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Cardiac magnetic resonance imaging derived quantification of myocardial ischemia and scar improves risk stratification and patient management in stable coronary artery disease

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Abstract

Background: *Quantification of myocardial ischemia and necrosis might ameliorate prognostic models and lead to improved patient management. However, no standardized consensus on how to assess and quantify these parameters has been established. The aim of this study was to quantify these variables by cardiac magnetic resonance imaging (CMR) and to establish possible incremental implications in cardiovascular risk prediction.*

Methods: *This study is a retrospective analysis of patients with known or suspected coronary artery disease (CAD) referred for adenosine perfusion CMR was performed. Myocardial ischemia and necrosis were assessed and quantified using an algorithm based on standard first-pass perfusion imaging and late gadolinium enhancement (LGE). The combined primary endpoint was defined as cardiac death, non-fatal myocardial infarction, and stroke.*

Results: *845 consecutive patients were enrolled into the study. During the median follow-up of 3.64 [1.03; 10.46] years, 61 primary endpoints occurred. Patients with primary endpoint showed larger extent of ischemia (10.7 ± 12.25% vs. 3.73 ± 8.29%, $p < 0.0001$) and LGE (21.09 ± 15.11% vs. 17.73 ± 10.72%, $p < 0.0001$). A risk prediction model containing the extent of ischemia and LGE proved to be superior in comparison to all other models (χ^2 increase: from 39.678 to 56.676, integrated discrimination index: 0.3851, $p = 0.0033$, net reclassification index: 0.11516, $p = 0.0071$). The beneficial effect of revascularization tended to be higher in patients with greater extents of ischemia, though statistical significance was not reached.*

Conclusions: *Quantification of myocardial ischemia and LGE was shown to significantly improve existing risk prediction models and might thus lead to an improvement in patient management.* (Cardiol J 2017; 24, 3: 293–304)

Key words: cardiac magnetic resonance imaging, quantification of ischemia and necrosis, coronary artery disease, risk stratification, prognosis and outcomes

Introduction

Coronary artery disease (CAD) is still a leading cause for morbidity and mortality worldwide [1]. Most CAD patients present with clinically stable ischemic heart disease. For these patients, current practice guidelines strongly support the use of stress imaging modalities for diagnosis and correct risk stratification prior to invasive coronary X-ray angiography [2–4]. There exists inconsistency

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across the different imaging modalities on how to assess and report the extent and severity of myocardial ischemia and necrosis [5]. This fact may explain the variability in management decisions and the high frequency of absent obstructive CAD on diagnostic coronary angiography [6]. Therefore, the need to reach consensus concerning the assessment and reporting of ischemia has been identified [7]. Moreover, the presence of moderate to severe ischemia is a mandatory appropriateness criterion for percutaneous coronary intervention (PCI) in stable CAD [8]. Cardiac magnetic resonance imaging (CMR) is an established non-invasive method for the diagnosis of CAD [9]. It offers several advantages in comparison to other imaging techniques, such as a high spatial and temporal resolution, clear image contrast and lack of ionizing radiation [10, 11]. It is viable to reliably detect and visualize myocardial ischemia as well as necrotic tissue in one single exam [11]. It has been shown to provide important prognostic information in patients with known or suspected CAD [12–19]. There remains however, a gap in the current evidence base and that gap is a lack of standardization for the quantification of ischemia [20]. Consequently, a majority of available studies treat ischemia and necrosis as categorical variables without taking into account, extent or severity. It has been suggested that this additional information may serve as an important factor for correct risk stratification in CAD [5, 21]. The objective of the present study was to elaborate a CMR algorithm for the quantification of ischemia and necrosis based on standard first-pass perfusion imaging and to establish it's implications on risk prediction improvement.

Methods

Patients

The presented analysis was conducted retrospectively on a patient cohort which was established within a former project. Patients with known or suspected CAD medium to high risk were referred for adenosine perfusion CMR were consecutively screened for enrollment. Appropriateness criteria for stress CMR in the referenced institutions were the following: evaluation of symptoms being consistent with stable CAD and medium to high pre-test probability, inconclusive previous stress test and suspected progress of known CAD. All patients were considered eligible for enrollment unless they exhibited predefined exclusion criteria such as cardiac or respiratory instability, concomitant limiting disease, e.g. cancer, high degree heart valve or pulmonary disease, pregnancy, inability to give informed consent, age < 18 years, or myocardial infarction within the last 3 months. The study was approved by the institutional ethics committee. All patients gave informed written consent.

CMR examination

Cardiac magnetic resonance imaging was performed on a 1.5-T whole-body clinical magnetic resonance scanner (Intera, Philips Medical Systems, Best, the Netherlands) using a cardiac 5-element phased array surface receiver coil. CMR imaging was conducted according to well established standards in conformity with current guidelines [22–24].

CMR analysis

Functional imaging of the left and right ventricle was performed using a steady-state free precession sequence (repetition time 5.1 ms, echo time 2.2 ms, flip angle 55°, voxel size 1.6 × 1.6 mm, slice thickness 8 mm, no interslice gap, acquisition in end-expiration breath-hold, 32 cardiac phases). For perfusion imaging, 3 slices in short-axis orientation (basal, mid-ventricular, and apical) were acquired. A balanced fast-field echo sequence (repetition time 2.6 ms, echo time 1.3 ms, saturate pre-pulse with 100-ms delay, flip angle 50°, 40 dynamics, voxel size 2.8 × 2.9 mm, slice thickness 10 mm) was used. Adenosine was given intravenously at a constant rate of 140 μg/kg/min for 3 min. First-pass perfusion imaging with 0.1 mmol/kg of a gadolinium based contrast agent (Dotarem®, Guerbet, Villepinte, France) was performed after an adequate vasodilator response was achieved (defined as an increase in heart rate above 10% or a decrease in systolic blood pressure above 10% [24]). In cases when sufficient vasodilator response could not be observed within 3 min, infusion rate was increased by steps of 10% until the predefined response was achieved. Ten minutes after first first-pass imaging, a second perfusion study using the same parameters was performed to allow for better discrimination between perfusion defects and artifacts. Perfusion defects visible under stress as well as under rest conditions were considered to be artifacts (such as dark rim phenomena) and thus were excluded from the analyses.

Ten minutes after the second perfusion study, a 3-dimensional (3D) inversion-recovery gradient-echo sequence (repetition time 7.1 ms, echo time 3.2 ms, voxel size 1.6 × 1.6 mm, slice thickness 8 mm) was acquired in continuous short axis covering the entire left ventricle for evaluation of late

gadolinium enhancement (LGE). Inversion time was individually adjusted for complete nulling of the myocardium.

Perfusion and LGE imaging was interpreted and quantified by two experienced readers in consensus. The readers were blinded to the patient's history and symptoms. Adenosine perfusion images were evaluated according to the 16-segment model [25]. Regional hypoenhancement present during adenosine perfusion without corresponding LGE was considered to be a reversible perfusion deficit. In the presence of LGE, a perfusion defect was considered reversible if the perfusion defect extended beyond the area of LGE.

Endo- and epicardial contours were drawn manually into each slice of the perfusion series in order to yield the global myocardial area. The extent of myocardial necrosis was assessed on corresponding LGE series using a semi-automatic approach. Myocardial necrosis was defined as signal intensity of above 5 standard deviations of remote myocardium as previously reported [26]. LGE patterns unlikely to be of ischemic origin (e.g. spotty, intramural or epicardial) were excluded from further quantification. The extent of necrosis was expressed as a percentage of global myocardial area.

Late gadolinium enhancement delineation was then copied into the perfusion series and compared to the extent of reversible ischemia. Two criteria had to be fulfilled to define a perfusion defect: an area of regional hypoenhancement had to below 5 standard deviations from remote myocardium in the dynamic with maximum contrast in the myocardium; the hypoenhancement had to be present in 5 sequential phases. The dynamic with the greatest extent of perfusion defect was then used for quantification which was achieved by manual delineation of the perfusion defect. Ischemia quantification was expressed as percentage of global myocardium. The observers manually excluded artifacts such as dark rim phenomena. Figure 1 provides several examples.

For analyses, the software provided by the manufacturer of the CMR system (ViewForum, Philips Medical Systems) was used.

Follow-up

Follow-up information was acquired from patients by telephone interview or from outpatient clinic, hospital chart review or by contact with the patients' general practitioner or hospital. Primary endpoint was defined as cardiac death, non-fatal myocardial infarction, or stroke. Cardiac death was defined as death from any cardiac cause (e.g. myocardial infarction, ventricular fibrillation or other lethal arrhythmia, heart failure) or sudden unexplained death. Non-fatal myocardial infarction was defined according to the current universal definition [27].

Statistical analysis

Continuous variables were tested for normal distribution by the D'Agostino-Pearson test. In cases of normal distribution, variables were reported as mean ± standard deviation and a 2-tailed t-test was applied for comparison. Variables without normal distribution were reported as median with percentiles [5; 95] and compared by the Mann-Whitney rank sum test.

Univariate regression analyses using Cox proportional hazard models were performed to estimate the predictive value of the variables. Hazard ratio and corresponding 95% confidence interval are provided.

To test for incremental predictive power, the following approach was applied: Multivariate models based on significant variables were defined and compared. Chi-square values were calculated with Cox's proportional hazard overall model fit. Integrated discrimination index and net reclassification index were assessed as well. In cases of a significant increase in these variables, a particular model was judged superior [28]. In order to avoid over-fitting, the variable 'history of CAD' was created as a combination of the variables which include previous myocardial infarction, previous PCI and previous coronary artery bypass graft.

Cumulative event curves were compared using the Kaplan-Meier method using a log-rank test.

Overall, a p value ≤ 0.05 was judged significant. Statistical analysis was performed using commercially available software (Stata13, College Station, USA, MedCalc, Mariakerke, Belgium).

Results

Patients

922 consecutive patients were enrolled in the study. 72 (7.8%) were lost to follow-up. Five patients (0.5%) were excluded due to insufficient CMR image quality. Thus, the study group consisted of 845 patients. Median age was 64.0 [39; 78] years, 32.1% were female. Median follow-up was 3.64 [1.03; 10.56] years. According to the established Morise score [29], 71 (8.4%) patients were assigned to the low risk group (< 9 points), 505 (59.8%) patients were assigned to the intermediate risk group (9–15 points) and 269 (31.8%) patients were assigned to the high risk group. Clinical and

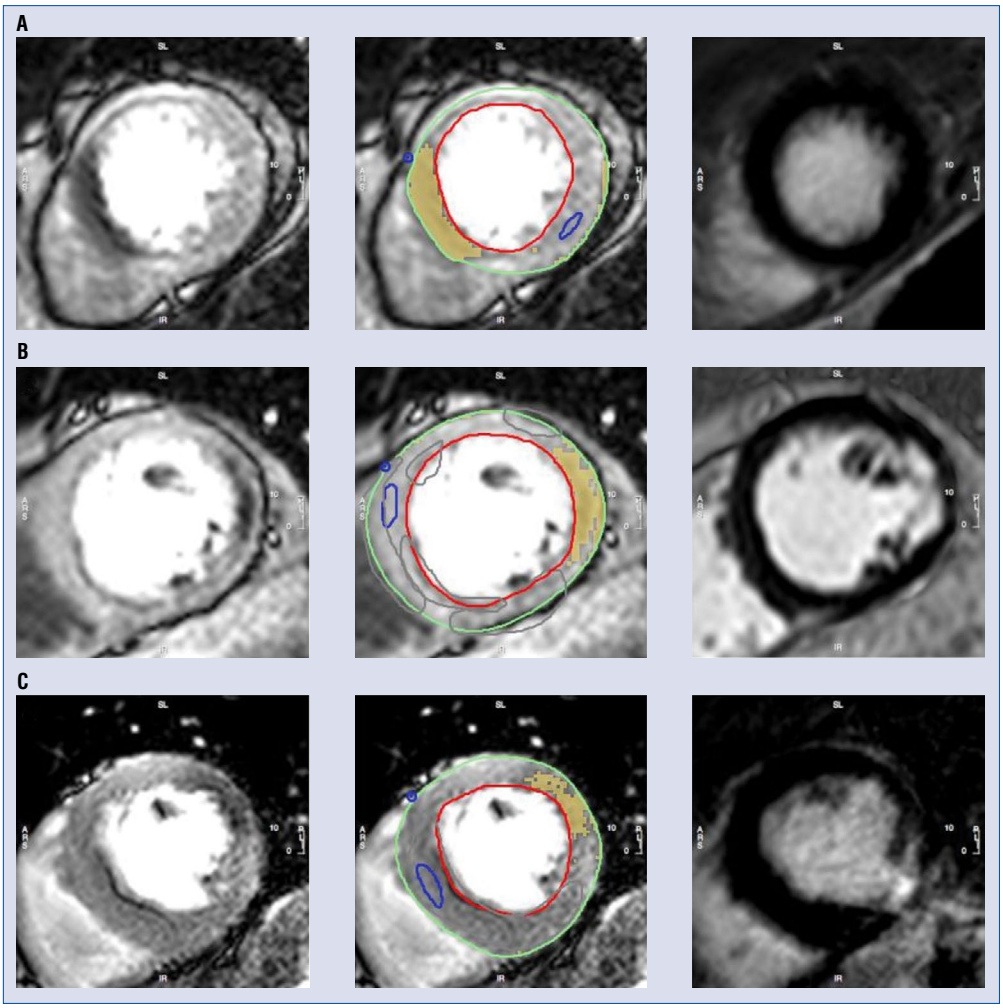

Figure 1. Examples of assessment of myocardial ischemia and necrosis; **A.** Adenosine perfusion imaging (midventricular slice) with a septal perfusion deficit (native and after delineation) and no underlying late gadolinium enhancement; **B.** Adenosine perfusion imaging (basal slice) with perfusion deficit in the lateral segments (native and after delineation) and matching late gadolinium enhancement; **C.** Perfusion deficit in the anterolateral segments (native and after delineation) and late gadolinium enhancement inferolateral. The perfusion deficit exceeds the area of myocardial scar.

demographic patient characteristics, including cardiovascular risk factors and prior cardiac events are provided in Table 1.

CMR examination and analysis

Median left ventricular end-diastolic volume was 130 [85; 208] mL; median left ventricular ejection fraction (LVEF) was 68 [42; 81] %. Among the 845 patients that formed the study group, LGE was present in 178 (20.9%) patients and reversible perfusion deficit in 200 (23.7%) cases. Table 1 gives further insight into particular CMR results.

Follow-up and comparison of patients with and without event

During the follow-up period, 61 primary endpoints occurred. 29 (47.5%) were cardiac deaths, 26 (42.3%) non-fatal myocardial infarctions and 6 (9.8%) were strokes.

Table 1 provides a comparison of patients with and without primary endpoint during follow-up. Patients with occurrence of primary endpoint were significantly older, often had more diabetes mellitus, a history of cardiac events and an impaired LVEF. Patients with primary endpoint exhibited significantly larger extents of ischemia (3.73 ± 8.29% vs. 10.7 ± 12.25%, $p < 0.0001$) and LGE (17.73 ± 10.72% vs. 21.09 ± 15.11%, $p < 0.0001$).

Univariate and multivariate analysis of endpoint prediction

Several demographic, clinical and CMR derived variables were analyzed concerning the

Table 1. Patient characteristics and cardiac magnetic resonance imaging (CMR) results including a comparison of patients with and without event.

	Total (n = 845)	No event (n = 784)	Event (n = 61)	P
Age [years]	64.0 [39; 78]	63 [39; 78]	68 [41; 81]	**0.0007**
Female sex	271 (32.1%)	258 (32.9%)	13 (21.3%)	0.08
Cardiovascular risk factors:				
BMI [kg/m^2]	26.51 [21.22; 33.93]	26.5 [21.22; 33.94]	26.7 [21.04; 34]	0.71
Hypertension	579 (68.5%)	534 (68.1%)	45 (74.1%)	0.42
Smoking	186 (22.0%)	168 (21.4%)	18 (29.3%)	0.21
Hyperlipidemia	491 (58.1%)	452 (57.7%)	39 (63.8%)	0.44
Diabetes mellitus	166 (19.6%)	144 (18.4%)	22 (36.2%)	**0.002**
Family history	207 (24.5%)	194 (24.7%)	13 (20.7%)	0.60
Morise score < 9	71 (8.4%)	68 (11.5%)	3 (4.9%)	0.58
Morise score 9–15	505 (59.8%)	469 (59.8%)	36 (59.0%)	
Morise score > 15	269 (31.8%)	247 (31.5%)	22 (36.1%)	
History of CAD:	363 (43.0%)	321 (41%)	42 (68.3%)	**< 0.0001**
Previous MI	180 (21.3%)	151 (19.3%)	29 (48.3%)	**< 0.0001**
Previous PCI	275 (32.6%)	240 (30.6%)	35 (56.7%)	**< 0.0001**
Previous CABG	89 (10.5%)	78 (9.9%)	11 (18.3%)	**0.007**
Symptoms:				
CCS I	106 (12.5%)	103 (13.1%)	3 (4.9%)	
CCS II	459 (54.3%)	422 (53.8%)	37 (60.7%)	
CCS III	280 (33.1%)	259 (33.0%)	21 (34.4%)	
CCS IV	0 (0%)	0 (0%)	0 (0%)	
CMR characteristics:				
LVEDV [mL]	130 [85; 208]	129.5 [85; 201.5]	137 [77; 276]	0.063
LVEF [%]	68 [42; 81]	68.2 [44; 80]	60.5 [27.5; 84.92]	**0.0001**
RVEDV [mL]	131 [84.4; 198]	131 [86.4; 199.2]	120 [75; 189.5]	**0.008**
RVEF [%]	65 [53; 76]	65 [54; 76]	67 [48; 77.3]	0.621
Wall motion score	17 [17, 29.5]	17 [17; 28]	20 [17; 35.7]	**< 0.0001**
LGE	175 (20.7%)	142 (18.1%)	33 (54.1%)	**< 0.0001**
LGE in % of left myocardium	17.73 (10.72%)	16.87 (9.16%)	21.09 (15.11%)	**< 0.001**
Ischemia	200 (23.7%)	163 (20.8%)	37 (60.7%)	**< 0.0001**
Ischemia in % of left myocardium	4.23 (8.81%)	3.73 (8.29%)	10.70 (12.25%)	**< 0.0001**

BMI — body mass index; CABG — coronary artery bypass graft; CAD — coronary artery disease; CCS — Canadian Cardiovascular Society class; LGE — late gadolinium enhancement; LVEDV — left ventricular end-diastolic volume; LVEF — left ventricular ejection fraction; RVEDV — right ventricular end-diastolic volume; RVEF — right ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention

occurrence of primary endpoints (Table 2). There were strong associations for age, diabetes mellitus, history of prior cardiac events and LVEF. The highest hazard ratios were observed with the presence of LGE and the presence of reversible ischemia (4.89 and 4.48, respectively, p in both cases < 0.0001). Quantification of these variables also lead to highly significant results with an increase per percentage point of left myocardium of 1.07 for LGE and 1.04 for reversible ischemia (p < 0.0001).

Based on the univariate analysis, multivariate models were defined and their predictive power calculated using the stepwise approach (Table 3). Model 1 contained established clinical risk factors, including age, hypertension, smoking, hyperlipidemia, and diabetes mellitus, which resulted in a χ^2-value of 18.501 (p = 0.0001). After the addition of the variable 'history of CAD' in model 2, an increase of χ^2 could be observed (χ^2: 28.386, p < 0.0001). In model 3 LVEF was added to model 2,

Table 2. Univariate analysis of predictors of primary endpoint.

	Hazard ratio	95% confidence interval	P
Age, per year	1.04	1.016–1.066	**0.001**
Female sex	0.64	0.343–1.173	0.146
Cardiovascular risk factors:			
BMI, per kg/m^2	1.00	0.936–1.067	0.980
Hypertension	1.37	0.759–2.461	0.298
Smoking	1.35	0.767–2.385	0.297
Hyperlipidemia	1.24	0.728–2.129	0.424
Diabetes mellitus	2.46	1.437–4.198	**0.001**
Family history	0.814	0.431–1.537	0.526
Morise score	1.03	0.967–1.10	0.354
Symptoms:			
CCS, per higher class	1.28	0.856–1.907	0.231
History of CAD:	2.86	1.661–4.936	**0.0002**
Previous MI	3.33	2.007–5.536	**< 0.0001**
Previous PCI	2.811	1.683–4.695	**0.0001**
Previous CABG	2.09	1.086–4.024	**0.027**
CMR characteristics:			
LVEDV [mL]	1.004	1.000–1.009	0.062
LVEF [%]	0.96	0.946–0.976	**< 0.0001**
RVEDV [mL]	0.99	0.979–0.995	0.002
RVEF [%]	0.99	0.960–1.025	0.622
Wall motion score [Unit]	1.11	1.070–1.148	**< 0.0001**
LGE	4.89	2.923–8.181	**< 0.0001**
LGE, per % of left myocardium	1.07	1.05–1.086	**< 0.0001**
Ischemia	4.48	2.669–7.506	< 0.0001
Ischemia, per % of left myocardium	1.04	1.035–1.061	**< 0.0001**
Follow up:			
PCI within 45 days after CMR	1.16	0.0447–2.787	0.815

BMI — body mass index; CABG — coronary artery bypass graft; CAD — coronary artery disease; CCS — Canadian Cardiovascular Society class; CMR — cardiac magnetic resonance imaging; LGE — late gadolinium enhancement; LVEF — left ventricular ejection fraction; LVEDV — left ventricular end-diastolic volume; RVEDV — right ventricular end-diastolic volume; RVEF — right ventricular ejection fraction; MI — myocardial infarction; PCI — percutaneous coronary intervention

which lead to a further increase of χ^2 to 39.678 ($p < 0.0001$). Model 4 contained the variables which proved to be significant in previous models plus LGE and Ischemia as categorical variables resulting in a further χ^2 increase to 50.616, ($p < 0.0001$). Finally, in model 5, 'quantification of LGE' and 'ischemia' was added. This lead to a further increase in χ^2-value (56.676, $p < 0.0001$). LVEF lost its significance in latter model. Table 3 also provides results of the analyses of the integrated discrimination index estimate and the net reclassification index estimate. The assessment of these parameters supported the superiority of model 5 over model 4 and of both models over model 3.

Event rates and impact of revascularization in dependency of ischemia

Overall annual event rate was 1.88%. 200 patients exhibited reversible myocardial ischemia, which equals 23.67% of the total study cohort. Patients without ischemia had an event rate of 0.93%, in contrast to patients with ischemia who exhibited an event rate of 4.25% (log-rank test for equality of survivor function: χ^2: 38.50, $p < 0.0001$) (Table 4).

In order to evaluate the effect of revascularization subsequent to positive stress-testing in dependency of the extent of ischemia, patients who received interventional or surgical revascularization within 45 days after CMR were further analyzed

Table 3. Risk prediction models using a stepwise multivariate approach.

	HR	CI	P
	Model 1: Basic Model		
Age	1.035	1.012; 1.061	0.005
Hypertension	Excluded		
Smoking	Excluded		
Hyperlipidemia	Excluded		
Diabetes mellitus	2.270	1.326; 3.885	0.003
	Overall Model Fit: χ^2 18.501; p = 0.0001		
	Model 2: Basic Model + History of CAD		
Age	1.029	1.004; 1.055	0.023
Diabetes mellitus	2.004	1.166; 3.445	0.012
History of CAD	2.419	1.368; 4.277	0.002
	Overall Model Fit: χ^2 28.386; p < 0.0001		
	Model 3: Model 2 + Basic CMR Features		
Age	1.029	1.004; 1.054	0.025
Diabetes mellitus	1.761	1.007; 3.079	0.047
History of CAD	2.327	1.322; 4.095	0.003
LVEF	0.970	0.954; 0.986	0.0003
RVEF	Excluded		
	Overall Model Fit: χ^2 39.678; p < 0.0001		
	Model 4: Model 3 + Extended CMR Features		
Age	1.028	1.004; 1.053	0.023
Diabetes mellitus	1.887	1.077; 3.308	0.027
History of CAD	Excluded		
LVEF	0.975	0.959; 0.992	0.004
LGE (categorical)	2.104	1.024; 4.324	0.043
Ischemia (categorical)	2.139	1.054; 4.342	0.035
	Overall Model Fit: χ^2 50.616; p < 0.0001		
	Improvement Model 4 vs. Model 3:		
	IDI-estimate: 0.03110; SE: 0.01161; p: 0.00738		
	NRI-estimate: 0.14381; SE: 0.05419; p: 0.00796		
	Model 5		
	Model 3 + Quantified CMR Features		
Alter	1.028	1.004; 1.052	0.019
Diabetes mellitus	**2.170**	**1.261; 3.735**	**0.005**
History of CAD	Excluded		
LVEF	Excluded		
LGE, per %	1.056	1.036; 1.076	< 0.0001
Ischemia, per %	1.033	1.013; 1.053	0.001
	Overall Model Fit: χ^2 56.676; p < 0.0001		
	Improvement Model 5 vs. Model 3:		
	IDI-estimate: 0.03851; SE: 0.01311; p: 0.00330		
	NRI-estimate: 0.11516; SE: 0.04274; p: 0.00705		
	Improvement Model 5 vs. Model 4:		
	NRI-estimate: 0.01929; SE: 0.00742; p: 0.00932		

CI — confidence interval; CAD — coronary artery disease; CMR — cardiac magnetic resonance imaging; HR — hazard ratio; IDI — integrated discrimination index; LGE — late gadolinium enhancement; LVEF — left ventricular ejection fraction; NRI — net reclassification index; RVEF — right ventricular ejection fraction; SE — standard error

Table 4. Annual event rates of dependency in presence of myocardial ischemia.

Total study cohort (n = 845)	Ischemia (of any extent)	No ischemia
Number of subjects	200	645
Events in this category	24	37
Annual event rate	4.25%	0.93%
Log-rank test	χ^2: 38.50, p < 0.0001	

Table 5. Annual event rates and impact of revascularization of dependency for extent of ischemia.

Patients with myocardial ischemia > 5%	Total number of subjects (n = 192)	
	Revascularization	Conservative treatment
Number of subjects	42	150
Events in this category	5	30
Annual event rate	3.17%	4.46%
Log-rank test	χ^2: 0.59, p = 0.44	
Patients with myocardial ischemia > 10%	**Total number of subjects (n = 151)**	
	Revascularization	**Conservative treatment**
Number of subjects	35	116
Events in this category	4	21
Annual event rate	2.89%	4.06%
Log-rank test	χ^2: 0.50, p = 0.48	
Patients with myocardial ischemia > 15%	**Total number of subjects (n = 115)**	
	Revascularization	**Conservative treatment**
Number of subjects	28	87
Events in this category	3	17
Annual event rate	2.70%	4.44%
Log-rank test	χ^2: 0.85, p = 0.36	

(Table 5, Fig. 2). Of the 200 patients exhibiting reversible ischemia, 43 received revascularization (21.5%). Patients with ischemia > 5% of myocardial volume without revascularization showed an event rate of 4.46%. In patients with ischemia > 5% of myocardial volume who were revascularized an event rate of 3.17% was observed (χ^2: 0.59, p = 0.44, risk reduction of 0.692). Patients with ischemia > 10% of myocardial volume had annual event rates of 4.06% without revascularization and 2.89%, if revascularized (χ^2: 0.50, p = 0.48, risk reduction of 0.681). In patients with myocardial ischemia > 15%, primary endpoint rates were 4.44% without vs. 2.70% with revascularization (χ^2: 0.85, p = 0.36, risk reduction of 0.564).

Discussion

In the present study, a simple and intuitive approach to quantify the extent of myocardial ischemia and necrosis is described. The superiority of a risk prediction model containing these variables could be demonstrated.

As reported by Bingham et al. [19], the combination of several CMR parameters was superior regarding correct risk stratification over preimaging information alone. As the authors of latter manuscript discuss, it is difficult to identify the most predictive CMR variable because of collinearity especially of reversible ischemia and LGE. Thus, they concluded that CMR-derived results provide rather complementary than overlapping information. This finding is consistent with other recently published studies [30]. The present hypothesis was that a risk prediction model containing myocardial ischemia and LGE only as dichotomous variables could further be improved by quantification of these parameters. This could be demonstrated by the data contained in this study (statistical significant increase in χ^2-, NRI- and IDI-values). A large

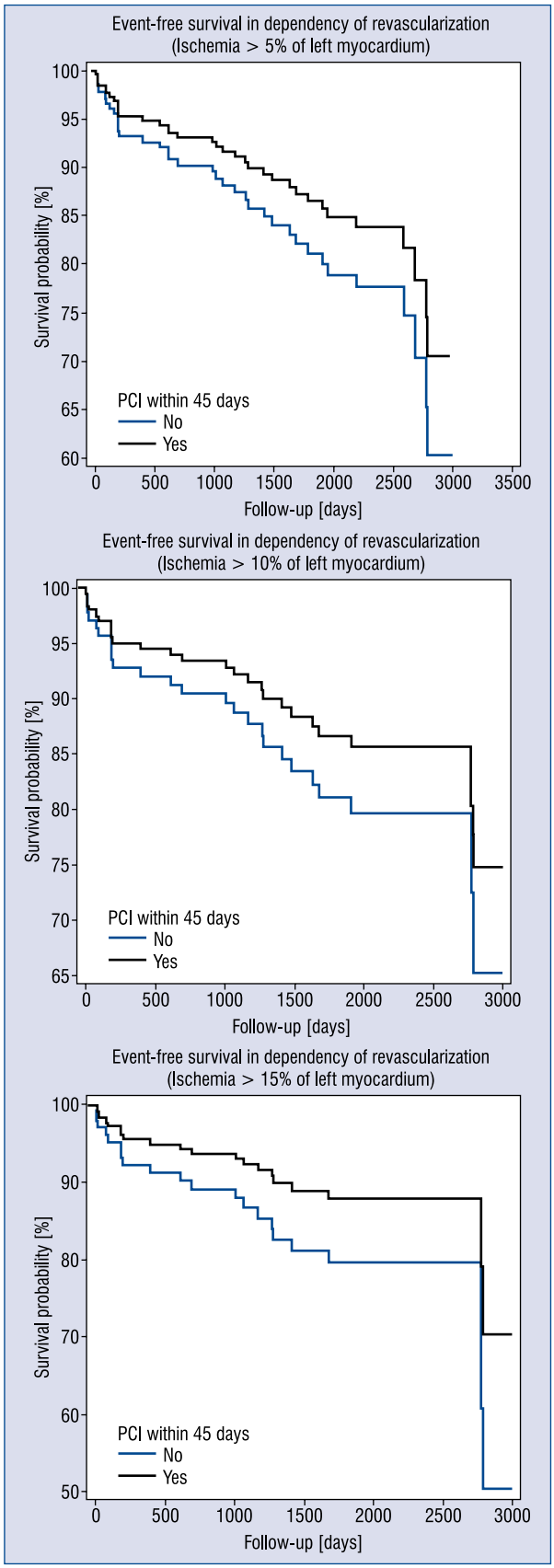

Figure 2. Kaplan-Meier plot showing event-free survival in dependence of ischemia and revascularization.

meta-analysis has recently been published [31]. The authors point out that presence of LGE itself is associated with a worse outcome in patients with CAD. They also explain that, in some of the studies that formed the evidence base, LGE lost its significance on multivariate testing when ischemia was assessed as well. They therefore, recommended further studies to determine whether LGE provides truly incremental prognostic information in patients undergoing stress CMR. It could be suspected that quantification of ischemia and LGE may contribute to a better understanding of the complex interactions. In this study, quantified LGE and myocardial ischemia maintained their statistical significance throughout all the evaluated models, a finding which supports the above mentioned suggestion.

There already exist approaches for the quantification of ischemia and LGE based on 2-dimensional (2D) myocardial perfusion CMR [20]. Some of them just report the number of affected segments according to the 16 segment model provided by current guidelines [20, 25], others have tried to take transmurality into account [32]. The presented presumption herein is that it is more intuitive and reliable to directly delineate the areas of perfusion deficit and LGE and relate them to the total left ventricular area. We acknowledge, that this approach may not reflect the true portion of affected myocardium due to the incomplete coverage of the left ventricle [33]. However, it is an easy to use algorithm which can be implemented in a daily clinical work-up routine and does not demand special analysis tools or additional sequences.

The feasibility of assessing the extent of myocardial perfusion deficit using a three dimensional first-pass myocardial perfusion approach has been demonstrated [20]. A recently published study with 45 patients reports a good correlation between 2D and the much more elaborated 3D myocardial perfusion CMR approach [32]. The authors demonstrate that the 2D approach tends to slightly underestimate the ischemic burden in comparison to the whole-heart analysis. Nevertheless, there was no significant difference concerning the assignment to designated further therapy. The authors of that trial therefore raise the question about relative benefits of whole-heart perfusion imaging that need to be explored in future studies. Overall, 2D first-pass perfusion stress CMR remains the current clinical standard which is supported by a robust evidence base.

In order to evaluate the potential improvement achieved by ischemia quantification with regard to patient management, the impact of revasculariza-

tion in dependency of the extent of ischemia was analyzed. Though the results of this study did not reach statistical significance, a tendency was observed. Patients with larger ischemia extent seem to benefit more from a revascularization strategy. Since the COURAGE trial was published in 2007 [32], the role of revascularization in the setting of stable CAD was a matter of debate. Several study efforts have been made to better identify the subgroup of CAD patients who will show a prognostic benefit from revascularization. For instance, a substudy of the COURAGE trial using myocardial perfusion singe photon emission computed tomography revealed that patients with moderate to severe myocardial ischemia (defined as ischemia > 10% of the left myocardium) seemed to benefit from revascularization over optimal medical treatment alone [34]. As a consequence, attempts have been made to comparably identify patients with moderate to severe ischemia throughout various imaging and diagnostic modalities. Hence, the presented approach of quantification may underestimate the real extent of ischemia in comparison to nuclear perfusion techniques due to incomplete coverage of the left ventricle. With regard to this problem, Shaw et al. [5] recently suggested an approach to overcome the difficulty of modality specific thresholds. They defined high risk CAD patients as those with a probability of having an adverse event being about 5% per year [5]. By this definition, they worked out a recommendation on how to identify high risk CAD patients across different imaging modalities. As a consequence, it could be demonstrated that patients with an event rate of 5% appear to benefit from revascularization [35, 36]. Most of the studies available on this topic used nuclear imaging techniques, whilst the evidence based on CMR imaging remains limited. However, results of this study are in concordance with these findings. Patients with myocardial ischemia above 5% had an annual event rate of 4.46%. It is of interest, that patients with small extents of ischemia exhibited event rates that were comparable to those with larger portions of ischemic myocardium (Table 4). It can be postulated that diffuse CAD causing a relatively small extent of ischemia which may lead to substantial increase in risk comparable to CAD with singe high-grade stenosis and larger extents of ischemia. In this study, the beneficial effect of revascularization seemed to be greater in the latter case. To further evaluate the role of ischemia detection and quantification in patients with stable CAD, studies using a prospective design are warranted, as with the ongoing ISCHEMIA trial [37].

Limitations of the study

There are several limitations that need to be addressed. The approach in quantifying reversible ischemia and LGE has not been sufficiently validated as yet. A prospective validation and comparison of the presented method in comparison with other techniques and modalities has not been done. The results of this study are concur with other studies in the field and are substantiated by an appreciable gain in prognostic prediction.

Moreover, a consensus method was chosen for ischemia and LGE quantification. Therefore, inter- and intra-reader variabilities cannot be reported. Nevertheless, image analysis was done by two experienced readers capable of attaining reasonable quality. In future evaluation, determination of procedures with specific operating figures will be necessary.

Because of the retrospective nature of our study, it was not possible to control for treatment effects such as the decision for or against revascularization in a particular patient. Therefore, treatment effects might be under or overestimated which might be an explanation as to why statistical significance could not be reached. Moreover, data on further testing after the CMR evaluation (e.g. results of subsequent coronary angiographies) were not complete. Thus, it presented an inability to assess important parameters such as diagnostic accuracy.

Conclusions

Quantification of myocardial ischemia and necrosis by CMR provides improved risk prediction in patients with stable CAD.

Conflict of interest: None declared

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