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Clinical implications of cardiac magnetic resonance imaging fibrosis

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Cardiac magnetic resonance (CMR) is a non-invasive imaging method that allows to characterize myocardial tissue. In particular, using the late gadolinium enhancement technique, it is possible to identify areas of focal fibrosis. Specific distribution patterns of this fibrosis allow us to distinguish ischaemic cardiomyopathy (iCMP) from non-ischaemic cardiomyopathy (nCMP) and sometimes to identify the aetiology of the latter. Diffuse fibrosis can also be identified using the parametric T1 mapping sequences. For this purpose, the native T1 of the tissue is measured before the administration of the contrast agent (c.a.) or the extracellular volume is calculated after c.a. Both focal and diffuse fibrosis evaluated with CMR appear to be strong prognostic predictors for the identification of threatening ventricular arrhythmias and sudden cardiac death. These evidence open the doors to a possible role of CMR in the selection of the patient to be sent to a defibrillator implant in primary prevention. In this review, we will briefly review the techniques used in CMR for the evaluation of fibrosis. We will then focus on the clinical role of myocardial tissue fibrosis detection in iCMP and nCMP.

Introduction

Cardiac magnetic resonance (CMR) is the gold standard non-invasive imaging technique for evaluating myocardial tissue. Indeed, CMR allows not only the quantification of biventricular volumes, mass, systolic and diastolic function, and intra- and extra-cardiac flows but also the identification of oedema, fibrosis, or accumulation of intra- and extracellular substances (such as iron, fat, or amyloid fibrils) allowing to obtain a large amount of information for the diagnosis and prognostic stratification of the patient with alterations in the myocardium.[1]

The different characteristics of the tissues in CMR are explored based on the signals emitted in response to radio frequency pulses. In particular, time T1 (or longitudinal relaxation time or spin-lattice time) represents the time necessary for the protons to rebalance the spins with respect to the surrounding molecules. Time T2 (or spin-spin time) is determined by how quickly the signal decays due to the loss of spin precession synchronism. Through the use of specific sequences, the tissue differences related to the T2 or T1 time differences can be enhanced. Through the use of T2 weighted images, for example, a high signal is obtained from tissues rich in water. In this way, it is possible to highlight the presence of tissue oedema. On the contrary, in the T1 weighted images, the signal from the water is low and the signal from the grease and paramagnetic substances is high. This last property is used to obtain images of tissue fibrosis with sequences acquired late after injection of a contrast medium based on gadolinium chelates (late gadolinium enhancement, 'LGE').

Gadolinium is a paramagnetic metal capable of significantly reducing the T1 time, consequently increasing the T1 signal in the tissue in a manner directly proportional to its concentration. Contrast agents (c.a.s) based on

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gadolinium chelates are very safe with a very low incidence of severe adverse events (<1 in 100 000). These are extracellular contrast media that do not cross the membranes of healthy myocytes, accumulate in areas where normal myocardial tissue is replaced by dense collagen matrix, and are slowly eliminated relative to the surrounding healthy tissue.[2]

In particular, before obtaining LGE sequences (acquired about 10–15 min after the administration of a Gd-based c.a. bolus), an inversion recovery sequence is performed with an inversion time set in such a way to cancel the signal of healthy myocardial tissue, which appears hypointense, i.e. dark. The gadolinium-rich fibrotic tissue will appear hyperintense.[2]

Due to their characteristics, the LGE sequences allow us to evaluate the presence of focal fibrous areas. On the contrary, the presence of diffuse fibrosis is studied in CMR with the parametric T1 mapping technique that allows us to obtain a point quantification of myocardial T1 values on the basis of the signal intensity of the single pixel. T1 mapping images are generated from multiple T1-weighted images acquired at different moments of the longitudinal relaxation time. Specifically, native T1 images are acquired without c.a. and can, therefore, also be used in patients with severe renal insufficiency; they allow the identification of focal and diffuse fibrosis on the basis of a high value of T1 in the tissue.[3] The T1 mapping images about 15 min after the contrast injection are instead used, concomitantly with the native T1 sequences, to obtain the non-invasive quantification of the extracellular volume (ECV) increased in the presence of focal and diffuse tissue fibrosis.[4]

In this brief review, we will examine the role of LGE and T1 mapping sequences in the identification of focal and diffuse myocardial fibrosis for diagnostic purposes and for prognostic stratification of the patient with iCMP and nCMP.

Ischaemic cardiomyopathy

Cardiac magnetic resonance has become an excellent non-invasive tool for patient assessment after acute myocardial infarction (AMI). Acute myocardial infarction is characterized by a subendocardial distribution of the LGE (myocardial region furthest from the epicardial coronaries), which can become transmural if the occlusion of the vessel is long-lasting. This pattern, typical of iCMP is different from that observed in nCMP forms in which the endocardium is often spared. In addition, in patients who come to observation for chest pain and elevation of markers of myocardial necrosis, MRI can distinguish AMI from myocarditis or stress cardiomyopathy.

After an AMI, the post-contrast hyperintensity of the signal must be assessed with caution because it is partially due to myocardial oedema, vasodilation, and cell necrosis with the possibility of significant reduction of the LGE area in the chronic phase (over 3–4 months) in which its extension definitively represents tissue fibrosis.[5,6] Other predictors, in particular the presence of microvascular obstruction, however, make CMR in the first week after a heart attack an excellent prognostic tool.[7]

In the chronic post-infarct phase, CMR is used clinically to identify viability for predicting recovery of left ventricular function after revascularization. Kim *et al*. demonstrated the ability of the transmural extension of the LGE to predict the recovery of the function of hypokinetic segments after revascularization. An LGE with transmurality <25% predicts recovery of function of about 80% of the myocardial segments. On the contrary, only 8% of the segments with transmurality >50% show an increase in post-angioplasty contractility.[8]

Myocardial fibrosis in the iCMP patient identified with LGE is a strong predictor of ventricular arrhythmias and sudden cardiac death (SCD). Thanks to the more accurate measurement of the ejection fraction of the left ventricle (LVEF) and the identification of the LGE, the RMC could allow us to better identify subjects at risk than using echocardiography alone.[9]

Pre- and post-contrast T1 mapping sequences also have great potential in evaluating iCMP. In fact, even if the research on T1 mapping has mainly focused on nCMP, the first T1 mapping images were created precisely for the characterization of myocardial infarction. In addition, in myocardial infarction, the ECV has a greater sensitivity than LGE and has a predictive role in mortality and adverse cardiac events.[10] However, future studies are needed to better understand the role of T1 mapping in iCMP patients.

Non-ischaemic cardiomyopathy

Non-ischaemic cardiomyopathy represents a heterogeneous group of myocardial diseases. However, myocardial tissue replacement with focal and diffuse fibrosis is common in all of these forms and is an important prognostic predictor of ventricular arrhythmias and SCD.[11]

In hypertrophic cardiomyopathy (HCM), LGE mainly affects the hypertrophic segments and has a commonly patchy or intramyocardial pattern of distribution. In particular, the extension of the LGE involving >15% of the myocardial mass was associated with a double risk of SCD.[12] Based on these data, the American College of Cardiology/American Heart Association recommends the assessment of LGE extension as an additional parameter in patients with HCM who are candidates for implantation of an implantable cardiac defibrillator (ICD) in which it is not possible to classify patients based on clinical, electrocardiographic, and echocardiographic parameters.[13] Furthermore, according to recent evidence, T1 mapping sequences for ECV measurement should always be acquired in patients with HCM because they appear to have an additional prognostic role compared with classic LGE sequences.[14]

In idiopathic dilated cardiomyopathy (DCM), even small areas of LGE significantly increase the risk of events with a prognosis that worsens as its extension increases. In subjects with DCM, LGE is often found in the interventricular septum with intramyocardial involvement. When this is associated with LGE at the lateral wall, the patient's risk of SCD is further increased.[15]

In addition, both native T1 and ECV proved to be important prognostic predictors in subjects with DCM. Puntmann *et al*.[16] enrolled 637 patients with DCM demonstrating that native T1, ECV, and the extension of the LGE are predictors of all causes of mortality and the composite end-point of mortality from heart failure and hospitalization. Despite the advances of CMR in predicting the risk of ventricular arrhythmias and SCD in subjects with DCM, an LVEF measured with echocardiography ≤35% continues to represent, according to the recommendations of the European Society of Cardiology, the fundamental criterion for implantation of an ICD.[17] However, the Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure trial (DANISH trial)[18] has shown that this criterion is ineffective in the prognostic stratification of these patients. The implantation of an ICD in primary prevention in subjects with DCM is in fact not associated with a reduction in the total mortality of these patients despite a reduction in the risk of SCD.[18] Moreover, it is known that most of the out-of-hospital cardiac arrests occur in patients with an LVEF >35%. Stecker *et al*. extrapolated all cases of SCD from the Oregon Sudden Unexpected Death study and retrospectively assessed LVEF among subjects undergoing cardiac function assessment prior to SCD. Two-thirds of these subjects did not meet the criteria for the implantation of an ICD.[19] In a large multicenter registry, the CarDiac magnEtic Resonance for prophylactic Implantable-cardioVerter defibrillAtor ThErapy in Non-Ischaemic dilated CardioMyopathy (DERIVATE) study,[20] a large number of clinical and MRI variables were evaluated for the prediction of major arrhythmic events in patients with non-ischaemic DCM. The study included over 1500 patients followed up with a follow-up of over 2 years. The multivariate analysis resulted in independent predictors of all causes of mortality, the age of the patient and the presence of 'midwall' fibrosis on CMR. An indexed end-diastolic volume (iLVEDV) >120.5 mL/m^2 measured with RMC and the presence of more than three segments with LGE 'midwall' were instead predictors of MACCE. From these data, a score was created that includes LVEDVi variables >120.5 mL/m^2, male sex, and the presence of LGE midwall in more than three segments. This score made it possible to reclassify about one-third of patients who meet the current criteria for ICD implantation in nCMP in subjects at low risk of MACCE. On the contrary, in 5% of patients with LVEF>35% on echocardiography, in which according to the current criteria an ICD is not indicated, MACCEs occurred.

Conclusion

Cardiac magnetic resonance is a technique that, in addition to providing an accurate morphofunctional evaluation of the heart chambers, allows us to characterize the myocardial tissue in a non-invasive way. In particular, the evaluation of focal and diffuse myocardial fibrosis with the techniques of LGE and T1 mapping appears of particular importance. In fact, in both iCMP and different forms of nCMP, the detection of myocardial fibrosis is an important prognostic parameter, especially due to its association with major ventricular arrhythmias and SCD. This information, even if not yet implemented in the guidelines, appears of considerable interest in the patient candidate to receive an ICD in primary prevention. In fact, the current criteria appear largely inefficient for identifying the patient at risk, especially in the patient with nCMP. The data from the DERIVATE[20] study, an international multicenter registry, confirm how the identification of fibrosis with RMC could significantly improve the process of selecting the patient who can benefit most from an ICD. Future randomized trials that include RMC are the natural next step before a possible modification of the international guidelines for ICD implantation.

Conflict of interest: None declared.

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