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Myocardium at Risk in ST-Segment Elevation Myocardial Infarction

Comparison of T_2-Weighted Edema Imaging With the MR-Assessed Endocardial Surface Area and Validation Against Angiographic Scoring

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OBJECTIVES The objective of this study was to assess the area at risk (AAR) in ST-segment elevation myocardial infarction with 2 different cardiac magnetic resonance (CMR) imaging methods and to compare them with the validated angiographic Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease Score (APPROACH-score) in a large consecutive patient cohort.

BACKGROUND Edema imaging with T_2-weighted CMR and the endocardial surface area (ESA) assessed by late gadolinium enhancement have been introduced as relatively new methods for AAR assessment in ST-segment elevation myocardial infarction. However, data on the utility and validation of these techniques are limited.

METHODS A total of 197 patients undergoing primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction were included. AAR (assessed with T_2-weighted edema imaging and the ESA method), infarct size, and myocardial salvage (AAR minus infarct size) were determined by CMR 2 to 4 days after primary angioplasty. Angiographic AAR scoring was performed by use of the APPROACH-score. All measurements were done offline by blinded observers.

RESULTS The AAR assessed by T_2-weighted imaging showed good correlation with the angiographic AAR ($r = 0.87$; $p < 0.001$), whereas the ESA showed only a moderate correlation either to T_2-weighted imaging ($r = 0.56$; $p < 0.001$) or the APPROACH-score ($r = 0.44$; $p < 0.001$). Mean AAR by ESA (20.0 ± 11.7% of left ventricular mass) was significantly ($p < 0.001$) smaller than the AAR assessed by T_2-weighted imaging (35.6 ± 10.9% of left ventricular mass) or the APPROACH-score (27.9 ± 10.5% of left ventricular mass) and showed a significant negative dependence on myocardial salvage index. In contrast, no dependence of T_2-weighted edema imaging or the APPROACH-score on myocardial salvage index was seen.

CONCLUSIONS The AAR can be reliably assessed by T_2-weighted CMR, whereas assessment of the AAR by ESA seems to be dependent on the degree of myocardial salvage, thereby underestimating the AAR in patients with high myocardial salvage such as aborted infarction. Thus, assessment of the AAR with the ESA method cannot be recommended. (Myocardial Salvage and Contrast Dye Induced Nephropathy Reduction by N-Acetylcystein [LIPSIA-N-ACC]; NCT00463749) (J Am Coll Cardiol Img 2011;4:967–76) © 2011 by the American College of Cardiology Foundation

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Acute occlusion of a coronary artery leads to a process of myocyte necrosis, which spreads from the subendocardium of the perfusion bed to the subepicardial layers, the so-called wave front phenomenon (1). Without reperfusion or relevant collaterals, this process ends in complete necrosis of the cardiomyocytes within the perfusion bed. Early reopening of the infarct-related artery can interrupt this process and lead to tissue salvage within the area at risk (AAR), albeit reperfusion itself might induce myocyte damaging processes known as reperfusion injury (2). In general, the resulting necrotic zone in reperfused acute myocardial infarction (AMI) is significantly smaller than the AAR before reperfusion. With angiographic jeopardy scores such as the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease Score (APPROACH-score) the AAR can be calculated (3). However, for direct measurement of the myocardial AAR, few techniques have been developed. In recent studies (4,5), AAR has often been measured by single-photon emission computed tomography (SPECT), which has limitations because of availability and handling in AMI. Two newer technologies for AAR assessment in AMI using cardiac magnetic resonance (CMR) have been recently introduced (6–8). The most widely used method for assessment of the AAR is T_2-weighted CMR. After initial validation in animals (6,9), the ability of this method to detect myocardial edema and, thereby, the AAR after ischemia has been demonstrated in humans (7,10,11). Furthermore, it has been demonstrated that edema can be seen as early as 30 min after ischemia onset (12), seems to be stable over 1 week (13), and can be assessed with good reproducibility between days 2 and 3 (14). Moreover, the amount of myocardial salvage as defined by this approach also predicts patient outcome (15).

ABBREVIATIONS AND ACRONYMS

AAR = area at risk

AMI = acute myocardial infarction

CMR = cardiac magnetic resonance

ESA = endocardial surface area

IQR = interquartile range

LGE = late gadolinium enhancement

LV = left ventricle

MSI = myocardial salvage index

SPECT = single-photon emission computed tomography

STEMI = ST-segment elevation myocardial infarction

Another method for estimating the AAR is the endocardial surface area (ESA) method, which is measured on contrast-enhanced magnetic resonance images. The ESA uses the hypotheses that necrosis first spreads to a final subendocardial extent and then only improves in transmurality according to the wave front phenomenon (8). The AAR is calculated by the relation of endocardial extent of late gadolinium enhancement (LGE) to the total endocardial circumference.

The ESA method has been applied in several trials (8,10,16). However, a comparison of T_2-weighted imaging versus the ESA method in a large consecutive patient cohort with ST-segment elevation myocardial infarction (STEMI) is lacking (10,13,16,17).

Therefore, the aim of the current trial was to study and compare the performance of T_2-weighted imaging versus ESA for assessment of the AAR and to validate these two CMR approaches against the angiographic APPROACH-score.

METHODS

This prospective trial is a subanalysis of the LIPSIA-N-ACC (Myocardial Salvage and Contrast Dye Induced Nephropathy Reduction by N-Acetylcystein) trial, which compared high-dose N-acetylcysteine versus placebo for reperfusion injury prevention in STEMI patients and did not show a difference between the treatment groups. The detailed design and main results of the trial have been previously published (18). In brief, between November 2006 and February 2008, 251 consecutive patients were enrolled and underwent primary percutaneous coronary intervention for STEMI (Fig. 1). Patients were eligible, if symptoms lasted $<$12 h and if ST-segment elevation of $\geq$0.1 mV in $\geq$2 extremity leads or $\geq$0.2 mV in $\geq$2 precordial leads was present. The study had been approved by the local ethics committee and all patients gave written informed consent.

Primary percutaneous coronary intervention. Primary angioplasty was performed as described previously (18). In brief, the use of bare-metal or drug-eluting stents was left to the discretion of the interventional cardiologist. Additional use of thrombectomy was recommended depending on relevant thrombus. All patients were treated with aspirin, heparin, and clopidogrel. The use of glycoprotein IIb/IIIa inhibitors, angiotensin-converting enzyme inhibitors, beta-blockers, and statins was strongly recommended.

Angiographic analysis. Angiographic AAR assessment was performed offline by 2 blinded observers using the modified APPROACH-score as described previously (8). This system is based on a score, which divides the left ventricle (LV) into regions according to pathological studies in humans evaluating the relative proportion of myocardium perfused by each coronary artery (19,20). Considering the location (proximal, mid, or dis-

tal) of the culprit lesion, vessel dominance, site of occlusion, and size of major branches of the infarcted artery, the score calculates the jeopardized myocardium for a given site of occlusion (Table 1, Fig. 2A) (3,8).

Cardiac magnetic resonance. CMR was performed using a 1.5-T scanner (Intera CV, Philips Medical Systems, Best, the Netherlands). The detailed scan protocol and sequence parameters have been described previously (18). In brief, visualization of myocardial edema was performed using a T_2-weighted triple inversion recovery breath-hold pulse sequence (Figs. 2B and 3A) (6,7,21). Early and LGE images covering the whole ventricle were acquired 1 and 15 min after intravenous administration of gadolinium-chelate (Gadovist, Bayer Schering Pharma, Berlin, Germany) with an inversion recovery gradient echo sequence. Inversion times were individually adjusted to optimize nulling of apparently normal myocardium (typical values 200 to 300 ms).

All measurements were performed by fully blinded operators at the CMR core laboratory, which has proven excellent reproducibility for infarct size (22), myocardial salvage, and microvascular obstruction assessment (14). Infarct size and AAR by T_2 edema were assessed by manual planimetry and expressed as percentage of LV mass (14,22,23). A central core of hypointense signal within the area of increased signal intensity, which is deemed to be intramyocardial hemorrhage (24), was included in the AAR assessment. Care was taken to exclude increased signal intensity from the blood pool adjacent to the endocardium due to slow flow. AAR by ESA was measured using ImageJ version 1.43u (National Institutes of Health, Bethesda, Maryland) as previously described (Fig. 3B) (8).

The following calculations were applied:

AAR assessed by T_2-weighted CMR = volume edema/volume LV mass × 100

AAR assessed by ESA = summed endocardial infarct length/total LV endocardial length × 100

%infarct size = volume infarct/volume LV mass × 100

myocardial salvage = area at risk − infarct size

myocardial salvage index = (area at risk − infarct size)/area at risk × 100

Statistical analysis. Categorical data are presented as counts or proportions with the corresponding percentages. All quantitative data are expressed as mean ± SD or median and interquartile range (IQR) on the basis of whether they had a normal distribution or not. Bland-Altman analyses were applied to compare the 3 AAR measurement methods. Correlation analyses were done by Pearson or Spearman tests, as indicated. Given the paired nature of the data, a repeated-measures analysis of variance with post hoc analysis and the use of the Bonferroni correction to account for multiple testing was used to detect differences among angio-

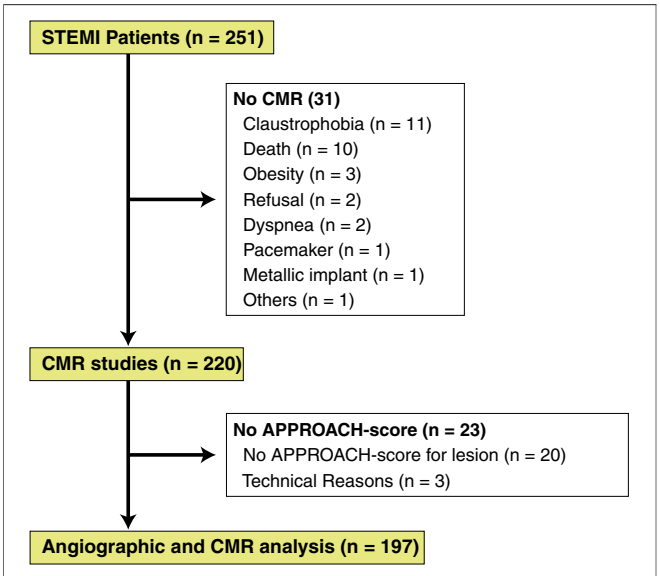

Figure 1. Study Flow

APPROACH-score = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease Score; CMR = cardiac magnetic resonance; STEMI = ST-segment elevation myocardial infarction.

Table 1. Modified Angiographic APPROACH-Score

Culprit Lesion Location	Infarct-Related Artery Side Branches	Diagonal for LAD Occlusion Only or Posterolateral for All Others		
		Small or Absent	Medium	Large
LAD	Distal	13.75	14.8	15.9
	Mid	27.5	29.7	31.8
	Proximal	41.25	44.5	47.75
Proximal LCx (RD)	Small or absent	9.25	12.5	15.75
	Medium	15.25	18.5	21.75
	Large	21.25	24.5	27.75
Proximal LCx (LD)	Small or absent	23.5	28	32.5
	Medium	29.5	34	38.5
	Large	35.5	40	44.5
Mid LCx (LD) or RCA (RD)	Small or absent	9.25	12.5	15.75
	Medium	15.25	18.5	21.75
	Large	21.25	24.5	27.75
Mid LCx (RD)		3.25	6.5	9.75

Results provided as percentage of left ventricular myocardium. Modified from Ortiz-Perez et al. (8).
APPROACH-score = Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease Score; LAD = left anterior descending artery; LCx = left circumflex artery; LD = left dominant; RCA = right coronary artery; RD = right dominant.

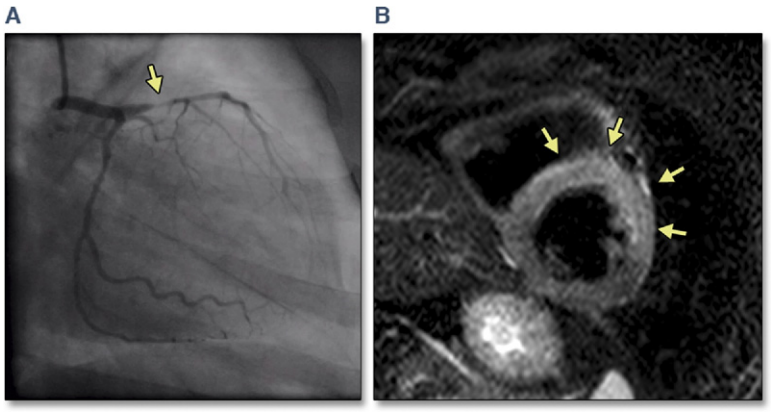

Figure 2. Coronary Angiogram With Culprit Lesion and Corresponding Edema in CMR

(A) Coronary angiogram with culprit lesion and corresponding edema in cardiac magnetic resonance (CMR). Coronary angiogram of a patient with occluded proximal left anterior descending coronary artery **(arrow)** and medium side branches resulting in an APPROACH-score of 44.5 %LV area at risk (AAR). **(B)** Corresponding T_2-weighted CMR study showing edema **(arrows)** in the anterior wall and parts of the interventricular septum (AAR: 49.0 %LV). %LV = percentage of left ventricular mass.

graphic AAR, ESA, and T_2-weighted imaging. A trend analysis using analysis of variance was used to analyze a possible influence of myocardial salvage index (MSI) on AAR assessment with the 3 methods.

Statistical analysis was performed using commercially available software (SPSS 17.0, SPSS Inc., Chicago, Illinois). A 2-tailed p value <0.05 was considered statistically significant.

RESULTS

Of 251 eligible STEMI patients, this study included 197 patients. The main reasons for exclusion from the study are listed in Figure 1. Demographic and clinical characteristics are shown in Table 2. The culprit vessel was the left anterior descending coronary artery in 87 (44.2%) patients, the left circumflex coronary artery in 12 (6.1%), and the right coronary artery in 98 (49.7%) patients. Time from symptom onset to angioplasty ranged from 45 to 720 min (median: 231 [IQR: 153 to 290]). The median time between reperfusion and CMR was 3 days (IQR: 2 to 4).

Comparison of AAR assessed by T_2-weighted imaging with LGE infarct size. All patients had a region of increased transmural signal intensity on T_2-weighted images in the territory of the corresponding culprit artery (Figs. 2 and 3). The T_2-weighted AAR (35.6 ± 10.9 %LV) was significantly larger than infarct size (18.2 ± 11.7 %LV; $p < 0.001$). In total, 11 patients had regional edema, but no LGE consistent with an aborted infarction (25) and 19 patients had evidence of prior infarction (with LGE in a different vascular territory).

The calculated myocardial salvage was 17.5 ± 11.6 %LV and the myocardial salvage index 49.3 ± 27.3.

Comparison of AAR assessed by T_2-edema versus APPROACH-score. AAR assessed with T_2-weighted imaging showed good correlation with the angiographic AAR ($r = 0.87$; $p < 0.001$). However, as shown by Bland-Altman analyses (Fig. 4A) there was a certain bias toward an overestimation of the AAR by T_2-weighted CMR in comparison to angiographic scoring (35.6 ± 10.9 %LV vs. 27.9 ± 10.5 %LV, difference: 7.7 ± 5.4; $p < 0.001$) with limits of agreement of ±10.6 %LV.

Comparison of AAR assessed by T_2-edema versus ESA. AAR by ESA showed only a moderate correlation with the AAR determined by T_2-weighted imaging ($r = 0.56$; $p < 0.001$). Furthermore, a significant difference between these 2 approaches (35.7 ± 10.9 %LV vs. 20.0 ± 11.7 %LV, difference 15.7 ± 10.7; $p < 0.001$) with limits of agreement of 21.4 %LV was evident (Fig. 4B).

Comparison of AAR assessed by ESA versus APPROACH-score. There was only moderate correlation between ESA and angiographic scoring ($r = 0.44$; $p < 0.001$). Consequently, the AAR was significantly different between these 2 approaches (20.0 ± 11.7 %LV vs. 27.9 ± 10.5 %LV, difference: 8.0 ± 11.8; $p < 0.001$) with higher values of the AAR using the APPROACH-score. The limits of agreement were 23.1 %LV in our Bland-Altman analysis (Fig. 4C).

Influence of MSI on AAR measurement. The extent of the AAR assessed by T_2-weighted CMR and the APPROACH-score was independent from the amount of MSI (mean 49.3 ± 27.3). Thus, no significant correlation between T_2-weighted imaging as well as the APPROACH-score with the MSI could be observed ($r = -0.21$, $p = 0.77$; $r = 0.08$, $p = 0.26$, respectively). In contrast, the ESA showed a significant negative correlation to the MSI ($r = -0.61$; $p < 0.001$). When categorized by quartiles of MSI, patients with a large MSI had a significantly smaller AAR as assessed by the ESA method, in comparison to T_2-weighted imaging and the APPROACH-score (Fig. 5).

Correlation of infarct size on AAR measurement. Only a weak correlation was seen between infarct size and T_2-weighted imaging ($r = -0.48$; $p < 0.001$) or APPROACH-score ($r = -0.34$; $p < 0.001$), whereas there was a strong correlation of ESA to infarct size ($r = -0.81$; $p < 0.001$). This was also observed when the infarct size was categorized in quartiles (Fig. 6).

DISCUSSION

This is the largest study to date to compare and validate the assessment of myocardium at risk with 2 different CMR methods in a large cohort of consecutive STEMI patients. We could show that AAR assessment with T_2-weighted CMR correlates well with angiographic scoring by the APPROACH-score, whereas AAR by ESA seems to be dependent on MSI and may not reflect the true AAR.

AAR assessment in AMI. The reliable assessment of the AAR in relation to infarct size enables determination of myocardial salvage and, consequently, of efficacy of reperfusion therapy in patients with STEMI. This is important for the evaluation of new therapeutic approaches in both interventional and pharmacological strategies for improvement of reperfusion success and reduction of reperfusion injury.

In the current study, we were able to show that there is excellent correlation between the AAR measured by T_2-weighted imaging and the angiographic APPROACH-score, which is an anatomically and prognostically validated measure of the extent of myocardial jeopardy. This is in line with a recently published study of 50 AMI patients, which also found that AAR estimated by T_2-weighted CMR was a predictor of the APPROACH-score (17). In contrast, AAR determination by ESA in our study showed only a moderate correlation to both T_2-weighted and the angiographic AAR. The main reason for these differences might be that the ESA method significantly underestimates the AAR in patients with major myocardial salvage. Ubachs et al. (16)

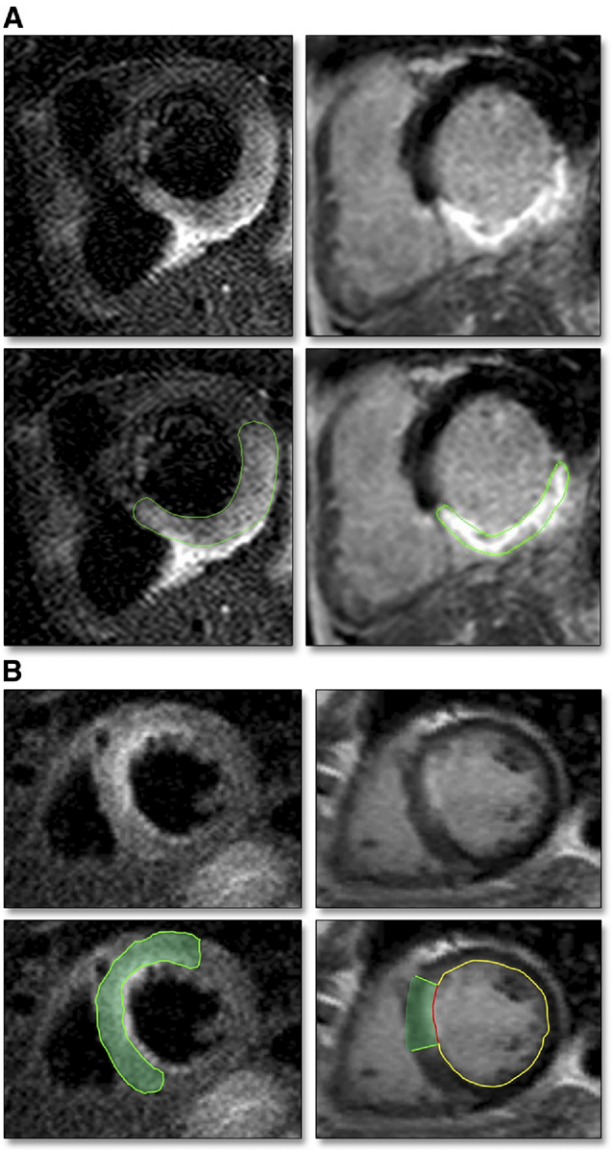

Figure 3. AAR by CMR

(A) Inferior acute myocardial infarction (AMI) with resulting inferior edema and late gadolinium enhancement (LGE) **(upper panels)** as well as corresponding edema and infarct size contours **(green, lower panels)**. In this patient, there was only minimal myocardial salvage. **(B)** Anteroseptal AMI with corresponding edema **(upper left panel)** and infarct size **(upper right panel)** assessed by CMR in a patient with high myocardial salvage index (MSI) showing a large difference of the AAR assessed with T_2-weighted edema imaging **(green, lower left panel)** versus the endocardial surface area (ESA) **(green, lower right panel)**. Abbreviations as in Figures 1 and 2.

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Table 2. Patient Characteristics

Characteristics	Patients (n = 197)
Age, yrs	65.4 ± 12.4
Male sex	136 (69)
Body mass index, kg/m^2	27.5 ± 4.0
Cardiovascular risk factors	
Current smoking	74 (38)
Hypertension	138 (70)
Hypercholesterolemia	62 (32)
Diabetes mellitus	49 (25)
Prior myocardial infarction	19 (10)
Prior coronary artery bypass grafting	3 (2)
Localization of myocardial infarction	
Anterior	87 (44)
Posterior	98 (50)
Lateral	12 (6)
Killip class on admission	
1	145 (74)
2	43 (22)
3	7 (3)
4	2 (1)
Concomitant medications	
Beta-blockers	196 (99.5)
ACE-inhibitors/angiotensin-1 antagonist	197 (100)
Aspirin	197 (100)
Clopidogrel	197 (100)
Statins	197 (100)
Aldosterone-antagonist	8 (4)
Glycoprotein IIb/IIIa inhibitor	187 (95)
Door-to-balloon time, min	26 (21–35)
Pain-to-balloon time, min	231 (153–290)

Values are mean ± SD, n (%), or median (IQR).
ACE = angiotensin-converting enzyme; IQR = interquartile range.

could similarly demonstrate in a small study cohort that the ESA is not suitable for AAR assessment in patients with early reperfusion as well as aborted infarction.

The characteristic CMR pattern of an aborted infarction is the detection of myocardium at risk in the absence of LGE (25). In these patients, the ESA allows no reliable assessment of the AAR, as the ESA method would generate an AAR of 0%, whereas the true salvaged AAR is 100%. Eleven patients in the present study showed no signs of infarction by LGE but did, however, show evidence of ischemic myocardium by T_2-weighted imaging. Consequently, LGE or ESA imaging does not allow for determination of AAR in aborted infarction, whereas T_2-weighted imaging does.

A recent study by Wright et al. (10) observed a better correlation between ESA and T_2-weighted imaging than our study did (r = 0.77). However, in our study, a significant portion of patients was treated within 2 h following symptom onset with consequently a high degree of myocardial salvage (28 patients), whereas in the study by Wright et al. (10) the shortest pain-to-balloon time was 120 min. Recent publications found the highest MSI in AMI reperfused the first 2 h after onset of symptoms (15,26).

We and others found only moderate correlation between angiographic risk scores and infarct ESA, in contrast to the results reported by Ortiz-Perez et al. (8). This might be due in part to different study populations, because Ortiz-Perez et al. (8) only studied patients with TIMI (Thrombolysis In Myocardial Infarction) flow grade 0 before intervention and patients with a pain-to-balloon times >60 min, indicating a lack of patients with high MSI.

Similar to a previous study (17), we found a systematic overestimation of T_2-weighted AAR in relation to angiographic AAR by the APPROACH-score. This might be explained by a significant increase of myocardial thickness in the infarcted region, which has been shown in experimental (27,28), patient (29), and imaging studies (30), as compared to noninfarcted areas. The APPROACH-score (3), however, is based on older autopsy studies (19,20,31) and was created to obtain prognostic information for overall coronary heart disease and is not exclusively dedicated to AMI patients. Thus, the APPROACH-score does not account for such an ischemia-related increased wall thickness. Notably, early postmortem analysis with microspheres in an animal model (6) and comparison to SPECT in humans (13) showed no significant differences in comparison to the T_2-weighted CMR–detected AAR.

Although it is possible to image the AAR with SPECT, determination of the AAR and myocardial salvage in routine clinical practice by SPECT is impractical and limited to specialized centers. Major limitations of SPECT include the need of the perfusion tracer injection before reperfusion, imaging with a gamma camera within a few hours, the need of 2 SPECT scans with radiation exposure. In contrast, CMR allows AAR delineation as well as estimation of the salvaged myocardium retrospectively in 1 scan after the acute event. Notably, the AAR by T_2-weighted imaging does not change during the first week after infarction, enabling myocardial salvage assessment after stabilization of the AMI patient (13). Additionally, CMR provides important in-

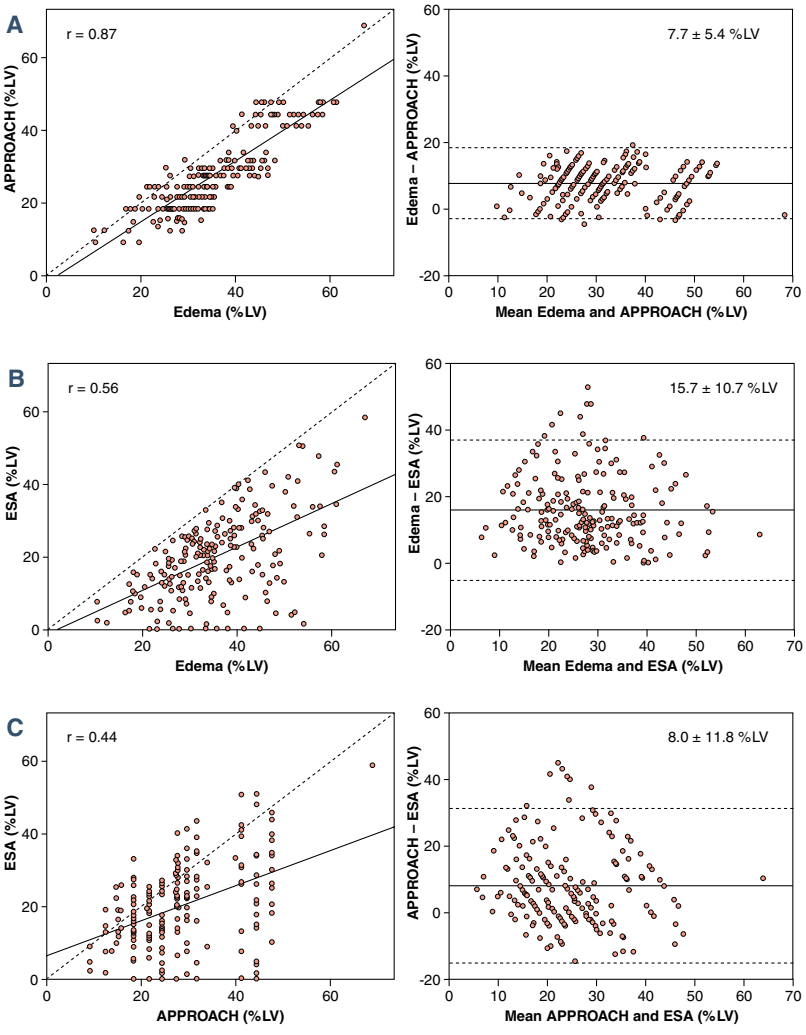

Figure 4. Comparison of the Different AAR Assessment Methods

Correlation **(left column)** and Bland-Altman analysis **(right column)** for angiographic and T_2-weighted AAR **(A)**, ESA, and T_2-weighted AAR **(B)**, as well as ESA and angiographic scoring (APPROACH) **(C)**. **Solid lines** in the **left column** show the line of best fit, **dotted lines** indicate an ideal correlation. In the Bland-Altman plot, the **central horizontal line** indicates the mean absolute difference or bias, and **upper and lower dotted lines** represent the limits of agreement (1.96 × SD). Abbreviations as in Figures 1, 2, and 3.

formation about ventricular anatomy, function, and microvascular status (32).

Study limitations. Some patients had to be excluded because of missing angiographic scoring for side branch lesions or codominant coronary anatomy. In addition, we did not assess several clinical variables such as the collateral blood flow or preconditioning, which might affect myocardial salvage. Several limitations of T_2-weighted edema imaging have to be mentioned such as signal intensity variability caused by phased-array coils (although we used a body coil in the data acquisition of the present analysis), high signal from slow moving ventricular chamber blood that can mimic and mask elevated T_2 in subendocardial myocardium, motion artifacts, and also the partly subjective nature of T_2-weighted image interpretation. Technical developments such as T_2-mapping may provide an even more robust and qualitative approach to edema imaging (33). In our study, we also performed quantitative analysis by manual drawing of the edema border contours, which might be inferior to a semiautomatic analysis. However, we have previously shown an excellent intra- and interobserver variability as well as reproducibility of T_2-weigted

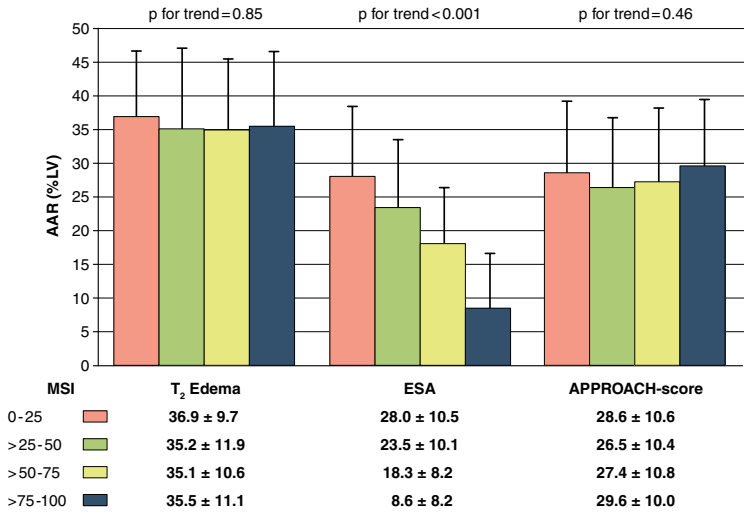

Figure 5. Impact of MSI on AAR Assessed by Different Measurements

Note a significant difference in AAR assessed by ESA with different levels of MSI. (MSI was divided in 4 groups: Group 1: 0% to 25% MSI; Group 2: >25% to 50% MSI; Group 3: >50% to 75% MSI; Group 4: >75% to 100% MSI). Abbreviations as in Figures 1, 2, and 3.

edema imaging and LGE measurements with manual planimetry (14,22), minimizing an influence on the data.

CONCLUSIONS

In conclusion, CMR can provide information on myocardium at risk and salvaged myocardium using T_2-weighted edema imaging, with a good correlation to the angiographic APPROACH-score. AAR determination by ESA seems to depend on myocardial salvage and underestimates the AAR, especially in patients with high myocardial salvage and, therefore, cannot be recommended for AAR assessment.

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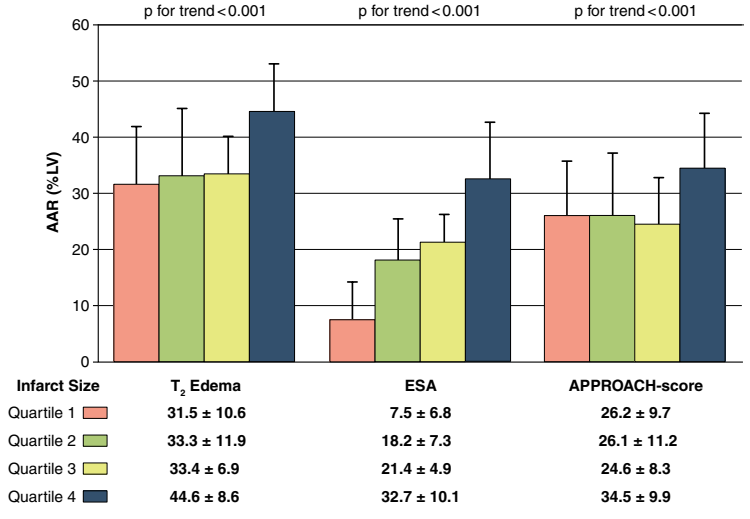

Figure 6. Mean AAR for Quartiles of Infarct Size

Mean AAR for quartiles of infarct size (mean infarct size: Quartile 1: 4.4 ± 3.2 %LV; Quartile 2: 12.6 ± 2.1 %LV; Quartile 3: 21.5 ± 3.0 %LV; Quartile 4: 34.0 ± 6.3 %LV). Although all methods showed significant increase of AAR with higher infarct size due to larger infarcts with higher AAR, a strong dependence of AAR to infarct size could only be observed with ESA. Abbreviations as in Figures 1, 2, and 3.

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Key Words: acute myocardial infarction ■ area at risk ■ cardiac magnetic resonance ■ myocardial salvage.