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Relation of Cardiac Ventricular Repolarization and Global Cognitive Performance in a Community Population

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Abstract

Atherosclerosis is a risk factor for dementia. Yet little is known about the association between cognitive performance and a widely used indicator of coronary heart disease, the resting electrocardiogram (ECG). We identified 839 older residents (mean age 81; 58% black) from a geographically defined biracial community in Chicago, Illinois, who underwent extensive cognitive performance testing and met ECG eligibility criteria, including a QRS duration less than 120 msec. We then examined multivariable regression coefficients that describe associations between global cognitive performance and 4 novel descriptors of ventricular repolarization waveforms. All analyses were adjusted for age, sex, education, and race. T wave non-dipolar voltage had a significant association with global cognitive performance ($p = 0.01$), and this association largely remained after adjustment for cardiovascular disease risk factors ($p = 0.03$). In contrast, global cognitive performance was not significantly associated with the rate-adjusted QT interval, the voltage change from beginning to end of the ST segment in lead V₅, or the spatial angle between mean QRS and T wave vectors. In conclusion, strengths of associations varied between novel ECG descriptors of ventricular repolarization and global cognitive performance. Nevertheless, the significant association observed with T wave non-dipolar voltage suggests that the cardiac effects of heart disease are associated with cognitive decline.

Keywords

cognitive performance; ventricular repolarization; T wave non-dipolar voltage

Previous investigations of ECGs and cognitive decline have focused on ventricular *excitation* (the QRS complex).^{1–4} Yet, recent evidence suggests that ventricular *repolarization* (ST segment and T wave) may be more sensitive to CHD.⁵ In addition, newer computerized processing techniques for standard 12-lead ECGs allow quantitative descriptions of repolarization waveforms. In general, quantitative disease markers are more

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powerful than qualitative ones.⁶ We hypothesized, therefore, that quantitative descriptors of ventricular repolarization would be associated with lower cognitive performance.

METHODS

The Chicago Health and Aging Project (CHAP) is a multi-wave, community-based longitudinal study of aging that was approved by our institutional review board. In 1993 we conducted a door-to-door census (including nursing homes) in a geographically defined area of Chicago, Illinois, and identified 8501 residents aged 65 years or older.⁷ Among these residents, 79% signed a written consent form to undergo in-home interviews that included brief tests of cognitive function. We combined these results with participants' age, race, and sex to draw a stratified random sample of participants for further detailed clinical evaluation that included a medical history, physical examination, phlebotomy, and extensive cognitive performance testing (see below). We have conducted this cycle of in-home interviews followed by clinical evaluations of a stratified random sample every 3 years since 1993; for each cycle since 2001, we have also identified additional age-eligible residents who either moved into the community or turned 65 years old after the census. Because resting ECGs were not obtained in the first 2 cycles, these analyses are based on data from the last 2 completed cycles (2001 – 2006, Figure 1).

Among the 1170 unique participants from these 2 cycles, we excluded 30 participants with incomplete cognitive testing and 151 with missing or poor quality ECGs. To limit our analyses to *primary* repolarization abnormalities, which have a normal ventricular conduction sequence, we excluded 150 participants with QRS duration of 120 ms or greater —after which no ECGs were consistent with Wolff-Parkinson-White pattern or the presence of a ventricular electronic pacemaker. Of these 839 unique participants, 123 participants had repeat observations, because they were randomly sampled once per eligible CHAP cycle. Because we accounted for correlations between repeat observations (see below), we pooled together single and repeat observations to yield 962 total ECGs. Atrial fibrillation or flutter was present in 5.4% of total ECGs (52 out 962). We did not exclude patients with these ECGs, because neither rhythm disturbance necessarily affects ventricular repolarization.

Masked to participants' sampling category, field investigators tested 17 measures of cognitive performance during clinical evaluations.⁸ To construct a global cognitive performance score, we first standardized each test score to a *z*-score (using the mean and standard deviation of the entire group) and then averaged the *z*-scores from the 17 component tests to yield a composite score. Higher scores indicated higher global cognitive performance.

Field investigators used strictly standardized procedures to record standard 12-lead resting ECGs (MAC® 1200, version 1.1, software version 5.1, GE Marquette, Milwaukee, Wisconsin). Then, masked to participants' cognitive performance data, central laboratory technicians (Epidemiological Cardiology Research Center, Wake Forest University, Winston-Salem, North Carolina) visually inspected ECGs for quality and processed them with the Marquette 12-SL Program (GE Marquette, Milwaukee, Wisconsin).

We *a priori* chose 4 novel ECG descriptors of ventricular repolarization that have been shown to predict incident CHD events.⁹ Technicians from the central laboratory derived these variables, which are neither in routine clinical use nor measureable by sole visual inspection, through special processing of participants' standard 12-lead ECG signals. First, QT_{rr} was calculated from a linear transformation of the QT interval based on the RR interval; this linear transformation is more accurate than those based on power functions.¹⁰ To reduce measurement error due to small waveform amplitudes in individual leads, QT

intervals were measured from composite waveforms (also known as median complexes) derived from multiple ECG leads. Second, quasi-orthogonal X, Y, and Z leads were constructed through a matrix transformation of the standard 12-lead ECG signals to generate mean QRS and T wave vectors in 3-dimensional space.¹¹ QRS/T angle was then calculated as the spatial angle between these mean vectors. Third, mathematical models (modified Chebyshev polynomials) were applied to composite waveforms from standard lead V₅ to calculate the linear change, or gradient, during the ST interval (STV₅ gradient).¹² Fourth, principal component analysis was applied to T wave signals from the 8 independent leads (I, II, V₁ to V₆) to derive 8 orthogonal components, or eigenvectors.¹³ The 3 largest of these 8 orthogonal components form an idealized and customized 3-dimensional coordinate system that represents the T wave energy that can be ascribed to a single electrical dipole (often diagrammatically represented by a vector between an anode and a cathode).¹⁴ The remaining T wave energy, which is represented by the 5 smaller orthogonal components, cannot be ascribed to a single electrical dipole and, therefore, represents *nondipolar* voltage. When repolarization is normal and uniform, T wave energy is largely dipolar; yet as repolarization becomes fragmented, as in cardiomyopathy, the amount of nondipolar T wave energy increases.¹⁴ We calculated T wave nondipolar voltage (TNDPV) as the square root of the sum of orthogonal components 4 through 8.

Hypertension was present if participants reported a history of high blood pressure, if they were currently taking antihypertensive medications, or if their measured systolic blood pressure was greater than 140 mmHg or diastolic blood pressure was greater than 80 mmHg. Diabetes was present if participants reported a history of having it or the use of medication to treat it. Smoking status was classified as never versus current or past. Total serum cholesterol was measured by routine enzymatic and colorimetric methods.

To determine the association between the 4 ECG descriptors and cognitive performance, we performed multiple linear regression with global cognitive performance as the dependent variable. We analyzed no additional candidate ECG descriptors. We selected other variables known to be associated with either cognitive performance or cardiovascular risk. These were age (years, centered at 75), sex, education (years, centered at 12 years), race (black/non-black), hypertension (yes/no), diabetes (yes/no), cigarette smoking (yes/no), cholesterol (mg/dL), and BMI (kg/m², centered at 25). Because the relationship between BMI and cognitive performance is curvilinear in our population,¹⁵ we also examined BMI x BMI in our model.

Age, sex, education, and race were included in our core model. Each ECG descriptor was then added singly to this core model. We then explored whether or not cardiovascular disease (CVD) risk factors modified the relationship between ECG descriptors and cognitive performance by adding the following terms: hypertension, diabetes, cigarette smoking, cholesterol, and BMI. Finally, because our population is comprised primarily of two races, we added interaction terms of ECG descriptors by race.

To calculate *p* values for the parameters in these models and we used sampling weights and a jackknife replication method of variance estimation.¹⁶ This variance calculation, together with our stratified Bernoulli sampling method, accounted for inherent correlations between repeat measurements.

RESULTS

Among 839 unique participants there were 962 clinical evaluations (Table 1). Of the 4 ECG descriptors, only TNDPV was significantly associated with global cognitive performance (*p* = 0.01, Table 2). The significance of this association was only slightly attenuated after adjustment for CVD risk factors (*p* = 0.03). The associations between the other 3

repolarization abnormalities (QTrr, QRS/T angle, and STV₅ gradient) and global cognitive performance were small and non-significant although each association was in the direction of more abnormal repolarization being associated with lower global cognitive performance scores; as QTrr and QRS/T angle widened and as STV₅ gradient became flatter and, therefore, more negative, global cognitive performance worsened slightly and non-significantly. All interaction terms of ECG descriptors by race were not significant and were, therefore, removed from both the core and fully-adjusted models.

DISCUSSION

We found varied significance of associations between 4 novel ECG repolarization descriptors and global cognitive performance in a random sample of older residents of a biracial community. Higher levels of TNDPV were significantly associated with poorer global cognitive performance both before and after adjustment for CVD risk factors whereas worsening abnormalities of QTrr, STV₅ gradient, and QRS/T angle were associated weakly and non-significantly.

Although focused on different ECG descriptors, other investigators also found varied associations with cognitive performance. Breteler et al¹ found that ECG evidence of MI was strongly associated with cognitive performance, but Newman et al³ found that none of several major ECG abnormalities were. Investigators who combined ECG abnormalities with a history of MI also found inconsistencies. Petrovich et al² found that neither historical nor ECG evidence of an MI was associated with cognitive performance. Yet Ikram et al⁴ found that men with unrecognized ECG evidence of MI have a two-fold increased risk of incident dementia when compared with men who have neither historical nor ECG evidence of MI.

The sources of the varied strengths of association found between cognitive performance and ECG abnormalities are not clear at present. Several possibilities deserve consideration. First, different investigators have grouped ECG abnormalities in various ways, because the pathogenesis of some ECG findings remains elusive. Second, studies have varied both according to design and to the distributions of factors affecting ECG abnormalities. For example, although the electrocardiographic acquisition, transmission, and analysis methods used in the present study are identical to those used in the Dietary Modification Trial of The Women's Health Initiative,⁹ differences in mean values observed for the same ECG descriptors are likely due to the different age, race, and gender mixes of the two populations.⁵ Finally, ECG abnormalities may simultaneously reflect both the physiology and function of the heart and, at least indirectly, factors that may affect both the heart and the brain. A major example is atherosclerosis. The atherosclerotic burdens present in the vascular beds of both organs are moderately correlated,^{17,18} and ECG abnormalities often reflect the presence of coronary heart disease, for which coronary atherosclerosis is the most important risk factor.¹⁹

This study does not answer whether ECG primary repolarization abnormalities are directly associated with coronary or cerebrovascular atherosclerosis. Though Ikram et al.²⁰ found a direct association of cerebral atherosclerosis with ventricular excitation abnormalities, the results of studies of repolarization abnormalities have been mixed. Among post-menopausal women the QRS/T angle was the most predictive of incident CHD.⁹ Yet since the T angle may be more affected by age than the QRS angle,²¹ the QRS/T angle may be less predictive of CHD in aged populations than deviation of the T-axis itself.²²

Strengths of this study include its population-based design, large size, high-participation rate, structured extensive neuropsychological testing, *a priori* planned analysis of limited

candidate variables, and preservation of continuous ECG data. Weaknesses include a cross-sectional design which means that we cannot establish that repolarization abnormalities preceded poor cognitive performance. Exclusion of 13% of our eligible sample due to ventricular excitation abnormalities may have caused selection bias. Since patients with excitation abnormalities are more likely to have CHD,⁵ these exclusions would likely tend to shift our results towards null associations.

The results of this study suggest that ventricular repolarization abnormalities have varying strengths of associations with cognitive performance. Nevertheless, we observed that TNDPV has an association with cognitive performance that is independent of CVD risk factors. Although limited to an association, this finding suggests that atherosclerosis is a generalized disorder that affects arterial beds of both the heart and brain—disease of the latter being a known risk factor for cognitive decline.^{23,24} In addition, given that higher levels of TNDPV are seen in cardiomyopathy of any cause, this finding also suggests that abnormal cardiac function has cognitive consequences. The lack of significant associations seen with 3 other repolarization abnormalities and cognitive performance, however, makes any conclusions based on TNDPV tenuous. Nevertheless, to facilitate comparative assessments and maximize the potential of using descriptors of ventricular repolarization as markers of disease, researchers should consider adopting an analysis of ungrouped ECG abnormalities that preserves their quantitative nature.⁶

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Figure 1. Flow Diagram of the Chicago Health and Aging Project (2001 – 2006)^a

^a Since 1993 sampling has occurred in 3-year cycles. This current report is based on 2 cycles that occurred from 2001 to 2006.

^b Stratified random samples were drawn based on age, sex, race, and brief cognitive testing conducted during interviews. There were no significant differences in comparisons between these weighted variables from the random samples and the sampling frames comprised of all participants who were interviewed.

^c In comparison to participants who underwent a clinical evaluation, those who did not performed slightly worse on cognitive tests conducted during the interview, had approximately 1 year less of education, and were more often black; but there were no differences between groups in age or sex.

TABLE 1Characteristics of 962 Clinical Evaluations from the Chicago Health and Aging Project^a

Characteristic	Available Data <i>n</i>	
Age, median (IQR) (years)	962	81 (76 to 85)
Women	962	603 (63%) ^b
Black	962	564 (59%) ^b
Education, median (IQR) (years)	962	12 (11 to 14) ^b
Current or former smoker	962	471 (49%)
Hypertension	941	746 (78%)
Diabetes mellitus	933	182 (19%)
Body mass index, median (IQR) (kg/m ²)	912	27 (24 to 31)
Total Serum cholesterol, median (IQR) (mg/dL)	836	205 (179 to 234)
TNDPV, median (IQR) (μV)	962	9.5 (8.2 to 11.1)
QTrr, median (IQR) (mS)	962	415 (406 to 427)
STV ₅ gradient, median (IQR) (μV)	962	30 (5 to 54)
QRS/T angle, median (IQR) (°)	962	75 (51 to 106)

Abbreviations: IQR, interquartile range; TNDPV, T wave non-dipolar voltage; QTrr, QT interval rate-adjusted through a linear function of RR interval; STV₅ gradient, voltage change from beginning to end of ST segment in lead V₅; QRS/T angle, spatial angle between mean QRS and T wave vectors.

^a Among 962 clinical evaluations there were 839 unique participants. Clinical evaluations from both eligible cycles (3 years apart), therefore, were included for 123 participants.

^b Among 839 unique participants, 528 (63%) were women, 486 (58%) were black, and median education level was 12 (IQR 11 to 15).

TABLE 2

Adjusted Associations of Electrocardiogram Primary Repolarization Abnormalities with Global Cognitive Performance Score among 962 Clinical Encounters from the Chicago Health and Aging Project

	Core Model ^a		Fully-adjusted Model ^b	
	Coefficient	<i>p</i> Value	Coefficient	<i>p</i> Value
TNDPV (μ V)	-0.0290	0.01	-0.0240	0.03
QTrr (mS)	-0.0019	0.14	-0.0014	0.31
QRS/T angle ($^{\circ}$)	-0.0010	0.19	-0.0005	0.56
STV ₅ gradient (μ V)	0.0020	0.14	0.0014	0.24

Abbreviations: TNDPV, T wave non-dipolar voltage; QTrr, QT interval rate-adjusted through linear function of RR interval; STV₅ gradient, voltage change from beginning to end of ST segment in lead V₅; QRS/T angle, spatial angle between mean QRS and T wave vectors.

^aCore model included terms for age, sex, education, and race.

^bIn addition to the terms used in the core model, the fully-adjusted model also included single terms for hypertension, diabetes, cigarette smoking, cholesterol BMI, and a quadratic term for BMI. Due to missing data (see Table 1), only 766 clinical encounters are included in the fully-adjusted model.