Review Article

Value of Cardiac Magnetic Resonance Image in the Approach of the Patient with Suspect Acute Coronary Syndrome and Normal Angiography

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Summary

It is estimated that patients presenting with chest pain, elevated serum troponin levels and electrocardiography abnormalities with normal or minimal angiographic coronary artery disease represents 2,6% to 19% of all initially diagnosed as having myocardial infarction. In this set is a challenge to the cardiologist make the appropriate diagnostic. Cardiac magnetic resonance has been used as an important tool to define between real myocardial infarct or a disease that simulate it, leading to an adequate treatment and improving the prognostic.

Introduction

Acute Myocardial Infarction (IAM) can be recognized by clinical examination, electrocardiographic findings, elevated markers of Myocardial Necrosis (MNM), imaging, or diagnosed by the pathological study that demonstrates death of heart cells - myocytes - by prolonged ischemia[1]. The main cause of IAM is rupture, ulceration, fissure, erosion or dissection of atherosclerotic plate leading to the formation of intraluminal thrombus in one or more coronary arteries, causing drop of the myocardial flow or distal embolization of platelets, causing myonecrosis. Usually the patient has Coronary Artery Disease (DAC), but in some cases coronary angiography may reveal the absence of obstructive lesions.

The angiographic appearance of the coronary arteries in patients with acute myocardial infarction without obstructive lesion may vary from normal to moderate coronary atherosclerotic lesions. Typically DAC is considered significant if an obstruction is greater than 50%, but this definition is arbitrary [2] and some authors classify as non-significant stenosis when less than 30%[3]. There are several published articles in the last decade showing that the predominance of IAM without significant DAC runs around 2.6% to 19%, depending on the criterion proposed for normal coronary angiography, as well as the presence of IAM with horizontal depression of ST (IAMCST) or IAM without horizontal depression of ST (IAMSST)[3-7]. Women are less prone to presenting obstructive coronary lesions in all forms of presentation of the ischemic myocardial disease, whether stable angina, IAM or sudden cardiac death[8]. women without obstructive coronariopathy are also more susceptible to new hospitalization with Acute Coronary Syndrome (SCA)/chest pain in 180 days of follow-up compared to men. All this reflects the anatomical and pathophysiological differences between genders[9].

The Cardiac Magnetic Resonance (RMC) has been an instrument of great value in the diagnostic investigation of this important and challenging group of patients with chest pain, elevated troponins (Tn) and normal coronary angiography or non significant RMC.

Keywords

Magnetic Resonance Spectroscopy/diagnostic use; Acute Coronary Syndrome; Chest Pain.

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Clinical Assessment

In order to establish appropriate therapy and prognosis, it is essential to define the correct diagnosis of this group of patients, i.e., if it is truly IAM or other disease mimicking IAM. For this, the first step should be a comprehensive clinical reassessment by history taking and physical examination.

There are several diseases that present themselves with chest pain, electrocardiogram (ECG) changes and elevated MNM (Table 1). The detection of MNM in the bloodstream is a sign of myocardial injury that may occur due to imbalance between supply and demand, toxic effects or hemodynamic stress, but does not necessarily indicate the presence of thrombotic SCA[11].Electrocardiographic changes emerge early in acute pericarditis. In this case, there is typically diffuse ST-segment elevation, except in aVR associated with depression of the PR segment. In the presence of pulmonary thromboembolism (TEP), patients usually present risk factors for venous thromboembolism, which needs to be investigated. The ECG shows very often deviation of the electrical axis of the heart to the right, complete right bundle branch block conduction delay or end the right branch and the standard S1Q3T3, unlike the cases of SCA. These are some examples of how simple clinical assessment can lead to the correct diagnosis.

Acute Coronary Syndrome and Normal Coronary Angiography

There are several causes of AMI with normal coronary angiography (Table 2). Coronary spasm (EC) is the etiology that initially comes to mind of the cardiologist. This is a sudden and intense vasoconstriction of epicardial arteries leading to occlusion or semiocclusion of the vessel[12]. In patients with

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Table 1

Causes of chest pain and elevated Tn
Acute Coronary Syndrome:
Acute heart failure
Pulmonary thromboembolism.
Acute aortic dissection
Severe aortic valve disease
Hypertensive emergency
Hypertrophic cardiomyopathy
Peripartum cardiomyopathy
Tachy-or bradyarrhythmias
Myocarditis
Perimiocardite
Takotstubo cardiomyopathy
Coronary vasculitis
Cardiac contusion

SCA, elevation of Tn and DAC that is not significant, the possibility of EC (challenge test with ergonovine or positive acetylcholine) must be considered13,14. EC can cause potentially fatal arrhythmias in patients with SCA and non significant DAC. Many agents can cause EC as ergotamine, diclofenac, Churg-Straus syndrome and Kounis syndrome and diseases such as pheochromocytoma, hyperthyroidism and Kawasaki disease. In more severe cases, vasospasm can affect three epicardial vessels causing cardiogenic shock. In patients with normal coronary angiography, altered vasoreactivity of epicardial coronary arteries in response to sympathetic stimulation is associated with increased risk of cardiovascular events[15]. In spite of the excellent prognostic of afterlife and coronary events in three years when compared to patients with obstructive SCA, eventually persistent angina is a great challenge in these patients, leading to the realization of kinecoronariography in some cases.[16]

Although there is no increased prevalence of Patent Foramen Ovale (FOP) in patients with IAM and normal coronariography[17], there is the possibility of AMI by paradoxal emboly[18]. Few cases of AMI due to paradoxal emboly through FOP have been reported and there may occur thromboembolism for two coronary arteries and associated to TEP. It is known that the FOP associated with Obstructive Sleep Apnea Syndrome can facilitate paradoxical embolism triggered by a Valsalva maneuver that induces negative intrathoracic pressure and sudden increase in the right atrial volume[19], and this association causing AMI has been previously described[20].

Although autopsy studies show evidence for coronary artery embolism in infective endocarditis in 60% of cases, rare cases of transmural IAM were described[21]. Non bacterial thrombotic endocarditis was also described as an ethiology of IAM. One should suspect thrombophilia alone or associated with other pathology in cases of IAM with normal coronary angiography, and the presence of FOP in this situation should be investigated. Eventually, IAM may be the first manifestation of thrombophilia and antiphospholipif[22] syndrome.. Coronary embolic event can also be derived from atrial mixoma and fiberelastome, as well as thrombus derived from the left ventricle in carriers of myocardiopathy or left atrium [23,24]. The risk of systemic emboly in carriers of valvar prothesis anticoagulated is of 0.5% to 1.7% year and most of the cases presents cerebrovascular event, but eventually there may occur IAM under this circumstance.[25]

Spontaneous Coronary Dissection (DCE) is a rare clinical entity. Clinical diagnosis is challenging and classically based on the angiographic demonstration of intimal-medial "flap" leading to the appearance of double lumen. Eventually the findings are negative, since coronary angiography cannot visualize the wall of the vessel [26, 27]. In these cases, intracoronary ultrasound and tomography by optical coherence can be fundamental.

Rarely marijuana use can trigger myocardial infarction. Postulated mechanisms include plaque rupture caused by sympathetic discharge, coronary vasospasm, coronary dissection and sudden hypotension. IAM was described as being caused by the association of marijuana with sildenafil. AMI triggered by cocaine occurs frequently in patients with normal coronary arteries. In such cases, the IAM involves several mechanisms being related to the blockade of norepinephrine receiving causing alpha-and beta-adrenergic effects. These include elevated heart rate and blood pressure and simultaneous EC with reduced supply of oxygen and consequent myocardial ischemia. Furthermore, there is evidence of effect of cocaine on platelet activation, increased platelet aggregation and potentiation of thromboxane production with thrombus formation. Young patients with chest pain and suspected ACS should be questioned about cocaine use. Cocaine use should be clarified by the patient or by the analysis of urine excretion[28].

Beriberic acute disease (Shoshin syndrome) may be presented as cardiogenic shock and seemingly serious myocardial ECG ischemia [29].Pseudoephedrine, common component in antiflue, dietetic supplements and Chinese herb teas, presents sympaticomimmetic effects with impact on the cardiovascular system. AMI with normal coronary started after intake of drugs with pseudoephedrine has been described.[30].

Table 2

Causes of acute myocardial infarction and normal coronary angiography
Coronary spasm
Obstruction of the coronary branch
Embolism (thrombus, tumor, calcified tissue)
Coronary plaque rupture with spontaneous thrombolysis
Thrombophilia
Spontaneous coronary dissection
Increased myocardial demand
Multiple mechanisms

Situations Mimicking Acute Myocardial Infarction

Takotsubo cardiomyopathy (CT) is characterized by reversible left ventricular systolic dysfunction and transient simulating SCA. Usually it appears after physical or emotional stress, predominantly in postmenopausal women, although it can also occur in young males. Often it presents with chest pain or dyspnea, ECG changes and elevated MNM suggesting that it was IAM. Normal coronary angiography typically exclude DAC and ventriculography revealed apical akinesia and compensatory hypercontractility of basal segments[31].

Myocarditis refers to clinical and histopathological manifestations of a wide range of immunopathological processes that affect the heart. Myocarditis can resemble the SCA, usually with preserved global left without significant DAC on coronary angiography ventricular function. Widening of the QRS complex and Q waves in the ECG are associated with worse prognosis in acute myocarditis. Pericarditis with depression of the PR segment and ST segment elevation can occur in the presence of diffuse extension of the inflammatory process to epicárdio[32].

Several studies showed that SCA is one of the most confused condition with TEP due to the considerable overlap of clinical findings. There are several case reports of TEP mimicking IAMCST, mainly in the anterolateral leads septais[33]. It is important to have in mind that eventually there may co-exist TEP and IAM due to the possibility of paradoxal emboly[34].

Acute aortic dissection involving the ascending aorta (type A) is a serious disease that mimics IAM. In almost half of the patients ECG shows acute changes including depression or ST-segment elevation and/or T wave inversion. Bonnefoy et al. found elevation in the levels of Tn above the cutting value for IAM at 10% of the patients with acute aortic dissection type A.[35]

Cardiovascular Magnetic Resonance In The Scenario Of Non Diagnostic Coronariography

Since coronary angiography does not establish the diagnosis, the next step will be necessary to define the etiology of the acute event to ensure proper treatment and to know the prognosis. RMC has been studied in this setting and has been shown as the best approach in this challenging situation[36-43].

Christiansen et al. investigated patients with SCA with High Tn and minimum DAC using an RMC through the technique of the delayed enhancement for evaluation of myocardial fibrosis. Twenty-three patients (54-8 years) who presented with chest pain, elevated Tn and minimal DAC were included. Patients with clinical pericarditis/myocarditis, tachyarrhythmia, prior MI or an alternative explanation for the elevation of Tn were excluded. Myocardial fibrosis was screened by the delayed enhancement technique using the inversion-recovery sequence after administration of gadolinium. Delayed enhancement consistent with myocardial fibrosis was seen in seven of 23 patients (30%) and primarily evidenced in the territory of the right coronary artery. Peak of Tn, clinical characteristics and volumetric parameters were similar in patients with or without delayed enhancement. One patient had delayed enhancement mesomiocardiac suggested that diagnosis of myocarditis. There was a linear relationship between fibrotic myocardial mass and peak Tn. During follow-up, cardiovascular events were more frequent in those with delayed enhancement (43% vs. 12.5%) [36].

Assomul et al. assessed 60 consecutive patients (average age of 44 years, 72% men) with episode of chest pain and high Tn and non-obstructed coronaries. Patients were recruited in the period of three months from the onset. All of them underwent RMC examination by kinemagnetic resonance, T2-weighted imaging for screening inflammation and delayed enhancement for detection of infarction/fibrosis. In 65% of patients a reason for lifting the Tn was identified. The most common cause myocarditis was (50%), followed by IAM (11.6%) and cardiomyopathy (3.4%). In 35% of patients without identifiable causative factor by RMC, the presence of infarction/fibrosis was significantly excluded[37].

Leurent et al. examined patients with a condition of acute chest pain, elevation of Tn and absence of significant coronary stenosis. During a period of three years, 107 consecutive patients (mean age 43.5 years, 62% males) underwent RMC at 3 tesla unit in a range of 6.9 days of onset of symptoms. The diagnosis was based on: deficit in contractility and pericardial effusion through kinemagnetic resonance; myocardial edema on T2-weighted images, and the presence of delayed enhancement on T1-weighted images. RMC was normal in 10.3% of the patients and contributed to the diagnosis in 89.7% of them, including myocardities in 59.9%, TC in 14% and AMI in 15.8%. Patients with normal MRI had lower peak Tn (2.6 ng/mL) compared to patients with abnormal RMC (9.7 ng/mL, $P = 0.01$), [38].

Chopard et al[39]. evaluated 87 patients consecutively (average of age 53 years old; 40.2 men) with SCA with elevation of Tn and normal coronariography. All of them underwent RMC at 3 tesla machine. Adverse events were recorded at one year follow up. A probable etiology for the acute symptoms was established by RMC in 63.2% of patients (22.7% IAM, acute myocarditis 26.4%, 11.5% CT). During follow-up, one patient in the IAM group had cerebral infarction (1.2%). In the myocarditis group had cardiogenic shock at presentation, an episode of congestive heart failure (1.2%) and nine patients had recurrent chest pain with elevated Tn (10.3%). Two patients in the CT group had cardiogenic shock in the initial phase (2.4%), and there was no other event in this group during follow-up. In the remaining 36.7% of patients, no clear diagnosis could be established by RMC and evolved without events during acompanhamento[39].

Stensaeth et al[40] evaluated the impact of RMC in the differential diagnosis of a prospective series of patients with suspected coronary IAMCST and without injuries. Among 1,145 patients with suspected IAMCST, 49 had normal coronary arteries and were selected for the study. CMR was performed whenever possible in the first 24 hours and included functional analysis, T2-weighted images and T1-weighted images before and after administration of gadolinium early (overall relative enhancement) and later. All patients

were followed for a period of approximately three months after the completion of the RMN. The incidence of patients with normal coronary arteries and IAMCST was 4.3% with a mean age of 45 ± 14 years (Group IAMCST 64 ± 13 years, P\0.001). There was a history recent infection in of them. MNM showed up moderately elevated on admission. There was a significant difference in the parameters of left ventricular end (P\0.001) diastolic volume, left ventricular mass (P\0.05), ratio of average T2 (P\0.05) and volume of delayed enhancement (P\0.05. The major diagnoses were myocardite (29%), pericarditis (27%) and TC (10%). In 18% of patients could not set the diagnóstico[40].

Gerbaud et al[41] evaluated 130 patients (mean age: 54 ± 17 years) who presented with acute chest pain and elevation of Tn and normal coronary angiography. All patients were conducted in accordance with the guidelines of the European Society of Cardiology including echocardiography and underwent RMC within 6.2 ± 5.3 days of the acute event. During follow-up, they were evaluated for the emergence of major cardiovascular events. The RMC contributed to the diagnosis in 100 of 130 patients (76.9%), and the findings were normal in the remaining 30 patients (23.1). RMC diagnosed 37 IAM (28.5%), 34 myocardites (26.1%), 28 TC (21.5%) and one patient with hypertrophic cardiomyopathy (0.8%). When there was a single diagnosis referrer cardiologist, cardiac MRI was concordant in 32 patients (76.2%). In those patients with at least two diagnostic hypotheses, RMC defined etiology in 61 patients (69.3%). In 10 patients (7.7%) were modified and the initial diagnosis in 42 patients (32.3%) were no changes in therapy. Mean follow-up was 34 months (range 24-49) in 124 patients. Major cardiovascular events occurred in 16 patients (12.9%), with no difference between those with abnormal or normal RMC. The authors concluded that in patients with acute chest pain associated with elevation of Tn and normal coronary conducting early RMC leads to important diagnostic and therapeutic applications. But his relationship with the occurrence of major cardiovascular events during midterm follow-up is not as obvious[41].

In Spain, Zaldumbide et al. studied 80 patients with suspected SCA and normal coronariography. RMC was performed by searching through T2-weighted and delayed enhancement after 10 minutes of infusion of gadolinium. In 51 patients (63%), the final diagnosis was acute myocarditis. In all these cases, we observed delayed enhancement in subepicardisc and mesocardic segments. In 12 patients (15%) was diagnosed AMI, all with standard subendocardial or transmural delayed enhancement. In nine patients (11%) than with segmental abnormality on initial echocardiographic study with subsequent normalization CMR showed no delayed enhancement CT findings considered characteristic. In addition, four patients were diagnosed with pericarditis, while in four other patients the etiology was not defined[42].

Batthi et al[43] developed a single-center prospective study in which they were allocated to undergo CMR 207 patients with chest pain, elevated Tn and absence of significant coronary artery disease (<50% stenosis). A comprehensive set of clinical data including risk factors for CAD and peak Tn were collected. Coronary atherosclerosis was graded as normal (0%), quasi-regular (1% -25%), and mild atherosclerosis (26% -50%). AMI was defined based on the pattern of delayed enhancement. Mean age was 55 ± 16 years, being 57% female. The average CAD risk factors was 1.6 ± 1.2 per patient. The Tn peak was approximately five times greater than the reference value. At coronary angiography, 45% had normal coronary arteries, 28%, quasi-normal, and 28%, mild atherosclerosis. The total number of AMI was 29.5% (61/207), and the specific etiology was set at 53% (109/207) of cases. No association between AMI and CAD risk factors or peak Tn was observed ($p = 0.26$ and $p = 0.17$, respectively). Although the rate of MI have shown a relationship with the degree of atherosclerosis, 25% of patients with normal coronary arteries were victims of IAM[43].

RMC and IAM

The RMC has been a very important tool in the evaluation of patients with chest pain, elevation of Tn, normal ECG and normal coronary angiography or modified or negligible. This is because the gadolinium presents a high spatial resolution may identify areas of fibrosis and enable distinction between reversible or irreversible ischemic injury regardless of the extent of the parietal contractility or time IAM[44]. The standard of late enhancement allows to differentiate between fibrosis related or not to IAM [45,46] (Figures 1, 2 and 3). The image of the delayed enhancement in acute myocardial infarction always involves the subendocardial region and may affect all or part of the heart muscle in the infarcted territory while this finding is not necessarily evidenced in other myocardial diseases. So if no subendocardial involvement, should consider another method of myocardial injury. Cardiac RMC can also differentiate infarction in acute or old by searching for edema using T2-weighted sequence.

RMC and Myocarditis

RMC has become the main tool in noninvasive diagnosis of myocarditis, providing greater reproducibility and definition of the disease, improving our understanding of the disease and the proper conduct of the patient. It is unknown the actual incidence and prevalence of mainly mild to moderate myocarditis, this because the symptoms of the acute phase of the disease are nonspecific and often omitted. Myocarditis can be acute, subacute or chronic and present focal myocardial injury or diffuse[47]. Acute myocarditis can simulate SCA, both IAMSST and IAMCST. Once suspected acute myocarditis, CMR should be performed preferably during the first 14 days. The presence of hyperintense signal compatible with edema increases sensitivity in patients with chest pain and elevation of Tn if RMC is performed immediately after the onset of symptoms[48].

RMC and CT

In the presence of CT, RMC allows the differential diagnosis of this entity from others such as myocarditis, cardiomyopathy and myocardial infarction, as well as view the transient increase in myocardial mass and resolution of edema while systolic function recovers. Studies have shown the utility of RMC contrast to differentiate small infarcts of myocarditis or CT. As a rule, although there is elevation of Tn as a sign of myocardial

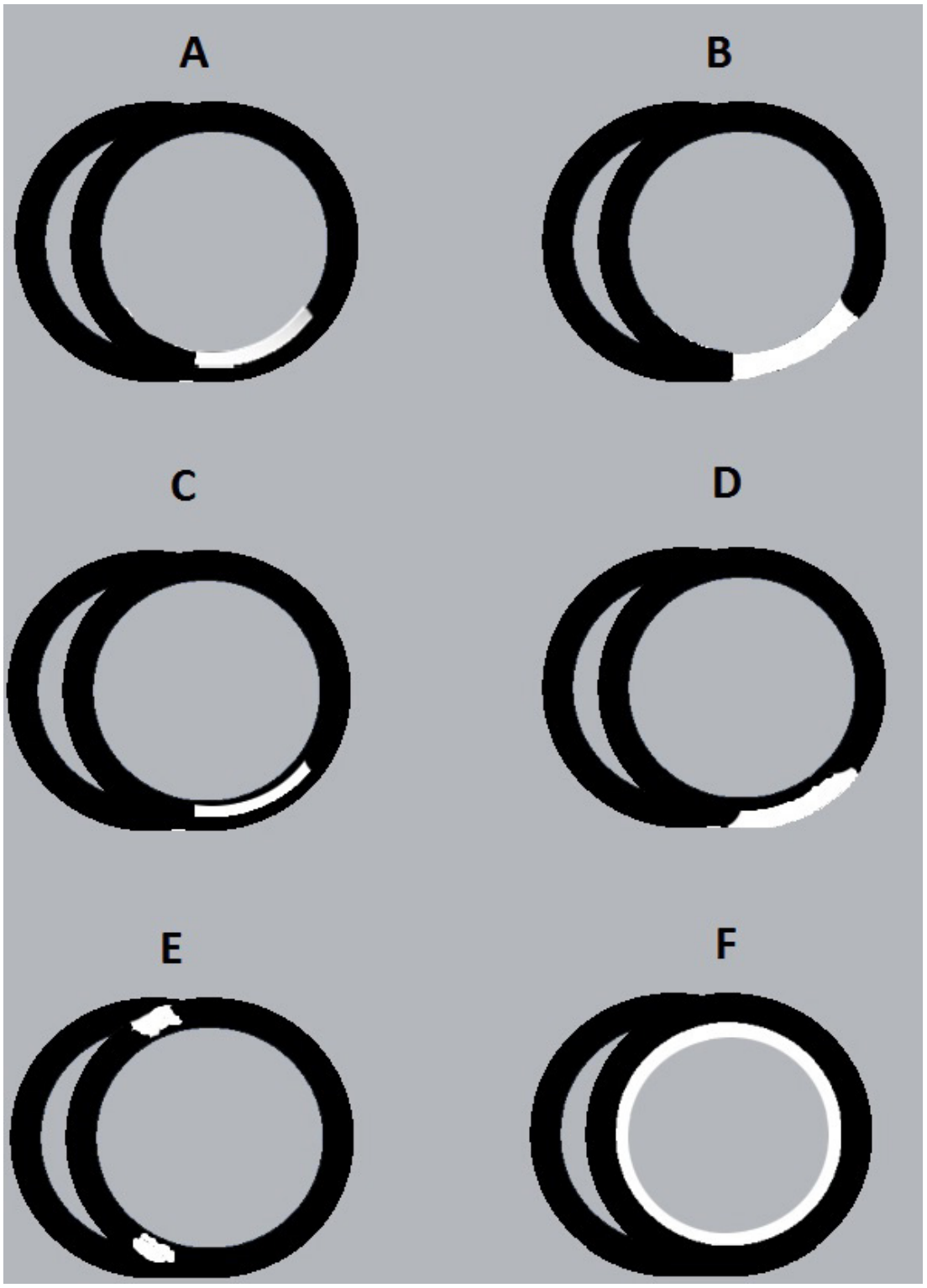

Figure 1 - *Patterns of delayed enhancement (A and B = Ischemic; C, D and E = Not ischemic): A - subendocardial infarction, B - transmural infarction; C - medium late enhancement – ventricular; D - Epicardial late enhancement; E - Late-enhancement in the septal insertion; F - Late enhancement global / diffuse*

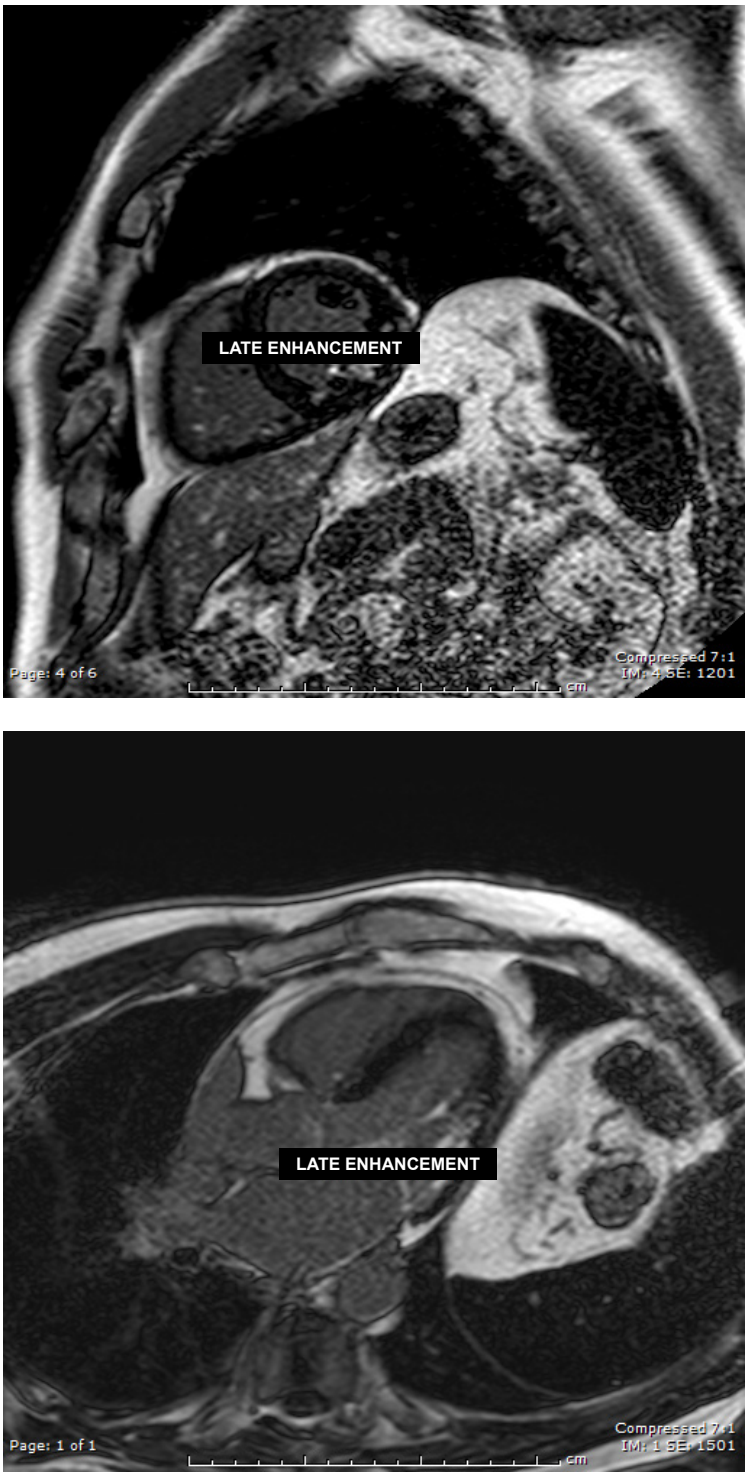

Figure 2 - *Presence of subendocardial late enhancement in the middle segment of the inferior-lateral wall in patients with acute myocardial infarction and coronary angioplasty circumflex artery.*

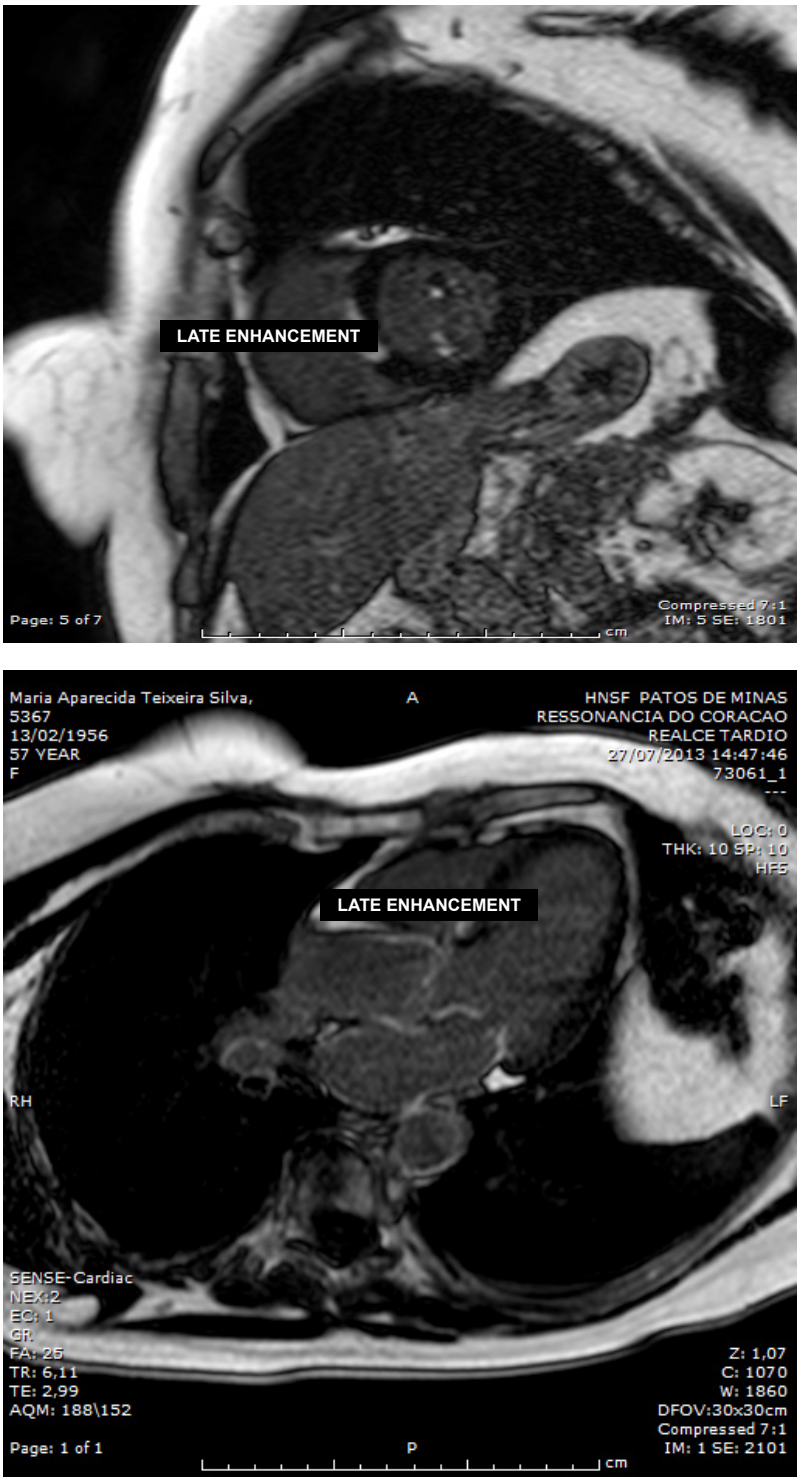

Figure 3 - *Presence of epicardial late enhancement in the basal segment of the septal wall in patient with chest pain, elevated markers of myocardial necrosis and normal coronary angiography, compatible with acute myocarditis*

injury in CT, delayed enhancement sequences are negative[49]. However, Avegliano et al.[50] described 8 patients with findings consistent with CT in which RMC realized early (immediately after coronariography) showed a unique morphological standard of delayed enhancement until then not described.[50] Nakamori et al[51] also found delayed enhancement in 10 (2.7%) of 368 segments analyzed in 5 (22%) of 23 patients with CT with the beginning of the symptoms up to 72 hours and that disappeared after a period of 12 months[51]. It is very important to establish the differential diagnostic between CT and myocarditis or IAM so that unnecessary therapies are avoided.[52] One must have in mind that the typical findings of CT are characterized by apical transitory hypokinesia and basal hyperkinesia, but some variants of CT have been reported. In reverse CT the apex presents akinetic and hyperkinetic basal segments. The mid-ventricular type is characterized by akinesia with or without ballooning the middle segments and apical and basal hyperdynamic pattern. Akinesia of other segments of the left or right ventricle were also described[53].

RMC and Pericarditis

Acute inflammation of the pericardium, with or without associated effusion can occur as an isolated disorder or be a manifestation of systemic disease. The signal intensity of pericardial thickening by RMC is variable in acute pericarditis process and there is no standard patognomônic[54].The detection of the pericardiac inflammatory process has become less challenging through modern RMC techniques. Both pericardial thickening and the presence of stroke can be evidenced through the techniques of weighted spin-echo T1- and cine-MRI as through technical STIR weighted spin-echo T2 allows visualization of the pericardial edema affected by acute inflammation. Also the study of acute pericarditis is feasible through the techniques of gadolinium enhancement. Both techniques of spin-echo and delayed enhancement are useful in this scenario. The application of fat suppression may be of interest to enhance the visualization of the inflammated pericardium[55] ..

Magnetic resonance angiography and TEP

You can perform the RMC for assessment of pulmonary arteries in suspected acute or chronic TEP when the results of other tests are doubtful, or in those patients in whom the use of iodinated contrast media or ionizing radiation is relatively contraindicado[56]. Stein et al.57 have evaluated the performance of magnetic angioresonance with or without reno resonance, for TEP diagnostic. Technically adequate magnetic resonance angiography had a sensitivity of 78% and specificity of 99%, but in 25% of patients the images were considered inadequate. They concluded that magnetic resonance angiography should be considered only at centers that routinely perform the technique with good results, and only in those patients in which the achievement of established methods is contraindicated[57]. Recently, Kalb et al.[58] evaluated the detection of TEP through standard pulmonary magnetic angioresonance with contrast injection and acquisition of images in apnea, through the recirculation technique of tridimensional contrast phase gradient-echo using low flip angle and through the sequence of image without delayed enhancement true fast with steady-state precession. They found that the combined three sequences increased the sensitivity to 84%. The specificity was 100% for all methods except for pulmonary magnetic resonance angiography (1 false positive) [58].

DISCUSSION

The SCA with normal coronary angiography is not a rare situation and often the cardiologist meets this challenge and need to deal with unknown etiology. In this scenario, the RMC assists in defining or exclusion of IAM, allowing the exclusion of some possible diagnoses and aiding in decision making.

It is known that patients with non-obstructive DAC tend to receive less requirements aimed at secondary prevention discharged when compared with patients with obstructive CZ, although the secondary prevention is given to all patients with DAC[59]. This conduct is not appropriate, since studies have shown that the rate of death and reinfarct occurs around 2% to 7.7% after IAM without obstructive DAC 2,3, 60 On the other hand, clinical cardiologists eventually treat patients will all kinds of therapy to prevent secondary, but treatment directed to atherosclerosis can be inappropriate.

The diagnosis of thromboembolism as a cause of IAM light therapy modification and improvement in prognosis. It is also very important to establish the diagnosis of myocarditis, since even with preserved ejection fraction this pathology cannot be considered benign[48].As mentioned previously, diagnosis through RMC benefitted one third of the patients leading to change in therapy.[41]

Therefore, as alleged, the RMC in the context of acute chest pain, elevated MNM and normal coronary angiography is an important tool that can impact the outcome of a significant number of patients, without increasing the risk of the procedure.

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