Accuracy of dynamic three-dimensional magnetic resonance perfusion imaging for the detection of coronary artery disease in patients with reduced ejection fraction

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Received: July 2, 2020 • Revised manuscript received: August 5, 2020 • Accepted: August 10, 2020

ABSTRACT

Background: To assess the accuracy of 3D cardiovascular magnetic resonance (CMR) perfusion imaging for the detection of coronary artery disease (CAD) against fractional flow reserve (FFR) and quantitative coronary angiography (QCA) in patients with reduced ejection fraction (EF).

Methods: Out of 447 patients who underwent 3D CMR perfusion imaging (at 1.5 and 3.0 T under adenosine stress and at rest) at 5 European centers, 86 cases with an EF ≤50% were identified (mean age 64 ± 11 yrs, 80% male). Significant CAD was defined as a FFR value <0.8 and a QCA >50%. 86 individuals matched for age, gender and major cardiovascular risk factors, were chosen as the control group.

Results: The prevalence of CAD defined by FFR (<0.8) was 59% (EF≤50%) vs. 54% (EF>50%), $P = 0.4$. In relation to FFR, 3D perfusion imaging yielded a sensitivity of 84.5% (95% CI 76.0–90.4) and specificity of 77.3% (95% CI 66.7–85.3). The sensitivity of perfusion imaging was higher in patients with an EF≤50% (90.2 vs. 78.3%, $P = 0.1$) whereas specificity showed the reverse (62.9 vs. 90.0%, $P = 0.005$). The diagnostic accuracy was comparable in both subgroups (AUC 79.1 vs. 83.7%, $P = 0.25$). According to QCA, the prevalence of CAD was 78 vs. 72% ($P = 0.4$). Perfusion imaging yielded a sensitivity and specificity of 82.1 vs. 62.9%, $P = 0.01$ and 79.0 vs. 95.8%, $P = 0.09$ respectively with a high diagnostic accuracy in both subgroups (AUC 82.0 vs. 80.5%).

Conclusion: 3D-CMR perfusion imaging yields a high sensitivity and diagnostic accuracy with regards to the detection of significant CAD irrespective of left ventricular (LV) systolic function.

KEYWORDS

Cardiac magnetic resonance perfusion imaging, Coronary artery disease, Heart failure, Late gadolinium enhancement

IMAGING 13 (2021) 1, 61–68
DOI: [10.1556/1647.2020.00007](https://doi.org/10.1556/1647.2020.00007)

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ABBREVIATIONS AND ACRONYMS

AUC: area under the curve; **CAD:** coronary artery disease; **CI:** confidence interval; **CMR:** cardiovascular magnetic resonance; **CVD:** cardiovascular disease; **EF:** ejection fraction; **FFR:** fractional flow reserve; **HF:** heart failure; **LGE:** late gadolinium enhancement; **LV:** left ventricular; **LVEDD:** left ventricular end-diastolic diameter; **LVEDV:** left ventricular end-diastolic volume; **LVEF:** left ventricular ejection fraction; **LVESV:** left ventricular end-systolic volume; **MIB:** myocardial ischemic burden; **QCA:** quantitative coronary angiography; **ROC:** receiver operator characteristics; **SD:** standard deviation; **SPECT:** single-photon emission computed tomography

Introduction

Perfusion imaging by cardiovascular magnetic resonance (CMR) has been demonstrated to be a reliable diagnostic tool for the assessment of hemodynamically significant coronary artery disease (CAD) in numerous studies [1–4]. Previous studies showed a high sensitivity and diagnostic accuracy of CMR perfusion imaging in the setting of single- and multi-center investigations, which also included a direct comparison with single-photon emission computed tomography (SPECT) [5, 6]. Ongoing technological improvement has led to 3D perfusion imaging, which solves the problem of limited LV coverage linked to the routinely used 3-slice 2D methods [7]. 3D CMR perfusion imaging has already been shown to have high diagnostic accuracy for detecting significant CAD in a multicenter setting [8] and could be beneficial in patients with heart failure who have been scarcely investigated with regards to the diagnostic performance of CMR perfusion imaging.

According to current clinical guidelines [9], CMR imaging is recommended for global evaluation of cardiac function and structure in patients with heart failure, as it represents the gold standard for determining LV function, volumes and mass, especially if echocardiographic data are inconclusive. Furthermore, the use of perfusion imaging provides a non-invasive approach to diagnose myocardial ischemia as the underlying etiology of an impaired LV function. Nonetheless, only limited data exists with regards to the feasibility and accuracy of CMR perfusion imaging in this clinical setting [10] where the detection of ischemia may be challenging due to LV remodeling including wall thinning, and the presence of scar tissue. In this setting, using a 3D method with high spatial resolution and full LV coverage, may potentially improve the diagnostic accuracy of perfusion analysis in selected patients.

In this study, we therefore aimed to assess the diagnostic performance of 3D CMR perfusion imaging with regards to the detection of significant CAD (as defined by fractional flow reserve (FFR) measurements (<0.8) or significant stenosis on quantitative coronary angiography (QCA)) in patients with depressed LV function ($EF \leq 50\%$). We selected individuals who underwent ischemia testing with suspected and known CAD as part of a multicenter trial, in comparison with a control group matched from the same study population.

Methods

Study population

The study cohort consisted of patients who had been recruited into 3 prospective studies [7, 8, 11] evaluating 3D CMR perfusion imaging for the detection of CAD in a multi-center setting. Pooling the available patient data resulted in a total of 447 individual data sets of patients from 5 European centers (University Hospital Zurich, Switzerland; University Hospital RWTH Aachen, Germany; German Heart Institute Berlin, Germany; King's College London, United Kingdom; University of Leeds, United Kingdom) who were scheduled for diagnostic coronary angiography due to suspected and known CAD and who underwent 3D perfusion imaging. 416 of these patients had already been included in the initial 3 studies, 31 patients with reduced LV function could be identified from pre-existing data-sets and were specifically analyzed for the current study in order to increase the number of patients in the subgroup of individuals with an impaired LV function. Out of the total of 447 patients, 86 patients with left ventricular ejection fraction (EF) of $\leq 50\%$ measured by CMR imaging were identified. A control group consisting of 86 patients with an $EF > 50\%$ matched for age, gender and major cardiovascular risk factors (arterial hypertension, diabetes, smoking, positive family history, obesity and hyperlipidemia) was selected from the same cohort. All patients had given written informed consent and the study had been approved by local ethics committees. Patients were excluded from study participation if contraindications to CMR imaging (e.g. claustrophobia, incompatible metallic implants) or adenosine administration (asthma, higher-degree AV-block) were present. Prior to the examination, patients were instructed to refrain from caffeine-intake for 24 h.

Cardiovascular magnetic resonance protocol

CMR imaging was performed at 1.5 and 3.0 T scanners of a single vendor (Philips, Best, The Netherlands) using either a 5-, 6-, 28- or 32 element coil for signal reception. A vector ECG was used for cardiac synchronization.

The imaging protocol consisted of cine sequences in standard cardiac geometries and LV function was measured by applying the disc-summation method in a short-axis geometry with full LV coverage. The 3D perfusion was planned with a short-axis geometry covering the LV from apex to base. Adenosine was used as the pharmacological stressor and administered intravenously at a dosage of 140 $\mu\text{g/kg/min}$ under continuous monitoring of blood pressure and heart rate. 3D stress first-pass perfusion imaging was performed after at least 3 min of adenosine infusion using a gadolinium-based contrast agent followed by a saline flush and image acquisition was performed during a single breath-hold. The identical 3D perfusion scan was repeated at rest.

A saturation-recovery gradient-echo pulse sequence (TR/TE/flip angle 1.9/0.8/15°, saturation pre-pulse delay 150 ms,

partial Fourier acquisition, 16 slices with 5 mm thickness, measured voxel size $2.3 \times 2.3 \times 10 \text{ mm}^3$) was used for 3D perfusion imaging. Employment of 10-fold data under-sampling resulted in a 7-fold net acceleration compared to standard CMR imaging techniques.

Late gadolinium enhancement scans were performed after another waiting period of 15 min in the identical short-axis geometry using a 3D inversion-prepared spoiled gradient echo sequence. A Look-Locker sequence was used to determine the optimal inversion recovery pre-pulse delay.

The imaging protocol has been previously described in detail [7, 8, 11].

Visual assessment of 3D CMR perfusion scans

All CMR examinations were analyzed visually at a core laboratory by reviewers who were blinded to patients' clinical and angiographic data using a dedicated workstation (ExtendedWorkSpace, Philips Healthcare, Best, The Netherlands) as part of the initial multicenter studies. The pre-existing data was used for our analysis. In the case of the additional 31 patients specifically added for our study, new analyses were performed according to protocol.

From all short axis slices acquired during perfusion imaging, those with a clearly definable left-ventricular (LV) cavity enhancement during contrast agent first-pass and >75% of circumferential LV myocardium being present were selected. Each slice was divided in 6 equally distributed segments and evaluated visually. A perfusion defect was defined as pathological if it persisted for at least 3 consecutive dynamics, displayed >25% of transmural and showed no defect on rest perfusion or late gadolinium enhancement (LGE) in the respective segment.

Measurement of myocardial ischemic burden

Quantification of myocardial ischemic burden (MIB) was performed by using a dedicated software (GTvolume, Gyrotools, Zurich, Switzerland) to assess myocardial hypo-enhancement as percentage of tissue volume.

In order to determine myocardial hypoenhancement, the dynamic frame of the stress perfusion displaying the maximum extent of regional myocardial hypoenhancement during peak signal enhancement of remote myocardium, was selected. Left-ventricular endo- and epicardial borders were traced manually by the observer to assess myocardial volume. Quantification of hypoenhanced areas was performed using a threshold-based algorithm with a cut-off value of >2 standard deviations below remote myocardium. Total volumes were calculated using the disc-summation method. MIB was defined as myocardial hypoenhancement relative to total myocardial mass and expressed as percentage. The late enhancement sequences were analyzed by using the same software (GTvolume, Gyrotools, Zurich, Switzerland). Myocardial scar volume was calculated by segmentation of late gadolinium enhancement images and quantification of hyperintense tissue. If myocardial scar was present in segments with hypoenhancement, the respective scar volume was subtracted before calculating MIB.

Fractional flow reserve and quantitative coronary angiography (QCA)

Coronary angiography was performed according to standard protocols. A 0.014-inch coronary pressure sensor tip wire (Volcano Therapeutics, San Diego, California or Pressure-Wire Certus, St. Jude Medical Systems AB, Uppsala, Sweden) was used for fractional-flow reserve (FFR) measurements in vessels with $\geq 2 \text{ mm}$ luminal diameter presenting with a ≥ 50 and $\leq 80\%$ diameter stenosis in 2 orthogonal views. A FFR value < 0.8 was considered to signify a functionally relevant stenosis. In cases of total occlusion or high-grade stenosis ($> 80\%$) no FFR measurements were performed due to their assumed hemodynamic relevance and a FFR value of 0.5 was assigned for statistical analysis.

QCA was performed off-line by an independent reviewer blinded to the results of CMR imaging.

Statistical analysis

Continuous variables are expressed as mean $\pm$ standard deviation, categorical variables as numbers and ratios. Student's *t*-test was used for comparisons between continuous variables and the Chi-Square test was applied for categorical variables. Sensitivity, specificity, positive predictive value and negative predictive value with corresponding 95% confidence intervals (95% CI) were calculated on a patient base according to standard definitions. Chi-Square tests were used to compare sensitivity and specificity between the subgroups. All tests were 2-tailed; a *P*-value ≤ 0.05 was considered to be significant.

Receiver–operator–characteristics (ROC) curve analysis was applied to determine the diagnostic accuracy (area under the curve (AUC)) of the investigated diagnostic methods. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.).

Results

Patient characteristics

Eighty-six patients with a left ventricular ejection fraction (LVEF) $\leq 50\%$ were identified in the overall study population. A total of 86 patients matched for age, gender and major cardiovascular risk factors (including arterial hypertension, diabetes mellitus, hyperlipidemia, body mass index, smoking status and positive family history) and an LVEF $> 50\%$ were used as the control group. Baseline clinical characteristics of the combined study cohort ($n = 172$, 80% male, mean age 63 ± 10) and of the 2 subgroups stratified according to LV function are summarized in Table 1. A significantly larger proportion of patients with a LVEF $\leq 50\%$ received heart failure medication including betablockers (92 vs. 57%, $P < 0.001$), ACE inhibitors (79 vs. 62%, $P = 0.01$) and diuretics (31 vs. 23%, $P = 0.02$). Furthermore, statins were more frequently administered in this subgroup (91 vs. 73%, $P = 0.003$) (see Table 1).

Table 1. Baseline patient demographics and clinical data stratified according to LV function.

	EF≤50% (n = 86)	EF>50% (n = 86)	P-value
Male (%)	69 (80)	69 (80)	1.0
Mean age (years)	64 ± 11	63 ± 9	0.6
BMI (kg/m ²)	27 ± 4	28 ± 4	0.5
BMI >25	61 (71)	64 (74)	0.6
<i>Cardiovascular risk factors, n (%)</i>			
Arterial hypertension	70 (81)	70 (81)	1.0
Diabetes mellitus	26 (30)	26 (30)	1.0
Hyperlipidemia	57 (66)	65 (76)	0.12
Smoking	43 (50)	43 (50)	1.0
Family history of CAD	24 (28)	24 (28)	1.0
<i>Medication, n (%)</i>			
Betablocker	79 (92)	49 (57)	<0.001
ACE inhibitor	68 (79)	53 (62)	0.01
Statin	78 (91)	63 (73)	0.003
Nitrates	8 (9)	16 (19)	0.3
Diuretics	27 (31)	20 (23)	0.02
ARBs	9 (11)	20 (23)	0.03
Ca antagonist	14 (16)	20 (23)	0.3
<i>Coronary artery disease, n (%)</i>			
QCA >50%	67 (78)	62 (72)	0.4
Single-vessel disease (QCA)	17 (20)	25 (29)	0.2
Multi-vessel disease (QCA)	50 (58)	37 (43)	0.05
FFR<0.8	51 (59)	46 (54)	0.4
SVD (FFR)	26 (30)	30 (35)	0.5
MVD (FFR)	25 (29)	16 (19)	0.1
<i>Left-ventricular function and parameters</i>			
LVEF (%)	41 ± 7	62 ± 6	<0.001
LVEDV (mL)	197 ± 66	135 ± 31	<0.001
LVESV (mL)	119 ± 55	53 ± 16	<0.001
LVEDD (mm)	57 ± 8	49 ± 5	<0.001
Septum (mm)	11 ± 2	11 ± 2	0.8
Lateral wall (mm)	9 ± 2	9 ± 2	0.6
<i>Hemodynamic parameters</i>			
Heart rate, bpm			
At rest	68 ± 11	66 ± 10	0.2
Max during stress	83 ± 14	83 ± 15	0.9
Systolic blood pressure, mmHg			
At rest	128 ± 21	128 ± 18	0.8
Max during stress	128 ± 22	127 ± 19	0.7
Diastolic blood pressure, mmHg			
At rest	75 ± 13	71 ± 8	0.05
Max during stress	73 ± 11	71 ± 9	0.4
<i>Perfusion MRI</i>			
Ischemia, n (%)	59 (69)	40 (47)	0.003
Ischemic burden (%)	19 ± 14	10 ± 13	<0.001
Scar, n (%)	55 (64)	13 (15)	<0.001
Scar burden (%)	10 ± 13	1 ± 3	<0.001
Myocardial ischemic burden (%)	9 ± 11	9 ± 13	0.4

Data are presented as n (%) or mean ± SD. P-value by Pearson's Chi-squared test or unpaired student's t-test. Myocardial ischemic burden (MIB) was calculated as Ischemic burden (IB) – Scar burden (SB)

CMR imaging data

Patients in the LVEF ≤50% group showed significantly lower mean EF values (41 ± 7% vs. 62 ± 6%, $P < 0.001$) with corresponding higher mean left-ventricular end-diastolic and end-systolic volumes (197 ± 66 vs. 135 ± 31 mL, $P < 0.001$

and 119 ± 55 vs. 53 ± 16 mL, $P < 0.001$). The hemodynamic parameters during pharmacologic provocation with adenosine showed no significant differences between both subgroups apart from slightly lower mean diastolic blood pressure values at rest in the LVEF >50% group (71 ± 8 mmHg vs. 75 ± 13 mmHg, $P = 0.05$).

Table 2. Diagnostic accuracy of 3D stress perfusion imaging stratified according to LV function.

	QCA				FFR			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
EF ≤ 50 ($n = 86$)	82.1 (71–90)	79.0 (57–92)	93.2 (84–97)	55.7 (37–72)	90.2 (79–96)	62.9 (46–77)	78.0 (66–87)	81.5 (63–92)
EF > 50 ($n = 86$)	62.9 (51–74)	95.8 (80–99)	97.5 (87–99)	50.0 (36–64)	78.3 (64–88)	90.0 (77–96)	90.0 (77–96)	78.3 (64–88)
<i>P</i> -value	0.01	0.09	0.3	0.6	0.1	0.005	0.1	0.7

Values are presented as %, values in parentheses are 95% confidence intervals. QCA indicates quantitative coronary angiography, FFR, fractional flow reserve

3D perfusion imaging revealed ischemia in 99 of 172 patients (58% overall; 69% (LVEF $\leq 50\%$) vs. 47% (LVEF $> 50\%$), $P = 0.003$) with an overall ischemic burden of $13\% \pm 14$ ($19 \pm 14\%$ (LVEF $\leq 50\%$) vs. $10 \pm 13\%$ (LVEF $> 50\%$), $P < 0.001$). The percentage of patients with scar tissue on late gadolinium enhancement imaging was significantly higher in the patients with a reduced LV function (64% (LVEF $\leq 50\%$) vs. 15% (LVEF $> 50\%$), $P < 0.001$) and a mean scar burden of $10 \pm 13\%$ (LVEF $\leq 50\%$) vs. $1 \pm 3\%$ (LVEF $> 50\%$), $P < 0.001$. By subtracting the scar burden from the ischemic burden, the myocardial ischemic burden was calculated and showed a mean value of $9 \pm 12\%$ for all patients. Stratified according to LV function, no statistically significant difference in MIB between both groups could be observed ($9 \pm 11\%$ (LVEF $\leq 50\%$) vs. $9 \pm 13\%$ (LVEF $> 50\%$), $P = 0.4$).

Diagnostic performance

Significant CAD (defined as FFR < 0.8) was diagnosed in 97 cases (56%) overall (59% (LVEF $\leq 50\%$) vs. 54% (LVEF $> 50\%$), $P = 0.4$).

The overall sensitivity of 3D perfusion imaging with FFR measurements as the reference standard on a per-patient base was 84.5% (95% CI 76.0–90.4) with a specificity of 77.3% (95% CI 66.7–85.3) and a diagnostic accuracy of 81.4% (95% CI 74.9–86.5). Positive and negative predictive values were 82.8% (95% CI 74.2–89.0) and 79.5% (95% CI 68.8–87.1), respectively.

If stratified according to LV-function, 3D perfusion yielded a high sensitivity in patients with an EF $\leq 50\%$ of 90.2% (95% CI 79.0–95.7) vs. 78.3% in those with an EF $> 50\%$ (95% CI 64.4–87.7, $P = 0.1$), but showed a significantly lower specificity (62.9% (EF $\leq 50\%$) (95% CI 46.3–76.8) vs. 90.0% (EF $> 50\%$) (95% CI 77.0–96.0, $P = 0.005$) compared to patients with a preserved LVEF, see Table 2. The diagnostic accuracy was comparably high in both subgroups, i.e. 79.1% (EF $\leq 50\%$) (95% CI 69.3–86.3) vs. 83.7% (EF $> 50\%$) (95% CI 74.5–90.1, $P = 0.25$). However, the positive predictive value showed a non-significant trend to be higher for patients with an EF $> 50\%$ (90.0%, 95% CI 77.0–96.0 vs. 78.0% (EF $\leq 50\%$), 95% CI 65.9–86.7, $P = 0.1$) whereas the negative predictive value

Fig. 1. Clinical case examples. *Left panel*: Three-dimensional stress CMR perfusion imaging in double-vessel disease with mildly reduced LV ejection fraction following subendocardial infero-septal and inferior infarction. 3D stress CMR perfusion imaging demonstrated an extensive, inducible perfusion deficit of the anterolateral and inferolateral wall (white arrows, Stress). Note the subendocardial infarction detected in the basal, infero-septal and inferior region (LGE) while on stress CMR imaging the inducible-proportion of the perfusion deficit clearly extended to the anterolateral/inferolateral wall. Invasive angiography identified a long-segment stenosis of the left circumflex artery (black arrow) which proved hemodynamically significant during FFR measurements. In addition, x-ray angiography demonstrated an occlusion of the mid right coronary artery with bridging collaterals. *Right panel*: 81-year-old male patient with mildly reduced LVEF (49%) and normal CMR stress perfusion imaging results in the absence of any myocardial scar or relevant coronary artery stenosis

was similar in both groups (81.5% (EF $\leq$ 50%), 95% CI 63.3–91.8 vs. 78.3% (EF $>$ 50%), 95% CI 64.4–87.7, $P = 0.7$, see Table 2). Representative imaging examples are provided in Fig. 1.

When CAD was defined morphologically by QCA ($>50\%$), the overall prevalence was 75% (78% (EF $\leq$ 50%) vs. 72% (EF $>$ 50%), $P = 0.4$). Under these circumstances, 3D-perfusion imaging yielded a sensitivity of 72.9% (95% CI 64.6–79.8), a specificity of 88.4% (95% CI 75.5–94.9) and a diagnostic accuracy of 0.8 (95% CI 0.7–0.9). If analyzed separately for both subgroups, the sensitivity and specificity were 82.1% (EF $\leq$ 50%), (95% CI 71.3–89.5) and 62.9% (EF $>$ 50%), (95% CI 50.5–73.8, $P = 0.01$) and 79.0% (EF $\leq$ 50%), (95% CI 56.7–91.5) and 95.8% (EF $>$ 50%), (95% CI 79.8–99.3), $P = 0.09$) respectively, see Table 2.

Myocardial ischemic burden

Using FFR measurements as the reference standard, MIB analysis yielded a diagnostic accuracy of 83.0% (95% CI 76.1–89.9) for the whole cohort. If stratified into subgroups, the AUC remained high irrespective of LV function (82.0% (EF $\leq$ 50%), 95% CI 70.8–93.1 vs. 84.4% (EF $>$ 50%), 95% CI 75.5–93.4).

By ROC curve analysis, a cut-off value of 4% optimally detected significant CAD in the whole cohort and both subgroups. The resulting sensitivities were 72.9% (all), 72.0% (EF $\leq$ 50%) and 73.9% (EF $>$ 50%), respectively and specificities 83.1% (all), 74.2% (EF $\leq$ 50%) and 90.0% (EF $>$ 50%), respectively.

Discussion

The present sub-study of a larger multicenter registry investigated the diagnostic performance of 3D CMR perfusion imaging in patients with reduced LV function. The main findings are (1) a high diagnostic accuracy for 3D stress perfusion imaging for the detection of significant CAD with FFR measurements as the reference standard irrespective of LVEF, (2) a high sensitivity but significantly lower specificity in patients with an impaired LV function, which could be explained by (3) a significantly higher scar burden in patients with reduced EF.

For patients with suspected CAD, CMR stress perfusion imaging has become an established diagnostic tool to assess the presence of significant coronary lesions especially in individuals with an intermediate pretest probability [12]. As was demonstrated by large studies such as CE-MARC [5] and MR-IMPACT [6], CMR perfusion imaging yields a high diagnostic accuracy, which in both studies was overall higher than for SPECT. Furthermore, CMR imaging provides other advantages for the management of cardiac patients including its avoidance of radiation exposure. The modality represents the gold-standard for the assessment of right- and left-ventricular function, volumes and mass but also allows a detailed tissue characterization of diseased myocardium, which renders CMR imaging a highly valuable tool in the

differential diagnosis of various cardiomyopathies. This is reflected by a class I level C recommendation for CMR imaging in the current ESC guidelines for heart failure [9] patients for the assessment of the aforementioned cardiac parameters. However, due to a lack of evidence, myocardial perfusion imaging only received a class IIb level B recommendation irrespective of the utilized modality. We therefore aimed to assess the diagnostic accuracy of CMR perfusion imaging in this scarcely investigated patient cohort using a 3D CMR perfusion imaging sequence, which offers full LV coverage and is highly reliable for the assessment of CAD with invasive measurements as the reference standard as documented in previous trials [7, 8, 11]. Of note, this imaging modality enables a quantitative ischemia assessment by calculating individual MIB values.

Our patient cohort consisting of 86 individuals with impaired LVEF and an equally large control group matched for age, gender and major CV risk factors, which represents the largest study population investigated for this research purpose so far. Sammut et al. [10] investigated a much smaller patient sample to assess the feasibility of quantitative perfusion analysis at 3T and larger, controlled trials are missing so far. Additionally, there are no trials using FFR measurements as the reference standard for CMR perfusion analysis in this selected patient cohort.

By choosing a cut-off value of 50% of LVEF, we adhered to the current ESC heart failure guidelines [9], which define any heart failure symptoms above this level in combination with elevated natriuretic peptides and structural heart disease or significant diastolic dysfunction as “Heart failure with preserved ejection fraction” (HFpEF). However, for this first evaluation of 3D CMR perfusion imaging in the context of impaired LV function, we didn’t further stratify according to existing heart failure definitions, i.e. heart failure with reduced ejection fraction (HFrEF) (LVEF $<$ 40%) and heart failure with mid-range EF (HFmrEF, LVEF 40–49%). Further analyses would be needed to assess any relevant differences with regards to the diagnostic accuracy of CMR perfusion imaging in these cohorts.

The prevalence of CAD in our entire patient cohort was 56% (using FFR as the reference method), which reflects an average value for an intermediate risk population referred for CAD assessment. There was no significant difference with regards to CAD prevalence, if stratified into two groups according to LV function (59% for EF $\leq$ 50% vs. 54%, $P = 0.4$). The diagnostic accuracy for the entire cohort was high (AUC 81.4%) and remained unaltered irrespective of LVEF (AUC 79.1 for EF $\leq$ 50% and 83.7% for EF $>$ 50%). In patients with a reduced LVEF, sensitivity was high (90.2 vs. 78.3%), whereas specificity was markedly lower in this subgroup (62.9 vs. 90.0%, $P < 0.005$). The significantly higher percentage of myocardial scar (64 vs. 15%, $P < 0.001$) may serve as a possible explanation in this case. In the presence of LV remodeling, i.e. scar tissue and consecutive wall thinning – a phenomenon frequently encountered in heart failure patients irrespective of the underlying etiology – the differentiation of ischemic but viable myocardium from myocardial scar may be challenging. As our data suggests, CMR

imaging's capability to correctly identify patients with significant ischemia isn't significantly reduced by the presence of myocardial scar, but a higher number of false positive test results has to be expected under these conditions.

Using a quantitative approach by calculating the MIB, mean values showed no significant difference between both groups (9 ± 22 (EF $\leq$ 50%) vs. 9 ± 13 (EF $>$ 50%), $P = 0.4$). With FFR measurements as the reference, the diagnostic accuracy of MIB values showed comparable values for the whole cohort and the subgroups (AUC 83.0% (all), 82.0% (EF $\leq$ 50%) and 84.4% (EF $>$ 50%) respectively). By using ROC analysis, an optimal cut-off value of 4% was determined and resulted in a sensitivity of 72.9% (all), 72.0% (EF $\leq$ 50%) and 73.9% (EF $>$ 50%) and specificity of 83.1% (all), 74.2% (EF $\leq$ 50%) and 90% (EF $>$ 50%), respectively. Therefore, in the EF $\leq$ 50% subgroup, MIB analysis could partially compensate for the reduced specificity in the case of qualitative perfusion analysis.

Further controlled investigations need to be performed to prospectively investigate the prognostic scope of CMR perfusion imaging in patients with impaired LVEF and to establish MIB cut-off value to improve the modality's diagnostic performance and guide further management in affected individuals.

Study limitations

Patients were recruited from a patient cohort already scheduled for coronary angiography, which may therefore be biased due to the selection of the referring physicians. FFR measurements were only performed in vessels with a luminal narrowing between 50 and 80%, which is in accordance with current guidelines. The cut-off value for an impaired EF ($\leq$ 50%) didn't take existing sub-classifications of heart failure (i.e. HFrEF and HFmrEF) into account and further investigations would be needed to assess the diagnostic accuracy of CMR perfusion imaging in these subgroups. There was no further analysis with regards to the underlying etiology of the LV function impairment, which resulted in a mixed patient cohort of ischemic and non-ischemic cardiomyopathies as a larger patient sample would be needed to assess potential differences between these etiological subgroups. Only a comparably small proportion of our study cohort was female (20%), which would necessitate further investigations to explore potential gender-based differences with regards to the diagnostic accuracy of 3D CMR perfusion imaging in the setting of impaired LV function.

Conclusion

3D-CMR first pass perfusion imaging yields a high sensitivity and diagnostic accuracy with regards to the detection of significant CAD irrespective of left-ventricular systolic function. Specificity appears to be lower in patients with LV function impairment, which may be attributed to the higher percentage of scar tissue. The analysis of myocardial

ischemic burden may be helpful in this setting, but potential cut-off values need to be further investigated in a prospective, controlled fashion.

Funding sources: The authors acknowledge support from the Swiss National Science Foundation, (grant #CR3213_132671/1); unrestricted research grants to the institution from Bayer Healthcare, Zurich, Switzerland; Philips Healthcare and the Swiss Heart Foundation, Bern, Switzerland.

Conflict of interests: T.F. Lüscher has received consulting honoraria from Philips Healthcare. The other authors report no conflicts.

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