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Electrocardiogram QRS duration and associations with telomere length: A cross-sectional analysis in Australian rural diabetic and non-diabetic population☆,☆☆

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Abstract Prolonged electrocardiogram QRS durations are often present in aging populations. Shorter telomere length is considered a biomarker of cellular aging. Decreased telomere length has been associated with coronary artery risk, and ventricular remodeling. However, the association between telomeres and cardiac conduction abnormalities, such as increased QRS duration are not well understood. A retrospective cross-sectional population was obtained from the CSU Diabetes Screening Research Initiative database where 273 participants had both ECG-derived QRS duration and DNA to permit leukocyte telomere length (LTL) determination. Telomere length was determined using the monochrome multiplex quantitative PCR method to measure mean relative LTL. Resting 12-lead electrocardiograms were obtained from each subject using a Welch Allyn PC-Based ECG system. Relative LTL was moderately negatively associated with QRS duration in type 2 diabetes mellitus (T2DM) patients ($R^2 = 0.055$), compared to controls ($R^2 = 0.010$). In general linear models with no adjustments a significant interaction between QRS duration and LTL is observed for a combined population of T2DM and non-diabetics. When we compared T2DM to non-diabetics, we found that T2DM increased the effect size for relative LTL on QRS duration in comparison to controls. Hence, for each 0.1 unit of relative LTL attrition, QRS duration in T2DM patients increased by 3.24 ms (95% CI, −63.00 to −1.84), compared to 1.65 ms in controls (95% CI, −40.44 to 7.40). In summary we have observed an association between LTL in a rural aging mixed population of T2DM and non-diabetes. We have observed an unadjusted association between QRS duration and LTL in T2DM. We noted that the control group demonstrated no such association. This highlights the complexity of T2DM when exploring disease phenotype–telomere interactions.

Keywords: Telomeres; QRS duration; ECG; Rural populations; Diabetes

Introduction

Leukocyte telomere length (LTL) is maximal at birth and decreases progressively with advancing age and chronic diseases such as cardiovascular disease [1–3]. Shorter LTL is considered a biomarker of cellular aging [4]. Telomere function is to maintain genome integrity during cell division [5]. Telomeres comprise of tandem repeats of "TTAGGG" DNA sequences at chromosomal ends, which range up to 20 kilobases in length [6]. Decreased LTL has been associated with coronary artery diseases risk, heart failure, fatal arrhythmias and reduction in ventricular mass [3,7–11]. However, the association between LTL and cardiac conduction abnormalities is not well understood.

Aging, hypertension and diabetes and longer telomeres in population studies have been shown to be associated with ventricular hypertrophy risk [12–15]. Telomere length predicts responses to cardiac remodeling signaling in translational models, yet paradoxically there are reports that longer telomere length is required for initial hypertrophic cellular responses [11,16]. Cardiac structural mass changes in cardiac hypertrophy are related to cardiac conduction defects [17,18]. Typically the signs on the electrocardiogram (ECG) of increased cardiac mass are

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represented by conduction slowing, predominately an increase in QRS duration on the ECG [19–21].

ECG abnormalities are frequent in community populations; they increase with age, and are associated with increased mortality [22,23]. Population studies have demonstrated that an increased QRS duration is associated with both all-cause mortality and cardiac specific mortality [24,25]. An increased QRS duration can also represent intra-ventricular conduction delay and/or ventricular conduction slowing and/or reduced coronary flow [26,27]. Myocardial conduction slowing is commonly associated with age related cardiovascular risk factors such as diabetes and hypertension [28,29]. To date the association between QRS duration and LTL has not been determined. Our aims are to explore the effects of QRS duration–telomere interactions on an aging population, with and without diabetes. These models will be adjusted for CVD risk factors.

Materials and methods

Study population and design cross-sectional analysis was performed on 273 participants aged 34 years and over, who had participated in a community health screening clinic at the Albury-Wodonga campus of Charles Sturt University. Participants in the study were from Albury-Wodonga and surrounding districts on the New South Wales-Victoria border (Southeast Australia). Inclusion criteria included having both a QRS duration measurement and a matching LTL measurement within the same subject. Participants where LTL could not be calculated from available DNA samples were excluded from the study analysis. Written informed consent was obtained from each recruited participant. The research protocol was approved by the institutional review board at Charles Sturt University.

Data collection

Demographic information was collected for age, smoking history, gender, height and weight (to calculate body mass index (BMI)) and the estimated amount of exercise in hours per week. Clinical history documenting pre-existing cardiovascular disease, treatment for hypertension (or being hypertensive during study screening – see below) and type 2 diabetes mellitus (T2DM) status were recorded [30]. We retrospectively extracted data from the community health screening program and performed a cross-sectional study using matching DNA in our bio-bank for LTL associations.

Blood pressure

Using a standard mercury sphygmomanometer (Welsh Allyn Australia P/L) blood pressure measurements were performed on subjects in a seated position. The blood pressure cuff placed on the upper arm, and the arm supported at the height of the heart, following a resting period of 5 min. Blood pressure measurements were repeated twice (1 min apart) in each subject and the average was recorded.

12-lead electrocardiogram (ECG)

Resting 12-lead electrocardiograms were obtained from each subject using a Welch Allyn PC-Based ECG system. This permitted automated QRS duration calculation from a 10 s epoch.

LTL measurement

Genomic DNA was extracted from 2 ml donated blood from each of the participants using the QIAamp DNA Blood Mini Kit (QIAGEN, Venlo, Netherlands). Nanodrop 1000 (Thermo Scientific, MA, U.S.) was used to verify DNA concentrations and purity. The monochrome multiplex quantitative PCR method [31] was applied to measure mean relative LTL using the QuantStudio 12 K Flex System (Life Technologies, CA, U.S.). Briefly, a relative measurement of LTL was presented with the ratio of amplification of telomeric DNA sequences (T) normalized by single copy gene (S) produced within each reaction well, in comparison to a common serial diluted standard DNA in the range of 3.75–60.00 ng/μl. Samples were detected in triplicate and mean of the three T/S ratios was recorded.

Statistics

Descriptive data including demographic variables are presented as proportions or means with standard error (SE). Student t-test or ANOVA was used to compare differences between continuous variables, and chi-square tests for categorical variables. General linear models were applied to estimate the association of risk factors in relation to QRS duration. All data analysis was performed using SPSS 22.0 (IBM, Armonk, New York, U.S.). A two-sided P-value <0.05 was considered statistically significant.

Results

There were 273 subjects available with corresponding QRS measures and LTL for analysis. Demographic information is summarized in Table 1. Subject's age ranged from 34 to 88 years. There was a mean of 3 years age difference between T2DM patients and controls. There was no difference in relative LTL between T2DM and controls. More than half of the study population (56.04%) self-reported as being hypertensive, and 52 participants (19.05%) self-reported having pre-existing cardiovascular disease. There were also no significant differences in mean QRS duration between T2DM and control subjects (P = NS).

Using a general linear model (Table 2), age was associated with increased QRS duration in all the samples ($P < 0.001$) at the rate of 0.38 ms per year. Similarly, each increased unit of waist circumference and BMI was associated with QRS duration of 0.20 ms (P = 0.009) and 0.46 ms (P = 0.023), respectively.

Relative LTL was negatively associated with QRS duration in T2DM patients ($R^2 = 0.055$), controls ($R^2 = 0.010$) and overall participants ($R^2 = 0.021$) (Fig. 1). Using general linear models with no adjustments demonstrated a significant interaction between QRS duration and LTL. When adjusted for diabetes this remained significant; however, this association was no longer significant when we adjusted independently for age and gender (Table 3). When we compared T2DM to non-diabetics, we found that