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Relationship between vectorcardiographic QRS_{area}, myocardial scar quantification, and response to cardiac resynchronization therapy

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ABSTRACT

Purpose: To investigate the relationship between vectorcardiography (VCG) and myocardial scar on cardiac magnetic resonance (CMR) imaging, and whether combining these metrics may improve cardiac resynchronization therapy (CRT) response prediction.
Methods: Thirty-three CRT patients were included. QRS_{area}, T_{area} and $QRST_{area}$ were derived from the ECG-synthesized VCG. CMR parameters reflecting focal scar core ($Scar_{2SD}$, $Gray_{2SD}$) and diffuse fibrosis (pre-T1, extracellular volume [ECV]) were assessed. CRT response was defined as ≥15% reduction in left ventricular end-systolic volume after six months' follow-up.
Results: VCG QRS_{area}, T_{area} and $QRST_{area}$ inversely correlated with focal scar ($R = -0.44$–-0.58 for $Scar_{2SD}$, $p \leq 0.010$), but not with diffuse fibrosis. $Scar_{2SD}$, $Gray_{2SD}$ and QRS_{area} predicted CRT response with AUCs of 0.692 ($p = 0.063$), 0.759 ($p = 0.012$) and 0.737 ($p = 0.022$) respectively. A combined ROC-derived threshold for $Scar_{2SD}$ and QRS_{area} resulted in 92% CRT response rate for patients with large QRS_{area} and small $Scar_{2SD}$ or $Gray_{2SD}$.
Conclusion: QRS_{area} is inversely associated with focal scar on CMR. Incremental predictive value for CRT response is achieved by a combined CMR-QRS_{area} analysis.

Introduction

Cardiac resynchronization therapy (CRT) is an effective treatment for patients with symptomatic heart failure (HF), reduced systolic left ventricular (LV) function, and wide QRS complex. Nevertheless, about one-third of patients eligible according to current guidelines fail to benefit from CRT. Suboptimal CRT response has been attributed to multiple factors including QRS duration (QRSd) <150 ms, non-left bundle branch block (non-LBBB) morphology, ischemic cardiomyopathy, and suboptimal LV lead position [1].

Parameters derived from the three-dimensional (3D) vectorcardiogram (VCG) have recently been shown to be more accurate than QRSd or morphology in predicting CRT response [2]. The VCG represents the electrical heart vector in three orthogonal directions (X, Y, and Z) and can be derived from a true VCG lead system or synthesized from the standard 12-lead ECG using a mathematical transformation matrix [3]. The 3D area of the VCG QRS- (QRS_{area}) and T-loop (T_{area}) are supposed to reflect unopposed electrical forces during ventricular depolarization and repolarization respectively. Both QRS_{area} and T_{area} have been shown to be strong predictors for LV reverse remodeling after CRT [2,4]. In a small study it was observed that QRS_{area} was relatively reduced in patients with ischemic cardiomyopathy, suggesting an association between QRS_{area} and myocardial scar [4].

Ischemic cardiomyopathy, the presence and size of scar burden, and positioning the LV lead in scar are negatively associated with CRT outcome [5]. CMR is able to characterize different types of myocardial scar including focal scar with delayed enhancement (DE-CMR) and diffuse fibrosis with T1 mapping. Recent work demonstrated that focal scar, but not diffuse fibrosis, was associated with poor CRT response [6].

Summarizing the above literature, it appears that certain electrical characteristics from the VCG and low myocardial scar burden is favorable for response to CRT. The association between VCG and myocardial scar as measured by CMR is however not known.

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The purpose of this study was therefore to investigate the association between VCG parameters and myocardial scar (both focal and diffuse) on CMR in HF patients with ventricular conduction disturbance, and whether combining VCG with CMR scar parameters improves prediction to CRT response.

Methods

Study population

Consecutive patients referred for CRT device implantation who underwent CMR imaging as part of their clinical workup were prospectively enrolled at Guys and St Thomas' NHS Trust hospital as previously described [6]. The South-East London Research Ethics Committee approved the study protocol and all patients gave written consent.

Vectorcardiography analyses

Standard 12-lead ECG's were recorded prior to CRT implantation in supine position using the ECG machine MAC 5500 HD (GE Healthcare, Chicago, IL). The digital PDF ECG files with vector graphics were used to extract the original digital ECG-signal. VCGs were semi-automatically synthesized from these digital ECG signals using custom software programmed in MATLAB 2016b (MathWorks, Natick, NA) [4]. The Kors transformation matrix was used to transform the 12-lead ECG to VCG [3]. The onset and end of the QRS-complex and T-wave were manually set on the three overlaid orthogonal leads (X, Y, and Z) of the VCG by two electrophysiologists blinded to CRT outcome. QRS_{area}, T_{area}, and $QRST_{area}$ were defined as the 3D areas of respectively the QRS-complex, T-wave, and QRST loop from the VCG between the loop and baseline in X, Y, and Z direction calculated as $QRS_{area} = (QRS^2_{area,x} + QRS^2_{area,y} + QRS^2_{area,z})^{1/2}$, $T_{area} = (T^2_{area,x} + T^2_{area,y} + T^2_{area,z})^{1/2}$, and $QRST_{area} = (QRST^2_{area,x} + QRST^2_{area,y} + QRST^2_{area,z})^{1/2}$ [4].

Cardiac magnetic resonance imaging

Patients underwent CMR prior to their CRT implantation using a 1.5T scanner with a 32–channel coil (Philips Healthcare, Best) as described previously [6]. Two independent CMR experts, blinded to CRT outcome, assessed the CMR images. In case of discrepancy, consensus between the reviewers was reached. LV mass was quantified using CMR42 (Circle Cardiovascular Imaging Inc., Calgary) software and used to index the delayed enhancement (DE-CMR) quantification of focal scar. The extent of scar core was automatically quantified using the 2-standard deviation (2SD) method, defined as the region with signal intensity (SI) >2SD above reference myocardium ($Scar_{2SD}$). The extent of Gray zone was quantified by the difference in SI between $Scar_{2SD}$ and $Scar_{3SD}$ ($Gray_{2SD}$).

Conceptually scar core comprises dense and non-viable fibrosis, creating zones of conduction block. Grayzone comprises an admixture of viable and non-viable myocytes, creating zones of slow conduction which may alter to electrical and mechanical remodeling. Both metrics are clinically relevant in the context of LV function and mortality. Given that the burden of scar core, i.e. homogeneously non-viable myocardium, is ubiquitously high amongst advanced heart failure patients, the assessment of the remaining viable tissue may play an important role in predicting the capacity of the LV to positively remodel with CRT. Grayzone is an independent predictor for mortality after myocardial infarction and is associated with ventricular arrhythmias [7,8], while focal scar is associated with clinical outcome and LV reverse remodeling after CRT [9,10].

All DE-CMR scar parameters were expressed as a percentage of LV mass (%LV). T1 relaxation maps were processed using a customized software plugin with Osirix (Pixmeo, Geneva), from which the diffuse fibrosis parameters pre-contrast T1 (pre T1) and extracellular volume index (ECV) was calculated [6]. A graphical representation of the VCG and CMR assessment is provided in Fig. 1.

Cardiac resynchronization therapy implantation and response determination

The LV lead was preferentially targeted in a posterolateral, lateral or anterolateral coronary sinus tributary, with pacing sites preferentially chosen in a basal position remote from CMR scar. Trans-thoracic echocardiography was assessed pre- and six months post-CRT implantation using a GE Vivid 7 scanner (General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2D images of LV dimensions and ejection fraction (LVEF) were acquired in standard apical 2- and 4-chamber views. LV end-diastolic and end-systolic volumes (LVEDV, LVESV) were used to estimate LVEF using the 2-dimensional modified biplane Simpson's method (EchoPac 6.0.1, General Electric Vingmed). CRT response was defined as an echocardiographic LVESV reduction of ≥15% of baseline after six months' follow-up. Echocardiography was performed by sonographers blinded to both VCG and CMR data.

Statistical analyses

Statistical analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, Illinois) and MATLAB. Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) and dichotomous variables in frequencies and percentages. Spearman correlation analyses were carried out between and within VCG and CMR parameters. Parameter differences between CRT responders vs. non-responders were compared using Mann Whitney *U* tests. Receiver operating characteristics (ROC) curves were generated to evaluate the diagnostic accuracy of all parameters in identifying CRT response and to find optimal cut-off values. These cut-off values were used to dichotomize the population to groups ≤cut-off and >cut-off, and the number of CRT responders for every subgroup were compared using Chi-squared analyses. The most promising VCG and CMR scar parameters were combined in a cross-tab to evaluate its joint effect on CRT response prediction. Differences within the crosstabs were evaluated using Fisher's exact tests. Significance was defined as p-value <0.05 using two-tailed analysis.

Results

Study population

Thirty-three consecutive patients with either non-ischemic ($n = 17$) or ischemic ($n = 16$) cardiomyopathy were included. Patient characteristics are provided in Table 1.

Cardiac resynchronization therapy response

Nineteen out of 33 patients (58%) showed a reduction in LVESV of ≥15% after six months follow-up. Mean $Scar_{2SD}$ and $Gray_{2SD}$ tended to be lower in CRT responders than in non-responders, although this difference was significant for $Gray_{2SD}$ ($p < 0.011$), but it did not reach a significance level for $Scar_{2SD}$ ($p = 0.065$). Pre-T1 and ECV however did not differ between CRT responders and non-responders ($p = 0.152$ and 0.706, respectively). QRS_{area}, but not T_{area} or $QRST_{area}$, was significantly higher in responders than in non-responders to CRT ($p = 0.021$; Table 2).

There was a positive correlation between $Scar_{2SD}$ and $Gray_{2SD}$ and ΔLVESV (R: 0.46–0.55, $p \le 0.008$), while there was no significant correlation between Pre-T1 and ECV and ΔLVESV. From the VCG parameters, QRS_{area} and $QRST_{area}$ inversely correlated with ΔLVESV (both R: −0.44, $p = 0.010$), while there was no correlation with ΔLVESV for QRSd and T_{area} (Fig. 2).

QRS_{area} and focal scar burden between non-ischemic ($n = 17$) and ischemic patients ($n = 16$) were additionally compared. QRS_{area} was lower ($p = 0.046$) in patients with ischemic cardiomyopathy (median: 62, IQR: 27–83) compared to patients with non-ischemic

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