Comparison of Electrocardiography Markers and Speckle Tracking Echocardiography for Assessment of Left Ventricular Myocardial Scar Burden in Patients with Previous Myocardial Infarction

Running title: Scar Burden in Myocardial Infarction

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Abstract

Myocardial scar burden is an important prognostic factor after myocardial infarction. This cohort study compared assessment of left ventricle scar burden between pathological Q-waves on electrocardiography (ECG), Selvester multi-parametric ECG scoring system for scar burden and global longitudinal strain (GLS) by speckle tracking echocardiography 6 months after myocardial infarction. The scar burden was defined by late gadolinium enhancement cardiac magnetic resonance as fraction of total left ventricle tissue. ECG measures were presence of pathological Q-waves and Selvester scores. GLS was the average of peak strain from 16 left ventricle segments. In 34 patients age 58 ± 10 years (mean $\pm$ SD), the scar burden was 19 (9, 26)% (median (quartiles)) and 79% had scar burden $>5\%$. Patients with scar burden $>5\%$ more frequently had pathological Q-waves (63% vs. 14%) and had worse Selvester scores (5 (3, 7) vs. 0 (0, 1)) and worse GLS ($-16.6 \pm 2.4\%$ vs. $-19.9 \pm 1.1\%$). Pathological Q-waves, Selvester scores, ejection fraction and GLS related to scar burden in univariable analyses. Sensitivity and specificity for detecting scar burden $>5\%$ was 63% and 86% (pathological Q-waves), 89% and 86% (Selvester score), 81% and 86% (ejection fraction), 89% and 86% (GLS) and 96% and 71% (combination of Q-waves, Selvester score and GLS). In conclusion, Selvester score and GLS related to scars 6 months after myocardial infarction, pathological Q-waves were only weakly associated with scar and GLS was associated with scar independently of ECG markers.

Keywords: Myocardial Infarction; Echocardiography; Electrocardiography; Magnetic Resonance Imaging

Myocardial scar burden is an important prognostic factor after acute myocardial infarction.¹ Late gadolinium enhancement cardiac magnetic resonance (LGE-CMR) is the reference method for quantification of scars following myocardial infarction.^{2,3} As LGE-CMR is costly, not available everywhere and has limitations or contraindications in several patient groups, bedside tools such as electrocardiography (ECG) and echocardiography are the most important first line methods for evaluation of infarct size in patients with prior myocardial infarction. Guidelines appreciate Q-waves on ECG as pathognomonic of prior myocardial infarction in patients with ischemic heart disease,⁴ and Q-waves relate to infarct size.⁵ The Selvester multi-parametric ECG scoring system combines the extent and morphology of Q-waves with other ECG indices to calculate scar burden.⁶ Longitudinal strain by 2-dimensional speckle tracking echocardiography is associated with the scar burden on LGE-CMR.⁷ No study has yet compared Q-waves, Selvester scores and longitudinal strain for quantification of scar burden after the acute phase of myocardial infarction. In this study, we related ECG indices and longitudinal strain to myocardial scar burden 6 months after acute myocardial infarction and used LGE-CMR as reference. We hypothesized that ECG indices and longitudinal strain relate to left ventricle scar burden.

Methods

The study population consisted of patients ≥ 18 years with a history of acute myocardial infarction confirmed by ECG and elevated troponin I or troponin T > 99 percentile, recruited in a single tertiary coronary care center. We collected peak Troponin I during the first days of the acute myocardial infarction and standard 12-lead ECG, 2-dimensional transthoracic echocardiography and LGE-CMR 6 months later. We excluded patients who (1) had incomplete datasets (ECG, echocardiography, and LGE-CMR 6 months after myocardial infarction); (2) had an ECG abnormality that interfered with the interpretation of Q-waves or Selvester score (left or right bundle branch block, left or right ventricular hypertrophy, left anterior or posterior fascicular block, or Wolff-Parkinson-White syndrome); (3) had atrial fibrillation; or (4) had significant valvular heart disease.

The Regional Committee for Medical Research (REK South, Oslo, Norway) approved the study. All subjects gave written informed consent.

We defined pathological Q-waves according to the third universal definition of myocardial infarction.⁴ A pathological Q-wave was (1) any Q-wave in leads V2-V3 ≥ 0.02 sec or QS complex in leads V2 and V3; (2) Q-wave ≥ 0.03 sec and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF or V4-V6 in any 2 leads of a contiguous lead grouping (I, aVL; V1-V6; II, III, aVF); (3) R-wave ≥ 0.04 sec in V1-V2 and R/S ≥ 1 with a concordant positive T wave in absence of conduction defect.

The Selvester scoring system uses Q-, R-, and S- wave amplitudes, Q- and R-wave durations, and R/Q and R/S ratios to calculate scar burden.⁶ An ECG can obtain a maximum score of 32 points. Each point corresponds to approximately 3% scar burden in the left ventricle in autopsy specimen.⁶ We calculated the 32-point Selvester score for each ECG.⁶

All patients had echocardiography 6 months after the acute myocardial infarction using Vivid 7 and Vivid E9 systems (GE Healthcare, Horten, Norway). Using commercial software (EchoPAC PC), we calculated ejection fraction by Simpson's biplane method and longitudinal strains by 2-dimensional speckle tracking echocardiography of the left ventricle from apical 4-chamber, 2-chamber and long-axis views. After manually marking the endocardial border and the myocardial thickness, the analysis software performed automatic tracking and estimation of deformation in 6 segments from each view. We converted the measurements from these 18 segments into the standard 16-segment model of the left ventricle⁸ and assessed the global longitudinal strain (GLS) as the average of the peak negative strains for each of the 16 segments. All images used for 2-dimensional speckle tracking echocardiography analysis had frame rate ≥ 50 s⁻¹.

LGE-CMR was performed immediately after echocardiography by a 1.5-Tesla magnetic resonance imaging scanner (Magnetom Sonata, Siemens, Erlangen, Germany). Multiple short-axis slices covering the entire left ventricle were acquired 10–20 min after intravenous injection of 0.2

mmol/kg gadopentetate dimeglumine (Magnevist, Schering, Berlin, Germany). To quantify the scar burden of the left ventricle, we marked the total myocardial area and area of infarcted myocardium manually on each short-axis image (PACS, Sectra, Sweden) and summed up total myocardial and scar volumes.⁹ The scar burden was defined as the infarct tissue as % of total myocardial tissue, estimated as the fraction between the areas.

We present data as mean $\pm$ standard deviation, median (quartiles) or dichotomously as appropriate and used 95% confidence intervals and 2-sided 5% p-values for statistical tests. We compared groups by Fisher's exact test, Independent-samples Mann-Whitney U Test and Student's T-test and used linear regression analyses to assess the impact from pathological Q-wave, Selvester score, ejection fraction and GLS on scar burden. We included constants in the linear regression analyses but performed a separate univariable regression analysis for the Selvester score without the constant to test the scar quantification capability of the Selvester score.⁶ We used the receiver operating characteristics curves to define optimal sensitivity, specificity, accuracy and for defining cut offs values for Selvester score, ejection fraction and GLS in logistic regression analyses.¹⁰ To avoid correlated independent variables in the multivariable analyses we did not include both ECG indices in the same models, because Q-wave is part of the Selvester score. In the combined analyses of ECG criteria and GLS for detecting scars >5% and >20%, the tests were regarded positive if 1 or more of the dichotomous variables indicated disease. We compared sensitivities of ECG criteria vs. of GLS and ECG criteria by pairwise McNemar chi square tests for scar burden >5% and >20% thresholds and specificities by pairwise tests in patients with scars burden below the thresholds.¹¹ We compared R-values between linear regression models by Fisher r-to-z transformation and assessed confidence intervals for sensitivities, specificities and accuracies by the efficient-score method.¹²

Results

Table 1 shows the patient characteristics stratified by 5% scar burden. All patients received beta-blockers at the time for examination. In the total material, the scar burden by LGE-CMR was 19

(9, 26)%. The median Selvester ECG score was 4 (1, 6), and average GLS was -17.2 ± 2.6 %. Peak Troponin I during acute phase of infarction correlated significantly with scar burden ($r=0.70$, $p<0.001$). Age and gender did not differ between those with scar $>5\%$ and $<5\%$. Selvester score was higher and pathological Q-waves more frequent in those with scar $>5\%$. The cardiac volumes did not differ between scar burden $>5\%$ and $<5\%$, but the ejection fraction and GLS were worse in those with scar burden $>5\%$. Figure 1 shows ECG, LGE-CMR and strain analysis from a study patient.

Table 2 shows the linear relations between scars and pathological Q-wave, Selvester score, ejection fraction and GLS. All indices related significantly to scar burden in the univariable analyses. There were no significant differences in the models between any of the linear univariable and multivariable analyses. Ejection fraction correlated strongly with GLS ($r=0.72$, $p<0.001$) and was therefore omitted from the multivariable analyses due to collinearity. Each point of Selvester score was associated with 3.9 (3.1, 4.7) % higher scar burden in the analysis without a constant ($p<0.001$). The optimal value for detecting scars $>5\%$ by receiver operating characteristic curve analyses were 55% for ejection fraction, 1.5 points for the Selvester score and -19.0% for GLS, with area under the curves of 0.82 (0.66-0.97) for ejection fraction and 0.93 (0.84-1.00) for Selvester score and for GLS. Table 3 shows sensitivity, specificity and accuracy for each index as markers of scars $>5\%$ and odds ratios for the logistic regression analyses. All indices were markers of scars $>5\%$ in the univariable analyses. Only GLS and Selvester score remained significant markers in the multivariable logistic analyses.

The scar burden was $>20\%$ in 17 (50%) of patients. As expected, the optimal cut off values were worse for 20% than for 5% scar burden (5 points for Selvester score and -15.1% for GLS). Pathological Q-waves (13/17 vs. 5/17, $p=0.015$) and Selvester score $>$ the optimal cut off value (11/17 vs. 4/17, $p=0.037$) were more frequent at high scar burden. The sensitivities, specificities and accuracies for 20% scar burden were 76 (50, 92) %, 71 (44, 89) % and 74 (55, 86) % for pathological Q-waves and 65 (39, 85) %, 76 (50, 92) % and 71 (52, 84) % for Selvester score. Table 4 shows the

sensitivities, specificities and accuracies for tests for scars >5% and >20% solely by ECG criteria (pathological Q-wave and/or Selvester score) and by ECG criteria in combination with GLS criteria. Both for 5% and 20% scar burden, the combination of ECG and GLS criteria detected all except 1 patient with scars > the thresholds levels, with 2 (29%) and 10 (59%) false positive cases respectively. None of the differences in sensitivities or specificities between test by ECG indices vs. by combination of ECG and GLS indices were statistically significant.

Discussion

The present study is the first to compare Q-wave, Selvester score and deformation indices as markers of scar burden by LGE-CMR 6 months after acute myocardial infarction. Pathological Q-waves, Selvester score and GLS related significantly to scar burden and were markers of scar burden >5% as individual indices. The Selvester score was a stronger marker than pathological Q-waves. The combination of ECG and GLS criteria had excellent sensitivities for detecting scar burden >5% and >20%. This advocates the use of GLS in the follow-up of patients after myocardial infarction.

Detecting small amounts of scars is important because the prognosis for patients with silent scars is similar to those with known scars.¹³ Cardiac volumes were similar in hearts with and without scar while ejection fraction was associated with scars. Troponin I correlated significantly with scar burden size, in line with previous studies.¹⁴

The accuracy of pathological Q-wave as a marker of scars will depend on the desired threshold for scar burden and the definition of pathological Q-wave.^{5,15-17} Similar to other studies,⁵ we found higher scar burden in hearts with pathological Q-waves and that pathological Q-wave was a significant marker of scar burden >5% and >20%. As demonstrated in our study, Q-waves have some shortcomings as a marker of prior myocardial infarction.^{4,5,16} Pathological Q-waves are associated with transmural scars¹⁸ but the presence of pathological Q-waves is more dependent on scar burden than transmural scars.¹⁵ Pathological Q-waves can be absent in small infarctions¹⁵⁻¹⁷ and in

transmural scars,⁵ and can be present in non-transmural scars¹⁹ and also in hearts with no scars on LGE-CMR.⁵ Due to this inconsistency, it has been suggested that the distinction between Q-infarction and non-Q-infarction is not clinically relevant and that the myocardial infarction should be judged on anatomical and functional considerations.²⁰ Our results showed that using Q-waves as the only diagnostic criterion would miss 37% of all patients with scar burden >5% and confirmed that pathological Q-waves can be present in patients with low scar burden. These considerations are increasingly more relevant since the majority of patients in the Western communities receive revascularization therapy,²¹ resulting in smaller infarcts as compared to the pre-reperfusion era.^{16,22,23}

The Selvester scoring system uses Q-waves in combination with other ECG characteristics to quantify scars.^{6,24} Studies have shown analysis of Selvester score to be feasible and reproducible.²² Quantification of scar burden by Selvester score compared to MRI has shown small systematic differences but wide range in limits of agreement (within the range of $\pm 20\%$ scar burden).²² Some have speculated that the relationship between Selvester score and scar burden is different after introduction of reperfusion therapies, because the scarred area has less distinct borders towards viable myocardium.²⁵ The increase in scar burden per point Selvester score in our study was close to the findings in an in-vivo study²⁶ and an autopsy study.⁶ The optimal Selvester score criterion value from the receiver operator characteristics curve was 1.5 points for scar burden >5% and 5.0 points for scar burden >20% in our study, in line with studies showing that the increase in scar burden per Selvester score point may be non-linear and lower in the era of reperfusion therapy.²³

Longitudinal strain relates to scar burden.^{7,27-29} We are, however, not aware of previous studies exploring GLS as a marker for LV scar burden as low as down to 5%. Compared to the sensitivity of 89% and specificity of 86% for detection of scar burden >5% by GLS in our study, others have found much lower sensitivity and specificity for detecting infarct of any size by wall motion score by echocardiography.³⁰

Opposed to studies of GLS and Selvester score in the acute phase of myocardial infarction,²⁸ the Selvester score in our study related significantly to scar burden in the analyses together with GLS. The combination of ECG criteria and GLS identified patients with scar burden >5% and >20% with only 1 false-negative test at each threshold. There were few extra false-positive tests, especially for identification of small scars. The lack of significant differences between the sensitivities and specificities might be due to the relatively low number of patients. Our findings suggest the combination of ECG and GLS as a feasible test for identification of patients with scars following myocardial infarction in clinical practice.

Our study is a relatively small observational study and there is therefore a need for larger studies including patients with a broader range of ejection fractions to confirm our findings. We used a standard definition of pathological Q-waves.⁴ Using another definition could have altered the results although studies have shown small differences in presence of pathological Q-waves in infarcted patients depending on definitions.⁵ We used presence of pathological Q-waves dichotomously and the clinical feasibility of pathological Q-wave for scar quantification was therefore limited. Because we used the standard Selvester scoring system, we did not include patients with ECG abnormalities that interfered with the interpretation of Q-waves or Selvester score. Future studies should explore the relation between regional ECG findings, regional strain and regional localization of myocardial scar.

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Conflicts of interest: None.

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Figure captions:

Figure 1. Electrocardiography (A), late enhancement magnetic resonance 4-chamber image (B) and segmental 4-chamber speckle tracking 2D-strain analysis (C) from a study patient. The white arrows in panel B and C denote findings from a scar in the apical lateral region. The apical (magenta) and mid (dark blue) inferior segmental strain curves in panel C show reduced systolic function compared to the other segments. The dotted white curve is the strain for the entire sample area. X-axis: Time. Y-axis: Longitudinal strain (%). AVC: Aortic valve closure.

Table 1. Patient characteristics stratified by scar burden <5% (n=7) and >5% (n=27) and p-value for difference between groups. Peak Troponin I is the maximal value during the acute phase of myocardial infarction.

Parameter	Scar burden <5% (n=7)	Scar burden >5% (n=27)	p-value
Age (years)	59 ± 14	57 ± 9	0.684
Female	2 (29%)	9 (33%)	1.000
Left ventricle end-diastolic volume (ml)	150 (104, 184)	135 (120, 164)	0.803
Left ventricle end-systolic volume (ml)	50 (30, 62)	58 (40, 78)	0.177
Ejection fraction (%)	60 ± 7	49 ± 10	0.013
Q-wave on electrocardiography	1 (14%)	17 (63%)	0.035
Selvester score	0 (0, 1)	5 (3, 7)	<0.001
Global longitudinal strain (%)	-19.9 ± 1.1	-16.6 ± 2.4	0.001
Peak Troponin I (microgram/l)	7 (2, 11)	48 (24, 96)	0.001
Percentage of scar on late gadolinium enhancement cardiac magnetic resonance (%)	0.6 (0.0, 4.0)	21.9 (16.2, 28.6)	<0.001

Table 2

Table 2. Relation between scar burden and pathological Q-waves, Selvester score and global longitudinal strain in linear univariable and multivariable analyses. See text for details.

	Beta	p-value	R-square (adjusted)
Univariable analyses			
Q-wave (scar-% increase if present)	11.6 (4.4, 18.8)	0.003	0.21
Selvester score (scar-% increase per point)	2.4 (1.2, 3.6)	<0.001	0.31
Ejection fraction (scar-% increase per ejection fraction-%)	-0.69 (-1.03, -0.35)	<0.001	0.31
Longitudinal strain (scar-% increase per strain-%)	3.2 (2.0, 4.4)	<0.001	0.45
Multivariable analysis of Q-wave and global longitudinal strain			
Q-wave (scar-% increase if present)	8.1 (3.6, 12.6)	0.008	0.55
Longitudinal strain (scar-% increase per strain-%)	2.8 (1.7, 3.9)	<0.001	
Multivariable analysis of Selvester score and global longitudinal strain			
Selvester score (scar-% increase per point)	1.5 (0.4, 2.5)	0.010	0.54
Longitudinal strain (scar-% increase per strain-%)	2.5 (1.4, 3.7))	<0.001	

Beta are values with 95% confidence intervals.

Table 3

Table 3. Sensitivity, specificity, accuracy and logistic regression analyses for presence of scar burden >5% by pathological Q-waves, Selvester score, ejection fraction and global longitudinal strain. See text for details.

	Sensitivity (%)	Specificity (%)	Accuracy (%)	Logistic regression		
				Log odds ratio	p-value	Cox&Snell R-square
Univariable analyses						
Q-wave	63 (42, 80)	86 (42, 99)	68 (49, 82)	2.3 (0.1, 4.6)	0.044	0.15
Selvester score	89 (70, 97)	86 (42, 99)	88 (72, 96)	3.9 (1.4, 6.3)	0.002	0.35
Ejection fraction	81 (61, 93)	86 (42, 99)	82 (65, 93)	3.3 (0.9, 5.6)	0.006	0.28
Global longitudinal strain	89 (70, 97)	86 (42, 99)	88 (72, 96)	3.9 (1.4, 6.3)	0.002	0.35
Multivariable analysis of Q-wave and global longitudinal strain						
Q-wave				2.6 (-0.4, 5.6)	0.085	
Global longitudinal strain				4.1 (1.3, 6.9)	0.005	0.42
Multivariable analysis of Selvester score and global longitudinal strain						
Selvester score				3.2 (0.3, 6.0)	0.029	
Global longitudinal strain				3.2 (0.3, 6.0)	0.029	0.45

Log odds ratios are values with 95% confidence intervals. Specificity, sensitivity and accuracy are % with 95% confidence intervals.

Table 4

Table 4. Sensitivities, specificities and accuracies of tests for scar burden >5% and >20% solely by electrocardiographic criteria (pathological Q-wave and/or Selvester score) and by electrocardiographic criteria in combination with global longitudinal strain. See text for details.

Scar threshold	Diagnostics variables	Sensitivity	Specificity	Accuracy
Scar >5%	Electrocardiography	89 (70, 97)	86 (42, 99)	88 (72, 96)
	Electrocardiography and global longitudinal strain	96 (79, 100)	71 (30, 95)	91 (75, 98)
Scar >20%	Electrocardiography	76 (50, 92)	59 (33, 81)	68 (49, 82)
	Electrocardiography and global longitudinal strain	94 (69, 100)	41 (19, 67)	68 (49, 82)

Sensitivity, specificity and accuracy are % with 95% confidence intervals.

Figure 1
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Note: This figure should be in color in print and on the web