

Clinical Significance of Late Enhancement and Regional Wall Remodeling Assessed by 3T Magnetic Resonance Imaging

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ABSTRACT

BACKGROUND: Clinical follow-up studies comparing left ventricular (LV) function and late gadolinium enhancement (LGE) by high-field 3T cardiac magnetic resonance (CMR) are of general interest due to the increased use of 3T scanners. In this study, the occurrence of LGE and LV regional wall remodeling (RWR) was assessed by 3T CMR in patients undergoing coronary angiography for suspected stable coronary artery disease (CAD).

MATERIALS AND METHODS: Analysis of myocardial viability by LGE was performed at the segmental level. LVRWR was identified by a significant reduction ($\geq 50\%$) of the wall thickness. Major adverse cardiovascular events (MACE) were registered during a median follow-up time of 58 (45–62) months.

RESULTS: Of the 87 patients (59 ± 9 years; 13 women) enrolled, nonviable myocardium was detected in 35 (40%) and significant CAD in 69 (79%). Nonviable myocardium was correlated to angiographic significant stenosis or occlusion. LVRWR was significantly related to a higher number of nonviable segments compared to those without LVRWR: ie, 6.0 ± 3.2 segments versus 2.6 ± 1.3 ; $P < 0.001$. In the nonviable group, LVEF was significantly reduced ($P < 0.001$) compared to the viable group: ie, $50 \pm 16\%$ versus $61 \pm 8\%$, and LVEF was significantly correlated to the number of nonviable segments ($r = -0.66$, $P < 0.001$). The number of nonviable segments by LGE was significantly associated with MACE by an odds ratio of 1.25 (95% CI, 1.05–1.49; $P = 0.013$).

CONCLUSION: The presence of nonviable myocardium as detected by LGE at 3T CMR is associated with angiographically significant CAD, and is associated with the development of LVRWR and reduced LVEF. Assessing the extent of nonviable myocardium by both LGE and LVRWR at the segmental level may therefore contribute to individualized risk stratification and treatment strategies.

KEYWORDS: ischemic heart disease, myocardial infarction, adverse remodeling, left ventricular systolic dysfunction, prognosis, major adverse cardiovascular events

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Introduction

Cardiac magnetic resonance (CMR) offers a unique method of studying left ventricular (LV) morphology and function in patients with coronary artery disease (CAD). This includes the use of contrast media, in which the late gadolinium enhancement (LGE) of the LV myocardium is indicative of nonviable

tissue and eventually the formation of scar.^{1,2} Irreversible injury of the myocardium following acute coronary artery occlusion is still an important cause of LV dysfunction and heart failure. A significant proportion of cases are clinically silent, ie, without symptoms that cause the patients to seek medical care.^{3,4} Important determinants in the development of heart failure



are the extent and transmuralty of the infarcted wall and development of adverse LV remodeling.^{5–8} Further, applying 1.5T CMR transmuralty of LV LGE has been shown to predict improvement of the myocardial function after revascularization,⁹ and thereby provide valuable information with regard to preoperative individualized decision making. Bearing in mind that cardiovascular disease is common, accounting for approximately 30% of all deaths in the US,¹⁰ the choice of optimized treatment strategy is of considerable importance to health care in general.

Achieving images at higher magnetic fields, eg, 3T rather than 1.5T, provides increased signal-to-noise ratio (SNR), which in turn may be translated into improved spatial resolution. Sequences that are widely used for CMR have been thoroughly evaluated at 3T. Although some particular artifacts are increased at high-field scanning compared to scanning at 1.5T, this is outweighed by the benefits of image quality and reduced imaging time.¹¹ Acceptable inter-observer reproducibility for solid-state free precession (SSFP) and LGE images at 3T has been shown as well.¹² On comparing LGE imaging at 3T versus 1.5T, the SNR has been shown to increase by 1.6–3.9 times, and the contrast-to-noise ratio by 1.9–3.3 times between an infarcted and a normal myocardium, depending on various sequences that were applied.¹³ Combined with the high spatial resolution of electrocardiogram (ECG)-triggered CMR acquisitions, this would be expected to give more detailed information about the localization and extent of the nonviable myocardium as well as LV regional wall remodeling (RWR) of the corresponding segments.

In the present study, the LV myocardium of patients with suspected ischemic heart disease was prospectively examined by high-field 3T CMR, whereas coronary angiography was used for demonstrating the extent and distribution of CAD. The medical history of each patient was then followed for a mean time of 58 months, and the major adverse cardiovascular events (MACE) were noted. The study was approved by the Regional Committee for Medical and Health Research (REK West), and conducted in accordance with the principles of the Declaration of Helsinki. We hypothesize that there is a positive correlation between the presence of nonviable myocardium and CAD, and that the extent of nonviable myocardium is associated with the development of LVRWR and decreased LV ejection fraction (LVEF).

Methods

Patients. Eighty-seven patients (59 ± 9 years; 13 women) with suspected stable CAD undergoing elective coronary angiography ($n = 72$) or coronary angiography due to unstable acute coronary syndrome including unstable angina pectoris or non-ST-elevation myocardial infarction ($n = 15$) were included. Patients with general contraindications to MR scanning were excluded from the study, and all patients presented with a clinical and hemodynamic stable condition. Prior to the procedures, all patients underwent a clinical examination, blood sampling including measurements

of creatinine, C-reactive protein (CRP), cholesterol, and glucose, and echocardiography. The Simpson method was applied for determining LVEF (%) by echocardiography.¹⁴ Patients also completed a self-administered questionnaire that provided information about medical history, risk factors, and prior medications. History of hypertension is with reference to subjects currently being treated with antihypertensive drugs, according to clinical criteria. Diabetes mellitus includes both type 1 and 2. Smokers include current smokers and those reporting having quit within the last 4 weeks.¹⁵ Information from the questionnaires was checked against medical records.

Coronary angiography was performed by experienced (>15 years) cardiologists, and a total of 16 coronary artery segments were evaluated for possible stenosis in all patients: ie, 15 segments as per the American Heart Association standardization criteria¹⁶ plus the right atrioventricular branch. Lesions with a diameter reduction of $\geq 30\%$ and $< 50\%$ were classified as non-significant CAD. Significant CAD was defined as a diameter of stenosis of $\geq 50\%$ in any of the main coronary arteries (left anterior descending (LAD), circumflex (CX), and right coronary artery (RCA)) including their main side branches. The extent of significant CAD was scored as no CAD, one-vessel disease, two-vessel disease, or three-vessel disease, according to the number of main vessels with significant stenosis. Presence of left main-stem artery stenosis with no RCA stenosis was classified as two-vessel disease or as three-vessel disease if RCA was hypoplastic. Known coronary stenoses or occlusions from previously performed coronary angiography were also included, even if revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) had been done.

The CMR examination was performed prior to, on the same day, or a few days following coronary angiography (median – 1 day (–1 to +1 days)). CMR was performed and evaluated blindly with regard to the angiographic findings by an experienced (>15 years) CMR reader.

Follow-up and clinical endpoints. The patients were included over a period of 26 months, and the median follow-up time was 58 (45–62) months. Information on clinical events was collected from the Cause of Death Registry at Statistics Norway and from the patient administrative systems at our university hospital, which is the primary hospital for the city of Bergen and secondary hospital for Western Norway. Data from the registries were checked against hospital medical records. The primary endpoint was MACE, and included fatal and nonfatal acute myocardial infarction (MI), re-angiography, and admission for major arrhythmias or heart failure. MI was classified according to the diagnostic criteria of the revised definition published in 2000.¹⁷ Events occurring within 24 hours after PCI or CABG were considered as procedure-related and were not included as endpoints. No patients were lost to follow-up.

CMR technique. Patients were examined with a 3T GE Signa Excite scanner (Milwaukee, WI, USA). A phased-array cardiac coil with eight elements was used. All images were obtained during breath-hold with ECG-triggering. For

evaluation of regional wall thickness during the heart cycle, CINE views of the left ventricle were taken. Vertical long-axis view and four-chamber view were obtained, as well as consecutive breath-hold short-axis views of the entire left ventricle. The parameters of the SSFP sequence were as follows: field of view (FOV) 330 × 330 mm; slice thickness 8 mm; matrix size: 192 × 192; flip angle 45°. In order to detect LGE of the LV myocardium, gadobutrol (Gadovist 1 mmol/mL; Bayer Schering Pharma, Leverkusen, Germany) was administered intravenously at a concentration of 0.2 mmol/kg. Twenty minutes later, images positioned correspondingly to that of the CINE views were acquired. The parameters of the 2D fast inversion-recovery gradient echo sequence were as follows: FOV 350 × 350 mm; slice thickness 8 mm; matrix size 256 × 128; flip angle 20°. The time of inversion (TI) was optimized for each examination, but commonly 250 milliseconds was used.

Analyses of the LV myocardium. The presence of LV myocardial LGE was defined as nonviable tissue, whereas the absence was defined as viable myocardial tissue. For assessing the distribution of LGE, a 17-segment bulls-eye model was applied.¹⁸ Hence, segments 1, 2, 3, 7, 8, 13, 14, and 17 corresponded to the myocardium supplied by LAD; segments 5, 6, 11, 12, and 16 to CX; and segments 4, 9, 10, and 15 to RCA, which then enabled comparison of viability with the angiographic findings of the corresponding coronary arteries. The numbers of segments showing LGE for each coronary territory were counted.

The extent of LGE across the wall was noted and allocated into subgroups: subendocardial nonviable myocardium (comprising <50% of wall thickness); transmural nonviable myocardium (comprising ≥50% of wall thickness); or combined subendocardial and transmural nonviable myocardium. LVRWR was defined as significant thinning of the myocardial wall (≥50% of the wall thickness compared to neighboring segment with viable myocardium).¹⁹ This was performed by assessing the SSFP short-axis views of the LV after identifying the end-diastolic phase.

The CMR examination was well tolerated by all patients, and neither the presence of steel threads in sternum after CABG nor stents in the coronary stents showed any significant image artifacts with regard to image quality.

Statistical analysis. Continuous variables are given as means (±1 standard deviation (SD)) or medians (25th–75th percentile), and categorical variables as counts (percentages). For comparisons of subgroups of patients, differences in continuous variables were explored using independent Student *t*-test, and proportions were compared by Pearson's Chi-square test (χ^2 cross-tabulations). Furthermore, correlations between variables were analyzed by simple linear regression or stepwise regression models.

Logistic regression analysis was applied to calculate the odds ratios (OR; with 95% confidence intervals) (CI) for risk factors related to MACE during follow-up.

A multivariable model was applied, adjusting for LVEF (%), number of nonviable segments by LGE, LVRWR (yes versus no), and diagnosis (stable versus unstable coronary syndrome).

$P < 0.05$ are considered significant, and values >0.05 are referred to as nonsignificant (ns). All statistical analyses were computed by PASW Statistics 18.0 (SPSS Inc, Chicago, IL, USA).

Results

Patient characteristics. Significant CAD was detected in 69 of 87 patients (79%). LGE in the LV wall demonstrating nonviable myocardium was detected in 35 (40%) patients. All nonviable segments were related to the presence of significant stenosis or occlusion as confirmed by coronary angiography; moreover, nonviable segments were not detected in

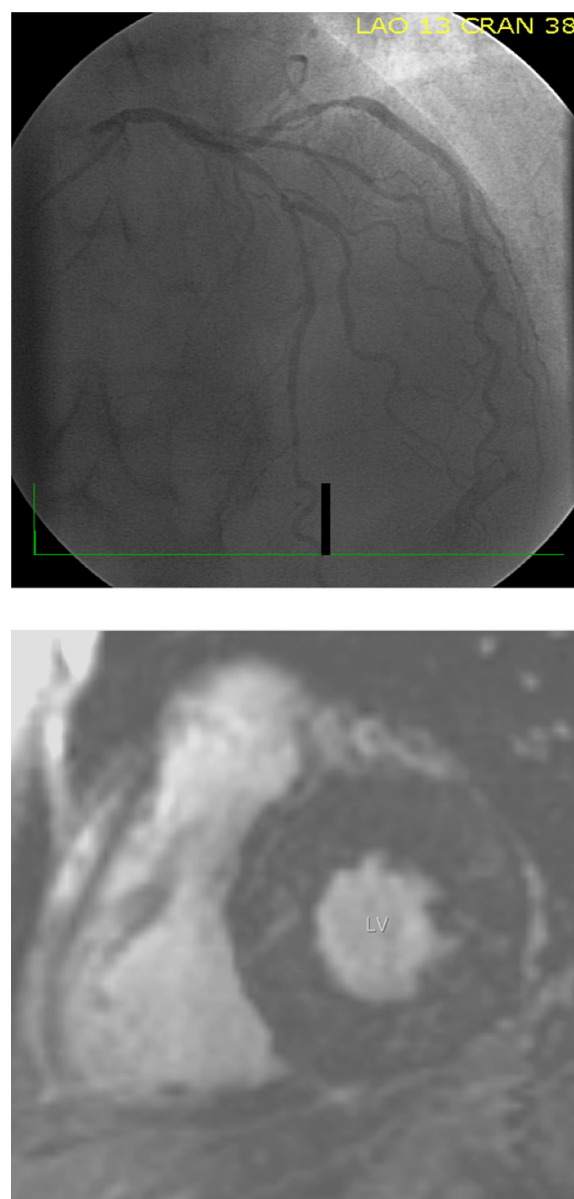


Figure 1. Viable myocardium.

Notes: Demonstration of viable myocardium in a 73-year-old male, as reflected by the absence of LGE at CMR (lower panel) despite significant CAD of LAD and CX arteries as shown by coronary angiography (upper panel).

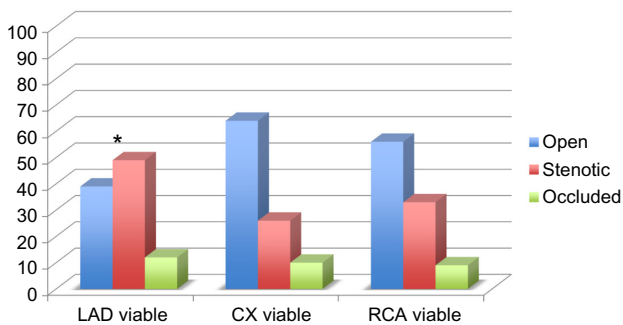


Figure 2. Viable segments (%) in relation to coronary stenosis.

Notes: This bar graph shows viable segments of the different coronary territories with corresponding numbers of either open (blue), stenotic (red), or occluded vessels (green) given in percentages. There was a significantly higher number of stenotic or occluded vessels ($P < 0.05$) in the LAD territory as compared to CX and RCA territories.

angiographically open vessels. Viable segments, on the other hand, were frequently found in territories with significant CAD (Figs. 1 and 2). The characteristics of the study population according to presence or absence of viable myocardium are summarized in Table 1. There was a significant gender difference, with more women in the viable group. Known chronic MIs (>3 months old), previous CABG, or PCI was overrepresented in the nonviable group, and LVEF was significantly decreased ($P < 0.05$): $50 \pm 16\%$ versus $61 \pm 8\%$. A considerable number of the patients underwent PCI (39%, $n = 34$), either directly or during a second intervention, whereas 12% ($n = 10$) were scheduled for succeeding CABG.

Nonviable segments and LVRWR. Transmurality as well as the segmental localization and distribution of nonviable myocardium was evaluated and compared to the angiographic

Table 1. Baseline demographic, clinical, and angiographic data.

VARIABLE	NONVIALE MYOCARDIUM n = 35	VIALE MYOCARDIUM n = 52	P-VALUES
Age (years)	59 ± 8	59 ± 9	ns
Female/Male ratio	2/33 (6%)	12/40 (23%)	0.031
Risk factors			
Smoking	13 (37%)	15 (29%)	ns
Diabetes mellitus	4 (11%)	5 (10%)	ns
Hypertension	14 (40%)	29 (56%)	ns
Hypercholesterolemia	16 (46%)	16 (31%)	0.081
BMI (kg/m^2)	27 ± 4	27 ± 4	ns
Previous CAD			
Myocardial infarction	24 (69%)	12 (23%)	<0.001
PCI	20 (57%)	18 (35%)	0.038
CABG	5 (14%)	1 (2%)	0.026
Cerebrovascular disease	0	3 (6%)	ns
Peripheral vascular disease	1 (3%)	2 (4%)	ns
Arrhythmia			
Atrial fibrillation	1 (3%)	5 (10%)	ns
Ventricular arrhythmias	1 (3%)	0	ns
CCSA			
Class 0	14 (40%)	17 (33%)	
Class 1	7 (20%)	12 (23%)	
Class 3	10 (29%)	21 (40%)	
Class 3	4 (11%)	2 (4%)	
LVEF (%)	50 ± 16	61 ± 8	<0.001
Angiographic findings			
0-vessel disease	0 (0%)	18 (35%)	<0.001
1-vessel disease	7 (20%)	9 (17%)	
2-vessel disease	10 (29%)	14 (27%)	
3-vessel disease	18 (51%)	11 (21%)	

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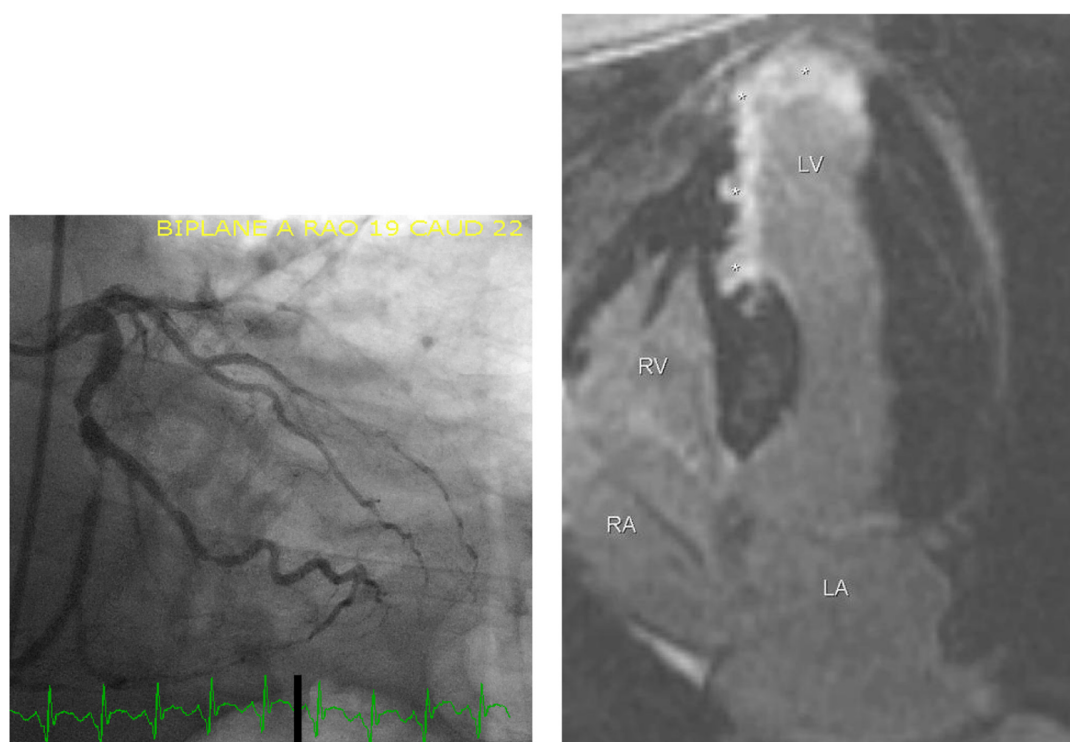
Table 1. (Continued)

VARIABLE	NONVIABLE MYOCARDIUM n = 35	VIABLE MYOCARDIUM n = 52	P-VALUES
Blood parameters			
Cholesterol (mmol/L)	4.4 ± 1.1	4.6 ± 1.0	ns
Glucose (mmol/L)	6.4 ± 1.3	6.4 ± 2.1	ns
CRP (mg/L)	6 ± 14	5 ± 11	ns
Creatinine (µmol/L)	103 ± 126	82 ± 17	ns
Medication at discharge			
Beta-blocking agents	29 (83%)	34 (65%)	0.074
ACE inhibitors	19 (54%)	9 (17%)	0.000
Other antihypertensives	5 (14%)	17 (33%)	0.053
Statins	30 (86%)	37 (71%)	ns
Further management			
No treatment	0 (0%)	7 (13%)	
Medication	14 (40%)	22 (42%)	
PCI	16 (46%)	18 (35%)	
CABG	5 (14%)	5 (10%)	

Abbreviations: ACE, angiotensin-converting enzyme; BMI, body mass index; CCSA, Canadian Cardiovascular Society angina classification; CRP, C-reactive protein. **Note:** P-values are based on Pearson Chi-square test for categorical data and one-way ANOVA for numerical data.

findings (Figs. 3 and 4). Of the 35 patients with nonviable myocardium, the number of these segments with regard to the corresponding blood supply territories was comparable: LAD $n = 18$ segments, CX $n = 17$, and RCA $n = 21$. Further, the

frequency of nonviable segments depicting subendocardial, transmural, or combined subendocardial and transmural nonviable myocardium was not statistically different for the three vessel territories. For the LAD territory, the presence of


Figure 3. Nonviable myocardium.

Notes: A 56-year-old male with occlusion of mid-LAD (upper panel) and the presence of nonviable myocardium, as demonstrated by LGE at CMR (lower panel). **Abbreviations:** LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; asterisks, LGE.

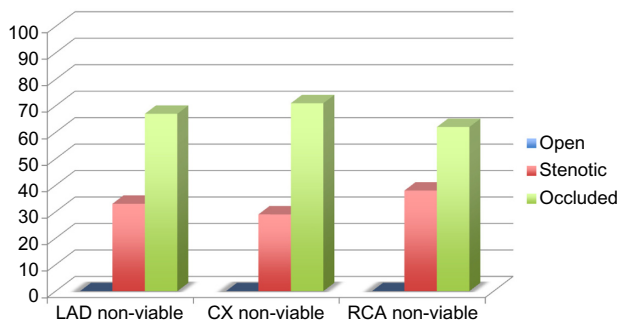


Figure 4. Nonviable segments (%) in relation to coronary stenosis.

Notes: This bar graph shows nonviable segments of the different coronary territories with corresponding numbers of either open (blue), stenotic (red), or occluded vessels (green) given in percentages.

subendocardial, transmural, and combined nonviable myocardium was 5% ($n = 1$), 67% (12), 28% (5); for the CX territory 12% ($n = 2$), 47% (8), 41% (7); and for RCA territory 0% ($n = 0$), 52% (11), 48% (10). When allocating the patients with nonviable myocardium into three subgroups according to the number of nonviable segments, ie, low 0–3 segments, medium 4–7 segments, and high ≥ 8 segments, in addition to the group with only viable myocardium, a significant negative correlation to LVEF was noted (Fig. 5). Moreover, the nonviable myocardium with evidence of LVRWR, 66% ($n = 23$), appeared mainly in the groups with medium and high numbers of nonviable segments (Fig. 5). Hence, in nonviable hearts with LVRWR, the average number of nonviable segments was 6.0 ± 3.2 , whereas the number of segments was significantly lower ($P < 0.001$), 2.6 ± 1.3 , in hearts without LVRWR. Further, in hearts with nonviable myocardium and LVRWR,

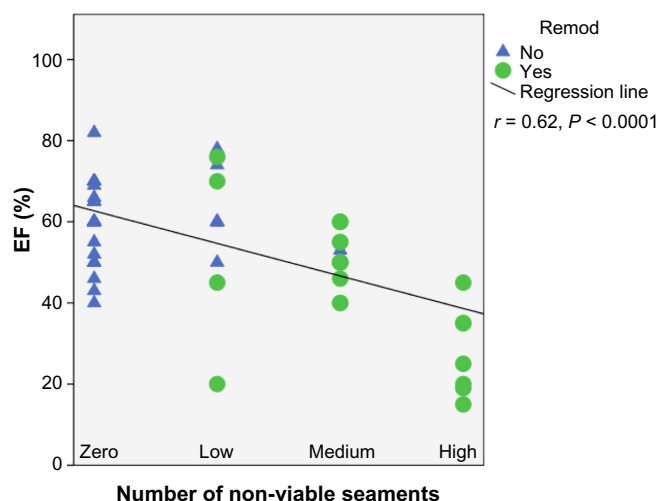


Figure 5. Correlation plot between number of nonviable segments and LV EF in relation to LV RWR.

Notes: This scatterplot shows the negative correlation between number of nonviable segments and LVEF in relation to LVRWR. Nonviable hearts are divided into four subgroups, ie, zero (0), low (0–3), medium (4–7), and high (≥ 8). Cases of LVRWR are depicted by green circles and of no RWR by blue triangles.

LVEF was significantly reduced ($P < 0.001$) compared to nonviable hearts without LVRWR, ie, $44 \pm 17\%$ versus $62 \pm 8\%$. When comparing patients with stable versus unstable angina, a significant difference in the presence of nonviable segments was found, ie, 1.5 ± 2.6 versus 3.9 ± 4.3 ($P = 0.007$), respectively.

Follow-up data. The incidence of MACE was significantly higher ($P < 0.05$) for those with nonviable myocardial segments than the group with only viable myocardial segments, ie, 19 patients out of 35 (54%) versus 15 out of 52 (29%). By applying logistic regression analysis, we found that in the multivariable model adjusting for LVEF (%), number of nonviable segments, LVRWR (yes versus no), and diagnosis, the number of nonviable segments was associated with MACE by an OR of 1.33 (95% CI, 0.98–1.80; $P = 0.063$), and also diagnosis was borderline significant with an OR of 0.27 (95% CI, 0.06–1.28; $P = 0.098$). In a simple regression model, number of nonviable segments by LGE correlated with LVEF by an r value of -0.66 , $P < 0.001$. Furthermore, in a multivariable stepwise regression model with LVEF as dependent variable, including number of nonviable segments by LGE, LVRWR (yes versus no), and diagnosis (stable versus unstable coronary syndrome), only the number of nonviable segments by LGE was found as a significant predictor for LVEF with $r = -0.66$, $B = -2.8$ (95% CI: -3.5 to -2.1 ; $P < 0.0001$).

Discussion

In the present study, stable patients with suspected CAD and referred for coronary angiography were examined with high-field 3T CMR. Being unaware of the angiographic results, the patients were allocated into a nonviable group and a viable group based on the presence or absence of LGE of the LV myocardium. In this patient cohort, with a mean age of 59 years, nonviable segments occurred only in territories supplied with vessels confirmed to be either occluded or significantly stenotic. On the other hand, viable segments were frequently noted in territories supplied with vessels showing significant lumen narrowing. Probably, sufficient collateral circulation from neighboring territories, which protects against myocardial necrosis, is an important mechanism for maintaining viability.

The presence of LGE in the myocardium has been shown to predict MACE in both ischemic and nonischemic hearts. Clinical studies of patients with hypertrophic cardiomyopathies, diabetes mellitus II, hypertension, and congenital conditions including the Senning-corrected systemic right ventricle and the Fontan-corrected single ventricle have demonstrated significant prognostic value of LGE as well.^{4,7,20–27} Hence, replacement of the normal contracting myocardium with fibrotic tissues may present common mechanisms for both ischemic and nonischemic heart diseases with regard to MACE. The fibrotic tissues, therefore, may represent a substrate for severe ventricular arrhythmias and may contribute to wall motion abnormalities and thereby to adverse remodeling of the LV.

A positive correlation between the amount of scar tissue and increased LV end-diastolic volume has been previously demonstrated.^{21,28} In the present study, the nonviable segments were directly related to LVRWR. A significant correlation between the number of nonviable segments and the development of LVRWR appeared. Most likely, this can be explained by the increased regional wall stress due to the replacement of myocardium with fibrotic tissues characterized by inferior compliance during the diastole and reduced contractile properties at systole. A corresponding theory has been suggested for hypertrophic cardiomyopathies, where increased deposition of fibrotic tissues facilitates an escalation of the condition.^{27,29} Further, in a study on patients treated with primary PCI, it was found that hearts exhibiting at least four LV segments with LGE was a strong predictor of adverse remodeling.^{28,30} This correlates well with the present patient cohort, where nonviable hearts with LVRWR had an average of 6.0 nonviable segments, whereas nonviable hearts without LVRWR had an average of 2.3 nonviable segments as defined by the presence of LGE. The LVRWR was reflected by a decrease in global LV systolic function, where EF was 44% compared to 62% for the nonviable group not showing evidence of LVRWR.

At 1.5T, it has been shown that in patients with ischemic heart disease and reduced LVEF there was a significant association between the extent of LGE and increase in mortality and the need of cardiac transplantation.³¹ As LVEF has been widely used a prognostic factor, we analyzed the relationship between LVEF and the number of nonviable segments by LGE, and found a significant negative correlation. Thus, LVEF could be used as a surrogate endpoint. On the other hand, in the multivariable logistic regression model, the number of nonviable segments by LGE was found to be a stronger predictor for MACE. Our findings suggest that LGE might be a useful tool for predicting prognosis. LGE was a stronger predictor than unstable coronary syndrome used as a variable in the analysis in spite of significantly more nonviable segments among unstable patients. Unstable coronary artery disease is known to carry a poorer prognosis than stable disease. However, invasive treatment modifies this risk factor by treating and thereby reducing the significance of unstable coronary plaques, and this probably explains why the nonmodifiable LGE remains as the strongest predictor.

Hence, considering nonviable myocardium of the LV myocardium as a valuable variable for the planning of revascularization and assessment of prognosis, the need for optimal and robust imaging tools is essential. Although increased image resolution and SNR is an advantage when using 3T CMR compared to 1.5T scanners, the increased magnetic field, however, is also potentially related to more image artifacts. This includes increased susceptibility, field inhomogeneity, and specific absorption rate (SAR) while using 3T scanners.³² However, these disadvantages have been considerably overcome, and presently 3T CMR is emerging as

a robust diagnostic technique.¹¹ Thus, comparison of LGE at 3T and 1.5T MR systems has shown similar or superior image quality.^{33–35} In this study, the images were assessable for all patients, and it was demonstrated that nonviable myocardium confirmed by LGE was prognostically significant with regard to hard endpoints at a 3T MR system similar to that noted for a number of 1.5T CMR studies.^{7,23,24}

Study limitations. The main limitations of this observational study are the small sample size and the restriction of the cohort to one large center. This may have influence on the demographics, treatment strategies, and enrolment criteria for being subjected to coronary angiography and CMR. A larger cohort would have enabled subgroup analyses and strengthened the statistical power of the results. In addition, patients with general contraindications to CMR were not included. Patients with implanted devices (eg, implantable cardioverter defibrillators/cardiac resynchronization devices) or considerably reduced kidney function were not examined. Thus, it is likely that a considerable proportion of those patients with notable advanced ischemic heart disease were excluded. This, in turn, may contribute to a selection bias and thereby influence the robustness of predicting clinical outcomes and survival patients with the most severe MIs.

Conclusion

Thus, in our study, applying a segment-based comparison of the presence of nonviable myocardium detected by 3T CMR and significant CAD as shown by coronary angiography, a positive correlation was confirmed. The extent of nonviable myocardium correlated with the presence of LVRWR and reduced LV systolic function. Although only a limited number of patients were examined and followed up, an increase of MACE was found in the group with nonviable myocardium corresponding to that found by others using 1.5T CMR. Hence, this study suggests that 3T CMR with detection of nonviable myocardium can be used as a noninvasive method for assessing patients with CAD, and may contribute to the individualized risk-stratification and treatment strategy of the patient.

Author Contributions

Conceived and designed the experiments: THL, SR, JEN. Analyzed the data: THL, MS, ON. Wrote the first draft of the manuscript: THL. Contributed to the writing of the manuscript: THL, MS, ON, JEN. Agree with manuscript results and conclusions: THL, MS, SR, ON, JEN. Jointly developed the structure and arguments for the paper: THL, MS, SR, ON, JEN. Made critical revisions and approved final version: THL, MS, SR, ON, JEN. All authors reviewed and approved of the final manuscript.

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