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Published in:
American Heart Journal

DOI:
[10.1016/j.ahj.2005.07.022](https://doi.org/10.1016/j.ahj.2005.07.022)

2005

[Link to publication](#)

Citation for published version (APA):

Engblom, H., Hedström, E., Heiberg, E., Wagner, G. S., Pahlm, O., & Arheden, H. (2005). Size and transmural extent of first-time reperfused myocardial infarction assessed by cardiac magnetic resonance can be estimated by 12-lead electrocardiogram. *American Heart Journal*, 150(5), 920-920.
<https://doi.org/10.1016/j.ahj.2005.07.022>

Total number of authors:
6

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The following pages constitute the final, accepted and revised manuscript of the article:

Engblom, Henrik and Hedstrom, Erik and Heiberg, Einar and Wagner, Galen S and Pahlm, Olle and Arheden, Hakan

“Size and transmural extent of first-time reperfused myocardial infarction assessed by cardiac magnetic resonance can be estimated by 12-lead electrocardiogram.”

Am Heart J. 2005 Nov;150(5):920.

Publisher: Elsevier.

Use of alternative location to go to the published version of the article requires journal subscription.

Alternative location: <http://dx.doi.org/10.1016/j.ahj.2005.07.022>

Section: Clinical investigations

**Size and Transmural Extent of First-Time Reperfused Myocardial Infarction
Assessed by Cardiac Magnetic Resonance can be Estimated by 12-lead ECG**

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Short title: AMI characteristics by CMR and ECG

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ABSTRACT

Background: The ability of the 12-lead ECG to quantify size and transmural extent of myocardial infarction (MI) is not fully explored. Q waves are still thought of as indicative of transmural MI, despite that several studies have rejected this association. We hypothesized that size and transmural extent of acute MI indeed can be estimated by QRS scoring on the 12-lead ECG using delayed contrast-enhanced magnetic resonance imaging (DE-MRI) as gold standard and that Q waves are not predictive of transmural MI.

Methods: Twenty-nine patients with first-time reperfused MI were studied. DE-MRI was performed and 12-lead ECG was recorded 8 ± 1 days after the acute event. MI size and transmural extent were determined by DE-MRI and compared with Selvester QRS score from the ECG recorded at the same day.

Results: There was a good correlation ($r = 0.79$, $p < 0.001$) between MI size by QRS scoring and DE-MRI. As local MI transmural extent increased as assessed by DE-MRI, the local QRS score increased progressively ($p < 0.001$). There was no significant difference in the number of Q-wave related QRS points between non-transmural and transmural MI (1.8 ± 0.6 vs. 2.9 ± 0.4 , $p = 0.14$). The global QRS score, however, differed significantly (3.1 ± 0.8 vs. 5.1 ± 0.6 , $p < 0.05$).

Conclusion: QRS score is significantly related to both MI size and transmural extent by DE-MRI in patients with first-time reperfused MI. Presence of Q waves, however, is not indicative of transmural MI in these patients. Thus, QRS scoring could potentially be used for diagnosing and characterising MI in patients with suspected recent MI.

INTRODUCTION

The incidence and prognosis of heart failure and ventricular arrhythmias after acute coronary occlusion are related to myocardial infarction (MI) size (1-4). The transmural extent of MI has been shown to be related to probability of functional recovery after acute revascularization (5). Thus, quantitative assessment of both MI size and transmural extent is important for clinical decision making in patients with acute MI.

In recent years, delayed contrast-enhanced magnetic resonance imaging (DE-MRI) has been shown to be highly accurate in quantifying and characterizing MI (6, 7). Thus, DE-MRI is an appropriate method for studying MI pathophysiology *in vivo* and is currently considered the gold standard for diagnosing and characterizing MI (8).

The 12-lead ECG has also been shown to be useful in estimating MI size (9). For this purpose the so called *Selvester QRS scoring system* was developed and validated by histopathology for different MI locations (10-13) and by DE-MRI for chronic anterior MI (14). However, the 12-lead ECG has previously been described as insensitive to MI transmural extent as no relationship was found between Q-wave MI and transmural MI by DE-MRI (15). The QRS scoring system considers not only Q waves but also other infarct-related deformities in the QRS complex such as changes in R- and S-wave amplitudes, R-wave durations, as well as R/Q- and R/S-ratio. How the Selvester QRS score relates to MI size and transmural extent of first-time reperfused MI assessed by DE-MRI has not yet been studied. Therefore the aim of the present study was to test the hypotheses that QRS score is related to MI size and transmural extent using DE-MRI as gold standard and that presence of Q waves is not indicative of transmural MI in patients with first-time reperfused MI.

METHODS

Study population

Twenty-nine patients (28 males, mean age 61 years, range 42-83 years) with first-time MI arriving at the Coronary Care Unit, Lund University Hospital, were prospectively included in the study. All patients had significant ST deviation, positive biochemical markers and symptoms suggestive of acute MI. All patients underwent successful primary percutaneous coronary intervention (PCI). Exclusion criteria comprised generally accepted contraindications for MRI such as pace-maker, defibrillators and cerebral aneurysm clips, as well as confounding factors for the quantitative ECG analysis including left or right bundle branch block, left anterior or posterior fascicular block, left ventricular hypertrophy and preexcitation. Patients with clinical history of prior MI, or signs of prior MI by ECG or DE-MRI, were also excluded.

Study protocol

The MRI examination took place 8 ± 1 days after admission. The culprit artery was assigned by the angiographer performing the PCI and later by a second angiographer, blinded to the assignment of the former. The admission ECG was used to localize the acute ischemia based on leads with ST deviation characteristic of acute MI. The quantitative ECG analysis (QRS scoring) was undertaken by an experienced ECG reader, blinded to the MR results. The MRI analysis was performed by 2 observers, blinded to each others results and to the ECG. The study protocol was approved by the local ethics committee at Lund University and all patients gave their written informed consent to participate in the study.

Cardiac magnetic resonance imaging

MR imaging was performed on either of two 1.5 T systems: Magnetom Vision (Siemens, Erlangen, Germany) with a CP body array coil, or Philips Intera CV (Philips, Best, the Netherlands) with a cardiac synergy coil. All subjects were placed in supine position. Short- and long-axis images were acquired, covering the left ventricle (LV) (16). The gradient-recalled echo (GRE) cine sequence and the segmented inversion-recovery (IR) GRE sequence were triggered by ECG, and images were acquired during breath-hold. The short-axis GRE cine images (slice thickness 8 mm, slice gap 2 mm) were used to measure LV dimensions and the corresponding end-diastolic delayed enhanced IR GRE images were used to measure the MI volume. A commercially available extracellular gadolinium-based contrast agent (*gadoteric acid*, Gd-DOTA, Guerbet, Gothia Medical AB, Billdal, Sweden) was administered intravenously (0.2 mmol/kg) 30 ± 9 (SD) minutes before image acquisition. DE-MRI using the IR-GRE sequence utilizes an increase in regional fractional distribution of extracellular MRI contrast media within the injured area to achieve contrast between infarcted and non-infarcted myocardium (17-20). The inversion time (TI) was adjusted to null the signal from the non-infarcted myocardium.

MRI analysis

The MR images were analyzed using freely available software developed and validated in-house (Segment 1.14, <http://segment.heiberg.se>)(21). The myocardium in each LV short-axis slice was manually segmented by tracing endocardial and epicardial borders. Regions of MI were visually identified as those with bright signal intensity and were segmented manually with an additional region of interest (Fig 1A).

The MI transmural extent was assessed by analyzing the radial extent of hyperenhancement between the endocardial and epicardial borders of the myocardial wall at 4.5° intervals around the circumference of LV short-axis DE-MR images (Fig 1B). The maximum transmural extent of the entire MI as well as the mean and maximum transmural extent in each of the 12 LV segments (Fig 1C) was calculated. MIs were labeled transmural if hyperenhancement extended throughout the entire LV wall at any point. Segments 1-6 are referred to as anterior, 7-9 as inferior and 10-12 as posterolateral. MI size as percent of the LV was calculated by summing the absolute amount of hyperenhanced tissue for all LV short-axis slices, divided by the total amount of LV tissue.

Electrocardiographic recordings and analysis

Standard 12-lead ECG was recorded at the time of patient admission and at the time of the MRI examination using a MEGACART-R (Siemens-Elema AB, Solna, Sweden). The frequency response was set at the range of 0.05-150Hz and the sampling rate was 500 Hz. The admission ECG was used to designate the location of the acute ischemia based on ST deviation patterns according to the method described by Aldrich et al (22). To estimate MI size from the ECG, the 50-criteria/31-point *Selvester QRS scoring system* was employed. Each QRS point has been designed to represent approximately 3 % of the LV (Appendix, Panel A) (10-13). Q-, R- and S-wave amplitudes, Q- and R-wave durations, and R/Q- and R/S-ratio were manually measured and checked against previously established criteria. The summed QRS points constitute the global QRS score. The estimated MI size as percent of the LV was acquired by multiplying global QRS score by 3. The *Selvester QRS scoring system* also generates a local QRS score for each of the 12 LV segments (Appendix,

Panel B). The local QRS scores were compared with MI transmural by DE-MRI in corresponding LV segments.

Statistical analysis

All results were expressed as mean \pm SD, except when comparing means where standard error of the mean was used. Linear regression analysis was used to assess the relationship between MI size by QRS scoring and DE-MRI. Bland-Altman plots (23) were used to assess differences in MI size between QRS scoring and DE-MRI. Two-tailed *t*-tests were used to compare the non-transmural and transmural MI groups with regards to global QRS score and the number of Q-wave related QRS points. The Jonckheere-Terpstra test for trend was used to assess the relationship between local QRS score and MI transmural by DE-MRI in the 12 LV segments. SPSS version 12.0 was used for all statistical analyses. P values less than 0.05 were considered to indicate statistical significance.

RESULTS

MRI and angiographic findings

In 41 % (11/29) of the patients, MI was found in the anterior LV wall, all showing left anterior descending artery (LAD) occlusion by angiography (Table 1). In 48 % (14/29) of the patients, MI was found in the inferior LV wall, all showing right coronary artery (RCA) occlusion. In 7 % (2/29) of the patients MI was located in the posterolateral LV wall resulting from occlusion of the left circumflex artery (LCX). There was complete agreement between the two angiographers assigning the culprit artery. In two patients no MI was found. The anterior, inferior and posterolateral MIs measured 9 ± 8 %, 8 ± 5 % and 17 ± 4 % of the LV, respectively.

ECG findings

The localization of the acute ischemia on the admission ECG corresponded with the main location of MI by DE-MRI in 96 % (26/27) of the patients (Table 1). One patient with posterolateral MI by DE-MRI was assigned inferior ischemia location on the admission ECG. However, in addition to inferior ST elevation, this patient had ST depression in V1 and V2 as well as ST elevation in V5 and V6 suggestive of posterolateral involvement. The anterior, inferior and posterolateral MIs measured 12 ± 7 %, 11 ± 9 % and 21 ± 8 % of the LV, respectively. In 21 % (6/29) of the patients there were no signs of MI on the ECG (QRS score = 0). Two of those patients had no MI by DE-MRI and for the remaining 4 patients MI size measured by DE-MRI was less than 2 % of the LV.

Relationship between infarct size by QRS scoring and DE-MRI

A good correlation ($r = 0.79$, $p < 0.001$) between MI size estimated by QRS scoring and measured by DE-MRI was found (Figure 2A). The correlation remained good when analysing MIs caused by LAD occlusion ($r = 0.86$, $p < 0.001$) and RCA occlusion ($r = 0.72$, $p = 0.004$) separately (Figure 2B,C). Since only two MIs caused by LCX occlusion were found, the correlation could not be assessed in this group separately (Figure 2D). MI size was overestimated by 3.3 ± 5.6 % (Figure 2A) by QRS scoring compared to DE-MRI. The overestimation was in the same range for MI caused by LAD (3.7 ± 6.1 %, Figure 2B), RCA (3.3 ± 5.6 %, Figure 2C) and LCX (4.1 ± 6.8 %) occlusions.

Relationship between local QRS score and infarct transmurality

Local QRS score was significantly correlated to MI transmurality by DE-MRI ($r = 0.71$, $p < 0.001$) in the 12 LV segments (Figure 3A). As MI transmurality increased the local QRS score increased progressively ($p < 0.001$) (Figure 3B).

Relationship between Q waves and infarct transmurality

Non-transmural MI was found in 45 % (13/29) of the patients of which 46 % (6/13) were assigned Q-wave points. Transmural MI was found in 48 % (14/29) of which 93 % (1/14) were assigned Q-wave points. No significant difference in number of Q-wave related QRS points was found between the non-transmural and transmural MI groups (1.8 ± 0.6 vs. 2.9 ± 0.4 , $p = 0.14$) (Figure 4A). The global QRS score, however, differed significantly between the non-transmural and transmural MI groups (3.1 ± 0.8 vs. 5.1 ± 0.6 , $p < 0.05$) (Figure 4B). Q-wave related local QRS points were absent in 35 % (13/37) of the LV segments showing 100 % MI transmurality at some

point. Thus, presence of Q waves was not indicative of transmural MI. Figure 5 shows three examples where it would be wrong to equate Q-wave MI with transmural MI.

DISCUSSION

The data shows that QRS score is significantly related to MI size and transmural by DE-MRI in patients with first-time reperfused MI. Presence of Q waves, however, is shown not to be indicative of transmural MI in these patients.

Pathophysiological considerations for infarct-related QRS changes

In 1954, Prinzmetal et al (24) concluded from their pathology studies that only transmural MI could give rise to pathologic Q waves in the 12-lead ECG. However, more recent literature has rejected the notion that Q waves can be used to differentiate transmural from non-transmural MI (25-27). Furthermore, studies in patients with first-time MI have not been able to show any differences in clinical outcome between Q-wave and non-Q-wave MI (28-30). Appearance of Q waves is only one possible electrocardiographic outcome after MI. Several depolarization abnormalities such as peri-infarction block and slow conduction can affect the QRS complex after MI. Pathological Q waves only appear when the MI causes the initial depolarization forces to be directed away from the leads in which the Q waves are seen, whether the MI is transmural or not.

Eight to ten percent of the MIs in general involve only the base of the LV and do not produce initial QRS changes (31). Thus, changes in the later part of the QRS complex must also be taken into consideration when performing quantitative assessment of MI from the ECG. In the present study no patient exhibited MI involving only the basal third of the LV. However, if reduction in S-amplitude in V1 and V2 would not have been taken into consideration in one of the patients with posterolateral MI, QRS score would have significantly underestimated the MI size.

Infarct transmurality

Moon et al (32) have previously shown that the dichotomous terms transmural and non-transmural MI are overly simplistic since an MI is rarely just one or the other. Therefore, in the present study, MI transmurality was not only assessed as transmurality for the entire MI but also as the mean MI transmurality for a given LV segment. Forty-six percent of the patients with non-transmural MI were assigned Q-wave criteria in the present study. Thus, equating non-transmural MI with non-Q-wave MI would be wrong in almost half of the patients. The mean global QRS score was found to differ between the non-transmural and transmural MI groups. However, given the considerable overlap in both Q-wave related QRS points and global QRS score between the groups (Figure 4), none of the ECG indices can be used to differentiate between non-transmural and transmural MI. Sievers et al (15) has previously showed that ECG findings cannot be used to differentiate between transmural and non-transmural MI or to determine MI location. However, only Q waves were considered in their study. Local QRS score, however, was significantly related to MI transmurality by DE-MRI in the 12 LV segments. This indicates that the *Selvester QRS scoring system* could potentially be used to identify patients likely to recover LV function after revascularization, since regional MI transmurality is shown to be important for functional recovery after revascularization (5).

Infarct size

The Selvester QRS scoring system was developed and validated before revascularization was clinically established (11-13). Residual viable myocardium within in the MI region is more likely to be found after revascularization in comparison to non-revascularized MI. Consequently, it is not clear how the Selvester

QRS scoring system performs in patients undergone acute reperfusion therapy. Several studies have shown that QRS scoring is associated with indirect estimated MI size after reperfusion (33-35). This is the first study, however, exploring the relationship between MI size by QRS scoring and DE-MRI in acute reperfused MI. There was a good correlation ($r = 0.79$, $p < 0.001$), which is comparable with the relationship found in previous histopathology reports ($r = 0.72-0.80$) (11-13). Even though all MIs exceeding 2 % of the LV were identified by the ECG, accurate characterization of MI size and transmural extent required DE-MRI.

In a previous study on chronic anterior MI the correlation between MI size by QRS scoring and DE-MRI was only moderate ($r = 0.40$) (14). The majority of those patients, however, had severe LV remodelling and apical aneurysms, limiting the diagnostic accuracy of the QRS scoring system.

Limitations

The study population in this study does not represent the MI population in general since all patients had first-time reperfused MI and no confounding factors for QRS scoring. The ability to predict MI size and location from 12-lead ECG, however, is of highest importance in patients with suspected first-time MI to rule out or confirm infarcted myocardium. There were few LV segments that had mean transmural extent between 76 and 100 %. Still, the trend with higher local QRS score as the MI transmural extent increased was highly significant. The clinical use of the QRS scoring system is still limited, since patients may develop conduction abnormalities due to MI, introducing confounding factors for QRS scoring.

The standard 17-segment model of the LV (36) was not used in the present study. The rationale for using the 12-segment LV model instead was that the QRS scoring

system was developed using the 12-segment model (37) and that the DE-MRI data was easily adopted to this model.

CONCLUSIONS

QRS score is significantly related to MI size and transmurality by DE-MRI in patients with first-time reperfused MI. Presence of Q waves, however, is not indicative of transmural MI in these patients. Thus, QRS scoring could potentially be used for diagnosing and characterising MI in patients with suspected recent MI.

ACKNOWLEDGEMENTS

The study was supported by the Swedish Medical Research Council, the Swedish Heart Lung Foundation and the Medical Faculty at Lund University.

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APPENDIX

Panel A			Panel B											
Lead	Criteria	Pts.	Ant-sep			Ant-sup			Inf			Post-lat		
			1	2	3	4	5	6	7	8	9	10	11	12
I [1]	$Q \geq 30$ ms	1				1	1					1		
	$R/Q \leq 1$	1				1	1	1						
	$R \leq 0.2$ mV	1				1	1	1						
II [2]	$Q \geq 40$ ms	2							1	2	2			1
	$Q \geq 30$ ms	1								1	1			1
aVL [2]	$Q \geq 30$ ms	1					2	1						
	$R/Q \leq 1$	1					1	2						
aVF [5]	$Q \geq 50$ ms	3							3	2	2		1	1
	$Q \geq 40$ ms	2							2	2	2			
	$Q \geq 30$ ms	1							2	2	1			
	$R/Q \leq 1$	2							2	3				1
	$R/Q \leq 2$	1							1	2				
V1(ant) [1] (post) [4]	Any Q	1		1	2									
	$R/S \geq 1$	1										1	1	1
	$R \geq 50$ ms	2							1	1		2	2	
	$R \geq 1.0$ mV	2							1	1		2	2	
	$R \geq 40$ ms	1							1			1	1	
	$R \geq 0.6$ mV	1							1			1	1	
	Q and $S \leq 0.3$ mV	1										1	1	1
V2(ant) [1] (post) [4]	Any Q	1	1	1	1									
	$R < RV1$	1	1	1	1									
	$R \leq 10$ ms	1	1	1	1									
	$R \leq 0.1$ mV	1	1	1	1									
	$R/S \geq 1.5$	1									1	1	1	
	$R \geq 60$ ms	2							1	1		1	2	1
	$R \geq 2.0$ mV	2							1	1		1	2	1
	$R \geq 50$ ms	1							1	1		1	1	
	$R \geq 1.5$ mV	1							1	1		1	1	
	Q and $S \leq 0.4$ mV	1							1			1	1	1
V3 [1]	Any Q	1	1	1			1							
	$R \leq 20$ ms	1	1	1			1							
	$R \leq 0.2$ mV	1	1	1			1							
V4 [3]	$Q \geq 20$ ms	1	1	1		1								
	$R/Q \leq 0.5$	2	2			1	1							
	$R/S \leq 0.5$	2	2			1	1							
	$R/Q \leq 1$	1	1			1								
	$R/S \leq 1$	1	1			1								
	$R \leq 0.7$ mV	1	1			1								
V5 [3]	$Q \geq 30$ ms	1	1	1		1								
	$R/Q \leq 1$	2	1			2	1							
	$R/S \leq 1$	2	1			2	1							
	$R/Q \leq 2$	1				1	1							
	$R/S \leq 2$	1				1	1							
	$R \leq 0.7$ mV	1				1	1							
V6 [3]	$Q \geq 30$ ms	1				1			1			1		
	$R/Q \leq 1$	2				1			2			2		
	$R/S \leq 1$	2				1			2			2		
	$R/Q \leq 3$	1				1			1			1		
	$R/S \leq 3$	1				1			1			1		
	$R \leq 0.6$ mV	1				1			1			1		
Global score:														
Local score:														

The *Selvester QRS scoring system* used to quantify the amount of MI from the 12-lead ECG. **Panel A)** The 50 QRS criteria. If more than one criterion within the same box was met, only the one generating the highest point was considered. The QRS points assigned in Panel A were summed to a global QRS score. **Panel B)** The distribution of QRS points into local QRS points per LV segment. Each QRS point assigned in Panel A has 3 corresponding local QRS points assigned in Panel B. For each LV segment (1-12) the local QRS points were summed to a local QRS score which was compared with MI transmuralities by DE-MRI in the corresponding LV segment.

ant, anterior; Ant-sep, anteroseptal; Ant-sup, anterosuperior; Inf, inferior; post, posterior; Post-lat, posterolateral

FIGURE LEGENDS

Figure 1

A) An example of a typical DE-MRI short-axis slice, where the myocardium and the MI (arrow) are delineated. **B)** Corresponding DE-MRI short-axis slice showing how the MI transmuralities were determined at each 4.5° around the circumference. **C)** Bulls-eye plot of the 12 LV segments for which local QRS score and MI transmuralities by DE-MRI were determined.

Figure 2

The relationship between infarct size by QRS scoring and DE-MRI. **Upper panel:** Linear regression plots for **(A)** all patients, **(B)** patients with left anterior descending artery (LAD) occlusion, **(C)** patients with right coronary artery (RCA) occlusion and **(D)** patients with left circumflex artery (LCX). **Lower panel:** Bland-Altman plots showing the differences in MI size between QRS scoring and DE-MRI in the corresponding patient groups. QRS scoring overestimated the MI size by $3.3 \pm 5.6\%$.

Figure 3

Relationship between local QRS score and mean MI transmuralities by DE-MRI in the 12 LV segments. The linear regression plot **(A)** and the bar graph **(B)** show that local QRS score increases progressively as infarct transmuralities increase as assessed by DE-MRI. Bars indicate mean local QRS score \pm standard error of the mean for different ranges of MI transmuralities.

Figure 4

Comparison between non-transmural and transmural MI with regards to **(A)** the number of Q-wave points and **(B)** global QRS score. The figure shows that there is no significant difference in number of Q-wave related QRS points between the non-transmural and transmural MI groups, but a significant difference in global QRS score. Given the considerable overlap in both Q-wave points and global QRS score, none of them could be used to differentiate between the two groups. Solid dots represent mean \pm standard error of the mean.

Figure 5

Three cases illustrating the importance of considering not only Q-waves for MI detection and quantification by ECG. **A)** A small transmural, non-Q-wave MI in the inferior LV wall. **B)** A non-transmural, Q-wave MI in the inferior LV wall. **C)** A transmural, non-Q-wave MI in the posterolateral LV wall. This patient had prominent R-waves and small S-waves in V1 and V2 suggestive of posterolateral MI. The MRI examination was aborted before long-axis images were acquired.

Arrows indicate either MI by DE-MRI or QRS changes generating QRS points.

2ch, two chamber long-axis view

Table 1. Patient characteristics

	Number (%)
Male	28 (97 %)
Age (range)	61 ± 9 (42-83)
Occluded artery	
LAD	13 (45 %)
RCA	14 (48 %)
LCx	2 (7 %)
Ischemia localization (ECG)	
Anterior	12 (41 %)
Inferior	15 (52 %)
Posterolateral	2 (7 %)
Primary MI location (MRI)	
Anterior	11 (38 %)
Inferior	14 (48 %)
Posterolateral	2 (7 %)
None	2 (7 %)
Primary MI location (QRS score)	
Anterior	11 (38 %)
Inferior	10 (34 %)
Posterlateral	2 (7 %)
None	6 (21 %)
Left ventricular mass (g)	155 ± 33 (96-236)

Figure 1

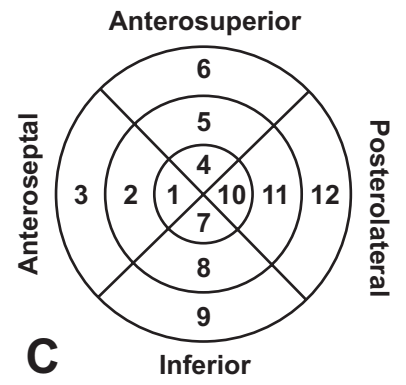
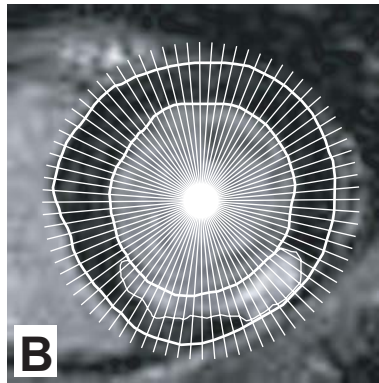
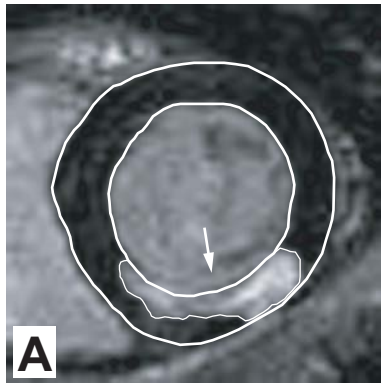


Figure 2

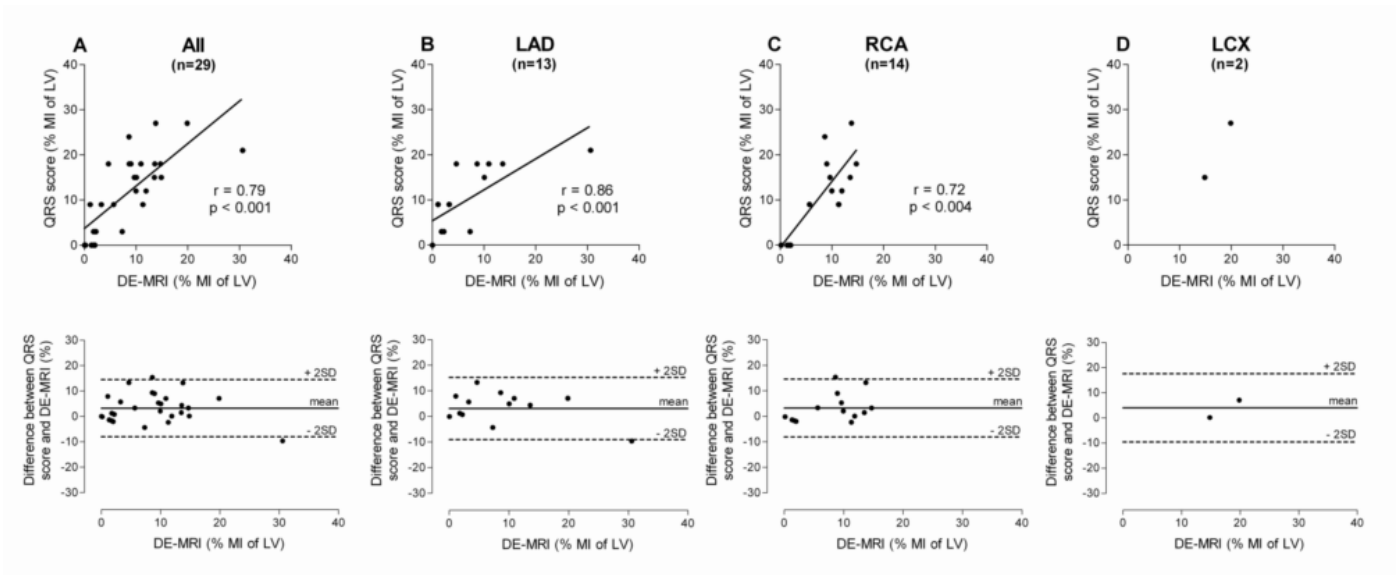


Figure 3

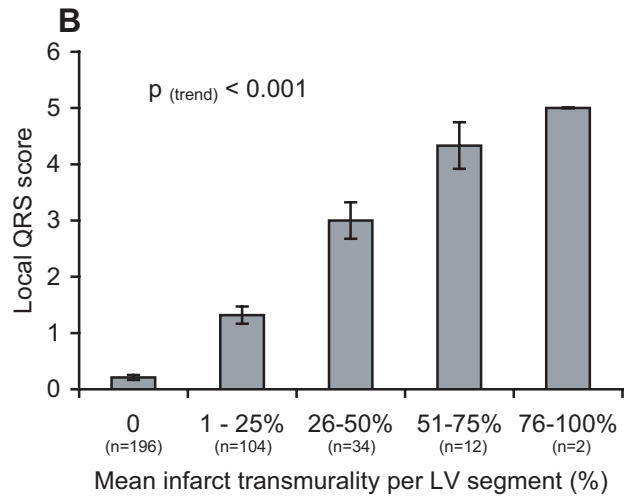
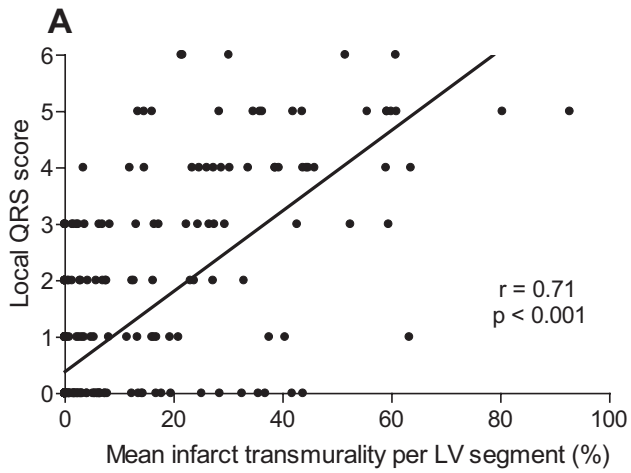


Figure 4

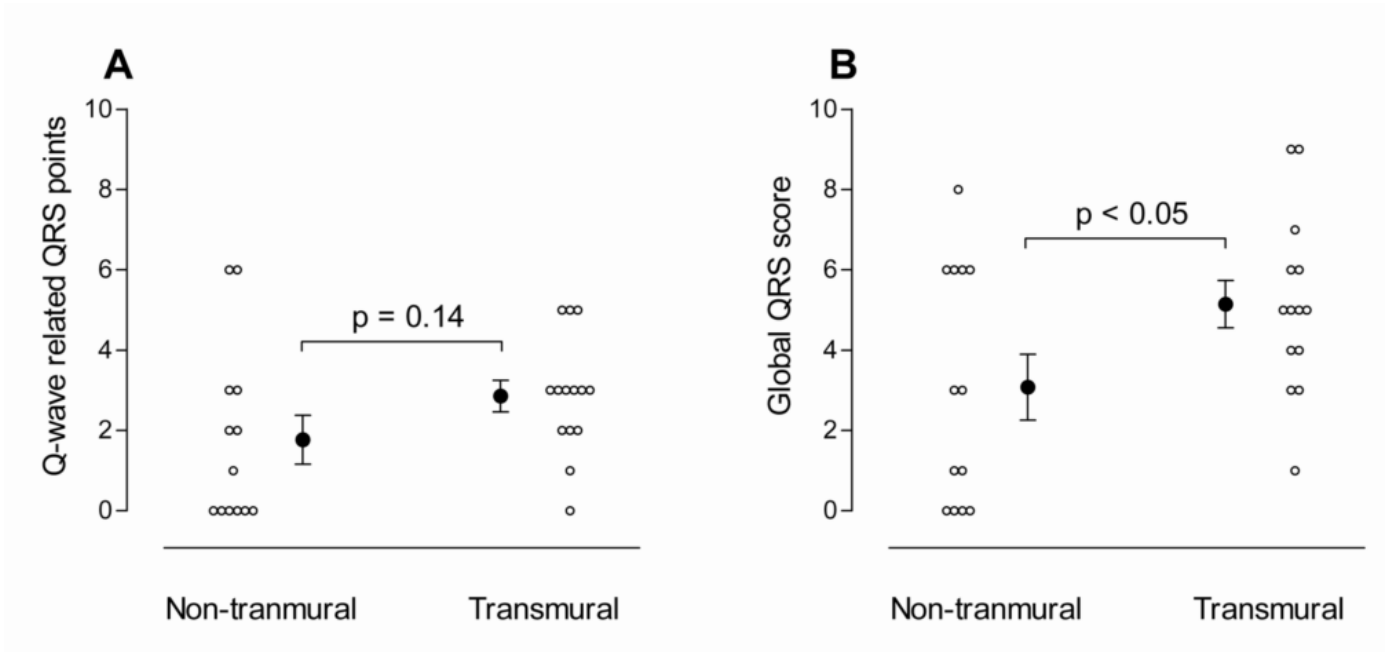


Figure 5

