

# Towards the Complete Characterization of Myocardial Infarcts by Magnetic Resonance Imaging

Javier Sanz

Cardiovascular Institute, Mount Sinai Hospital, New York, USA

Magnetic resonance imaging (MRI) offers a degree of versatility in the non-invasive study of multiple anatomical and physiopathological aspects of the cardiovascular system which is matched by few other imaging techniques.<sup>1</sup> The description of late enhancement, or temporary accumulation of contrast agents with gadolinium in the infarcted region, was one of the most important advances in the application of cardiac magnetic resonance.<sup>2</sup> During the nineties, the development and standardization of late enhancement techniques after gadolinium administration made it possible to visualize myocardial infarctions of any age and to precisely quantify the extent of necrotic tissue. Excellent spatial resolution was an added benefit. As a consequence, in a few years time-frame, magnetic resonance has become one of the most widely used techniques for the visualization of myocardial infarction. Clinical applications include the detection of myocardial necrosis and differentiation between non-viable dysfunctional tissue and tissue with a high probability of recovering contractility spontaneously (stunned tissue) or with revascularization (hibernating tissue).<sup>3</sup> In the field of research, late enhancement makes it possible to study *in vivo* the myocardial response to different assaults, ventricular remodeling, or the potential cardioprotective effects of various therapeutic interventions.<sup>4</sup> Nevertheless, late enhancement shows only some of the components of ischemic lesion, specifically initial cell death that is subsequently followed by the replacement of necrotic myocardium with scar tissue. If the injury is sufficiently severe, it is also possible to detect the resulting microvascular obstruction, which appears as unenhanced zones in the necrotic area. Other pathophysiologically important aspects of cardiac

status, such as tissue perfusion or the impact on contractile function, can also be evaluated using magnetic resonance<sup>5,6</sup> or other techniques.<sup>7</sup>

Myocardial edema is an important component of ischemic lesions which we have been aware of for decades. Interruption of coronary flow leads to alterations in capillary permeability and facilitates the development of interstitial edema. Similarly, loss of function of the sarcolemmal sodium-potassium pump and the accumulation of osmotically active metabolites (eg, lactic acid) in the intracellular space facilitates the entry of water into the myocyte. In later stages, when necrosis is present, impairment of cell membrane integrity allows communication between the intracellular and interstitial compartments, leading to even greater intracellular edema. The accumulation of water in ischemic myocardium is particularly pronounced if the blood flow is restored (reperfusion). Moreover, reperfusion of tissues exposed to prolonged ischemia and which have suffered severe microvascular injury may be associated with intramyocardial hemorrhage.<sup>8,9</sup> The feasibility of using magnetic resonance as a non-invasive means of detecting myocardial edema was described over 20 years ago. The increase of free water in different tissues is associated with more prolonged transversal relaxation time (or T2) in these tissues as well as an increase in proton density, resulting in increased signal contrast between edematous and normal myocardium on T2-weighted images.<sup>10</sup> Specifically, a linear relationship has been shown to exist between relaxation time and water content in myocardial tissue samples.<sup>11,12</sup>

However, image acquisition required considerable amounts of time in initial studies (5-10 min for a limited number of sections), which meant that MRI was basically limited to use as a research tool. Technological advances over the last decade including the availability of magnets with more powerful magnetic fields and gradients, improvements in the design of image sequences, and upgrades in the reception coils, have allowed demonstration of this phenomenon reliably *in vivo* and in clinical practice. It has been possible to demonstrate that the edema extends beyond the territory showing late enhancement, thereby indicating that the hyperintense region on T2-weighted images

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Correspondence: Dr J. Sanz,  
Cardiovascular Institute, Mount Sinai Hospital,  
One Gustave L, Levy Place, Box 1030, New York, NY 10029, USA  
E-mail: Javier.Sanz@mssm.edu

might represent myocardium exposed to ischemic aggression, irrespective of whether necrosis is present or not. Thus, tissue showing signal enhancement on T2-weighted images would represent non-infarcted, at-risk myocardium.<sup>13</sup> This concept has been elegantly validated in animal models, where there were no significant differences between the areas identified as at-risk using MRI in vivo and those identified by post mortem sampling after injection of autofluorescent microspheres.<sup>12,14</sup> Recent studies have shown that MRI can detect the increase in water content in ischemic myocardium in as little as 30 min after coronary occlusion, before myocardial damage becomes evident through elevated enzymes or the presence of late enhancement.<sup>15</sup> This technique would therefore be potentially useful in a clinical setting for detecting acute coronary syndrome in patients attending emergency departments with thoracic pain. In such cases, the additional assessment of the presence of edema can improve specificity and positive predictive value compared with other parameters such as segmental alterations in contractility, regional hypoperfusion or late enhancement.<sup>16</sup> Similarly, the combination of T2-weighted images and late enhancement can be extremely useful in differentiating acute or sub-acute chronic infarcts, for example in patients with negative enzymes and electrocardiographic Q waves but no clear history of a prior ischemic event.<sup>17</sup>

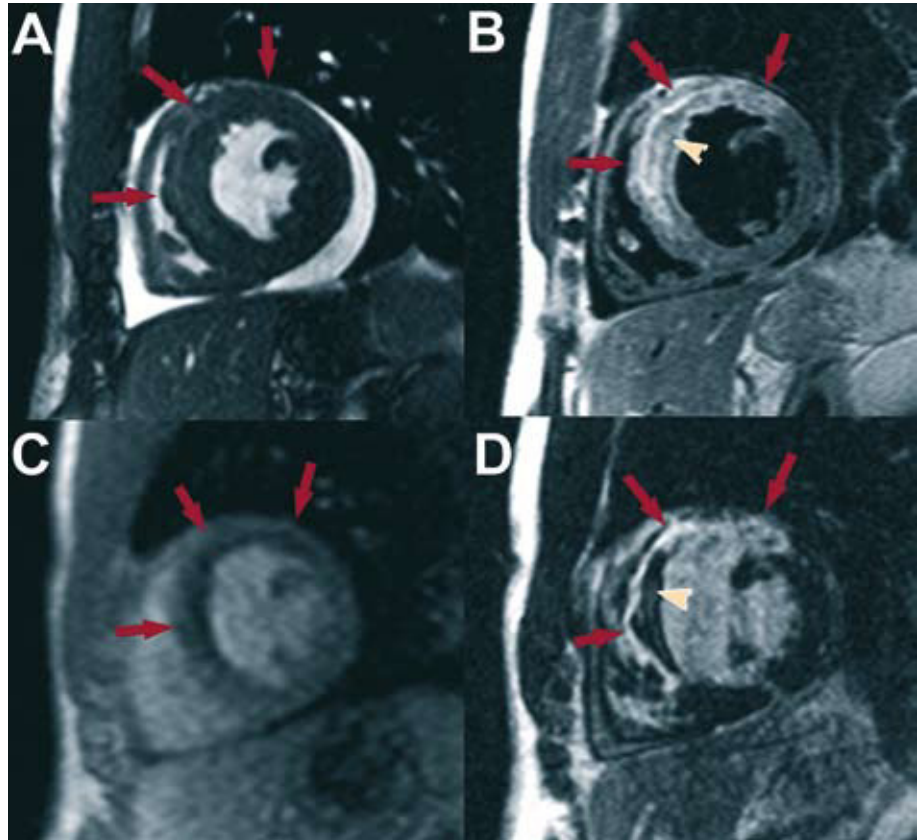
In an interesting and well-designed study published in this number of *Revista Española de Cardiología*, Monmeneu et al<sup>18</sup> add to existing evidence on the usefulness of MRI in detecting myocardial edema. From an initial group of 146 patients with TIMI 3 flow who had undergone mechanical reperfusion for a first infarct, the authors prospectively included 134 patients with no contraindications for MRI. The protocol applied in the first week after infarction included evaluation of ventricular function at rest and with low-dose dobutamine, presence of edema, first-pass resting perfusion, and delayed enhancement in a single examination (Figure). The assessment was repeated after 6 months in 70 participants. In the initial scan, images of sufficient quality to determine the presence and extent of myocardial edema were obtained for 117 (90.6%) patients. Of these, 68 (58.1%) and 45 (38.5%) had edema of  $\leq 4$  or  $>4$  myocardial segments (median), respectively. There were no significant clinical differences between these 2 patient subgroups except for larger infarct size measured using cardiac enzymes in the group with more edema. The location of the edema coincided with that of the infarcted area (and the peri-infarct region) and was most noticeable in segments with transmural necrosis. In a detailed comparison of segments with and without edema, the former showed significantly higher diastolic

thickness, less contractility both at rest and with dobutamine, low perfusion, more widespread necrosis, and greater prevalence of microvascular obstruction. Similarly, patients with  $>4$  edematous segments had larger infarctions, transmural, and microvascular obstruction, as well as increased left ventricular volume and mass and poorer ejection fraction than those with  $\leq 4$  segments. The alterations in ventricular size and function remained present at 6 months, although edema was not detected in the follow-up resonance. Finally, 23 (20%) patients showed lower signal intensity in the edematous zone, corresponding to the presence of microvascular obstruction in the late enhancement images.

There are several findings of interest in Monmeneu et al's study.<sup>18</sup> First, the study shows that it is feasible to test for myocardial edema after acute myocardial infarction in a clinical setting. The sequences used by the authors made it possible to obtain images of the entire left ventricle in a single apnea in three-quarters of the patients, and in multiple apneas in the remainder (the latter usually taking about 5 min). This approach is perfectly feasible in daily practice and is well-tolerated by most patients. Secondly, the study demonstrates that we now have available a non-invasive, robust imaging technique which can be used to quantify a component of myocardial ischemic lesion which could not be assessed up to this point. Some of the current clinical applications have been mentioned above; others will no doubt be developed in the near future.

The technique is also invaluable in the research field, where simultaneous knowledge of the extent of necrotic tissue and the at-risk area has immediate applications in the evaluation of, for example, cardioprotective treatments.<sup>4</sup> The authors also show that the presence of myocardial edema and the prolongation of T2 relaxation time after infarction is a transient phenomenon which gradually disappears during scarring. This confirms previous findings.<sup>19</sup> The reappearance of an augmented T2 signal in chronically infarcted tissue should therefore lead us to consider the possibility of a recent new ischemic episode. In addition, the authors describe areas of low signal intensity within the edema in about 20% of reperfused infarcts. These regions correspond not only to severe microvascular obstruction but also to concomitant intramyocardial hemorrhage.<sup>20</sup> The percentage is consistent with recent studies that also showed that this finding was independently associated with poorer ventricular remodeling.<sup>21</sup> Of particular interest in the present study is the detailed characterization of the functional and morphological features of the edematous segments in a homogeneous and well-selected patient population, ie, those with a first myocardial infarction and demonstrated

**Figure 1.** Mid-ventricular short-axis images obtained with magnetic resonance imaging at the same anatomic location, showing different pathophysiological aspects of myocardial ischemic injury. A: cine image in tele-systole demonstrating akinesis of the anterior and anteroseptal segments (arrows). B: T2-weighted image showing increased signal intensity in the same segments (arrows), indicating edema. The area of lower signal intensity within the edematous territory region (arrow head) corresponds to microvascular obstruction and intramyocardial hemorrhage. C: image obtained during contrast first pass through the myocardium demonstrating subendocardial hypoperfusion (arrows). D: post-contrast late enhancement delineating the extent of necrosis as a hyperintense region (arrows). The central hypointense area corresponds to microvascular obstruction (arrow head).



reperfusion. The data presented in this study will certainly be useful as a reference in the future.

Should MRI be performed in all patients with acute infarction? Will knowledge of the extent of myocardial edema change our therapeutic approach? It is probably premature to respond affirmatively to these questions. First, not all patients with an acute myocardial infarction are suitable for the test. In Monmeneu et al's study, the test was contraindicated in 8% of the initial group because of clinical instability or claustrophobia. In a further 10% of cases, it was not possible to obtain good quality images.<sup>18</sup> The imaging sequences used required inversion preparatory pulses which would make them susceptible to artifacts related to respiratory movement and particularly to cardiac rhythm disturbances. The authors demonstrated that patients with extensive edema showed the worst ventricular remodeling, contractile reserve, and myocardial perfusion not only in the week of the infarction, but also after 6 months.

Nevertheless, from the data presented it is not possible to determine if these findings are due simply to the fact that myocardial infarctions were also larger in this subgroup. In an experimental study of infarction in a porcine model performed in our laboratory, we were able to demonstrate that the extent of spared myocardium at risk, defined

as tissue that shows edema but not necrosis, is an independent predictor of functional recovery.<sup>4</sup> If this observation could be confirmed in humans, the clinical implications of assessing edema would be even more significant. Clearly, demonstration of these findings will require larger "real world" sample sizes, compared with the experimental model where factors such as duration of ischemia and reperfusion time, location of the coronary occlusion, etc, can be controlled and where other aspects such as ischemic preconditioning or comorbidities are not as relevant. Monmeneu et al's study does not, unfortunately, provide answers to this question. However, the authors' extensive experience means they are in a privileged position to perform this analysis, and we can only encourage them to continue this interesting line of research.

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