

Cardiac Magnetic Resonance Evaluation of Edema After ST-Elevation Acute Myocardial Infarction

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Introduction and objectives. The aims of the study were to characterize myocardial edema after ST-elevation acute myocardial infarction using cardiac magnetic resonance imaging and to investigate its impact on ventricular function and its subsequent evolution.

Methods. In total, 134 patients admitted to hospital for a first ST-elevation myocardial infarction who had a patent infarct-related artery underwent cardiac magnetic resonance imaging. Cine images (at rest and with low-dose dobutamine) and edema, perfusion and viability images were acquired. Imaging was repeated after 6 months.

Results. In the first week after infarction, edema was detected in at least one segment in 96.6% of patients (4 ± 2.1 segments per patient). Extensive edema (≥ 4 segments) was associated with large ventricular end-diastolic and end-systolic volumes ($P < .0001$), a small left ventricular ejection fraction at rest ($P = .001$) and with low-dose dobutamine ($P = .006$), a large number of segments showing hypoperfusion ($P = .001$) or microvascular obstruction ($P = .009$), a more extensive infarct ($P = .017$) and greater transmural extent of the infarct ($P = .003$). The association between the presence and extent of edema during the first week and functional, perfusion and viability variables was still observable after 6 months. No patient exhibited edema at 6 months.

Conclusions. Cardiac magnetic resonance imaging was useful for characterizing the myocardial edema that occurred after ST-elevation acute myocardial infarction. Extensive edema was associated with poor left ventricular characteristics. Edema was a transitory phenomenon that vanished within 6 months.

Key words: Edema. Magnetic resonance imaging. Myocardial infarction.

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Received November 17, 2008.

Accepted for publication April 15, 2009.

Valoración del edema tras un infarto agudo de miocardio con elevación del ST mediante resonancia magnética cardíaca

Introducción y objetivos. Los objetivos del estudio son caracterizar el edema miocárdico tras un infarto agudo de miocardio con elevación del ST mediante resonancia magnética cardíaca y analizar sus implicaciones en los parámetros ventriculares y su evolución temporal.

Métodos. Se practicó resonancia a 134 pacientes ingresados con un primer infarto con elevación del ST y arteria abierta. Se obtuvieron imágenes de cine (reposo y dobutamina a dosis bajas), edema, perfusión y viabilidad. Se repitió la prueba al sexto mes.

Resultados. En la primera semana del infarto se detectó edema en algún segmento en el 96,6% de los pacientes ($4 \pm 2,1$ segmentos por paciente). El edema extenso (≥ 4 segmentos) se asoció a mayores volúmenes ventriculares telediastólico y telesistólico ($p < 0,0001$), menor fracción de eyección en reposo ($p = 0,001$) y con dobutamina a dosis bajas ($p = 0,006$), mayor número de segmentos hipoperfundidos ($p = 0,001$) y con obstrucción microvascular ($p = 0,009$) e infartos más extensos ($p = 0,017$) y con mayor transmuralidad ($p = 0,003$). La presencia y la extensión del edema en la primera semana mantuvieron la asociación con las variables funcionales, de perfusión y viabilidad obtenidas a los 6 meses. No se detectó edema en ningún paciente al sexto mes.

Conclusiones. La resonancia magnética cardíaca permite caracterizar el edema miocárdico tras un infarto agudo de miocardio con elevación del ST. El edema extenso se asocia a peores parámetros ventriculares. Es un fenómeno transitorio que desaparece antes del sexto mes.

Palabras clave: Edema. Resonancia magnética nuclear. Infarto de miocardio.

INTRODUCTION

An increase in myocardial water content has been observed following acute myocardial infarction.^{1,2} Moreover, an inflammatory response is produced after reperfusion that can lead to an increase in

ABBREVIATIONS

CMR: cardiac magnetic resonance
 EF: ejection fraction
 LGE: late gadolinium enhancement
 LV: left ventricle
 MVO: microvascular obstruction
 STEMI: ST-segment elevation acute myocardial infarction

interstitial water. Hence, myocardial edema is a phenomenon directly related to acute ischemia and particularly, to reperfusion injury.³

Cardiac magnetic resonance (CMR) imaging has become the ideal technique for comprehensive study of patients with ischemic heart disease^{4,5} and is currently the only method that can provide an analysis of myocardial edema *in vivo*.⁶ Nevertheless, assessment of this factor in the clinical setting is not a widespread practice.

The aims of this study are to characterize myocardial edema that occurs following ST-segment elevation acute myocardial infarction (STEMI) by CMR imaging, to analyze its implications in several ventricular parameters, such as systolic function, ventricular remodeling, microcirculation, and the extent of necrosis, and to determine its evolution over time.

METHODS

From December 2001 to January 2008, patients admitted to a tertiary hospital with a first STEMI

and a patent infarct-related artery were prospectively included in the study. From the initial group of 160 patients, 14 were excluded because of TIMI flow <3 after revascularization (to avoid the influence of epicardial flow alteration on microvascular perfusion), 9 because of death, reinfarction, or severe clinical instability, and 3 because of claustrophobia. Thus, the final series was composed of 134 patients. The research project was approved by the local ethics committee and all patients gave their informed consent to participate.

Cardiac magnetic resonance imaging (1.5 T unit, Magnetom Sonata, Siemens, Erlangen, Germany) was performed 8.5 (4.7) days after STEMI (at least 48 h after revascularization), according to the protocol used in our department,^{7,8} which includes cine sequences at rest and following low-dose dobutamine administration, edema detection, first-pass myocardial perfusion at rest, and late gadolinium enhancement (LGE) imaging (Figure 1).

Edema detection was carried out using short-axis, black blood, T2-weighted STIR (short TI inversion recovery) sequences in the same view as the cine sequences, all in mid-diastole. A half-Fourier acquisition single-shot turbo spin echo (HASTE) multisection sequence was used (TR, 2 R-R intervals; TE, 33 ms; TI, 170 ms; slice thickness, 8 mm; interslice interval, 2 mm; flip angle, 160°; matrix, 256×151; bandwidth, 781 Hz/pixel).⁹ If the quality of the images obtained was insufficient, a segmented turbo-spin echo (TSE) sequence was obtained with 1 slice per breath-hold (TR, 2 R-R intervals; TE, 100 ms; TI, 170 ms; slice thickness, 8 mm; interval, 2 mm; flip angle, 180°; matrix, 256×146; bandwidth, 235 Hz/pixel).^{10,11}

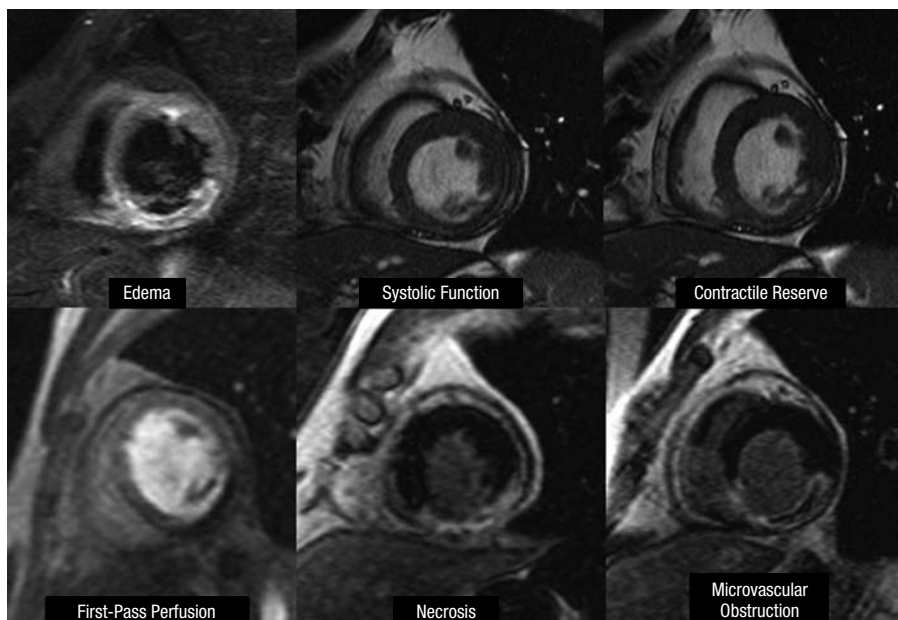


Figure 1. Different types of information obtained from cardiac magnetic resonance sequences. The example shows images from the same patient with an inferior infarct in similar short-axis views (study in the first week following the infarct).

Cardiac Magnetic Resonance Image Analysis

An experienced observer blinded to the patients' clinical data analyzed all the studies using QMASS MR 6.1.5 software (Medis, Leiden, The Netherlands).

Analysis of Myocardial Edema

The edema images were analyzed separately on different days, apart from the other CMR images, without the observer knowing whether they came from the study performed in the first week or at 6 months, or the status of ventricular function, perfusion, or necrosis, information that could affect the results of the analysis. The areas of high T2 signal intensity were identified by visual inspection using restrictive criteria (ie, excluding segments for which there was some doubt that the high-signal area might be due to an artifact), and segments were classified as edematous or non-edematous. A dichotomous analysis was performed, in which the value of 4 segments was used for the extent of edema; this value coincided with the median and was found to be the best cut-off point for predicting an ejection fraction (EF) <50% following receiver operating characteristic (ROC) curve analysis ($P<.05$). The finding of a low-signal-intensity area surrounded by a high-signal-intensity area in these images was considered to indicate an area of microvascular obstruction (MVO), in the same way as in the LGE sequences.

Morphological and Functional Analysis

The following were quantified: left ventricular (LV) end-diastolic and end-systolic volumes (mL/m²), EF determined by the Simpson method (%), and LV mass (g/m²) determined by manually outlining the endocardial borders in all short-axis cine slices. Segment localization was performed by applying the 17-segment model,¹² excluding the apical segment from the analysis. In each segment, we measured the end-diastolic wall thickness (the abnormal cut-off point used in the dichotomous analysis was ≤ 5.5 mm),^{7,13} resting wall thickening, and wall thickening following low-dose dobutamine (the abnormal cut-off point used in the dichotomous analysis was ≤ 2 mm).⁸

Perfusion Analysis

The perfusion deficit was assessed visually as the number of segments showing persistent delay (in at least 3 consecutive temporal images) in the myocardial enhancement pattern during first-pass contrast.^{8,14} In addition, a quantitative analysis

of perfusion was carried out following the regular protocol used by our group,^{5,7} obtaining absolute and normalized values of the slope and signal intensity.

Analysis of Necrosis and Microvascular Obstruction

Signal intensity was measured in LGE sequences. Necrosis was defined as a signal intensity exceeding the intensity of remote uninfarcted myocardium by more than 2 standard deviations. The size of the infarct was considered to be the percentage of LV mass showing LGE.⁸ In the analysis by segments, the percentage of transmuralities of each infarcted segment was calculated. In the dichotomous analysis, necrosis was considered to be transmural when the percentage of transmuralities was >50%. Microvascular obstructions were defined as areas with an absence of signal located within an area of LGE.¹⁵

At 6 months, a new CMR was carried out to determine the status of edema by reassessment of all the parameters. The first 70 patients of our series were analyzed. After confirming the absence of edema in all cases, patient enrollment was halted.

In an analysis of a subgroup of 20 patients, 320 segments, the interobserver agreement was 96% ($\kappa=0.91$; 95% CI, 0.86-1) and the intraobserver agreement was 97% ($\kappa=0.92$; 95% CI, 0.88-1).

Statistical Analysis

Continuous data are expressed as the mean (SD); between-group comparisons for paired and unpaired samples were performed with the Student *t* test. Discrete data are expressed as percentages; between-group comparisons were done with the χ^2 test. A *P* value less than .05 was considered significant. Statistical analyses were carried out with SPSS, version 11.0 (Chicago, IL, USA).

RESULTS

Images allowing proper assessment of the presence of edema were obtained in 117 (90.6%) of 134 patients. In the first week following STEMI, edema was detected in any segment in 113 (96.6%) patients, with a mean of 4 (2.1) segments per patient (median, 4 [2-5]). HASTE sequences provided high-quality images in 89 (76%) patients, whereas TSE sequences had to be used in 28 (24%).

As to the extent of edema, more than 4 segments were affected in 45 (38.5%) patients and 4 or fewer segments were affected in 68 (58.1%) patients. The baseline characteristics of the overall group and the differences between patients with and without extensive edema are shown in Table 1.

TABLE 1. Clinical Characteristics of the Study Group

	Complete Group (n=117)	Edema >4 Segments (n=45)	Edema ≤4 Segments (n=68)	P
Age, mean (SD), y	58 (12)	54 (11)	61 (12)	.003
Men, %	83	91	79	.05
Diabetes mellitus, %	17	9	21	.054
Hypertension, %	46	40	49	NS
Hypercholesterolemia, %	36	44	33	NS
Smoking, %	61	71	55	NS
Door-to-revascularization time, d	2.6 (3.9)	2.1 (3.5)	3 (4.2)	NS
Door-to-CMR time, d	8.5 (4.7)	7.5 (3.2)	9.1 (5.4)	.06
Anterior infarct, %	59	70	53	.07
Thrombolysis, %	62	58	63	NS
Primary angioplasty, %	24	33	19	NS
Stent implantation, %	83	93	78	NS
Peak CK-MB mass, ng/mL	232 (185)	326 (216)	178 (135)	<.0001
Peak troponin I, ng/mL	66 (37)	79 (36)	57 (34)	.001
Antiplatelet agents, %	98	98	99	NS
Anticoagulants, %	5	7	5	NS
Antiarrhythmia agents, %	1	2	0	NS
Antidiabetic agents, %	9	2	13	NS
Beta-blockers, %	67	69	66	NS
Calcium channel blockers, %	4	2	5	NS
Nitrates, %	2	0	3	NS
Diuretics, %	11	4	16	NS
ACE inhibitors, %	71	62	76	NS
ARA-II, %	15	20	11	NS
Statins, %	83	80	85	NS

ACE inhibitors indicates angiotensin converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; CK-MB, creatine kinase cardiac isoenzyme; CMR, cardiac magnetic resonance.

Analysis by Segments

Edema was detected in 446 (23.9%) of 1863 assessable segments and was distributed mainly in infarcted segments (57% had edema) and segments adjacent to the infarct (10% had edema), whereas it was unusual to find edema in remote segments (1% had edema). Moreover, the presence of edema was significantly more common in segments with transmural necrosis (57% had edema) than in those without (27% had edema). The differences between segments with and without edema in the first week following infarction are shown in Table 2. Segments with edema showed greater wall thickness, less wall thickening, worse perfusion data, a higher presence of necrosis with more transmural, and a higher presence of MVO in LGE sequences.

Analysis by Patients

Patients who had more extensive edema in the first week following STEMI also had larger end-systolic and end-diastolic LV volumes, EF (at rest and following low-dose dobutamine), greater LV mass, a larger number of hypoperfused segments, a larger

number of segments with >50% necrosis, greater infarcted mass, and a larger number of segments with MVO in LGE sequences (Table 3).

The presence of areas of lower T2 signal intensity within the area of edema was observed in 23 patients; this group had a larger number of segments with MVO in LGE sequences than the 94 patients in whom this feature was not seen (3.8 [2] vs 0.5 [1.4]; $P<.0001$). In addition, the presence of MVO in edema images was almost invariably associated with the appearance of MVO in LGE images, although the absence of this feature in the former did not rule it out (Figure 2). Thus, hypointense areas within the edema are an indicator of severe MVO. In addition to the statistical association between these images, there was considerable agreement in their location and appearance. At 6 months following STEMI, CMR imaging was repeated in 70 patients to verify whether edema persisted or not; edema was found to have resolved in all patients (Figure 3). The presence of extensive edema in the first week was related to poorer LV parameters at 6 months: end-diastolic volume (86 [25] vs 73 [18] mL/m²; $P=.014$), end-diastolic volume (48 [26] vs 33 [15] mL/m²; $P=.014$), EF (47% [15%] vs 57% [14%]; $P=.013$), and EF with

TABLE 2. Analysis by Segments. Cardiac Magnetic Resonance in the First Week Following Infarction

	Edema in the First Week (n=446)	No Edema in the First Week (n=1417)	P
Wall thickness, mm	8.9 (2.7)	8.6 (2.9)	.049
Wall thickening at rest, mm	2.8 (3.1)	5.1 (3.7)	<.0001
Wall thickening after dobutamine, mm	3.5 (3.7)	5.9 (4.6)	<.0001
Abnormal perfusion (visual), %	32	8	<.0001
Slope, %/s	16 (10)	20 (14)	<.0001
Normalized slope	0.8 (0.2)	0.9 (0.2)	<.0001
Signal intensity, %	189 (88)	209 (108)	<.0001
Normalized signal intensity	0.8 (0.2)	0.9 (0.1)	<.0001
Necrosis (any degree), %	75	28	<.0001
Necrosis transmurality			
≤50%	23	52	<.0001
>50%	77	48	
MVO in LGE images, %	19	3	<.0001

CMR indicates cardiac magnetic resonance; LGE, late gadolinium enhancement; MVO, microvascular obstruction.

TABLE 3. Analysis by Patients. Cardiac Magnetic Resonance in the First Week Following Infarction

	Complete Group (n=117)	Edema >4 Segments (n=45)	Edema ≤4 Segments (n=68)	P
Infarction size, % LV mass	20 (10)	23 (11)	18 (9)	.017
Mean transmurality of infarct, %	28 (16)	34 (17)	24 (13)	.003
End-diastolic volume index, mL/m ²	78 (23)	88 (25)	71 (18)	<.0001
End-systolic volume index, mL/m ²	38 (18)	47 (19)	32 (14)	<.0001
LV mass, g/m ²	72 (20)	77 (23)	69 (17)	.03
EF, %	52 (12)	47 (10)	55 (12)	.001
EF with dobutamine, %	56 (13)	51 (11)	58 (12)	.006
Number of segments per patient with:				
Wall thickening at rest ≤2 mm	4.8 (3.48)	5.3 (3)	4.6 (3.6)	NS
Wall thickening with dobutamine ≤2 mm	4.3 (3.1)	4.8 (2.8)	4 (3.4)	NS
Wall thickness ≤5.5 mm	1.7 (2.5)	1.2 (1.9)	2.1 (2.9)	.05
Abnormal first-pass perfusion	1.9 (2.5)	2.9 (2.8)	1.3 (2)	.001
MVO in LGE images	1.1 (2)	1.8 (2.4)	0.7 (1.6)	.009

CMR indicates cardiac magnetic resonance; EF, left ventricular ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle; MVO, microvascular obstruction.

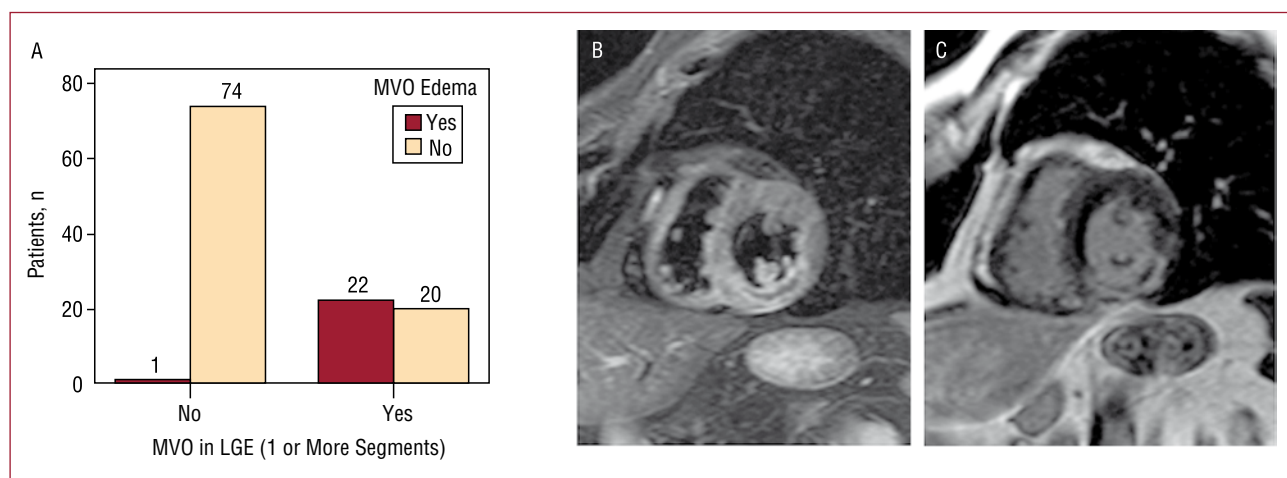


Figure 2. A: bar chart showing the number of patients in whom images of microvascular obstruction (MVO) were observed in edema sequences with respect to those with MVO in late gadolinium enhancement (LGE) sequences. B: typical image of MVO within an area of edema. C: in the same patient, a similar image is seen in LGE sequences.

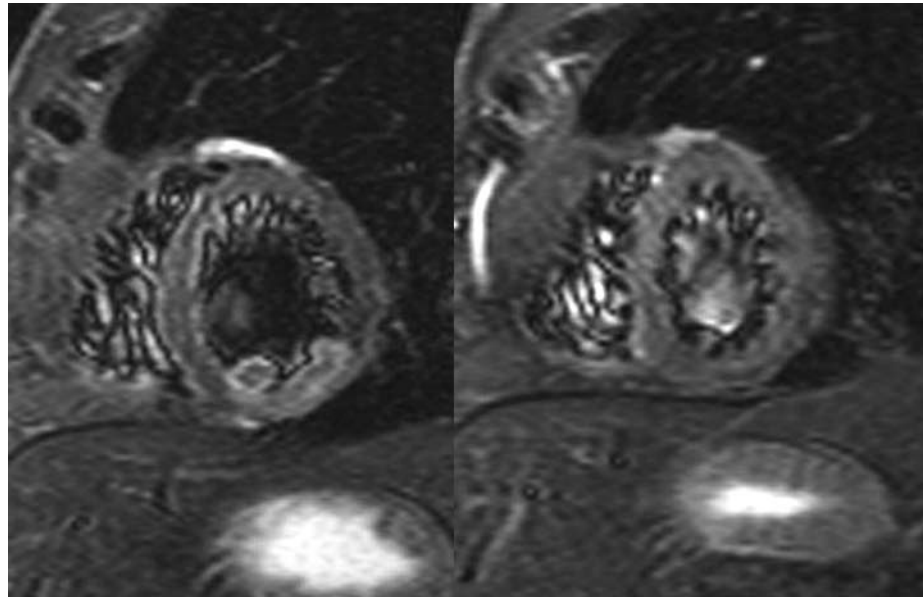


Figure 3. T2-weighted short-axis views in a patient with early edema following infarction in the inferior and medial inferolateral segments (left), which had disappeared at 6 months (right).

low-dose dobutamine (51% [16%] vs 60% [14%]; $P=.03$). In addition, the ventricular mass tended to be larger in the first week than at 6 months (72 [20] vs 67 [27] g/m^2 ; $P=.16$), which could indicate that the measures of ventricular mass in the early phase following infarction might be somewhat overestimated because of the presence of myocardial edema.

DISCUSSION

The main findings of this study show that analysis of edema following STEMI can be noninvasively carried out in most patients in the clinical setting and integrated within the usual magnetic resonance imaging study. In these patients, edema is an almost universal, although transitory, finding in the early phases. Extensive edema is related to larger LV volumes and poorer systolic function, more severe microcirculation alterations, and larger infarcts that have greater transmuralities. In all patients studied, edema disappeared at 6 months following STEMI.

Analysis of Myocardial Edema

The appearance of edema after STEMI is a common event that has been demonstrated in animal studies⁶ and in patients.^{1,2} The mechanism underlying the development of myocardial edema in these patients seems to be an alteration of the energy-regulated transmembrane ion transport system following ischemic injury, which leads to an increase in cellular sodium.¹⁶ Edema increases after reperfusion because blood having normal

osmolarity flows through tissue with increased osmolarity; subsequently, the condition gradually resolves.

A linear correlation has been demonstrated between the T2 signal intensity and myocardial water content.¹⁷ However, analysis of myocardial edema has been difficult up to the present time, when recent advances in CMR imaging have made it possible. Variants of enhanced T2-weighted TSE sequences combined with black blood preparations have been used to increase the contrast between myocardium and blood. In addition, a STIR pulse sequence is applied to suppress the fat signal. The HASTE sequence uses very short echo spacing and a half-Fourier technique to allow single-shot imaging, in which all the imaging information is obtained with a single excitation pulse. This technique is less sensitive to respiratory or patient movement because of its short acquisition time, and the entire LV can be covered in one breath-hold.⁹ In contrast, in TSE sequences, a single slice is obtained with each breath-hold; thus, these sequences were not obtained in all patients to avoid lengthy studies and the risk of image artifacts caused by the movements of the patient.^{6,10}

The extent of edema we found was somewhat smaller than that reported in other studies,^{18,19} likely because of 2 factors: *a*) segments showing hyperintensity that might have been due to slow flow or the effect of the distance to the antenna were eliminated from the analysis; and *b*) edema was assessed at an early time point, but not immediately (mean door-to-CMR time, 8.5 days), and the size of the hyperintense area may have undergone some reduction.¹⁹

Relationship of Edema to Morphologic and Functional Parameters

The relationship between myocardial edema and contractile dysfunction explains the impact of the extent of edema on LV volumes and systolic function.^{20,21} Thus, our findings showing a relationship between edema and greater LV thickness and greater wall thickening are consistent with the histologic data obtained in animal studies.^{18,22}

Relationship of Myocardial Edema to Microcirculation Alterations

We observed a close relationship between the presence of edema and poorer first-pass perfusion parameters, particularly in the first week following STEMI; at 6 months, perfusion has improved in the majority of patients, as was previously described by our group.⁷ Since all our patients were revascularized and had a patent infarct-related artery at the time CMR was performed, we consider that the reperfusion defects found were due to microcirculation alterations. Another method for analyzing the presence of MVO by CMR is to use LGE sequences. In both cases, these are dynamic alterations, as is edema.²³⁻²⁵ Although many mechanisms have been proposed to explain reperfusion injury,²⁶ the presence of edema in itself can favor this phenomenon by its compressive effect on the small vessels and capillaries.²⁷

We found a clear relationship between the image of a hypointense center within the edema and the known features of MVO in LGE sequences. Despite the fact that edema secondary to infarction is related to a loss of membrane permeability, leading to an increase in cellular sodium, sodium accumulation depends on microvascular integrity and would be slower in areas with MVO.²⁸ Moreover, this phenomenon would be favored by the presence of hemoglobin degradation products, as has been seen in experimental animal studies.²⁹ Therefore, these unenhanced edema sequences provide a fast, preliminary approximation of the existence of severe MVO.

Relationship of Myocardial Edema to Necrosis

The relationship that was seen between the magnitude of edema and the size and transmural extent of the infarct provides evidence that the extent of edema expresses the extent of myocardial injury; this is further supported by the effect on the functional parameters. Experimental animal studies have shown a good correlation between the hyperintense area on T2-weighted images measured after a recent infarction and the area at risk.¹⁸ The main advantage of these images is that they can be acquired after

revascularization and enable differentiation between myocardium with edema, but without necrosis, that is, salvaged myocardium, and necrotic myocardium.¹⁹

Complete resolution of edema within 6 months following STEMI is plausible, although there is no consensus on this point in the literature.³⁰⁻³² The influence of early edema on the CMR parameters at 6 months was notable. Normalization of the early hyperintensity is related to water loss in the edematous tissue, but also to progressive collagen deposit, which occurs during the healing process. The amount of tissue collagen inversely correlates with T2 signal intensity,³³ and this renders the signal of the chronic myocardial scar less intense in these sequences. Thus, the presence of edema is useful for detecting recent myocardial injury, particularly because LGE cannot differentiate between acute and chronic myocardial infarction.^{30,34}

Limitations of the Study

One interesting aspect of this technique is that it allows analysis of salvaged myocardium following revascularization. This is achieved by measuring the hyperintense area in T2-weighted images (area at risk) and subtracting the area of necrosis. However, this analysis was not performed in our study. The reasons are related to potential problems with these sequences, such as a poorer signal-to-noise ratio than in most CMR images and, occasionally incorrect interpretation of unsuppressed slow-flow blood, which sometimes results in poor definition of the border of the hyperintense area and requires continuous visual corrections in automatic analyses. Thus, we considered that simple visual inspection of the number of affected segments by an experienced observer was a reliable measurement method with greater practical utility. Furthermore, despite the fact that CMR was performed in our patients as soon as possible, the mean delay of more than 1 week between the event and CMR study may have meant that the extent of edema seen was smaller than it would have been if CMR had been performed immediately after the infarct, as has been indicated in a recent study.¹⁹

Lastly, we did not analyze the existence of events or the prognostic value of this technique with respect to other more consolidated findings, such as the extent of late enhancement. This aspect will be the subject of a later analysis with a larger series of patients.

CONCLUSIONS

Cardiac magnetic resonance imaging enables characterization of myocardial edema after a STEMI in clinical practice. A greater extent of edema was

associated with larger ventricular volumes, poorer systolic function, more severe microcirculation abnormalities following reperfusion, and more extensive infarcts with greater transmural. Edema is a transitory phenomenon that disappears within 6 months following infarction.

ACKNOWLEDGMENTS

To Dr Arturo Evangelista, for his interest in this subject, which inspired us to perform this study.

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