Obesity and Cardiovascular disease. Results from the Netherlands Epidemiology of Obesity Study

Elffers, T.W.

CHAPTER 6

Carotid intima media thickness, pulse wave velocity and the spatial QRS-T angle

T.W. Elffers , S. Trompet, R. de Mutsert , A.C. Maan, P.W. Macfarlane,
H.J. Lamb, F.R. Rosendaal, J.W. Jukema

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ABSTRACT

Background

The spatial QRS-T angle (spQRSTa) reflects ventricular electrophysiological heterogeneity and has previously been studied as prognostic factor for cardiovascular events and mortality. To gain more insight in mechanisms involved in spQRSTa widening, we investigated associations between a) several cardiovascular risk factors; b) carotid intima-media thickness (cIMT), as a marker of subclinical atherosclerosis; c) pulse wave velocity (PWV), as a marker of arterial stiffness, and the spQRSTa. Also, we wished to investigate the ability of spQRSTa to discriminate between normal and high cIMT or high PWV.

Methods

We performed cross-sectional analyses within the Netherlands Epidemiology of Obesity (NEO) study cohort (n=6671). Participants with electrocardiographic evidence of atrial flutter, fibrillation or other arrhythmias were excluded, as well as participants with missing spQRSTa measurements. SpQRSTa was determined from 12-lead electrocardiograms, cIMT was assessed with ultrasonography and PWV was determined with velocity-encoded magnetic resonance imaging. Risk factors were assessed over three groups of spQRSTa, based on sex-specific percentiles (<p75, p75-p95, >p95). Associations of cIMT and PWV with spQRSTa were investigated with linear regression analysis. Ability of spQRSTa to discriminate between normal and high (>p75, p95 or p99) cIMT or PWV was assessed using the area under the receiver operating characteristic curve.

Results

We included 6342 participants, of whom 6278 had cIMT and 2369 had PWV measurements. Several cardiovascular risk factors were associated with a wider spQRSTa. Compared with participants with a normal glucose metabolism (mean spQRSTa: 54°), spQRSTa was wider in participants with impaired (58°) or high (66°) fasting glucose, or type II diabetes mellitus (61°). Furthermore, both greater cIMT and PWV were associated with a wider spQRSTa in crude models (difference in spQRSTa per SD cIMT: 2.7°, 95%CI: 1.6 - 3.8; per SD PWV: 2.9°, 1.3 - 4.4), but not in models adjusted for classical cardiovascular risk factors (cIMT: 0.5°, -0.7 -1.6; PWV: 0.6°, -1.3- 2.4). Addition of spQRSTa to the variables age, sex, BMI, systolic blood pressure and smoking did not improve discriminative ability for either cIMT or PWV.

Conclusions

Several cardiovascular risk factors were associated with spQRSTa, and a wider angle was found in participants with impaired fasting glucose or type II diabetes mellitus, compared with normal glucose metabolism. Furthermore, associations between greater cIMT and PWV and wider spQRSTa were present. These findings may partly explain the fact that spQRSTa, an electrocardiographically and cheaply determinable variable, is a prognostic factor for cardiovascular morbidity and mortality.

INTRODUCTION

The spatial QRS-T angle (spQRSTa) can be computed from a regular electrocardiogram (ECG) and can be used to assess overall heterogeneity of the ventricular action potential morphology. A wider spQRSTa reflects a more heterogeneous or abnormal repolarization of the ventricles, or ventricular electrophysiological heterogeneity. Several cardiovascular risk factors have been associated with a wider spQRSTa [1-7]. In individuals with type II diabetes mellitus (T2DM), the spQRSTa has been reported to be wider, and a wider spQRSTa has also been associated with poorer glycaemic control [7]. An abnormal spQRSTa is the result of changes in action potential duration in certain areas of the heart. These changes in action potential duration can be the result of, amongst others infarction, ischemia, or fibrosis and can ultimately lead to arrhythmias and cardiovascular events [8,9]. The spQRSTa has already gained recognition as a prognostic factor for cardiovascular events and mortality in several populations [3,6,10-15]. However, little is known of the associations between subclinical atherosclerosis or arterial stiffness and the spQRSTa. Since an abnormal spQRSTa could be the result of damaged areas of the myocardium, associations of subclinical atherosclerosis and arterial stiffness with the spQRSTa are plausible. In peritoneal dialysis patients, both intima-media thickness and coronary artery calcification were predictors of wider spQRSTa, even when classical cardiovascular risk factors were taken into account [16]. This study aimed to identify cardiovascular risk factors associated with a wider spQRSTa in a large study population. Furthermore, we explored associations between subclinical atherosclerosis and arterial stiffness and spQRSTa. When such associations were present, we investigated whether they remained present after adjustment for known cardiovascular risk factors. The spQRSTa can be derived from the ECG, which is widely used and easily obtainable in clinical practice, whereas carotid intima-media thickness (cIMT) and pulse wave velocity (PWV) are less easily measured. Therefore, we investigated the added value of the spQRSTa, as a marker of underlying cardiovascular pathology, in cardiovascular risk prediction by investigating the ability of spQRSTa to discriminate between normal and high cIMT or high PWV.

METHODS

Study design and population

The Netherlands Epidemiology of Obesity (NEO) study is a prospective, population-based cohort study with 6671 participants included between 2008 and 2012. Men and women aged between 45 and 65 years living in the area of greater Leiden (the Netherlands) and with a BMI ≥27 kg/m^2 were eligible to participate. In addition, all inhabitants aged between 45 and 65 years from one municipality (Leiderdorp) were invited to join irrespective of their BMI, allowing for a reference distribution of BMI. Participants completed a questionnaire on demographic and clinical information prior to the visit to the NEO study center. Participants were invited to a baseline visit at the NEO study centre after an overnight fast. Participants with ECG evidence of atrial, junctional or ventricular premature beats, atrial flutter or fibrillation, and other arrhythmias were excluded (n=237). Also participants with missing spQRSTa values were excluded (n=92). More information on the study design and population has been published elsewhere [17]. The Medical Ethics Committee of the Leiden University

Medical Center (LUMC) approved the design of the study. All participants gave their written informed consent.

Ethnicity was self-reported in eight categories on the questionnaire and then grouped into white and other. Education level was grouped as low (none, primary school or lower vocational education) and high education (intermediate secondary education, middle-level vocational education, higher secondary education, higher professional education, university or other). Tobacco smoking was categorized into current, former, or never smokers. Participants were asked to bring all medication they were currently using to the study visit. Height and weight were measured without shoes and 1 kg was subtracted from the weight to correct for the weight of clothing. BMI was calculated by dividing the weight in kilograms by the height in meters squared. Brachial blood pressure was measured in a seated position on the right arm using a validated automatic oscillometric device (OMRON, Model M10-IT, Omron Health Care Inc, IL, USA). Blood pressure was measured three times with 5 minutes rest between consecutive measurements. The mean systolic and diastolic blood pressure was calculated. Blood samples were drawn after an overnight fast of 10 hours. Fasting glucose, triglyceride, total cholesterol and high-density lipoprotein cholesterol concentrations were measured with the enzymatic colorimetric method (Roche Modular Analytics P800, Roche Diagnostics Mannheim, Germany). Low-density lipoprotein cholesterol concentrations were calculated using the Friedewald equation.

Categories of glucose metabolism

We defined four categories of glucose metabolism. I): Normal glucose metabolism, defined as fasting plasma glucose concentration <6.1 mmol/l and no self-reported T2DM or medication use. II): Impaired fasting glucose, defined as fasting plasma glucose concentration 6.1-7.0 mmol/l and no self-reported T2DM or medication use. III): High fasting plasma glucose, defined as fasting plasma glucose concentration ≥7.0 mmol/l and no self-reported T2DM or medication use. IV): T2DM, defined as self-reported T2DM or medication use for diabetes mellitus.

Electrocardiography

A 12-lead resting ECG was obtained using a Mortara Eli-350 electrocardiograph (Mortara Instrument Inc., Milwaukee, WI, USA) after a resting period of at least 10 minutes. ECGs were stored in a MegaCare ECG management system (Dräger, formerly Siemens). The raw data were extracted and transferred to the University of Glasgow ECG core lab where ECGs were automatically processed and Minnesota codes were assigned using the University of Glasgow ECG analysis program [18]. Moreover, standard 10-second ECGs were stored in an 8-lead (I, II, V1-V6), 5000 sample comma-separated-value file. The Kors matrix was used to calculate vector cardiograms from the eight independent ECG leads [19]. ECGs and vector cardiograms were analyzed using the automatic MATLAB-based (The MathWorks, Natick, MA) program BEATS and the semiautomatic program LEADS [20,21]. BEATS was used to detect the timings of all QRS complexes and calculated R-R intervals (ms). The QRS and T integral vectors were approximated by calculating the numerical sum of x-y-z deflections (amplitudes of positive deflections are added and those of negative deflections subtracted). The spatial

QRS-T angle was defined as the angle (°) between the integral QRS vector and the integral T vector. In a subgroup (n=962), spQRSTa was assessed by two researchers, with an intraclass correlation coefficient (95% CI) of 0.99 (0.98 - 0.99).

Measures of atherosclerosis and arterial stiffness

Carotid intima-media thickness was assessed by ultrasonography of the far wall of the left and right common carotid arteries along a 15 mm long section 10 mm proximal to the bifurcation in recumbent position. A 7.5–10 MHz linear-array transducer (Art.Lab version 2.1, Esaote, Maastricht, The Netherlands) in B-mode setting was used to visualize the distal common carotid arteries and a wall track system was used to detect the lumen-intima and media-adventitia boundaries. The cIMT was measured in three predefined angles per side (180, 135 and 90 degrees for the right common carotid artery and 180, 225 and 270 degrees for the left common carotid artery) during six heartbeats. Mean cIMT was calculated for each individual by averaging all 36 cIMT measurements within each individual.

PWV of the aorta was assessed in a random group of 30% of all NEO study participants without contraindications for magnetic resonance imaging (most notably metallic devices, claustrophobia, or a body circumference of more than 1.70 m). PWV was determined on a 1.5 Tesla (T) whole-body MRI scanner (Gyroscan ACS/NT15, Philips, Best, the Netherlands) using multi-slice, two-one-directional in-plane velocity-encoded MRI. PWV was calculated by the ratio of the distance along the aortic center line (Δx) and the transit-time of the propagating systolic pulse wave between two measurement sites (Δt) (proximal aorta and distal aorta summed). The heart was imaged in short-axis view using an ECG-triggered balanced turbo-field-echo sequence. Data were analysed using in-house software (MASS and FLOW; Leiden University Medical Center, Leiden, the Netherlands).

Statistical analyses

In the NEO study, participants with a BMI of 27 kg/m^2 or higher were oversampled. To correctly represent baseline associations in the general population [22], adjustments for the oversampling of participants with a BMI ≥ 27 kg/m^2 were made. This was done by weighting all participants towards the BMI distribution of participants from the Leiderdorp municipality [23], whose BMI distribution was similar to the BMI distribution of the general Dutch population [24]. All results are based on weighted analysis. Consequently, the results are considered to apply to a population-based study without oversampling of participants with a BMI ≥ 27 kg/m^2.

The baseline characteristics of study participants were presented as mean (SD) or percentage in Table 1. Since one of the study aims was to describe cardiovascular risk factors associated with a wider spQRSTa, characteristics of the participant are also presented stratified by three groups of spQRSTa in Table 1. The three groups of spQRSTa were based on sex-specific percentiles, namely <75th percentile (<p75, representing a normal spQRSTa), 75-95th percentile (p75-p95 representing a borderline abnormal spQRSTa) and >95th percentile (>p95 representing an abnormal spQRSTa). For men, <p75 corresponded with spQRSTa <76.0° and >p95 corresponded with spQRSTa > 119.8°. For women, <p75 corresponded with spQRSTa

<63.9° and >p95 corresponded with spQRSTa > 103.4°. Mean spQRSTa was determined for the four glucose metabolism categories as described above. Then, associations between cIMT and PWV and spQRSTa were investigated in the whole study population and in men and in women separately, with weighted linear regression analyses, and were expressed as difference (95% CI) in spQRSTa (°) per standard deviation (SD) increase in cIMT (mm) or PWV (m/s). Furthermore, the ability of spQRSTa to discriminate between normal and high cIMT or PWV was assessed using the area under the receiver operating characteristic curve (AUC). To define normal/high cIMT and PWV, both liberal and more conservative cut-offs were used, namely p75, p95 and p99. AUC was also assessed for a combination of simple risk factors, namely age, sex, BMI, systolic blood pressure and smoking, and it was investigated whether addition of the spQRSTa to these variables led to improvement of the AUC. Data were analysed using STATA (Statacorp, College Station, Texas, USA) version 14.

RESULTS

Participants with ECG evidence of atrial, junctional or ventricular premature beats, atrial flutter or fibrillation, and other arrhythmias were excluded (n=237). Also 92 participants with missing spQRSTa values were excluded. The baseline characteristics of the 6342 included participants are presented in Table 1, over three groups of the spQRSTa (<p75, p75-p95 and >p95). SpQRSTa increased with increasing age, HbA1c, use of glucose lowering medication, systolic and diastolic blood pressure, use of antihypertensive therapy and use of lipid lowering medication.

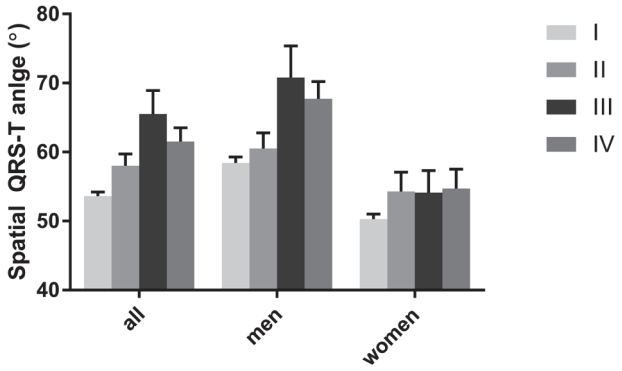

Figure 1. Mean spatial QRS-T angle over the different glucose metabolism categories

All results are based on analyses weighted towards the body mass index distribution of the general population. Data are presented as mean(se)
Glucose metabolism categories I: no diabetes mellitus and fasting glucose<6.1 mmol/l, II: fasting glucose 6.1-7.0 mmol/l, III: fasting glucose >7.0 mmol/l and no diabetes mellitus or use of glucose lowering medication, IV: type II diabetes mellitus or use of glucose lowering medication
All: category I, n=4908; II, n=727; III, n=206; IV, n=423. Men: I, n=2171; II, n=420; III, n=121; IV, n=227. Women : I, n=2737; II, n=307; III, n=85; IV, n=196

Table 1. Baseline characteristics of 6342 participants aged 45-65 years from the Netherlands Epidemiology of Obesity study population

		Spatial QRS-T angle		
	All, 100%	<p75(1)	p75-p95 (2)	>p95 (3)
Age, years	56 (6)	55 (6)	56 (6)	58 (6)
Sex, men, %	43	43	43	44
Ethnicity, white, %	95	95	93	97
Education, high, %	46	46	46	40
Current smoking, %	16	15	18	17
BMI, kg/m2	26.3 (4.4)	26.2 (4.2)	26.6 (4.9)	27.2 (5.7)
Fasting glucose, mmol/l	5.5 (1.0)	5.4 (0.9)	5.5 (1.1)	5.7(1.2)
HbA1c, %	5.4 (0.5)	5.3 (0.4)	5.4 (0.6)	5.5 (0.6)
Glucose-lowering medication, %	3	2	4	5
Systolic blood pressure, mmHg	130.2 (17.0)	129.1 (16.1)	132.5 (19.2)	136.5 (19.3)
Diastolic blood pressure, mmHg	83.2 (10.3)	82.6 (9.9)	84.8 (11.3)	85.3 (10.7)
Use of antihypertensive therapy, %	23	21	29	36
LDL-cholesterol, mmol/l	3.5 (1.0)	3.6 (0.9)	3.5 (1.0)	3.5 (1.1)
Triglycerides, mmol/l	1.2 (0.9)	1.2 (0.8)	1.3 (0.9)	1.3 (0.8)
Use of lipid lowering medication, %	11	9	13	18

BMI, body mass index; HbA1c, glycated haemoglobin; LDL-cholesterol, low-density lipoprotein cholesterol; p, percentile. Data are presented as mean (SD), percentages or difference (95% confidence interval)
Results are based on analyses weighted towards the body mass index distribution of the general population <p75, n=4570; p75-p95, n=1401; >p95, n=371

As shown in Figure 1, the mean spQRSTa increased across glucose metabolism categories I, II and III in the total study population (from 54° to 58° to 66°), in men (from 58° to 60° to 71°), and in a less pronounced way in women (from 50° to 54° to 54°). Mean (SD) spQRSTa in glucose metabolism category IV was 61° (34) in all, 68° (42) in men and 55° (42) in women.

Measurements of cIMT and PWV were available in 6278 and 2369 participants, respectively. As shown in Figure 2, in the total group, greater cIMT was associated with wider spQRSTa in the crude model 1 (difference in spQRSTa per SD increase in cIMT: 2.7°; 95% CI: 1.6 -- 3.8) and in the sex and age-adjusted model 2 (1.1°; 95% CI: 0.0 - 2.3), but, as was expected, not in model 3 adjusted for classical cardiovascular risk factors (0.5°; 95% CI: -0.7- 1.6). In men, associations were somewhat stronger than in women, e.g., in model 1 in men the difference in spQRSTa per SD increase in cIMT was 3.0° (95%CI: 1.3- 4.8) and in women this was 1.2° (95%CI: -0.2 - 2.6). Also, in men no association was present between cIMT and spQRSTa in model 3. Furthermore, higher PWV was associated with a wider spQRSTa in the total group in model 1 (difference in spQRSTa per SD increase in PWV: 2.9°; 95% CI: 1.4 - 4.4) and in

model 2 (2.1°; 95% CI: 0.3 - 3.9), but not in model 3 (0.6°; 95% CI: -1.3 - 2.4). When the study group was stratified by sex, we found in men that PWV was associated with the spQRSTa in model 3 (2.6°; 95% CI: 0.0 - 5.2), whereas this association was not present in women (-0.7°; 95% CI: -3.4 - 1.9).

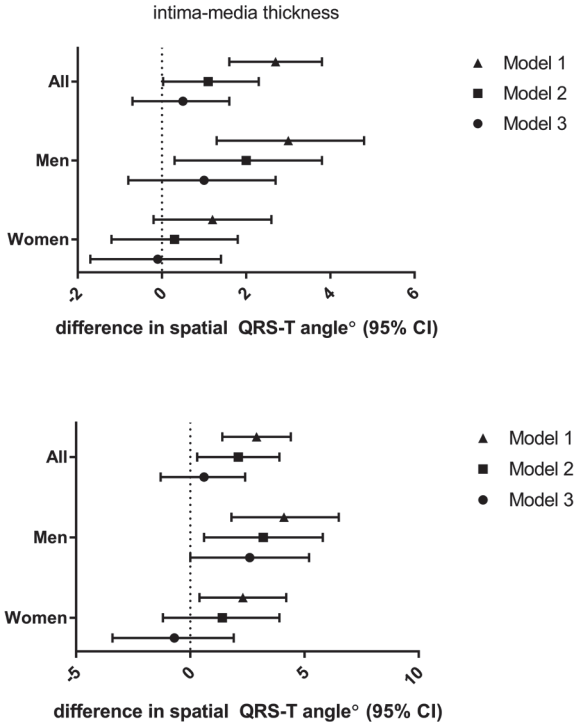

Figure 2. Associations of carotid intima-media thickness and pulse wave velocity with the spatial QRS-T angle in all, in men and in women
Results are presented as difference (95% confidence interval) per standard deviation increase in carotid intima-media thickness or pulse wave velocity. All results are based on analyses weighted towards the body mass index distribution of the general population.
Model 1: crude, model 2: adjusted for age (and sex), model 3: adjusted for age, (sex,) systolic blood pressure and antihypertensive medication use, body mass index, fasting plasma glucose and use of glucose-lowering medication, low-density lipoprotein cholesterol, triglycerides and lipid-lowering medication

SpQRSTa showed poor discriminative ability for cIMT >p75 (AUC: 0.56; 95%CI: 0.55 – 0.58), cIMT >p95 (0.56; 0.53 – 0.58) and cIMT >p99 (0.56; 0.53 – 0.58) as well as for PWV >p75 (0.52; 0.50 – 0.53), PWV >p95 (0.50; 0.49 – 0.52) and PWV >p99 (0.50; 0.49 – 0.52). As presented in Table 2, addition of spQRSTa to the variables age, sex, BMI, systolic blood pressure and smoking did not improve discriminative ability for either cIMT or PWV.

Table 2. Discriminative ability of spQRSTa and risk factors for normal/high cIMT or PWV

	AUC (95% confidence interval)					
	cIMT			PWV		
	p75	p95	p99	p75	p95	p99
spQRSTa	0.56 (0.55 - 0.58)	0.56 (0.53 – 0.58)	0.56 (0.53 – 0.58)	0.52 (0.50 – 0.53)	0.50 (0.49 – 0.52)	0.50 (0.49 – 0.52)
Age, sex, BMI, systolic blood pressure, smoking	0.68 (0.66 – 0.69)	0.67 (0.65 – 0.70)	0.61 (0.56 – 0.66)	0.63 (0.61 – 0.64)	0.57 (0.56 – 0.59)	0.57 (0.56 – 0.59)
Age, sex, BMI, systolic blood pressure, smoking & spQRSTa	0.68 (0.66 – 0.69)	0.67 (0.65 – 0.70)	0.61 (0.56 – 0.66)	0.63 (0.61 – 0.64)	0.57 (0.56 – 0.59)	0.57 (0.56 – 0.59)

Results are presented as area under the receiver operating characteristic curve with 95% confidence interval. Results are based on analyses weighted towards the body mass index distribution of the general population

AUC, area under the curve; BMI, Body Mass Index; p, percentile; cIMT, carotid intima media thickness; PWV, pulse wave velocity; spQRSTa, spatial QRS-T angle cIMT: p75, 0.7 mm; p95, 0.8 mm; p99, 0.9 mm. PWV: p75, 7.2 m/s; p95, 9.1 m/s; p99, 10.3 m/s

DISCUSSION

In this large cohort study with over 6000 ECGs we found the cardiovascular risk factors age, BMI and blood pressure to be associated with a wider spQRSTa. In addition, spQRSTa was wider in participants with impaired fasting glucose, high fasting glucose or T2DM, compared with participants with a normal glucose metabolism. Furthermore, we found associations of greater cIMT and PWV with a wider spQRSTa. As expected, after adjustment for classical cardiovascular risk factors, associations attenuated. Furthermore, adding spQRSTa on top of age, sex, BMI, systolic blood pressure and smoking was not useful in a model used for discriminating between normal and high cIMT or PWV.

Several studies have previously found cardiovascular risk factors, including also blood pressure, LDL-cholesterol, triglycerides, metabolic syndrome score, T2DM and increased fasting plasma glucose to be associated with a wider spQRSTa [1-7]. Moreover, it has been reported that the spQRSTa is on average wider in men then in women, which is confirmed here [25-27]. We also demonstrated a wider spQRSTa in participants with fasting plasma glucose of 6.1-7.0 mmol/l and an even wider spQRSTa in participants with fasting plasma glucose >7.0 mmol/l. In participants with T2DM (history or medication use), the spQRSTa is somewhat narrower compared with participants with fasting plasma glucose >7.0mmol/l, which is most likely due to the high percentage of glucose-lowering medication use in the T2DM subgroup (74%). One possible explanation for the wider spQRSTa found in diabetic individuals, and also already in individuals with impaired fasting glucose, involves the increased sympathetic nervous system activity that can be seen in these individuals and could contribute to the changes in myocardial repolarization [28]. Furthermore, T2DM and pre-diabetes have been associated with premature atherosclerosis, peripheral artery disease and stiffening of the blood vessels. Several mechanisms are involved in diabetic cardiomyopathy, among which interstitial fibrosis, hypertrophy, cardiac autonomic neuropathy, changes in myocardial substrate and energy metabolism, myocardial damage and changes (functional or structural) of the small coronary vessels [29,30].

Several studies have investigated adverse outcomes that are associated with, or can be predicted by a wider or abnormal spQRSTa. After adjustment for several classical cardiovascular risk factors, abnormal or wider spQRSTa was associated with cardiovascular events in women [14], with coronary heart disease events and congestive heart failure in postmenopausal women [11,12], with all-cause mortality (especially sudden cardiac death) in dialysis patients [10], with increased risk of cardiac mortality but not non-fatal cardiac events in an older general population [13], and with all-cause and cardiovascular mortality in US adults without known heart disease [3]. In a large population-based study, abnormal spQRSTa was associated with increased risk of coronary heart disease and total mortality in women, but not in men [15].

Furthermore, in a large clinical population, abnormal spQRSTa was associated with cardiovascular mortality, after adjustment for age and sex, but not for other classical cardiovascular risk factors [6]. Associations of atherosclerosis and arterial stiffness with spQRSTa, which are observed in this present study, have to our knowledge not been demonstrated before. As expected, the observed associations between cIMT and PWV and

a wider spQRSTa in this study attenuated after adjustment for classical cardiovascular risk factors. It is plausible that these risk factors are common causes of both increased cIMT or PWV and a wider spQRSTa, leading to this attenuation of the observed associations after adjustment for these risk factors. Furthermore, the spQRSTa did not show potential added value when added to some simple cardiovascular risk factors in a model used for discriminating between participants with normal and high cIMT or PWV. Although spQRSTa was not able to discriminate between participants with normal or high cIMT or PWV, spQRSTa was shown to be useful in cardiovascular risk stratification in several studies, as described above.

Strenghts and limitations

A strength of this study is the large number of participants with measurement of the spQRSTa in combination with cIMT (n=6278) and PWV (n=2369) that was included. A limitation is that this study consists of cross-sectional analyses, which hampers conclusions on causal mechanisms.

Conclusion

Cardiovascular risk factors are associated with a wider spQRSTa. Furthermore, greater cIMT and PWV were associated with a wider spQRSTa. The spQRSTa was not found to be useful in a model used for discriminating between participants with normal and high cIMT or PWV.

The spQRSTa can be computed from the electrocardiogram, a low-cost and widely used medical tool, especially in the field of cardiology. Several studies have previously found the spQRSTa to be a prognostic factor for cardiovascular disease and mortality [3,6,10-15]. Other mechanisms that could contribute to widening of the spQRSTa should be further elucidated to examine the role of the spQRSTa as marker and predictor of cardiovascular disease.

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REFERENCES

1. de Torbal A, Kors JA, van Herpen G, Meij S, Nelwan S, Simoons ML, et al. The electrical T-axis and the spatial QRS-T angle are independent predictors of long-term mortality in patients admitted with acute ischemic chest pain. Cardiology. 2004;101:199-207.
2. Voulgari C, Tentolouris N, Papadogiannis D, Moyssakis I, Perrea D, Kyriaki D, et al. Increased left ventricular arrhythmogenicity in metabolic syndrome and relationship with myocardial performance, risk factors for atherosclerosis, and low-grade inflammation. Metabolism. 2010;59:159-65.
3. Whang W, Shimbo D, Levitan EB, Newman JD, Rautaharju PM, Davidson KW, et al. Relations between QRS|T angle, cardiac risk factors, and mortality in the third National Health and Nutrition Examination Survey (NHANES III). Am J Cardiol. 2012;109:981-7.
4. Voulgari C, Moyssakis I, Perrea D, Kyriaki D, Katsilambros N, Tentolouris N. The association between the spatial QRS-T angle with cardiac autonomic neuropathy in subjects with Type 2 diabetes mellitus. Diabet Med. 2010;27:1420-9.
5. Atsma F, Bartelink ML, van der Schouw YT, Kors JA, Grobbee DE. Elevated blood pressure and electrocardiographic frontal T axis and spatial QRS-T angle changes in postmenopausal women. J Electrocardiol. 2008;41:360-4.
6. 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.
7. Voulgari C, Tentolouris N, Moyssakis I, Dilaveris P, Gialafos E, Papadogiannis D, et al. Spatial QRS-T angle: association with diabetes and left ventricular performance. Eur J Clin Invest. 2006;36:608-13.
8. Hurst JW. Thoughts about the ventricular gradient and its current clinical use (part II of II). Clin Cardiol. 2005;28:219-24.
9. Macfarlane PW, Edenbrandt L, Pahlm O. 12-Lead vectorcardiography. Butterworth Heinemann. 1995.
10. de Bie MK, Koopman MG, Gaasbeek A, Dekker FW, Maan AC, Swenne CA, et al. Incremental prognostic value of an abnormal baseline spatial QRS-T angle in chronic dialysis patients. Europace. 2013;15:290-6.
11. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic predictors of incident congestive heart failure and all-cause mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113:481-9.
12. Rautaharju PM, Kooperberg C, Larson JC, LaCroix A. Electrocardiographic abnormalities that predict coronary heart disease events and mortality in postmenopausal women: the Women's Health Initiative. Circulation. 2006;113:473-80.
13. Kardys I, Kors JA, van der Meer IM, Hofman A, van der Kuip DA, Witteman JC. Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J. 2003;24:1357-64.
14. Triola B, Olson MB, Reis SE, Rautaharju P, Merz CN, Kelsey SF, et al. Electrocardiographic predictors of cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. J Am Coll Cardiol. 2005;46:51-6.
15. Zhang ZM, Prineas RJ, Case D, Soliman EZ, Rautaharju PM, Group AR. Comparison of the prognostic significance of the electrocardiographic QRS/T angles in predicting incident coronary heart disease and total mortality (from the atherosclerosis risk in communities study). Am J Cardiol. 2007;100:844-9.

16. Jaroszynski A, Czekajska-Chechab E, Drelich-Zbroja A, Zapolski T, Ksiazek A. Spatial QRS-T angle in peritoneal dialysis patients: association with carotid artery atherosclerosis, coronary artery calcification and troponin T. Nephrol Dial Transplant. 2009;24:1003-8.
17. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. Eur J Epidemiol. 2013;28:513-23.
18. Macfarlane PW, Devine B, Clark E. The University of Glasgow (Uni-G) ECG Analysis Program. Comput Cardiol. 2005:451–4.
19. Kors JA, van Herpen G, Sittig AC, van Bemmel JH. Reconstruction of the Frank vectorcardiogram from standard electrocardiographic leads: diagnostic comparison of different methods. Eur Heart J. 1990;11:1083-92.
20. Man SC, Maan AC, van der Wall EE, Schalij MJ, Swenne CA. Beats: an interactive research oriented ECG analysis system. Comput Cardiol. 2010;37:1007-10.
21. Draisma HHM, Swenne CA, van der vooren H, Maan AC, Hooft van Huysduynen B, van der Wall EE, et al. LEADS: an interactive research oriented ECG/VCG analysis system. Comput Cardiol. 2005;32:515-8.
22. Korn EL, Graubard BI. Epidemiologic studies utilizing surveys: accounting for the sampling design. Am J Public Health. 1991;81:1166-73.
23. Lumley T. Analysis of complex survey samples. J Stat Softw. 2004; 9:1-19.
24. Ministerie van VWS. Hoeveel mensen hebben overgewicht? NdMG. 2014.
25. Scherptong RW, Henkens IR, Man SC, Le Cessie S, Vliegen HW, Draisma HH, et al. Normal limits of the spatial QRS-T angle and ventricular gradient in 12-lead electrocardiograms of young adults: dependence on sex and heart rate. J Electrocardiol. 2008;41:648-55.
26. Rautaharju PM, Zhou SH, Gregg RE, Startt-Selvester RH. Heart rate, gender differences, and presence versus absence of diagnostic ST elevation as determinants of spatial QRS|T angle widening in acute coronary syndrome. Am J Cardiol. 2011;107:1744-50.
27. Smetana P, Batchvarov VN, Hnatkova K, Camm AJ, Malik M. Sex differences in repolarization homogeneity and its circadian pattern. Am J Physiol Heart Physiol. 2002;282:H1889-97.
28. Scherrer U, Sartori C. Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. Circulation. 1997;96:4104-13.
29. Boudina S, Abel ED. Diabetic cardiomyopathy, causes and effects. Rev Endocr Metab Disord. 2010;11:31-9.
30. Aneja A, Tang WH, Bansilal S, Garcia MJ, Farkouh ME. Diabetic cardiomyopathy: insights into pathogenesis, diagnostic challenges, and therapeutic options. Am J Med. 2008;121:748-57.