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REVIEW

Imaging of myocarditis and inflammatory cardiomyopathies

Imagerie de la myocardite et des cardiomyopathies inflammatoires

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Summary Myocarditis encompasses a wide range of myocardial inflammatory diseases, including acute myocarditis, chronic myocarditis and inflammatory cardiomyopathies, and myocardial inflammation associated with other cardiomyopathies. Because of this heterogeneity in clinical presentation, and the infrequent use of endomyocardial biopsy, cardiac imaging has gradually acquired a key role in the non-invasive detection of myocardial inflammation, the assessment of aetiology and the management of specific therapies. This article summarizes the issue of myocarditis and myocardial inflammation in clinical practice, and reviews the role of different non-invasive imaging techniques in the exploration of myocardial inflammation.

Abbreviations: 18F-FDG, 18F-fluorodeoxyglucose; CMR, cardiac magnetic resonance imaging; CT, computed tomography; ECV, extracellular volume; EGE, early gadolinium enhancement; EMB, endomyocardial biopsy; LGE, late gadolinium enhancement; MRI, magnetic resonance imaging; PET, positron emission tomography; TTE, transthoracic echocardiography.

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Tomographie par émission de positons

Résumé Les myocardites regroupent un vaste ensemble de maladies inflammatoires du myocarde comprenant la myocardite aiguë, la myocardite chronique et les cardiomyopathies inflammatoires, et l'inflammation du myocarde associée à d'autres cardiomyopathies. En raison de l'hétérogénéité des présentations cliniques et du faible recours à la biopsie endomyocardique, l'imagerie cardiaque a progressivement pris un rôle essentiel dans la détection non invasive de l'inflammation myocardique, l'évaluation des étiologies et la gestion des traitements spécifiques. Cet article résume la question de la myocardite et de l'inflammation du myocarde en pratique clinique et examine le rôle des différentes techniques d'imagerie non invasives dans l'exploration de l'inflammation du myocarde.

Background

Myocarditis is defined as an inflammatory disease of the myocardium, diagnosed by established histological, immunological and immunohistochemical criteria [1]. The clinical spectrum of myocarditis is wide, and includes acute myocarditis, chronic myocarditis and inflammatory cardiomyopathies, and myocardial inflammation associated with other cardiomyopathies. Because of this heterogeneity in clinical presentation, and the infrequent use of endomyocardial biopsy (EMB) — the gold-standard diagnostic tool — the actual incidence of myocarditis is difficult to determine, ranging from 2% to 42% in autopsic series of cases of sudden death in young people [2], and from 9% to 16% in EMB series of cases of unexplained dilated cardiomyopathy in adults [3,4].

Aetiologies

Acute myocarditis is characterized histologically by the classical Dallas criteria as evidence of inflammatory infiltrates within the myocardium, associated with myocyte degeneration and necrosis of non-ischaemic origin [5]. The most common causes are infections — mainly of viral origin — infection-negative lymphocytic myocarditis, eosinophilic myocarditis, caused by systemic hypereosinophilic syndromes or drug-induced hypersensitivity reactions, and giant-cell myocarditis [6]. Immune checkpoint inhibitor therapy in cancer patients has emerged recently as a rare cause of acute myocarditis, with a high fatality rate [7]. Myocarditis can also occur in systemic immune-mediated diseases [8].

Myocardial inflammation can be present as a more focal disease, by inflammatory sites, with chronic evolution, as is typically the case in cardiac sarcoidosis. Cardiac manifestations of sarcoidosis contribute to a major part of the disease's morbimortality [9]. Recently, it has been suggested that some cases pf sarcoidosis may present as exclusive involvement of the heart [10]. Cardiac sarcoidosis can be asymptomatic [11]. Reliable assessment of cardiac involvement is therefore mandatory, given the major prognostic impact and potential morbidity of immunosuppressive treatment. The prevalence of cardiac sarcoidosis is difficult to establish because of the absence of symptoms in some patients. Clinical prevalence is about 5% [12], but autopsic series have found cardiac involvement in 20—25% of patients with sarcoidosis [12—16]. As many as 25% of patients with cardiac sarcoidosis may have an isolated cardiac localization, without other organ involvement [10]. In addition, cardiac involvement may vary according to geographical location; it has been found to account for > 50% of sarcoidosis-related deaths in Japan [14,15].

Finally, myocardial inflammation can be associated with other causes of cardiomyopathies. Cardiac inflammation and viral presence have been reported in 39% and 74% of patients with genetic or familial dilated cardiomyopathy, respectively, and are associated with adverse outcome [17]. Myocardial inflammation has been reported as one of the pathophysiological processes explaining the presence of intramyocardial fibrosis in the advanced forms of Fabry disease [18]. Subclinical myocardial inflammation is common in systemic sclerosis, and leads to focal and diffuse myocardial fibrosis [19]. Patients with arrhythmogenic cardiomyopathy can present with associated myocarditis of viral or autoimmune origin [20,21]. Myocarditis and sarcoidosis can even mimic the arrhythmogenic right ventricular cardiomyopathy phenotype in genotype-negative patients, in so-called phenocopies [22,23]; therefore, making an accurate diagnosis has important therapeutic consequences.

Pathogenesis

Usually, acute myocarditis resolves in about 50% of cases, but some patients can develop chronic myocarditis, even after an unnoticed acute phase. Chronic myocarditis is caused by either microbial agent persistence and/or development of pathogenic cardiac autoantibodies, with ongoing myocardial inflammation, destruction and remodelling, and can evolve towards a myocarditis-induced cardiac dysfunction, called inflammatory cardiomyopathy [24]. In these presentations, the classical histological Dallas criteria are not always met and lack sensitivity, and myocarditis is better defined by immunological and immunohistochemical criteria [24,25].

Cardiac sarcoidosis is a particular cause of chronic inflammatory cardiomyopathy, often presenting with a dilated left ventricle and new ventricular arrhythmias, high-degree heart block or lack of response to usual care in 1—2 weeks [6,26]. The pathological hallmark of sarcoidosis is the presence of epithelioid-cell rich granulomas without necrosis, which may affect all cardiac structures, but are generally located at the myocardium. After the initial inflammatory phase, the involution of granulomas leads to the development of myocardial tissue scarring [14]. The most frequent myocardial localization of granulomas is the left ventricular free wall, followed by the interventricular septum, which may be responsible for arrhythmic events or conduction disturbances, and therefore represents a potential trigger for sudden cardiac death. Clinical presentation of advanced cardiac sarcoidosis consists of cardiomyopathy with loss of function or tachyarrhythmias and bradyarrhythmias (palpitations, syncope and death).

Diagnostic approaches to myocardial inflammation, and their limitations

Clinical presentation and electrocardiography

Myocarditis affects individuals of all ages, although it is most frequent in the young. Clinical presentations are very heterogeneous, ranging from chest pain or palpitations associated with transient electrocardiogram changes to life-threatening cardiogenic shock and ventricular arrhythmia [24].

One of the most common clinical presentations of acute myocarditis is that of myocardial infarction with normal coronary arteries. Chest pain frequently starts within 1—4 weeks of a respiratory or gastrointestinal infection. The electrocardiogram shows ST-segment elevation or depression, or T wave inversions. In this context, coronary artery disease must be ruled out as a priority, and coronary angiography or computed tomography (CT) shows non-obstructive coronary arteries. In this infarct-like clinical presentation, acute myocarditis is frequently associated with a significant rise in serum troponin concentrations as a result of cardiomyocyte necrosis, with a time course similar to acute myocardial infarction.

Screening for cardiac sarcoidosis, with clinical evaluation and an electrocardiogram at least, should be performed systematically in patients with sarcoidosis. The presence of fragmented QRS or a bundle branch block pattern has been shown to be associated with cardiac involvement [27]. A third-degree atrioventricular block may appear in 23—30% of cases [28], and ventricular tachycardia in up to 23% of cases [29].

Biology

Increased concentrations of troponins are commonly seen in myocarditis, but normal concentrations do not exclude the diagnosis, particularly when there are specific causes, such as sarcoidosis. C-reactive protein concentration is often raised in myocarditis, but this does not confirm the diagnosis, as the concentration is often increased in acute pericarditis [24]. Serum cardiac autoantibodies, directed, for example, against beta-adrenergic receptors or sarcomeric proteins, have been described in patients with myocarditis [30], but, to date, no commercially available cardiac autoantibody tests have been validated against the results obtained in research laboratories [24].

Routine viral serology testing is not specific to a viral aetiology [31], and is not recommended in the management of acute myocarditis [24]. Hypereosinophilia and positivity for specific serum autoantibodies are indicative of hypereosinophilic syndrome-related and systemic immune-mediated myocarditis, respectively [8].

Endomyocardial biopsy

EMB remains the cornerstone of the diagnosis of myocarditis [24]; it is of particular interest in life-threatening clinical presentations, such as new-onset heart failure with haemodynamic compromise, ventricular arrhythmias, high-degree heart block or failure to respond to usual care [32], where a specific treatment, such as immunosuppressive therapy, has to be discussed (e.g., in case of infection-negative giant cell myocarditis or cardiac sarcoidosis) [24]. In general, immunosuppression should be started only after ruling out active infection on EMB by viral polymerase chain reaction [24].

Nonetheless, apart from in these particular situations, EMB is not performed systematically in general practice in the diagnostic work-up of myocarditis, as it is invasive, with a certain amount of complications [32], and because its diagnostic accuracy is not always optimal (e.g., in focal inflammatory processes, such as sarcoidosis) [25,26,33].

In suspected cardiac sarcoidosis, EMB fails to prove cardiac involvement in numerous cases, with a yield of about 20% [13,34], as granulomas have a patchy distribution.

Hence, imaging plays a crucial role in the non-invasive detection of myocardial inflammation, and for determining aetiologies and managing specific therapies. The contribution of cardiac imaging techniques to the management of myocarditis is under the scope of this review.

Transthoracic echocardiography

Transthoracic echocardiography (TTE) is a first-line test when myocarditis is suspected. Echocardiographic findings are not specific, but it is particularly useful in order to rule out differential diagnoses and stratify prognosis [24].

Differential diagnosis

When acute myocarditis is suspected, TTE can rule out differential diagnoses in the first instance, including myocardial infarction, but also aortic dissection, pericardial disease or valvular heart disease. The differential diagnosis is sometimes difficult, because the typical presentation of acute myocarditis, mimicking acute coronary syndrome, does not necessarily have wall motion abnormalities, and may therefore have the same echocardiography as myocardial inflammation.

In the chronic presentation of myocardial inflammation, the role of TTE in the differential diagnosis is quite challenging, as it does not always enable specific arguments to be made for cardiac sarcoidosis (which can mimic hypertrophic

cardiomyopathy or non-specific left ventricular dysfunction) or another inflammatory cardiomyopathy (which can mimic non-specific right or left ventricular dysfunction).

Morphological and functional abnormalities

However, when myocarditis is suspected, TTE is the most commonly used initial non-invasive imaging technique. Non-specific findings in infectious myocarditis include left ventricular global dysfunction, resulting in a decreased ejection fraction and/or regional dysfunction with left ventricular wall motion abnormalities. The left ventricle can be dilated, and increased ventricular wall thickness can also be observed because of myocardial oedema, and is particularly common in the fulminant form. Fulminant myocarditis usually presents with global left ventricular dysfunction and a non-dilated but thickened ventricle [35]. Intracardiac thrombi have also been reported. Left ventricular diastolic dysfunction is frequent and classical, but non-specific. Right ventricular involvement is possible. Pericardial effusion is common, defining myopericarditis. Finally, it has to be emphasized that a normal echocardiogram does not exclude the diagnosis.

Echocardiographic findings in cardiac sarcoidosis are also non-specific, ranging from normal cardiac function to dilated or restrictive cardiomyopathies. Left ventricular dysfunction can be global or regional, with regional wall motion abnormalities, usually not respecting coronary distribution. Because of oedema or infiltration, wall thickening can occur and simulate left ventricular hypertrophy. A bright aspect of the myocardium can be seen. Areas of wall thinning are also commonly observed, especially in the ventricular septum, probably as a result of scarring. A typical, but uncommon, finding is the thinning and akinesia of the basal septum, contrasting with normal contraction of the rest of the septal wall and the presence of ventricular aneurysm in the inferolateral wall [36]. Left atrial hypertrophy is difficult to detect, but can be present. Diastolic dysfunction is common. Pericardial effusion, mitral or tricuspid regurgitation and pulmonary hypertension can also be found. Tamponade and constrictive pericarditis are exceptional. The right ventricular dilatation and dysfunction at the end stage of the disease, as well as the predominance of basal septum abnormalities in terms of contractility, are important findings on echocardiography.

Other forms of chronic myocarditis and inflammatory cardiomyopathies may have multiple presentations, dilated or hypertrophied, with or without ventricular systolic dysfunction, making the TTE approach challenging because of its non-specificity.

Strain imaging

Strain imaging can be a useful diagnostic and prognostic tool in patients with suspected myocarditis. Global longitudinal strain is usually measured using speckle-tracking echocardiography, and is a more sensitive marker of systolic dysfunction than left ventricular ejection fraction. Strain imaging can also be used for right ventricular function evaluation, using strain of the lateral free wall. However, the use of strain imaging has been less validated for the evaluation of right ventricular function than for left ventricular function [37].

Strain is decreased in patients with acute myocarditis, and remains decreased in patients with persistent inflammation; it also correlates with lymphocytic infiltrates [38]. Strain imaging identifies remaining subtle left and right ventricular dysfunction in patients with a history of non-severe myocarditis and a normal left ventricular ejection fraction [39].

Strain imaging can also be used in cardiac sarcoidosis, especially for the detection of subtle systolic dysfunction in the early phase of the disease, when the standard variables remain normal [36].

Cardiac magnetic resonance imaging

Morphological and functional abnormalities

Cardiac magnetic resonance (CMR) imaging is an accurate tool for assessing left and right ventricular morphology and kinetics. CMR is prominent in right ventricular assessment, as it does not suffer from acoustic windows, and allows perfect plane acquisitions. CMR is useful in the measurement of left ventricular volumes and ejection fraction, as inter- and intraobserver reproducibilities are known to be limited to 5%. It is of special value for longitudinally following left ventricular healing and remodelling.

Pericardial effusion is a frequent finding in inflammatory cardiomyopathy; it can feature on echocardiography, but CMR detects even the smallest effusion, location and extent. Pericardial effusion appears bright on cine magnetic resonance imaging (MRI), and as hypoenhancement in dark-blood T1- or T2-weighted imaging. Furthermore, CMR may provide information about the pericardium itself, including not only the inner thickening, but also inflammation and fibrosis.

One major reason for performing CMR in the assessment of inflammatory cardiomyopathy is to provide insight into differential diagnoses, including arrhythmogenic right ventricular cardiomyopathy, and non-compaction, infiltrative and hypertrophic cardiomyopathy. Of note, during the acute and inflammatory phase, it is common to observe some thickened areas in the ventricular wall (myocarditis, sarcoidosis, as for acute myocardial infarction) — these are not to be overseen with hypertrophic cardiomyopathy. Careful reading of T2-weighted and late gadolinium enhancement (LGE) imaging helps to avoid such a misdiagnosis (Fig. 1).

Tissue characterization

To date, diagnosis of myocarditis is pragmatic, and is based on Lake Louise Criteria [40,41] when two out of three hallmarks for inflammation are met. Lake Louise Criteria include oedema by T2-weighted imaging, hyperaemia by early gadolinium enhancement (EGE) and necrosis/oedema by LGE.

Oedema (T2-weighted imaging)

Like most tissues, myocardium shows inner properties in terms of longitudinal (T1) and transverse (T2) relaxation

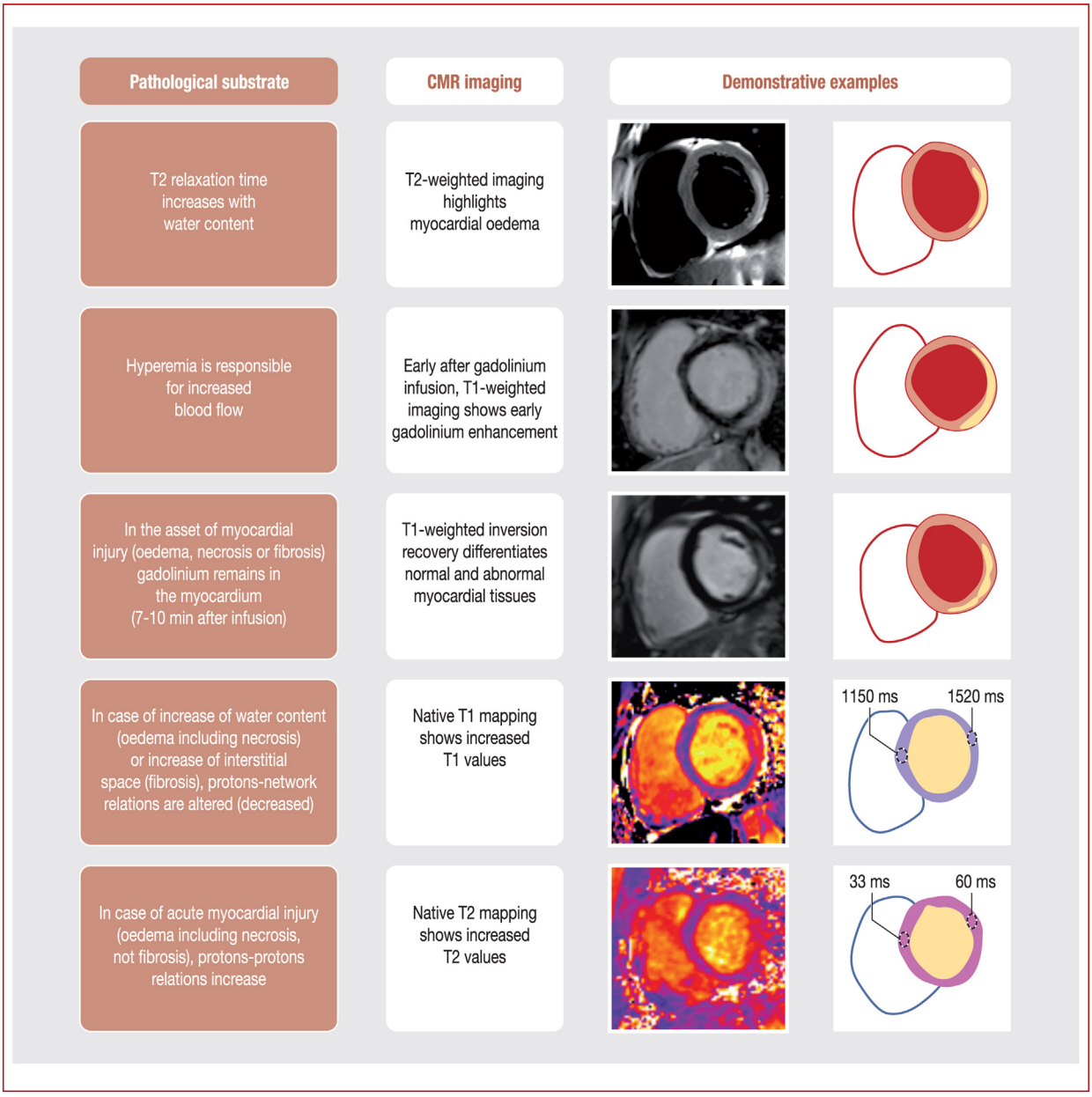

Figure 1. Pathological substrate and typical appearance by cardiac magnetic resonance (CMR) imaging in patients with acute myocarditis.

time, which vary with pathology. There is a linear and specific relationship between the increase in the water content of myocardial tissues and T2 relaxation [42]. Therefore, T2-weighted imaging with myocardial oedema appearing in hyperenhancement is likely to be obtained. These sequences are, nevertheless, subject to many artefacts and pitfalls [43]. In addition, they are dramatically altered by motion/breathing artefacts, and suffer from poor contrast. The Lake Louise Criteria recommend a semiqualitative assessment of T2-weighted hyperenhancement as a ratio of myocardial signal intensity to skeletal muscle that is > 1.9 (Fig. 1).

Hyperaemia and capillary leak (early gadolinium enhancement)

EGE is a T1-weighted imaging technique, performed about 1 minute after gadolinium infusion. EGE is positive when the signal intensity ratio to skeletal muscle exceeds 4 (Fig. 1). In sarcoidosis, and potentially in some of the most aggressive cases of myocarditis, massive oedema may lead to extracapillary obstruction and a global decrease in perfusion. Nowadays, the relationship of EGE to hyperaemia is questionable; EGE is rather time consuming to implement, and is challenged by T2-weighted and LGE for the diagnosis of

oedema; as a consequence, EGE is rarely used in the clinical settings but is still used for research purposes.

Necrosis and replacement fibrosis (late gadolinium enhancement)

LGE imaging is basically a T1-weighted imaging of the heart, powered by gadolinium infusion (that provides T1 contrast) and an inversion-recovery sequence design to null the signal of the normal myocardium. Given the fact that myocardial conditions, such as oedema, necrosis or replacement fibrosis, are responsible for gadolinium accumulation, LGE imaging will provide dramatic contrast between abnormal and normal myocardium (Fig. 1). Evidence for LGE providing specific insights into myocarditis abound, and its feasibility is unequivocal [40,44–46].

Diagnosis: updated Lake Louise Criteria

While the clinical use of EMB and Lake Louise Criteria is broadly debated [47], new CMR approaches are arising. Myocardial T1 and T2 mapping techniques are parametric imaging tools, and provide direct quantification of tissue-specific magnetization characteristics. Indeed, T1 and T2 relaxation times are given after a simple drawing of a region of interest on the myocardium.

T2 mapping informs about myocardial oedema, and thus provides direct quantification of myocardial active inflammation (Fig. 1) [48,49]. Nevertheless, mapping techniques suffer from a lack of standardization, as they are susceptible to magnet vendor, acquisition scheme and post-processing methods. Above all, field strength alters normal values, from 50 ± 5 ms at 1.5 Tesla to 45 ± 5 ms at 3 Tesla [49].

T1 mapping informs about longitudinal relaxation. Native (i.e. contrast-free) T1 relaxation time increases with oedema and/or an increase of interstitial state (Fig. 1). Compared with LGE, which depends on relative contrast between normal and abnormal myocardium, T1 mapping explores interstitial/diffuse fibrosis. Normal values range from 950 ± 50 ms at 1.5 Tesla to 1150 ± 75 ms at 3 Tesla [49,50].

Extracellular volume (ECV) measurement requires post-contrast T1 mapping and haematocrit value, in an effort to approach a physiological variable, showing good agreement with collagen volume fraction [51]. ECV is meant to be more reproducible, but as a novel technique its applicability is limited by the low quantity of clinical evidence.

In clinical practice, CMR is the cornerstone for the assessment of myocardial infarction with normal coronary arteries, which encompasses myocarditis, ischaemia and takotsubo cardiomyopathy, among others. In the case of ischaemic cardiomyopathy, CMR findings will occur in a single coronary territory with T2-weighted hyperenhancement, subendocardial hypoenhancement on first-pass imaging and subendocardial-to-transmural hyperenhancement on LGE. By comparison, in myocarditis, T2-weighted and LGE hyperenhancement are not related to a coronary territory, and first-pass imaging is normal. Lake Louise Criteria present high sensitivity (81%) and specificity (71%) in the diagnosis of acute myocarditis [52]. Nevertheless, a CMR scan should not be performed too early (< 48 hours) or too late after the onset of symptoms, at the risk of lower sensitivity. Some patterns of LGE have been associated with different viruses; parvovirus B19 myocarditis had subepicardial inferolateral LGE; while anteroseptal LGE was associated with either human herpesvirus 6 or the combined presence of the two viruses [53]. To improve diagnostic performance, two meta-analyses showed that native T1 mapping—but not ECV or T2 mapping—had significantly better sensitivity than Lake Louise Criteria [48,54]. Furthermore, the combination of T1 and T2 mapping readouts permits discrimination between active and healed myocarditis [55].

T2-weighted, native T1 and T2 mapping and LGE findings are sensitive for myocardial inflammation, but are not specific. Thus, they are useful in almost all inflammatory cardiomyopathies, such as rheumatoid arthritis, systemic sclerosis [19,56], takotsubo cardiomyopathy [57], lupus, peripartum cardiomyopathy [40], immunotoxic cardiomyopathy [7] and acute rejection in cardiac transplant recipients [58].

Cardiac sarcoidosis is accountable for the bright LGE pattern affecting the middle and epicardial left ventricular layers. Wicks et al. showed the combination of CMR with positron emission tomography (PET) to be useful for diagnosis and prognosis, despite poor intermodality agreement on the location of cardiac abnormalities [59]. T2 mapping was found to be useful for distinguishing between sarcoidosis with and without cardiac involvement [60], showing increased T2 values of 66 ± 5 ms in cardiac sarcoidosis compared with 56 ± 2 ms. Furthermore, T2 may decrease with effective therapy [61].

Follow-up and prognosis

The presence of LGE is associated with increased mortality and cardiovascular events in cardiac sarcoidosis [62]. More recently, a body of evidence described the prognostic impact of LGE presence in myocarditis as well. LGE appears to be a major prognostic marker by its location (midwall layer of the septum) [44,46] and extent (per 10% increase, corresponding to a 79% increase in the risk of a major acute cardiac event) [46]. ECV also has some prognostic value, even in the absence of LGE, as an ECV $\geq$ 35% portended a 6-fold increased hazard for a major acute cardiac event [63].

While mid- and long-term prognoses after myocarditis seem favourable, the consequences and sequelae of myocarditis are still poorly described. Filipetti et al. showed that left ventricular remodelling reached 21% patients out of a cohort of young myocarditis patients with preserved ejection fraction, and was related to a composite of adverse cardiac events during follow-up [45]. As mentioned previously, some patients with acute myocarditis will develop later dilated cardiomyopathy [17]. Further studies should determine the role of imaging in detecting these patients.

Positron emission tomography

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a fluorine-18-labelled analogue of glucose, which accumulates after injection into cells in proportion to their metabolic activity; it is therefore an ideal tool to highlight a metabolically active process, such as myocardial inflammation (Fig. 2). PET is a three-dimensional imaging modality that enables whole

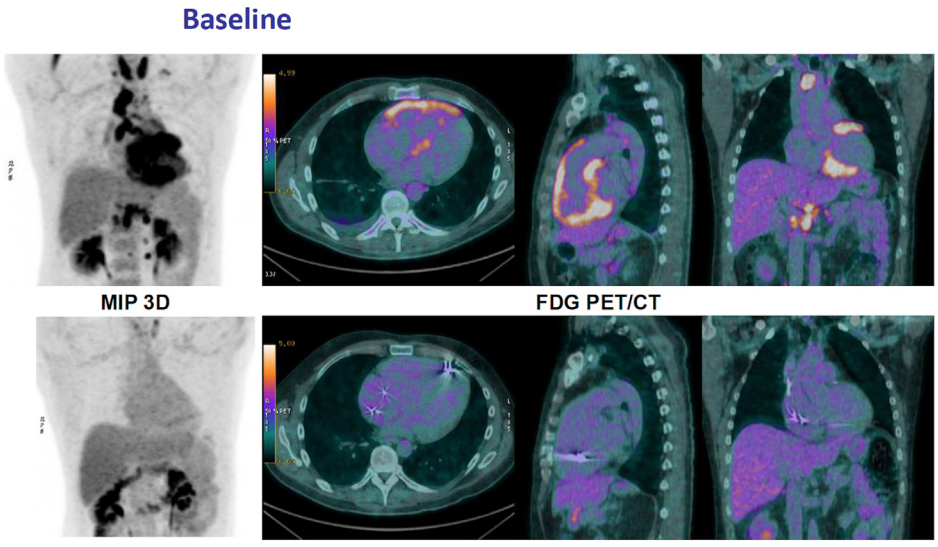

Figure 2. Diagnosis and follow-up of cardiac sarcoidosis by ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT). Patient referred to an intensive care unit for sustained ventricular tachycardia originating from the right ventricle. ^{18}F-FDG PET-CT pattern is typical of sarcoidosis involving the lungs, lymph nodes (mediastinum, bilateral hilar lymphadenopathy and subdiaphragmatic areas) and myocardium. At baseline (upper panel) ^{18}F-FDG cardiac uptake predominates at the right ventricle, a location associated with an increased risk of ventricular arrhythmias. After 6 months of steroid therapy (lower panel), all abnormalities have disappeared. 3D: three-dimensional; MIP: maximum intensity projection.

body scans; it is now coupled systematically to CT, which, in addition to the attenuation correction, provides anatomical and geographical information.

Dietary preparation

Before ^{18}F-FDG PET-CT, it is mandatory that patients undertake adequate dietary preparation, consisting of a high-fat no-carbohydrate diet (including glucose infusion) followed by prolonged fasting (at least > 12 hours), to suppress physiological myocardial glucose uptake [64]. Under these conditions, the myocardium uses free fatty acids as the main energy substrate, and the ^{18}F-FDG uptake, when present, truly accounts for ongoing inflammation.

Diagnosis

Although some studies have suggested a potential role for ^{18}F-FDG PET-CT in the monitoring of acute myocarditis, with good correlation between myocardial ^{18}F-FDG signalling and macrophage infiltration [65], its lack of specificity, and the need for strict dietary preparation for reliable interpretation have limited its use in this indication.

However, ^{18}F-FDG PET-CT is extremely interesting in the exploration of chronic and focal inflammation, as can be seen in cardiac sarcoidosis [66], Fabry disease [67], systemic sclerosis [68] or an inflammatory process accompanying arrhythmogenic right ventricular cardiomyopathy [69].

The role of advanced cardiac imaging was first acknowledged in the expert consensus statement on cardiac sarcoidosis from the Heart Rhythm Society [70]. In addition, recommendations pertaining to advanced imaging (PET and MRI) in cardiac sarcoidosis have been issued very recently by the Cardiovascular Council of the Society of Nuclear Medicine and Molecular Imaging and the American Society of Nuclear Cardiology [10], and by the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging and the American Society of Nuclear Cardiology [36]. These recommendations clarify the role of imaging in the diagnostic strategy for and prognostic assessment of cardiac sarcoidosis. First of all, these guidelines determine that it is justified to investigate cardiac sarcoidosis by advanced imaging in patients with biopsy-proven extracardiac sarcoidosis and symptoms (unexplained syncope/presyncope/significant palpitations) and/or abnormal electrocardiogram and/or inconclusive echocardiogram (class IIa); or suspected relapse in a patient with a history of cardiac sarcoidosis. The typical pattern of cardiac sarcoidosis is the presence of focal or multifocal ^{18}F-FDG uptake in the absence of background myocardial uptake or when this uptake is mild and diffuse. The presence of a focal uptake limited to the laterobasal segment of the left ventricle is generally considered to be non-specific, as it is frequent even when the high-fat no-carbohydrate diet has been correctly applied. In a meta-analysis that evaluated the diagnostic performance of ^{18}F-FDG PET in cardiac sarcoidosis, the pooled sensitivity and specificity were 89% and 78%, respectively [71]. To overcome the limitation of non-specific ^{18}F-FDG cardiac uptake based on qualitative image analysis, some authors assessed the diagnostic performance of quantitative analysis based on standard uptake value or maximal standard uptake value, but failed to demonstrate an additional diagnostic value [72]. A study also evaluated kinetic variables derived from dynamic PET acquisitions, with promising results [73]. Of note, the right ventricle may be involved, and may sometimes be the main location.

Whenever possible, perfusion imaging should be combined with ^{18}F-FDG to allow identification of specific

patterns suggestive of either active or quiescent disease. Evidence of myocardial perfusion abnormalities associated with cardiac sarcoidosis, and their reversibility after pharmacological vasodilation, suggesting that microvascular alterations may be a possible cause of perfusion abnormalities in addition to scar tissue, were reported with thallium by single photon emission tomography decades ago [74—76]. Indeed, the reversibility of perfusion defects after dipyridamole infusion was correlated with their improvement after corticosteroid therapy, suggesting that the acute response under vasodilation was a good predictor of steroid efficacy, and thus could help to select those patients with cardiac sarcoidosis who might benefit most from corticotherapy [77].

The pattern of perfusion and inflammation abnormalities is related to the stage of the disease. Mismatched segments represented by normal perfusion and active inflammatory lesion are suggestive of the early stage of disease, matched abnormal segments represented by abnormal perfusion and active inflammatory lesion are suggestive of advanced stage of disease, whereas inverse mismatched segments represented by abnormal perfusion and no inflammatory lesion are suggestive of end-stage disease [78]. In addition, in a retrospective analysis of 18 patients, Isiguzo et al. reported that a mismatch between perfusion and inflammation identified active cardiac sarcoidosis with a specificity of 62% and a sensitivity of 80%. A mismatch threshold of > 6% allowed improvement of the specificity to 100%, with a sensitivity of 70% [79].

Follow-up and prognosis

The combined information provided by both ^{18}F-FDG and myocardial perfusion PET analysis can provide additional prognostic information. Recently, Blankstein et al. evaluated the prognostic value of combined assessment of rest perfusion and inflammation in 118 patients with suspected cardiac sarcoidosis and no history of coronary artery disease [66]. In this study, 17 (14%) patients presented an isolated abnormal perfusion, and 34 (28%) presented an abnormal perfusion associated with increased ^{18}F-FDG cardiac uptake. This latter pattern (abnormal perfusion and ^{18}F-FDG uptake) was associated with a 2.9-fold increase in the rate of adverse events (death or sustained ventricular tachycardia), whereas those who had either perfusion defects or ^{18}F-FDG abnormal uptake had a 2.4-fold increase in events. Interestingly, those patients with right ventricular involvement had a 3-fold increase in the rate of adverse events.

After initiation of immunosuppressive treatment in patients with cardiac sarcoidosis, it has been shown that a decrease in ^{18}F-FDG uptake is associated with an increase in left ventricular ejection fraction [80]. Because of the high sensitivity, it is generally recommended to use ^{18}F-FDG PET imaging to guide immunosuppressive therapy, and thereafter to monitor treatment response [36,81] (Fig. 2).

Alternative approaches

Positron emission tomography-magnetic resonance imaging

Considering the reciprocal performance of PET and MRI in the diagnosis, quantification and monitoring of myocardial inflammation, PET-MRI legitimately appears to be the future tool of choice in the exploration of myocarditis.

Cardiac sarcoidosis provides a unique example of how PET and MRI can complement each other. Indeed, the inflammation that characterizes granulomas during the active phase of the disease is detected with great sensitivity by ^{18}F-FDG; also, tissue remodelling associated with the development of granulomas, leading progressively to the formation of fibrosis, is well characterized by MRI. Some settings more specifically require the use of combined ^{18}F-FDG PET and MRI (e.g. in the early phase of cardiac involvement). The introduction of hybrid systems combining PET and MRI is a real opportunity for sarcoidosis imaging. Several studies performed on limited numbers of patients have already suggested a promising role in assessing cardiac involvement, whatever the stage of the disease [82,83]. Further studies are required to validate the potential additional value in larger series.

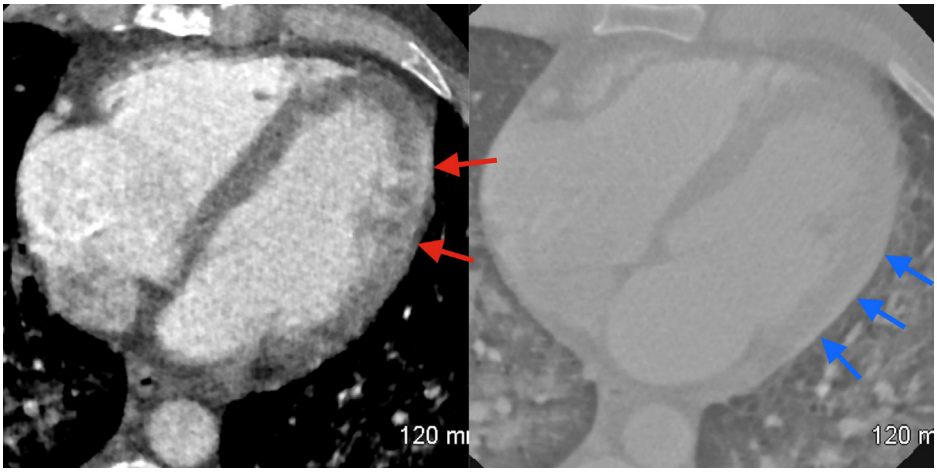

Figure 3. Early (left side, red arrows) and late (right side, blue arrows) iodine enhancement by spectral computed tomography in a patient with acute myocarditis.

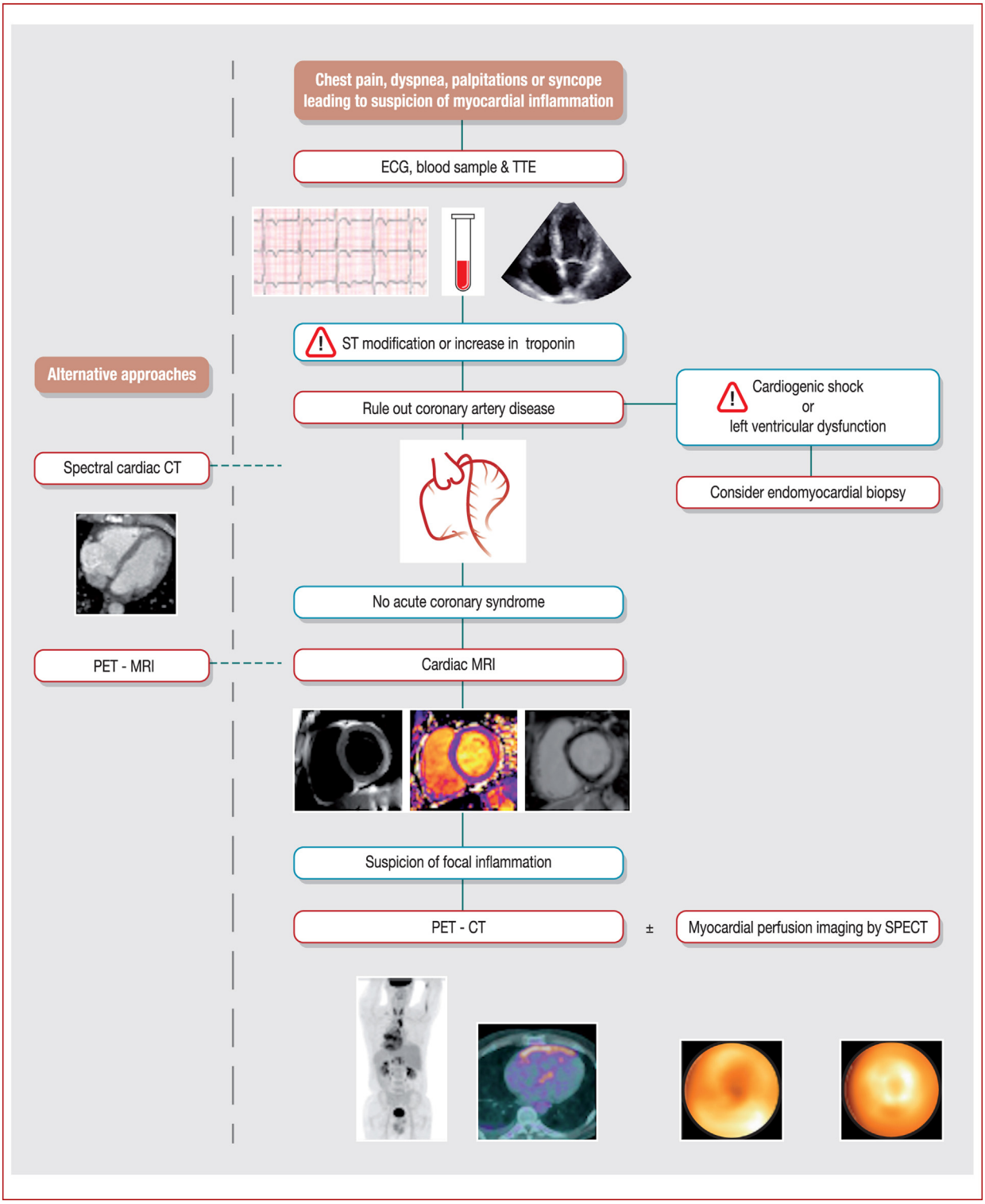

Figure 4. Algorithm for the application of non-invasive cardiac imaging in the diagnosis of myocardial inflammation. CT: computed tomography; ECG: electrocardiogram; MRI: magnetic resonance imaging; PET: positron emission tomography; SPECT: single photon emission computed tomography; TTE: transthoracic echocardiography.

Computed tomography

A recent study has shown the potential value of cardiac CT as an alternative to CMR for tissue characterization based on late iodine enhancement [84]. This study showed spectral CT to have good accuracy in the evaluation of inflamed myocardium in acute myocarditis, with typically subepicardial late iodine enhancement (Fig. 3), enabling acute coronary syndrome to be ruled out with coronary CT angiography during the same examination.

Summary and future directions

The heterogeneity of clinical presentations and the limitations of EMB make non-invasive imaging an essential tool for the exploration of myocardial inflammation, whether acute and diffuse or focal and chronic. TTE remains the first-line examination, but because of its lack of specificity in this indication, it is mainly used to guide initial management and rule out differential diagnoses. CMR is quickly positioned in the management algorithm as a sensitive tool for diagnosis and follow-up. PET has the advantage of high sensitivity for the exploration of focal and chronic inflammation, such as is observed in cardiac sarcoidosis. A synthesis algorithm is presented in Fig. 4.

Alternative approaches providing both sensitivity and specificity for the diagnosis, monitoring and prognostic evaluation of myocardial inflammation should appear in the coming years. These approaches already include spectral CT and PET-MRI. Many other innovations are yet to come, based on the principle of molecular imaging, in the field of echocardiography [85], but also in the field of PET, with the emergence of new tracers to predict ventricular remodelling induced by myocarditis inflammation [86].

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Disclosure of interest

The authors declare that they have no competing interest.

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