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Imaging (Q Truong, Section Editor)

Updates on the Role of Imaging in Cardiac Sarcoidosis

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Abstract

Purpose of review The non-specific symptom profile and subclinical nature of disease along with variable region of cardiac involvement in systemic sarcoidosis make the diagnosis particularly challenging. The yield of endomyocardial biopsy, a gold standard for diagnosis, is not high unless coupled with additional imaging modalities to detect regional involvement. This review is focused on highlighting the major recent advances in imaging modalities and diagnosis of cardiac sarcoidosis.
Recent findings There has been much interest and increasing research focused on developing newer and improved imaging modalities to establish diagnosis. CMR and ^{18}F- FDG-PET are now considered imaging modalities of choice in most centers worldwide, but the data comparing both methodologies head-to-head is limited. Nevertheless, novel radiotracers (i.e. ^{68}Ga-DOTANOC, ^{18}F-Flurpiridaz, ^{13}N-Ammonia) and hybrid combination PET/CMR imaging are coming to spotlight with improved sensitivity and specificity for earlier detection of myocardial sarcoid.
Summary As CMR and PET are showing increased utilization in cardiac sarcoidosis, ^{201}Th-

SPECT, ^{99m}Tc MDP SPECT, ^{67}Ga Scintigraphy, and ^{82}Rb PET are falling out of favor. Newer imaging modalities, radionuclide tracers, and hybrid PET/CMR combinations have been promising in better detecting cardiac sarcoidosis and are currently being evaluated in larger trials.

Introduction

Sarcoidosis has been present as a clinical entity over last 150 years. It was first described by Hutchinson in 1869 as a cutaneous manifestation [1]. The disease was named 30 years later, when Caesar Boeck, a Norwegian dermatologist in 1899, described nodular skin lesions of epithelioid cells. He named the cells "sarcoid" as he thought the appearance was similar to sarcoma cells [2]. Over time, knowledge about the disease process grew through contributions of numerous physicians and scientists. It was discovered that the disease's hallmark was inflammation and granuloma formation in multiple organ systems. Cardiac sarcoidosis (CS) was first described by Bernstein in 1929, when he incidentally found epicardial granulomas in a post-mortem patient which were identical to their skin granulomas [3]. In 1937, G. Gentzen reported the first death directly attributed to myocardial sarcoidosis [4]. Subsequently, a case of myocardial sarcoidosis was diagnosed clinically and confirmed at autopsy by Adickes et al. [5]. There remains a paucity of data regarding different aspects of cardiac sarcoidosis and some may argue that the lack of information is due to the under-diagnosis of this condition. Additionally, the non-specific nature of symptoms and subclinical nature of disease often hinder prompt diagnosis.

The prevalence of CS amongst patients with systemic sarcoidosis has been reported to be 20 to 27% in the USA and as high as 58% in Japan [6–8]. Yet, autopsy studies indicate that subclinical cardiac involvement may be present in up to 80% of cases [9]. In the USA, 13 to 25% of deaths from sarcoidosis have been attributed to CS, while in Japan, 47 to 85% of deaths from sarcoidosis have been attributed to cardiac involvement [10].

The diagnosis of CS has traditionally been confirmed by endomyocardial biopsy (EMB) from the affected region, with demonstration of non-caseating granulomas. However, the diagnosis becomes challenging due to variation in extent and distribution of affected region. Most of the data regarding distribution and extent of lesions are based on autopsy findings and establishing a diagnosis in the living remains difficult [11–13]. No single diagnostic imaging study has been identified to have sufficient sensitivity and specificity to reliably confirm or rule out CS. Although the imaging has been increasingly used, expert consensus still refers to EMB as the gold standard for diagnosis of CS.

The healthcare burden carried by sarcoidosis patients remains substantial. In a recent US-based population study of patients with sarcoidosis, the mean annual associated health care cost was $119,878 for patients in the 95th–99th percentile and $375,436 for patients in the top percentile, with higher-cost patients being associated with high odds-ratio (OR) of cardiac arrhythmia (OR 1.493; $P < 0.001$), having an inpatient admission (OR = 9.771; $P < 0.001$) and use of biologic therapies [14]. Therefore, an intelligent radio-pathologic algorithm is fundamental to an early and prompt diagnosis of this condition. There has been considerable progress in imaging studies over the recent years. These advances in imaging may not only allow for earlier diagnosis of CS but also for clinicians to follow therapeutic response. This review aims to highlight the most recent advances made in cardiac imaging for establishing a diagnosis and their utility in tracking therapeutic responses in patients with cardiac sarcoidosis.

Diagnostic imaging techniques

A. Two-dimensional (2D) echocardiography

Considering the advancements in modern medicine, cardiac imaging has now become integral to the diagnosis of CS [15]. Two-dimensional Doppler echocardiography is non-invasive, readily available at many institutions, and

relatively inexpensive compared to other modalities. These characteristics make it an attractive initial screening test. Echocardiography offers detailed structural and functional properties of the myocardium and is the initial imaging study of choice for evaluation of patients with suspected or known CS [16, 17••]. Among patients with an established diagnosis, a majority have pathologic abnormalities [18, 19] on echocardiography including but not limited to hypokinesia, dyskinesia, [20, 21] chamber dilation, reduced ejection fraction, structural valvular regurgitation, and wall thinning or thickening [18, 20–22]. Specifically, localized thinning of the basal interventricular septum is present in approximately 90% of patients with CS [9]. Ventricular aneurysms, which commonly affect the infero-posterior wall in this patient population, can easily be distinguished from ischemic aneurysms, as the abnormalities do not follow typical coronary artery distributions.

Left ventricular systolic and diastolic dysfunction are also a common finding, seen in 32% [23] and 14% [19] of patients respectively. Diastolic dysfunction is more common amongst patients who also suffer from pulmonary sarcoid involvement; likewise, early mitral annular tissue velocity of the septal wall has been shown to be lower in this population [24]. Left ventricular systolic dysfunction, when present, may be global, segmental, or regional due to the variable granulomatous involvement of the myocardium. Regional wall motion abnormalities are also common, typically affecting the anterior and apical segments [21]. Longitudinal strain of the left ventricle may be a valuable predictor of therapeutic response as well as adverse outcomes as demonstrated in one small retrospective study of 117 patients in Greece [25, 26]. Right ventricular dysfunction, which may be due to direct granulomatous inflammation of the myocardium but most commonly secondary to pulmonary hypertension from sarcoid lung involvement, is present in up to 5.7% of patients [27].

Pericardial manifestations are not uncommon, with effusions occurring in 19% of patients [28]. These effusions are typically hemodynamically insignificant with rare occurrences of cardiac tamponade. Constrictive pericarditis may develop as well [29].

Valvular dysfunction may be also present and is typically classified as primary or secondary. Primary dysfunction results from direct granulomatous involvement of the valve leaflets. Secondary valvular dysfunction may result from a change in left ventricular geometry, with mitral regurgitation being most prevalent lesion [30]. Valvular lesions, are helpful in diagnosing CS but are unfortunately non-specific and can be associated with a myriad of other cardiac etiologies.

More specific findings, such as granulomatous inflammation, can also be detected on echocardiography via macroscopic echogenic lesions referred to as having a "snowstorm-speckled" pattern [7, 31]. Tissue Doppler derived global and left ventricular longitudinal strain patterns can be detected earlier with greater sensitivity using speckle tracking strain analysis [32–35] along with techniques like pulmonary capillary contrast assessment and cycle-dependent variation of myocardial integrated backscatter analysis [36]. Backscatter analysis specifically measures acoustic properties within the myocardium, which allows for differentiation between affected and normal tissue and is able to detect these abnormalities before conventional echocardiography [36].

Overall echocardiography is a valuable tool in the management of suspected or diagnosed CS. It is far from perfect however. Even in combination with electrocardiogram (ECG), ambulatory rhythm monitoring and thorough

history taking, this imaging modality still has a relatively low sensitivity (85%) and specificity (55%) for diagnosing CS [37].

B. Cardiac magnetic resonance

Both the Heart Rhythm Society (HRS) expert consensus statement and a recent positional statement from the Cardiovascular and Inflammation and Infection Committees of the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology recommend either cardiac magnetic resonance (CMR) or 18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), for patients with any significant abnormality on echocardiography and suspected CS, with CMR being a preferred initial imaging choice [38, 39••]. Diagnosis of CS with CMR has a 100% sensitivity and specificity of 78%, greatly surpassing echocardiography [39••, 40].

In a recent Danish study of 197 screened patients with systemic sarcoidosis, of patients with positive Japanese Ministry of Health and Welfare (JMHW) criteria, 53% were diagnosed by CMR alone compared to 29% with EMB [41]. Part of current diagnostic guidelines for CS, as published by the Heart Rhythm Society, includes late gadolinium enhancement (LGE) on CMR which is present in 97% of patients diagnosed. Similar to 2D-echocardiography, CMR allows for increased image clarity without added radiation risks, as well as the ability to differentiate between ischemic and non-ischemic lesions. Allergic reaction rates are also low, with only 0.005% of patients in a 37,788-patient cohort experiencing severe allergic reaction to gadolinium [42]. Additionally, in patients with a known glomerular filtration rate (GFR) greater than 30 ml/min, gadolinium contrast is considered to be low risk, and with recent advancements and development of newer contrast agents, reported complications (i.e., nephrogenic systemic fibrosis) are even lower [43]. Compared to echocardiography, CMR offers superior visualization of granulomatous infiltration, fibrosis, perfusion defects, and even microvasculitis [44]. As previously mentioned, the presence of LGE on CMR is a diagnostic criterion for CS in several established society guidelines. Late gadolinium enhancement is caused by delayed clearance of gadolinium in fibrotic myocardium [45]. The presence of myocardial scarring detected by LGE on CMR in a non-vascular distribution or in two orthogonal views without the presence of another known LGE process, like myocarditis or hypertrophic obstructive cardiomyopathy, is indicative of CS. The most prevalent myocardial fibrosis patterns detected as LGE on CMR in patients with diagnosed CS include sub-epicardial and mid-wall enhancements of the basal septum or inferolateral wall [46]. This modality of imaging also offers great detail of the right ventricle, often difficult to visualize using conventional 2D-echocardiography. It has been previously documented that right ventricular structural and functional changes may correlate directly with myocardial infiltration or be a result of pulmonary sarcoid involvement [47]. Isolated right ventricular involvement is rare, with large majority of patients rather having concomitant extensive left ventricular involvement. Right-sided involvement may often be patchy/multifocal [48], septal, or present with insertion point enhancement [49•]. Ventricular insertion point enhancement has been documented [50•] and directly correlates with pulmonary arterial pressures, right ventricular mass, volume, and ejection fraction. In cases of

predominant right ventricular involvement, CS can be differentiated from arrhythmogenic right ventricular cardiomyopathy by several features: an older age of onset, a non-familiar pattern, wider QRS complexes, septal involvement with atrioventricular conduction disease, multiple arrhythmogenic foci, concomitant left ventricular disease, and the presence of mediastinal lymphadenopathy, all favoring sarcoid [51].

In diagnosis of CS, T2-weighted CMR sequences have been able to identify areas of definitive myocardial fibrosis for endomyocardial biopsy, increasing the successful detection of pathologic tissue [52]. Although LGE is not a diagnostic criterion by the modified JMHW guidelines, it has been shown that LGE is up to twice as sensitive than JHMW criteria [40, 49]. Additionally, presence of LGE on CMR was directly correlated with significantly higher rates of sudden cardiac death, ventricular arrhythmias, and all-cause mortality (11.9 vs 1.1%) in a meta-analysis of 10 studies (760 patients) [53]. Myocardial scarring identified on CMR via LGE has also been proven to be a potent independent risk factor for death, ventricular arrhythmias, and defibrillator discharges [54•]. Right ventricular involvement was also found to be predictive of ventricular tachyarrhythmias, probably because of higher coexisting left ventricular disease and resulting systolic dysfunction [48, 55, 56]. Newer techniques including circumferential strain (Ecc) and strain change per second (Ecc rate) to better detect focal myocardial damage have shown promising results in small patient samples, particularly in LGE-positive segments [57]. Given these mentioned findings, cardiac magnetic resonance imaging will remain a valuable tool in the evaluation process for suspected CS.

C. 18-fluorodeoxyglucose positron emission tomography

18-Fluorodeoxyglucose positron emission tomography or ^{18}F-FDG PET takes advantage of the high glycolytic activity of the immunologic cells within cardiac sarcoid granulomas. 18-Fluorodeoxyglucose, a glucose analog, is retained within these metabolically active cells enabling high sensitivity imaging [58]. Unfortunately, the myocardium is also a very metabolically active tissue, requiring patient pre-imaging preparation to improve pathologic cellular detection. Many techniques have been developed to suppress normal myocardial tissue uptake of the ^{18}F-FDG. Some strategies require high-fat and low-carbohydrate pre-imaging diets, intravenous unfractionated heparin administration, and long-term fasting. Additionally, ^{18}F-FDG requires comparison-resting perfusion scans to determine active inflammation from scar tissue (SPECT or PET) and a low-dose CT scan for attenuation correction making this imaging modality a high radiation exposure option [59].

Despite several disadvantages and radiation risks associated with ^{18}F-FDG PET, several studies have shown increased sensitivity and specificity when compared to other imaging modalities, including Gallium-67 uptake studies, Thallium-201 perfusion studies, and 99mTc imaging [60–62]. Some of its main advantages when compared with CMR are the ability to perform the tests in patients with implantable cardioverter-defibrillators and the ability to distinguish active inflammation from scar [63]. A recent small study out of France on patients with biopsy-proven sarcoidosis and suspected cardiac involvement reported 100% sensitivity and 91% specificity of FDG-PET/CT findings according to JMHW criteria [64].

There are limited studies comparing CMR to ^{18}F-FDG PET, but one small study suggested that 18F-FDG PET has higher sensitivity (88%) when compared to CMR (75%). This study was quite small however, with only eight patients, and the results were not statistically significant [58, 65•]. A list of studies utilizing CMR and PET in patients with systemic sarcoidosis, known or suspected CS, and their respective sensitivities/specificities for cardiac involvement identification can be seen in Table 1. Initial reports also assume benefit of PET to reliably monitor disease progression and therapeutic monitoring of anti-inflammatory or immunosuppressive therapy [90] for CS, response to ablation therapy in ventricular arrhythmia patients using lesion metabolic activity (LMA) which correlated with a 20-fold higher risk of MACE in non-responders ($p = 0.007$) and may even parallel systolic function ($p = 0.003$) [91•], and association with higher adverse event rates in those with high-degree AVB [92]. Novel ECG parameters of ventricular remodeling (septal and inferolateral) and diffuse QRS fragmentation have also been found to have a strong association with myocardial FDG uptake on PET scans in sarcoidosis patients in a recent Finnish study of 133 patients [93]. FDG PET has also been shown to diagnose CS in asymptomatic patients [94] as this modality allows for detection of inflammation and infiltration via metabolic activity at the cellular level [95•]. In addition, in cases where myocardial LGE usually persists and T2-weighted edema CMR imaging may be unreliable, PET can reveal reduced FDG uptake that can signify a successful response to therapy in myocardial CS [96, 97].

Imaging classification for CS includes normal results (normal perfusion and 18F-FDG uptake), progressive disease (a moderate perfusion defect and increased 18F-FDG uptake), and fibrous disease (severe perfusion defect and minimal or no ^{18}F-FDG uptake) [66]. Additionally, other quantitative techniques with ^{18}F-FDG PET have been developed, like FDG-volume intensity detection, coined cardiac metabolic activity (CMA), which has been independently associated with adverse cardiac events in patients with CS [98•]. In summary, both imaging modalities, ^{18}F-FDG PET and CMR, are very useful in CS and can be used in conjunction to diagnose and evaluate CS. Fibrosis can be identified as LGE on CMR, and inflammatory infiltration can be detected via increased ^{18}F-FDG uptake on PET. Each modality can highlight different pathophysiologic processes in CS, and for this reason, both studies are valuable tools to diagnose and monitor the progression of the disease process.

D. Other imaging modalities: Thallium-201 myocardial perfusion single photon emission computed tomography (^{201}Th-SPECT), technetium 99m-methylene diphosphonate single-photon emission computed tomography (^{99m}Tc MDP SPECT), 67-gallium citrate (^{67}Ga) scintigraphy, and rubidium-82 positron emission computed tomography (82-Rb PET)

Like ^{18}F-FDG PET, Thallium-201 myocardial perfusion single photon emission-computed tomography or ^{201}Th-SPECT is a form of radionuclide imaging used in the evaluation of CS. ^{201}Th-PET has a documented left ventricular perfusion defect detection rate of approximately 30% [22, 99] and has been also valuable in detection of abnormal right ventricular perfusion [100]. Similar to CMR and ^{18}F-FDG PET, perfusion defects on ^{201}Th-SPECT that do not follow coronary artery anatomy and exist in the presence of normal coronary studies are consistent with granulomatous disease [101]. Although this diagnostic process is similar to other myocardial perfusion imaging modalities, its reliability is

Table 1. Summary of trials looking at cardiac involvement in sarcoid patients and respective CMR/PET sensitivity/specificity data

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
Yamagishi [60]	2003	13 N-NH3/18F-FDG PET, ≥ 5 h fast	17	CS	82	–	Thirteen patients (76%) exhibited ^{13}N-NH_3 defects, and 14 patients (82%) exhibited increased 18F-FDG uptake in the heart in contrast to 35% exhibiting myocardial 201-Tl defects and only 18% with abnormal 67-Ga accumulation in the heart
Okumura [66]	2004	18F-FDG PET, ≥ 12 h fast	22	Systemic sarcoidosis	100	90.9	FDG-PET more sensitive than 67-Ga (36.3%) and 99m-Tc (63.6%); Total SUV demonstrated a good linear correlation with serum ACE levels, total DS had a negative correlation with LVEF
Ishimaru [67]	2005	18F-FDG PET, ≥ 6 h fast, heparin	32	Systemic sarcoidosis	100	81.5	Focal myocardial FDG uptake was a characteristic feature in sarcoidosis patients vs controls; 67-Ga did not detect any abnormalities even in 10 patients who had abnormal Holter monitoring and met JMHW criteria
Smedema [40]	2005	CMR	58	Systemic sarcoidosis	100	78	Diagnosis made with CMR in 21% of patients using modified JMHW criteria; LGE present in basal/lateral segments in 73%
Ohira [65•]	2008	18F-FDG PET, ≥ 6 h fast, heparin/CMR	21	Systemic sarcoidosis, suspected CS	87.5/75	38.5/76.9	FDG PET and CMR obtained in 21 consecutive patients; in the sub-analysis between patients with and without steroid therapy, the sensitivity of 18F-FDG PET was lower in patients with steroid therapy (75%) than those without (100%), the opposite was seen

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
							with CMR steroid therapy (100%) than those without (50%); focal uptake on FDG PET correlated with abnormal ACE levels, no such association seen with CMR
Mehta [68•]	2008	82-Rb and 18F-FDG PET/CMR	62	Systemic sarcoidosis	86/36	–	Overall prevalence of CS was 39%; recommendation for CMR and PET imaging in CS patients with uncertain results of other non-invasive testing proposed; patients with abnormal baseline testing who refused to undergo PET or CMR were excluded; PET/CMR not performed on 38 patients deemed not to have CS at initial screening
Matoh [69]	2008	CMR (in conjunction with 201-TI, 99m-Tc sestamibi and 18F-FDG PET—data not reported here)	12	Systemic sarcoidosis	42	–	5 of 12 patients showed abnormalities (diffuse or focal) on CMR, mainly limited to mid- to epi-myocardium; %DEA significantly correlated with LV function; 18F-FDG PET only performed on 3 patients
Langah [70]	2009	18F-FDG PET, > 18 h fast	65	Systemic sarcoidosis, suspected CS	85	90	Prolonged fasting PET demonstrated superior sensitivity and accuracy over 67-Ga; prolonged fasting was used to suppress myocardial physiologic glucose uptake with rationale that it more effectively suppresses serum insulin and glucose levels thereby reducing physiological myocardial glucose influx
Patel [49]	2009	CMR	81		75	78	

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
				Systemic sarcoidosis			DE-CMR identified myocardial abnormalities in significantly more patients when compared with JMHW, 26 vs 12% respectively
Tahara [71]	2010	18F-FDG PET, ≥ 12 h fast	24	Systemic sarcoidosis	100	76	Coefficient of variation (CoV) is a useful marker if active myocardial inflammation in CS patients and improves specificity
Youssef [72]	2012	18F-FDG PET, ≥ 12 h fast	164	Systemic sarcoidosis or suspected CS	89	78	Pooled prevalence of CS was 50%, FDG PET demonstrated superior sensitivity and specificity with significant heterogeneity (38–100%)
			24		79	70	Ontario Registry group
Manabe [73]	2013	18F-FDG PET, > 6 h fast, heparin	50	Systemic sarcoidosis, suspected CS	95.8	61.5	> 60% of patients with abnormal uptake, frequently focal and seen in basal anteroseptal and lateral wall segments and 24% had uptake in right ventricular region; AV block predicted interventricular septum tracer uptake; patients with abnormal ECG had higher number of PET positive regions
McArdle [74]	2013	18F-FDG PET, > 12 h fast, HFLC diet, ± heparin	27	Diagnosed and silent CS	100	83	Looked at consecutive patients presenting with AVB or VT and known CS with clinically silent CS patients as controls; SUV values (both max and LV) were significantly higher in CS patients presenting with VT; no significant differences seen in AVB group
Soussan [75]	2013		58	Suspected CS	83	78	

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
		18F-FDG PET, HFLC diet, 4 h before imaging					HFLC diet is reliable and efficiently eliminated the myocardial physiological uptake except in the papillary muscle (15% of controls)
		CMR	35		100	72	Moderate agreement between CMR and PET (k = 0.5); CMR may not permit to differentiate between inflammation and a fibrotic scar
Ahmadian [76]	2014	18F-FDG PET, ≥ 12 h fast, HFLC diet	31	Known/suspected CS	91	93	CMA was the only independent predictor significantly greater in visually FDG-positive studies, particularly when EF < 50% and a history of preceding adverse clinical event; CMA uptake may correlate with systolic dysfunction and clinical HF; study underpowered to assess relationship between CMA and arrhythmic events
Blankstein [77]	2014	18F-FDG PET, ≥ 3 h fast, HFLC diet	118	Known/suspected CS	71	45	Abnormal PET findings were predictive of adverse events, and the presence of both a perfusion defect and abnormal FDG (29% of patients) was associated with hazard ratio of 3.9 ($p < 0.01$) and remained significant after adjusting for LVEF and clinical criteria
Manabe [78]	2014	18F-FDG PET, ≥ 6 h fast, HFLC diet, heparin	59	Systemic sarcoidosis, suspected CS	93	69	Right ventricular non-diffuse FDG uptake was strongly suspicious for sarcoid involvement and was associated with a broader LV regional involvement more

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
							frequently meeting the JMHW criteria
Wicks [79] Abstract presented at BCS. Combined PET-CMR is superior to isolated PET or CMR alone, although with notable poor inter-modality agreement between SUV and LGE (k = 0.021)	2014	Hybrid PET-CMR	51	Systemic sarcoidosis or suspected CS	89/100[a]	42	(probable CS group)
Yokoyama [80]	2015	18F-FDG PET, ≥ 18 h fast, LC diet	125	Suspected CS	97.3	83.6	Myocardial SUVmax was significantly higher in patients with CS, was the only significant predictor of CS, and decreased significantly with in patients who received steroid therapy (p = 0.03)
Gormsen [81]	2016	18F-FDG PET, ~ 15 h fast 68-Ga-DOTANOC PET	19 19	Known/suspected CS	33 100	87.5 100	Large proportion of FDG-PET images were inconclusive compared to none in DOTANOC group; inter-observer variability was a significant caveat for the latter (k = 0.46)
Lapa [82]	2016	68-Ga-DOTANOC PET,	15		70	100	DOTANOC PET demonstrated high concordance with CMR, matching

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
		no special diet indications		Systemic sarcoidosis, suspected CS			LGE and T2-weighted edema within areas of myocardial inflammation
Ohira [83]	2016	18F-FDG PET, 12 h fast, variable diet, heparin CMR	30	Newly diagnosed conduction disease and suspected CS	87.5 75	38.5 76.9	Compared FDG PET and CMR in patients with newly diagnosed CSD of unclear etiology that had imaging within 12 weeks of diagnosis; patients with chronic CSD were more likely to be positive only on CMR, while those with new onset AVB were likely to be positive on PET
Aikawa [84]	2017	Delayed enhanced contrast CT LGE-CMR	24	CS or suspected CS	94 100	33 25	Compared DE-CT with LGE CMR as standard on a group of 24 patients; delayed enhancement CT shows high sensitivity in patients with known or suspected CS but low specificity despite exclusion of patient with previous MI; DE-CT had sufficient image quality to allow for assessment of hyper-enhanced myocardium
Norikane [85]	2017	18F-FDG PET, ≥ 18 h fast, LC diet 18F-FLT PET, no diet instructions	20	Systemic sarcoidosis	85 92	100 100	Study compared the new radiotracer to 18F-FDG PET and FLT was deemed to be as effective in detecting CS although FLT uptake in lesions was significantly lower but no inconclusive scans reported or prolonged fasting required with FLT
Kouranos [86•]	2017	CMR	321	Systemic sarcoidosis	96.9	100	Largest cohort evaluating cardiac involvement and combined diagnostic utility of cardiac tests

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
							in patients with systemic sarcoidosis; CMR identified 9.3% of patients with silent cardiac involvement and was most valuable in diagnosis and prognosis of general sarcoidosis population
Dweck [87]	2018	Hybrid CMR/18F-FDG PET, no carb 24 h, 12 h fast	25	Suspected CS	100	94	Approximately one-third of patients had both FDG and LGE uptakes being highly suggestive of CS; TNMRmax values were also higher in these patients with threshold values > 1.2 being highly accurate; CMR-negative PET-positive patients were felt to represent failed myocardial suppression
Wicks [88•]	2018	18F-FDG PET, ≥ 12 h fast, HFLC diet CMR Hybrid CMR/18F-FDG PET	51	Known/suspected CS	60–85 82 94	56 78 44	Hybrid PET-CMR was superior in detecting CS (odds ratio = 12.4) and predicting adverse event rate, especially if both PET and CMR were positive (71%); the presence of LGE was an independent predictor of major adverse cardiac events after adjusting for LVEF with HR = 8.04
Lebasnier [64]	2018	18F-FDG PET, > 12 h fast, HFLC diet	30	Systemic sarcoidosis, suspected CS	100	91	Myocardial glucose metabolism was significantly heterogeneous in patients with CS who showed significantly higher normalized CoV values compared to patients without CS ($p = 0.0007$)
Smedema [89]	2017	Contrast-enhanced CMR	30	CS, infarct patients	87	70	CMR was helpful in differentiating patients with CS from patients

Table 1. (Continued)

Author/study	Year	Method(s) of imaging and protocol details	Number of patients	Population	Sens	Spec	Comments
							with ischemic cardiomyopathy and previous MI

Sensitivity/specificity were calculated by authors using either EMB or JMHW guidelines. Comments were only added to include pertinent information relevant to study and/or methods utilized. Values separated by "/" are indicative of PET/MRI results in this exact order respectively, unless otherwise specified. Where mentioned in imaging method and protocol section, heparin was used to additionally suppress myocardial physiologic glucose uptake

sens sensivitity, *spec* specificity, *CS* cardiac sarcoidosis, *JMHW* Japanese Ministry of Health and Welfare (1993), *^{13}N-NH3* ^{13}N-ammonia, *^{18}F-FDG PET* 18-fluorodeoxyglucose positron emission tomography, *^{18}F-FLT* another radiotracer, 3'-deoxy-3'-^{18}F-fluorothymidine, *HFLC* high fat low carbohydrate diet, *LC* low carbohydrate diet, *^{68}Ga-DOTANOC PET* Ga-68-labeled-somatostatin-analogues positron emission computed tomography, *CT* computed tomography, *^{82}Rb PET* Rubidium-82 positron emission computed tomography, *CMR* cardiac magnetic resonance imaging, *CSD* conduction system disease, *DE* contrast-delayed enhancement, *LGE* late gadolinium enhancement, *%DEA* the DE area traced manually with percentage against total LV area, *TNMRmax* maximum target-to-normal myocardium ratio, *CoV* coefficient of variation, *SUVmax* maximum standard uptake value, *DS* defect score, *VT* ventricular tachycardia, *MI* myocardial infarction, *EF* ejection fraction, – missing data

[a]Here, 89% corresponds with sensitivity of PET-CMR in probable CS patients and 100% with PET-CMR in those with confirmed CS

questionable. There is evidence suggesting that microvascular vasoconstriction may be responsible for the perfusion defects seen on ^{201}Th-SPECT, as reversibility of perfusion defects has been documented between post-injection rest and delayed imaging studies [101]. Evidence which depicts a relationship between abnormal ^{201}Th-SPECT studies and clinical cardiac dysfunction is also lacking. Given this information, in the absence of clinical cardiac signs or symptoms, ^{201}Th-SPECT is not recommended as a routine screening tool for CS.

There are other radionuclide imaging modalities available, although they have fallen out of favor in light of more sensitive and specific imaging techniques. Technetium 99m-methylene diphosphonate single photon emission-computed tomography (^{99m}Tc MDP SPECT) Scintigraphy and 67-Gallium Citrate (^{67}Ga) Scintigraphy are amongst the sparsely used and now somewhat antiquated imaging techniques. Although ^{67}Ga scintigraphy has been incorporated into the modified diagnostic criteria in the JMHW guidelines, most centers do not pursue such imaging, as studies have demonstrated its inferiority, in terms of sensitivity and diagnostic accuracy to ^{18}F-FDG PET [102]. Similarly, perfusion abnormalities visualized on ^{99m}Tc MDP SPECT are not diagnostic of CS and their clinical significance has yet to be established [103].

Rubidium-82 positron emission computed tomography (82-Rb PET) is another less often used radionuclide imaging modality. It does offer some advantages when compared to when compared to ^{99m}Tc MDP SPECT. It has greater sensitivity (91%) and specificity (90%) with lower radiation exposure [104, 105]. Rest and stress 82-Rb PET imaging is roughly equivalent to the average person's annual natural radiation exposure in the USA [105, 106]. Additionally, 82-Rb PET was able to outperform ^{99m}Tc MDP SPECT in terms of diagnostic accuracy in patients with body mass index greater than 30 kg/m^2 and in women with large breast size, 85 and 67%, respectively [105, 107], and offer more information on myocardial blood flow (MBF) [108, 109], which may aid in the detection of inflammatory and fibrotic myocardial disease.

E. Novel PET tracers: ^{18}F-flurpiridaz positron emission computed tomography (^{18}F-Flurpiridaz PET), ^{13}N-ammonia positron emission computed tomography (^{3}N-Ammonia PET), and ^{68}Ga-DOTANOC

Along with the advent of newer imaging modalities, novel radionuclide tracers have been developed which may greatly surpass their antiquated counterparts in terms of diagnostic accuracy for cardiac pathophysiology. ^{18}F-Flurpiridaz positron emission computed tomography (^{18}F-Flurpiridaz PET) and ^{13}N-Ammonia positron emission computed tomography (^{13}N-Ammonia PET) are two novel radionuclide tracers that are in development which may greatly aid in early detection of CS. ^{18}F-Flurpiridaz binds to mitochondrial complex 1 which allows for high-resolution myocardial perfusion imaging (MPI) [110]. Similar to *82-Rb PET*, ^{18}F-Flurpiridaz PET offers enhanced clarity in obese patients or in women with large breasts, but with reduced radiation levels. Based on the clinical studies available, when compared to SPECT MPI which is the current standard of care, it appears that ^{18}F-Flurpiridaz PET may provide higher resolution imaging, increased diagnostic certainty, reduced patient radiation exposure, and more accurate risk stratification [110–112]. ^{13}N-Ammonia PET adds diagnostic value as it allows for quantification of myocardial flow reserve (MFR), particularly in patients with normal MPI which can potentially unmask

clinically significant cardiac pathophysiology. In a Phase 2 trial focused on detection of coronary artery disease (> 50% stenosis by coronary angiography), ^{18}F-Flurpiridaz had a higher sensitivity (78.8 vs 61.5%) and a stronger negative predictive value when compared to SPECT [112]. Considering their proposed increased detection rates of perfusion defects, it can be implied that these imaging modalities may offer potentially superior diagnostic accuracy for CS as perfusion defects (non-coronary artery distribution) are common. Currently, ^{18}F-Flurpiridaz, ^{13}N-Ammonia, in addition to other tracers (i.e., 11C-PBR28, F18-FSPG and DOTATAE) are undergoing further clinical trials investigating their potential use in CS patients and are demonstrated in Table 2.

Lastly, ^{68}Ga-DOTANOC is an alternative radionucleotide tracer that binds to somatostatin receptors on inflammatory cells, specifically in sarcoid granulomas, which requires a less rigorous fasting protocol compared to ^{18}F-FDG PET and has shown promising results in a small Danish study where ^{68}Ga-DOTANOC tracer use yielded 100% diagnostic accuracy, proving it to be a viable alternative to ^{18}F-FDG PET [113]. It has also shown greater sensitivity in disease activity monitoring when compared to conventional CMR; the reasoning being that LGE on CMR primarily depicts myocardial scarring, while ^{68}Ga-DOTANOC is actively bound to activated macrophages, lymphocytes, and epithelioid cells. Unfortunately, with ^{68}Ga-DOTANOC PET, immunosuppressive therapy at the time of imaging may alter results, increasing the rate of false-negative reports [114].

F. Simultaneous hybrid cardiac imaging: ^{18}F-FDG PET/CMR

Recently, some centers have taken on a hybrid imaging approach by combining ^{18}F-FDG PET with CMR [115]. A small single-center study (N = 51) compared simultaneous ^{18}F-FDG PET and LGE on CMR to current accepted diagnostic imaging modalities (^{18}F-FDG PET alone and CMR alone). This study found that simultaneous hybrid imaging was superior to conventional imaging in terms of sensitivity (94%), specificity (44%), positive predictive value (76%), and negative predictive value (80%). The sensitivity for ^{18}F-FDG PET is 85% and LGE on CMR is 82%. The prevalence of CS in this patient population was 65% (N = 33) [88]. Simultaneous hybrid cardiac imaging allows for high-resolution morphologic and functional data collection via LGE-CMR [95•] while retaining the ability to assess for myocardial viability, perfusion, inflammatory metabolism processes, and abnormal cardiac deposition via ^{18}F-FDG PET. Compared to PET-CT, ^{18}F-FDG PET CMR offers many advantages, including attenuation correction without additional radiation, detection of edematous tissue, and improved image quality in regard to myocardial viability, perfusion, cardiac morphology, and function [95•]. Recent studies also predict that hybrid cardiac imaging may allow clinicians to differentiate between active and inactive disease, as both positive PET and LGE on MRI suggest active CS, while PET-negative and LGE MRI-positive imaging may correlate with inactive disease with residual fibrosis [95•]. This mentioned benefit may aid in the monitoring of CS and response to therapy [116]. As both ^{18}F-FDG PET and CMR are indicated imaging studies for the evaluation of CS [83], and there is no clear consensus on which modality is superior [104, 117], simultaneous hybrid cardiac imaging should be considered.

Table 2. Ongoing imaging trials in patients with cardiac sarcoidosis

Investigator/s	Compl date	Name	Location	Type	Number	Topic	Outcomes
Murthy et al.	2019	Non-Invasive				characterization in cardiac sarcoidosis	USA
Clinical trial	8	Diagnostic use of 11C-PBR28 as a radiotracer for PET CT scanning	Ratio of	11C-PBR28 in the myocardium			
Ripa et al.	2019	Somatostatin receptor imaging in cardiac sarcoidosis	Denmark	Observational, prospective, cohort	60	Accuracy of Cu-64 labeled DOTA-TATE for diagnosing cardiac sarcoidosis using PET/CT or PET/MRI	Sensitivity and specificity of DOTA-TATE to in detecting CS
Birnie, Nery, Beanlands	2025	Cardiac sarcoidosis multi-center prospective cohort	Canada	Observational, prospective, cohort	1500	Registry of current diagnostic approaches, treatment and prognosis, and a randomized clinical trial of the effect of corticosteroid treatment on the clinical course of cardiac sarcoidosis	Clinically manifest patients, clinically silent disease, total mortality, CV mortality, HF hospitalization, change in LVEF from baseline, change in disease activity on PET, AFib and ventricular arrhythmia burden, % ventricular pacing
Iagaru et al.	2020	PET/MRI imaging of cardiac sarcoidosis	USA	Clinical trial	20	Detection of cardiac sarcoidosis or inflammation using 18F-FSPG PET/MRI	Number of participants with F18 FSPG Uptake on PET/MRI indicating cardiac involvement by sarcoidosis
Le Guludec et al.	2025	Perfusion analysis using rubidium in cardiac sarcoidosis	France	Clinical trial	53	Diagnostic and therapeutic impact of rubidium-82 PET in cardiac sarcoidosis	Percentage of patients who have two different diagnostic and therapeutic attitude before knowing Rb-82 PET result and after knowing Rb-82 PET

Table 2. (Continued)

Investigator/s	Compl date	Name	Location	Type	Number	Topic	Outcomes
							result; analysis of the cost for the use of Sestamibi SPECT and 82Rb-PET as MPI agents in CS
Di Carli et al.	2018	Somatostatin receptor imaging in patients with suspected cardiac sarcoidosis	USA	Clinical trial	15	Diagnostic use of DOTATE for diagnosing cardiac sarcoidosis	Visual signal of OctreoScan or DOTA-TATE in the heart; early versus delayed imaging; correlate localization and number of increased foci; monitoring effect of treatment
Hanneman et al.	2019	PET MRI study in patients with cardiac sarcoidosis	Canada	Observational, prospective, cohort	60	Diagnostic use of simultaneous combined 18F-FDG PET and cardiac MRI imaging	The incremental value of combined 18F-FDG PET and CMR imaging in the evaluation of patients with suspected cardiac sarcoidosis or cardiac inflammation; looking at the differences in circulating plasma biomarkers between cardiac with suspected, cardiac sarcoidosis, and healthy people; the prognostic significance of PET-MRI imaging findings in patients with cardiac inflammation
Miller et al.	2018		USA	Clinical trial	15		

Table 2. (Continued)

Investigator/s	Compl date	Name	Location	Type	Number	Topic	Outcomes
		Optimizing acquisition parameters and interpretive methods of ^{18}FDG-PET/CT With Rb-82				Optimizing acquisition parameters and interpretive methods of FDG-PET/CT with RB-82	Visual interpretation of FDG uptake, severity of myocardial inflammation, and extent
Broadhurst et al.	2018	PET-detected myocardial inflammation is a characteristic of cardiac sarcoid but not of ARVC	UK	Observational, prospective	20	PET imaging in cardiac sarcoid and ARVC	Myocardial inflammation or fibrosis by CMR and PET/CT

Ongoing study by Birnie et al. although non-imaging predominant was included because of importance for establishing a registry for CS patients

Comp Date completion date of the study, *CS* cardiac sarcoidosis, *CV* cardiovascular, *CT* computed tomography, *PET* positron emission tomography, *CMR* cardiac magnetic resonance imaging, *^{18}F-FDG PET* 18-fluorodeoxyglucose positron emission tomography, *ARVC* arrhythmogenic right ventricular cardiomyopathy, *MPI* myocardial perfusion imaging, *SPECT* single-photon emission computed tomography, *DOTA-TATE* DOTA-octreotide, an amino acid peptide covalently bound to DOTA, *11C-PBR28* novel radiotracer, *^{82}Rb* Rubidium-82; *HF* heart failure, *Afib* atrial fibrillation

Framework of combined PET/CMR studies establishes a new monumental mark in our role as imagers and caregivers for these patients. The combination of CMR and FDG-PET imaging may add significant incremental benefit for many patients. Vita et al. demonstrated this in a recent paper with utilization of CMR, FDG-PET, and combination of both in assessment of the likelihood of CS and guidance of patient management. The combination of FDG-PET and CMR image data reclassified 45% (high probable and higher likelihood groups) of patients compared with single-modality imaging [118•, 119]. On the contrary, Dweck et al. postulated in a recent prospective combined PET/MRI study only 32% of their patients with both PET and MRI (LGE)-positive tests to suffer from active CS. As mentioned previously, it is important to keep in mind that PET-negative findings with positive LGE in MRI can be rather considered as inactive CS with remaining scar [87, 95•].

Conclusion

Awareness about CS is growing with increased understanding of the disease process and case detection in autopsy studies. Due to the nature of cardiac involvement, diagnosis of CS remains a challenging task for the clinician. Even with detailed history and clinical exam with basic cardiac workup including ECG and transthoracic echocardiography, the diagnosis is frequently missed. This has prompted extensive research in cardiac imaging for prompt detection of cardiac involvement. There has been promising development in cardiac imaging studies in recent years, resulting in increasing pre-mortem identification of CS cases. CMR and ^{18}F-FDG-PET have shown high sensitivity and specificity, making them the imaging modalities of choice. Newer imaging modalities with novel agents like ^{18}F-Flurpiridaz PET, ^{13}N-Ammonia PET, and ^{68}Ga-DOTANOC are currently undergoing testing and have showed promise in initial small studies. However, further research is needed to establish a unified approach and increase detection rates of CS. Recent advancements in imaging techniques continue to shape the narrative on how best to diagnose this disease. At this point in time, there does not seem to be a gold standard non-invasive test that accomplishes the goals of being readily available, inexpensive, sensitive, and specific for diagnosis of CS.

Like many other diseases in medicine, CS requires awareness and clinical suspicion of the disease coupled with knowledge of the strengths and weaknesses of each imaging modality. This knowledge can help guide the clinician to order the best test or tests to make the diagnosis and monitor treatment of CS. As knowledge about the disease increases and diagnostic techniques are refined, one can hope for earlier diagnosis of the condition which hopefully will lead to better patient outcomes.

Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Authorship Declaration
All authors listed meet the authorship criteria according to the latest guidelines the International Committee of Medical Journal Editors. All the authors have contributed equally and are in agreement with the manuscript.

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- •• Of major importance

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This 21-patient study found that FDG-PET was superior to CMR for ruling out cardiac sarcoidosis with a sensitivity of 87.5% and specificity of 38.5%, compared to CMR with sensitivity of 75% and specificity of 76.9%. Specificity of FDG-PET was lower in this study compared to previous data.

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