
Universiteit
Leiden
The Netherlands

Role of cardiac biomarkers in cognitive impairment and functional decline

Mahin Rad, S.

Citation
Mahin Rad, S. (2018, November 29). *Role of cardiac biomarkers in cognitive impairment and functional decline*. Retrieved from https://hdl.handle.net/1887/67289

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/67289

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/67289 holds various files of this Leiden University dissertation.

Author: Mahin Rad, S.
Title: Role of cardiac biomarkers in cognitive impairment and functional decline
Issue Date: 2018-11-29

CHAPTER 5

SPATIAL QRS-T ANGLE AND COGNITIVE IMPAIRMENT

Manuscript based on this chapter is submitted as:

Mahinrad, S., Ferguson, I., Macfarlane, P.W., Clark, E.N., Stott, D.J., Ford, I., Mooijaart, S.P., Trompet, S., van Heemst, D., Jukema, J.W. & Sabayan, B. Spatial QRS-T angle and cognitive function in old age.

Abstract

An abnormally wide spatial QRS-T angle on an ECG is a marker of heterogeneity in electrical activity of cardiac ventricles and is linked with cardiovascular events. Growing evidence suggests that cardiac dysfunction might signal future risk of cognitive impairment. In this study, we investigated whether spatial QRS-T angle associates with future cognitive decline in older subjects at high cardiovascular risk. We included 4172 men and women (mean age 75.2 ± 3.3 years) free of cardiac arrhythmias from PROSPER cohort. Spatial QRS-T angle was calculated from baseline 12-lead ECGs using a matrix transformation method. Different domains of cognitive function including reaction time, processing speed, immediate memory and delayed memory were measured at baseline and repeatedly during a mean follow-up time of 3.2 years. Using linear mixed models, we calculated annual changes of cognitive scores in sex-specific thirds of spatial QRS-T angle. Our results showed that participants with wider spatial QRS-T angle had a steeper decline in reaction time (β = 0.0004, p = 0.055), processing speed (β = -0.0106, p = 0.004), immediate memory (β = -0.0049, p = 0.001) and delayed memory (β = -0.0055, p = 0.013). All associations were independent of arrhythmias, cardiovascular risk factors, comorbidities, medication use, cardiovascular events and other ECG abnormalities including QRS duration, QTc interval, T wave abnormalities and left ventricular hypertrophy. In conclusion, abnormal cardiac electrical activity characterized by wide spatial QRS-T angle associates with accelerated cognitive decline independent of conventional cardiovascular factors. These findings suggest a link between a non-traditional ECG measure of pre-clinical cardiac pathology and future cognitive decline.

Introduction

The electrical activity of the heart is generated by waves of myocardial depolarization and repolarization leading to a harmonized cardiac muscle contraction and relaxation[1]. Alterations in the sequence of ventricular depolarization and repolarization are not only associated with cardiovascular events[2, 3] but may also precede cerebrovascular events and increase risk of stroke[4]. Apart from overt cerebrovascular accidents, ventricular depolarization inhomogeneity has shown to be closely related to a higher load of cerebral small vessel disease[5]. In the last couple of years, mounting evidence has supported a major contribution of small and large vessel disease in development and progression of cognitive impairment[6, 7]. Indeed cardiac and cerebrovascular dysfunction is a common phenomenon in patients with cognitive deficit[6]. Hence, it has been suggested that early changes in cardiac function might signal future risk of cognitive impairment and such markers can assist in identification of high-risk populations[8].

The spatial QRS-T angle is a non-invasive subclinical marker of electrical activity of cardiac ventricles[9]. It quantifies the deviation in the direction of cardiac ventricular depolarization and repolarization in a three-dimensional space[10]. A wide spatial QRS-T angle reflects the pathophysiological changes in the ionic channels affecting the repolarization profiles, or structural abnormalities affecting the sequence of depolarization[11]. A wider spatial QRS-T angle has been associated with incident coronary heart disease[2], all-cause and cardiovascular mortality[12] and ischemic stroke[13]. Since a wide spatial QRS-T angle is a marker of greater inhomogeneity of electrical activity of cardiac ventricles, we aimed to study the independent link between spatial QRS-T angle and cognitive decline in older subjects at high risk of cardiovascular disease.

Methods

Study design and participants

The study population consists of the participants from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). PROSPER was a multicenter randomized clinical trial which aimed to assess the effect of pravastatin in prevention of vascular events in older subjects with pre-existing cardiovascular risk factors or diseases[14]. In brief, a total of 5804 men and women at high cardiovascular risk (defined as being due to smoking, hypertension or diabetes mellitus) or with a history of vascular disease (defined as stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction [MI] and vascular surgery), aged 70 to 82 years, were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. The mean follow-up time was 3.2 years. The study was approved by the institutional ethics committees of the three collaborating centers and all participants gave written informed consent. The original PROSPER study was approved by the Medical Ethics Committees of the three collaborating centres and complied with the Declaration of Helsinki. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

From the baseline electrocardiogram (ECG) recordings, we excluded participants with missing spatial QRS-T angle measurements and those with evidence of atrial fibrillation, atrial flutter, ectopic atrial rhythms, supraventricular arrhythmias, junctional rhythms, intermittent conduction defect and other arrhythmias (n= 520). Furthermore, we included only participants with at least two cognitive measurements: the baseline and one follow-up measurement. Hence, a total of 4172 participants were included for analysis. Compared to the excluded participants, the included participants were younger and had a lower prevalence of cardiovascular risk factors and co-morbidities (Supplementary Table 1). We included participants from both treatment groups since it has been shown that treatment with pravastatin does not affect cognitive function[15].

Spatial QRS-T angle measurement

Standard 12-lead ECGs were recorded using a Burdick Eclipse 850i electrocardiograph in the resting supine position. All the ECGs were recorded in the morning of the first enrolment visit (at baseline) before initiation of statin treatment. A fully computerized automated method was used to ensure reproducibility of the measurements. The digital ECG recordings were transferred to the University of Glasgow ECG Core Lab in Scotland and interpreted using the University of Glasgow (Uni-G) ECG analysis program software[16]. The software provided an interpretation of the ECG recordings, Minnesota Codes, and numerous measurements including the QRS complex and T waves[16-18]. To calculate the spatial QRS-T angle, we first reconstructed the Frank XYZ vectocardiographic leads from the 12-lead ECG recordings using the inverse Dower method[19]. We then measured the spatial QRS-T angle as the angle between the maximum QRS vector and the maximum T vector. The maximum QRS and T vectors were defined as the point of maximum magnitude of the spatial QRS vector and the spatial T vector within the 3-dimensional QRS loop and T loop, respectively[9]. Since the cut-point for spatial QRS-T angle has varied among previous studies[9], we first classified the spatial QRS-angle based on the sex-specific tertiles in three groups of low (0°-38° for women and 0°-45° for men), middle (39°-75° for women and 46°- 84° for men) and high (76°-180° for women and 85°-180° for men). Secondly, based on a cut-point used in previous studies for older subjects[12, 20], we classified the spatial QRS-T angle levels in three groups of normal (0° to 104°), borderline (105° to 134°), and abnormal (135° to 180°). The QT interval was calculated from the onset of QRS complex to the T offset and was corrected for heart rate (QTc interval) using the Hodges formula[21]. T wave abnormalities were defined as Minnesota Codes 5-1, 5-2 and 5-3[17]. Left ventricular hypertrophy (LVH) was defined by using the Sokolow-Lyon voltage criteria[22].

Cognitive function assessment

In PROSPER, the mini-mental state examination test (MMSE) was used at baseline for screening purposes and participants with poor cognitive function (MMSE score <24) were

excluded from enrolment in the study[23]. Four cognitive tests were used to assess different domains of cognitive function. The cognitive tests included the Stroop test, the letter-digit coding test (LDCT), immediate picture-word learning test (PLTi) and delayed picture-word learning test (PLTd). A detailed description of the cognitive assessments has been published elsewhere[23]. In brief, the Stroop test measures the selective attention and reaction time. The outcome variable is the total number of seconds to complete the test; a higher score indicates worse performance. The LDCT measures the processing speed and the outcome variable is the total number of correct digits entered in 60 seconds; a higher score indicates better performance. The PLTi and PLTd tests measure immediate and delayed memory, respectively. The outcome variables are the accumulated number of correctly recalled pictures for the immediate and delayed trials; a higher score indicates better performance. Cognitive function was assessed at baseline, after 9, 18, 30 months and at the end of the study which varied between 36 and 48 months. During each visit, different versions of cognitive tests were used to avoid learning effects[23].

Statistical analysis

Differences in baseline characteristics of participants in the three groups of spatial QRS-T angle were compared using the ANOVA test for continuous variables and Chi-squared test for categorical variables. Linear regression models were used to test the cross-sectional association between spatial QRS-T angle and cognitive function at baseline. The dependent variable was the score of each cognitive test at baseline. Using analysis of covariance, we calculated the adjusted mean score of cognitive tests in sex-specific thirds of spatial QRS-T angle. The Stroop test scores were log-transformed because they were not normally distributed. Linear mixed models (random regression model with random intercepts and slopes) were used to test the longitudinal association between spatial QRS-T angle and changes in cognitive scores over time. The models incorporated spatial QRS-T angle, time (in years) and the interaction term between time and spatial QRS-T angle. Subjects were defined as random factors and all other variables were defined as fixed factors. To assess the mean annual change of cognitive scores in thirds of spatial QRS-T angle, we computed the

estimates of interaction between time and sex-specific thirds of spatial QRS-T angle using linear mixed models. To calculate the estimate of change in cognitive scores per 10 degree increase in spatial QRS-T angle, we divided the spatial QRS-T angle levels by ten. All probability values were calculated using continuous values of spatial QRS-T angle. Both cross-sectional and longitudinal analyses were first adjusted for age, sex, education (age at which the participant left school), country of enrolment and version of cognitive tests where appropriate (model 1). In the next step, adjustment for cardiovascular diseases, cardiovascular risk factors and medication use (diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors [ACEI] and angiotensin receptors blockers [ARB]) were added (model 2). In longitudinal analysis, further adjustment for statin treatment groups was added in model 2. To test the effect of other ECG parameters on the longitudinal associations, adjustments for T wave abnormalities, QTc interval, QRS duration and LVH were added in model 3.

To test the effect of cardiovascular events on the longitudinal associations, a series of sensitivity analyses were performed in which we stratified for the participants according to who did and who did not develop incident atrial fibrillation, heart failure hospitalization, coronary events, fatal or non-fatal stroke or transient ischemic attack (TIA) and non-fatal MI during follow-up. To test whether the difference between participants who did and who did not develop cardiovascular events is significant, p for interactions were calculated using linear mixed models. Finally, in a series of additional analyses, we tested the effect of baseline cardiovascular co-morbidities and use of anti-arrhythmic medications on longitudinal associations by excluding participants who had history of hypertension, history of diabetes mellitus, history of MI, history of stroke or TIA, and participants using anti-arrhythmic medications.

Results

Of the 4172 participants in this study, the mean age was 75.2 ± 3.3 years and 1998 (47.9%) participants were male. A total of 2593 (62.2%) had history of hypertension, 427 (10.2%) had history of diabetes mellitus, 541 (13.0%) had history of MI and 430 (10.3%) had history of stroke or TIA. The mean systolic blood pressure was 154.5 ± 21.8 mmHG, mean diastolic blood pressure was 83.7 ± 11.3 mmHG and mean body mass index was 26.9 ± 4.1 kg/m^2. Subjects with higher spatial QRS-T angle were slightly older, had higher prevalence of cardiovascular diseases and risk factors, were more likely to have T-wave abnormalities, had higher QTc interval and QRS duration, used ACEI more frequently and used beta-blockers less frequently (Table 1). Moreover, participants with higher spatial QRS-T angle were more likely to develop incident atrial fibrillation, heart failure hospitalization, coronary events, and non-fatal MI during follow-up period (Table 1).

Table 2 shows the cross-sectional association between spatial QRS-T and cognitive function at baseline. In model 1, higher spatial QRS-T angle was marginally associated with worse Stroop performance (β = 0.002; p = 0.049) and LDCT score (β = -0.042; p = 0.064). After full adjustments for cardiovascular risk factors, cardiovascular co-morbidities and medication use, higher spatial QRS-T angle was not associated with any of the cognitive tests scores at baseline.

Table 3 and Figure 1 show the longitudinal association between spatial QRS-T angle and cognitive decline over a period of 3.2 years. In model 1, higher spatial QRS-T angle was marginally associated with a steeper decline in the Stroop performance (β = 0.0004; p = 0.055). Higher spatial QRS-T angle was significantly associated with a steeper decline in the LDCT (β = -0.0106; p = 0.004), PLTi (β = -0.0049; p = 0.001) and PLTd (β = -0.0055; p = 0.013) scores during follow-up. After full adjustment for cardiovascular risk factors, cardiovascular co-morbidities and medication use, the mean annual change of cognitive scores in thirds of spatial QRS-T angle remained essentially the same (Table 3, model 2). Adjustment for baseline level of cognitive scores did not essentially change these results (data not shown).

Table 1. Baseline characteristics of participants in thirds of Spatial QRS-T angle

Characteristics	Spatial QRS-T angle thirds			
	Low n=1383	Middle n=1393	High n=1396	*p* Value
Demographics				
Age, y, mean (SD)	75.04 (3.29)	75.09 (3.30)	75.33 (3.37)	0.049
Age left school, y, mean (SD)	15.22 (2.15)	15.25 (2.11)	15.12 (2.08)	0.253
Cardiovascular diseases and risk factors				
History of vascular disease, n (%)	543 (39.3)	568 (40.8)	713 (51.1)	<0.001
History of stroke or TIA, n (%)	126 (9.1)	140 (10.1)	164 (11.7)	0.068
History of MI, n (%)	116 (8.4)	156 (11.2)	269 (19.3)	<0.001
History of DM, n (%)	123 (8.9)	134 (9.6)	170 (12.2)	0.011
History of hypertension, n (%)	841 (60.8)	883 (63.4)	869 (62.2)	0.373
LVH, n (%)*	41 (3.0)	112 (8.0)	157 (11.3)	<0.001
BMI, kg/m^2, mean (SD)	26.87 (4.17)	26.69 (3.97)	27.19 (4.25)	0.006
SBP, mmHG, mean (SD)	152.17 (21.48)	154.78 (21.51)	156.58 (22.33)	<0.001
DBP, mmHG, mean (SD)	83.09 (11.40)	83.67 (10.74)	84.35 (11.61)	0.012
Current smoking, n (%)	373 (27.0)	362 (26.0)	351 (25.1)	0.547
ECG parameters				
Heart rate, beats/min, mean (SD)	65.70 (11.06)	65.48 (11.47)	66.67 (11.62)	0.014
T wave abnormality, n (%)†	184 (13.3)	353 (25.3)	560 (40.1)	<0.001
QTc interval, sec, mean (SD)	0.424 (0.02)	0.426 (0.03)	0.433 (0.03)	<0.001
QRS duration, sec, mean (SD)	0.095 (0.02)	0.094 (0.01)	0.105 (0.02)	<0.001
Medications				
Beta-blocker, n (%)	413 (29.9)	379 (27.2)	325 (23.3)	<0.001
Diuretic, n (%)	538 (38.9)	561 (40.3)	557 (39.9)	0.747
ACE inhibitor, n (%)	188 (13.6)	208 (14.9)	268 (19.2)	<0.001
ARB, n (%)	26 (1.9)	24 (1.7)	39 (2.8)	0.107
Calcium channel blocker, n (%)	324 (23.4)	350 (25.1)	376 (26.9)	0.103
Incident cardiovascular events during follow-up				
Atrial fibrillation, n (%)	105 (7.6)	105 (7.5)	141 (10.1)	0.021
Heart failure hospitalization, n (%)	34 (2.5)	37 (2.7)	75 (5.4)	<0.001
Coronary events, n (%)	110 (8.0)	123 (8.8)	191 (13.7)	<0.001
Non-fatal MI, n (%)	99 (7.2)	99 (7.1)	137 (9.8)	0.011
Fatal/non-fatal stroke or TIA, n (%)	89 (6.4)	91 (6.5)	99 (7.1)	0.756

Abbreviations: TIA: Transient Ischemic Attack; MI: Myocardial Infarction; DM: Diabetes Mellitus; LVH: Left Ventricular Hypertrophy; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ACE inhibitors: Angiotensin Converting Enzyme inhibitors; ARBs: Angiotensin Receptor Blockers.

To further explore the effect of other ECG parameters affecting the sequence of ventricular repolarization/depolarization on the longitudinal associations, adjustment for T wave

abnormalities, QTc interval, QRS duration and LVH were added in model 3. Further adjustment for these parameters did not essentially change the results, meaning that higher spatial QRS-T angle remained significantly associated with a steeper decline in LDCT, PLTi and PLTd test scores (all $p < 0.05$) and marginally associated with a steeper decline in the Stroop test performance ($p = 0.052$) (Table 3). Furthermore, we tested whether an interaction exists between spatial QRS-T angle and these ECG parameters in relation to cognitive function and found no significant interaction (all p for interactions > 0.05). The estimate (β) and 95% confidence intervals that were assessed using continuous levels of spatial QRS-T angle are presented in Supplementary Table 2. When we categorized the spatial QRS-T angle according to a cut-point that is reported in literature (Normal: 0° to 104°, Borderline: 105° to 134° and Abnormal: 135° to 180°), the abnormal group was associated with a steeper decline in the Stroop, LDCT, PLTi and PLTd tests performances (Supplementary Table 3).

Table 2. Cognitive function in relation to spatial QRS-T angle at baseline

	Spatial QRS-T angle thirds			
	Low	Middle	High	
	n=1383	n=1393	n=1396	*p V*alue*
Stroop, seconds, mean (SE)				
Model 1	63.45 (0.61)	62.90 (0.61)	64.64 (0.61)	0.049
Model 2	66.04 (1.57)	65.46 (1.57)	66.84 (1.52)	0.166
LDCT, digits coded, mean (SE)				
Model 1	24.21 (0.18)	24.06 (0.18)	23.87 (0.18)	0.064
Model 2	23.21 (0.45)	23.05 (0.45)	22.99 (0.44)	0.171
PLTi, pictures remembered, mean (SE)				
Model 1	9.50 (0.05)	9.55 (0.05)	9.46 (0.05)	0.299
Model 2	9.40 (0.12)	9.46 (0.12)	9.39 (0.12)	0.436
PLTd, pictures remembered, mean (SE)				
Model 1	10.38 (0.07)	10.47 (0.07)	10.35 (0.07)	0.530
Model 2	10.25 (0.17)	10.35 (0.17)	10.28 (0.17)	0.876

**p* values were calculated using continuous values of spatial QRS-T angle. Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable; Model 2: adjusted for all the variables in model 1 + history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status and antihypertensive medications. Abbreviations: LDCT: letter digit coding test; PLTi: picture-word learning test immediate; PLTd: picture-word learning test delayed.

Table 3. Cognitive function in relation to spatial QRS-T angle during follow-up

	Spatial QRS-T angle thirds			
	Low	Middle	High	
	n=1383	n=1393	n=1396	*p* Value*
Stroop, seconds, mean annual change (SE)				
Model 1	0.488 (0.13)	0.622 (0.13)	0.775 (0.13)	0.055
Model 2	0.491 (0.13)	0.625 (0.13)	0.781 (0.13)	0.054
Model 3	0.492 (0.13)	0.622 (0.13)	0.781 (0.13)	0.052
LDCT, digits coded, mean annual change (SE)				
Model 1	-0.350 (0.03)	-0.345 (0.03)	-0.461 (0.03)	0.004
Model 2	-0.350 (0.03)	-0.346 (0.03)	-0.462 (0.03)	0.004
Model 3	-0.350 (0.03)	-0.346 (0.03)	-0.463 (0.03)	0.004
PLTi, pictures remembered, mean annual change (SE)				
Model 1	0.007 (0.01)	-0.009 (0.01)	-0.034 (0.01)	0.001
Model 2	0.007 (0.01)	-0.009 (0.01)	-0.034 (0.01)	0.001
Model 3	0.007 (0.01)	-0.010 (0.01)	-0.035 (0.01)	0.001
PLTd, pictures remembered, mean annual change (SE)				
Model 1	-0.060 (0.02)	-0.054 (0.02)	-0.094 (0.02)	0.013
Model 2	-0.060 (0.02)	-0.054 (0.02)	-0.095 (0.02)	0.013
Model 3	-0.060 (0.02)	-0.054 (0.02)	-0.095 (0.02)	0.012

**p* values were calculated using the interaction term between continuous values of spatial QRS-T angle and time. Means represent the mean annual decline in the score of each cognitive test. Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable; Model 2: adjusted for all the variables in model 1+ history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status, antihypertensive medications and statin treatment groups. Model 3: adjusted for all the variables in model 2 + LVH, T wave abnormalities, QTc interval and QRS duration. Abbreviations: LDCT: letter digit coding test; PLTi: picture-word learning test immediate; PLTd: picture-word learning test delayed.

Over a period of 3.2 years, a total of 351 participants developed incident atrial fibrillation, 146 participants were hospitalized for heart failure, 424 participants developed coronary events, 279 participants developed stroke or TIA and 335 participants developed non-fatal MI. A total of 3235 subjects were free of these cardiovascular events during follow-up. Figure 2 shows the longitudinal association of spatial QRS-T angle and cognitive function stratified by incident cardiovascular events during follow-up. We did not observe a significant

difference in annual changes of cognitive function between participants who did and those who did not develop incident atrial fibrillation, coronary events, stroke or TIA, heart failure hospitalization, non-fatal MI during follow-up (all p for interactions > 0.05). Finally, when we excluded participants with additional cardiovascular co-morbidities at baseline and participants taking anti-arrhythmic medications, the longitudinal results did not change except that after exclusion of participants with history of hypertension (n=1579, >37% of the population) higher spatial QRS-T angle was not associated with steeper decline in Stroop and LDCT tests performances (Supplementary Table 4).

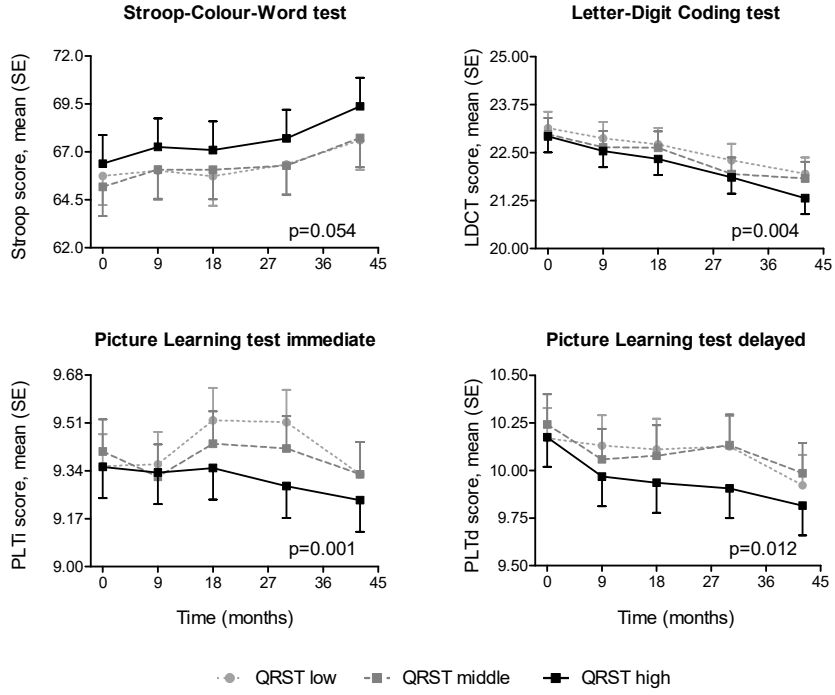

Figure 1. Cognitive function in relation to spatial QRS-T angle during follow-up. Data represent mean (standard error) decline in the score of each cognitive test in three groups of spatial QRS-T angle. The time point at the end of the study is the mean of end time points (36 to 48 months). Analyses were adjusted for age, country, education, version of cognitive tests where applicable, history of diabetes, history of vascular disease, body mass index, smoking status, systolic blood pressure, diastolic blood pressure, antihypertensive medications and statin treatment groups.

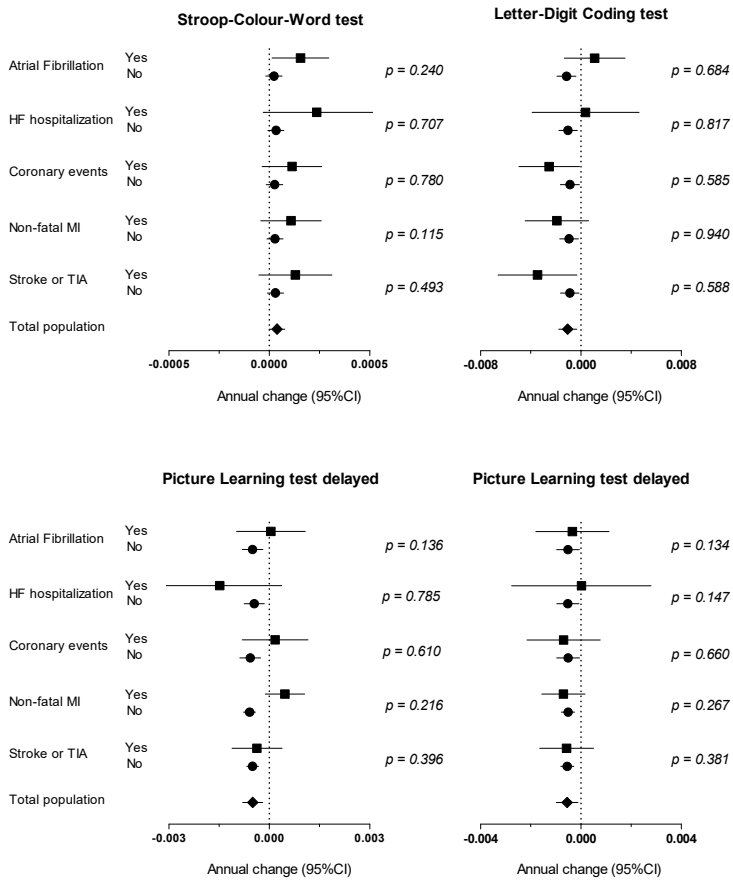

Figure 2. Association of spatial QRS-T angle and annual changes of cognitive function stratified for cardiovascular events during follow-up. Data represent annual change (95% confidence interval) in cognitive function per each unit (degree) increase in spatial QRS-T angle (the X axis), stratified for subjects who did and those who did not develop cardiovascular events during follow-up. Dark circles and squares correspond to the annual change (estimate) and the lines correspond to the 95% confidence intervals. P-values show the p for interaction. Analyses were performed in the fully adjusted model. Abbreviation: MI: myocardial infarction; HF: heart failure hospitalization and TIA: transient ischemic attack

Discussion

Our findings suggest that a wide spatial QRS-T angle, as a reflection of greater heterogeneity in electrical activity of cardiac ventricles, associates with accelerated decline in cognitive

function of older subjects at high cardiovascular risk. These associations were independent of arrhythmias, cardiovascular risk factor and co-morbidities, medication use, incident cardiovascular events and other ECG parameters.

Previous research has shown that different ECG-parameters measuring either the excitation or relaxation phase of the cardiac ventricles are related to cerebrovascular accidents and cognitive impairment. Pathologic Q waves in men suggesting unrecognized MI have a two-fold increased risk of dementia and carry a higher burden of cerebral small vessel disease[5]. Similarly, patients with Alzheimer's disease and mild cognitive impairment have higher values of QT dispersion and QT corrected dispersion[24]. Our current study suggests that an abnormal spatial QRS-T angle might precede the decline in cognitive function in a large cohort of older adults at high cardiovascular risk. Furthermore, the persistence of longitudinal associations in subjects without cardiac arrhythmias suggests that even subtle alterations in the ventricular electrical activity are linked to cognitive decline.

The observed association between spatial QRS-T angle and cognitive decline can be explained through a number of mechanisms. First, the spatial QRS-T angle and cognitive decline may both reflect cardiovascular damage and hence share a common cause. Previous research has shown that spatial QRS-T angle is a strong non-invasive predictor of cardiovascular morbidity and mortality2, 25, 26 and a wide angle is linked with higher electric instability of the cardiac ventricles that might increase the risk of cardiac arrhythmias and ischemia10. The role of cardiovascular risk factors and diseases in development of cognitive impairment is well established8. In line with this, our results show that subjects with higher spatial QRS-T angle have higher prevalence of cardiovascular co-morbidities and are more likely to develop incident cardiovascular events during follow-up. Furthermore, exclusion of subjects with a history of hypertension at baseline attenuated the longitudinal relation of spatial QRS-T angle and executive function. However, the relation between spatial QRS-T angle and memory function was independent of measured cardiovascular co-morbidities and incident cardiovascular events during follow-up. This might suggest that the association of spatial QRS-T angle and cognitive function is not limited to vascular pathologies. An abnormal

spatial QRS-T angle might reflect cardiac changes that results in hemodynamic stress and altered brain perfusion, which might in turn lead to global cognitive decline. In line with this, a wide QRS-T angle have been associated with cardiac abnormalities such as ventricular remodeling, diastolic dysfunction, impaired ionic channel and calcium homeostasis in the heart27. Such alterations may cause subtle hemodynamic instability, which may over time, lead to cerebral small vessel disease and ultimately to parenchymal damage manifesting as cognitive impairment8. In fact, recently we found that even early alterations in cardiac hemodynamic stability are linked with features of accelerated brain ageing28. Nevertheless, we cannot rule out the effect of residual confounding and unmeasured cardiovascular factors in our study, which might affect both cognitive function and spatial QRS-T angle 29. Finally, it is also possible that a wide QRS-T angle mirrors the already established cerebrovascular damage in the brain which may in turn contribute to cognitive impairment13.

It is important to mention that the spatial QRS-T angle is superior to other traditional ECG parameters measuring cardiac electrical activity since it quantifies the spatial aspects of ventricular action potential that are not measured by other ECG-parameters20. Furthermore, the spatial QRS-T angle is a more robust parameter since it is less susceptible to measurement errors and noises due to determination of the T wave end on the surface of ECG10, 30. Other ECG measures of ventricular electrical activity such as QT dispersion and QTc interval are highly dependent on the determination of ECG wave points31. Moreover, the spatial QRS-T angle is distinct from other well-known markers of cardiac dysfunction such as troponin and B-type natriuretic peptide. Such plasma markers of cardiac dysfunction such as B-type natriuretic peptide (BNP) or troponin are released from cardiac muscles in response to cardiac wall stretch and/or cardiac muscle damage32. However, the spatial QRS-T angle is increased as a result of cardiac ionic channel disturbances and inhomogeneity of cardiac electrical activity10. As such, it might be considered as a non-invasive marker for detection of subtle cardiac abnormalities in an early stage.

In our analysis, we did not find a cross-sectional association between spatial QRS-T angle and cognitive function at baseline. This might be due to the characteristics of

participants in the original PROSPER cohort in which subjects with poor cognitive function were excluded14. Since our population consists of older subjects with a fairly preserved cognitive function at baseline, the observed association between QRS-T angle and cognitive function might be underestimated. Nevertheless, a wide spatial QRS-angle was associated with a significant decline in all four cognitive tests during follow-up, strengthening the temporal order of the associations. Furthermore, the threshold for abnormal spatial QRS-T angle varied among studies20, 26, 33 and there is no established cut-off point. When we repeated our analysis using a cut-off point from previous literature12, 20, the results did not essentially change. Future research should determine the optimal age and gender specific threshold for abnormal spatial QRS-T angle.

The strengths of this study include the large sample size (more than 4000 participants), prospective multicentre design and the use of different cognitive tests assessing various domains of cognitive function. Furthermore, the non-invasive nature of ECG makes the QRS-T angle a suitable tool for use in routine clinical practice and supports its use for cardiovascular prevention strategies as well as efforts to prevent cognitive decline. Although measurement of spatial QRS-T angle requires a computer program, the implementation of this program using modern electrocardiographs is quite easy20. One limitation is that the participants had pre-existing cardiovascular risk factors or disease which might limit generalizability of our findings to a healthy older population. Another limitation is that PROSPER had a relatively short duration of follow-up which results in small magnitude of associations and jeopardizes the clinical significance of our findings. Moreover, only 10% of the population developed incident events during follow-up which might have under-powered our analysis in finding moderating effects of cardiovascular events on the reported associations. Finally, this was a secondary analysis of a randomized-controlled trial and was not designed to investigate a causal association between ECG abnormalities and cognitive decline.

In conclusion, we found that wider spatial QRS-T angle as a reflection of electrical instability in cardiac ventricles associates with accelerated cognitive decline independent of

several conventional cardiovascular risk factors and comorbidities. These findings provide insight into the link between early electrical abnormalities of the heart and development of cognitive decline in future. Further work should investigate the prognostic accuracy of a widened QRS-T angle and future cognitive decline, with the aim of early intervention into subtle cardiovascular abnormality in order to prevent cerebrovascular alterations and cognitive impairment.

Supplementary Material

Supplementary Table 1. Baseline characteristics of included and excluded participants

Characteristics	Included n=4172	Excluded n=1632	*p* Value
Socio-demographics			
Age, y, mean (SD)	75.2 (3.3)	75.8 (3.4)	<0.001
Male, n (%)	1998 (47.9)	806 (49.4)	0.305
Age left school, y, mean (SD)	15.2 (2.1)	15.0 (1.8)	<0.001
Cardiovascular risk factors			
History of vascular disease, n (%)	1824 (43.7)	741 (45.4)	0.245
History of stroke or TIA, n (%)	430 (10.0)	219 (13.4)	0.001
History of MI, n (%)	541 (13.0)	235 (14.4)	0.097
History of DM, n (%)	427 (10.2)	196 (12.0)	0.050
SBP, mmHg, mean (SD)	154.5 (21.8)	155.0 (21.8)	0.431
DBP, mmHg, mean (SD)	83.7 (11.3)	83.9 (11.9)	0.480
BMI, kg/m ^{2},mean (SD)	26.9 (4.1)	26.6 (4.3)	0.015
Current smoking, n (%)	1086 (26.0)	472 (28.9)	0.025
Antihypertensive medications			
Beta-blockers, n (%)	1117 (26.8)	385 (23.6)	0.013
Diuretics, n (%)	1656 (39.7)	702 (43.0)	0.021
ACE inhibitors, n (%)	664 (15.9)	287 (17.6)	0.122
ARBs, n (%)	89 (2.1)	27 (1.7)	0.241
Calcium channel blockers, n (%)	1050 (25.2)	408 (25.0)	0.895

Abbreviations: TIA: transient ischemic attack; MI: myocardial infarction; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; ACE inhibitors: angiotensin converting enzyme inhibitors; ARBs: angiotensin receptor blockers.

Supplementary Table 2. The estimates (β) and 95% confidence intervals for cross-sectional and longitudinal analyses

	Cross-sectional Estimate (95% CI)	Change over time Estimate (95% CI)	Additional annual change Estimate (95% CI)
Stroop test, seconds			
Model 1*	0.002 (0.00001, 0.004)	0.004 (0.0006, 0.007)	0.0004 (-0.000007, 0.0008)
Model 2*	0.001 (-0.001, 0.003)	0.004 (0.0007, 0.007)	0.0004 (-0.000006, 0.0008)
LDCT, digits coded			
Model 1	-0.042 (-0.086, 0.002)	-0.312 (-0.37, -0.25)	-0.0106 (-0.018, -0.003)
Model 2	-0.031 (-0.076, 0.013)	-0.312 (-0.37, -0.25)	-0.0106 (-0.018, -0.003)
PLTi, pictures remembered			
Model 1	-0.006 (-0.018, 0.006)	0.022 (-0.002, 0.047)	-0.0049 (-0.008, -0.002)
Model 2	-0.005 (-0.017, 0.007)	0.022 (-0.002, 0.047)	-0.0049 (-0.008, -0.002)
PLTd, pictures remembered			
Model 1	-0.005 (-0.022, 0.011)	-0.031 (-0.067, 0.005)	-0.0055 (-0.098, -0.001)
Model 2	-0.001 (-0.018, 0.016)	-0.031 (-0.067, 0.005)	-0.0055 (-0.098, -0.001)

*estimates and 95% CIs for the natural log-transformed values of Stroop test. The term *cross-sectional* represents the cross-sectional association between spatial QRS-T angle and cognitive function at baseline. The term *changes over time* represents the annual changes of cognitive scores during follow-up. The term *additional annual change* represents the extra yearly change in cognitive scores per 10 degree increase in the spatial QRS-T angle values. Model 1 is adjusted for age, sex, country, education and version of cognitive tests where appropriate; Model 2 is additionally adjusted for history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status, antihypertensive medications and statin treatment groups. Abbreviations: LDCT: Letter Digit Coding test; PLTi: Picture-Word Learning test immediate; PLTd: Picture-Word Learning test delayed.

Supplementary Table 3. Cognitive function in relation to spatial QRS-T angle during follow-up, using cut-offs from previous studies

	Spatial QRS-T angle thirds			
	Normal (0°-104°) 3223	Borderline (105°-134°) 370	Abnormal (135°-180°) 579	*p* Value*
Stroop, seconds, mean annual decline (SE)				
Model 1	0.536 (0.08)	0.933 (0.25)	0.954 (0.20)	0.055
Model 2	0.540 (0.08)	0.941 (0.25)	0.956 (0.20)	0.054
LDCT, digits coded, mean annual decline (SE)				
Model 1	-0.362 (0.02)	-0.463 (0.05)	-0.467 (0.04)	0.004
Model 2	-0.363 (0.02)	-0.465 (0.05)	-0.467 (0.04)	0.004
PLTi, pictures remembered, mean annual decline (SE)				
Model 1	-0.002 (0.008)	-0.028 (0.02)	-0.059 (0.02)	0.001
Model 2	-0.002 (0.008)	-0.028 (0.02)	-0.059 (0.02)	0.001
PLTd, pictures remembered, mean annual decline (SE)				
Model 1	-0.054 (0.01)	-0.100 (0.03)	-0.132 (0.03)	0.013
Model 2	-0.055 (0.01)	-0.101 (0.03)	-0.133 (0.03)	0.013

*p-values were calculated using the interaction term between continuous values of spatial QRST angle and time. Means represent the mean annual decline in the score of each cognitive test. Model 1: adjusted for age, sex, country, education and version of cognitive tests where applicable; Model 2: adjusted for all the variables in model 1+ history of vascular disease, history of diabetes, systolic and diastolic blood pressure, body mass index, smoking status, antihypertensive medications and statin treatment groups. Abbreviations: SE: Standard error; LDCT: Letter Digit Coding test; PLTi: Picture-Word Learning test immediate; PLTd: Picture-Word Learning test delayed.

Supplementary Table 4. Cognitive function in relation to spatial QRS-T angle during follow-up, after exclusion of participants with cardiovascular co-morbidities at baseline

	Spatial QRS-T angle thirds			*p* Value*
	Low	Medium	High	
Stroop, seconds, mean (SE)				
No history of hypertension (n=1579)	0.785 (0.20)	0.707 (0.21)	1.008 (0.20)	0.152
No history of DM (n=3745)	0.422 (0.13)	0.624 (0.13)	0.725 (0.13)	0.035
No history of MI (n=3631)	0.487 (0.14)	0.582 (0.14)	0.836 (0.14)	0.029
No history of stroke or TIA (n=3742)	0.415 (0.14)	0.593 (0.14)	0.724 (0.14)	0.045
No anti-arrhythmic use (n= 4079)	0.524 (0.13)	0.637 (0.13)	0.737 (0.13)	0.117
LDCT, digits coded, mean (SE)				
No history of hypertension (n=1579)	-0.431 (0.04)	-0.355 (0.04)	-0.418 (0.04)	0.943
No history of DM (n=3745)	-0.326 (0.03)	-0.323 (0.03)	-0.459 (0.03)	0.002
No history of MI (n=3631)	-0.359 (0.03)	-0.338 (0.03)	-0.446 (0.03)	0.029
No history of stroke or TIA (n=3742)	-0.345 (0.03)	-0.347 (0.03)	-0.472 (0.03)	0.002
No anti-arrhythmic use (n= 4079)	-0.355 (0.03)	-0.347 (0.03)	-0.461 (0.03)	0.009
PLTi, pictures remembered, mean (SE)				
No history of hypertension (n=1579)	0.010 (0.02)	-0.035 (0.02)	-0.037 (0.02)	0.017
No history of DM (n=3745)	0.007 (0.01)	0.001 (0.01)	-0.028 (0.01)	0.008
No history of MI (n=3631)	0.004 (0.01)	-0.007 (0.01)	-0.037 (0.01)	0.001
No history of stroke or TIA (n=3742)	0.007 (0.01)	-0.001 (0.01)	-0.034 (0.01)	0.002
No anti-arrhythmic use (n= 4079)	0.006 (0.01)	-0.008 (0.01)	-0.034 (0.01)	0.002
PLTd, pictures remembered, mean (SE):				
No history of hypertension (n=1579)	-0.010 (0.03)	-0.111 (0.03)	-0.074 (0.03)	0.030
No history of DM (n=3745)	-0.061 (0.02)	-0.042 (0.02)	-0.088 (0.02)	0.040
No history of MI (n=3631)	-0.066 (0.02)	-0.058 (0.02)	-0.094 (0.02)	0.025
No history of stroke or TIA (n=3742)	-0.053 (0.02)	-0.047 (0.02)	-0.096 (0.02)	0.009
No anti-arrhythmic use (n= 4079)	-0.059 (0.02)	-0.052 (0.02)	-0.095 (0.02)	0.014

**p* values were calculated using continuous values of spatial QRS-T angle. All analyses were performed in the fully adjusted models (model 2). Abbreviations: SE: standard error; LDCT: Letter Digit Coding test; PLTi: Picture-Word Learning test immediate; PLTd: Picture-Word Learning test delayed; DM: diabetes mellitus; MI: myocardial infarction; TIA: transient ischemic attack.

References

1. Katz AM. *Physiology of the heart*. Lippincott Williams & Wilkins; 2010.
2. 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;113:473-480
3. Pietrasik G, Goldenberg I, Zdzienicka J, Moss AJ, Zareba W. Prognostic significance of fragmented qrs complex for predicting the risk of recurrent cardiac events in patients with q-wave myocardial infarction. *The American journal of cardiology*. 2007;100:583-586
4. Soliman EZ, Howard G, Cushman M, Kissela B, Kleindorfer D, Le A, et al. Prolongation of qtc and risk of stroke: The regards (reasons for geographic and racial differences in stroke) study. *Journal of the American College of Cardiology*. 2012;59:1460-1467
5. Ikram MA, van Oijen M, de Jong FJ, Kors JA, Koudstaal PJ, Hofman A, et al. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. *Stroke; a journal of cerebral circulation*. 2008;39:1421-1426
6. Gorelick PB, Scuteri A, Black SE, Decarli C, Greenberg SM, Iadecola C, et al. Vascular contributions to cognitive impairment and dementia: A statement for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation*. 2011;42:2672-2713
7. Prins ND, van Dijk EJ, den Heijer T, Vermeer SE, Koudstaal PJ, Oudkerk M, et al. Cerebral white matter lesions and the risk of dementia. *Archives of neurology*. 2004;61:1531-1534
8. van Buchem MA, Biessels GJ, Brunner la Rocca HP, de Craen AJ, van der Flier WM, Ikram MA, et al. The heart-brain connection: A multidisciplinary approach targeting a missing link in the pathophysiology of vascular cognitive impairment. *Journal of Alzheimer's disease : JAD*. 2014;42 Suppl 4:S443-451
9. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. Qrs-t angle: A review. *Annals of noninvasive electrocardiology : the official journal of the International Society for Holter and Noninvasive Electrocardiology, Inc*. 2014;19:534-542
10. Voulgari C, Tentolouris N. Assessment of the spatial qrs-t angle by vectorcardiography: Current data and perspectives. *Curr Cardiol Rev*. 2009;5:251-262
11. Aro AL, Huikuri HV, Tikkanen JT, Junttila MJ, Rissanen HA, Reunanen A, et al. Qrs-t angle as a predictor of sudden cardiac death in a middle-aged general population. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2012;14:872-876
12. 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). *The American journal of cardiology*. 2012;109:981-987

13. Gandhi K, Aronow WS, Desai H, Palaniswamy C, Singh T, Amin H, et al. Patients with ischemic stroke have a higher prevalence of a planar qrs-t angle >90 degrees than patients with transient ischemic attack. *Med Sci Monit*. 2010;16:CR588-592
14. Shepherd J, Blauw GJ, Murphy MB, Cobbe SM, Bollen EL, Buckley BM, et al. The design of a prospective study of pravastatin in the elderly at risk (prosper). Prosper study group. Prospective study of pravastatin in the elderly at risk. *The American journal of cardiology*. 1999;84:1192-1197
15. Trompet S, van Vliet P, de Craen AJ, Jolles J, Buckley BM, Murphy MB, et al. Pravastatin and cognitive function in the elderly. Results of the prosper study. *Journal of neurology*. 2010;257:85-90
16. Macfarlane P, Devine B, Clark E. The university of glasgow (uni-g) ecg analysis program. *Computers in Cardiology, 2005*. 2005:451-454
17. Macfarlane PW, Latif S. Automated serial ecg comparison based on the minnesota code. *J Electrocardiol*. 1996;29 Suppl:29-34
18. Macfarlane PW, Murray H, Sattar N, Stott DJ, Ford I, Buckley B, et al. The incidence and risk factors for new onset atrial fibrillation in the prosper study. *Europace*. 2011;13:634-639
19. Edenbrandt L, Pahlm O. Vectorcardiogram synthesized from a 12-lead ecg: Superiority of the inverse dower matrix. *J Electrocardiol*. 1988;21:361-367
20. 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. *European heart journal*. 2003;24:1357-1364
21. Luo S, Michler K, Johnston P, Macfarlane PW. A comparison of commonly used qt correction formulae: The effect of heart rate on the qtc of normal ecgs. *J Electrocardiol*. 2004;37 Suppl:81-90
22. Wagner GS, Macfarlane P, Wellens H, Josephson M, Gorgels A, Mirvis DM, et al. Aha/accf/hrs recommendations for the standardization and interpretation of the electrocardiogram: Part vi: Acute ischemia/infarction: A scientific statement from the american heart association electrocardiography and arrhythmias committee, council on clinical cardiology; the american college of cardiology foundation; and the heart rhythm society: Endorsed by the international society for computerized electrocardiology. *Circulation*. 2009;119:e262-270
23. Houx PJ, Shepherd J, Blauw GJ, Murphy MB, Ford I, Bollen EL, et al. Testing cognitive function in elderly populations: The prosper study. Prospective study of pravastatin in the elderly at risk. *Journal of neurology, neurosurgery, and psychiatry*. 2002;73:385-389
24. Zulli R, Nicosia F, Borroni B, Agosti C, Prometti P, Donati P, et al. Qt dispersion and heart rate variability abnormalities in alzheimer's disease and in mild cognitive impairment. *Journal of the American Geriatrics Society*. 2005;53:2135-2139
25. 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;113:481-489
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;2:73-78

27. Selvaraj S, Ilkhanoff L, Burke MA, Freed BH, Lang RM, Martinez EE, et al. Association of the frontal qrs-t angle with adverse cardiac remodeling, impaired left and right ventricular function, and worse outcomes in heart failure with preserved ejection fraction. *Journal of the American Society of Echocardiography : official publication of the American Society of Echocardiography*. 2014;27:74-82 e72
28. Sabayan B, van Buchem MA, Sigurdsson S, Zhang Q, Harris TB, Gudnason V, et al. Cardiac hemodynamics are linked with structural and functional features of brain aging: The age, gene/environment susceptibility (ages)-reykjavik study. *Journal of the American Heart Association*. 2015;4:e001294
29. Jefferson AL, Himali JJ, Beiser AS, Au R, Massaro JM, Seshadri S, et al. Cardiac index is associated with brain aging: The framingham heart study. *Circulation*. 2010;122:690-697
30. Kors JA, van Herpen G, van Bemmel JH. Qt dispersion as an attribute of t-loop morphology. *Circulation*. 1999;99:1458-1463
31. Statters DJ, Malik M, Ward DE, Camm AJ. Qt dispersion: Problems of methodology and clinical significance. *J Cardiovasc Electrophysiol*. 1994;5:672-685
32. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Jr., Ganiats TG, Holmes DR, Jr., et al. 2014 aha/acc guideline for the management of patients with non-st-elevation acute coronary syndromes: A report of the american college of cardiology/american heart association task force on practice guidelines. *Journal of the American College of Cardiology*. 2014;64:e139-228
33. 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). *The American journal of cardiology*. 2007;100:844-849