Original Research

Gender Effects on Novel Indexes of Heterogeneity of Repolarization in Patients with Stable Coronary Artery Disease

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Introduction: There appear to be important gender differences with respect to the incidence and clinical course of arrhythmias. It has been shown that women with coronary artery disease (CAD) have a lower rate of ventricular arrhythmias and sudden cardiac death (SCD) than men. The T peak-to-end (Tpe) interval and the Tpe/QT ratio represent novel markers of arrhythmic risk that possibly correspond to the spatial dispersion of ventricular repolarization. We sought to examine the effect of gender on these indexes in patients with stable CAD.

Methods: We studied 119 patients (age 62 ± 9 years, 85 men) with stable CAD. We recorded the demographic and clinical characteristics as well as electrocardiographic indexes of repolarization, such as corrected QT interval (QTc), Tpe interval, and Tpe/QT ratio. The QT interval was measured in each of the 12 leads while Tpe interval was measured in the precordial leads.

Results: There were no significant differences in the demographic and clinical characteristics between men and women. The QTc intervals were comparable between the 2 groups (389 [368-419] ms in men, 374 [348-421] ms in women; p=0.39). A significant difference was observed with respect to Tpe (80 [58-86] ms in men vs. 48 [39-65] ms in women, p=0.008) and Tpe/QT ratio (0.20 [0.17-0.23] in men vs. 0.14 [0.12-0.22] in women, p=0.034).

Conclusions: Women with CAD have a lower Tpe interval and a lower Tpe/QT ratio compared to men. The decreased dispersion of ventricular repolarization may contribute to the lower incidence of ventricular arrhythmias and SCD in women with CAD.

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Accumulating evidence suggests that there are important differences between the two genders with regard to cardiac electrophysiological mechanisms and clinical arrhythmia profile.[1-3] Coronary artery disease (CAD) is the condition most commonly associated with sudden cardiac death (SCD).[4] It has been shown that women with known CAD have a substantially lower risk for SCD than men,[5] while women with CAD and implantable cardioverter defibrillators (ICDs) are less susceptible to ventricular arrhythmias than are men.[6] The development of simple noninvasive arrhythmic risk indexes in this setting seems to be of special interest.

A well-known pathogenetic factor for malignant ventricular arrhythmias and SCD is the dispersion of repolarization, which reflects the heterogeneity rather than the total duration of repolarization.[7] The T peak-to-end (Tpe) interval and the Tpe/QT ratio represent novel electrocardiographic indexes of arrhythmic risk that possibly correspond to the spatial disper-

sion of ventricular repolarization.[7-9] In this study, we sought to investigate the impact of gender on the aforementioned electrocardiographic indexes in the setting of stable CAD.

Methods

Study population

In this observational study, consecutive patients with stable CAD who were seen in the outpatient clinic were screened. The presence of CAD was based on the patients' history and validated medical records, or official reports from specific tests for myocardial ischemia. In patients with a history of myocardial infarction the diagnosis was evident, while in patients with a history of angina a positive exercise stress test or a positive scintigraphic perfusion imaging study was required. Exclusion criteria were recent acute coronary syndrome within the past 6 months, recent percutaneous coronary intervention or cardiac surgery, any physical disability, congestive heart failure with NYHA class >II, presence of atrial fibrillation, history of channelopathies, history of syncope, presence of nonsustained ventricular tachycardia on Holter monitoring, presence of bundle branch block, QRS duration >120 ms, presence of second or third degree atrioventricular block, previous implantation of a pacemaker or a defibrillator, administration of antiarrhythmic drugs, administration of drugs that prolong the QT interval, hormone replacement therapy, thyroid dysfunction, renal failure, and electrolyte disturbances. All participants were able to perform their normal daily activities and their functional capacity was satisfactory.

Thirty-four patients were excluded according to the above criteria, while another 8 patients were excluded because their ECG tracings were inappropriate for QT and/or Tpe analysis. A total of 119 patients were finally included in the analysis (mean age 62 ± 9 years, 85 men). Two patient groups were studied, classified according to sex (men vs. women).

Study data

Demographic and clinical as well as electrocardiographic indexes of repolarization were carefully recorded. Specifically, the QT and the QTpeak intervals were measured manually on ECG recordings at a paper speed of 50 mm/s. The QT interval was assessed as the time between the first deflection of the QRS and the point of return of the T wave to the isoelectric line. The Tpe interval was calculated as QT minus QTpeak. The QT interval was measured in as many of the 12 leads as possible, while the Tpe interval was assessed in the precordial leads.[8] The Tpe and the Tpe/QT ratio were calculated using the corresponding values from each lead (Tpe/QT ratio was calculated separately for each lead). The measurements were obtained from three consecutive complexes in each lead and the resulting average value was used. In order to avoid diurnal variations, we obtained the ECG recordings during the same time interval (from 9 to 11 am). The QT interval corrected for heart rate (QTc) was calculated using Bazett's formula ($QTc=QT/RR^{1/2}$).[10] The Tpe, QTc, and Tpe/QT values reported were the maximum obtained values. All measurements were performed by one experienced investigator who was unaware of the clinical characteristics of the study participants. To identify intraobserver variability, the ECG tracings of 10 randomly selected patients were reexamined 10 days after the initial evaluation. Intraobserver variation was less than 5%.

Statistical analysis

Continuous variables are expressed as mean ± SD, or as median [25th-75th percentile] if their values were not normally distributed. Normality of distributions was evaluated using the Kolmogorov-Smirnov test. Categorical variables are presented as absolute numbers and frequencies. Comparisons of continuous variables were performed using the unpaired t-test or the non-parametric Mann-Whitney U test, as appropriate. Comparisons between categorical variables were performed using the chi-square test. A two-tailed p-value <0.05 was considered significant. All analyses were performed using SPSS software (version 13.0, SPSS Inc., Chicago IL, USA).

Results

The demographic and clinical characteristics of the female (n=34) and male patients (n=85) with CAD are presented in Table 1 and were comparable between the 2 groups. The QTc intervals were similar between the 2 groups (389 [368-419] ms in men, 374 [348-421] ms in women, p=0.73). Women had a higher resting heart rate compared to men (Table 2). Moreover, a significant difference was noted with respect to Tpe (80 [58-86] ms in men vs. 48 [39-65] ms

Table 1. Demographic and clinical characteristics of the patients.

	Men (n=85)	Women (n=34)	p
Age (years)	62.1 ± 8.7	64.1.7 ± 8.6	0.24
Previous MI	48 (56.5%)	17 (50%)	0.54
Diabetes	14 (16.5%)	6 (17.6%)	0.87
Hypertension	30 (35.3%)	14 (41.2%)	0.67
CHF	12 (14.1%)	7 (20.5%)	0.41
LVEF	43.2 ± 7.3	43.7 ± 7.2	0.91
Drug therapy:			
B-blockers	69 (81.2%)	26 (76.4%)	0.61
ACEI/ARB	46 (54.1%)	20 (58.8%)	0.69
Statins	79 (92.9%)	30 (88.2%)	0.47
Nitrates	27 (31.8%)	12 (35.2%)	0.83
Aspirin	72 (84.7%)	30 (88.2%)	0.77
Clopidogrel	57 (67.1%)	21 (61.7%)	0.67
Diltiazem	6 (7.1%)	4 (11.7%)	0.47

ACEI – angiotensin-converting enzyme inhibitors; ARB – angiotensin receptor blockers; CHF – congestive heart failure; LVEF – left ventricular ejection fraction; MI – myocardial infarction.

in women, p=0.008), and Tpe/QT ratio (0.20 [0.17-0.23] in men vs. 0.14 [0.12-0.22] in women, p=0.018) (Table 2).

Discussion

In this study we demonstrated that women with CAD have a lower Tpe interval and a lower Tpe/QT ratio compared to men. To our knowledge, no study to date has examined these novel indexes, which provide an estimate of the dispersion of ventricular repolarization in patients with stable CAD. It could therefore be speculated that the decreased heterogeneity of repolarization contributes to the lower incidence of malignant arrhythmias and SCD in women with CAD compared to men.

Tpe represents a novel index of arrhythmic risk. Regardless of the controversy as to whether it is a marker of transmural or global dispersion of repolarization,[8,9,11] it has been clearly associated with in-

Table 2. Electrocardiographic parameters. Values are presented as median [25th-75th percentile].

	Men (n=85)	Women (n=34)	p
HR (min⁻¹)	66 [57-75]	75 [60-82]	0.02
QTc (ms)	389 [368-419]	374 [348-421]	0.39
Tpe (ms)	80 [58-86]	48 [39-65]	0.008
Tpe/QT	0.20 [0.17-0.23]	0.14 [0.12-0.22]	0.034

HR – heart rate; QTc – corrected QT interval; Tpe – T peak-to-end interval.

creased risk for malignant ventricular arrhythmias in a variety of conditions, including long QT syndrome (both acquired and congenital), short QT syndrome, Brugada syndrome, acute ST-elevation myocardial infarction, and hypertrophic cardiomyopathy.[8,12-19] Most of these conditions, such as Brugada syndrome,[20] are associated with a substantial dispersion of ventricular repolarization that is a substrate of re-entry. Moreover, afterdepolarizations may trigger and perpetuate ventricular arrhythmias in this setting.[21]

Spatial dispersion of repolarization reflects the heterogeneity of repolarization, which creates voltage gradients, thus promoting life-threatening ventricular arrhythmias. Tpe represents a promising marker of total dispersion of ventricular repolarization (transmural, apicobasal, or global).[8] However, the Tpe/QT ratio appears to be a more sensitive arrhythmogenic index, since it remains constant despite changes in the heart rate (dynamic changes in Tpe and QT interval occur in a proportional and parallel fashion).[8,12,19]

Taking into account the aforementioned considerations, we focused on the measurement of the novel indexes Tpe and Tpe/QT in order to investigate the effects of gender on the dispersion of ventricular repolarization in patients with stable CAD. We did not measure the older index, QTc dispersion, since accumulated evidence has cast doubt on whether it actually represents the dispersion of ventricular repolarization.[22]

In the Framingham study the age-adjusted risk of SCD among patients with CAD was significantly lower in women, a difference not explained by the risk factor burden.[5] Moreover, Lampert et al, in a population of CAD patients treated with an ICD, demonstrated that episodes of ventricular arrhythmia, as well as the number of more severe arrhythmias (electrical storms or shock-treated episodes), were more frequent in men.[6] It has also been shown that the rate of inducibility of sustained ventricular tachycardia during an electrophysiological study (patients enrolled in the MUSTT study having CAD, left ventricular ejection fraction ≤40%, and episodes of nonsustained ventricular tachycardia) is lower in women.[23]

There seems to be a complex interaction between gender and electrophysiological parameters in various clinical settings. It has been postulated that different effects of the sex hormones on ion channels, as well as the sex differences in autonomic tone, are the main underlying mechanisms.[1-3] In healthy subjects, women have a higher heart rate at rest and a longer QTc interval.[1-3] With regard to ventricular arrhyth-

mias, women are more prone to acquired QT prolongation and drug-induced *torsades de pointes*, but less susceptible to malignant ventriclular arrhythmias in the setting of CAD and heart failure.[1-3,6,24]

In our study no significant differences in QTc interval were noticed between the 2 sexes. This finding is in line with previous studies in CAD or post-myocardial infarction patients who underwent ICD implantation.[6,23] It could be speculated that the pathological substrate, as well as the extent of myocardial disease, are more important determinants of QTc than gender.[6] Furthermore, it underscores the importance of markers that represent the heterogeneity of repolarization and not simply its duration.

With regard to gender differences in the Tpe interval and Tpe/QT ratio, there are already published data, but not from patients with structural heart disease. Smetana et al showed that healthy men have longer Tpe intervals and Tpe/QT ratios than healthy women.[25] Along the same lines, Mayuga et al, in a study of 40 healthy adults (20 women), demonstrated that men had significantly longer Tpe intervals in the precordial leads V_3-V_6.[26] However, in a larger study of 1081 healthy subjects (83% men) Tpe was similar between the 2 genders, although there was a trend for longer intervals in women.[27]

Limitations

We feel that our study adds to the evidence linking male gender and arrhythmic risk in CAD patients. However, some potential limitations are apparent. Firstly, we have to acknowledge that this was a small study. Secondly, half of our patients had a previous history of myocardial infarction (ST-elevation or non ST-elevation). Previous myocardial infarction is a well known marker of arrhythmic risk. Subgroup analyses were not feasible due to the small number of the patients. Thus, our results cannot be extrapolated to patients with CAD and no previous myocardial infarction. Thirdly, other echocardiographic parameters apart from LV ejection fraction are not available. Fourthly, we do not have angiographic data regarding the extent and severity of CAD in the 2 studied groups. In addition, we have to acknowledge that lower doses of beta-blockers may contribute to the higher resting heart rates in women. However, we do not have data on the specific dosage of these agents. Undoubtedly, heart rate may affect the Tpe interval but, as mentioned before, Tpe/QT ratio remains constant despite changes in the heart rate. Finally, since our study was an observational cross-sectional study we did not evaluate the potential dynamic change in the ECG indexes over time, or their potential prognostic role for future events.

Conclusion

In conclusion, we demonstrated that women with CAD have a lower Tpe interval and a lower Tpe/QT ratio compared to men with CAD. Thus, it could be concluded that the decreased dispersion of ventricular repolarization contributes to the lower incidence of malignant ventricular arrhythmias and SCD in women with CAD. Whether these novel ECG indexes have a prognostic role for future arrhythmic events should be investigated by further studies. Also, the clinical utility of these indexes in tailoring therapeutic interventions as well as the effects of specific drugs on these indexes remain to be elucidated.

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