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Editorial

Why do we need metabolic information in cardiovascular diseases?

¿Por qué necesitamos la información metabólica en las enfermedades cardiovasculares?

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Over the past 2 decades, cardiac magnetic resonance imaging (CMR) has become consolidated as the criterion standard for evaluating myocardial injury in patients with ischemic heart disease,[1–3] nonischemic cardiomyopathy,[4] and aortic disease. CMR allows anatomical and functional assessment of both ventricles, the heart valves, and the aorta without anatomical limitations or exposure to ionizing radiation. However, the extensive use of this technique is mainly due to its excellent capacity for in vivo tissue characterization. Several studies have shown that delayed gadolinium uptake enables precise assessment of myocardial fibrosis in both ischemic and nonischemic cardiomyopathies, and is a prognostic marker of adverse events during follow-up.[2,5] In addition, the development of T_1 and T_2 mapping has allowed detection of fibrosis and diffuse inflammation, thus facilitating early subclinical diagnosis of affected areas in various cardiomyopathies. CMR mapping allows differentiation between several constituents that can affect myocardial tissue (fat, iron, fibrosis, edema, and amyloid), thereby assisting in the diagnosis of diverse cardiomyopathies and in determining the physiological mechanism of myocardial injury. In this line, it is known that in patients with left ventricular hypertrophy, a low T_1 is associated with Fabry disease and a very high T_1 with amyloid infiltration.[6] Furthermore, patients with light chain (AL) amyloidosis are known to have more severe myocardial inflammation than those with transthyretin amyloidosis because the native T_2 (which determines the presence of myocardial edema) is higher in AL patients. This may also explain their worse prognosis despite smaller degrees of infiltration.[7] All this information is valuable, as an early diagnosis enables prompt establishment of the optimal therapeutic approach, which can lead to increased survival.[8–10] In addition, detection of subtle ultrastructural changes can herald a good response to treatment. For example, T_2^* normalization is associated with a favorable treatment response in patients with hemochromatosis,[11] and a decrease in native T_1 is associated with a good response to tafamidis treatment in amyloidosis patients.[12,13] There are, however, certain limitations to CMR mapping, as the values obtained depend on the sequences used, the magnetic field of the MR magnet, and the acquisition protocol. Thus, large-scale prognostic and multicenter studies that demonstrate its usefulness in daily clinical practice are still lacking.

This growing interest in achieving a prompt diagnosis of cardiovascular disease and the development of new therapeutic strategies in recent years has stimulated the study of inflammation affecting the myocardium, pericardium, cardiac valves, and vascular structures. In patients with ischemic heart disease, the size and transmurality of myocardial necrosis are the main predictors of cardiovascular events and left ventricular remodeling.[2] However, remote myocardial inflammation also plays a key role in ventricular remodeling,[14] and prompt identification of patients requiring closer follow-up and more intensive treatment would be of great value. Furthermore, myocardial necrosis transmurality is overestimated in the acute phase of infarction due to myocardial edema,[1] and for this reason 47% of segments with transmurality around 50% of wall thickness show improved contractility (viable myocardium) over follow-up. Therefore, early identification of viable myocardium or remote myocardial inflammation has prognostic implications.

In patients with nonischemic cardiomyopathies, myocardial inflammation is associated with dilated cardiomyopathy, heart failure, and sudden death. Viruses are the main cause of myocarditis and inflammatory cardiomyopathy, and these pathogens can induce an immune response that causes inflammation even after they have disappeared. Other agents, such as certain drugs, toxic substances, and autoimmune disorders[15] can also lead to myocarditis. When persistent myocardial inflammation is identified in patients with chronic heart failure (>3 months) and no evidence of significant coronary disease, medical treatment can be individualized, such as administration of beta interferon, corticosteroids, immunosuppressant agents, or conventional heart failure therapy,[15] all of which can considerably improve the disease course. Nonetheless, despite the advances in CMR for assessing myocardial inflammation, its performance is still limited compared with that of endomyocardial biopsy for the diagnosis of myocarditis in the chronic phase: diagnostic accuracy is 45% for a native T_1 increase and 72% for a native T_2 increase.[16] Likewise, in patients with cardiac sarcoidosis, it is important to differentiate between residual fibrosis, which does not require immunosuppressant/antiinflammatory treatment and active inflammation, for which it is needed. Both entities are visualized as foci of delayed gadolinium enhancement on CMR.[4]

Valvular inflammation is associated with more rapid progression of aortic stenosis[17] and with intrinsic degeneration of a biological prosthesis.[18] In patients with suspected infective endocarditis, analysis of metabolic activity by positron emission tomography (PET) combined with computed tomography (CT) allows reclassification of 90% of patients and provides a conclusive

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diagnosis (definite/ruled out) in 95% of cases.[19] Similarly, there is evidence of an arterial inflammatory state in early stages of atherosclerosis.[20] Therefore, identification of arterial plaques with inflammatory activity would enable prompt diagnosis of lesions with a greater probability to progress and a potential to produce cardiovascular events at follow-up.

In response to these situations, the last decade has witnessed the development of hybrid CMR and PET image fusion systems (PET/MR) with the aim of combining the information on tissue characterization provided by CMR and the metabolic data provided by PET. PET/MR involves less radiation exposure than PET/CT and it enables measurement of myocardial flow in stress testing. This technology is quite new, and the first related expert position paper was published only a short time ago.[21] The development of cardiac PET/MR was made possible by the availability of motion correction algorithms, attenuation correction, optimized myocardial PET signal uptake, and standardized examination protocols.[21]

In a recent article published in *Revista Española de Cardiología,* Barrio et al.[22] investigated the added value of PET/MR over CMR and PET performed separately in the assessment of various cardiovascular diseases. The study included 30 patients with chronic ischemic heart disease to evaluate myocardial viability and 19 patients with noncoronary heart disease (infiltrative cardiomyopathy, pericarditis, cardiac tumors, infective endocarditis, and myocarditis). Patients were examined on a 3T CMR system, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) radiotracer was used for PET. Patients with electronic devices, claustrophobia, or pregnancy, and those with a persistent glucose concentration $>$ 200 mg/dL despite correct preparation were excluded, as these factors can alter radiotracer distribution and affect the results. Among the patients included, 82% were men and the mean age was 57 years; 87.8% of the studies were amenable to interpretation. The final study population (after exclusion of patients with noninterpretable studies or nonrecoverable images) included 19 coronary and 18 noncoronary patients.

In the assessment of ischemic heart disease, the authors performed analyses by segment and by patient. In the patient-by-patient assessment, separate CMR and PET analyses enabled determination of myocardial viability in 57.9% of cases and hybrid PET/MR was useful in 42.1% of cases. PET/MR fusion led to correct reclassification of 87.5% of patients with inconclusive findings on CMR or PET. In their article, the authors discuss the limitations of these findings, such as the absence of follow-up data to ensure normalization of contractility. In addition, the patient's viable or nonviable status was based on the total of segments; that is, taking into account that segments with different degrees of necrosis transmurality and therefore, different degrees of viability, could be present in the same patient.

As to nonischemic heart diseases, PET/MR was useful in 88.9% of the cases. In infective endocarditis (6 patients), CMR imaging alone was inconclusive in all cases, and PET/MR fusion was required to reach a correct diagnosis in 5 of the 6 patients. The main advantage of CMR in this population was that ventricular and valvular function could be assessed in the same study. Now it remains to be seen whether PET/MR can provide better diagnostic performance than PET/CT in this condition, which has been well demonstrated in several publications[19] and included in clinical practice guidelines. In cardiac tumors, PET/MR yielded diagnostic information on their distribution, extension, degree of infiltration, and metabolism (malignancy) in all cases. Lastly, in cardiomyopathy and myocarditis, PET/MR was helpful for determining inflammatory activity and guiding biopsies.

The study by Barrio et al.,[22] used a concordance analysis to assess the usefulness of combined PET/MR over that of PET or CMR alone in each patient subgroup (coronary and noncoronary), with excellent results ($\kappa = 0.913$). Furthermore, among cases with a diagnostic confirmation over clinical follow-up (10 coronary and 16 noncoronary), the diagnostic accuracy of PET/MR was 80% and 87.5%, respectively.

The study be Barrio et al.,[22] a pioneer effort from a clinical perspective, shows that cardiac PET/MR studies are feasible and amenable to interpretation in most cases (87.5%). Furthermore in patients with inconclusive diagnoses based on information from CMR or PET alone, 85% can receive definite diagnoses with the use of PET/MR. This study provides interesting data on a promising technique that yields anatomic information, functional data, tissue characterization, and metabolic information in the same examination. We are, however, at the dawning of this technique, and prospective studies are needed to validate its prognostic value and determine its potential superiority over PET/CT, a standardized technique that is more consolidated and more widely used.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest related to this article.

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