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Value of the QRS-T area angle in improving the prediction of sudden cardiac death after acute coronary syndromes

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ABSTRACT

Background: Prediction of sudden cardiac death (SCD) after acute coronary syndromes (ACS) remains a challenge. Although electrophysiology measures obtained by 3-D vectorcardiography (VCG) shortly after ACS may be useful predictors of SCD, they have not been adopted into clinical practice. The main objective of our study was to assess whether the VCG-derived QRS-T area angle (between area vectors) and the QRS-T angle (between maximum vectors) have additional value beyond standard risk factors in predicting SCD after ACS.

Methods and results: We studied 643 consecutive ACS patients for whom data on VCG and echocardiography during the index hospitalization were available. Seventy-seven patients (12%) died, 37 (6%) from SCD and 21 (3%) from other cardiac causes during the 30-month follow-up. After adjusting for 9 standard risk factors (age, sex, diabetes, previous stroke, left ventricular ejection fraction; and estimated glomerular filtration rate, heart rate, systolic blood pressure < 100 mm Hg, and Killip class > 1 on admission), QRS-T area angle and QRS-T angle were shown to have independent predictive value for both SCD and all cardiac deaths. Reclassification analysis showed that both measures had additional predictive value beyond the 9 standard risk factors. For SCD, net reclassification improvements for QRS-T area angle and QRS-T angle were 46% and 45% and relative integrated discriminative improvements were 16% and 13% (vs the average ~ 11% of the 9 standard risk factors).

Conclusions: The VCG-derived QRS-T area angle and QRS-T angle improved prediction of SCD after ACS beyond standard risk factors. Further evaluation of their clinical utility and cost-effectiveness is therefore warranted.

1. Introduction

Although improved in-hospital treatment of acute coronary syndromes (ACS) and subsequent secondary prevention has led to a reduction in the number of overall cardiovascular deaths, sudden cardiac death (SCD) remains a major health problem [1–4]. Current recommendations suggest that postponement of the risk evaluation [by echocardiographic assessment of left ventricular (LV) function] to 40 days after ACS [5], and LV ejection fraction (LVEF) ≤35% at this time point is currently the gold standard for selecting who should receive an implantable cardioverter defibrillator (ICD) for primary prevention of SCD [5]. This delay carries a risk of patients dying before the evaluation [6], and a continued search for early risk markers is therefore warranted [7].

Different measures (such as degrees or cosine) of the angle between the main depolarization and repolarization forces have been shown to correlate with SCD and other cardiovascular events in various cohorts, and thus have potential as predictive indicators [8]. There are in fact two angles between these electrical forces: 1) the angle between the peak or maximum QRS and T vectors, which can be measured by electrocardiography (ECG) or 3-D vectorcardiography (VCG), and is usually called the QRS-T angle; and 2) the angle between the QRS area and T area vectors, which can only be measured by 3-D VCG, and which we call the QRS-T area angle [9]. However, neither the QRS-T angle nor the QRS-T area angle have been adopted into clinical practice as predictors of SCD, probably because standardization and automation of the methodology and agreement on prognostic threshold values are lacking.

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The aim of this study was to assess the incremental value of the QRS-T area angle, the QRS-T angle, and other non-invasive electrophysiology measures obtained by 3-D VCG beyond that of standard demographic and clinical variables in predicting SCD and all cardiac deaths after ACS.

2. Methods

2.1. Study population

This study comprises 643 consecutive ACS patients <80 years who were admitted to a tertiary center coronary care unit, in whom VCG and echocardiography was recorded during index hospitalization, and who were discharged between September 15, 1995 and September 15, 1999. They did not have left bundle branch block or permanent ventricular pacing at inclusion. They were followed for 30 months, a period chosen to minimize the influence of incident confounders. Confirmation of survival or date of death was obtained from the Swedish National Population Registry using personal identification numbers. Information about the cause of death was collected through hospital records including death certificates by one of the authors (MH) who had no information about VCG and echocardiography data. The study cohort has been described in detail elsewhere [10]. The study protocol was approved by the Regional Ethical Review Board in Gothenburg and complied with the Declaration of Helsinki. Patients provided consent before participating in the study.

2.2. Primary and secondary end-points

The primary end-point was SCD defined as: 1) established SCD, here unsuccessful cardiac resuscitation with subsequent death, 2) probable SCD, i.e. unexpected death without obvious extra-cardiac cause occurring within 24 h of onset of any symptom, or 3) where circumstances clearly indicated sudden death applying recently recommended principles [7]. The secondary end-point was all cardiac deaths (including SCD).

2.3. Clinical data

Clinical data were collected from hospital records and by interview with an experienced study nurse. Previous medical history, on-going medication, clinical characteristics, delay time from symptom onset, and ECG pattern on admission were recorded. Diabetes mellitus and hypertension were defined in the presence of a history, records and/or pharmacotherapy for these diseases. Body mass index (BMI) was calculated as body weight in kg/(height in m) [2]. Glomerular filtration rate was estimated by the Cockcroft–Gault formula.

2.4. VCG recording and analysis

A MIDA (myocardial infarction dynamic analysis) 1000 or 1200 system (Ortivus, Danderyd, Sweden) was connected to 8 electrodes positioned according to a Frank orthogonal lead system (X, Y, and Z) modified for the supine position. The methods for recording, interval measurements, and other analyses performed off-line followed the same principles and definitions as described previously and were performed using customized software [9,11–12].

Three-dimensional QRS, T and P vector loops were acquired as shown in Fig. 1a; this figure shows a relatively large, wide and, in this case, almost triangular QRS loop, whereas the T loop is much smaller, narrow, and elliptical, and the P loop is small and close to the origin. In a standard ECG, these loops are projected onto extremity and chest leads in the frontal and transverse planes resulting in 12 different QRST complexes. In VCG, they are recorded in the X, Y and Z directions resulting in 3 complexes: $QRST_X$, $QRST_Y$ and $QRST_Z$. These QRST complexes are used for calculating the QRS and T areas and their vectors, and one 3-D QRST complex is constructed from their sum. The 3-D QRST complex is used for measuring the QRS, QT, and T peak-end (Tp-e) intervals, as for a standard ECG.

The maximum diameters within the QRS and T loops are the maximum QRS and T vectors, and the angle between them is the QRS-T angle (Fig. 1b). The QRS-T area angle is the angle between the QRS and T area vectors (Fig. 1c). The ventricular gradient is the sum of these two vectors and therefore is itself a vector (Fig. 1c). Fig. 1d shows that the QRS-T area angle was wider than the QRS-T angle at a group level in this ACS cohort (at angles <135°), although individual variability also was apparent. All VCG-derived measures and their definitions are described in Table 1.

Averaged 3-D QRST complexes and vector loops were constructed from all cardiac cycles from a sampling period of 1 to 2 min. The sampling period used for calculations was selected when the ST vector magnitude had reached a steady state [mean (SD) 28 (14) h after the start of the VCG recording (median 39 h 40 min after onset of chest pain in a subgroup of 572 patients for whom the exact start of chest pain had been identified)] and just before the end of the recording, thus describing the electrophysiological status after the acute phase [12]. Averaged complexes and loops from samples with >75% cardiac cycles with the dominant QRS morphology during the sampling period were accepted; ventricular extra systoles were thus excluded. The signal-averaged QRST complexes were used to provide a high signal-to-noise ratio and ensure good signal quality. On the averaged QRST complexes, customized software made automated annotations of QRS onset and end, and T peak and end (of which T end usually is the most difficult to define). The annotation (fiducial) points were therefore verified and manually corrected by two authors (ML and AR) blinded to all clinical and follow-up data. They had a low inter-observer variability when tested in a subsample with a QTc interval difference < 1%. When the annotation points had been confirmed, all subsequent analysis was automatic.

2.5. Echocardiography

During the index hospitalization (within five days of hospital admission), an experienced investigator performed 2-D echocardiography as previously described [13], calculated the biplane LVEF by the disk sum method, and checked tracings for accuracy in motion mode.

2.6. Statistics

Mann–Whitney U test (continuous variables) and Fisher's exact test (dichotomous variables) were used for crude group comparisons of baseline characteristics, in-hospital findings and treatment.

Logistic regression was used for calculation of unadjusted and adjusted odds ratios with corresponding confidence intervals. The adjustment was made for the following 9 clinical variables: age, sex, diabetes, previous stroke; estimated glomerular filtration rate, heart rate, systolic blood pressure < 100 mm Hg, and Killip class > 1 on admission; and LVEF within 5 days of admission. The assumption of linearity regarding continuous variables was checked by entering the squared transformation of the variable tested into the model and considering a significant change in the −2 log likelihood as a sign of nonlinearity. Variables not fulfilling this assumption (QRS area and T elevation) were transformed using the natural logarithm for the analyses.

Receiver operating characteristic (ROC) curves were constructed for selected variables and the cutoff value was defined as the point on the ROC curve closest to 100% for sensitivity and specificity. The Kaplan–Meier estimate was used to visualize cumulative risk over time, but time was not used in statistical calculations [net reclassification improvement (NRI) or regression models].

Assessment of the added predictive value of VCG measures was based on the change in area under the ROC curve (AUC, or c statistic), the reclassification measures of the category-less NRI, and the relative integrated discrimination improvement (RIDI) [14]. Category-less NRI was chosen to avoid effects of category definitions as described by