Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 59 (2010) 159 – 165
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Increased left ventricular arrhythmogenicity in metabolic syndrome and relationship with myocardial performance, risk factors for atherosclerosis, and low-grade inflammation

Christina Voulgari[a], Nicholas Tentolouris[a,*], Dimitrios Papadogiannis[a], Ioannis Moyssakis[b], Despoina Perrea[c], Despoina Kyriaki[a], Nicholas Katsilambros[a]

[a]*First Department of Propaedeutic Medicine, Laiko General Hospital, Athens University Medical School, Athens 115 27, Greece*
[b]*Cardiology Department, Laiko General Hospital, Athens 115 27, Greece*
[c]*Laboratory for Experimental Surgery and Surgical Research, Athens University Medical School, Athens 115 27, Greece*

Received 24 November 2008; accepted 19 June 2009

Abstract

Metabolic syndrome (MetS) is a clustering of cardiovascular risk factors recently associated with left ventricular dysfunction. Limited data exist on the association between MetS and ventricular arrhythmogenicity. This study examined differences in ventricular arrhythmogenicity assessed by classic (QT interval) and newer (spatial QRS-T angle [spQRS-Ta]) electrocardiographic markers in subjects with and without MetS. A total of 306 subjects, 153 with and 153 without MetS, matched for sex and age were examined. The spQRS-Ta, which vectorcardiographically quantifies the deviation between the directions of ventricular depolarization and repolarization, was measured using a computer-based electrocardiograph. Left ventricular mass index and myocardial performance were evaluated echocardiographically. The spQRS-Ta was significantly higher in subjects with in comparison with those without MetS. Left ventricular mass index, QT interval, and its dispersion were not different between the 2 groups. Left ventricular myocardial performance was worse in subjects with MetS and was associated with higher values of the spQRS-Ta. Multivariate linear regression analysis demonstrated MetS status as the strongest predictor of ventricular arrhythmogenicity. Addition of the high-sensitivity C-reactive protein in the model increased the explained variance of the spQRS-Ta by 11%. In conclusion, ventricular arrhythmogenicity is present in MetS and is associated with myocardial dysfunction, risk factors for atherosclerosis, and low-grade inflammation. The independent association between the spQRS-Ta and MetS implies that the clustering of the metabolic disturbances has additional prognostic information than its individual components in terms of ventricular arrhythmogenicity and may explain in part the excess cardiovascular risk in subjects with MetS.

Metabolic syndrome (MetS) is defined as a clustering of cardiovascular risk factors, such as central obesity, insulin resistance, increased blood pressure, hyperglycemia, and dyslipidemia [1]. It is also considered a systemic proinflammatory state and is associated with substantial cardiovascular risk above and beyond its individual metabolic components [2]. Recent data suggest that individuals with MetS have a 2-fold higher risk for cardiovascular disease (CVD) than those without and thus can be identified as elusive high–cardiovascular-risk patients [3]. Ventricular arrhythmogenicity assessed by prolongation of left ventricle (LV) repolarization and depolarization time has been associated with arrhythmia provocation and sudden cardiac death [4]. Although the challenge for the identification of patients at risk for arrhythmia is compelling, the role of noninvasive risk stratification is not well defined. Prolongation of QT interval and its dispersion are considered poor surrogate markers for arrhythmogenesis [5]. The *spatial QRS-T angle* (spQRS-Ta), defined as the angle between the directions of ventricular depolarization and repolarization obtained by vectorcardiography (VCG), is a novel marker of ventricular arrhythmogenicity akin to the concept of the ventricular gradient [6,7]. Higher values of the spQRS-Ta are associated with the classic cardiovascular risk factors [8-10]; and prospective data demonstrated that widening of the spQRS-Ta, but not QT prolongation, was the dominant

* Corresponding author. Tel.: +30 210 745 6448; fax: +30 210 746 2640.
E-mail address: ntentol@med.uoa.gr (N. Tentolouris).

0026-0495/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2009.06.028

predictor of CVD and mortality [8]. These findings suggest that evaluation of electrophysiologic abnormalities by spQRS-Ta determination predicts better CVD events. Recent data suggest that the MetS is associated with alterations in LV function as a result of increased triglyceride content and fuel utilization in myocardium [11]. However, there are limited data on the association between ventricular arrhythmogenicity and MetS, assessed by determination of the spQRS-Ta and QT interval. The research hypothesis we examined herein is that ventricular arrhythmogenicity, as a result of the clustering of risk factors and the myocardial alterations that accompany MetS, may be present in this condition. The relationship between ventricular arrhythmogenicity and myocardial performance, as well as the demographic, clinical, and metabolic variables, was also examined.

1. Research design and methods

1.1. Subjects

A total of 620 subjects attending the outpatient clinics of our hospital were screened for the study. Inclusion criteria required that subjects were free of clinically apparent macrovascular disease (CVD of any cause, cerebrovascular disease, and peripheral vascular disease); *chronic kidney disease*, defined as estimated glomerular filtration rate (GFR) of less than 60 mL/min [12]; infections; and inflammatory diseases. Patients with type 1 diabetes mellitus, those treated with nonsteroid anti-inflammatory medications or corticosteroids in the previous 3 months, and current smokers were excluded. From those screened, 153 were found to have MetS according to the National Cholesterol Education Program–Adult Treatment Panel (NCEP-ATP) III criteria [13]. Subsequently, they were matched for sex, age, presence of type 2 diabetes mellitus (T2DM), and hypertension with 153 persons without MetS. Diagnosis and classification of diabetes mellitus were based on the American Diabetes Association criteria [14]. The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of our hospital, and written informed consent was obtained from participants.

All participants underwent a thorough clinical examination in the morning of the study, and a detailed history for the current use of medications and concomitant diseases was obtained. Blood pressure was measured 3 consecutive times, 1 minute apart, in the sitting position, using an appropriate cuff size. The mean value of the last 2 measurements was used in the analysis. Arterial hypertension was defined according to the current guidelines, and the type of the antihypertensive treatment was recorded [13]. Body weight, height, and waist circumference (WC) were measured in light clothing; and body mass index (BMI) was calculated. Ankle brachial pressure index was measured and calculated with a pulsed, continuous Doppler (MD16; Hokanson, Bellevue, WA).

1.2. Analytical assays

Blood was collected after an overnight fast of 10 to 12 hours. Fasting serum glucose, lipids, and creatinine were measured on an automated analyzer (Technicon, Dublin, Ireland); and low-density lipoprotein (LDL) cholesterol levels were calculated. Plasma high-sensitivity C-reactive protein (hs-CRP) was determined using ADVIA 1650 (Bayer HealthCare LLC, Elkhart, IN). Microalbuminuria was assessed by measuring albumin-to-creatinine ratio (ACR) in a random urine sample on a DCA 2000 analyzer (Bayer HealthCare). Glomerular filtration rate was calculated using the formula of Cockcroft-Gault. Glycated hemoglobin A_{1c} (HbA_{1c}) was measured also on a DCA 2000 analyzer. Plasma insulin was measured with radioimmunoassay (Biosure, Brussels, Belgium). Insulin resistance was estimated using the homeostasis model assessment equation (HOMA-IR).

1.3. Electrocardiographic methodology

In all subjects, a 12-lead digital electrocardiogram (ECG) was recorded in the supine resting position for 5 minutes using a computer-based ECG system (Cardio Perfect, version 1.3.1.216; Cardio Control, Rijswijk, the Netherlands) [15]. The amplitude of the mean spatial T vector (spatial T amplitude) and the amplitude of the mean spatial QRS vector (spatial QRS amplitude) were calculated [16]. Afterward, the spQRS-Ta was computed by adding the mean vector representing all of the electrical forces produced by depolarization and the mean vector representing all of the electrical forces produced by repolarization as described previously [17]. Besides spQRS-Ta, the angle between the maximum QRS and T vectors in the frontal, horizontal, and right sagittal planes was also computed [17]. QT measurements were made from the simultaneously sampled standard 12 ECG leads. QT mean was then heart rate corrected (QTc) using both the Bazett formula ($QT_{C[B]} = QT\ \sqrt{RR}$) [18] and the Fridericia equation ($QT_{C[F]} = QT/RR_{1/3}$) [19,20]. *QT dispersion* was defined as the difference between the maximum QT and the minimum QT interval across the 12 digital ECG leads [21].

1.4. Echocardiographic study

Complete 2-dimensional Doppler echocardiographic examination was performed with a Hewlett Packard Sonos 1000 ultrasound system (Hewlett Packard, Palo Alto, CA) by the same cardiologist. The Penn convention was used for calculation of LV mass, which was normalized for the body surface area (LV mass index [LVMi]) [22]. Left ventricular hypertrophy (LVH) was defined using echocardiographic criteria [23]. The myocardial performance index (Tei index) of the LV, a composite index for the evaluation of both LV systolic and LV diastolic function, was also evaluated [24].

1.5. Statistical analysis

Statistical analysis was performed using the SPSS statistical package (SPSS 12.0, Chicago, IL). All variables were tested for normal distribution of the data. Data are shown as mean ± SD, unless it is stated otherwise. A Student *t* test was used to assess differences in continuous variables between the studied groups, whereas a χ^2 test was used for categorical variables. Differences in nonparametric variables were compared using the Mann-Whitney *U* test. Univariate linear regression analysis was performed to look for the relationship between spQRS-Ta and the variables of interest in the study population. Afterward, multivariate linear regression analyses were performed (backward stepwise method) to look for independent associations between the spQRS-Ta and the variables of interest. A total of 8 models of multivariate linear regression analysis have been created. Model 1 included the variables that were found to be associated significantly with the spQRS-Ta in univariate analysis and included age, BMI, heart rate, HbA_{1c}, LDL cholesterol, HOMA-IR, ACR, LVH, Tei index, hs-CRP, use of β-blockers, use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs), and use of statins; models 2 to 8 included the variables of the model 1 that were associated significantly with the spQRS-Ta and MetS status (model 2), the sum of the components of the MetS on a scale from 0 to 5 (model 3), high WC (model 4), low high-density lipoprotein (HDL) cholesterol (model 5), high triglycerides (model 6), high blood pressure (model 7), and high serum glucose or diabetes (model 8). All independent variables in the multivariate analyses models were tested for multicollinearity. *P* values < .05 (2-tailed) were considered statistically significant.

2. Results

2.1. Demographic, clinical, and metabolic parameters of the study subjects

Individuals with and without MetS did not differ in terms of sex, age, prevalence rates of T2DM and hypertension, use of statins, and ACR. Individuals with MetS had higher values of blood pressure, BMI, and WC. Furthermore, the values of plasma glucose, triglycerides, hs-CRP, HbA_{1c}, and HOMA IR were higher, whereas those of HDL cholesterol were lower, in the participants with MetS (Table 1).

2.2. Echocardiographic, ECG, and VCG parameters of the study subjects

Subjects with and without MetS did not differ in terms of LVMi, heart rate, QT and QTc interval duration, or QT dispersion. The values of the Tei index were higher, suggesting worse cardiac performance, in the subjects with MetS. The values of the spatial *T* amplitude were lower, whereas those of the spatial *QRS* amplitude were higher, in the individuals with MetS. From the VCG components of the ventricular gradient, only the spQRS-Ta was higher in subjects with MetS (Table 2). The spQRS-Ta was not significantly different between men and women irrespective of the MetS status (data not shown).

Table 1
Demographic and clinical characteristics of the study subjects according to the MetS status

	Without MetS	With MetS	*P* value
n (%)	153 (50)	153 (50)	–
Male/female, n (%)	77 (50.3)/76 (49.7)	77 (50.3)/76 (49.7)	1.00
Age (y)	58.6 ± 9.8	59.7 ± 8.7	.31
BMI (kg/m^2)	26.9 ± 3.3	29.3 ± 4.4	<.001
WC (cm)	94.3 ± 11.8	105.5 ± 11.8	<.001
Waist-to-hip ratio	0.89 ± 0.08	0.90 ± 0.08	.36
Systolic blood pressure (mm Hg)	123.0 ± 19.7	137.4 ± 25.8	<.001
Diastolic blood pressure (mm Hg)	71.3 ± 11.5	75.8 ± 12.7	.002
Ankle brachial index	1.02 ± 0.14	1.02 ± 0.14	.78
Glucose (mmol/L)	6.9 ± 2.4	8.1 ± 2.8	<.001
HbA_{1c} (%)	6.3 (4.7-12.8)	6.9 (4.7-13.7)	.002
Total cholesterol (mmol/L)	5.7 ± 0.9	5.8 ± 1.1	.20
HDL cholesterol (mmol/L)	1.3 ± 0.3	1.0 ± 0.2	<.001
LDL cholesterol (mmol/L)	3.7 ± 0.8	3.8 ± 1.0	.54
Triglycerides (mmol/L)	1.2 ± 0.4	2.0 ± 1.0	<.001
hs-CRP (mg/L)	1.1 ± 0.7	2.1 ± 0.2	<.001
HOMA-IR[a]	3.0 (1.1-15.9)	4.8 (1.1-13.2)	<.001
ACR (mg/mmol)[a]	1.5 (0.34-11.2)	1.8 (0.34-12.5)	.38
Microalbuminuria (yes), n (%)	31 (20.3)	35 (22.9)	.64
GFR (mL/min)	91.4 ± 28.9	84.9 ± 18.7	.29
Diabetes mellitus (yes), n (%)	74 (49.0)	83 (54.2)	.49
Hypertension (yes), n (%)	34 (22.2)	38 (23.0)	.59
Use of statins (yes), n (%)	24 (16)	35 (23)	.31
LVH (yes), n (%)	55 (35.9)	65 (42.5)	.24
Sum (scale 0-5) of the components of the MetS[a]	2 (0-2)	4 (3-5)	<.001

Data are mean values ± SD or number (percentage). *P* values for the comparison between groups with and without MetS by independent-samples *t* test for continuous variables, χ^2 for categorical variables, or Mann-Whitney *U* test for nonparametric data.

[a] Median values (interquartile range).

2.3. Association between the spatial QRS-T angle and studied variables

Univariate linear regression analysis showed significant relationships between the spQRS-Ta and age, BMI, WC, MetS status and NCEP-ATP III score, diabetes and hypertension status, fasting glucose, HbA_{1c}, HOMA-IR, heart rate, systolic blood pressure, use of ACE-I and/or ARBs, use of β-blockers, HDL cholesterol, LDL cholesterol,

Table 2
Electrocardiographic, ECG, and VCG data (mean ± SD) of the subjects without and with MetS

	Without MetS	With MetS	*P* value
Heart rate (ms)	67.5 ± 9.7	68.9 ± 10.2	.23
LVMi (g/m^2)	122.3 ± 19.7	124.8 ± 15.9	.21
Tei index	0.37 ± 0.02	0.40 ± 0.03	<.001
QT max (ms)	410.7 ± 26.2	412.9 ± 29.3	.47
QT mean (ms)	387.8 ± 29.6	386.0 ± 34.1	.62
$QTc_{(F)}$ mean (ms)	402.2 ± 25.1	401.9 ± 28.7	.64
$QTc_{(B)}$ mean (ms)	411.4 ± 28.9	409.4 ± 30.8	.63
QT dispersion (ms)	41.4 ± 14.8	42.0 ± 20.1	.77
FQRS-T angle (°)	19.7 ± 3.2	19.5 ± 2.2	.19
HQRS-T angle (°)	54.9 ± 3.7	57.3 ± 3.5	.63
RsQRS-T angle (°)	98.0 ± 4.2	96.4 ± 3.7	.77
SpQRS amplitude (μV)	1191.9 ± 333.5	1285.4 ± 404.3	.02
SpT amplitude (μV)	408.4 ± 146	365.9 ± 132.8	.008
SpQRS-T angle (°)	14.2 ± 7.2	22.1 ± 10.9	<.001

QT max indicates maximum QT interval; QT mean, mean QT interval; QTc: heart rate–adjusted QT interval (F: using the Fridericia formula; B: using the Bazett formula); FQRS-T angle, frontal plane QRS-T angle; HQRS-T angle, horizontal plane QRS-T angle; RsQRS-T angle, right sagittal plane QRS-T angle; SpQRS amplitude, spatial QRS amplitude; SpT amplitude, spatial T amplitude.

use of statins, hs-CRP, ACR or presence of microalbuminuria, LVH, and Tei index (Table 3). No significant relationships were found between the spQRS-Ta and sex, diastolic blood pressure, total cholesterol and triglycerides levels, use of other classes of antihypertensive medications, and GFR. Multivariate linear regression analysis, after adjustment for the variables that were associated significantly with the spQRS-Ta in univariate analysis (Table 4, model 1), demonstrated independent significant associations between the spQRS-Ta and BMI, HbA_{1c}, LDL cholesterol, ACR, hs-CRP, Tei index, and use of statins. Noteworthy, addition of the hs-CRP in the model increased its predictive value by 11%. The MetS status and score were both associated significantly and independently with the spQRS-Ta, although the highest association was noted for MetS status per se. From the particular components of the MetS, high WC, low HDL cholesterol, high blood pressure levels or hypertension, and high blood glucose or diabetes were associated independently with the spQRS-Ta (Table 4, models 2-8). The independent association between the spQRS-Ta and the MetS status and the NCEP-ATP III score remained after exclusion of the patients with diabetes from analysis (standardized regression coefficient [β] = 0.258, $P < .001$ and $\beta = 0.216$, $P = .003$, respectively).

3. Discussion

The main findings of the present study are as follows: (1) LV arrhythmogenicity is present in uncomplicated subjects with MetS, assessed by determination of the spQRS-Ta; (2) ventricular arrhythmogenicity in MetS correlates with most of its metabolic components and increases along with their clustering as well as with low-grade inflammation; and (3) subjects with MetS have worse myocardial performance.

Recent studies demonstrated that individuals with high spQRS-Ta values are more prone to life-threatening arrhythmias and that high spQRS-Ta values predict cardiac events in the general population [8,9] and in elderly subjects [25]. Moreover, a population-based study demonstrated that the spQRS-Ta is an independent predictor of cardiovascular death [26]. Thus, inclusion of this simple ECG marker may add substantially in terms of cardiovascular risk stratification. Widening of the spQRS-Ta is considered to reflect several underlying cardiac abnormalities, including LVH, ischemia, fibrosis, and functional myocardial changes, which induce aberrations in ionic channel functions and are indicators of abnormal sequence of ventricular repolarization [8-10]. Metabolic syndrome consists of a clustering of disturbances, most of which are established risk factors for CVD [1,2]. The independent association between MetS and the spQRS-Ta in the present study suggests that the abnormalities encompassed in MetS affect LV arrhythmogenicity. This was demonstrated mainly for the MetS per se, for the sum of its components (NCEP-ATP III score), and for each one of its particular metabolic components, with the

Table 3
The association between various parameters with the spatial QRS-T angle in the study subjects by univariate linear regression analysis

	B	SE (B)	β	*P* value
Independent variables				
Age (1 y)	0.122	0.061	0.115	.045
Sex (male vs female)	0.033	1.156	0.002	.977
WC (1 cm)	0.192	0.043	0.249	<.001
BMI (1 kg/m^2)	0.580	0.126	0.255	<.001
Heart rate (1 beat/min)	0.197	0.057	0.195	.001
Systolic blood pressure (1 mm Hg)	0.105	0.023	0.251	<.001
Total cholesterol (1 mmol/L)	0.887	0.589	0.091	.114
LDL cholesterol (1 mmol/L)	3.025	0.580	0.287	<.001
HDL cholesterol (1 mmol/L)	−0.177	0.043	0.231	<.001
HbA_{1c} (1%)	2.706	0.348	0.417	<.001
HOMA-IR (1 U)	1.568	0.307	0.362	<.001
ACR (1 mg/mmol)	0.408	0.185	0.141	.029
Microalbuminuria (yes vs no)	5.034	1.344	0.211	<.001
hs-CRP (1 mg/L)	1.407	0.256	0.402	<.001
LVH (yes vs no)	2.559	1.442	0.118	.048
Tei index (1 U)	73.34	14.00	0.288	<.001
MetS status (yes vs no)	7.976	1.061	0.396	<.001
Sum (scale 0-5) of the components of the MetS	1.626	0.572	0.203	.005
High waist (yes vs no)	2.742	1.486	0.116	.067
Low HDL cholesterol (yes vs no)	2.732	1.372	0.128	.048
High triglycerides (yes vs no)	1.667	1.371	0.078	.226
High blood pressure or hypertension	3.178	1.389	0.149	.024
High blood glucose or diabetes	4.445	1.700	0.205	<.001
Use of ACE-I/ARBs (yes vs no)	−7.254	3.323	−0.236	.032
Use of β-blockers (yes vs no)	−4.155	3.573	−0.098	.048
Use of statins (yes vs no)	−6.309	3.787	−0.128	.027

Parentheses show the units of increment or the categories of the independent variables. B indicates unstandardized regression coefficient; SE, standard error.

Table 4
The association between various parameters with the spatial QRS-T angle by multivariate linear regression analysis

	B	SE (B)	β	P value	Adjusted R^2
Independent variables					
Model 1					
BMI (1 kg/m^2)	0.312	0.143	0.143	.030	
HbA_{1c} (1%)	1.451	0.475	0.223	.003	
LDL cholesterol (1 mmol/L)	1.630	0.654	0.157	.010	
ACR (1 mg/mmol)	0.408	0.185	0.141	.029	
hs-CRP (1 mg/L)	1.407	0.256	0.402	<.001	
Tei index (1 U)	9.622	2.900	0.366	.002	
Use of statins (yes vs no)	−6.440	2.533	−0.261	.015	0.549
Model 2					
MetS status (yes vs no)	5.594	1.367	0.253	<.001	0.604
Model 3					
Sum (scale 0-5) of the components of the MetS	1.626	0.572	0.203	.005	0.576
Model 4					
High waist (yes vs no)	2.742	1.486	0.116	.067	0.558
Model 5					
Low HDL cholesterol (yes vs no)	2.732	1.372	0.128	.048	0.560
Model 6					
High triglycerides (yes vs no)	1.667	1.371	0.078	.226	0.545
Model 7					
High blood pressure or hypertension (yes vs no)	3.178	1.389	0.149	.024	0.570
Model 8					
High blood glucose or diabetes (yes vs no)	4.445	1.700	0.205	.010	0.572

Parentheses show the units of increment or the categories of the independent variables. Additional variables tested in model 1: age, heart rate, HOMA-IR, LVH, use of β-blockers, and use of ACE-I and/or ARBs. Models 2 to 8 were adjusted in addition for the variables included in model 1.

exception of serum triglycerides. The association between the aforementioned variables with the spQRS-Ta raises questions about the underlying pathologic processes.

The basic underlying abnormality in MetS is insulin resistance [2]. Indeed, in our study, participants with MetS had a 2-fold higher HOMA-IR than subjects without MetS. Insulin resistance results in ectopic fat accumulation [1,2]. Although muscle and liver are considered as the main such loci, increased lipid content in cardiac myocytes (cardiac steatosis) has been recently demonstrated in insulin-resistant states [11,27]. An inverse relationship was demonstrated recently between the amount of the myocardial lipid content and LV function, which improves by reduction in myocardial lipid burden [28]. Our findings confirm those of a previous study, which showed worse myocardial performance in subjects with MetS [29]; and moreover, we showed that the myocardial dysfunction in subjects with MetS is associated with ventricular arrhythmogenicity, assessed by the spQRS-Ta. Therefore, we conclude that the electrophysiologic abnormalities in the participants with MetS may be due to either the direct effects of hyperinsulinemia on myocardial membrane activity or its electrophysiologic alterations that accompany the biochemical and functional abnormalities caused by the shift in myocardial substrate utilization [11].

Noteworthy, data from a recent study showed that subjects with MetS have prolongation of repolarization of the LV assessed by determination of the duration of QTc interval [30]. In the present study, we did not find significant differences in mean QT interval and its dispersion or differences in QTc interval between participants with and without MetS. This finding was sustained for QTc assessed by both the Bazett formula (which depends more on heart rate) and the Fridericia equation (which does not depend on heart rate) [5]. The diverged results between the 2 studies may be related to differences in the characteristics of the participants. In the former study [30], participants with MetS were significantly more often male and older than those without MetS, factors affecting QT interval duration.

Although QT prolongation has been associated with arrhythmia provocation [31,32], many studies failed to demonstrate the predictive value of its moderate prolongation (≤410 milliseconds) and arrhythmogenic risk in asymptomatic population-based cohorts [33,34]. In many studies, QT prolongation has been found to have a nonsignificant association with sudden cardiac events and mortality specifically when evaluated in subjects without coronary artery disease [5,8,33,34]. The spQRS-Ta is probably more sensitive in detecting moderate deviations of electrophysiologic heterogeneity because it is less susceptible to noise and problems of definition than the QT interval [4,5,21]. Moreover, with its calculation, an accurate determination of waveform recognition points and in particular the end of the T wave is less critical than with the QT interval determination [35,36].

Another study showed increased T-axis deviation in subjects with MetS [37]. Increased T-axis deviation is a well-studied VCG parameter that predicts cardiovascular events in older (>55 years) subjects [38,39]. Unlike the T axis, which reflects the main orientation of electrical heart activity during repolarization, the spQRS-Ta takes into account depolarization; and its power lies on the ability to discriminate between primary factors (heterogeneity of action potential morphology throughout the ventricles) and secondary factors contributing to electrophysiologic heterogeneity and to the better localization of arrhythmogenic areas in the heart [40].

Participants with MetS in our study had higher hs-CRP concentrations than those without MetS. Increased hs-CRP levels in individuals with MetS offer additional prognostic information in terms of CVD prediction [41]. Our findings of a strong association between the spQRS-Ta and hs-CRP corroborate previous observations showing significant relationship between hs-CRP and QT prolongation in healthy subjects [42]. Further support for the association between hs-CRP and repolarization abnormalities comes

from the fact that reduction of hs-CRP by statins in mice attenuates the prolonged duration of action potential of cardiomyocytes and improves myocardial repolarization [43]. This effect is mediated by decrease in potassium currents in ventricular cardiomyocytes and possibly explains the negative relationship between the spQRS-Ta and the use of statins observed in our study. Moreover, MetS is characterized by chronic sympathetic nervous system predominance mainly as a result of chronic hyperinsulinemia [44]. Sympathovagal imbalance induces repolarization heterogeneity [45] and may explain in part the increased spQRS-Ta values in MetS. In agreement with previous reports, we showed a negative relationship between the use of β-blockers and ACE-I/ARBs and the prolongation of repolarization in univariate analysis [46].

Microalbuminuria is associated with LVH, myocardial fibrosis and dysfunction, as well as LV prolongation of repolarization [47]. We showed that the spQRS-Ta was independently associated with LDL cholesterol levels, an established risk factor for CVD. Moreover, we have shown previously that the spQRS-Ta is increased in subjects with T2DM and that it was associated significantly with HbA_{1c} in both diabetic and nondiabetic individuals [10]. This relationship was confirmed in the present study and suggests that the higher, but still in the reference range, blood glucose levels affect the electrical activity of the LV [10]. Because diabetes affects myocardium, we repeated analyses after exclusion of the participants with T2DM; and we showed that the independent relationship between the spQRS-Ta and MetS remained, suggesting that diabetes has not confounded our results.

3.1. Limitations

The cross-sectional design of the study does not allow us to draw conclusions in terms of causality between MetS and the spQRS-Ta. Prospective studies are needed to examine if interventions aiming at regression of the MetS restore these abnormalities. In addition, selection biases due to inclusion of subjects with T2DM cannot be excluded. Because MetS is very common in patients with T2DM, it is possible that subjects with T2DM but without MetS were recruited in the study; and this is a limitation on the generalization of our results. Furthermore, subjects with macrovascular disease were excluded; therefore, our findings cannot be extrapolated to the general population. This probably explains the relatively low spQRS-Ta values in the study groups. Not all participants underwent exercise stress testing or imaging studies to exclude coronary artery disease. It cannot, therefore, be ruled out that some patients with subclinical coronary artery disease may have been included in the study. Moreover, the Tei index has been criticized because it cannot discriminate systolic and diastolic function of the LV. However, in subjects without known cardiac disease, abnormalities of LV function primarily reflect a diastolic abnormality [23]. The strong relationship between the Tei index and the spQRS-Ta in individuals with MetS suggests an association between the underlying diastolic dysfunction and the electric activity of the LV.

In conclusion, this study has shown that ventricular arrhythmogenicity is present in subjects with MetS. Ventricular arrhythmogenicity is associated with the classic risk factors for atherosclerosis, low-grade inflammation, and worse myocardial performance. The independent association between the spQRS-Ta and MetS status and NCEP-ATP III score implies that the clustering of the metabolic disturbances has additional prognostic information than its individual components in terms of electrical activity perturbations of the LV and may explain in part the excess cardiovascular risk in MetS.

References

[1] Sakkinen PA, Wahl P, Cushman M, et al. Clustering of procoagulation, inflammation and fibrinolysis variables with metabolic factors in insulin resistance syndrome. Am J Epidemiol 2000;152:897-907.
[2] Reilly MP, Rader DJ. The metabolic syndrome: more than the sum of its parts? Circulation 2003;108:1546-51.
[3] Dekker JM, Girman C, Rhodes T, et al. Metabolic syndrome and 10-year cardiovascular disease risk in the Hoorn Study. Circulation 2005;112:666-73.
[4] Antzelevitch C. Heterogeneity and cardiac arrhythmias: an overview. Heart Rhythm 2007;4:964-72.
[5] Rautaharju PM. Why did QT dispersion die? Card Electrophysiol Rev 2002;6:295-301.
[6] Batchvarov V, Kaski JC, Parchure N, et al. Comparison between ventricular gradient and a new descriptor of the wavefront direction of ventricular activation and recovery. Clin Cardiol 2002;25:230-6.
[7] Malik M, Hnatkova K, Batchvarov VN. Post infarction risk stratification using the 3-D angle between QRS complex and T-wave vectors. J Electrocardiol 2004;37:201-8.
[8] Rautaharju PM, Kooperberg C, Larson JC, et al. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation 2006;113:473-80.
[9] Kardys I, Kors JA, van der Meer IM, et al. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J 2003;24:1357-64.
[10] Voulgari Ch, Tentolouris N, Moyssakis I, et al. Spatial QRS-T angle: association with diabetes and left ventricular performance. Eur J Clin Invest 2006;36:608-13.
[11] Szczepaniak LS, Victor RG, Orci L, et al. Forgotten but not gone: the rediscovery of fatty heart, the most common unrecognized disease in America. Circ Res 2007;101:759-67.
[12] National kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(suppl 1):S1-266.
[13] Chobanian AV, Bakris GL, Black HR, et al. National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
[14] The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2006;29:S43-48.
[15] Edenbrandt L, Pahlm O. Vectorcardiogram synthesized from a 12-lead ECG: superiority of the inverse Dower matrix. J Electrocardiol 1988;21:361-7.

[16] Dilaveris P, Pantazis A, Gialafos E, et al. Determinants of electrocardiographic and spatial vectorcardiographic descriptors of ventricular repolarization in normal subjects. Am J Cardiol 2001;88: 912-4.
[17] Zabel M, Acar B, Klingenheben T, Franz MR, Hohnloser SH, Malik M. Analysis of 12-lead T-wave morphology for risk stratification after myocardial infarction. Circulation 2000;102:1252-7.
[18] Bazett HC. An analysis of the time-relations of electrocardiograms. Heart 1920;7:353-70.
[19] Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Med Scand 1920;53:469-86.
[20] Franz MR. Bazett, Fridericia, or Malik? Heart Rhythm 2008;5:1432-3.
[21] Malik M, Batchvarov VN. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000;36:1749-66.
[22] Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol 1986;57:450-8.
[23] Mancia G, De Backer G, Dominiczak A, et al. Guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2007;28:1462-536.
[24] Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997;10:169-78.
[25] Kors JA, Kardys I, van der Meer IM, et al. Spatial QRS-T angle as a risk indicator of cardiac death in an elderly population. J Electrocardiol 2003;36:113-4.
[26] Yamazaki T, Froelicher VF, Myers J, Chun S, Wang P. Spatial QRS-T angle predicts cardiac death in a clinical population. Heart Rhythm 2005;2:73-8.
[27] Hayden MR, Chowdhury N, Govindarajan G, et al. Myocardial myocyte remodeling and fibrosis in the cardiometabolic syndrome. J Cardiometab Syndr 2006;1:326-33.
[28] Hammer S, van der Meer RW, Lamb HJ, et al. Progressive caloric restriction induces dose dependent changes in myocardial triglyceride content and diastolic function in healthy men. J Clin Endocrinol Metab 2008;93:497-503.
[29] Turhan H, Yasar AS, Yagmur J, Kurtoglu E, Yetkin E. The impact of metabolic syndrome on left ventricular function: evaluated by using the index of myocardial performance. Int J Cardiol 2009;132:382-6.
[30] Faramawi MF, Wildman RP, Gustat J, Rice J, Abdul Kareem MY. The association of the metabolic syndrome with QTc interval in NHANES III. Eur J Epidemiol 2008;23:459-65.
[31] Dekker JM, Crow RS, Hannan PJ, Schouten EG, Folsom AR. Heart rate–corrected QT interval prolongation predicts risk of coronary heart disease in black and white middle-aged men and women: the ARIC Study. J Am Coll Cardiol 2004;43:565-71.
[32] de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly: the Rotterdam Study. Eur Heart J 1999;20: 278-82.
[33] Karjalainen J, Reunanen A, Ristola P, Viitasalo M. QT interval as a cardiac risk factor in a middle aged population. Heart 1997;77:543-8.
[34] Goldberg RJ, Bengtson J, Chen Z, Anderson KM, Locati E, Levy D. Duration of the QT interval and total and cardiovascular mortality in healthy persons (The Framingham Heart Study Experience). Am J Cardiol 1991;67:55-8.
[35] Rautaharju PM, Zhang ZM. Linearly scaled, rate-invariant normal limits for QT interval. Eight decades of incorrect application of power functions. J Cardiovasc Electrophysiol 2002;13:1211-8.
[36] Wilson FN, Macleod AG, Barker PS, Johnston FD. The determination and significance of the areas of the ventricular deflections of the electrocardiogram. Am Heart J 1934;10:46-61.
[37] Faramawi MF, Sall M, Kareem MYA. The association of the metabolic syndrome with T-wave axis deviation in NHANES III. Ann Epidemiol 2008;18:702-7.
[38] Kors JA, de Bruyne MC, Hoes AW, et al. T axis as an indicator of risk of cardiac events in elderly people. Lancet 1998;352:601-5.
[39] Rautaharju PM, Nelson JC, Kronmal RA, et al. Usefulness of T-axis deviation as an independent risk indicator for incident cardiac events in older men and women free from coronary heart disease (The Cardiovascular Health Study). Am J Cardiol 2001;88:118-23.
[40] Grant RP. Clinical electrocardiography: the spatial vector approach. New York: McGraw Hill Book Company; 1957.
[41] Cushman M, Arnold AM, Psaty BM, et al. C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: the cardiovascular health study. Circulation 2005;112:25-31.
[42] Kim E, Joo S, Kim J, et al. Association between C-reactive protein and QTc interval in middle-aged men and women. Eur J Epidemiol 2006;21:653-9.
[43] Tang Q, Huang J, Qian H, et al. Antiarrhythmic effect of atorvastatin on autoimmune myocarditis is mediated by improving myocardial repolarization. Life Sci 2007;80:601-8.
[44] Tentolouris N, Liatis S, Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. Ann N Y Acad Sci 2006;1083: 129-52.
[45] Cua M, Shvilkin A, Danilo Jr P, Rosen MR. Developmental changes in modulation of cardiac repolarization by sympathetic stimulation: the role of beta- and alpha-adrenergic receptors. J Cardiovasc Electrophysiol 1997;8:865-71.
[46] Malmqvist K, Kahan T, Edner M, Bergfeldt L. Comparison of actions of irbesartan versus atenolol on cardiac repolarization in hypertensive left ventricular hypertrophy: results from the Swedish Irbesartan Left Ventricular Hypertrophy Investigation Versus Atenolol (SILVHIA). Am J Cardiol 2002;90:1107-12.
[47] Weir MR. Microalbuminuria and cardiovascular disease. Clin J Am Soc Nephrol 2007;2:581-90.