

CONTINUING EDUCATION PROGRAM: FOCUS...

Is it possible to do without the study of myocardial perfusion in 2013?



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Abstract The analysis of myocardial perfusion is a key step in the cardiac MRI examination. In routine work, this exploration carried out at rest is based on the qualitative first pass study of gadolinium with an ECG-triggered saturation recovery bFFE sequence. In view of recent knowledge, the analysis of the myocardial perfusion under vasodilator stress may be carried out by scintigraphy or MRI, the latter benefiting from the absence of exposure to ionizing rays and a lower cost. Besides coronary disease, the perfusion sequence provides a rich semiology to compare with the clinics and the data from other sequences. Arterial Spin Labeling (ASL) is an alternative technique used in the animal to quantify myocardial perfusion.

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In human clinical practice, myocardial perfusion is mainly studied in imaging by scintigraphy or MRI. We will concentrate on MRI, even if the isotopic examinations are still most common in cardiology in France and throughout the world.

The first pass perfusion sequence acquired in real time during the injection of gadolinium is an integral part of the conventional cardiac MRI protocol.

It is also the key MRI sequence under vasodilator stress in the diagnosis of myocardial ischemia. The interpretation is usually qualitative (visual).

It should not be confused with the late enhancement sequence, carried out 10 to 20 minutes after the injection of contrast product, that aims at identifying the pathological myocardium retaining the gadolinium (necrosis, fibrosis, inflammation).

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In all cases, the analysis of myocardial perfusion is integrated with the data from other sequences. This comprehensive analysis (CINE, edema, perfusion, late enhancement sequences), without blind zone, is the great advantage of MRI over other techniques.

In this article, we will discuss the principles for perfusion analysis, then illustrate the main applications, before concluding with the alternative techniques used in the small animal.

Technique

Rest perfusion

This basic sequence in the conventional examination involves a multi-slice acquisition with saturation recovery (SR), most often in balanced fast field echo gradient (bFFE) [1]. It consists of a high temporal resolution sequence, that produces a signal highly dependent on the relaxation time T1, and its shortening induced by gadolinium for which the cavity and myocardial transit is monitored in real time.

The operator plans a number of slices that depends on the R-R space of the ECG. This number will be increased in patients with low cardiac frequency. With current 1.5T machines and a patient with around machines 60–70 beats per minute, it is possible to place four to five slice planes in an R-R space (typically, two to three slices in the short axis, one slice in the 4-chamber view, and a last one along the LV axis). The slices are defined according to the disorder suspected.

In certain cases, it is possible to place five slices in a single plane (the search for a shunt may, for example, benefit from a stack of joint slices in the 4-chamber view).

The injection protocol may vary according to the patient's habits and the disorder suspected. In our centre, we routinely inject a full dose of gadolinium chelate at 5 cc/s (0.1 mmole/kg or 0.2 mL/kg if it consists of a semi-molar product or 0.1 mL/kg if it consists of a molar product). In all cases, the gadolinium is pulsed by saline solution (30 cc in the adult).

It is possible to stick to this dose to obtain a late enhancement of quality.

However, certain teams recommend the use of a "double dose" of gadolinium to optimize the sequences of late enhancement, and re-inject the same quantity of contrast product after the acquisition of the first pass perfusion sequence.

The sequence can be carried out with free breathing. An apnea may be solicited (without stress, the patient is simply asked to stop breathing for about 20s) when the gadolinium appears in the superior vena cava, especially if one wants to quantify the perfusion phenomenon with an input function.

The right cavities, the arterial vessels, the pulmonary veins, and then the left cavities become opaque in this order (Fig. 1). Finally, the myocardium is enhanced according to an often-visible epi-endocardial gradient, in particular in case of hypertrophy of the myocardium. Following an apnea of about 20s, the patient may gently start breathing again before the end of the sequence that lasts for a total of about 50s.

Perfusion under vasodilator stress

The principle is to reveal any perfusion asymmetry between different coronary distribution territories of the myocardium. A vasodilator (adenosine or dipyridamole) is administered to a patient well informed of the adverse effects (flush, headaches) and closely monitored (visual surveillance, ECG, arterial pressure, PaO₂) after checking for the absence of any contraindication [2]. The drug acts on the healthy arterial trunks, provided that the patient has not taken or received one of its inhibitors, in particular coffee (the consumption of coffee in the morning is the main practical restriction for this examination). The dilation of the healthy vessels induces a vascular steal syndrome to the detriment of the ischemic territories. The first pass perfusion sequence carried out in the conditions described above reveals a hypoperfusion (relative hyposignal) of the ischemic territories (Fig. 2).

The detection of such an anomaly suggests the indication of revascularization and also guides the procedure towards the ischemic territory after comparison with the imaging of the coronary network.

Technically, several variants are possible. The above protocol is applied. It is simply necessary to adapt the number of slices acquired to the heart rate that will increase with the injection of the vasodilator.

Stress perfusion should always come before rest perfusion, since the diagnosis of ischemia (relative hyposignal) is easier at the first pass of gadolinium. In most teams, the stress perfusion is completed with a rest perfusion. The purpose of this double injection (2 × 0.05 mmol/kg of semi-molar contrast) is to make sure of the absence of artifact (hyposignal in bands in the septum that does not change from one sequence to the next) by slice-by-slice comparison of the two sequences.

The interpretation of the examination is always confronted with the analysis of the global and segmental kinetics as well as a late enhancement.

There is increased certainty that the vasodilatation has stopped (return to a state of rest) when adenosine is used, whose tolerance is excellent and whose half-life is very short, than with dipyridamole whose half-life is longer and whose effect has to be cancelled by the injection of theophylline. The disadvantage of adenosine is due to the price, much higher than that of dipyridamole. Regadenoson is now proposed in this indication. We have not yet used it.

Other authors consider that if the stress perfusion is normal, it is not useful to re-inject the patient to obtain a rest acquisition.

There are at least two alternatives to vasodilators in MRI:

- the physical exertion stress test (when the patient is able to undergo it) is the most effective and physiological way to assess the coronary reserve. However, the stress is not easy to implement in an MRI environment and this test is not carried out on a routine basis. When the patient is able to undergo a significant stress, he is now more willingly directed towards nuclear medicine, where the post-stress measurement will be compared with the measurement at rest;
- certain teams use "high dose" dobutamine. It constitutes a purer ischemic stress than the vasodilator, by increasing

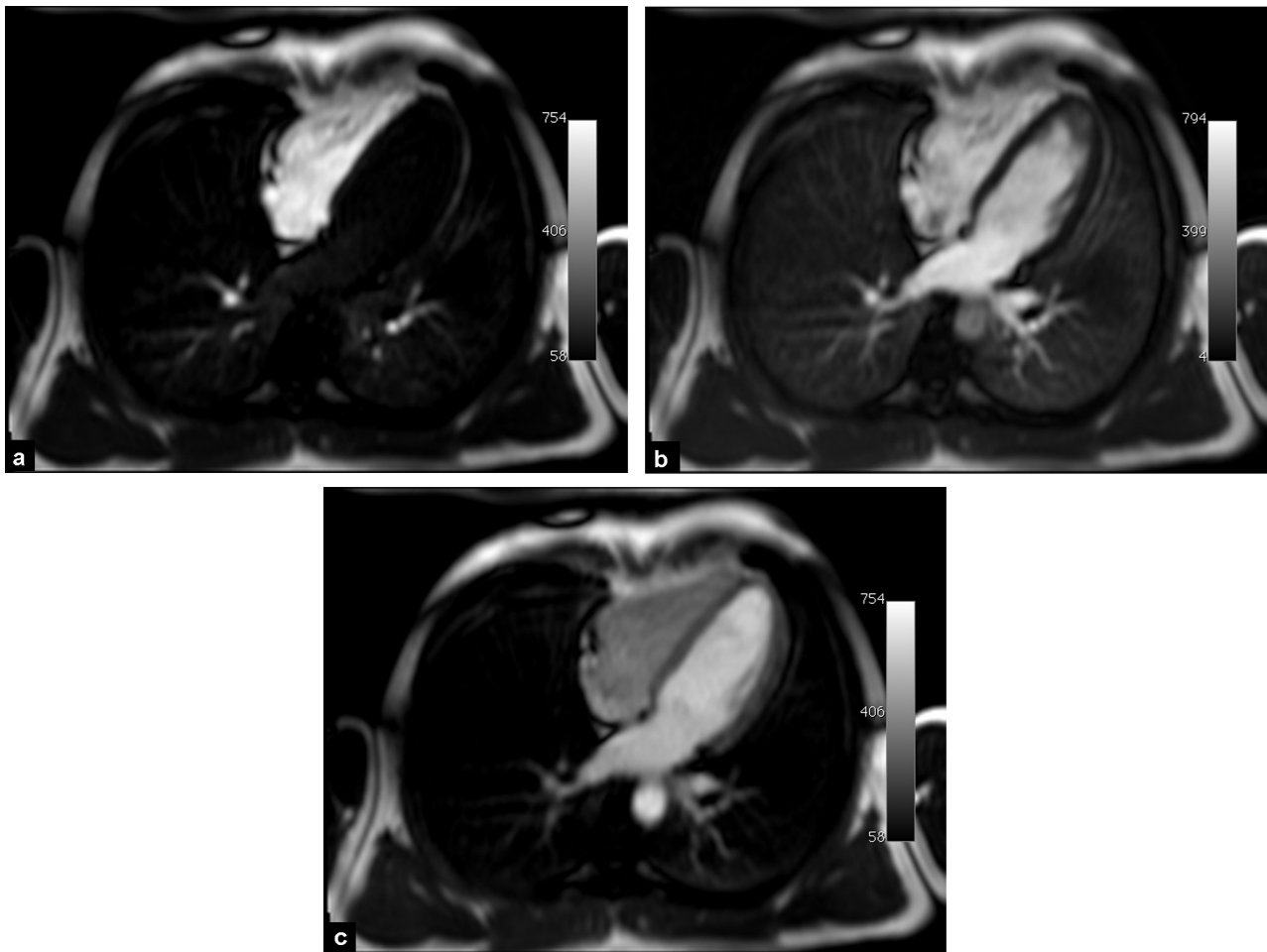


Figure 1. Slices in the 4-chamber view (horizontal long axis) extracted from a first pass perfusion sequence. Normal examination showing the kinetics of the contrast product. a: opacification of the right cavities; b: opacification of the left cavities; c: homogenous myocardial enhancement.

the myocardial work. In this case, the first pass perfusion is not studied but the global contractility (evolution of the ejection fraction) and segmental contractility (appearance of a segmental kinetic disorder in case of ischemia).

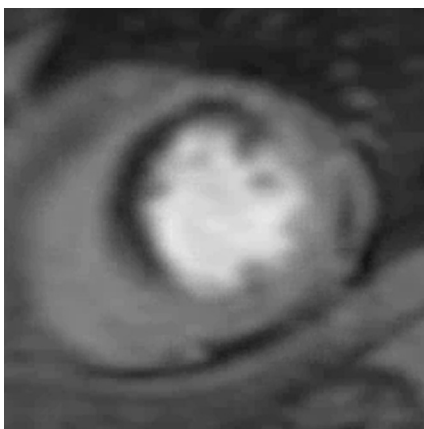


Figure 2. Slice in the short axis of the heart extracted from a perfusion sequence under vasodilator stress. Anterior septal ischemia. The anterior territory (anterior interventricular artery) presents a distinct hypointense under stress, attesting to a detrimental perfusion asymmetry.

Applications

Ischemic stress

This is the main indication for perfusion sequences. The search for ischemia by MRI has given rise to a great many studies that place it at least at the diagnostic level of gated SPECT imaging. The main advantage of the MRI is the absence of exposure to ionizing radiation [3]. The main limit in this context is the difficulty of including stress.

Radiologists are familiar with the other limits or contraindications for MRI: obesity and claustrophobia (the latter often induced by the former), non-magneto compatible implant, in particular a pacemaker or implantable defibrillator, intra-orbit foreign metal body, ferromagnetic vascular clips, kidney failure or allergic antecedents contraindicating the injection of gadolinium chelate.

Among the many studies backing up the use of the MRI in the detection of coronary disease, two of them have to be mentioned.

Watkins et al. [4] carried out a monocentric trial to compare MRI under adenosine with Fractional Flow Reserve (FFR), a robust hemodynamic reference to determine the significance of arterial stenosis. By way of a reminder, FFR is the invasive measurement (during a coronary angiography)

of a mean pressure gradient between the thoracic aorta and an endocoronary point located downstream from the stenosis studied. A stenosis is considered to be significant if the difference in mean pressure between these two points exceeds 25%. The FFR is considered to be normal when it exceeds 75%, abnormal when below.

The results of this study support the use of MRI. In fact, the evaluation by patients provides the following results: of the 76 patients who had a lesion that was judged positive by MRI, 74 had at least one vessel with a FFR less than 75% (2 false positives). Of the 25 patients where the MRI did not detect an anomaly, four had a pathological FFR (false negatives). The sensitivity per patient was 95%, the specificity 91%, the positive predictive value 97%, the negative predictive value 84%. The study by segment provided similar results with a sensitivity of 91%, a specificity of 94%, a positive predictive value of 91% and a negative predictive value of 94%.

In the English, bi-centric CE-MARC (Clinical Evaluation of MAgnetic Resonance in Coronary heart disease) study, recently published in *The Lancet*, Greenwood et al. [5] compared MRI including perfusion under stress by adenosine with gated SPECT (tetrofosmine labeled with ^{99m}technetium) in angina patients with at least one cardiovascular disease risk factor. The coronagraphy was the reference. The MRI protocol chosen was very complete (as opposed to a past "MR Impact" study that only took into account the perfusion analysis), associating a CINE analysis, coronary MR-angiography, and late enhancement with rest-stress perfusion sequences.

The positivity criterion for the MRI was composite: an anomaly in the segment kinetics or a first pass perfusion anomaly under vasodilator stress, or coronary stenosis revealed by MR-angiography, or typical subendocardial late enhancement typical of necrosis, resulting in the examination being considered positive.

The results of the CE-MARC study support the use of MRI. The reference method and technique have even disadvantaged MRI. In fact, in the patients with a normal coronary angiography and scintigraphy and a (non-transmural) subendocardial sequela of infarction by MRI, the authors consider the result as a false positive of MRI in spite of the obvious coronary disease. The sensitivity (86.5%) and the negative predictive value (90.5%) of MRI was significantly higher ($P < 0.0001$) than that of the scintigraphy (66.5% and 79.1% respectively). However, the specificity and positive predictive value of the tests did not present a significant difference.

MRI is currently little used in France in the diagnosis of coronary disease and myocardial ischemia. The main reasons for this underuse are the mediocre position of our country in terms of the number of machines but, even more so, the parsimonious use of French MRI machines in the exploration of the heart. Finally, too few radiologists or cardiologists are invested in this field. The remuneration of stress MRI when compared with that of nuclear medicine procedures may also be mentioned.

Post-infarction

MRI is an examination that is increasingly requested after myocardial infarction (often towards D2 for practical

reasons, at the risk of mildly overestimating the volume of necrosis), whether revascularization was or was not carried out [6]. The main purpose of this examination is to assess the residual viability of the myocardium. CINE sequences (whether or not associated with a stress inotropic agent by dobutamine) and late enhancement allow for an optimum study of the myocardial viability (segmental and transmural extension) and guide the care. In this context, the semiology provided by first pass perfusion sequences is important. In fact, these sequences provide information about the microvascularization of the myocardium that is not analyzable by coronagraphy (or coronary CT-scan), examinations limited to the study of the epicardial arterial trunks.

Delayed subendocardial perfusion may be observed that does not persist at the late time. In this case, we speak of "slow flow".

At a more severe stage, this perfusion anomaly that is visible in first pass perfusion persists and remains distinctly visible in the late enhancement sequences. This pattern defines "no-reflow" when there has been revascularization, or microvascular damage in the contrary case (infarction seen late). The impaired segments are not viable and this situation announces ventricular remodeling (Fig. 3).

The no-reflow is a major prognostic element whose search may justify the systematic use of MRI in post-infarction [7]. The perfusion sequence may also identify an intracavity thrombus that is difficult to diagnose by sonography, requiring anticoagulation (Fig. 4). The first pass diagnosis is confirmed at the late times, in particular in the phase-sensitive inversion recovery sequences.

Non-ischemic cardiomyopathy

Hypertrophic cardiomyopathy

The first pass perfusion sequence may reveal a delay in subendocardial perfusion at the hypertrophic zones. This anomaly is correlated with functional angina pectoris, which may be observed in this context (Fig. 5).

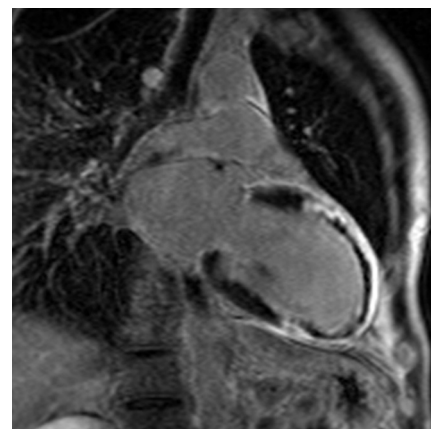


Figure 3. Cardiac slice in the vertical long axis plane. Late enhancement sequence revealing extensive anterior infarction with a no-reflow phenomenon. The perfusion anomaly was visible as of the first pass and remains visible at late time, attesting to a microvascularization anomaly and a poor prognosis.

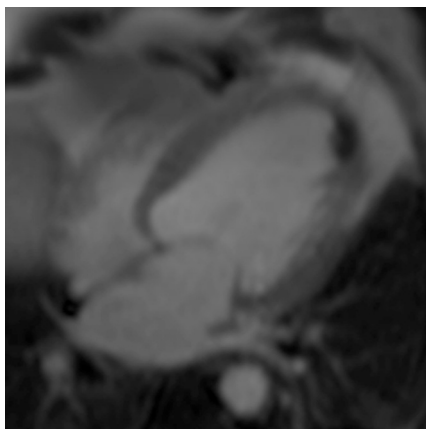


Figure 4. Demonstration as of the first pass perfusion sequence (4-chamber view) of a small thrombus lining the bottom of inferior lateral infarction. This diagnosis will be confirmed by sequences with late enhancement, in particular the PSIR sequence.

MRI is often requested after the detection of hypertrophy by cardiac sonography to eliminate amyloidosis [8,9]. In this case, we observe modifications in the first pass enhancement kinetics of the myocardium, shortening of the inversion time TI and late diffuse enhancement affecting both the ventricle walls and the atrial or septal walls.

Myopericarditis

MRI is currently the reference technique for the diagnosis of myopericarditis [10]. The first pass and late enhancement sequences are necessary for the diagnosis. The perfusion sequence may reveal enhancement of the layers of the pericardium and subepicardial hyperhemia (Fig. 6). This epicardial hypersignal of inflammatory origin, most often apico-lateral, may give rise to errors in interpretation. In fact, the normal signal of the subendocardial topography may be erroneously considered to be a hyposignal of ischemic origin. In this context of thoracic pain with electric anomalies and increase in troponine, imaging of the coronaries is most often carried out (coronagraphy or coronary CT-scan). The absence of coronary artery disease and linear

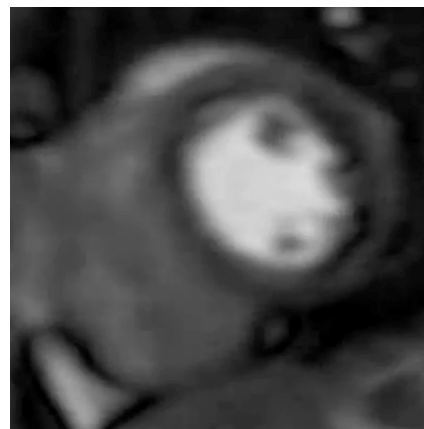


Figure 6. Image extracted from a first pass perfusion sequence in a young patient suffering from acute myopericarditis (healthy coronaries). Note the lateral and, to a lesser degree, anterior hyperhemia on the epicardial side that may be mistaken for an image of subendocardial ischemia.

or nodular, subepicardial late enhancement helps confirm the diagnosis of myopericarditis and set up adapted surveillance.

Angeitis

Cardiac impairment is possible within a context of anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis, such as Churg-Strauss disease [11] or Wegener's granulomatosis [12]. Suspicion of cardiac impairment in this context should lead to an exploration by MRI. The analysis of the first pass perfusion may be pathological, revealing focal perfusion anomalies without vascular systematization.

The same type of anomaly may be observed in thrombotic thrombocytopenic purpura and MRI may be more efficient than scintigraphy in this context [13].

Congenital heart disease

Analysis of the first pass perfusion directed toward a suspected anomaly may be of use in this context. For example,

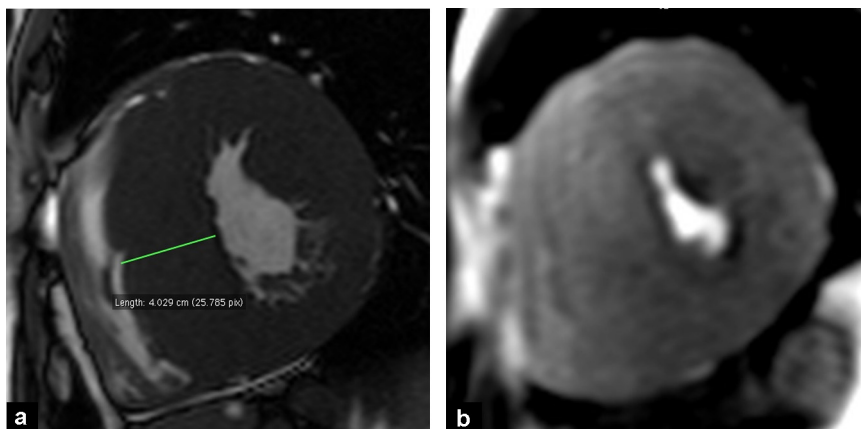


Figure 5. Severe hypertrophic cardiomyopathy. Imaging in the short axis of the heart. a: balanced FFE sequence revealing the pathological thickness of the myocardium in diastole; b: slice extracted from a perfusion sequence showing the delayed subendocardial perfusion that is habitual in this disease.

one or several slices will be placed in 4-chamber view to demonstrate a shunt.

Alternatives

3T

In spite of the theoretical advantages, the 3T field has still not demonstrated its superiority over the 1.5T in the analysis of myocardial perfusion [14]. It should be noted that, in certain recent studies, first pass perfusion quantification techniques have been proposed with assessment of the input function [15].

Arterial Spin Labeling (ASL)

In the small animal, the myocardial perfusion cannot be analyzed by the perfusion of gadolinium due to the high heart rate. However, the analysis of perfusion is of prime importance in cardiovascular pharmacology to analyze the effect of new treatments. Among the strategies developed, measurement of the T1 relaxation time by arterial spin labeling seems to be highly efficient [16]. Briefly, the principle is to obtain two T1 mappings, one with global saturation, the other with a selective saturation. The difference between the two relaxation curves represents the myocardial perfusion (Fig. 7). The ability to quantify the myocardial perfusion is of great value in diffuse myocardial disease, such as that observed with hypertension or diabetes.

In short, can we do without the analysis of myocardial perfusion?

No, analysis of myocardial perfusion is a basic element in cardiac exploration by MRI. It is the key sequence of MRI under vasodilator stress, in the search for myocardial ischemia, an examination that takes into account recent knowledge and should develop considerably. The new

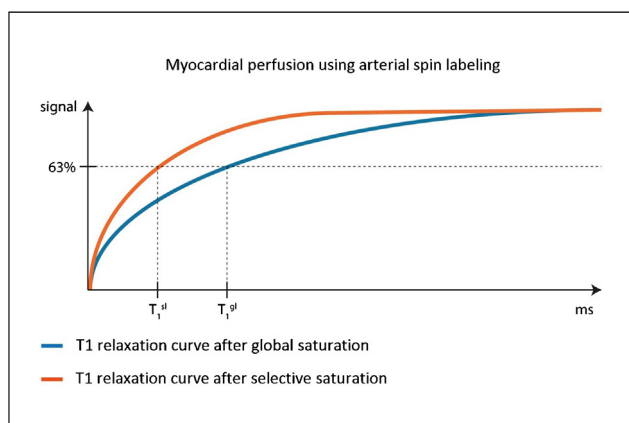


Figure 7. Diagram illustrating the principle of arterial spin labeling to measure myocardial perfusion in the small animal. Two T1 relaxation curves are obtained, one after global saturation, the other after selective saturation. The myocardial perfusion is determined from these two curves.

techniques aim at the relative or absolute quantification of myocardial perfusion.

TAKE-HOME MESSAGES

- Any cardiac MRI examination should include rest perfusion.
- The analysis of perfusion under vasodilator stress by MRI is an alternative to scintigraphy.
- Rest-stress perfusion should always be compared with the clinical data and the results of other sequences: in particular global and segmental kinetics, edema, late enhancement.
- The main indication for myocardial perfusion MRI is the search for arguments indicating a coronary disease. If the examination is positive, the planning of the treatment depends on its results.

Clinical case

This 74-year-old man was referred to cardiology for an assessment of rapidly progressing dyspnea, associated with a distinct change in his general condition. He has a past history of stroke and renal infarction. The transthoracic sonography of the heart reveals diffuse hypertrophy and an alteration in the left ventricular ejection fraction.

Cardiac MRI is carried out in cardiac synchronization before and after the injection of contrast product. The LVEF in MRI is low at 35%, and the myocardial mass has increased to 137 g/m². A global alteration in the bi-ventricular kinetics is noted (Fig. 8).

Questions

1. What is your diagnostic hypothesis in this clinical context?
2. What is the best MRI sequence in this disease?
3. Describe the perfusion imaging anomalies in this patient. Do they suggest the diagnosis proposed in Question 1?

Answers

1. Global hypokinetic hypertrophy in this age group should suggest cardiac amyloidosis, a disorder in which MRI is often very efficient.
2. The key sequences are the T1 scouting that often reveals a shortening of the myocardial inversion time and late enhancement that is positive, very distinct, without vascular systematization, with subendocardial predominance. This late enhancement is specific in that it not only reaches the left ventricular myocardium but also the right ventricle, the atria and the interatrial septum.
3. In this context, the first pass perfusion imaging is often helpful, demonstrating, as in this patient, a non-systematized subendocardial hyposignal (c). The diagnosis strongly indicated by the MRI was confirmed by the biopsy.

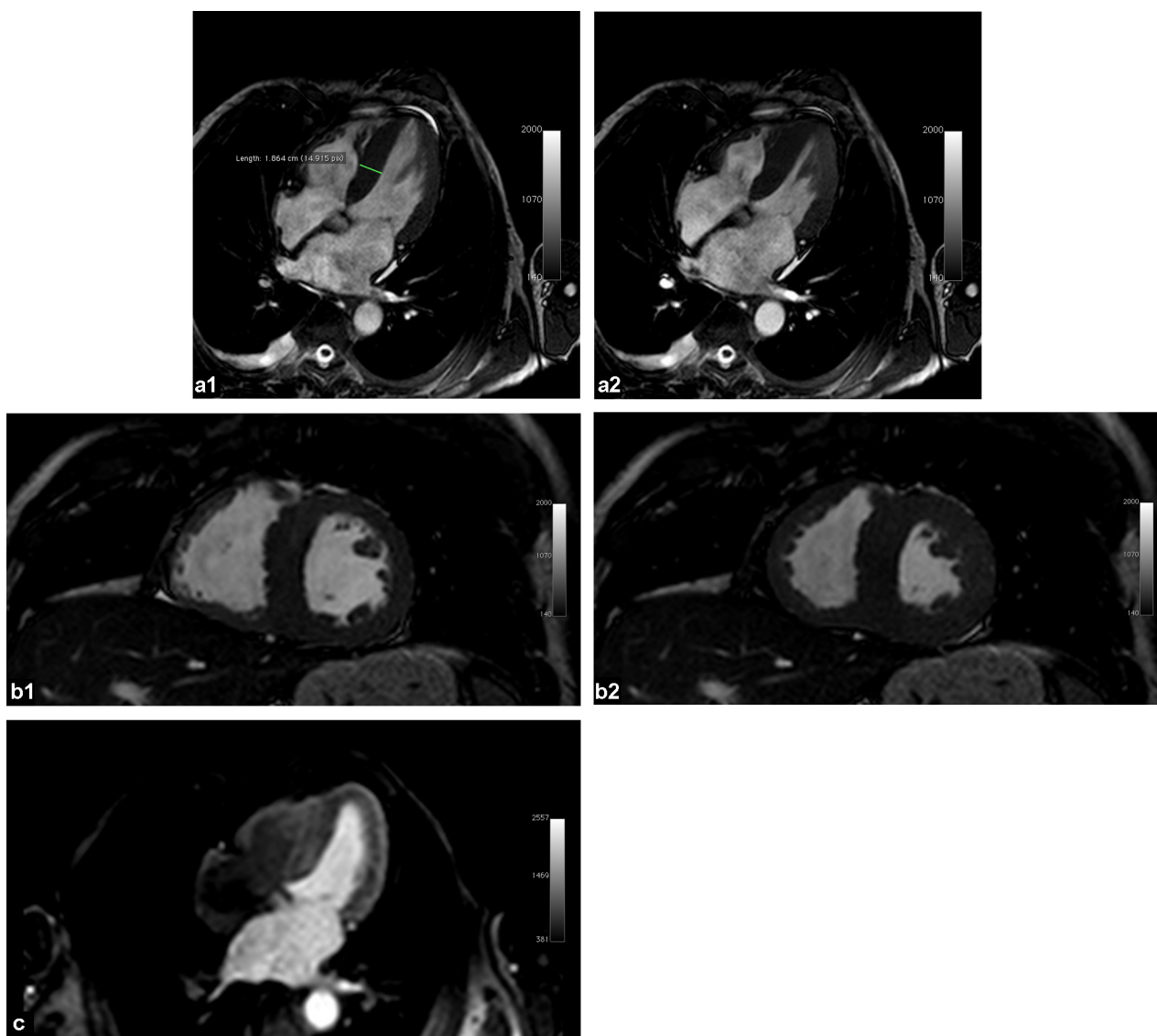


Figure 8. Cardiac MRI before and after the injection of contrast product. a: 4-chamber view at diastole (a1) and systole (a2); b: short axis view at diastole (b1) and systole (b2); c: first pass perfusion in the 4-chamber view.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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