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ScienceDirect

Journal of Electrocardiology 48 (2015) 101 – 111

JOURNAL OF Electrocardiology

www.jecgonline.com

Electrocardiographic repolarization-related predictors of coronary heart disease and sudden cardiac deaths in men and women with cardiovascular disease in the Atherosclerosis Risk in Communities (ARIC) study

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Abstract

Introduction: We evaluated repolarization-related predictors of coronary heart disease (CHD) death and sudden cardiac death (SCD) in men and women with cardiovascular disease (CVD) in the Atherosclerosis Risk in Communities (ARIC) study.

Methods and results: Hazard ratios (HR) from Cox regression were computed for 11 ECG measures of repolarization in 1384 subjects (50% women) 45 to 65 years of age. The average follow-up was 14 years. Based on electrophysiological considerations the spatial angle between Tpeak and normal repolarization reference vector [Θ(Tp|Tref)], STJV6 amplitude, QRS duration and Tonset and Tpeak vector magnitude ratio (ToV/TpV) were considered as primary candidates for independent mortality predictors, and as an alternative set TaVR and TV1 amplitudes and the spatial angle between the initial and terminal T vectors [Θ(Tinit|Tterm)]. From the primary set [Θ(Tp|Tref)] was a strong independent predictor for CHD death (nearly 4-fold increased risk in men and 2-fold increased risk in women) and for SCD [Θ(Tinit|Tterm)] in men (3.4-fold increased risk) and (ToV/TpV) in women (7.76-fold increased risk). From the alternative set of independent predictors TaVR amplitude negativity reduced to less than 150 μV (1.5 mm) was a strong mortality predictor with an approximately 3-fold increased risk for CHD death and SCD in men and women.

Conclusions: The strongest independent predictors of CHD death were [Θ(Tp|Tref)] in men and TaVR in women and of SCD were [Θ(Tp|Tref)] in men and ToV/TpV in women. Overall, TaVR amplitude negativity reduced to less than 150 μV (1.5 mm) was the most consistent mortality predictor in all subgroups. These ECG variables may warrant consideration for identification of high risk men and women for more intense preventive intervention.

Keywords: ECG; Coronary heart disease; Sudden cardiac death; Risk factors; Repolarization; QT

Introduction

Evaluation of electrocardiographic (ECG) variables for classification of conditions such as old myocardial infarction (MI) and left ventricular hypertrophy (LVH) based largely on QRS measurements has been among the main areas of interest in clinical ECG research. From repolarization variables ST deviation in acute MI also been a prominent research topic. Prolongation of rate-adjusted QTend interval (QTea) has also received considerable attention [1]. Other repolarization features have been generally considered as "non-specific" findings of limited clinical utility. However, QRS/T angle has been associated with increased mortality risk in the general clinical population [2] and in patients with acute coronary syndrome [3,4]. General population cohorts without known heart disease have also found excess mortality risk for wide QRS/T angle [5–8] and for isolated T wave inversion [9,10] and abnormal T wave axis [11,12].

A previous investigation in participants free from cardiovascular disease (CVD) from the Atherosclerosis Risk in Communities (ARIC) study [13] found spatial angles reflecting

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http://dx.doi.org/10.1016/j.jelectrocard.2014.10.004
0022-0736/

deviant spatial direction of the repolarization sequence and T wave amplitudes in V1 and aVR independent predictors of coronary heart disease (CHD) death and sudden cardiac death (SCD). Mortality risk for these independent predictors was higher in women than in men, and prolonged QTea was a significant independent predictor in men only. Prolonged QTea is known to have notable limitations [14–16], and the need for improved predictors of the risk of adverse cardiac events has been generally recognized, including the Federal Drug Agency (FDA) [17,18].

The objective of the present investigation was to evaluate repolarization-related ECG variables as predictors of CHD death and SCD in men and women with manifest CVD.

Methods

Study population

The Atherosclerosis Risk in Communities (ARIC) study was designed as a prospective investigation of the cause and natural history of atherosclerosis, its clinical manifestations, and the community burden of CHD. Risk factors were measured and outcomes evaluated in a population-based probability sample of adults 45 to 65 years of age at the 1987 to 1989 baseline examination; follow-up of the cohort is ongoing. Study population and definition of prevalent diseases at the baseline and outcomes have been described previously [19–21].

Deaths were classified into definite or possible CHD death, non-CHD death, and unclassified death. In this analysis, SCD was defined as definite or possible CHD death that occurred within 1 hour after the onset of acute symptoms. CHD at baseline was classified by angina pectoris using the questionnaire of Rose et al. [22] or MI defined by a self-reported episode requiring hospitalization for >1 week, MI diagnosed by a physician, or major Q waves at the baseline ECG by Minnesota Code (MC) [23] (MC 1.1), or previous coronary artery bypass graft or coronary angioplasty. Prevalent (baseline) heart failure was determined on the basis of evidence of use of heart-failure-related medications and classified according to Gothenburg criteria [24]. Adjudication or endpoint events were performed centrally by ARIC Morbidity and Mortality Classification Committee.

After exclusion of ECGs of participants with bundle branch blocks, artificial pacemakers, Wolf–Parkinson–White pattern, ECG wave detection errors or lead reversals detected in visual inspection of all of the study ECGs using computer graphics terminals, source data were available from 15,005 ARIC participants from whom 13,621 were considered CVD-free leaving a subgroup of 1384 participants with CVD at the baseline (691 men and 693 women). CVD included CHD according to the criteria above, hospitalized heart failure or cerebrovascular disease (stroke or transient ischemic attack). From 1384 participants with CVD the race was classified as white in 931, African-American in 451 and "other" in 2 subjects. The outcome data for CHD and SCD were available for the present study from a mean follow-up period of 14 years.

Electrocardiographic procedures

Standardized procedures were used for recording the 12-lead ECGs with MAC Personal Computer (Marquette Electronics, Milwaukee, Wisconsin) in each clinical center. ECGs were processed in a central ECG laboratory initially using the Dalhousie Novacode ECG program [25]. All ECGs were later reprocessed with the GE Marquette 12-SL program (GE Marquette, Milwaukee, Wisconsin). The quasiorthogonal XYZ leads were derived from the 8 linearly independent component-leads of the 12-lead ECG signals using the Kors' transformation [26] and these leads were used as the source data to derive ECG parameters for the repolarization model. Gender-specific formulas for rate adjusted QTpeak (QTpa) and QTend (QTea) were derived by regressing lnQT on lnRR whereby $QTpa = QTp - 295 \times (RR^{0.40} - 1)$ for men and $QTpa = QTp - 303 \times (RR^{0.40} - 1)$ for women and $QTea = QTe - 316 \times (RR^{0.33} - 1)$ for men and $QTea = QTe - 435 \times (RR^{0.33} - 1)$ for women. RR interval in the above formulas is in seconds. All other intervals throughout the manuscript are in milliseconds.

Definitions of repolarization parameters

A set of 11 repolarization-related ECG variables were chosen for evaluation based on previous data of their value as risk predictors. QRS duration was included among these repolarization-related parameters because even moderate QRS prolongation may induce secondary repolarization abnormalities.

The conceptual model used to derive the repolarization parameters for the present study has been described in detail in previous publications [6,27]. A refined algorithm was used in the present study to derive the key QT subinterval, ECG estimate of the epicardial repolarization time (RT_{epi}) computed as a function of QTpa. Briefly, $RT_{epi} = QTpa - ((Cos\Theta(Tp|Tref) - 1)*TpTxd/2$, where $\Theta(Tp|Tref)$ is the spatial angle between Tp vector and Tref, the reference direction in normal spatial repolarization with unit x,y,z components (0.626,0.463, −0.627) in men and (0.741,0.563,−0.367) in women derived in CVD-free normal reference group. (Symbol '*' in these algorithms denotes multiplication). TpTxd in turn, is the interval from Tp to Txd, where Txd is the inflexion point (the minimum slope) at global T wave downstroke. Thus, ECG estimate of RT_{epi} is obtained from QTpa by modifying it by the degree of deviation of direction of the initial repolarization from the direction of normal repolarization. Left ventricular RT at time point Txd (RTxd) is obtained with an algorithm similar to that for RT_{epi}, whereby $RTxd = QTpa + ((Cos\Theta(Tp|Tref) + 1)*TpTxd/2$. RTxd is considered as a representative value for RT_{endo} when the maximum number of left ventricular myocytes is simultaneously leaving their phase 3 repolarization within the same RT increment. In addition to $\Theta(Tp|Tref)$ noted above, a number of other spatial angles between various QRS and T vectors and other interval and amplitude variables were used in various phases of the study. Their definitions are listed in the footnotes of the corresponding tables. The definitions of the main variables of the repolarization are summarized in Table 6 in the beginning of Discussion emphasizing in simple terms their meaning and significance.