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Late gadolinium enhancement—cardiovascular magnetic resonance identifies coronary artery disease as the aetiology of left ventricular dysfunction in acute new-onset congestive heart failure

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Aims We evaluated the ability of late gadolinium enhancement (LGE) using cardiovascular magnetic resonance (CMR) to identify acute new-onset heart failure (HF) with left ventricular systolic dysfunction (LVSD), whether or not in relation to underlying coronary artery disease (CAD), in patients with no clinical evidence of associated ischaemic cardiomyopathy.
Methods and results Hundred consecutive patients admitted with acute new-onset decompensated HF and EF $<40\%$, with no clinical or electrocardiographic data suggestive of CAD. The patients were classified according to the presence or absence of significant CAD (stenosis $\geq 70\%$ in at least one major vessel). Twenty-one patients (21%) had significant CAD. Seventy-nine (79%) had no lesions. Eighteen of the 21 patients (85%) with CAD had subendocardial/transmural LGE. In the diagnosis of CAD, LGE has a sensitivity of 85.7% (95% CI, 80–91) and specificity of 92.4% (95% CI, 87–96), respectively, with a negative predictive value of 96% (95% CI, 90–99). It has an area under the receiver operating characteristic curve of 0.906 (95% CI, 0.814–0.998).
Conclusion In patients with new-onset HF and LVSD for whom there are no clinical and exploratory data suggestive of ischaemic heart disease, CMR with LGE is an excellent means of ruling out significant CAD and is a valid alternative to angiography.

Introduction

Given the high prevalence of coronary artery disease (CAD) among patients with heart failure (HF) and left ventricular systolic dysfunction (LVSD), the aetiological study is based on the exclusion of underlying CAD.[1] However, HF associated with idiopathic-dilated cardiomyopathy (DCM) or ischaemic cardiomyopathy (ICM) can be clinically indistinguishable. The symptoms of angina and the risk factors generally associated with CAD are neither exclusive nor constant. In addition, the frequent occurrence of left bundle branch block on the electrocardiogram makes diagnosis even more difficult as it impedes the detection of Q waves suggestive of previous myocardial infarction.[2] Coronary angiography is routinely performed to exclude the presence of obstructive CAD in this setting. Although the risk of complications with coronary angiography is low, these can be serious,[3] and a non-invasive approach in the diagnosis of CAD may therefore be preferable, especially in patients who present with no symptoms of myocardial ischaemia. According to data from the EuroHeart Survey on acute HF, more than a third of patients admitted with acute HF have no previous history of HF, and although acute coronary syndrome may be the most common cause of new-onset acute HF, it is only responsible for less than half the cases.[4] This would also seem to support the use of a non-invasive approach to the diagnosis of CAD in this clinical scenario.

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It was recently demonstrated that the detection of necrotic areas in the myocardium of patients with chronic HF by cardiovascular magnetic resonance (CMR) with late gadolinium enhancement (LGE) makes it possible to identify patients with underlying CAD,[5,6] even in those patients with no history of myocardial infarction and/or clinical findings suggestive of CAD.[7] These results suggest that CMR with LGE could be of great use in the initial non-invasive assessment of HF with LVSD of uncertain aetiology, given that the absence of LGE of subendocardial distribution virtually excludes the presence of significant CAD in these patients.[8,9] However, the results of the only study that had assessed exclusively patients with new-onset HF were contradictory.[10]

The aim of our study was to evaluate the ability of LGE by CMR to identify acute new-onset HF with LVSD, whether or not in relation with underlying CAD, in patients with no clinical evidence of associated ischaemic heart disease. In addition, we evaluated whether or not the absence of LGE on CMR rules out the presence of significant CAD in this clinical scenario.

Methods

Population studied

We prospectively included 100 consecutive patients, admitted with acute new-onset HF with LVSD, with no previous history of CAD, no Q waves on the electrocardiogram consistent with criteria established for infarction,[11] and no clinical data at the time of diagnosis to suggest CAD (angina-like symptoms and significant elevation of biological markers for myocardial necrosis). The diagnosis of HF and LVSD was made on the basis of compatible clinical presentation and echocardiographic evidence of LVSD (EF $<$ 40%) with increased left ventricular end-diastolic diameter ($>$95th percentile according to size).

A coronary angiogram was performed on all patients in order to determine the presence of significant CAD (stenosis $\geq$70% in at least one major coronary artery) being the patients classified under two groups, according to the angiogram results:

(i) Patient with LVSD with significant CAD (CAD+),
(ii) Patient with LVSD without significant CAD (CAD−).

All patients had CMR with LGE. We excluded for the study patients with contraindications for CMR, or clinical data suggesting hypertrophic cardiomyopathy, infiltrative heart disease, or myocarditis.

The study was approved by our institution's Ethics Committee and all the participants gave their written informed consent to take part in the study.

Cardiovascular magnetic resonance

The CMR images were obtained using a 1.5 Tesla acquisition system (Sonata Magneton; Siemens, Erlangen, Germany) as described elsewhere.[7] Briefly, cine sequences were obtained using steady-state free precession sequences in the long axes and the short axes from the mitral valve to the apex. The contrast medium was gadolinium-DTPA (0.15 mmol/kg) administered into a peripheral vein. For the study of late enhancement, 3D inversion-recovery gradient-echo pulse sequences were used, acquired 10 min after the administration of the contrast, in short axis and in long axis and a maximum number of sections as determined by the ventricular volume.[12] The inversion time to null normal myocardium and to detect the presence of gadolinium in the ventricular wall was repeatedly adjusted.

Analysis of images

The short-axis cine sequences were used to calculate the left ventricular volumes and the ejection fraction, using specific software for cardiac analysis (Argus, Siemens). LGE was analysed using a 17-segment model[13] and the extent in each of the segments was evaluated semi-quantitatively assigning the following values: 0, absence of enhancement; 1, subendocardial enhancement (less than or equal to 50% of the wall thickness); 2, transmural enhancement (more than 50% of the wall thickness). The presence of other patterns of LGE was assessed (midwall, linear, or focal). The extent and distribution of the LGE was evaluated by two independent observers, with discrepancies being resolved by consensus. We analysed the intra- and inter-observer agreement in the evaluation of the location and extent of the LGE in 10 studies at random (170 segments) in patients in the group with CAD using the Cohen's kappa index (inter-observer agreement $\kappa = 0.72$; intra-observer 1 and 2 agreement $\kappa = 0.78$ and $\kappa = 0.81$, respectively).

The SCORE for the diagnostic test was considered as the total number of damaged segments located on the CMR along with the semi-quantitative variable which indicates the extent of LGE in each segment. The scores for each of the 17 segments were added together to obtain the SCORE with a range from 0 (no segments with enhancement) to 34 (17 segments with a score of 2).

The coronary angiography was performed by one cardiologist only who was blind to the results of the CMR.

Data analysis

All the continuous variables are expressed as mean $\pm$ standard deviation. The dichotomous variables are described as absolute and relative frequencies in the format of *n* (%). The non-paired *t*-test was used for the comparison of the continuous variables between groups. The Chi-square test, and Fisher's exact test when appropriate, was used for comparison between groups of the non-continuous variables. A bilateral probability $<$0.05 was considered statistically significant.

As a measure of accuracy of CMR in the complete spectrum of cut-off points, receiver operating characteristic (ROC) curve corresponding to the diagnostic test was constructed using non-parametric methods, the area under the curve (AUC) was estimated as the Wilcoxon statistic W, and a confidence interval for the estimation was obtained for a 95% level of confidence.[14]

The choice of the optimal cut-off point for the result of the CMR was made weighing up the cost to the patient's health of a possible false positive or a false negative (FN) and taking into account the prevalence of the disease estimated from the data, according to the Zweig method.[15] Once the cut-off point was selected, the binary diagnostic test designed on the basis of this point was evaluated. Specific estimations were obtained for the sensitivity, specificity, and diagnostic accuracy of the test using the usual methods for the inference for proportions.[16] The positive and negative likelihood ratios have also been calculated as non-dependent prevalence indicators.

Results

Baseline characteristics

Based on the coronary angiography results, 21 of the 100 patients (21%) had significant CAD (group CAD+), the remaining 79 (79%) presenting no evidence of significant lesions (group CAD−). Seven of the 21 patients with CAD had proximal left anterior descending (LAD) disease (33%) and 15 had multivessel disease (71%). The baseline characteristics of the study sample and of each group are presented in *Table 1*. Compared to the patients with no CAD, there was a higher prevalence of diabetes and dyslipidaemia

Table 1 Baseline characteristics of the study sample

Characteristics	Sample	Group CAD+	Group CAD−	*P*-value
Number of patients	100 (100)	21 (21)	79 (79)	–
Age	60.4 ± 14.1	64.3 ± 12.4	59.4 ± 14.4	0.17
Gender (M/F)	68 (68)/32 (32)	15 (71)/6 (28)	53 (67)/26 (33)	0.70
BMI (kg/m^2)	27.7 ± 5.6	27.5 ± 3.3	27.7 ± 4.1	0.84
Cardiovascular risk factors (CVRF)				
Hypertension	43 (43)	7 (33)	36 (45)	0.25
Diabetes mellitus	33 (33)	14 (66)	19 (24)	<0.01
Dyslipidaemia	32 (32)	11 (52)	21 (26)	0.03
Smoking	32 (32)	7 (33)	25 (34)	0.90
Hb (mg/dL)	14.2 ± 1.7	14.3 ± 1.9	14.2 ± 0.8	0.77
Creatinine (mg/dL)	1.1 ± 0.8	1.1 ± 0.2	1.1 ± 0.8	0.78
Treatment on discharge				
Antiplatelet drugs	36 (36)	17 (81)	19 (24)	<0.01
Beta-blockers	87 (87)	17 (81)	70 (89)	0.76
ACE inhibitors/ARB	88 (88)	17 (81)	71 (90)	0.48
Statins	43 (43)	18 (86)	25 (31)	<0.01
Diuretics	90 (90)	15 (71)	75 (95)	0.01
ECG				
AF	31 (31)	6 (29)	25 (32)	0.65
LBBB (%)	28 (28)	5 (24)	23 (29)	0.56
QRS (ms)	113 ± 31	108 ± 25.4	119 ± 32.5	0.48
CMR				
EF (%)	29.1 ± 7.8	32.5 ± 6.1	28.1 ± 8.2	0.01
LVEDD (mm)	60.9 ± 8.6	56.1 ± 6.4	62.1 ± 8.7	<0.01
LVEDV (mL/m^2)	123.7 ± 44.2	110.6 ± 30.5	127.2 ± 47.2	0.04
LA (mm)	40.1 ± 7	37.8 ± 6.1	40.7 ± 7.1	0.09

BMI, body mass index; Hb, haemoglobin; CVFR, cardiovascular risk factors; ACE inhib.; angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor antagonist; LBBB, left bundle branch block; EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LA, left atrium.

Table 2 Findings on the late gadolinium enhancement magnetic resonance

Characteristics	Sample	Group CAD+ (N 21)	Group CAD− (N 79)	*P*-value
Enhancement location, *n* (%)				
Absent	69 (69)	2 (9.5)	67 (85)	0.01
Subendocardial/transmural	24 (24)	18 (85.7)	6 (7.5)	<0.01
Midwall	14 (14)	6 (28)	8 (10)	0.08
Midwall+subendocardial/transmural	7 (7)	5 (23)	2 (2.5)	0.01
Score LGE	1.79 ± 4.1	7.2 ± 5.9	0.36 ± 1.4	<0.01

CMR, cardiovascular magnetic resonance; EF, ejection fraction.

in CAD(+) group with a larger number of risk factors for CAD.

Table 2 shows the MRI findings. Eighteen of the 21 (85.7%) patients in CAD(+) group presented subendocardial or transmural LGE (*Figure 1*), while this occurred in only 6 of the 79 (7.5%) patients in CAD(−) group ($P < 0.001$). None of the three patients in the CAD(+) (3 of 21, 14%) who did not show subendocardial and/or transmural enhancement had CAD in proximal segments of major or dominant arteries; in one, 80% stenosis was documented in the mid-segment of LAD and 70% in the first marginal branch, with an LVEF of 32%. A second patient had 80% stenosis in the proximal non-dominant right coronary artery and a 70% lesion in the distal segment of the circumflex artery (EF 35%). The last of the three had a 70% lesion in the mid-segment of LAD which was not considered to be the cause of the generalized contractile abnormalities (EF 30%). Fourteen patients (14%) presented a non-ischaemic enhancement pattern of midwall distribution, 6 of the 21 patients in CAD(+)group and 8 of the 79 in CAD(−) group (28 vs. 10.1%, NS). Five of the six patients with CAD had both LGE patterns (*Figure 1*). All of six patients had non-proximal one vessel disease.

Determination of the optimum cut-off point and calculation of the discriminatory efficacy of the test

The AUC for ROC curve which measures the discriminatory efficacy of this test was 0.906 (95% CI, 0.814–0.998). Therefore, the estimated likelihood of an individual selected at random from the group of patients with coronary disease having an LGE score higher than a healthy patient is 0.906, which indicates that it is a highly effective test (*Figure 2*).

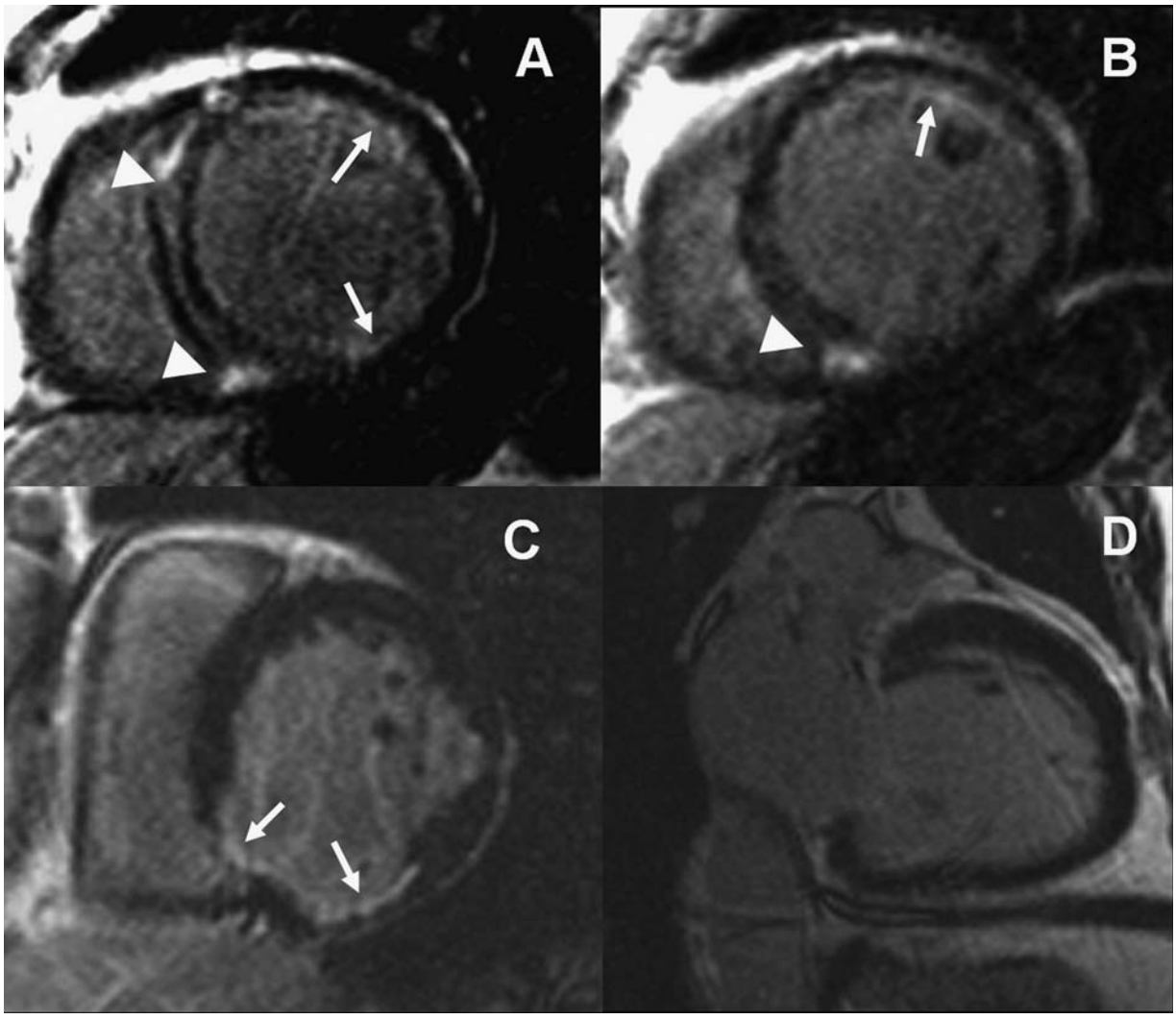

Figure 1 Cardiovascular magnetic resonance late gadolinium enhancement patterns. (*A* and *B*) Short axis, midwall enhancement, linear in septum and focal in area of right inferior ventricular-septal junction (arrow head) coexisting with subendocardial enhancement in anterior, lateral, and inferior segments (arrows) in a patient with coronary artery disease (CAD). (*C*) Short axis. Transmural enhancement in inferior segments and inferior septum (arrows) in a patient with CAD. (*D*) Absence of enhancement in a patient with no CAD.

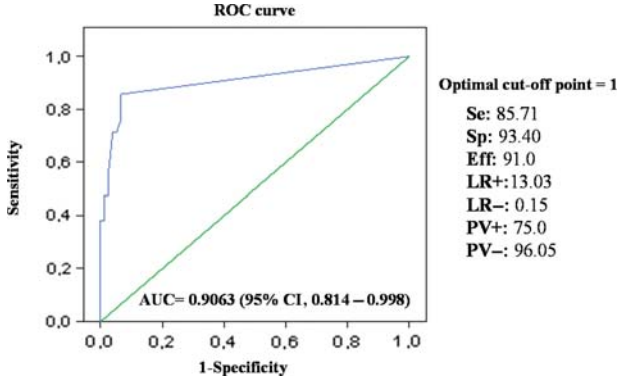

Figure 2 Receiver operator characteristic curve for late gadolinium enhancement SCORE for the diagnosis of coronary artery disease. S, sensitivity; Sp, specificity; EFFI, efficacy; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PV+, positive predictive value; PV−, negative predictive value; FP, false positive; FN, false negative. AUC: area under the curve.

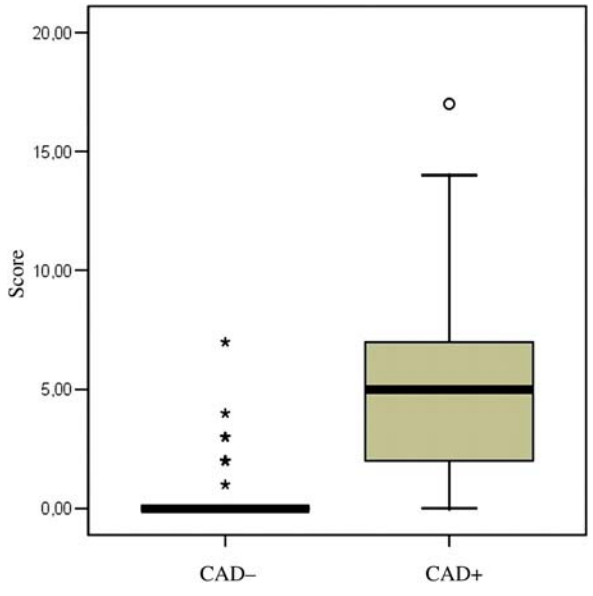

Figure 3 Comparison of late gadolinium enhancement SCORE in patients with coronary artery disease (CAD) and those without CAD. The box defines the interquartile range with the median indicated by the crossbar.

Table 3 Late gadolinium enhancement in the diagnosis of coronary disease

			Significant coronary disease		Total
			Yes	No	
LGE transmural or subendocardial	Yes	Number	18	6	24
		% coronary disease	85.7%	7.5%	24%
	No	Number	3	73	76
		% coronary disease	14.3%	92.4%	76%
Total		Number	21	79	100
			21%	79%	

LGE, late gadolinium enhancement.

A Box-and whisker diagram has been constructed to provide a clearer view of the distribution of the SCORE in patients with and without CAD (*Figure 3*).

The optimal cut-off point was selected considering the 2:1 ratio between the cost of a FN and the cost of a false positive, since in this type of diagnostic test, the risk of a FN is much higher as it implies not applying the treatment corresponding to a patient with CAD. Applying the Zweig method,[16] the value score=1 is obtained as optimal cut-off point, which means that the presence of at least one damaged segment with subendocardial enhancement is needed to be a positive result for the test.

Diagnostic efficacy of late enhancement

The diagnostic performance of LGE for the detection of CAD was analysed with the optimal cut-off point. The diagnostic sensitivity was 85.71% (95% CI, 80–91), indicating a 14.3% likelihood of a FN. The specificity was 92.4% (95% CI, 87–96). The overall accuracy of the test, or overall rate of correct results, was 91% (95% CI, 84–95) (*Table 3*).

The positive likelihood ratio was 13.03, which indicates that the odds ratio for CAD is 13 times greater after a positive LGE or, in other words, for every 13 times that the LGE is positive in patients with CAD, it will be positive once in patients who do not have the disease.

The apparent prevalence in the population group considered is 21%, and for that prevalence, the positive predictive value was 75.0% (95% CI, 71–86), and the negative predictive value (PV−), 96.05% (95% CI, 90–99). These results indicate that, although the sensitivity of the test is 85.7% (95% CI, 80–91), taking the low prevalence of CAD in this population group into account, the PV− of the test is very high, which means that, if the LGE is negative, we can rule out coronary disease with a likelihood of error of $<5\%$.

However, since the predictive values cannot be exported from one context to another due to their dependence on the prevalence, *Table 4* may help provide a clearer picture of the predictive values of LGE in different situations. It may be seen in the table that the NPV continue to be quite high for the usual prevalence levels.

Table 4 Variations in PV+ and PV− for the late gadolinium enhancement according to the prevalence

Prevalence	PV+	PV−
0.1	0.59	0.98
0.2	0.7	0.96
0.3	0.85	0.94
0.4	0.9	0.91
0.5	0.93	0.87
0.6	0.95	0.81
0.7	0.97	0.74

PV+, positive predictive value; PV−, negative predictive value.

Discussion

We investigated the capability of LGE with subendocardial and/or transmural distribution pattern using CMR to identify the presence of CAD in patients with acute new-onset HF of uncertain aetiology, LVSD, and increased LV diameters. It can be concluded from the data in *Table 3* that the detection of subendocardial and/or transmural enhancement had a sensitivity of 86% and a specificity of 92% in the diagnosis of obstructive CAD in our group of patients, the overall accuracy of the test being 91.7%. Our results confirm the usefulness of LGE in the diagnosis of CAD in patients with LVSD[5–7] and show for the first time its clinical applicability in patients with acute new-onset HF. Grouping together the studies published to date,[6,7] LGE of subendocardial or transmural distribution has been detected in 94% of patients with ICM with or without a history of previous infarct, while this LGE distribution pattern was only detected in 9% of the patients with DCM. The only contradictory result in relation to the capability of the technique to identify patients with HF associated with underlying CAD was published very recently by Schietinger *et al.*[10] That study selected a sample of 26 patients with new-onset HF and LVSD. CAD was documented in five patients (stenosis $>50\%$) and endocardial and/or transmural LGE was only documented in two of the five patients (40%). All the patients in the CAD group in whom LGE was not detected had multivessel CAD. The results of this study should be viewed with caution given the limited number of patients studied, non-dilated LV (mean end-diastolic volume 183 ± 62 mL) in CAD group, the different criteria of usual definition of ICM, and no information about vessel stenosis localization. We previously reported the correlation between the extent of LGE and standardized definition of ICM.[17]

In our study, 3 out of 21 (14%) patients did not present subendocardial or transmural LGE, despite showing obstructive coronary stenosis on the coronary angiogram. Although in two of the previous studies,[5,18] 100% of the patients

classified in the ICM group had subendocardial and/or transmural enhancement, all the patients in the ICM group studied by Wu *et al*.[18] and McCrohon *et al*.[5] had a previous history of MI. In contrast, as patients in our CAD(+) group had no previous history of MI, the presence of CAD might not be associated with the existence of myocardial necrosis, thus hampering the detection of scar tissue by LGE. These are consistent with previous studies which have included patients without previous MI.[6,7] In our previous study on patients with chronic HF with no history of infarct, 5 of the 26 patients with significant CAD did not present LGE,[7] or 1 of the 40 in the Casolo series.[6] Nevertheless, although absence of LGE in patients with ischaemic left ventricular dysfunction has been previously reported[7,19] when CAD is associated with HF and LVSD, myocardial necrosis, silent, or overt, is present in most cases.[17] Furthermore, the presence of CAD in these patients may not be the cause of their LVSD, especially in the absence of stenosis in proximal segments of the main coronary arteries, which means that there are unlikely to be large areas of hibernating myocardium.[20,21] In our study, in view of the data obtained on LV function and from the coronary angiograms, coronary disease would not in itself explain the systolic dysfunction presented by these CAD(+) patients with no LGE.

Six out of 79 patients (7.5%) presented subendocardial and/or transmural LGE with a pattern of distribution indistinguishable from that presented by the patients classified in CAD(+) group, despite not having obstructive coronary stenosis on the coronary angiogram. The presence of LGE in patients with HF with no history of MI varies from 10–15% according to the different series[5–7] and could be explained by the presence of a previous silent infarct, in spite of the fact that there is no evidence of obstructive stenosis in the coronary arteries.[22] Thus, LGE-CMR can provide more information than coronary angiography, as it is able to identify patients with scarring but no lesions in their coronary arteries. This is an important factor from a clinical point of view because of its associated therapeutic and prognostic implications.[23–25]

The presence of LGE of midwall or subepicardial distribution has been described in patients with DCM,[5] but also in hypertrophic cardiomyopathy, myocarditis, amyloidosis, glycogenosis, arrhythmogenic right ventricular dysplasia, sarcoidosis, cardiomyopathies associated with myopathies and Chagas disease.[8] In our series, this pattern was presented in patients in both groups, and midwall and subendocardial patterns coexisted in 5 of the 18 patients in the CAD(+) group, suggesting that non-ischaemic DCM and CAD can coexist. This finding, which confirms our previous data,[7] shows that this LGE distribution pattern is not pathognomonic of DCM as initially described.[5] In fact, these LGE distribution patterns are non-specific and simply indicate that there is expansion of the myocardial extracellular matrix, which may be associated with infiltration, inflammation, oedema, and fibrosis.[8] It has recently been demonstrated that the presence of LGE of midwall distribution has an adverse prognostic value in patients with non-ischaemic dilated cardiomyopathy.[26]

Clinical implications

In clinical practice, coronary angiography is the norm in the diagnostic assessment of patients with acute HF and LVSD, with the aim of excluding underlying coronary disease because of its associated therapeutic and prognostic implications. Although the risk of complications with coronary angiography is low, a non-invasive approach is preferable, especially in patients in whom CAD is unlikely. In this clinical scenario, the detection of LGE on CMR is a useful tool in the aetiological diagnosis of LVSD. In fact, the absence of LGE virtually rules out the presence of severe CAD, and the need to perform a coronary angiogram can therefore be avoided in a considerable number of patients. Moreover, LGE–CMR can provide more information than coronary angiography, as it is able to identify patients with scarring but no lesions in their coronary arteries.[23–25]

Limitations

Patients with infiltrative cardiomyopathy, hypertrophic cardiomyopathy, significant valve disease, or myocarditis were excluded from the study since, although these patients might also have concomitant coronary heart disease, these conditions can give rise to the presence of LGE. Our results are therefore not applicable to these forms of presentation of HF.

The absence of LGE in patients with LVSD of ischaemic origin indicates the existence of potentially recoverable viable myocardium after revascularization.[26] It could be argued that large areas of hibernating myocardium with no associated necrosis may lead to severe LVSD and HF without LGE. However, this clinical scenario is highly unlikely, especially in the absence of clinical and exploratory data suggestive of underlying CAD.

Conclusions

In patients with new-onset acute HF and LVSD in whom there is no clinical and exploratory data suggestive of ischaemic disease, CMR with LGE is an excellent means of excluding obstructive coronary disease and is a valid alternative to coronary angiography in this clinical context.

Conflict of interest: none declared.

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