Relationship between vectorcardiographic QRS\textsubscript{area}, myocardial scar quantification, and response to Cardiac Resynchronization Therapy

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Running title:
Vectorcardiography and cardiac magnetic resonance imaging defined scar
Structured 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<sub>area</sub>, T<sub>area</sub> and QRST<sub>area</sub> were derived from the ECG-synthesized VCG. CMR parameters reflecting focal scar core (Scar<sub>2SD</sub>, Gray<sub>2SD</sub>) 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<sub>area</sub>, T<sub>area</sub> and QRST<sub>area</sub> inversely correlated with focal scar (R=-0.44--0.58 for Scar<sub>2SD</sub>, p≤0.010), but not with diffuse fibrosis. Scar<sub>2SD</sub>, Gray<sub>2SD</sub> and QRS<sub>area</sub> 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<sub>2SD</sub> and QRS<sub>area</sub> resulted in 92% CRT response rate for patients with large QRS<sub>area</sub> and small Scar<sub>2SD</sub> or Gray<sub>2SD</sub>.

**Conclusion:** Incremental predictive value for CRT response is achieved by a combined CMR-QRS<sub>area</sub> analysis.

**Keywords**
Vectorcardiography, myocardial scar, cardiac magnetic resonance imaging, cardiac resynchronization therapy
Highlights

- The relationship between vectorcardiography (VCG) and myocardial scar defined by cardiac magnetic resonance imaging (CMR) is elucidated.
- VCG QRS\textsubscript{area} significantly inversely correlates with focal scar, suggesting that myocardial scar leads to a smaller QRS\textsubscript{area}.
- By combining QRS\textsubscript{area} and CMR focal scar assessment, CRT response prediction improves beyond that by either VCG or scar parameters alone.
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Conflict of interests
There are none conflict of interests.
**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 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\textsubscript{area}) and T-loop (T\textsubscript{area}) are supposed to reflect unopposed electrical forces during ventricular depolarization and repolarization respectively. Both QRS\textsubscript{area} and T\textsubscript{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\textsubscript{area} was relatively reduced in patients with ischemic cardiomyopathy, suggesting an association between QRS\textsubscript{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.

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. 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. The Kors transformation matrix was used to transform the 12-lead ECG to VCG. 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. $\text{QRS}_{\text{area}}$, $\text{T}_{\text{area}}$, and $\text{QRST}_{\text{area}}$ were defined as the 3D areas of respectively the QRS-, T-wave, and QRST loop from the VCG between the loop and baseline in X, Y, and Z direction calculated as $\text{QRS}_{\text{area}} = (\text{QRS}_{\text{area,x}}^2 + \text{QRS}_{\text{area,y}}^2 + \text{QRS}_{\text{area,z}}^2)^{1/2}$, $\text{T}_{\text{area}} = (\text{T}_{\text{area,x}}^2 + \text{T}_{\text{area,y}}^2 + \text{T}_{\text{area,z}}^2)^{1/2}$, and $\text{QRST}_{\text{area}} = (\text{QRST}_{\text{area,x}}^2 + \text{QRST}_{\text{area,y}}^2 + \text{QRST}_{\text{area,z}}^2)^{1/2}$.

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. 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 ($\text{Scar}_{2\text{SD}}$). The extent of Gray zone was quantified by the difference in SI between Scar$_{2\text{SD}}$ and Scar$_{3\text{SD}}$ ($\text{Gray}_{2\text{SD}}$).
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 cardiac resynchronization therapy (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 Figure 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 (Matlab 2016B, MathWorks, Natick, MA). Continuous variables are expressed
as mean±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 Scar2SD and Gray2SD tended to be lower in CRT responders than in non-responders, although this difference was significant for Gray2SD (p<0.011), but it did not reach a significance level for Scar2SD (p=0.065). Pre-T1 and ECV however did not differ between CRT responders and non-responders (p=0.152 and 0.706, respectively). QRSarea, but not Tarea or QRSTarea, was significantly higher in responders than in non-responders to CRT (p = 0.021; Table 2).

There was a positive correlation between Scar2SD and Gray2SD and ΔLVESV (R: 0.46-0.55, p≤0.008), while there was no significant correlation between Pre-T1 and ECV and ΔLVESV. From the VCG parameters, QRSarea and QRSTarea inversely correlated with ΔLVESV (both R: -0.44, p = 0.010), while there was no correlation with ΔLVESV for QRSd and Tarea (Figure 2).

QRSarea and focal scar burden between non-ischemic (n = 17) and ischemic patients (n = 16) were additionally compared. QRSarea was lower (p = 0.046) in patients with
ischemic cardiomyopathy (median: 62, IQR: 27-83) compared to patients with non-ischemic cardiomyopathy (median: 106, IQR: 58-145), while focal scar burden did not differ between the two groups (all $p >0.136$).

**ROC analyses for CMR and VCG parameters identifying CRT response**

Pre-T1 and ECV were poor predictors for CRT response, while $\text{Scarc}_{2SD}$ and $\text{Grays}_{2SD}$ were substantially better at predicting CRT response ([AUC: 0.692, $p=0.063$] and [AUC: 0.759, $p=0.012$] respectively). $\text{QRS}_{\text{area}}$, but not $\text{QRSd}$, $T_{\text{area}}$ or $\text{QRST}_{\text{area}}$, significantly predicted CRT response (AUC: 0.737, $p = 0.022$) (Figure 3, Table 3).

**Association between VCG and myocardial scar**

There was no association between pre-T1 or ECV and $\text{QRS}_{\text{area}}$ or $T_{\text{area}}$ (all $p>0.142$). All VCG parameters inversely correlated with $\text{Scarc}_{2SD}$ and $\text{Grays}_{2SD}$. The strongest VCG-CMR association was found between $\text{QRS}_{\text{area}}$ and focal scar parameter $\text{Scarc}_{2SD}$ (Figure 4).

**Combining VCG and CMR scar parameters**

The study population was dichotomized using the cut-off values for $\text{Scarc}_{2SD}$, $\text{Grays}_{2SD}$ and $\text{QRS}_{\text{area}}$ derived from the ROC analyses in Table 3. The percentage of CRT responders was significantly higher in patients with low $\text{Grays}_{2SD}$ and low $\text{Scarc}_{2SD}$ versus patients with high focal scar parameters (Figure 5A). The percentage of CRT response was also higher in patients with high $\text{QRS}_{\text{area}}$ as compared to those with low $\text{QRS}_{\text{area}}$ (Figure 5B). Crosstab analyses between $\text{QRS}_{\text{area}}$ and $\text{Grays}_{2SD}/\text{Scarc}_{2SD}$ showed that the percentage CRT response was highest (92%) in patients with a combination of high $\text{QRS}_{\text{area}}$ (>66 mV.ms) and low $\text{Grays}_{2SD}$ ($\leq 5.91\%$ LV mass)/low $\text{Scarc}_{2SD}$ ($\leq 20.29\%$ LV mass). The four subgroups in $\text{Scarc}_{2SD} + \text{QRS}_{\text{area}}$ combinations differed significantly from each other (overall: $p<0.001$; Figure 5C). For $\text{Grays}_{2SD} + \text{QRS}_{\text{area}}$ combinations, the subgroup [low $\text{Grays}_{2SD} + \text{high} \text{QRS}_{\text{area}}$] was significantly different from the other three subgroups, while the subgroups [low $\text{Grays}_{2SD} + \text{low} \text{QRS}_{\text{area}}$] and [high $\text{Grays}_{2SD} + \text{high} \text{QRS}_{\text{area}}$] were not significantly different.

**Discussion**

The present study is the first to investigate the relationship between VCG parameters and CMR defined scar, and between these parameters and CRT response. The principal findings of this study are that $\text{QRS}_{\text{area}}$ significantly correlated inversely with focal scar,
suggesting that myocardial scar leads to a smaller $\text{QRS} \text{area}$, Additionally, by combining $\text{QRS} \text{area}$ and CMR focal scar assessment, CRT response prediction improves beyond that by either VCG or scar parameters alone.

**The role of VCG in clinical context**

The VCG technique was first described almost a century ago. VCG measures the electrical activity of the heart as a vector loop consisting of momentary magnitudes and directions in 3D space for each time point in the heart cycle. Various VCG systems have been introduced, from which the Frank VCG system (employing seven recording electrodes) was the most common VCG system in clinical care in the 1960s together with the current 12-lead ECG system.(11) After two periods of discontinuation in clinical practice, interest in the use of VCG regained in the late 1980s, and mathematical matrices were developed to synthesize the VCG from the 12-lead ECG.(3) Advantages of VCG parameters over the 12-lead ECG-derived morphology definitions (like LBBB) is that VCG parameters are objective continuous parameters and therefore more suitable for statistical analyses. $\text{QRS} \text{area}$ and $\text{T} \text{area}$ defined as the 3D integral of the QRS- and T-wave loop respectively, resemble dispersion of depolarization and repolarization, and are the most common VCG parameters recently investigated in CRT.(2, 4, 12-14)

**The association between VCG and CMR scar**

The usefulness of VCG for identification of myocardial scar has been investigated by Bizarro et al. almost four decades ago.(15) In this small study, automatically generated VCG parameters from both the QRS- and T-loop were able to identify 85% of the patients with autopsy-confirmed scar. Ever since, the majority of studies have focused on comparing features from the 12-lead ECG with myocardial scar.(16, 17) However, the use of these ECG criteria in estimating scar extent is complex and particularly debatable in patients ventricular conduction disturbances.(17)

In the present study, correlation analyses suggested that $\text{QRS} \text{area}$ decreased with focal scar burden (encompassing dense scar core), and to a lesser extent scar border zone; but VCG parameters were not significantly associated with measures of diffuse fibrosis. This suggests that scar tissue with higher density affects the VCG 3D loop the most. A low $\text{QRS} \text{area}$ theoretically resembles less dispersion and subsequently a small amount of unopposed forces during ventricular depolarization. The size of these forces likely
depends on the uniformity of slow conduction and the amount of viable myocardium. A lower number of viable myocardial cells, lateralization of connexins, and increased axial resistivity after myocardial infarction may lead to a decrease of total electrical forces during the cardiac cycle and therefore an overall decrease of VCG amplitude, and subsequently low QRS_{area} and T_{area}.

QRS_{area} is not only affected by the severity of focal myocardial scar, but may also be affected by the etiology of heart failure alone. Van Deursen et al.\( ^4 \) reported lower QRS_{area} in patients with ischemic cardiomyopathy compared to patients with non-ischemic cardiomyopathy.

**The role of VCG in CRT response prediction**

The significant association of a large QRS_{area} with more LV reverse remodeling after CRT is in line with earlier studies demonstrating a significant association of QRS_{area} with CRT response.\( ^{2,4} \) QRS_{area} has been shown to be associated with delayed electrical activation on the LV lateral wall.\( ^{19} \) QRS_{area} is thought to represent unopposed ventricular contraction forces. A larger QRS_{area} therefore reflects a greater degree of ventricular electrical dyssynchrony which is amenable to CRT.\( ^{4,20} \)

The strength of QRS_{area} in predicting CRT response is particularly demonstrated in the recent multicenter prospective MARC study where numerous clinical, echocardiographic, blood, and electrocardiographic biomarkers were studied and related to LV reverse remodeling.\( ^2 \) From all these biomarkers, only QRS_{area} and echocardiographic interventricular mechanical delay and apical rocking remained significantly associated with LV reverse remodeling in the multivariable model. Although in their data T_{area} showed a significant association with LV reverse remodeling in the unadjusted model (\( p \)-value <0.001), significance was not preserved in the multivariate model.\( ^2 \) Interestingly, T_{area} proved to predict CRT response slightly better than QRS_{area} in retrospective studies by Engels and Vegh et al.\( ^{4,13} \) The sum of the absolute QRST integral (SAI QRST) has also been investigated as a predictor for LV reverse remodeling. In 234 CRT recipients from the SMART-AV trial by Tereshchenko et al.\( ^{14} \) found that patients with a high QRST_{area} had significantly greater odds of LV reverse remodeling than those with lower QRST_{area}. QRST_{area} was also associated with \( \Delta \text{LVESV} \) reduction in our data but was not a significant CRT response predictor in the
ROC analyses ($p = 0.074$). Altogether these results indicate that the role for $T_{area}$ in CRT response prediction is not fully understood yet. (4, 13, 14)

**The relevance of myocardial scar regarding CRT response**

The association between focal scar burden and poor CRT response has been investigated in numerous studies. Chalil et al. demonstrated that CRT recipients with a scar size of $<33\%$ showed significantly more favorable clinical response to patients with $\geq 33\%$ scar. Patients with a posterolateral scar, the common site for LV lead placement, also had a higher risk of cardiovascular death and HF hospitalization. (9) Leyva et al. concordantly studied the use of DE-CMR to guide LV lead placement remote from scar tissue in a large cohort of 559 patients. In their data, patients with DE-CMR confirmed scar showed the highest risk of cardiovascular death and lowest echocardiographic CRT response, confirming the importance of pacing remote from scar. (5)

After the introduction of T1 mapping in CMR, a few studies additionally investigated the potential role of diffuse fibrosis in CRT response. (6, 21) The association between diffuse fibrosis and focal scar and LV reverse remodeling was studied by Chen et al. prospectively in CRT candidates with ischemic and non-ischemic etiologies of HF. (6) In a multivariate model only focal scar burden, but not diffuse fibrosis, was able to predict LV reverse remodeling significantly. Höke et al. investigated the association of diffuse fibrosis with CRT response prediction specifically in the non-ischemic cohort (21). In their data both focal scar as well as diffuse fibrosis were associated with LV reverse remodeling after CRT. These findings indicate that diffuse fibrosis may have a potential role in CRT response prediction in patients with non-ischemic cardiomyopathy.

**Combining VCG with CMR for a better CRT response prediction**

The present study demonstrates that combining parameters reflecting both electrical and tissue substrate for CRT may be an approach to further improve CRT response prediction. Almost all (92\%) patients with a low extent of focal scar and a large $QRS_{area}$ were CRT responders. This finding is important, since myocardial scar burden and $QRS_{area}$ are inversely related to each other. Apparently, CRT response prediction is better when incorporating focal scar metrics in addition to $QRS_{area}$ compared to using $QRS_{area}$ alone. Potential explanations for the negative effect of scar on CRT may be that 1) scar is inherent to non-viable myocytes and therefore reduces the amount of normal
myocardium that can be resynchronized, 2) pacing in scar may reduce resynchronization as electrical propagation may be inhibited by slow conducting (scarred) myocardium.

**Clinical implications**

The present study supports the earlier findings that QRS$_{area}$ may improve the selection of CRT candidates and extents this idea by demonstrating that further improvement in selection may be obtained by combining scar characterization using CMR and VCG analysis. The refined positive predictive value using such combined VCG-CMR focal scar index is highly encouraging, in particular in the ischemic cardiomyopathy cohort, in whom the CRT response is commonly low.(22)

**Limitations**

This study incorporated a relative small number of patients from a single center with the inherent limitation of such study design. Nevertheless, the consecutive patient's cohort reflects a broad real-world experience. QRS$_{area}$ in the present study is slightly lower compared to previous publications,(5, 6) which may be explained by the lower QRS duration and fewer LBBB morphologies in our study population compared to the populations from Maass et al.(6) and Engels et al.(4) The optimal thresholding values for the scar VCG parameters should be taken in the context of the study and a larger population study is needed to validate these optimal thresholding values and different cut-offs may be required in ischemic and non-ischemic cardiomyopathy.

**Conclusion**

Focal scar CMR parameters and QRS$_{area}$ are independent predictors for CRT response and are inversely associated with each other. The highest percentage of CRT response was observed in patients with low focal scar CMR values and high QRS$_{area}$, indicating that combined CMR-VCG parameters may improve prediction to CRT response.
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### Table 1

**Patient characteristics**

| Characteristics                  | QRSarea p-value |
|----------------------------------|-----------------|
| Total patient no.                | 33              |
| Age (years)                      | 65±12           | 0.569           |
| Male                             | 27 (82%)        | 0.479           |
| Ischemic cardiomyopathy          | 16 (49%)        | 0.045*          |
| NYHA (II/III/IV)                 | 1 (3%) / 31 (94%) / 1 (3%) | 0.270           |
| LVEF (%)                         | 24±8            | 0.681           |
| ECG QRS duration (ms)            | 150±22          | 0.016*          |
| ECG LBBB morphology              | 12 (36%)        | <0.001*         |
| CRT response (reduction ∆LVESV ≥15%) | 19 (58%)       | 0.021*          |

Values are displayed as mean and standard deviation or n (%). The association between patient characteristics and QRSarea was investigated using Spearman correlation analyses for continuous variables and Mann Whitney u or Kruskal Wallis tests for dichotomous variables.

BMI=body-mass-index, EDV=end-diastolic volume, ESV=end-systolic volume, LBBB=left bundle branch block, LV=left ventricular, LVEF=LV ejection fraction, NYHA=New York Heart Association.
Table 2
Parameter value differences between responders and non-responders to CRT

| T1 mapping (diffuse fibrosis) | CRT non-responders (n=14) | CRT responders (n=19) | p-value |
|--------------------------------|---------------------------|-----------------------|---------|
| Pre-T1 (ms)                   | 1063 (984-1098)           | 1065 (1002-1105)      | 0.706   |
| ECV (%)                       | 0.33 (0.29-0.37)          | 0.29 (0.24-0.35)      | 0.152   |
| DE-CMR (focal scar)           |                           |                       |         |
| Gray_{2SD} (%)                | 7.27 (5.48-10.37)         | 3.83 (1.69-6.10)      | 0.011*  |
| Scar_{2SD} (%)                | 26.16 (18.69-28.84)       | 13.29 (4.55-26.83)    | 0.065   |
| VCG parameters                |                           |                       |         |
| QRSd (ms)                     | 145 (125-161)             | 151 (144-168)         | 0.199   |
| QRS_{area} (mV.ms)            | 59 (33-78)                | 106 (62-163)          | 0.021*  |
| T_{area} (mV.ms)              | 41 (32-63)                | 42 (25-90)            | 0.577   |
| QRST_{area} (mV.ms)           | 33 (29-68)                | 57 (34-85)            | 0.077   |

Responders are defined as reduction of LVESV ≥15%. P-values are based Mann Whitney u-tests. Continuous variables are displayed as median and interquartile ranges. *indicates significance (p-value ≤0.05).
Table 3

ROC analyses predicting CRT response (ΔLVESV ≥15%) for CMR and VCG parameters

|                      | AUC    | CI          | p-value | Threshold | Sensitivity | Specificity |
|----------------------|--------|-------------|---------|-----------|-------------|-------------|
| **T1 mapping (diffuse fibrosis)** |         |             |         |           |             |             |
| Pre-T1 (ms)          | 0.461  | 0.258-0.663 | 0.702   | <1063     | 47%         | 50%         |
| ECV (%)              | 0.650  | 0.455-0.846 | 0.145   | <0.32     | 68%         | 72%         |
| **DE-CMR (focal scar)** |         |             |         |           |             |             |
| Gray<sub>2SD</sub> (%) | 0.759  | 0.586-0.933 | 0.012*  | <5.91     | 74%         | 71%         |
| Scar<sub>2SD</sub> (%) | 0.692  | 0.503-0.881 | 0.063   | <20.29    | 68%         | 72%         |
| **VCG**              |         |             |         |           |             |             |
| QRS<sub>d</sub> (ms) | 0.635  | 0.438-0.832 | 0.190   | >148      | 63%         | 57%         |
| QRS<sub>area</sub> (mV.ms) | 0.737  | 0.564-0.910 | 0.022*  | >66       | 74%         | 71%         |
| T<sub>area</sub> (mV.ms) | 0.560  | 0.358-0.762 | 0.560   | >39       | 63%         | 50%         |
| QRS<sub>T</sub> (mV.ms) | 0.684  | 0.493-0.875 | 0.074   | >36       | 74%         | 64%         |

*indicates significance (p-value ≤0.05).
Figure 1
Graphical representation of CMR and VCG assessment approach.
**Figure 2**

Scatter plots of VCG and CMR scar parameters vs. ΔLVESV (%). Correlation coefficients are based on Spearman correlation analyses.
**Figure 3**

ROC analyses predicting CRT response ($\Delta$LVESV $\geq$15\%) for CMR focal scar parameters (upper left) and VCG parameters (upper right). Accompanying details of the ROC analyses are provided in Table 3.
**Figure 4**

Scatter plots of CMR scar parameters vs. VCG parameters. Correlation coefficients are based on Spearman correlation analyses. All focal scar CMR parameters correlated inversely with the VCG parameter.
**Figure 5**

2D bar graphs showing CRT response percentage per focal scar CMR (A) and VCG (B) parameter when dividing the study population using the cut-off value as determined by ROC analyses in Table 3. *P*-values in A and B are based on Chi-squared tests.

3D bar graphs demonstrating CRT response percentage when combining QRS\textsubscript{area} with focal scar CMR parameters (C). *P*-values in each graph are based on Fisher’s exact tests.