ORIGINAL ARTICLE

Heart Rate Turbulence and T-Wave Alternans in Patients with Coronary Artery Disease: The Influence of Diabetes

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Background: Patients with diabetes mellitus (DM) have a higher risk of sudden cardiac death. Factors associated with the risk profiles of coronary artery disease (CAD) patients with DM are not well established. Heart rate turbulence (HRT) and T-wave alternans (TWA) are often used to predict arrhythmia events.

Methods and Results: HRT and TWA were measured in two independent groups: the ARTEMIS cohort study and the REFINE-ICD randomized trial. ARTEMIS assesses risk 3–12 months after coronary angiography in patients with CAD. The initial 1001 patients in ARTEMIS, 526 with and 475 without DM, are included in this analysis. REFINE-ICD compares usual care versus usual care plus ICD therapy in patients with left ventricular (LV) ejection fraction (EF) values of 36–50% assessed 2–15 months after myocardial infarction. The initial 275 patients screened in REFINE ICD are included in this analysis. Abnormal HRT plus TWA was more common in patients with versus without DM in ARTEMIS (125/526, 24% vs 63/475, 13%; $P < 0.001$) and REFINE-ICD (43/55, 78% vs 55/220, 25%; $P < 0.001$), respectively. Abnormal HRT plus TWA was also more common in patients with LVEF values $< 50\%$ (28%) vs $\geq 50\%$ (18%; $P < 0.001$) in ARTEMIS and LVEF values below the population median of 42% (60/138, 43%) versus above the median (38/137, 28%; $P < 0.01$) in REFINE-ICD.

Conclusions: Abnormal HRT plus TWA is more common in CAD patients with DM compared with the patients without DM and is related to the severity of LV dysfunction.

Clinical Trial Registration Information: <http://www.clinicaltrials.gov>, NCT01426685; <http://www.clinicaltrials.gov>, NCT00673842.

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diabetes; coronary artery disease; myocardial infarction; sudden cardiac death; heart rate turbulence; T-wave alternans

Patients with type 2 diabetes (DM) have a higher risk for coronary artery disease (CAD) related death than patients without DM.^{1,2} DM is also associated

with a higher risk for sudden cardiac death after myocardial infarction (MI).³ Two noninvasive arrhythmia risk markers, heart rate turbulence

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(HRT) and T-wave alternans (TWA) measured from Holter recordings and/or exercise ECG, have emerged as predictors of life-threatening arrhythmic events in patients with CAD.^{4–6} The factors associated with DM that contribute to arrhythmia risk profiles of these patients are not well established, but are important to ascertain. We hypothesized that CAD patients with DM will have a greater likelihood of abnormal HRT plus TWA than similar patients without DM. To investigate this, we evaluated the relationship of DM with abnormal HRT plus TWA in two independent cohorts of CAD patients.

METHODS

Study Populations

The study populations consist of two independent CAD patient groups. Both studies are ongoing and the institutional review boards have approved the protocols. All subjects provide written informed consent, and Holter data are collected/analyzed using established standards.^{7,8}

ARTEMIS

The Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection (ARTEMIS) cohort study includes patients with angiographically documented CAD (NCT01426685). Risk assessment is performed 3–12 months after coronary angiography. The presence of DM is determined by a fasting capillary plasma glucose level ≥ 7.0 mmol/L on two occasions, a 2-hour value > 12.2 mmol/L on the oral glucose tolerance test, or the use of antihyperglycemic medication and a prior diagnosis of DM. The ARTEMIS database included a consecutive series of type II diabetic patients who have undergone a clinically indicated coronary angiography within 6 months before the enrolment into the study. For these patients, a control group is recruited from the same database of consecutive patients without type II diabetes who are matched according to age, sex, history of prior MI and heart failure, and type of coronary intervention (percutaneous coronary intervention, bypass graft surgery, or medical treatment). A total of 1500 CAD patients with diabetes and 800 CAD patients without diabetes will be enrolled and followed for at least 5 years. The primary endpoint is sudden cardiac

death. The secondary endpoint is cardiac death or hospitalization for heart failure or MI. The first 1001 consecutively recruited CAD patients were included in this analysis. Of these, 526 had DM and 475 did not.

REFINE-ICD

The Risk Estimation Following Infarction Non-invasive Evaluation–Implantable Cardioverter Defibrillator (ICD) efficacy (REFINE-ICD) trial is a randomized comparison usual care versus usual care plus an ICD in post-MI patients with left ventricular ejection fraction (LVEF) values of 36% to 50% and abnormal HRT plus TWA measured from 2 to 15 months after MI (NCT00673842). The presence of DM was based on the use of antihyperglycemic medication and clinical diagnosis of DM. The REFINE-ICD trial is based on the results of the REFINE and CARISMA cohort studies.^{9,10} Subjects in REFINE-ICD with LVEF values in the specified range undergo Holter screening. Those with both abnormal HRT plus TWA are then eligible to be randomized (1:1) to usual care versus usual care plus an ICD. The primary outcome is total mortality. The secondary outcomes are quality of life and the cost-effectiveness. A total of 1400 patients will be randomized and followed an average of 5 years. The initial 275 patients screened are included in this analysis. Of these 55 had DM and 220 did not. Only 36% of these 275 screened patients were finally eligible and randomized to the REFINE-ICD study.

Assessment of Ejection Fraction

Standard techniques are used to assess LVEF in both groups. In ARTEMIS, LVEF is measured by echocardiography.^{11,12} In REFINE-ICD, LVEF is assessed via radionuclide ventriculography (83/275, 30%), a modified Simpson's technique for biplane echocardiography (165/275, 60%), or cardiac magnetic resonance (27/275, 10%).

Risk Assessment

Subjects in both studies undergo a 24-hour ambulatory ECG recording that is analyzed independent of clinical data or subject outcome.

In both studies, HRT slope is defined as the highest slope of the regression line over any of the five successive sinus beat RR intervals during first 20 sinus beat RR intervals after a ventricular

premature depolarization,¹³ and determined from the averaged RR intervals following the ventricular premature depolarizations. In ARTEMIS, HRT slope is considered abnormal, if ≤ 2.5 milliseconds per RR interval. In ARTEMIS, exercise ECGs and Cardiosoft, Version 6.5 software are used to assess for TWA (GE Healthcare, Fairfield, CT, USA). TWA is analyzed using the moving modified average technique (MMA) by a core laboratory in Germany.^{14,15} TWA was considered present when the MMA voltage is $\geq 60 \mu\text{V}$.

Holter assessments in REFINE-ICD include a rest phase, a six-minute hall walk, a second rest phase, and the remainder of the 24-hour recording. Abnormal HRT is defined by an onset value of $\geq 0\%$ or a slope value of < 2.5 ms per beat of the RR interval.⁷ TWA is evaluated using the MMA method. Abnormal TWA is defined by an MMA value of $\geq 20 \mu\text{V}$ at rest or immediately following the 6 minute walk test, or an MMA value $\geq 47 \mu\text{V}$ during the 6-minute walk test or at other times.^{8,16} All TWA recordings are assessed by experienced technicians and verified by an expert. Only visible TWA is considered to be present. HRT and TWA are assessed using the MARS version 8.0 software (GE Healthcare) in REFINE-ICD.

Statistical Analyses

The Student's *t*-test and chi-square test were used to assess for significant differences in continuous and categorical variables, respectively. The association of DM with abnormal HRT plus TWA was assessed in multivariable logistic regression models that included age, gender, LVEF, and other clinical data. Analyses were performed using the IBM Statistics software 20 (Armonk, NY, USA) in ARTEMIS and Stata 12 software (College Station, TX, USA) in REFINE-ICD. P-values < 0.05 were considered significant.

RESULTS

Clinical Characteristics of Patients with and without Diabetes

Clinical characteristics of the subjects in ARTEMIS are shown in Table 1. Age, gender, LVEF, or a history of prior MI did not differ significantly between subjects with and without DM. The ARTEMIS subjects with DM had more frequently hypertension, more severe angina pectoris

symptoms, and were more frequently on beta-blocker, angiotensin converting enzyme (ACE)/angiotensin receptor (ATR) inhibitor, calcium-blocker, long-acting nitrate and diuretic medication than those without DM. In the REFINE ICD cohort, there were no statistically significant differences in gender or LVEF between subjects with and without DM (male/female, 46/9 [84%/16%] vs 183/37 [83%/17%], $P = 0.94$; LVEF, $42 \pm 4\%$ vs $43 \pm 4\%$, $P = 0.074$, respectively), but patients with DM were older on average than patients without DM (66 ± 8 years vs 61 ± 10 years, $P = 0.0005$, respectively).

Presence of Abnormal HRT+TWA in Study Patients with and without Diabetes

Abnormal HRT plus TWA (both abnormal) was significantly more common in CAD patients with DM than in CAD patients without DM in ARTEMIS (Table 2). Similarly, abnormal HRT+TWA occurred significantly more frequently in post-MI patients with DM than those without DM in the initial 275 patients screened in REFINE-ICD study (Table 2).

Individual Contribution of HRT and TWA to Abnormal HRT Plus TWA in Patients with Diabetes

Abnormal HRT was significantly more common in DM (41% in ARTEMIS cohort, 78% in REFINE ICD cohort) versus non-DM patients (25% in ARTEMIS cohort, 29% in REFINE ICD cohort) ($P < 0.001$) (Table 2). Abnormal TWA did not occur significantly more frequently in patients with DM compared with non-DM patients in ARTEMIS (61% vs 59%, respectively, $P = 0.39$) (Table 2). However, abnormal TWA was significantly more common in DM versus non-DM patients in REFINE-ICD (87% vs 64%, respectively, $P = 0.001$) (Table 2).

Association of Left Ventricular Ejection Fraction with Abnormal HRT and TWA

Abnormal HRT plus TWA was significantly more common in the ARTEMIS patients with LVEF $< 50\%$ than in those with LVEF $\geq 50\%$ and in the REFINE ICD patients with LVEF $\leq 42\%$ than in those with LVEF $> 42\%$ (Table 3). In the ARTEMIS cohort, HRT tended to be more

Table 1. Clinical Characteristics of the Subjects in the ARTEMIS Cohort

	No Diabetes (n = 475)	Diabetes (n = 526)	P
Age (years)	66 ± 8	67 ± 8	0.18
Male/female	336/139 (71/29)	376/150 (71/29)	0.80
Ejection fraction (%)	65 ± 8	64 ± 10	0.20
History of prior AMI	209 (44)	247 (47)	0.38
History of hypertension	269 (57)	426 (81)	<0.001
CCS class I/II/III/IV	311 (65)/ 137 (29)/ 19 (4)/ 0 (0)	275 (52)/ 196 (37)/ 45 (9)/ 1 (0.2)	<0.001
Medication			
Antithrombotic medication	467 (98)	511 (97)	0.22
Beta-blockers	403 (85)	479 (91)	<0.01
Lipid lowering medication	431 (91)	483 (92)	0.54
ACE-/ATII-inhibitors	259 (55)	366 (70)	<0.001
Calcium-blockers	80 (17)	169 (32)	<0.001
Nitrates	153 (32)	229 (44)	<0.001
Diuretic drugs	91 (19)	246 (47)	<0.001

The values are means ± SD or the number of the patients (percentages in parentheses). ACE = angiotensin converting enzyme; ATII = angiotensin II receptor 1; AMI = acute myocardial infarction; CCS class = Canadian Cardiac Society classification for angina pectoris symptoms; DM = diabetes mellitus. ARTEMIS = Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection.

Table 2. Presence of Abnormal Heart Rate Turbulence and T-Wave Alternans in Study Patients with and without Diabetes

ARTEMIS	No Diabetes (n = 475)	Diabetes (n = 526)	P
Abnormal HRT plus TWA	13%	24%	<0.001
Abnormal HRT	25%	41%	<0.001
Abnormal TWA	59%	61%	0.39
REFINE ICD	No Diabetes (n = 220)	Diabetes (n = 55)	P
Abnormal HRT plus TWA	25%	78%	<0.001
Abnormal HRT	29%	78%	<0.001
Abnormal TWA	64%	87%	0.001

HRT = heart rate turbulence; TWA = T-wave alternans.

frequently abnormal in patients with LVEF < 50% than in patients with LVEF ≥ 50%. However, the occurrence of abnormal TWA did not differ statistically significantly between the patients with normal and those with abnormal LVEF. In REFINE ICD, abnormal HRT occurred significantly more frequently in patients with LVEF ≤ 42% compared with patients with LVEF values > 42%, while the frequency of TWA was similar in patients with higher and lower LVEF values (Table 3).

Multivariate Determinants of Abnormal HRT Plus TWA

In ARTEMIS, DM was tested in the logistic regression analysis model including age, gender, LVEF, history of hypertension, CCS (Canadian Cardiac Society) class, beta-blocker, ACE/ATR inhibitor, calcium-blocker, long-acting nitrate and

diuretic medication. In this model, DM, LVEF, age, and gender retained their statistically significant association with abnormal HRT plus TWA (Table 4).

In REFINE ICD, DM was a very strong univariate predictor of abnormal HRT plus TWA with an odds ratio (OR) of 10.75, 95% CI 5.3–21.8, $P < 0.001$. When age, gender, LVEF as a continuous variable, type of MI (STEMI/NSTEMI) and DM were included in a multivariable logistic regression model DM remained strongly and independently associated with abnormal HRT plus TWA. Apart from DM, only LVEF remained significant in that multivariable model (Table 4).

DISCUSSION

The present observations in two independent cohorts of patients with CAD show that DM is

Table 3. Association of Left Ventricular Ejection Fraction with Abnormal Heart Rate Turbulence and T-Wave Alternans

ARTEMIS	LVEF $\geq$ 50%	LVEF < 50%	P
Abnormal HRT plus TWA	18%	28%	<0.001
Abnormal HRT	32%	44%	0.052
Abnormal TWA	54%	62%	0.23
REFINE ICD	LVEF > 42%	LVEF $\leq$ 42%	P
Abnormal HRT plus TWA	28%	43%	<0.01
Abnormal HRT	30%	47%	<0.01
Abnormal TWA	64%	72%	0.14

The values are percents. HRT = heart rate turbulence; LVEF = left ventricular ejection fraction; TWA = T-wave alternans. The median value (42%) was used as a cut-point for LVEF in REFINE ICD.

Table 4. Multivariate Determinants of Abnormal Heart Rate Turbulence Plus T-Wave Alternans

ARTEMIS	Relative Risk	95% Confidence Interval	P
Diabetes	1.82	1.28–2.59	0.001
LVEF (as continuous variable)	0.98	0.96–0.99	0.01
Age (as continuous variable)	1.04	1.02–1.06	0.001
Female gender	1.67	1.17–2.38	0.005
REFINE ICD	Relative Risk	95% Confidence Interval	P
Diabetes	10.3	4.9–21.8	< 0.001
LVEF (per 10% increase)	0.4	0.2–0.8	0.01

HRT = heart rate turbulence; LVEF = left ventricular ejection fraction; TWA = T-wave alternans.

significantly associated with a higher propensity toward abnormal HRT plus TWA.

In post-MI patients with mild to moderate left ventricular dysfunction, the combination of abnormal HRT and TWA has been shown to indentify the patients at high risk for cardiac death or resuscitated cardiac arrest.⁹ Blunted HRT has been observed to be a predictor of mortality in several populations of post-MI patients.^{13,17} Abnormal HRT has also been shown to predict a higher risk of sudden cardiac death after MI, even after adjustments with relevant clinical risk markers, including LVEF.⁴ A recent study also showed that abnormal HRT is associated with a higher risk of mortality in DM patients with a prior MI.¹⁸ Interestingly, in the present patient cohorts the more common occurrence of abnormal HRT plus TWA (both abnormal) in patients with DM was driven by the more common occurrence of abnormal HRT in patients with DM compared with patients without DM. HRT has a significant association with baroreflex sensitivity and its origin is considered to be an autonomic response to perturbations of blood pressure after a

ventricular premature depolarization.^{13,17,19} There are previous animal studies, which have shown that dogs with impaired baroreflex sensitivity (HRT turbulence being a surrogate measure of baroreflex sensitivity) have an increased risk of developing ventricular fibrillation at the time coronary occlusion.²⁰ Cardiac autonomic neuropathy is an important and relatively early complication of DM and it contributes significantly to the cardiovascular risk of these patients.^{21–23} HRT slope has been shown to be a sensitive and specific marker for the detection of cardiac autonomic neuropathy in patients with DM.²⁴ It is plausible to speculate that cardiac autonomic neuropathy may be the link between abnormal HRT and increased risk for sudden cardiac death in patients with DM.

The presence of clinically important TWA has been shown to be associated with the risk for life-threatening ventricular tachyarrhythmias in several patient populations.^{5,6,8,25–28} Although microvolt TWA has been observed to be a predictor of arrhythmic events in post-MI patients,^{5,29} there has been some controversy regarding the prognostic value of microvolt TWA when the patients are

treated according to modern guidelines with routine use of beta-blocker therapy.³⁰ Although earlier studies have indicated that TWA predicts the first appropriate electrical shock in patients with ICDs,³¹ the more recent data suggest that TWA has limited accuracy in predicting the fatal or near fatal arrhythmic events in patients with ischemic cardiomyopathy and prophylactic defibrillators.³² In the present study, the prevalence of abnormal TWA was relatively high in both CAD populations, but did not differ significantly between the DM and non-DM patients in the larger ARTEMIS cohort supporting the concept that the presence of DM alone does not increase the occurrence of abnormal TWA.³³

It is noteworthy that post-MI patients with severe LV dysfunction with sufficient number of risk factors and high all-cause mortality do not significantly benefit from prophylactic ICD implantation.³⁴ DM has been shown to contribute to the risk models, which predict all-cause death during the years after primary prevention ICD therapy.³⁵ Therefore despite its association with the risk for sudden cardiac death, DM does not necessarily modulate the long-term benefit of ICD therapy in patients with severe LV dysfunction. Based on our present findings and previous observations,³ one might speculate that DM may be more closely associated with risk for arrhythmic death than all-cause mortality in post-MI patients with mild to moderate left ventricular dysfunction. This is being evaluated in ongoing and future studies. In ARTEMIS and REFINE ICD, the likelihood of abnormal HRT plus TWA was related to the degree of LV dysfunction. This observation is in accordance with previous findings, which have shown that patients with decreased LVEF have more frequently abnormal HRT and TWA.^{33,36} However, in our present analysis DM retained a strong independent association with abnormal HRT plus TWA despite adjustment for relevant clinical factors including LVEF. This suggests that DM yields incremental independent information about arrhythmic risk profile in individuals with CAD.

The present analysis has some limitations. It is based on the association of abnormal arrhythmia risk markers HRT plus TWA with DM. We did not have data on QT interval available for the present analysis. Our study is not a randomized comparison and causation can only be inferred. It is possible that factors other than those measured

and adjusted for may explain part or all of this relationship. In addition, this analysis is from two ongoing studies and no endpoint data are available. Hence, it is only speculative that these markers will predict a higher risk of sudden cardiac death and represent arrhythmia risk profile in these patient groups. Yet, the consistency of the observations provides support for the notion that DM increases the risk of sudden cardiac death due to a higher incidence of abnormal autonomic tone.

In conclusion, patients with CAD and DM have more frequently abnormal HRT plus TWA than patients with CAD, but without DM. Ongoing data collection and outcomes assessment in ARTEMIS, REFINE ICD, and other studies will aid in clarifying the role of these noninvasive risk markers and DM as arrhythmia risk indicators.

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