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Intramyocardial hemorrhage in spontaneously reperfused myocardial infarction

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ABSTRACT

Objective. The presence of intramyocardial hemorrhage (IMH) is frequent in patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PPCI). We aim for the presence IMH using cMRI in patients who presented AMI and did not undergo PPCI or thrombolysis. Cardiac magnetic resonance has proven to be a highly sensitive method for detect its presence in the ischemic damaged tissue. **Material and methods.** Patients admitted with diagnosis of ST elevation myocardial infarction > 24 h after initial presentation and without reperfusion therapy were enrolled in the study. All patients underwent cardiac magnetic resonance for detecting edema, microvascular obstruction and intramyocardial hemorrhage, followed by coronary angiography. **Results.** Seven male patients, with median age of 53 years, were enrolled. Cardiac magnetic resonance showed that all patients had microvascular obstruction and edema. Two of them had intramyocardial hemorrhage in association with spontaneous reperfusion demonstrated by angiography. **Conclusion.** The results of our study show that in patients with acute myocardial infarction, intramyocardial hemorrhage occurs not only after therapeutic, but also after spontaneous reperfusion. This is the first time that its presence is demonstrated by cardiac magnetic resonance.

Key words. Ischemic heart disease. Cardiac magnetic resonance. Myocardial infarction. Spontaneous reperfusion. Reperfusion damage. Intramyocardial hemorrhage.

Hemorragia intramiocárdica en el infarto miocárdico con reperfusión espontánea

RESUMEN

Introducción. *La hemorragia intramiocárdica es una de las manifestaciones del daño por reperfusión y se encuentra con frecuencia en pacientes con oclusión aguda coronaria que son sometidos a terapia de reperfusión.* ***Objetivo.*** *Determinar su presencia a través de resonancia magnética, en pacientes con infarto agudo del miocardio que no recibieron tratamiento de reperfusión.* ***Material y métodos.*** *Se enrolaron en el estudio aquellos pacientes con diagnóstico de síndrome coronario agudo con elevación del ST de más de 24 h de evolución, que no recibieron tratamiento de reperfusión por llegar fuera de ventana terapéutica. Antes de ser sometidos a coronariografía percutánea todos los pacientes fueron estudiados con resonancia magnética en busca de edema, obstrucción intravascular y hemorragia intramiocárdica.* ***Resultados.*** *Se incluyeron siete pacientes, la mediana de edad fue de 53 años. Todos ellos presentaron obstrucción intravascular y edema intramiocárdico demostrados por resonancia magnética. En dos de ellos se pudo observar, además, la presencia de hemorragia intramiocárdica, la cual estuvo asociada a un proceso de reperfusión espontánea demostrado por el estudio angiográfico.* ***Conclusiones.*** *Los resultados de este trabajo muestran que la hemorragia intramiocárdica se presenta no sólo como resultado de los procedimientos de reperfusión terapéutica (angioplastia primaria o trombólisis) sino también durante los procesos de reperfusión espontánea. Se trata del primer trabajo que demuestra, mediante resonancia magnética, su presencia en este tipo de pacientes.*

Palabras clave. *Hemorragia intramiocárdica. Cardiopatía isquémica. Cardiorresonancia magnética. Infarto de miocardio. Daño por repercusión.*

INTRODUCTION

The most efficacious way to restore coronary flow in patients with acute myocardial infarction (AMI), particularly those with ST elevation myocardial infarction (STEMI), is primary percutaneous coronary intervention (PPCI) followed by thrombolysis. However, in some patients, myocardial reperfusion can cause undesirable effects which have been described as reperfusion damage.[1] Angiographically it is characterized by non-reflow phenomenon of the infarct related vessel; by cardiac magnetic resonance (cMRI) it is shown as microvascular obstruction (MVO) and intramyocardial hemorrhage[2,3] (IMH), for which cMRI has proven to be highly sensitive.[4,5] Van den Boss demonstrated, in an animal model, signal voids on T2*-weighted scanning in all animals with reperfused MI, because of the presence of haemorrhage, as confirmed by histology.[6] MVO is detected after the injection of contrast during late enhancement sequences and is defined as any region of hypoenhancement within the hyperenhanced, infarcted area, due to the lack of contrast medium penetration in the hypoenhancement area.[7] Also it has been described that MVO can be visualized by T2-weighted.[8,9] In addition this imaging modality can also identify hemoglobin degradation products due to leakage of red blood cells through the damaged endothelial walls using T2* sequences. This particular sequence has proven to be highly accurate in detection of patients with hemochromatosis.[10]

Reperfused AMI frequently appears reddish on pathological examination because of IMH, which is caused by vascular cell damage with the leakage of blood from the infarct-related vessel.[3] Reperfusion hemorrhage has been found in humans after surgical revascularization, PPCI or thrombolysis.[11] Unfavorable mechanical consequences of IMH may include increased myocardial stiffness, propensity to free left ventricular wall rupture and delayed healing process.

There is lack of data regarding the prevalence of IMH in patients with spontaneously reperfused AMI. The aim of the study is to evaluate the presence of IMH using cMRI in patients who presented after STEMI and did not undergo primary PPCI or thrombolysis in the first 24 h of presentation.

MATERIAL AND METHODS

Seven individuals admitted to our institution with a diagnosis of STEMI[12] and without history of primary

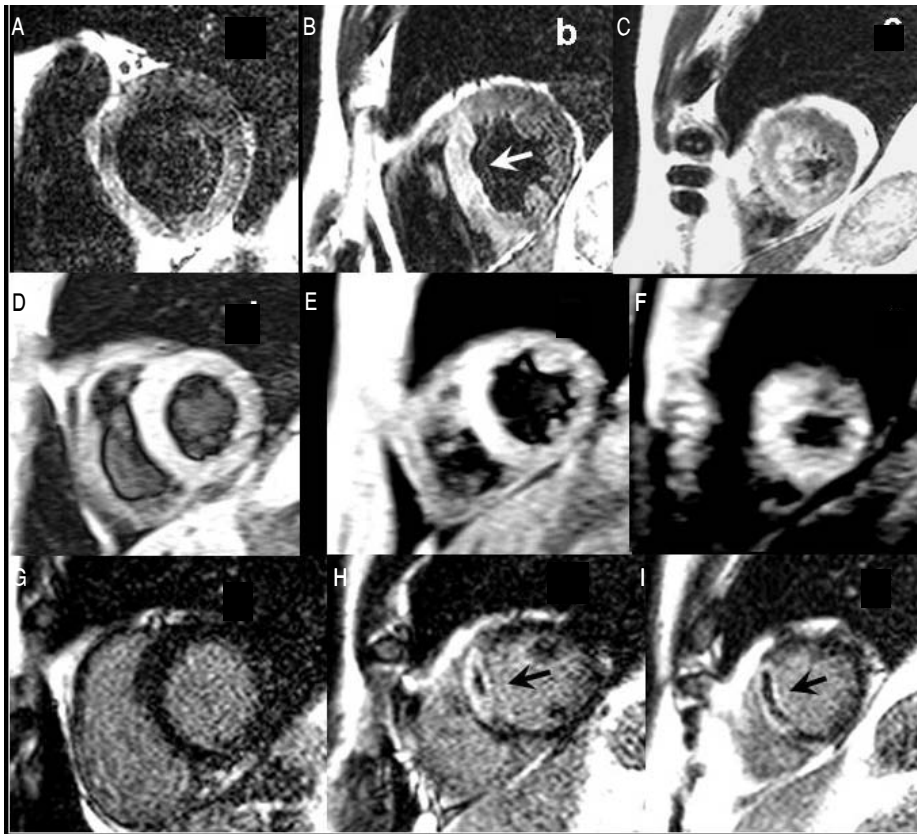

Figure 1. *cMRI sequences in a patient with no reperfused anterolateral infarction. In T2 sequence (**A-C**) edema (hyperenhancement) in the anteroseptal region is noticed (white arrow). T2* sequence (**D-F**) shows homogeneity in all the segments without data suggesting intramyocardial hemorrhage. LE images (**G-I**) show hypointensity areas corresponding to microvascular obstruction (black arrows).*

PPCI, thrombolysis, prior AMI or coronary artery bypass graft were enrolled. All patients underwent cMRI followed by coronary angiography +/- PPCI during their admission > 24 h after initial presentation. cMRI studies were done using a 1.5 T scanner (Magnetom Avanto, Siemens Medical Solutions, Erlangen Germany) The cMRI protocol included scout imaging and a horizontal long axis, vertical long axis and short axis localizers. The cMRI protocol included a functional study of the left ventricle (LV) using an ECG-triggered breath-hold segmented steady-state free precession (SSFP); cine images in the horizontal and vertical long axis views, with the following parameters: TR 5.7 msec, TE, 1.2 msec, flip angle, 80°, slice thickness of 8 mm, temporal resolution 45 msec. Then, contiguous short-axis slices were acquired, parallel to the atrio-ventricular grove to cover the entire LV, with 3-5 mm inter-slice gap. T2-weighted spin-echo sequence (short T1 inversion recovery [STIR], repetition time [TR] 2 RR interval, echo time [TE] 64 ms, slice thickness 10 mm, matrix 256 x 256), was used to asses myocardial edema. T2* weighted images were used to detect products of degradation of hemoglobin (detection of hypo-intense areas into T2 positive zones). During the first pass sequence 0.1 mmol/kg of gadopentetatedimeglumine (Magnevist, Schering, Germany) was injected. Then inversion recovery (I-R) sequence was performed in long and short axis using a breath hold ECG triggered 2D gradient echo sequence at 3, 10 and 15 min after the injection of contrast media with the following parameters TR/TE, 700/1.1 msec; flip angle, 40°. We used a scout to determine the inversion time (TI, non-selective inversion pulse), with the inversion time set to null the signal of normal myocardium. In the LE sequence, the infarcted area was characterized by the usual high signal area adjacent to non-infarcted nulled myocardium and the MVO corresponded to a low intensity signal area surrounded by myocardial scar.[13] MVO was evaluated in the I-R sequence at 3-5 min and LE at 10-15 min. Post processing and interpretation was done in a separate Leonardo Siemens workstation, Erlangen Germany. Assessment of severity of CAD was done after coronary angiogram.

Table 1. Clinical characteristics and outcomes.

Patients	No IMH (n = 5)		IMH (n = 2)	
Age (year)	50	(39+61)	60	(53-68)
Male(%)	5	(100)	2	(100)
Medical history				
Current smoker (%)	3	(60)	1	(50)
Hypertension (%)	1	(20)	0	(0)
Diabetes (%)	2	(40)	0	(0)
Dislipidemia (%)	2	(40)	0	(0)
Previous angina (%)	0	(0)	0	(0)
Clinical presentation				
Killip	4	(80)	0	(0)
Pain (hours before admission)	55.31	(20.56-59.59)	34.58	(20.56-49.0)
Anterior STEMI (%)	5	(100)	2	(100)
SBP mmHg (range)	140	(100-150)	112.5	(110-115)
DBP mmHg (range)	90	(60-96)	75	(70-80)
Heart rate	95	(70-100)	86	(72-80)
Peak CK (mg/dL)	1015	(185-2,288)	451	(303.7-600)
Peak troponin (mg/dL)	29.5	(5.9-150)	9.5	
Outcome intra-hospital				
Death (%)	1	(20)	0	(0)
Angina post AMI (%)	0	(0)	0	(0)
Heart failure (%)	0	(0)	0	(0)
VF (%)	1	(20)	0	(0)
ARF (%)	2	(40)	0	(0)

IMH: intramyocardial hemorrhage. SBP: systolic blood pressure. DBP: diastolic blood pressure. AMI: acute myocardial infarction. VT: ventricular fibrillation by extended monitoring. ARF: acute renal failure serum creatinine > 1.5 mg/dL.

RESULTS

All seven patients were male, with median age of 53 years (range 39-68 years). cMRI studies showed that all patients had edema and MVO (Figure 1) and two of them (29%) IMH. Table 1 describes clinical characteristics and outcomes of all patients. During hospital stay one patient without IMH developed acute renal failure, ventricular fibrillation and expired. The remaining 6 patients were discharged from the hospital after stabilization of their hemodynamic status and all completed a six-month follow-up with bi-monthly visits without any adverse cardiac event defined as re-infarction, need for subsequent PPCI or death. The first patient with IMH was a 68 year-old male with spontaneously reperfused antero-septal myocardial infarction (Figure 2). In the T2 imaging, edema was noticed in the septum and anterior wall. It was also observed central hypointensity in the apical anterior and apical-septal segments. T2* showed low attenuation signal in the mid anterior, mid antero-septal, mid infero-septal,

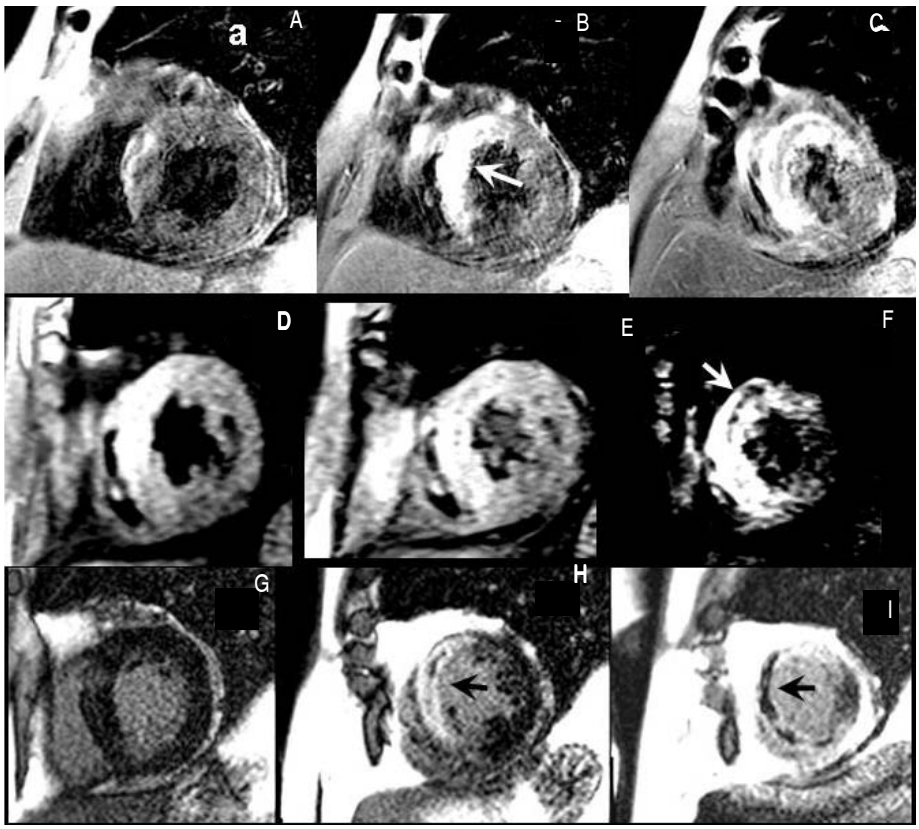

*Figure 2. cMRI sequences in a patient with spontaneously reperfused anterolateral infarction. In T2 sequence (**A-C**) edema (hyperenhancement) in the anteroseptal region is shown (white arrow). In T2* sequences (D-F) one area of hypointensity corresponding to the presence of intramyocardial hemorrhage is observed (white arrow). LE images (**G**-I) show hypointensity related to microvascular obstruction in the same region (black arrow).*

Table 2. Magnetic resonance findings.

Patients	Overall, n = 7	No IMH, n = 5	IMH, n = 2
Left ventricular ejection fraction (%)	40 (26-59)	43 (26-53)	49.5 (40-59)
Ventricular mass (g)	110 (80-135)	110 (105-127)	107.5 (80-135)
Left ventricular end diastolic volume (cc)	131 (116-158)	131 (116-150)	140.5 (123-158)
Left ventricular end systolic volume (cc)	96 (53-100)	86 (60-100)	74.5 (53-96)
Stroke volume (cc)	52 (34.3-70)	59 (34.3-68)	66.5 (63-70)
Diastolic diameter (mm)	53 (46-58)	53 (46-55)	54 (50-58)
Systolic diameter (mm)	34 (26-43)	34 (26-40)	37 (31-43)
Interventricular septum (mm)	10 (8-11)	10 (8-11)	9.5 (9-10)
Posterior wall (mm)	8 (6-10)	8 (7-10)	7.5 (6-9)
Microvascular obstruct	7	5	2

Table 3. Angiographic findings and IMH.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
IMH	Yes	Yes	No	No	No	No	No
IRA stenosis (%)	75%	0%	78%	100%	100%	99%	82%
TIMI flow	3	3	3	0	0	1	3
PCI of the IRA	No	No	Yes	Yes	Yes	Yes	Yes
TIMI flow post-PCI	-	-	3	3	2	3	3
Thrombus TIMI grade*	0	0	0	5*	5*	0	0

IMH: intramyocardial hemorrhage. PCI: percutaneous coronary intervention. IRA: infarct related artery.

apical-anterior and apical-septal segments. LE images showed MVO in the same segments with hipointensity in the T2* sequence. Coronary angiography showed 75% stenosis of the left anterior descending artery with distal TIMI-3 flow. The second patient with IMH was a 53 year-old male with antero-lateral infarction. In the T2 sequence, edema was noticed in the mid antero-lateral, apical anterior and apical lateral segments. T2* sequence showed low attenuation signal in the apical anterior segment. LE images showed apical anterior and apical lateral microvascular obstruction. Table 2 describes magnetic resonance findings. Coronary angiography demonstrated no evidence of coronary artery stenosis. Findings are shown in table 3.

None patient had history of prior antiplatelet medications. At the time of admission, all received treatment with parenteral heparin and aspirin. Clopidrogel was added in the four patients undergoing interventional treatment.

DISCUSSION

The results of our study show that in patients with myocardial infarction, IMH occurs not only after therapeutic reperfusion, but also after a spontaneous one.

Although timely reperfusion salvages myocardium and reduces mortality, successful restoration of epicardial artery patency after prolonged occlusion does not always lead to adequate reperfusion at the microvascular level. Reperfused AMI is characterized by myocite swelling due to osmotic process, intracellular calcium overload, MVO and IMH.[14] As IMH is caused by leakage of blood into the extravascular space, as a consequence of ischemic microvascular damage, it only occurs in reperfused AMI.

Nevertheless, myocardial reperfusion not only takes place as a consequence of fibrinolytic or interventional treatment, but it also can happen spontaneously or physiologically as it was evidenced in two patients of our study. In these patients coronary angiography showed antegrade TIMI 3 flow without collateral circulation and cMRI demonstrated the presence of IMH.

This is the first time that the presence of IMH is demonstrated after spontaneously reperfused STEMI by cMRI.

In our group of patients, T2* sequence showed IMH in 2 of the 7 patients which had not received thrombolysis or primary PCI. In medical literature, we have found that with this cMRI sequence, the IMH is seen in 33-38% of patients after successful primary PCI15; when T2W sequences are used, IMH has been found in up 49% of the cases10. However, it must be considered that the current value of breath-hold T2W spin-echo imaging technique is limited by its sensitivity to artifacts caused by cardiac or respiratory motion.

There are studies showing an overlap among the location, size, and shape of hypointensity regions by *ex vivo* T2 MR images and the pathologic specimen.[4]

Finally, it is important mention that the evidence of IMH after late reperfused myocardial infarction may have prognostic implications. In a recent study, incidence of adverse cardiac events was higher in the IMH group that in non-IMH group during the first year following STEMI. Cox regression analysis identified the presence of IMH lesions as an independent predictor of adverse clinical outcome.[16]

In our case-series study, we completed a six-month follow-up and, except for the noted case, there was only one death which occurred during the index admission in a patient without IMH. Therefore, the long term conclusions about the prognosis of IMH still need to be confirmed in a larger cohort. Nevertheless, it is probably that unfavorable mechanical consequences of IMH could consist in increased myocardial stiffness, propensity to wall rupture and delayed healing process.[17] Future studies addressing the prognostic significance of hemorrhage AMI will define the role of some drugs

currently used for AMI therapy and will clarify whether it represents a substrate at increased risk for post AMI rupture and unfavorable remodeling.

CONCLUSION

The results of our study show that in patients with acute myocardial infarction IMH occurs not only after therapeutic reperfusion, but also after a spontaneous one. This is the first time that its presence is demonstrated.

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