical disease/ion channel defect including long QT, arrhythmogenic right ventricular dysplasia, Brugada syndrome; OHT = orthotopic heart transplant; VT = ventricular tachycardia at rates >120 beats/min; VF = rapid polymorphic ventricular tachycardia or ventricular fibrillation, both with hemodynamic compromise, appropriate ICD use, or cardioversion.

Some of the sources of indeterminate studies were related to the nature of the patients. Respiratory sinus arrhythmia or low-grade ventricular ectopy precluded analysis at resting heart rates in 168 (52%), but rapidly normalized such that 83% were normalized at heart rates less than 90% and 92% at heart rates <100 beats/min. Continued heart rate irregularity, primarily from ventricular ectopy, persisted at heart rates >100 in 10% (Fig. 2). The presence of preexisting ventricular arrhythmia was associated with indeterminate studies (OR 2.0 ± 1.1–3.4, P = 0.017). Rapid heart rate rise also contributed to indeterminate studies in 74 (23%) of the tests. Both adequate and indeterminate studies were obtained in each diagnostic category. Within the relatively narrow age cohort studied, age was neither associated with indeterminate studies, excessive noise, or excessive heart rate increase.

Repeated Studies

Fourteen patients underwent repeated studies. In 13 cases the initial study had been negative and the repeat study was also negative. In one case the initial study was positive with an onset heart rate of 89, while the duplicate was indeterminate secondary to ventricular ectopy and high noise levels. Once patients had positive studies they were not routinely scheduled for repeat studies. Only the initial study was used for outcome analysis.

Significance of TWAs

The onset of TWA at heart rates <130 was associated with previous or subsequent sustained ventricular arrhythmia, or cardiac arrest, which included appropriate ICD use, by multivariate analysis. TWA was associated with an eightfold increased risk of cardiac arrest (Fig. 3); however, only identified 26% of the cardiac arrest patients. When we broadened the category of "high risk" to include patients with CHD referred for revision, patients who require defibrillator implantation, patients with cardiac syncope (e.g., long QT), and patients who are considered for heart transplant, the study identified 83 (27%) of these patients. Therefore, TWA remained associated with the clinical status. This finding was retained even if the onset heart rate criteria were made more stringent by decreasing to 120 or 110 beats/min and when limited to the patients who were classified in a more stringent definition of high risk, only including patients with CHD, CM, and primary electrical disease (Table IV).

When controlling for diagnoses, symptoms, ventricular function, and age, TWA remained associated with each clinical outcome. The clinical classification of CHD, CM, and EM contained 72 (86%) of the high-risk patients and an even higher proportion of the more serious outcomes and hence those diagnoses were, not surprisingly, strongly associated with outcome. Limiting analysis to CHD, CM, and EM patients the association between positive TWA and outcome was retained by multivariate analysis. In this subgroup, already clinically identified as being at higher risk than the patients with apparently normal hearts, the marginal value of TWA was lower, as determined by the lesser area under the receiver operating curve.

This clinical and statistical correlation was primarily a negative association. The overall specificity was high, while the sensitivity was low. The absence of TWA, even given the high rate of indeterminate studies, remained associated with the absence of ventricular arrhythmias, arrest, or a low-risk clinical classification.

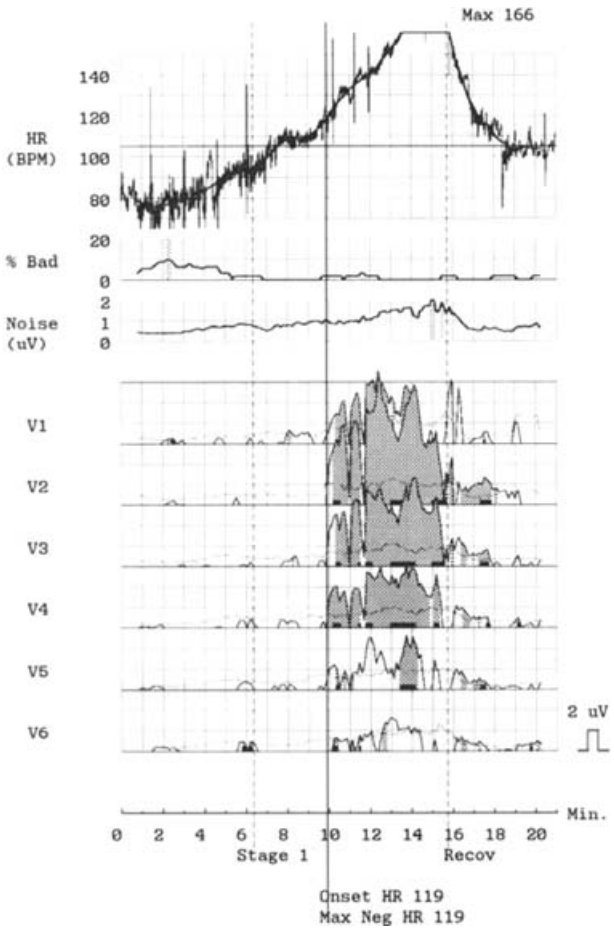

Figure 1. *Example of sustained microvolt t-wave alternans. Significant t-wave alternans with an onset heart rate of 119. The patient is a 19-year-old male who, 3 years previously, presented with sustained palpitations and witnessed cardiac arrest with documented ventricular fibrillation. He has had stable cardiomyopathy with left ventricular shortening fraction of 23%, normal left ventricular dimensions, and no significant ectopy on subsequent ICD monitoring. The maximum alternans amplitude (V_{alt}) is 7.25 μV in lead V2 with an alternans ratio of 18.2. Significant alternans is present in three adjacent precordial leads.*

Discussion

The association between TWA and cardiac arrest, sustained ventricular arrhythmias or a more loosely defined clinically higher risk population, was robust and present at both restrictive (TWA onset HR < 110) and permissive (TWA onset HR < 130 thresholds). As a univariate predictor TWA was particularly useful as a negative predictive tool with specificity of 96–100% and negative predictive values of 76–94% depending upon the specific outcomes examined. When additional clinical features are added, the presence of TWA continues to add information, though the incremental value is more limited. In this cohort, while TWA was associated with an eightfold increased risk of cardiac arrest, 76% of the events occurred in patients without observed TWA.

These results are quite comparable to other uses of TWA and to other tools used in the CHD, ischemic heart disease with ventricular dysfunction, and hypertrophic CM populations (Table V).[5–10] They share similar features of limited sensitivity (even in high-risk populations) and relatively high negative predictive values. While TWA remains useful as additional clinical features are added, the incremental diagnostic precision associated with the presence/absence of TWA generally decreases. This statistical finding highlights the concept that a wide variety of clinical data contribute to effective decisions. Practically the observation of TWA in the pediatric and CHD population may best be viewed as a reason for enhanced vigilance, even if the precise nature of that vigilance is not defined.

The 28% incidence of indeterminate studies using bicycle exercise in this cohort was more than that achieved using bicycle exercise in a study of normal children (16%)[3] but comparable to that of children and adolescents with tetralogy of Fallot (37%).[4] Each of these pediatric studies had resting data invalidated by sinus arrhythmia and exercise data limited by rapid heart rate increases. These values are also comparable to what is reported with exercise in adult cohorts.[7,11] The comparable frequency of indeterminate studies suggests that the choice of treadmill versus bicycle exercise in evaluating TWAs may be based on procedural considerations.

Limitations

The cohort studied, while sequential, is a selected population with an uncertain ability to generalize to a broader patient cohort. The clinical choice to refer for exercise testing almost certainly includes some selection biases that are not addressed in this study. For example, this study did not include OHT patients with high-grade rejection. This is primarily due to the fact that asymptomatic OHT patients are referred for exercise testing while symptomatic patients are referred directly to biopsy or therapy. While 11 of 84 patients with nuclear perfusion studies had potential ischemia, those studies were predominately done in OHT and coronary disease patients, where the incidence of TWA and of other significant events was low, limiting the ability to evaluate nuclear perfusion abnormalities as an outcome. This discussion demonstrates that the pretest clinical assessment of patients is equally important to the test results in evaluating risk in patients.

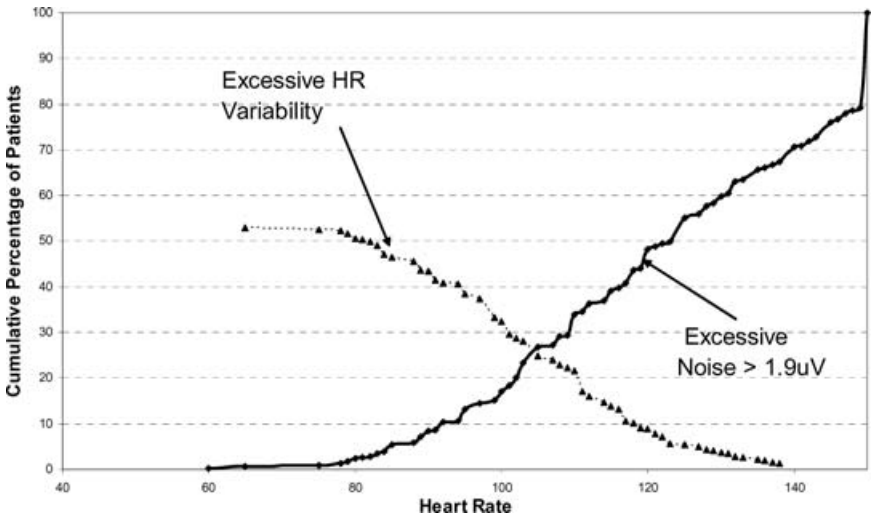

Figure 2. *Sources of inability to assess for t-wave alternans. Combinations of respiratory sinus arrhythmia and low-grade ventricular ectopy, both of which are typically suppressed at higher heart rates, create excessive heart rate variability in over 50% of pediatric and congenital heart disease patients at rest, with a sigmoidal decline in frequency so that by a heart rate of 120 less than 10% of studies cannot be reliably interpreted (the percentage of patients below the dashed line). Noise levels, in contrast are steadily increasing with increasing heart rate and exercise, so that by 120 beats/min 45% of subjects have noise levels in excess of 1.9 μV, precluding detecting low amplitude t-wave alternans (the percentage of patients above the black line). In practice, individual patients may have neither source (or both) prior to the clinical relevant heart rate zone.*

The cohort examined is a heterogeneous group, by design and by practice. Unlike large, high-risk, and relatively homogenous adult cohorts studied, the practice of pediatric cardiology routinely involves large numbers with apparently normal hearts at exceptionally low risk of actual events, but with potentially serious symptoms. There is a wide range of congenital heart patients and smaller numbers of patients with more specific diagnoses. Each of those groups has specific challenges. The CHD population generally has low annual risk of events in childhood and adolescence, with increased (but still relatively low) risk as they move in their adult life. The subclassification within and between groups was chosen to be relatively limited and reflect practical clinical practice: hence not all apparently normal hearts had echocardiograms; a range of CHD patients were included, sustained ventricular arrhythmias clinically known to represent automatic arrhythmias were included. By including these patients, this analysis should be more generalizable to daily pediatric cardiology practice than by limiting the analysis to a tiny cohort where multiple other measures would already have allowed an accurate assessment of risk. The results support this choice, as both TWA and clinical features permitted reasonable risk stratification.

The most significant limitation is that some of the outcomes evaluated predated the date of the TWA determination. Hence while there is an ability to show an association between TWA and

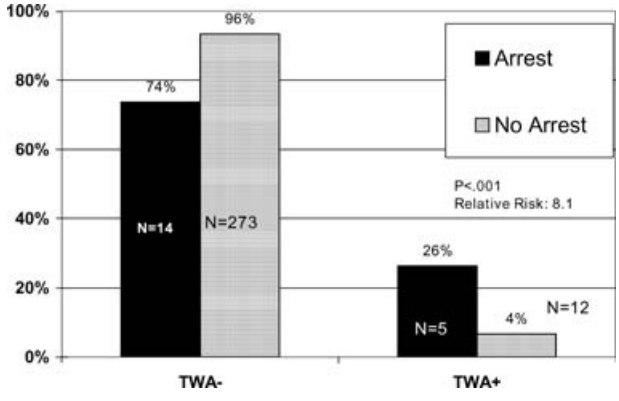

Figure 3. *T-wave alternans associated with cardiac arrest. Nineteen patients had cardiac arrest or electrogram confirmed ventricular tachycardia/ventricular fibrillation treated with ICD therapy. Compared to 285 without arrest there was an eightfold relative risk of having sustained t-wave alternans with an onset heart rate of less than 120. Despite this, 74% of patients with cardiac arrest had negative t-wave alternans.*

Table IV.

Predictive Value of Positive T-Wave Alternans

OR	P		95% CI	ROC	Sens	PPV	Spec	NPV
Cardiac arrest								
TWA onset <130	5.0	0.005	1.6–15.4	0.59	–	–	100	94%
TWA onset <110	6.7	0.009	1.6–28.1	0.57	–	–	100	94%
Ventricular arrhythmia								
TWA onset <130	6.1	<0.001	2.6–14.6	0.59	21%	58%	96%	81%
TWA onset <110	7.9	0.001	2.2–28.1	0.55	13%	64%	98%	82%
High risk								
TWA onset <130	12.8	<0.001	4.6–35.7	0.60	23%	79%	98%	77%
TWA onset <110	15.0	0.001	3.2–71.5	0.56	13%	82%	99%	77%
Clinical classification alone as predictor of high risk								
CM	7.9	<0.001	2.7–22.9	0.88	60%	75%	92%	85%
EM	11.4	<0.001	3.4–38.2					
CHD	2.4	<0.070	0.92–6.5					
Normal	0.07	<0.001	0.018–0.30					
Multivariate model of higher risk in CHD, CM, and EM*								
TWA onset <130	5.6	0.004	1.7–18.6	0.67	68%	68%	64%	64%
TWA onset <110	10.8	0.032	1.22–95.6	0.66	66%	67%	66%	65%

*Age, ventricular function, and symptoms were entered into the model. Symptoms were retained at P $\sim$ 0.05 in each model.
OR = odds ratio; ROC = area underneath receiver operator curve; Sens = sensitivity; PPV = positive predictive value; Spec = specificity; NPV = negative predictive value; CM = cardiomyopathy including dilated, hypertrophic, and primary electrical disease; CHD = congenital heart disease.

Table V.

Representative Predictive Values

Author	Year	Cohort	Test	Outcome	Sens	Spec	PPV	NPV	ROC	RR/HR
Alexander	2006	Peds/CHD	TWA-alone	VT/Intervention	23%	98%	79%	77%	60%	12.8
			TWA-with clinical	VT/Intervention	68%	64%	68%	64%	67%	5.6
Khairy	2004	TOF: screening	VEST	SCD/VT	86%	79%	25%	99%	80%	4.1
		TOF: clinical indication	VEST	SCD/VT	76%	80%	67%	87%	79%	3.8
Alexander	1999	CHD: clinical	VEST	Death/VT	60%	67%	20%	93%	66%	3.2
			VEST with clinical	Death/VT	87%	62%	24%	97%	79%	6.1
Rashba	2004	CAD: EF < 40	VEST	Death/VT	80%	35%	35%	80%		1.9
			TWA	Death/VT	82%	43%	40%	84%		2.2
			Combined	Death/VT	88%	42%	39%	89%		4.7
Berul	1999	Mixed adults	TWA	Induced VT	78%	69%	75%	65%	67%	
McKenna	2002	HCM	Two or more	Death	45%	90%	23%	93%		
Stelling	1990	CHD: clinical indication	SAECG RMS < 100 μV	Induced VT	91%	70%	62%	93%		11.8

Comparison of the current data (top rows) with representative populations.
CAD = coronary artery disease; CHD = congenital heart disease; Clinical = clinical indications for study; EF = ejection fraction; HCM = hypertrophic cardiomyopathy; NPV = negative predictive value; Peds = pediatrics; PPV = positive predictive value; ROC = diagnostic accuracy or area beneath the receiver operator curve; RR/HR = relative risk or hazard ratio; SAECG = signal averaged ECG using criteria of the RMS voltage of the terminal 40 ms <100 μV; SCD = sudden cardiac death or appropriate ICD use; Sens = sensitivity; Spec = specificity; TWA = microvolt t-wave alternans; VEST = programmed ventricular stimulation.[5–10]

outcome, the predictive power may be more statistical than practical.

Conclusions

Microvolt TWAs can be acquired in over 70% of pediatric and congenital heart patients using treadmill exercise. The presence of TWAs is broadly associated with the expected outcomes of cardiac arrest, sustained ventricular arrhythmias, and a clinical classification of being at "high risk." This association is statistically relatively strong: it is valid with the adult criterion of 110 beats/min for onset HR or with a less rigid criterion of 130 beats/min, which may be more appropriate for children under age 18. TWA remains a contributor to outcome even when controlling for clinical features such as depressed function and symptoms. In this broad cohort, the presence of TWA was primarily associated with diagnoses viewed as having elevated risk of ventricular arrhythmias (primarily CM and CHD). Hence, while the presence of TWA helps identify patients at risk, the diagnosis of CHD, or of dilated, hypertrophic, or EM is more useful in identifying high-risk patients. However, if the population is already identified as being "at risk" then the presence of TWA appears to aid in stratification. This association is more powerful for its specificity and hence its ability to predict who will not have events, than it is for its sensitivity in identifying severe outcomes.

Both technical features of excessive noise levels at the heart rates of interest, and physiologic challenges of high heart rate variation and sometimes rapid early heart rate increases result in a high number of indeterminate studies.

While further experience in more carefully defined cohorts will be useful, TWA is likely to remain an imprecise tool that the clinician may choose to include in developing a clinical plan. This limitation is not surprising given that the test characteristics of even more "precise" tools like programmed stimulation in CHD have comparable predictive values, and low specificity, even if they have higher sensitivity.[5,6]

These data suggest that evaluation for TWA may be justified in pediatric patients with heart disease at perceived risk of ventricular arrhythmias. The role of TWA in otherwise low-risk groups is unlikely to be justified. When TWA is used, an onset heart rate of <130 beats/min appears to be significant. Like other tools used for risk stratification, the finding represents an incompletely independent marker of the patients' cardiac status and needs to be placed in clinical context.[12]

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