ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2017) **18**, 1073–1089
doi:10.1093/ehjci/jex146

POSITION PAPER

A joint procedural position statement on imaging in cardiac sarcoidosis: from the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology

Writing group: Riemer H.J.A. Slart[1,2]*, Andor W.J.M. Glaudemans[1], Patrizio Lancellotti[3,4], Fabien Hyafil[5,6], Ron Blankstein[7], Ronald G. Schwartz[8,9], Wael A. Jaber[10], Raymond Russell[11], Alessia Gimelli[12], François Rouzet[5], Marcus Hacker[13], Olivier Gheysens[14], Sven Plein[15], Edward J. Miller[16], Sharmila Dorbala[7]†, and Erwan Donal[17,18]†

Document reading group: Roberto Sciagra[19], Jan Bucerius[20,21,22], Hein J. Verberne[23], Oliver Lindner[24], Christopher Übleis[25], Denis Agostini[26], Alberto Signore[27], Thor Edvardsen[28], Danilo Neglia[12], Rob S. Beanlands[29], Marcelo Di Carli[7], Panithaya Chareonthaitawee[30], Vasken Dilsizian[31], Prem Soman[32], and Gilbert Habib[33]

EACVI Reviewers: This document was reviewed by members of the EACVI Scientific Documents Committee for 2014–2016 and 2016–2018: Victoria Delgado, Nuno Cardim, Bernard Cosyns, Frank Flachskampf, Bernhard Gerber, Kristina Haugaa, Massimo Lombardi, Pier Giorgio Masci.

[1]Department of Nuclear Medicine and Molecular Imaging, University of Groningen, University Medical Center Groningen, Hanzeplein 1, P.O. Box 30001, 9700 RB, Groningen, The Netherlands; [2]Department of Biomedical Photonic Imaging, University of Twente, Enschede, The Netherlands; [3]Department of Cardiology, GIGA-Cardiovascular Sciences, University Hospital Sart Tilman, Liège, Belgium; [4]Gruppo Villa Maria Care and Research, Anthea Hospital, Bari, Italy; [5]Department of Nuclear Medicine, Centre Hospitalier Universitaire Bichat, Département Hospitalo-Universitaire FIRE, Inserm 1148, Assistance Publique - Hôpitaux de Paris, Université Paris Diderot, Paris, France; [6]Department of Nuclear Medicine, Klinikum rechts der Isar, Technische Universität München, München, Germany; [7]Division of Nuclear Medicine and Molecular Imaging, Department of Radiology, Division of Cardiovascular Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA; [8]Cardiology Division, Department of Medicine, University of Rochester Medical Center, Box 679, Rochester, NY, USA; [9]Nuclear Medicine Division, Department of Imaging Sciences, University of Rochester Medical Center, Rochester, NY, USA; [10]Cleveland Clinic Lerner College of Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, USA; [11]Cardiovascular Institute, Rhode Island Hospital, Alpert School of Medicine of Brown University, Providence, RI, USA; [12] Fondazione Toscana/CNR Gabriele Monasterio, Pisa, Italy; [13]Division of Nuclear Medicine, Department of Biomedical Imaging and Image-guided Therapy, Medical University Vienna, Vienna, Austria; [14]Nuclear Medicine and Molecular Imaging, University Hospitals Leuven, Belgium and Department of Imaging and Pathology, KU Leuven, Belgium; [15]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK; [16]Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, CT, USA; [17]Service de Cardiologie, et CIC-IT INSERM 1414, - CHU Rennes, - Rennes, France;

This article is being published concurrently in the European Heart Journal – Cardiovascular Imaging (10.1093/ehjci/jex146) and the Journal of Nuclear Cardiology (• • •).

* Corresponding author. Tel: +31 50 3613541; Fax: +31 50 3611687. E-mail: r.h.j.a.slart@umcg.nl

† The authors contributed equally to this study.

[18]LTSI, Université de Rennes 1 - INSERM, UMR 1099, - Rennes, France; [19]Nuclear Medicine Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy; [20]Department of Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands; [21]Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands; [22]Department of Nuclear Medicine, University Hospital RWTH Aachen, Aachen, Germany; [23]Department of Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands; [24]Institute of Radiology, Nuclear Medicine and Molecular Imaging, Heart and Diabetes Center NRW, Bad Oeynhausen, Germany; [25]Department of Clinical Radiology, Ludwig-Maximilians Universität München, München, Germany; [26]Department of Nuclear Medicine, CHU Cote de Nacre, CAEN, France; [27]Nuclear Medicine Unit, Department of Medical-Surgical Sciences and of Translational Medicine, Faculty of Medicine and Psychology, 'Sapienza' University of Roma, Rome, Italy; [28]Department of Cardiology, Oslo University Hospital, Rikshospitalet and University of Oslo, Oslo, Norway; [29]Division of Cardiology, Department of Medicine, University of Ottawa Heart Institute, Ottawa, Canada; [30]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA; [31]Department of Diagnostic Radiology and Nuclear Medicine, University of Maryland School of Medicine, Baltimore, MD, USA; [32]Division of Cardiology, Heart and Vascular Institute, University of Pittsburgh Medical Center, A-429 Scaife Hall, 200 Lothrop Street, Pittsburgh, PA, 15213, USA; and [33]Department of Cardiology, Aix-Marseille Université, Marseille 13284, France La Timone Hospital, 13005, Marseille, France

Received 2 May 2017; editorial decision 5 May 2017; accepted 16 May 2017

This joint position paper illustrates the role and the correct use of echocardiography, radionuclide imaging with ^{18}F-fluorodeoxyglucose positron emission tomography, radionuclide myocardial perfusion imaging and cardiovascular magnetic resonance imaging for the evaluation and management of patients with known or suspected cardiac sarcoidosis. This position paper will aid in standardizing imaging for cardiac sarcoidosis and may facilitate clinical trials and pooling of multi-centre data on cardiac sarcoidosis. Proposed flow charts for the work up and management of cardiac sarcoidosis are included.

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Preamble

This procedural position paper on the use of imaging in the management of patients with known or suspected cardiac sarcoidosis has been developed under the auspices of the Cardiovascular and the Inflammation & Infection Committee of the European Association of Nuclear Medicine (EANM), the European Association of Cardiovascular Imaging (EACVI) of the European Society of Cardiology (ESC), and the American Society of Nuclear Cardiology (ASNC), highlighting the close collaboration between the societies on this topic.

Introduction

Sarcoidosis is a multisystem inflammatory granulomatous disease of unknown origin. Granulomas in sarcoidosis are compact, centrally organized collections of macrophages and epithelioid cells that are surrounded by lymphocytes. Granulomas from sarcoidosis are most often located in the lungs or its associated lymph nodes, but any organ can be affected.

Sarcoidosis affects approximately 10 out of 100 000 persons each year.[1] Cardiac sarcoidosis is reported to involve only 2–5% of patients with systemic sarcoidosis,[2,3] even though autopsy studies indicate a considerably greater prevalence of 27%.[4,5] There is also evidence indicating that sarcoidosis can be clinically confined to the heart.[6] *Cardiac involvement* may range from silent myocardial granulomas to symptomatic conduction disturbances, ventricular arrhythmias, progressive heart failure, and sudden death, accounting for 13–25% of disease-related deaths.[5] The clinical course of cardiac sarcoidosis varies from benign to life-threatening with severe heart failure and sudden cardiac death.[7] The management of cardiac sarcoidosis involves both immunosuppressive therapy for the treatment of sarcoidosis and cardiac-specific therapies to manage ventricular

dysfunction and device therapy (pacemaker/ICD) for heart blocks and heart rhythm disturbances. The decision for drug therapy alone or the implantation of an ICD for primary prevention in the early stage of cardiac sarcoidosis remains challenging. Nevertheless, it is felt that early initiation of immunosuppressive therapy may prevent progression of cardiac dysfunction and improve clinical outcomes.[8]

To date, the diagnosis and long-term management of cardiac involvement remain controversial. Cardiac sarcoid granulomas affect the whole heart but in a focal manner. Also, acutely inflamed epithelioid cell granulomas as well as chronic fibrotic stage granulomas, may exist in different parts of the heart of any given patient. Consequently, blind endomyocardial biopsy of the right side of the interventricular septum has a low diagnostic yield, 20–30%, and it is unreliable to assess whole heart burden of inflammation or fibrosis. Molecular imaging of increased metabolic activity in the granulomas using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) provides the advantages of whole heart evaluation and the ability to identify granulomas with active inflammation. Cardiovascular magnetic resonance (CMR) on the other hand is highly sensitive to detect fibrosis. The Japanese Ministry of Health, Labour and Welfare (JMHW) criteria have been widely used for the diagnosis of cardiac sarcoidosis. But, they do not include FDG-PET or CMR.[9] The Heart Rhythm Society (HRS) consensus document has included FDG-PET and CMR in the diagnostic criteria for cardiac sarcoidosis.[10] However, procedural details of imaging are not covered in that document.

The purpose of this joint procedural position paper is to describe the role and the correct use of the different imaging techniques including radionuclide imaging (FDG-PET, radionuclide myocardial perfusion imaging, MPI), CMR, and echocardiography for the management of patients with known or suspected cardiac sarcoidosis. We further hope that this position paper will aid in standardizing imaging for cardiac sarcoidosis with conventional and novel imaging techniques and facilitate clinical studies and pooling of multi-center data on cardiac sarcoidosis.

Role of different imaging techniques in cardiac sarcoidosis

Echocardiography

Rationale

Echocardiography is widely available and often provides the first suspicion for cardiac sarcoidosis.

Image acquisition

Several traditional and advanced echocardiographic approaches can be used with standard acquisition and interpretation protocols.[11–18] Stress echocardiography has a limited role in the diagnosis of cardiac sarcoidosis; it may be helpful to exclude epicardial coronary artery disease as a cause of left ventricular systolic dysfunction and focal regional wall motion abnormalities.

Interpretation and reporting

Cardiac sarcoidosis can manifest with normal function or with dilated or restrictive cardiomyopathy.[19–21] The ventricle may be globally hypokinetic or the patchy nature of sarcoid infiltration of the heart may result in regional wall motion abnormalities in a non-coronary distribution. Mild wall thickening may be present related to oedema or infiltration. In some cases, the increase in myocardial wall thickness (>13 mm) can simulate LV hypertrophy. Increased ventricular wall echogenicity (bright aspect), particularly the ventricular septum or the LV free wall, is frequent; and can reflect scar formation and granulomatous inflammation. More commonly, areas of wall thinning are seen, especially in the ventricular septum, probably as a result of scar. A typical but uncommon finding is the thinning (<7 mm) and akinesia of the basal septum, while the distal septum and apex are contracting normally, and the presence of ventricular aneurysm in the inferolateral wall[20,22–24] (*Figure 1*). Echocardiographic features of cardiac sarcoidosis echo can also mimic arrhythmogenic right ventricular dysplasia/cardiomyopathy.[25,26] In the early stage of the disease, reduced longitudinal myocardial function (2D speckle tracking or tissue Doppler imaging-derived strain)[27–32] or alterations in acoustic properties of the myocardium,[33,34] particularly in the basal interventricular septum, may be present in the absence of other 2D echo features. About 20% of patients with cardiac sarcoidosis have atrial lesions characterized by atrial wall hypertrophy (easier diagnosis by transoesophageal echocardiography).[35] On rare occasions, an appearance similar to hypertrophic cardiomyopathy can be observed.[36,37] Any degree of diastolic dysfunction is a common but non-specific finding.[38] Small pericardial effusions, mitral or tricuspid regurgitation secondary to papillary muscle dysfunction, pulmonary hypertension secondary to lung implication, and/or ventricular dys-synchrony are other echo parameters that can be potentially observed in cardiac sarcoidosis. Tamponade and constrictive pericarditis have been infrequently found.[19] The right ventricular dilatation and dysfunction at the end-stage disease in cardiac sarcoidosis as well as the predominance of basal septum abnormalities in terms of contractility are important findings on echocardiography.[25]

Diagnostic accuracy

Echocardiography can detect cardiac structural abnormalities from cardiac sarcoidosis. But in patients with extra-cardiac sarcoidosis, echocardiographic abnormalities are highly variable, ranging from 4 to 55%, even without clinical symptoms or ECG abnormalities.[3,10] The measurement of LV systolic and diastolic function and evaluation of valvular disease severity are not-specific for sarcoidosis.[39] Although newer techniques such as Doppler, strain, and speckle tracking echocardiography are useful in detecting abnormal myocardial function, these imaging techniques cannot delineate tissue characteristics and therefore cannot differentiate between various types of cardiomyopathies.[40] Using the criteria of RV systolic dysfunction in the absence of pulmonary hypertension, and/or significant diastolic dysfunction inappropriate for the patient's age, echocardiography yields a sensitivity of 10–47% and a specificity of 82–99% for the diagnosis of cardiac sarcoidosis.[10,41]

In summary, standard 2D transthoracic echocardiography is a common initial test in patients with suspected cardiac sarcoidosis. However, findings are frequently non-specific for inflammation and not sensitive for early changes from sarcoidosis. The primary role of

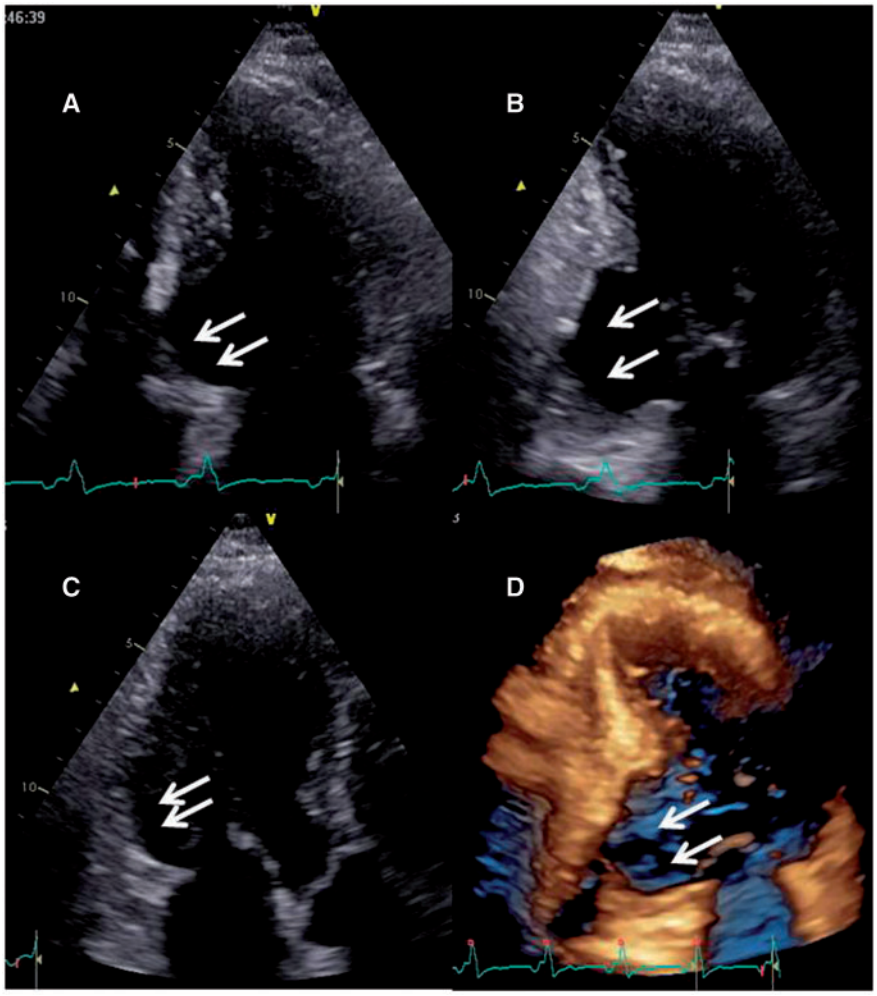

Figure 1 Example of echocardiography in cardiac sarcoidosis. Echocardiographic images showing (*A*) a basal thinned basal septal wall (4-chamber view showing, arrows); (*B–D*) aneurysmal dilatation involving inferior (*B, D*) and posterolateral (*C*) walls. D is a 3D image displaying the inferior aneurysm (arrows).

echocardiography in cardiac sarcoidosis, at this time, is to assess and follow LV function.

Radionuclide imaging

Radionuclide imaging with ^{67}Gallium-citrate SPECT and FDG-PET have been used to diagnose myocardial inflammation. ^{67}Gallium-citrate is specific for inflammation, but has relatively low sensitivity and poor spatial resolution compared with FDG-PET, especially for detecting extra-pulmonary sarcoidosis involvement.[42] Therefore, the use of ^{67}Gallium-citrate SPECT to diagnose cardiac sarcoidosis is limited to centres without access to FDG PET. FDG-PET has emerged as a powerful and most commonly used technique not only to assess the extent of systemic sarcoidosis but also to assess extent and activity of myocardial involvement.[43] In addition, recent studies have demonstrated the importance of identifying perfusion defects in patients with cardiac sarcoidosis, as this group of patients is at highest risk for death or ventricular arrhythmias.[44,45] FDG-PET in conjunction with MPI is therefore the currently recommended radionuclide method for evaluation of cardiac sarcoidosis.

^{18}F-fluorodeoxyglucose positron emission tomography

Rationale

Active inflammatory cells have high glycolytic activity to sustain their energy demands; the accumulation of FDG in these activated macrophages and CD4+ T lymphocytes is the underlying mechanism for *in vivo* visualization of active granulomatous sarcoid lesions in various

organs.[46] Low carbohydrate diet and prolonged fasting of the subject are recommend to suppress myocardial FDG uptake to facilitate visualizing FDG uptake in these inflammatory cells of cardiac sarcoidosis. The role of FDG-PET for the diagnosis of extra-cardiac sarcoidosis is well established; in contrast, its role in cardiac sarcoidosis management, and therapy is currently under active investigation.

Patient preparation and image acquisition

Metabolic imaging to identify the non-caseating granulomas of cardiac sarcoidosis takes advantage of enhanced FDG uptake based on the high glycolytic activity of inflammatory cells.[47,48] However, the surrounding normal myocardium can also use glucose as an energy substrate, and therefore it is important to minimize physiological myocardial glucose utilization to optimize the target to background ratio of FDG-PET for identifying active cardiac sarcoid lesions. Patient preparation for cardiac FDG-PET imaging for sarcoidosis is based on increasing the provision of fatty acids to the heart and decreasing physiological uptake of glucose by the myocardium.[103] The current SNMMI/ASNC/SCCT guidelines recommend preparation with a fat-enriched diet lacking carbohydrates for 12–24 h prior to the scan, a 12–18 h fast, and/or the use of intravenous unfractionated heparin approximately 15 min prior to ^{18}F-FDG injection.[49] Careful patient preparation is critical to optimize FDG-PET image quality. Details of patient preparation are listed in Supplementary data online, *Supplement 1a and 1b*.

The FDG-PET imaging protocol involves cardiac image acquisition 90 min (minimum of 60 min) after intravenous injection of 2.5–5 MBq/kg of FDG.[50–52] (*Table 2*). Following FDG injection and before the images are obtained, the patient should continue to fast and should not be physically active, as either of these will enhance myocardial glucose uptake. In addition, limited whole body FDG imaging is recommended to allow for the assessment of extra-cardiac disease activity (lung, lymph nodes, liver, spleen, kidneys, bones) and identify potential sites amenable for biopsy. Imaging procedures, including dietary preparation and image acquisition parameters should be documented and standardized on repeat studies, to enable reliable quantitation and comparison of changes. Exercise and/or myocardial ischemia can enhance myocardial FDG uptake. For this reason, stress testing should be avoided and patients should be advised not to exert themselves on the day of cardiac sarcoid FDG imaging. Also, note that patients with systolic LV dysfunction may have increased glucose uptake due to metabolic changes, which is likely diffuse rather than focal.

Interpretation and reporting

Interpretation of FDG-PET for cardiac sarcoidosis requires an understanding of the metabolic preparations necessary to differentiate the pathological glucose uptake that is the hallmark of sarcoidosis-related inflammation from physiological myocardial glucose uptake. It is also important to note that none of the interpretive strategies described below have been validated experimentally, due to the lack of a gold standard, and there is little data available on comparing the various methods. The most common method of interpreting FDG-PET for the evaluation of cardiac sarcoidosis relies on the use of traditional nuclear cardiology display systems as well as nuclear medicine display systems.[53] Typically short-axis, horizontal, and vertical long-axis images of the FDG and rest MPI are displayed together with the image intensity normalized to the maximum counts per pixel of the respective data set. These normalized images are reviewed for four imaging patterns[54]:

(1) No FDG uptake ('none')
(2) Diffuse FDG uptake ('diffuse')
(3) Focal FDG uptake ('focal')
(4) Focal on diffuse FDG uptake ('focal on diffuse').

The presence of 'focal' or 'focal on diffuse' FDG uptake is abnormal and may be consistent with cardiac inflammation from sarcoidosis, while interpretation of diffuse uptake is challenging as it can be non-specific (possibly related to poor suppression of normal myocardial glucose uptake) or may represent multiple sarcoid granulomas with heterogeneous FDG uptake in a diffuse distribution. The normal FDG image pattern for an appropriately prepared patient is no myocardial FDG uptake where the LV blood pool is brighter than the

Table 1 Sensitivity and specificity of FDG PET for detecting cardiac sarcoidosis

References	Year	Patients	EMB*	Sensitivity	Specificity	Remarks
Yamagishi *et al.*[53]	2003	17	0/17	100	n.a.	Only patients with histologic evidence of extra-cardiac sarcoidosis were included
Okumura *et al.*[55]	2004	22	3/22	100	90.9	Diagnosis JMHW
Ishimaru *et al.*[54]	2005	62	0/62	100	81.5	Included 30 healthy controls and 32 patients with suspected sarcoidosis. Diagnosis 28 out of 32 with histologic evidence of extra-cardiac sarcoidosis.
Nishiyama *et al*[42]	2006	18	0/18	100	100	Diagnosis JMHW
Ohira *et al.*[69]	2008	21	2/21	87.5	38.5	Diagnosis JMHW
Langah *et al.*[57]	2009	65	1/65	85	90	Diagnosis JMHW
Youssef *et al.*[70]	2012	164	n.a.	89	78	Meta-analysis of 7 studies Diagnosis JMHW
Blankstein *et al.*[45]	2014	118	13/118	42.1	79.7	Based on patients that had both abnormal FDG and ^{82}Rubidium PET studies. Diagnosis JMHW

*endomyocardial biopsy.

Table 2 Procedure guidelines for radionuclide myocardial perfusion and FDG imaging for cardiac sarcoidosis

Imaging sequence	Myocardial perfusion imaging and FDG PET at baseline Myocardial perfusion imaging and FDG PET at follow-up	Standard
Myocardial perfusion imaging		
Preparation	None	Standard
	Preparation for FDG PET, if performed on the same day	
Technique	PET or SPECT	Standard
Perfusion radiotracers	^{99m}Tc-sestamibi/tetrofosmin, ^{201}Tl, ^{13}N-ammonia, ^{82}Rb	Standard
Protocols	Standard radiotracer dose and rest MPI protocols as per ASNC, EANM, ESC	Standard
	Attenuation correction when available	Standard
	Gated SPECT/PET MPI	Standard
Review	Review MPI along with FDG PET	
FDG PET imaging		
Preparation	Dietary preparation to minimize physiological myocardial glucose utilization	Standard
Type of PET scan	Hybrid PET/CT	Standard
	Dedicated PET	Acceptable
CT scan	Low dose chest CT scan for attenuation correction without iodinated contrast	Standard
Imaging mode	3D	Standard
	2D	Acceptable
Dose	2.5–5 MBq/kg for 3 D mode or	Acceptable
	5–10 mCi for 3 D imaging and 10-20 mCi for 2 D imaging	Acceptable
FDG uptake period after injection	90 min	Standard
	60 min	Minimum
Scan field of view	Dedicated cardiac scan and whole body to include neck through pelvis at baseline	Standard
	Dedicated cardiac scan and whole body to include neck through pelvis at follow up	Standard
Scan duration	10 min for 3D cardiac PET	Standard
	20 min for 2D cardiac PET	Standard
	3 min per bed position partial whole body PET	Standard
Scan type	Static FDG PET	Standard
	Gated FDG PET	Optional
Scan reconstruction	Iterative reconstruction (OSEM)	Standard
	Attenuation correction	Standard
	With and without attenuation correction for hybrid PET/CT in individuals with intracardiac devices	Standard
Scan interpretation	Visual using cardiac imaging planes	Standard
	Whole body imaging using SUV scale	Standard
	Myocardial SUV max	Standard
	Volume of myocardium above specific SUV threshold	Standard
	Interpretation by physicians experienced in nuclear cardiology, CT and FDG imaging	Standard
Special considerations	In individuals with recent intracardiac device placement or ablation wait 4–6 weeks for FDG PET	Optional

myocardium, although low intensity FDG uptake in the lateral wall is also often considered a normal finding, particularly when such uptake is homogenous in intensity and is not associated with any resting perfusion defects.[54] In addition to evaluating for abnormal FDG uptake in the LV, it is also important to evaluate for areas of focal FDG uptake in the right ventricle, which may be associated with a worse prognosis.[45] Lastly, the use of FDG-PET combined with MPI will be particularly helpful to judge the orientation of the image when only focal FDG uptake is present.

The use of traditional nuclear cardiology display systems to interpret relative FDG-PET images for cardiac sarcoidosis has two limitations. First, since these display schemes normalize image intensity to the most intense pixel, it is difficult to judge the absolute intensity of myocardial FDG uptake. This may be important for understanding the severity of myocardial inflammation and for evaluating the response to treatment, particularly if only the intensity but not the distribution of FDG uptake changes between studies. Secondly, the issue of normalization is especially important when the FDG signal is only mildly increased above background. This can falsely cause these areas of low absolute uptake to appear artificially intense in the normalized display.

A review of the images for non-inflammatory pathological FDG activity (cancer, other infections, etc.) is accomplished using limited whole body hybrid PET/CT. Hybrid FDG-PET/CT imaging, however, may be problematic in individuals with intra-cardiac devices due to apparent focal increase in FDG uptake at the site of lead insertion related to errors from CT based attenuation correction and/or focal inflammation. In individuals with intra-cardiac devices and suspected

cardiac sarcoidosis, the non-attenuation corrected FDG images could be reviewed to overcome this limitation.

In addition to a visual review of the relative scaled FDG images and hybrid PET-CT images, FDG images should be assessed using a semi-quantitative scale and standardized uptake values (SUV). SUVs are defined as the (radioactivity concentration in the region of interest in Bq/mL/(injected dose in Bq/patient weight in g).[55] Various metrics for quantification of FDG uptake in cardiac sarcoidosis have been reported, including the maximal SUV values in the heart (SUVmax),[45,55] the total SUV value of the heart,[55] mean SUV of the heart,[56] heart-to-blood pool SUV ratios,[57] coefficient of variance of SUVs,[58] and the volume,[59] and volume-activity[44,59] of voxels with intensities of FDG SUVs above various thresholds. While these methods have not been rigorously compared head-to-head, there is data to suggest that they perform better than visual assessment of normalized images to assess treatment response.[44,59,60] A standard FDG-PET for cardiac sarcoidosis is typically reported in conjunction with rest MPI (see Supplementary data online, *Supplement 2*).

Myocardial perfusion imaging

Cardiac sarcoidosis may alter coronary microcirculation leading to myocardial perfusion defects. Myocardial perfusion abnormalities, including reversible perfusion defects with adenosine or dipyridamole, have been reported in cardiac sarcoidosis.[56,61,62] However, unlike with coronary artery disease, perfusion abnormalities related to sarcoid granulomas typically do not match with coronary territories. In the chronic phase, when epithelioid-cell granulomas have been replaced by fibrosis, perfusion defects become irreversible and may be associated with segmental motion abnormalities according to the transmural extent of the fibrotic scar.

The evaluation of the diagnostic performance of perfusion SPECT and perfusion PET in cardiac sarcoidosis is very scarce and limited.[54–56] The potential additional value of myocardial blood flow quantification by PET in the diagnosis and evaluation of cardiac sarcoidosis remains to be investigated. Due to the limited sensitivity and specificity of MPI alone, and due to the fact that abnormal MPI alone cannot distinguish scar from active sarcoidosis, MPI is currently used for the evaluation of cardiac sarcoidosis only in conjunction with FDG-PET.

When combined with FDG-PET, standard PET or SPECT MPI protocols are recommended.[63–66] PET MPI has advantages over SPECT for the identification of small perfusion defects, as seen in patients with cardiac sarcoidosis. When SPECT imaging is used, attenuation correction and gated imaging are recommended to avoid interpreting segments with attenuation artifacts as segments of true mismatch.[67] Perfusion and FDG abnormalities associated with cardiac sarcoidosis are not specific for inflammation or scar from sarcoidosis. Consequently, it is mandatory to rule out alternative diagnoses such as CAD before interpreting myocardial perfusion images.

Combined assessment of perfusion and inflammation

The combined assessment of perfusion and inflammation, preferably in hybrid imaging setting, is likely to provide additional information about the status of cardiac sarcoidosis (scar or inflammation) and risk from cardiac involvement (*Figure 2*). In this section we will only consider the assessment of inflammation by FDG-PET/CT combined with MPI since ^{67}Gallium-citrate scintigraphy is no longer regarded as a method of choice.

Perfusion defects in patients with cardiac sarcoidosis can represent areas of scar or inflammation, while abnormal FDG uptake represents inflammation (*Table 3*). FDG and MPI patterns have been described as 'early' (only FDG-positive), 'progressive inflammatory' (FDG-positive without major perfusion defects), 'peak active' (high SUV FDG uptake with small perfusion defects), 'progressive myocardial impairment (high SUV FDG uptake with large perfusion defects) or 'fibrosis-predominant' (FDG negative, but with perfusion defects)[55] (*Figure 2B*). Another staging system utilizes a nomenclature analogous to the Scadding system for staging pulmonary sarcoidosis, specifically, Stage 0 (normal FDG, normal perfusion), Stage 1 (FDG-positive, normal perfusion), Stage 2 (FDG positive with perfusion defects in the same myocardial segments), Stage 3 (FDG positive with perfusion defects in different segments), or Stage 4 (normal FDG, but perfusion defects).[68]

Notably, the pattern of perfusion and inflammation abnormalities in relation to the disease status is not validated histologically or by outcomes. However, this relationship may be important both for diagnosis, and for the determination of prognosis and establishing treatment,[44,45,55] see next sections. It is noteworthy that both resting perfusion defects as well as increased FDG uptake may be caused by inflammation as well as associated microvascular compression and local ischemia; for this reason some perfusion defects may actually improve following immunosuppressive therapy.

Diagnostic accuracy

FDG-PET is an accurate tool for the detection of cardiac involvement in sarcoidosis. Several studies reported on the sensitivity and specificity of FDG-PET to detect cardiac sarcoidosis.[1] These studies have included patients with and without endomyocardial biopsy proven cardiac involvement. However, as with the data from the other imaging methods, most of these studies were observational in nature, included small sample size, lacked an adequate reference standard, were limited by referral bias, and used different protocols.

The sensitivity of FDG-PET for detecting cardiac sarcoid is 85–100% for most studies while the specificity is more variable (39–100%) using the JMHW criteria as the gold standard (*Table 1*).[53–55,57,69,70] A recent meta-analysis of 7 studies demonstrated an overall sensitivity of 89% and a specificity of 78% for FDG-PET.[70] However, these estimates are biased as the lower specificity of PET in some studies may reflect the fact that this test is more sensitive for identifying cardiac sarcoidosis than the JMHW criteria. Indeed, the requirement of histologically proven extra-cardiac sarcoidosis by the JMHW criteria limits identification of isolated cardiac sarcoidosis, whereby the disease is confined only to the heart,[71] particularly if endomyocardial biopsy is negative. Likewise, the lower sensitivity of FDG-PET in some studies may reflect the reduced specificity of the JMHW criteria. Several studies have compared FDG-PET, either alone or combined with PET MPI, to ^{67}Gallium imaging and have demonstrated improved accuracy for detecting cardiac sarcoid.[42,53,54,57,72] Despite the high diagnostic accuracy of FDG-PET, it is currently not included in the most recent updated (2006) diagnostic criteria of the JMHW,

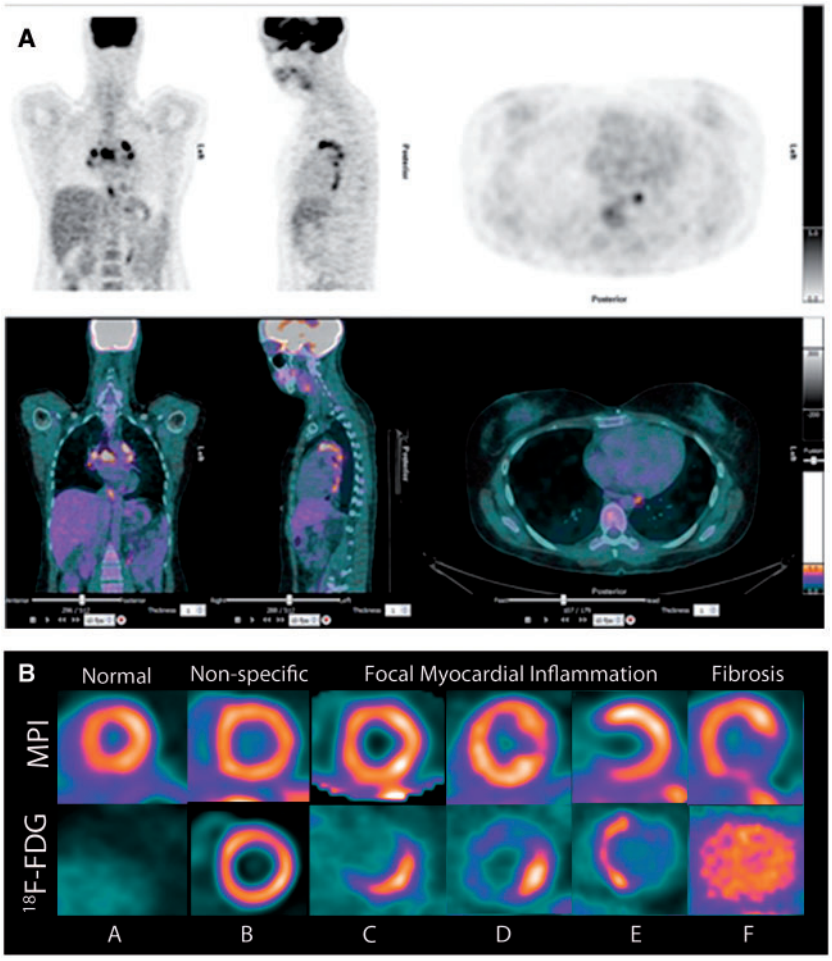

Figure 2 (*A*) Example of FDG and myocardial perfusion PET in sarcoidosis. The whole body hybrid FDG PET/CT study (A) showed multiple foci of inflammation in the mediastinum, but no active inflammation in the myocardium; hybrid imaging confirms regions of FDG uptake in the mediastinal lymphnodes and not the myocardium. Assessment of systemic disease activity is an advantage of FDG PET compared with echocardiography or CMR. (*B*) Patterns of myocardial perfusion imaging (MPI) and FDG imaging of myocardial inflammation. This figure shows rest MPI in the top row and FDG imaging of myocardial inflammation in the bottom row. A pattern of no myocardial FDG uptake is normal if MPI is normal (A), or fibrosis when MPI is abnormal (*F*, the pattern of FDG uptake represents blood pool activity). A pattern of diffuse myocardial FDG uptake represents a non-specific finding that may be seen with incomplete suppression of physiological myocardial glucose utilization and is not diagnostic for cardiac sarcoidosis (B). A pattern of focal myocardial FDG uptake is consistent with active myocardial inflammation without (*C*, *D*, no perfusion defect) or with coexistent fibrosis (*E*, perfusion defect). Of note, Pattern C, isolated focal FDG uptake in the basal lateral wall in the absence of a perfusion defect, abnormal wall motion, or delayed enhancement on CMR may have reduced specificity for active myocardial inflammation.

published by the Japan Society of Sarcoidosis and Other Granulomatous Disorders.[9] The more recent Heart Rhythm Society Consensus Recommendations[10] suggest that clinical diagnosis of cardiac sarcoidosis is probable if there is histological proof of extra-cardiac sarcoidosis and one or more findings which include a pattern consistent with cardiac sarcoidosis on imaging (including dedicated cardiac PET, late gadolinium enhancement (LGE) on CMR, positive ^{67}Gallium imaging), unexplained reduced left ventricular ejection fraction (LVEF) <40%, unexplained sustained (spontaneous or induced ventricular tachycardia, VT), second degree atrio-ventricular (AV) heart block (Type 2, also called Mobitz Type II) or third degree heart block, steroid/immunosuppression responsive cardiomyopathy or heart block, and other causes for the cardiac manifestation(s) have been reasonably excluded.

In summary, FDG-PET is the best clinically available tool for imaging myocardial inflammation. Careful preparation to suppress physiological myocardial glucose utilization is essential for FDG-PET imaging of cardiac sarcoidosis. Combined assessment of perfusion and inflammation is necessary to provide optimal information for the diagnosis, risk assessment, and management of cardiac sarcoidosis.

Table 3 Interpretation of combined rest perfusion and FDG imaging

Rest perfusion	FDG	Interpretation
Normal perfusion and metabolism		
Normal	No uptake	Negative for cardiac sarcoidosis
Normal	Diffuse	Diffuse (usually homogeneous) FDG most likely due to suboptimal patient preparation
Normal	Isolated lateral wall uptake	May be a normal variant
Abnormal perfusion or metabolism		
Normal	Focal	Could represent early disease
Defect	No uptake	Perfusion defect represents scar from sarcoidosis or other etiology
Abnormal perfusion and metabolism		
Defect	Focal in area of perfusion defect	Active inflammation with scar in the same location
Defect	Focal on diffuse with focal in area of perfusion defect	Active inflammation with scar in the same location with either diffuse inflammation or suboptimal preparation
Defect	Focal in area of normal perfusion	Presence of both scar and inflammation in different segments of the myocardium

Adapted from Blankstein *et al.*[45]

Cardiovascular magnetic resonance

Rationale

CMR can provide a wide range of potentially unique information in inflammatory and infiltrative heart disease. Specific CMR imaging sequences with characteristic findings in cardiac sarcoidosis have been reported. Although evidence from large-scale prospective clinical studies for the use of CMR in cardiac sarcoidosis is lacking, several smaller studies have demonstrated its potential to detect cardiac involvement in sarcoidosis and predict adverse clinical outcome.

Image acquisition

Patient preparation for CMR is detailed in Supplementary data online, *Supplement 3*. Standardized acquisition protocols are available for all modern cardiac enabled MRI scanners[73] and in suspected cardiac sarcoidosis typically include low resolution localizer images, cine imaging in multiple planes, oedema sensitive (T2-weighted) and late gadolinium enhancement (LGE) imaging, with parametric mapping as an emerging addition. Images should be acquired with standardized methods[73] and in standardized and reproducible imaging planes, allowing reliable correlation between different components of the study. T2 weighted images, most commonly using Short Tau Inversion Recovery (T2-STIR) methods, are sensitive to the free water content of tissue and can thus detect myocardial inflammation and oedema in cardiac sarcoidosis[74] (*Table 4*). T2-STIR methods suffer from relatively low sensitivity however due to low contrast to noise ratio and can also be affected by artefacts from slow moving blood at the endocardial surface. LGE imaging uses dual inversion saturation recovery pulse sequences to delineate myocardial tissue with expanded extracellular space as occurs in infiltration, scaring or fibrosis. Granulomatous infiltration in cardiac sarcoidosis can be sensitively detected with this method as focal hyperenhancement.[7,76–81] Cine CMR is most commonly performed with Steady State Free Precession (SSFP) methods, acquiring a stack of images covering the entire heart in the left ventricular short-axis and additional long-axis sections. Cine CMR is the most accurate imaging method for the measurement of left and right heart dimensions and contractile function. In later stages of cardiac sarcoidosis contractile function can be impaired and is sensitively detected and followed up with CMR. Cine CMR also allows detection of ventricular aneurysms, pericardial effusion and valve pathology. Increasingly, parametric T1 and T2 mapping provide quantitative measures of tissue inflammation, oedema and diffuse fibrosis, but are only beginning to be used in sarcoidosis, so that, experience with these newer methods is limited.

Interpretation and reporting

The most commonly found CMR abnormality in patients with sarcoidosis is focal hyperenhancement on LGE images, usually readily detectable by visual inspection. Mid-wall or sub-epicardial enhancement in the basal ventricular wall, the lateral wall and septum is considered the most common pattern in cardiac sarcoidosis, but subendocardial or transmural enhancement in other myocardial locations has also been described[82] (*Figure 3*). Importantly, LGE findings are not specific to sarcoidosis and the differential diagnosis from myocarditis and other inflammatory conditions can be challenging. Using thresholding methods, the extent of hyperenhancement on LGE can be quantified to give a measure of disease extent, but no consensus exists so far for to the optimal threshold for diagnosis. Oedema sensitive images may show areas of high signal in patients with cardiac sarcoidosis, suggestive of inflammation and oedema. However, reliable detection of oedema can be difficult as T2 weighted images have a relatively low signal to noise ratio and can be prone to artifacts, in particular from slow flow at the endocardial boundary. A careful review of the images is therefore mandatory. By calculating the ratio of signal in skeletal muscle and the myocardium,

Table 4 Recommended CMR protocol and analysis in sarcoidosis

	Pulse sequence	Imaging planes	Analysis and tips
Morphology and function	1. Steady State Free Precession (SSFP) cine imaging	i. Whole heart coverage in LV short-axis plane from the mitral valve to the apex.	Use real time acquisition in patients with poor breath holding.
	- Slice thickness 6–8 mm, with 2–4 mm inter-slice gaps to equal 10 mm.	ii. 4 chamber plane	Report regional and global LV and RV function as well as aneurysms and other morphological abnormalities.
	- Temporal resolution ≤45 ms between phases	iii. Vertical long-axis plane	
	- Parallel imaging as available	iv. LV outflow tract (LVOT) plane	
T2-weighted imaging	1. Black blood T2-W STIR (Short Tau Inversion Recovery)	Same planes as for cine imaging (short- and long-axis views)	Report presence of focal signal enhancement suggestive of oedema.
	2. Bright blood T2-W sequences		Beware slow flow artefacts at endocardial border in particular in long-axis planes.
	a. T2-prepared single-shot SSFP sequence		
	b. Turbo spin echo-steady SSFP hybrid		
Late Gadolinium Enhancement	1. 2D/3D segmented inversion recovery gradient or SSFP pulse sequence	Same planes as for cine imaging (short- and long-axis views)	PSIR is less dependent on correct TI.
	2. Phase-Sensitive Inversion-Recovery (PSIR) pulse sequence		Use Single Shot for patients with irregular heart rhythm, and/or difficulty breath holding.
	3. Single-shot imaging (SSFP readout)		
	- Slice thickness same as for cine imaging		Report presence of focal hyperenhancement.
	- In-plane resolution, ~1.4–1.8 mm		
	- Inversion time to null normal myocardium.		Consider using thresholding methods.
	- Acquisition duration per R-R interval below 200 ms, less in the setting of tachycardia.		
	- Read-out usually every other heart beat unless tachycardia or bradycardia		
	- Images acquired during diastolic stand-still.		
	- Acquired at least 10 min after gadolinium injection		
T2 mapping (optional)	1. T2-prepared single-shot SSFP sequence acquired with different T2 prep time	Typically LV short-axis	Acquire prior to contrast administration.
			Review maps for presence of focal signal enhancement suggestive of oedema.
T1 mapping (optional)	1. Look Locker imaging (MOLLI or ShMOLLI or equivalent)	Typically LV short-axis	Performed prior to contrast and at 2–4 time points post-contrast bolus.
	2. Saturation Recovery Single-Shot Acquisition (SASHA)		Alternatively, constant infusion of contrast can be used rather than bolus.
			Review maps for presence of focal signal enhancement suggestive of oedema/fibrosis.

Modified from Kramer *et al.*[75]

a semi-quantitative measure of oedema can be derived. In sarcoidosis, cine CMR provides quantitative measurements of volumes and EF and shows similar abnormalities as seen on 2D echocardiography. A CMR report in suspected sarcoidosis should include a description of extracardiac findings (including lung nodules, splenic or hepatic perfusion defects), measurements of right and left ventricular size, volumes, and function, comments on pericardial and valve pathology, presence of oedema and a description of the location and size of lesions seen on LGE.

Diagnostic accuracy

Multi-parametric CMR is a sensitive tool for the detection of cardiac involvement in sarcoidosis. However, to date CMR has only been used in relatively small observational studies and as for other imaging

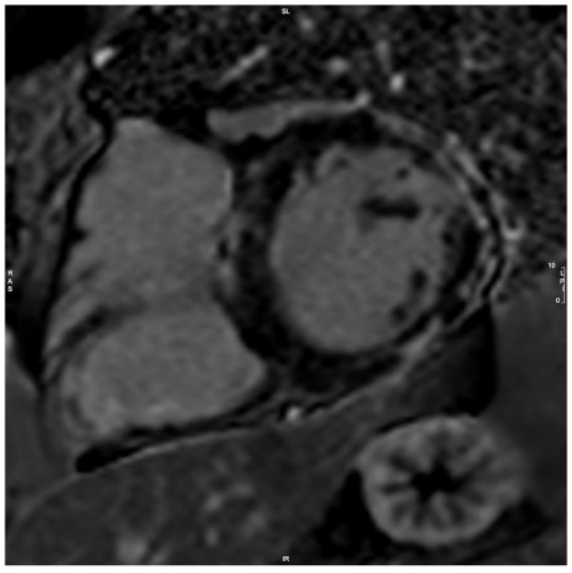

Figure 3 Example of cardiac sarcoidosis diagnosed with CMR. Late gadolinium enhanced CMR image from an Afro-Caribbean male who presented with pulmonary sarcoidosis and suspected cardiac involvement. The image shows focal mid-myocardial contrast enhancement in the basal inferior and lateral wall and septum. (Image courtesy Dr Tevfik Ismail, King's College London, United Kingdom.)

modalities, prospectively designed diagnostic accuracy studies against histological endpoints are lacking. Similar to FDG-PET studies, estimates of the diagnostic accuracy of CMR in cardiac sarcoidosis are hampered by the lack of a gold standard.

The first report on the diagnostic accuracy of CMR for cardiac sarcoidosis showed a sensitivity of 100% and specificity of 78% vs. the JMHW criteria.[80] The relatively low specificity can be explained as the CMR data were compared using the low diagnostic sensitive JMHW criteria. Patel *et al.*, showed that CMR compared with the JMHW criteria resulted in a higher incidence of cardiac involvement in sarcoidosis (i.e. >2-fold increase in cardiac sarcoidosis diagnosis vs. JMHW criteria), leading to a significant improvement in prognostication of adverse events by CMR when compared with JMHW criteria.[82]

The most consistently reported finding on CMR is focal LGE, described in numerous smaller reports[7,77–81] and two larger studies, which found LGE in 39 of 155 (25.5%) and 41 of 205 (20%) patients with extra-cardiac sarcoidosis,[76,83] and a systematic review and meta-analysis.[84] Importantly, LGE was seen in patients who did not meet standard JMHW guidelines, suggesting that CMR is a more sensitive test to detect cardiac involvement in sarcoidosis than established diagnostic criteria, however specificity may be variable. Although small reports have suggested that some lesions on LGE regress following steroid therapy,[85] this needs to be further evaluated.

Oedema sensitive T2 weighted imaging and T2 mapping have only been used in cases series and small feasibility studies. In 32 patients with sarcoidosis, increased signal in the interventricular septum on T2-weighted images was more common in patients with complete heart block than patients with normal conduction.[74] T2 mapping has been used in a study of 28 patients and showed reduced T2 values in regions of LGE, which the authors speculate may reflect an inactive phase of the disease.[86]

The above limitations related to evaluating the diagnostic accuracy of CMR, similar to the ones for FDG-PET underscore the importance of evaluating the prognostic findings provided by various imaging results, as the ultimate identification of patients who have a higher risk of adverse events may be most important for guiding therapy. Finally, as discussed in 'Approach to sarcoidosis imaging procedures' section, with the exception of a few small reports, focal LGE by CMR has consistently been linked with adverse clinical outcome.[76,77,87,88]

Of equal importance, the absence of LGE in patients with suspected cardiac sarcoidosis is generally associated with a favourable prognosis,[76] although some studies have shown conflicting findings.[77]

In summary, CMR is a multi-parametric imaging modality that can accurately delineate cardiac morphology and function and interrogate tissue characteristics. CMR is a valuable tool for the diagnosis and risk assessment of cardiac sarcoidosis. Whether CMR can be used to assess response to therapy is unclear, as CMR findings are limited by a relatively low specificity to distinguish scar from active inflammation. However, the relatively high sensitivity of the technique contributes to the exclusion of cardiac sarcoidosis.

Computed tomography

CT plays a limited role in the evaluation and management of patients with systemic sarcoidosis. Although, cardiac CT has no established role for the diagnosis of cardiac sarcoidosis, coronary CT angiography may play an important role in excluding CAD in individuals with LV dysfunction and regional wall motion abnormalities.

Imaging to guide biopsy

Cardiac involvement is often difficult to diagnose because endomyocardial biopsy is limited by sampling error and complication risk cannot be ignored.[45,89,90] The diagnosis of isolated cardiac involvement is therefore difficult and laboratory abnormalities are non-specific. If the likelihood of an inflammatory cardiomyopathy remains high despite a negative endomyocardial biopsy, pursuing the diagnosis with repeated and image-guided biopsies of the myocardium or mediastinal lymph nodes is worthwhile and may markedly improve the detection rate of cardiac sarcoidosis.[91] Biopsy guided by electromechanical mapping has also been used for the diagnosis of isolated cardiac sarcoidosis.[92] Although focal myocardial LGE, high T2 signal on CMR, and increased glucose uptake on cardiac FDG-PET are non-specific signs of myocardial damage or inflammation, in patients with histologically proven extra-cardiac sarcoidosis they provide sensitive signs of sarcoid involvement of the heart.[54,82] In patients with biopsy-proven cardiac sarcoidosis, abnormal LGE and FDG-PET findings were observed in 94% and 80% of patients, respectively.[91] However, without histopathological verification, even typical abnormalities on CMR or PET may not provide a definitive diagnosis and decisions regarding long-term

immunosuppression in such patients with suspected, but not proven, cardiac sarcoidosis remains challenging and must be individualized. The role of hybrid PET/CT and PET/MRI to guide biopsy remains to be evaluated (see 'Future directions' section).

In summary, abnormal cardiac findings on CMR and/or FDG-PET are frequent and suggest localized areas of myocardial damage and/or inflammation in patients with cardiac sarcoidosis. In a clinical setting suggestive of cardiac sarcoidosis, 'hot' mediastinal or cervical lymph nodes on FDG-PET provide a biopsy target that may improve the success rate of identifying sarcoid histopathology. The potential role of image-guided endomyocardial biopsy to improve the yield for histopathological diagnosis of cardiac sarcoidosis requires further evaluation.

Imaging to initiate and monitor therapy

Immunosuppressive therapy is frequently used to treat cardiac sarcoidosis. Sarcoidosis experts, using a Delphi study method, agreed on the treatment of cardiac sarcoidosis with immunosuppressive therapy for the following clinical scenarios: LV dysfunction, ventricular arrhythmias, hypermetabolic activity on cardiac FDG-PET, presence of conduction defects, LGE on CMR, or right ventricular dysfunction in the absence of pulmonary hypertension.[93] But, due to high side effect profile of immunosuppressive drugs, image guided initiation and tailoring of therapy are critical.

A multimodality imaging approach may be necessary for the decision making about pacemaker or ICD.[10] Per HRS guidelines,[10] ICD is indicated, if LVEF remains <35% after immunosuppressive therapy (Class I) or if LGE is present in patients with LVEF 35–49% after immunosuppression (Class IIb).

Echocardiography and/or CMR features are not very specific for inflammation. However, they may help in the assessment of LV remodeling, left as well as right ventricular function, pulmonary artery hypertension and in the follow-up of end stage heart failure from cardiac sarcoidosis before and after heart transplantation.[25] The use of echocardiography and CMR (and LGE) to assess changes in inflammation in response to therapy is limited.[94]

Observational studies suggest an important role for FDG-PET to monitor efficacy of immunosuppressive therapy.[53] Osborne

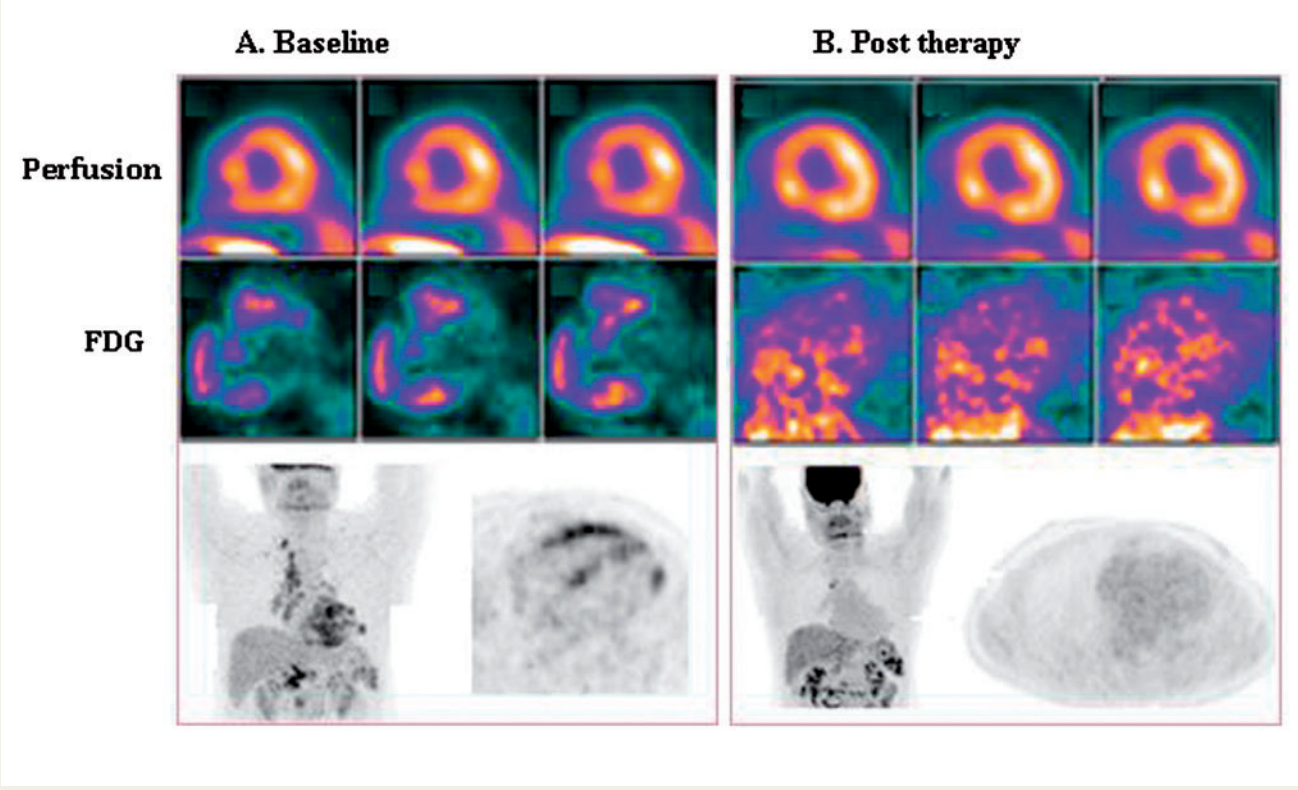

Figure 4 Example of FDG and myocardial perfusion PET in sarcoidosis: Assessing response to therapy with FDG PET. A 48 year old man with mild exertional dyspnea with exercise that progressed to more severe dyspnea and with lightheadedness and dizziness. His ECG should complete heart block with ventricular escape rate of 45 bpm, catheterization revealed no coronary artery disease, and his left ventricular ejection fraction was 52%. A cardiac MRI suggested four areas of inflammatory/infiltrative processes in the basal septal and anteroseptal regions. A CT scan of the chest revealed enlarged mediastinal lymph nodes and bilateral pulmonary nodules. An endomyocardial biopsy showed non-specific mild hypertrophy. A mediastinoscopy with biopsy of a mediastinal lymph nodes confirmed extensive (confluent) non-necrotizing granulomas consistent with sarcoidosis. An FDG PET scan was performed prior to initiation of Prednisone therapy. It revealed multiple foci of inflammation in the left and right ventricular walls (SUV max 5.7) as well as in the mediastinum. Oral prednisone 40 mg per day was initiated and an ICD was implanted. Three months after high dose steroid therapy, a repeat FDG PET scan showed that myocardial (SUV max 1.5) and mediastinal inflammation is substantially decreased (blood pool FDG activity is noted), but splenic and abdominal lymph node inflammation persisted. No myocardial perfusion defects were noted suggesting no regions of fibrosis.

et al. examined 23 patients who underwent serial FDG-PET exams during treatment for cardiac sarcoidosis. They showed that a quantitative reduction in the intensity (i.e. SUV max) or extent (i.e. volume of inflammation above a pre-specified SUV threshold) was associated with improvement in LVEF.[59] Although clear response to therapy is seen in some case, (*Figure 4*) the use of visual analysis to assess serial changes in response to therapy may be limited particularly when there is partial response (see 'Myocardial perfusion imaging' section). Quantitative metrics of SUVmax as well as volume of myocardial pixels with SUV above a certain threshold, and changes in extent and severity of myocardial perfusion, may be preferred to assess response to therapy. Whether steroid induced glucose metabolic changes influence FDG uptake by the myocardium is not known. The duration of treatment is based on clinical response and can be guided by disease activity on FDG PET, *Figure 6*.[88] The optimal timing to repeat FDG-PET imaging is not known. We suggest repeating FDG PET approximately 4–6 months after initiation of therapy.

In summary, in the absence of specific guidelines, in asymptomatic patients with cardiac sarcoidosis, echocardiography is useful to follow-up LVEF and to evaluate for new wall motion abnormalities, wall thinning. A quantitative FDG-PET with MPI may be useful to monitor progression of scar and inflammation and assess response to active immunosuppressive therapies. Prospective randomized clinical trials of imaging guided management of immunosuppressive therapy are warranted.

Prognosis

Several groups of investigators have studied the value of structural and functional myocardial changes of cardiac sarcoidosis detected on echocardiography, CMR and FDG-PET in predicting prognosis (*Table 5*). The extent of LV dysfunction and dilatation at baseline are important predictors of survival.[23] Further, a reduced global longitudinal strain is an independent predictor of adverse events among patients with suspected cardiac sarcoidosis.[25] The presence of LGE on CMR, including focal LGE,[76] and the extent of LGE (LGE mass ≥ 20% of LV mass), is associated with a higher risk of death or VT and a lower likelihood of improvement in LV function.[83,99] The

Table 5 Summary of studies examining the prognostic value of CMR and FDG PET in cardiac sarcoidosis

Study	Number/type of patients	Patients with abnormal LGE/PET N (%)	Median F/U (months)	Overall number of Events	Number of events in patients without LGE/normal PET	Conclusions
Patel *et al.*[82]	81 w/extra cardiac disease	21 (26%)	21m	8 [5 death, 2 VT, 1 AVB]	2 [1 cardiac death; 1 non-cardiac death]	(+)CMR associated with events; more sensitive than clinical criteria
Greulich *et al.*[76]	155 w/extra cardiac disease	39 (25%)	31m	12 [death/SCD/ICD Rx]	1 [1 non-cardiac death]	(+) CMR is a strong predictor of potentially lethal events
Nagai *et al.*[77]	61 w/extra cardiac disease	8 (13%)	50m	1 [1 AVB]	2 [2 non-cardiac death]	both patients with and w/out LGE had low event rates
Nadel *et al.*[95]	106 w/extra cardiac or cardiac disease	32 (30%)	37m (mean)	4 SCD	1	LGE → higher rate of SCD/VT/VF
				8 VT/VF [8 no cardiac deaths]	[1 SCD]	ICD in cardiac sarcoidosis → associated with lower mortality
Murtagh *et al.*[83]	205 w/extra cardiac disease AND EF > 50%	41 (20%)	36m (mean)	12 death/VT [8 deaths; 4 VT]	2 [2 deaths]	LGE → higher rate of death/VT, even with preserved EF
Blankstein *et al.*[45]	118 w/extra cardiac disease	37 (31%)	18m	31 (27 VT and 8 deaths)	4 VT events and 3 deaths, 1 in a patient who also had VT	Focal PD and FDG uptake on cardiac PET identifies patients at higher risk of death or VT
Ahmadian *et al.*[44]	34 w/extra cardiac disease	23 (61%)	3m	11 VT, AVB, heart failure.	1	Quantification of FDG uptake in CS by CMA is an important tool for prognostication in patients with known or suspected cardiac sarcoidosis.

CS, cardiac sarcoidosis; PD, perfusion defects; LGE, late gadolinium enhancement; VT, ventricle tachycardia; VF, ventricle fibrillation; SCD, sudden cardiac death; AVB, atrioventricular block; ICD, implantable cardioverter defibrillators; EF, ejection fraction; CMA, Cardiac Metabolic Activity.

prognostic value of other CMR findings have been less well studied and no reports are available for T2 weighted CMR. In one study, LVEF was a weaker prognosticator than LGE.[83] Importantly, patients who do not have any late enhancement had an extremely low event rate, with very few cardiac events reported. Therefore, CMR may be used not only to exclude the presence of cardiac sarcoidosis in the vast majority of patients with suspected disease, but also to identify patients who have an excellent prognosis, with a strong value of LGE. Also, patients with a combination of (a) increased myocardial inflammation (i.e. focal uptake of FDG) and (b) resting perfusion defects are at high risk for death or VT (four-fold increased risk),[45] independent of LVEF, clinical criteria, and the presence of active extra-cardiac disease.[44,45] In addition, the presence of focal uptake of FDG by the right ventricle was found to be associated with an extremely high event rate. Notably, the presence or absence of active extra-cardiac sarcoidosis was not associated with adverse events.

Based on the published studies to date, the event rate in patients referred for cardiac PET is higher than those referred for CMR. This difference can be explained by the fact that patients referred for PET are more likely to already have an ICD (which is sometimes a contraindication for CMR) and prior history of VT. Therefore, this most likely reflects a referral bias based on the fact that patients referred for PET imaging have higher degree of disease activity.[97,98]

In summary, while there is a paucity of data in this regard, it seems plausible that the findings provided by echocardiography (which provides an estimate of myocardial remodeling and function), CMR (which provides an estimate of the extent of scar), PET imaging with FDG (which provide an estimate of the overall magnitude and extent of myocardial inflammation), and MPI (which provides an estimate of microvascular dysfunction and/or scar) may be complementary, both for diagnosing and treating disease, as well as for providing an estimate of the risk of future adverse events.

Approach to sarcoidosis imaging procedures

The approach to cardiac sarcoidosis imaging may include multiple imaging tests (*Figure 5*). The main indications for advanced imaging in cardiac sarcoidosis: (i) suspected cardiac involvement in patients with biopsy-proven extracardiac sarcoidosis and symptoms (unexplained syncope/presyncope/significant palpitations), and/or abnormal ECG and/or inconclusive echocardiogram[10]; (ii) suspected relapse in a patient with a history of cardiac sarcoidosis; (iii) treatment monitoring in patients diagnosed with cardiac sarcoidosis. In addition, advanced imaging may contribute to (iv) prognostic assessment that may impact on therapeutic management and follow up.[19,99,100] Radionuclide imaging, particularly FDG-PET with SUV quantitation and in conjunction with myocardial perfusion imaging, may be useful to not only detect myocardial inflammation but also to monitor progression of scar and inflammation and assess response to active immunosuppressive therapies (*Figure 6*).

Future directions

The future of cardiac sarcoidosis imaging relies on development of novel inflammation specific radiotracers, hybrid imaging devices,

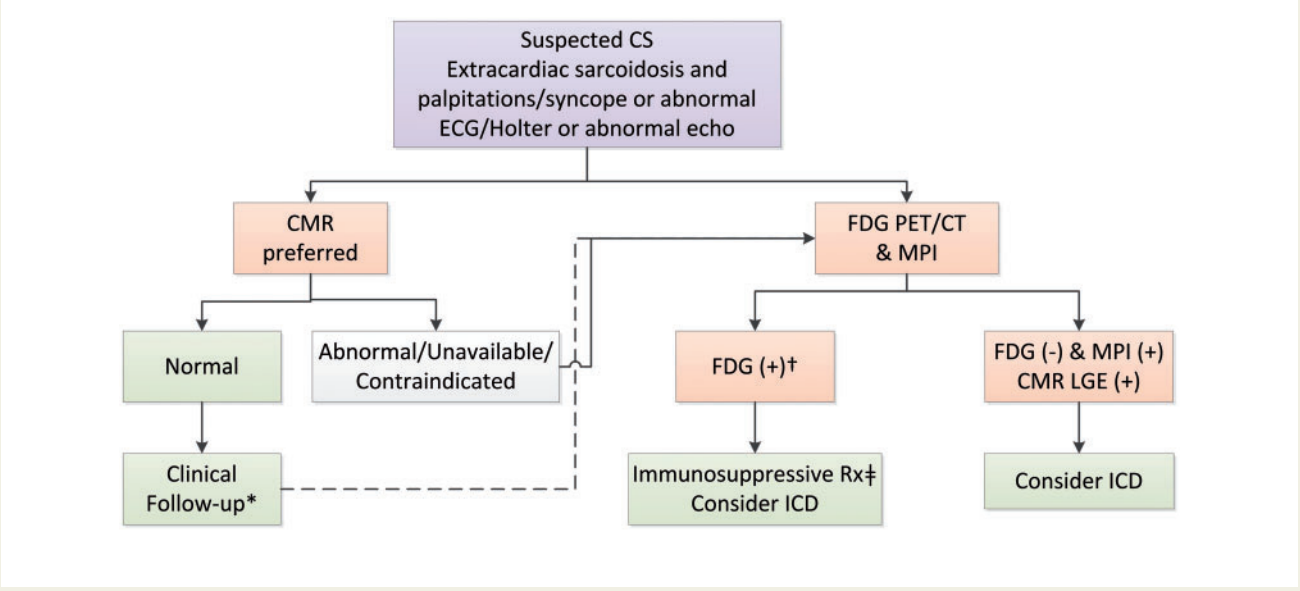

Figure 5 Non-invasive imaging approach to initial evaluation of patients with suspected cardiac sarcoidosis. CS, cardiac sarcoidosis; CMR, cardiovascular magnetic resonance imaging; ECG, electrocardiogram; Echo, echocardiogram; FDG, ^{18}F-fluorodeoxyglucose; ICD, implantable cardioverter defibrillator; LGE, late gadolinium enhancement; MPI, myocardial perfusion imaging; Rx, therapy. †Identify coexistent inflammation; FDG PET/CT may be preferred first test in individuals with known systemic sarcoidosis where systemic sarcoidosis activity needs to be assessed. *If clinical suspicion is high or symptoms persist, FDG PET/CT and MPI may be considered in patients with normal CMR. ‡Immunosuppressive Rx may be considered taking into account the amount of inflammation. Patients with ICD are excluded for CMR.

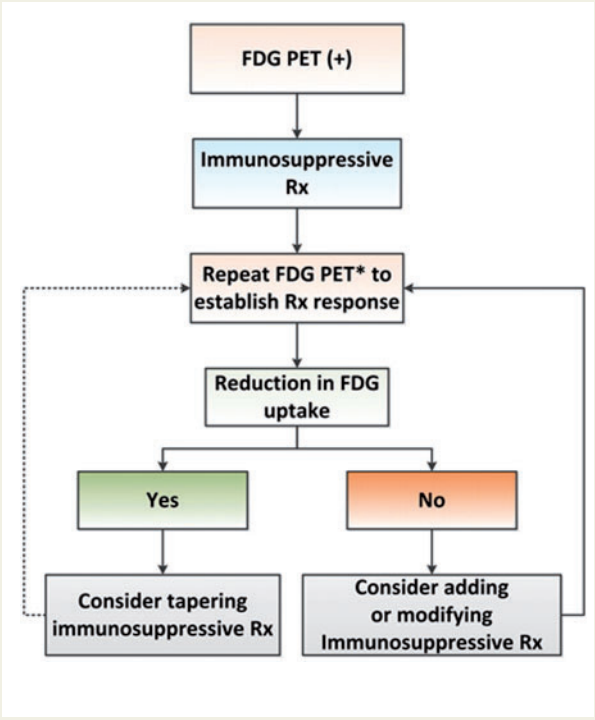

Figure 6 Use of FDG PET imaging to guide immunosuppressive therapy in cardiac sarcoidosis. In cardiac sarcoidosis patients with positive FDG-PET imaging, repeat FDG-PET imaging can be repeated to judge treatment response, however whether the result of FDG-PET can be used to taper immunosuppressive therapy is currently unclear and evidence is lacking to adjust treatment based on imaging. *The optimal timing of repeat FDG-PET imaging is not well established, but approximately 4–6 months following treatment initiation is commonly employed, or when significant changes in therapy are being considered. FDG: ^{18}F-fluorodeoxyglucose; Rx: therapy.

as well as multi-disciplinary and multi-institutional collaborations using standardized imaging methods. Novel somatostatin receptor binding radiopharmaceuticals such as ^{68}Ga-DOTATOC/TATE/NOC, radiotracers of inflammation (^{11}C-PBR28) and ^{18}F-FLT (fluorothymidine) as well as novel CMR contrast agents such as Ferumoxytol (contrast agent consisting of ultrasmall superparamagnetic particles of iron oxide (USPIOs) that are taken up by macrophages, are under evaluation (clinicaltrials.gov). In addition, novel hybrid imaging systems combining PET and MRI (PET/MRI camera) provide highly complementary information on tissue characterization and metabolic information in one single session.[101,102] Due to the lack of a gold standard for the diagnosis of cardiac sarcoidosis, the lack of specificity of the imaging findings, and the potential risk of high-dose immunosuppressive therapies, sarcoidosis is challenging to diagnose and manage. A multidisciplinary heart team approach involving experienced imagers (echocardiography, CMR, and radionuclide imaging), internal medicine physicians, cardiologists, heart failure physicians, pulmonary physicians, electrophysiologists, rheumatologists, pathologists, and others will be critical to manage sarcoidosis.

Conclusions

Sarcoidosis is a complex systemic disease that often requires multidisciplinary expertise and approach for diagnosis and management. Detection of cardiac sarcoidosis is important to prevent life-threatening arrhythmias and to preserve LV function in affected individuals. A multi-imaging approach that can identify disease activity, prognosis and response to therapy is needed to improve further the management of patients with cardiac sarcoidosis. Optimal imaging based on standardized procedural guidelines for acquisition, interpretation, and quantification is paramount.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflicts of interest: none declared.

References

1. Ungprasert P, Carmona EM, Utz JP, Ryu JH, Crowson CS, Matteson EL. Epidemiology of Sarcoidosis 1946-2013: a population-based study. *Mayo Clin Proc* 2016;**91**:183–8.
2. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H, Jr., Bresnitz EA *et al.* Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001;**164**:1885–9.
3. Lynch JP, III, Hwang J, Bradfield J, Fishbein M, Shivkumar K, Tung R. Cardiac involvement in sarcoidosis: evolving concepts in diagnosis and treatment. *Semin Respir Crit Care Med* 2014;**35**:372–90.
4. Perry A, Vuitch F. Causes of death in patients with sarcoidosis. A morphologic study of 38 autopsies with clinicopathologic correlations. *Arch Pathol Lab Med* 1995;**119**:167–72.
5. Silverman KJ, Hutchins GM, Bulkley BH. Cardiac sarcoid: a clinicopathologic study of 84 unselected patients with systemic sarcoidosis. *Circulation* 1978;**58**:1204–11.
6. Nelson JE, Kirschner PA, Teirstein AS. Sarcoidosis presenting as heart disease. *Sarcoidosis Vasc Diffuse Lung Dis* 1996;**13**:178–82.
7. Kim JS, Judson MA, Donnino R, Gold M, Cooper LT, Jr., Prystowsky EN *et al.* Cardiac sarcoidosis. *Am Heart J* 2009;**157**:9–21.
8. Yazaki Y, Isobe M, Hiroe M, Morimoto S, Hiramitsu S, Nakano T *et al.* Prognostic determinants of long-term survival in Japanese patients with cardiac sarcoidosis treated with prednisone. *Am J Cardiol* 2001;**88**:1006–10.
9. Jpn Ministry Health Welfare. Diagnostic standard and guidelines for sarcoidosis. *Jpn J Sarcoidosis and Granulomatuous Disord (Japanese)* 2007;**27**:89–102.
10. Birnie DH, Sauer WH, Bogun F, Cooper JM, Culver DA, Duvernoy CS *et al.* HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm* 2014;**11**:1305–23.
11. Cardim N, Galderisi M, Edvardsen T, Plein S, Popescu BA, D'andrea A *et al.* Role of multimodality cardiac imaging in the management of patients with hypertrophic cardiomyopathy: an expert consensus of the European Association of Cardiovascular Imaging Endorsed by the Saudi Heart Association. *Eur Heart J Cardiovasc Imaging* 2015;**16**:280.
12. Cosyns B, Plein S, Nihoyanopoulos P, Smiseth O, Achenbach S, Andrade MJ *et al.* European Association of Cardiovascular Imaging (EACVI) position paper: multimodality imaging in pericardial disease. *Eur Heart J Cardiovasc Imaging* 2014;**16**:12–31.
13. Flachskampf FA, Wouters PF, Edvardsen T, Evangelista A, Habib G, Hoffman P *et al.* Recommendations for transoesophageal echocardiography: EACVI update 2014. *Eur Heart J Cardiovasc Imaging* 2014;**15**:353–65.
14. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA *et al.* Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2013;**14**:611–44.
15. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T *et al.* EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging* 2012;**13**:1–46.
16. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;**16**:233–70.

17. Mor-Avi V, Lang RM, Badano LP, Belohlavek M, Cardim NM, Derumeaux G *et al*. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese. *Society of Echocardiography. J Am Soc Echocardiogr* 2011;**24**:277–313.
18. Popescu BA, Stefanidis A, Nihoyannopoulos P, Fox KF, Ray S, Cardim N *et al*. Updated standards and processes for accreditation of echocardiographic laboratories from The European Association of Cardiovascular Imaging: an executive summary. *Eur Heart J Cardiovasc Imaging* 2014;**15**:1188–93.
19. Aggarwal NR, Snipelisky D, Young PM, Gersh BJ, Cooper LT, Chareonthaitawee P. Advances in imaging for diagnosis and management of cardiac sarcoidosis. *Eur Heart J Cardiovasc Imaging* 2015;**16**:949–58.
20. Focardi M, Picchi A, Nikiforakis N, Bargagli E, Fossi A, Maggiorelli C *et al*. Assessment of cardiac involvement in sarcoidosis by echocardiography. *Rheumatol Int* 2009;**29**:1051–5.
21. Lewin RF, Mor R, Spitzer S, Arditti A, Hellman C, Agmon J. Echocardiographic evaluation of patients with systemic sarcoidosis. *Am Heart J* 1985;**110**:116–22.
22. Burstow DJ, Tajik AJ, Bailey KR, DeRemee RA, Taliercio CP. Two-dimensional echocardiographic findings in systemic sarcoidosis. *Am J Cardiol* 1989;**63**:478–82.
23. Chiu CZ, Nakatani S, Zhang G, Tachibana T, Ohmori F, Yamagishi M *et al*. Prevention of left ventricular remodeling by long-term corticosteroid therapy in patients with cardiac sarcoidosis. *Am J Cardiol* 2005;**95**:143–6.
24. Jain A, Starek PJ, Delany DL. Ventricular tachycardia and ventricular aneurysm due to unrecognized sarcoidosis. *Clin Cardiol* 1990;**13**:738–40.
25. Patel MB, Mor-Avi V, Murtagh G, Bonham CA, Laffin LJ, Hogarth DK *et al*. Right heart involvement in patients with sarcoidosis. *Echocardiography* 2016;**33**:734–41.
26. Vasaiwala SC, Finn C, Delpriore J, Leya F, Gagermeier J, Akar JG *et al*. Prospective study of cardiac sarcoid mimicking arrhythmogenic right ventricular dysplasia. *J Cardiovasc Electrophysiol* 2009;**20**:473–6.
27. Degirmenci H, Demirelli S, Arisoy A, Ermis E, Araz O, Bakirci EM *et al*. Myocardial deformation and total atrial conduction time in the prediction of cardiac involvement in patients with pulmonary sarcoidosis. *Clin Respir J* 2017;**11**:68–77.
28. Joyce E, Ninaber MK, Katsanos S, Debonnaire P, Kamperidis V, Bax JJ *et al*. Subclinical left ventricular dysfunction by echocardiographic speckle-tracking strain analysis relates to outcome in sarcoidosis. *Eur J Heart Fail* 2015;**17**:51–62.
29. Kul S, Ozcelik HK, Uyarel H, Karakus G, Guvenc TS, Yalcınsoy M. Diagnostic value of strain echocardiography, galectin-3, and tenascin-C levels for the identification of patients with pulmonary and cardiac sarcoidosis. *Lung* 2014;**192**:533–42.
30. Orii M, Hirata K, Tanimoto T, Shiono Y, Shimamura K, Yamano T *et al*. Myocardial damage detected by two-dimensional speckle-tracking echocardiography in patients with extracardiac sarcoidosis: comparison with magnetic resonance imaging. *J Am Soc Echocardiogr* 2015;**28**:683–91.
31. Saeed IM, Coggins T, Main ML, Bateman TM. Cardiac sarcoidosis with visually normal wall motion: role of cardiac MRI, FDG PET, and strain echocardiography. *Eur Heart J Cardiovasc Imaging* 2015;**16**:1275.
32. Tigen K, Sunbul M, Karaahmet T, Tasar O, Dundar C, Yalcinsoy M *et al*. Early detection of bi-ventricular and atrial mechanical dysfunction using two-dimensional speckle tracking echocardiography in patients with sarcoidosis. *Lung* 2015;**193**:669–75.
33. Hyodo E, Hozumi T, Takemoto Y, Watanabe H, Muro T, Yamagishi H *et al*. Early detection of cardiac involvement in patients with sarcoidosis by a non-invasive method with ultrasonic tissue characterisation. *Heart* 2004;**90**:1275–80.
34. Yasutake H, Seino Y, Kashiwagi M, Honma H, Matsuzaki T, Takano T. Detection of cardiac sarcoidosis using cardiac markers and myocardial integrated backscatter. *Int J Cardiol* 2005;**102**:259–68.
35. Hourigan LA, Burstow DJ, Pohlner P, Clarke BE, Donnelly JE. Transesophageal echocardiographic abnormalities in a case of cardiac sarcoidosis. *J Am Soc Echocardiogr* 2001;**14**:399–402.
36. Nureki S, Miyazaki E, Nishio S, Ehara C, Yamasue M, Ando M *et al*. Interventricular septal thickening as an early manifestation of cardiac sarcoidosis. *Int Heart J* 2014;**55**:181–3.
37. Yazaki Y, Isobe M, Hayasaka M, Tanaka M, Fujii T, Sekiguchi M. Cardiac sarcoidosis mimicking hypertrophic cardiomyopathy: clinical utility of radionuclide imaging for differential diagnosis. *Jpn Circ J* 1998;**62**:465–8.
38. Skold CM, Larsen FF, Rasmussen E, Pehrsson SK, Eklund AG. Determination of cardiac involvement in sarcoidosis by magnetic resonance imaging and Doppler echocardiography. *J Intern Med* 2002;**252**:465–71.
39. Youssef G, Beanlands RS, Birnie DH, Nery PB. Cardiac sarcoidosis: applications of imaging in diagnosis and directing treatment. *Heart* 2011;**97**:2078–87.
40. Soejima K, Yada H. The work-up and management of patients with apparent or subclinical cardiac sarcoidosis: with emphasis on the associated heart rhythm abnormalities. *J Cardiovasc Electrophysiol* 2009;**20**:578–83.
41. Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M *et al*. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. *Chest* 2008;**133**:1426–35.
42. Nishiyama Y, Yamamoto Y, Fukunaga K, Takinami H, Iwado Y, Satoh K *et al*. Comparative evaluation of 18F-FDG PET and 67Ga scintigraphy in patients with sarcoidosis. *J Nucl Med* 2006;**47**:1571–6.
43. Treglia G, Annunziata S, Sobic-Saranovic D, Bertagna F, Caldarella C, Giovanella L. The role of 18F-FDG-PET and PET/CT in patients with sarcoidosis: an updated evidence-based review. *Acad Radiol* 2014;**21**:675–84.
44. Ahmadian A, Brogan A, Berman J, Sverdlov AL, Mercier G, Mazzini M *et al*. Quantitative interpretation of FDG PET/CT with myocardial perfusion imaging increases diagnostic information in the evaluation of cardiac sarcoidosis. *J Nucl Cardiol* 2014;**21**:925–39.
45. Blankstein R, Osborne M, Naya M, Waller A, Kim CK, Murthy VL *et al*. Cardiac positron emission tomography enhances prognostic assessments of patients with suspected cardiac sarcoidosis. *J Am Coll Cardiol* 2014;**63**:329–36.
46. Koiwa H, Tsujino I, Ohira H, Yoshinaga K, Otsuka N, Nishimura M. Images in cardiovascular medicine: Imaging of cardiac sarcoid lesions using fasting cardiac 18F-fluorodeoxyglucose positron emission tomography: an autopsy case. *Circulation* 2010;**122**:535–6.
47. Kubota R, Yamada S, Kubota K, Ishiwata K, Tamahashi N, Ido T. Intratumoral distribution of fluorine-18-fluorodeoxyglucose in vivo: high accumulation in macrophages and granulation tissues studied by microautoradiography. *J Nucl Med* 1992;**33**:1972–80.
48. Newsholme P, Newsholme EA. Rates of utilization of glucose, glutamine and oleate and formation of end-products by mouse peritoneal macrophages in culture. *Biochem J* 1989;**261**:211–8.
49. Dorbala S, Di Carli MF, Delbeke D, Abbara S, DePuey EG, Dilsizian V *et al*. SNMMI/ASNC/SCCT guideline for cardiac SPECT/CT and PET/CT 1.0. *J Nucl Med* 2013;**54**:1485–507.
50. Jamar F, Buscombe J, Chiti A, Christian PE, Delbeke D, Donohoe KJ *et al*. EANM/SNMMI guideline for 18F-FDG use in inflammation and infection. *J Nucl Med* 2013;**54**:647–58.
51. Morooka M, Moroi M, Uno K, Ito K, Wu J, Nakagawa T *et al*. Long fasting is effective in inhibiting physiological myocardial 18F-FDG uptake and for evaluating active lesions of cardiac sarcoidosis. *EJNMMI Res* 2014;**4**:1.
52. Scholtens AM, Verberne HJ, Budde RP, Lam MG. Additional heparin preadministration improves cardiac glucose metabolism suppression over low-carbohydrate diet alone in (1)(8)F-FDG PET imaging. *J Nucl Med* 2015;**57**:568–73.
53. Yamagishi H, Shirai N, Takagi M, Yoshiyama M, Akioka K, Takeuchi K *et al*. Identification of cardiac sarcoidosis with (13)N-NH(3)/(18)F-FDG PET. *J Nucl Med* 2003;**44**:1030–6.
54. Ishimaru S, Tsujino I, Takei T, Tsukamoto E, Sakaue S, Kamigaki M *et al*. Focal uptake on 18F-fluoro-2-deoxyglucose positron emission tomography images indicates cardiac involvement of sarcoidosis. *Eur Heart J* 2005;**26**:1538–43.
55. Okumura W, Iwasaki T, Toyama T, Iso T, Arai M, Oriuchi N *et al*. Usefulness of fasting 18F-FDG PET in identification of cardiac sarcoidosis. *J Nucl Med* 2004;**45**:1989–98.
56. Mc Ardle BA, Birnie DH, Klein R, de Kemp RA, Leung E, Renaud J *et al*. Is there an association between clinical presentation and the location and extent of myocardial involvement of cardiac sarcoidosis as assessed by (1)(8)F- fluorodoexyglucose positron emission tomography? *Circ Cardiovasc Imaging* 2013;**6**:617–26.
57. Langah R, Spicer K, Gebregziabher M, Gordon L. Effectiveness of prolonged fasting 18f-FDG PET-CT in the detection of cardiac sarcoidosis. *J Nucl Cardiol* 2009;**16**:801–10.
58. Tahara N, Tahara A, Nitta Y, Kodama N, Mizoguchi M, Kaida H *et al*. Heterogeneous myocardial FDG uptake and the disease activity in cardiac sarcoidosis. *JACC Cardiovasc Imaging* 2010;**3**:1219–28.
59. Osborne MT, Hulten EA, Singh A, Waller AH, Bittencourt MS, Stewart GC *et al*. Reduction in (1)(8)F-fluorodeoxyglucose uptake on serial cardiac positron emission tomography is associated with improved left ventricular ejection fraction in patients with cardiac sarcoidosis. *J Nucl Cardiol* 2013;**21**:166–74.
60. Waller AH, Blankstein R. Quantifying myocardial inflammation using F18-fluorodeoxyglucose positron emission tomography in cardiac sarcoidosis. *J Nucl Cardiol* 2014;**21**:940–3.
61. Chapelon-Abric C, de ZD, Duhaut P, Veyssier P, Wechsler B, Huong DL *et al*. Cardiac sarcoidosis: a retrospective study of 41 cases. *Medicine (Baltimore)* 2004;**83**:315–34.
62. Le GD, Menad F, Faraggi M, Weinmann P, Battesti JP, Valeyre D. Myocardial sarcoidosis. Clinical value of technetium-99m sestamibi tomoscintigraphy. *Chest* 1994;**106**:1675–82.
63. Dilsizian V. Highlights from the updated joint ASNC/SNMMI PET myocardial perfusion and metabolism clinical imaging guidelines. *J Nucl Med* 2016;**57**:1327–8.

64. Holly TA, Abbott BG, Al-Mallah M, Calnon DA, Cohen MC, DiFilippo FP *et al.* Single photon-emission computed tomography. *J Nucl Cardiol* 2010;**17**:941–73.
65. Sciagra R, Passeri A, Bucerius J, Verberne HJ, Slart RH, Lindner O *et al.* Clinical use of quantitative cardiac perfusion PET: rationale, modalities and possible indications. Position paper of the Cardiovascular Committee of the European Association of Nuclear Medicine (EANM). *Eur J Nucl Med Mol Imaging* 2016;**43**:1530–45.
66. Verberne HJ, Acampa W, Anagnostopoulos C, Ballinger J, Bengel F, De BP *et al.* EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. *Eur J Nucl Med Mol Imaging* 2015;**42**:1929–40.
67. Kapur A, Latus KA, Davies G, Dhawan RT, Eastick S, Jarritt PH *et al.* A comparison of three radionuclide myocardial perfusion tracers in clinical practice: the ROBUST study. *Eur J Nucl Med Mol Imaging* 2002;**29**:1608–16.
68. Berman JS, Govender P, Ruberg FL, Mazzini M, Miller EJ. Scadding revisited: a proposed staging system for sardiac sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2014;**31**:2–5.
69. Ohira H, Tsujino I, Ishimaru S, Oyama N, Takei T, Tsukamoto E *et al.* Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. *Eur J Nucl Med Mol Imaging* 2008;**35**:933–41.
70. Youssef G, Leung E, Mylonas I, Nery P, Williams K, Wisenberg G *et al.* The use of 18F-FDG PET in the diagnosis of cardiac sarcoidosis: a systematic review and metaanalysis including the Ontario experience. *J Nucl Med* 2012;**53**:241–8.
71. Okada DR, Bravo PE, Vita T, Agarwal V, Osborne MT, Taqueti VR *et al.* Isolated cardiac sarcoidosis: a focused review of an under-recognized entity. *J Nucl Cardiol* 2016;(Epub ahead of print).
72. Okumura W, Iwasaki T, Ueda T, Seki R, Miyajima A, Hatori T *et al.* Usefulness of 18F-FDG PET for diagnosis of cardiac sarcoidosis. *Kaku Igaku* 1999;**36**:341–8.
73. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. *J Cardiovasc Magn Reson* 2013;**15**:91.
74. Orii M, Hirata K, Tanimoto T, Ota S, Shiono Y, Yamano T *et al.* Comparison of cardiac MRI and (18)F-FDG positron emission tomography manifestations and regional response to corticosteroid therapy in newly diagnosed cardiac sarcoidosis with complete heart block. *Heart Rhythm* 2015;**12**:2477–85.
75. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols, society for cardiovascular magnetic resonance: board of trustees task force on standardized protocols. *J Cardiovasc Magn Reson* 2008;**10**:35.
76. Greulich S, Deluigi CC, Gloekler S, Wahl A, Zurn C, Kramer U *et al.* CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. *JACC Cardiovasc Imaging* 2013;**6**:501–11.
77. Nagai T, Kohsaka S, Okuda S, Anzai T, Asano K, Fukuda K. Incidence and prognostic significance of myocardial late gadolinium enhancement in patients with sarcoidosis without cardiac manifestation. *Chest* 2014;**146**:1064–72.
78. Patel AR, Klein MR, Chandra S, Spencer KT, Decara JM, Lang RM *et al.* Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function: an observational study. *Eur J Heart Fail* 2011;**13**:1231–7.
79. Smedema JP, Snoep G, van Kroonenburgh MP, van Geuns RJ, Cheriex EC, Gorgels AP *et al.* The additional value of gadolinium-enhanced MRI to standard assessment for cardiac involvement in patients with pulmonary sarcoidosis. *Chest* 2005;**128**:1629–37.
80. Smedema JP, Snoep G, van Kroonenburgh MP, van Geuns RJ, Dassen WR, Gorgels AP *et al.* Evaluation of the accuracy of gadolinium-enhanced cardiovascular magnetic resonance in the diagnosis of cardiac sarcoidosis. *J Am Coll Cardiol* 2005;**45**:1683–90.
81. Watanabe E, Kimura F, Nakajima T, Hiroe M, Kasai Y, Nagata M *et al.* Late gadolinium enhancement in cardiac sarcoidosis: characteristic magnetic resonance findings and relationship with left ventricular function. *J Thorac Imaging* 2013;**28**:60–6.
82. Patel MR, Cawley PJ, Heitner JF, Klem I, Parker MA, Jaroudi WA *et al.* Detection of myocardial damage in patients with sarcoidosis. *Circulation* 2009;**120**:1969–77.
83. Murtagh G, Laffin LJ, Beshai JF, Maffessanti F, Bonham CA, Patel AV *et al.* Prognosis of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction: risk stratification using cardiovascular magnetic resonance. *Circ Cardiovasc Imaging* 2016;**9**:e003738.
84. Hulten E, Agarwal V, Cahill M, Cole G, Vita T, Parrish S *et al.* Presence of late gadolinium enhancement by cardiac magnetic resonance among patients with suspected cardiac sarcoidosis is associated with adverse cardiovascular prognosis: a systematic review and meta-analysis. *Circ Cardiovasc Imaging* 2016;**9**:e005001.
85. Shimada T, Shimada K, Sakane T, Ochiai K, Tsukihashi H, Fukui M *et al.* Diagnosis of cardiac sarcoidosis and evaluation of the effects of steroid therapy by gadolinium-DTPA-enhanced magnetic resonance imaging. *Am J Med* 2001;**110**:520–7.
86. Yang Y, Safka K, Graham JJ, Roifman I, Zia MI, Wright GA *et al.* Correlation of late gadolinium enhancement MRI and quantitative T2 measurement in cardiac sarcoidosis. *J Magn Reson Imaging* 2014;**39**:609–16.
87. Murphy RC, Hammarstrom S, Samuelsson B. Leukotriene C: a slow-reacting substance from murine mastocytoma cells. *Proc Natl Acad Sci USA*1979;**76**:4275–9.
88. Vignaux O, Dhote R, Duboc D, Blanche P, Dusser D, Weber S *et al.* Clinical significance of myocardial magnetic resonance abnormalities in patients with sarcoidosis: a 1-year follow-up study. *Chest* 2002;**122**:1895–901.
89. Ardehali H, Howard DL, Hariri A, Qasim A, Hare JM, Baughman KL *et al.* A positive endomyocardial biopsy result for sarcoid is associated with poor prognosis in patients with initially unexplained cardiomyopathy. *Am Heart J* 2005;**150**:459–63.
90. Ratner SJ, Fenoglio JJ, Jr, Ursell PC. Utility of endomyocardial biopsy in the diagnosis of cardiac sarcoidosis. *Chest* 1986;**90**:528–33.
91. Kandolin R, Lehtonen J, Graner M, Schildt J, Salmenkivi K, Kivisto SM *et al.* Diagnosing isolated cardiac sarcoidosis. *J Intern Med* 2011;**270**:461–8.
92. Nery PB, Keren A, Healey J, Leug E, Beanlands RS, Birnie DH. Isolated cardiac sarcoidosis: establishing the diagnosis with electroanatomic mapping-guided endomyocardial biopsy. *Can J Cardiol* 2013;**29**:3–1015.
93. Hamzeh NY, Wamboldt FS, Weinberger HD. Management of cardiac sarcoidosis in the United States: a Delphi study. *Chest* 2012;**141**:154–62.
94. Cain MA, Metzl MD, Patel AR, Addetia K, Spencer KT, Sweiss NJ *et al.* Cardiac sarcoidosis detected by late gadolinium enhancement and prevalence of atrial arrhythmias. *Am J Cardiol* 2014;**113**:1556–60.
95. Nadel J, Lancefield T, Voskoboinik A, Taylor AJ. Late gadolinium enhancement identified with cardiac magnetic resonance imaging in sarcoidosis patients is associated with long-term ventricular arrhythmia and sudden cardiac death. *Eur Heart J Cardiovasc Imaging* 2015;**16**:634–41.
96. Ise T, Hasegawa T, Morita Y, Yamada N, Funada A, Takahama H *et al.* Extensive late gadolinium enhancement on cardiovascular magnetic resonance predicts adverse outcomes and lack of improvement in LV function after steroid therapy in cardiac sarcoidosis. *Heart* 2014;**100**:1165–72.
97. Betensky BP, Tschabrunn CM, Zado ES, Goldberg LR, Marchlinski FE, Garcia FC *et al.* Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. *Heart Rhythm* 2012;**9**:884–91.
98. Schuller JL, Zipse M, Crawford T, Bogun F, Beshai J, Patel AR *et al.* Implantable cardioverter defibrillator therapy in patients with cardiac sarcoidosis. *J Cardiovasc Electrophysiol* 2012;**23**:925–9.
99. Blankstein R, Waller AH. Evaluation of Known or Suspected Cardiac Sarcoidosis. *Circ Cardiovasc Imaging* 2016;**9**:e000867.
100. Hulten E, Aslam S, Osborne M, Abbasi S, Bittencourt MS, Blankstein R. Cardiac sarcoidosis-state of the art review. *Cardiovasc Diagn Ther* 2016;**6**:50–63.
101. Schneider S, Batrice A, Rischpler C, Eiber M, Ibrahim T, Nekolla SG. Utility of multimodal cardiac imaging with PET/MRI in cardiac sarcoidosis: implications for diagnosis, monitoring and treatment. *Eur Heart J* 2014;**35**:312.
102. Wada K, Niitsuma T, Yamaki T, Masuda A, Ito H, Kubo H *et al.* Simultaneous cardiac imaging to detect inflammation and scar tissue with F-fluorodeoxyglucose PET/MRI in cardiac sarcoidosis. *J Nucl Cardiol* 2015;
103. Harisankar CN, Mittal BR, Agrawal KL, Abrar ML, Bhattacharya A. Utility of high fat and low carbohydrate diet in suppressing myocardial FDG uptake. *J Nucl Cardiol* 2011;**18**:926–36.