The Use of ^{18}F-FDG PET in the Diagnosis of Cardiac Sarcoidosis: A Systematic Review and Metaanalysis Including the Ontario Experience

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Cardiac sarcoidosis is a potentially fatal complication of sarcoidosis. The 1993 guidelines of the Ministry of Health, Labour, and Welfare (MHLW) of Japan have been used as the diagnostic gold standard and for comparison with imaging modalities. ^{18}F-FDG PET is not currently included in the guidelines. However, studies have shown promising data using ^{18}F-FDG PET. We conducted a systematic review of studies that evaluated the accuracy of ^{18}F-FDG PET for the diagnosis of cardiac sarcoidosis compared with MHLW guidelines. Data from a prospective Ontario provincial registry are also reported and included in the metaanalysis. **Methods:** PubMed, Embase, and the Cochrane Central Register of Controlled Trials were searched for studies that satisfied predetermined criteria. Quality evaluation using the Quality Assessment for Diagnostic Accuracy Studies was performed by 2 independent masked observers. Data were extracted and analyzed to measure study-specific and pooled accuracy for ^{18}F-FDG PET compared with the MHLW as the reference. **Results:** A total of 519 titles was identified; 7 studies, including the Ontario registry, were selected for inclusion. Metaanalysis of these 7 studies was conducted, with a total of 164 patients, most of whom had been diagnosed with systemic sarcoidosis. The prevalence of cardiac sarcoidosis was 50% in the whole population. Pooled estimates for ^{18}F-FDG PET yielded 89% sensitivity (95% confidence interval [CI], 79%–96%), 78% specificity (95% CI, 68%–86%), a 4.1 positive likelihood ratio (95% CI, 1.7–10), and a 0.19 negative likelihood ratio (95% CI, 0.1–0.4). The overall diagnostic odds ratio was 25.6 (95% CI, 7.3–89.5), and the area under the summary receiver operator characteristic curve was 93% $\pm$ 3.5. The Ontario study yielded sensitivity and specificity of 79% and 70%, respectively. **Conclusion:** The high diagnostic accuracy determined for ^{18}F-FDG PET in this metaanalysis suggests potential value for diagnosis of cardiac sarcoidosis compared with the MHLW guidelines. These results may affect patient care by providing supportive evidence for more effective use of ^{18}F-FDG PET in the diagnosis of cardiac sarcoidosis. Large-scale multicenter studies are required to further evaluate this role.

Key Words: cardiac sarcoidosis; meta-analysis; ^{18}F-FDG PET

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Sarcoidosis is a multisystem granulomatous disease of unknown etiology occurring in 10.9 per 100,000 Caucasians and 35.5 per 100,000 African Americans (*1,2*). Noncaseating granulomas are the pathologic hallmark of sarcoidosis and most often occur within pulmonary parenchyma and lymph nodes but may involve the heart and other tissues (*3,4*). Autopsy studies have estimated the prevalence of cardiac involvement to be at least 25% in patients with sarcoidosis (*5,6*), and cardiac sarcoidosis accounts for 13%–25% of disease-related deaths (*7*), because of complications such as heart failure, ventricular tachyarrhythmia, or conduction disturbances (*8,9*). Cardiac sarcoidosis can exist without clinically apparent sarcoidosis elsewhere (*10*). This is believed to be uncommon but has not been well studied.

The diagnosis of cardiac sarcoidosis can be challenging. Only 40%–50% of patients with cardiac sarcoidosis identified at autopsy had clinical evidence of myocardial disease (*6*). The 1993 guidelines published by the Ministry of Health, Labour, and Welfare (MHLW) of Japan (*11*) have been used most frequently as the clinical gold standard for the diagnosis of cardiac sarcoidosis and as the reference for comparison of imaging techniques, including PET and MRI (*12*). In 2006, the Japan Society of Sarcoidosis and Other Granulomatous Disorders published a revised version of the guidelines in which gadolinium-enhanced MRI was added as a minor criterion for the clinical diagnosis (*13*).

Although findings on the imaging techniques in the guidelines may suggest cardiac sarcoidosis, no individual

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finding is pathognomonic for the disease. Thus, there is a need for more robust methods of diagnosis. One area of major interest is functional imaging of inflammatory disease activity using ^{18}F-FDG PET, in conjunction with perfusion imaging to assess fibrogranulomatous replacement of the myocardium. In a recent case review study, increased ^{18}F-FDG uptake corresponded to active granulomatous sarcoid lesions on autopsy (*14*).

As with any diagnostic test, the routine clinical use of ^{18}F-FDG PET in cardiac sarcoidosis requires sufficient supporting data. To date, evaluation of the diagnostic accuracy of ^{18}F-FDG PET for cardiac sarcoidosis has been limited to small single-center studies. No systematic review or metaanalysis has been conducted. Of note, ^{18}F-FDG PET has not been included in the most updated MHLW guidelines for cardiac sarcoidosis diagnosis. Hence, we undertook a systematic review and metaanalysis evaluating the accuracy of ^{18}F-FDG PET in diagnosing cardiac sarcoidosis. Data from a prospective registry in the province of Ontario (the Cardiac FDG-PET Registry [CADRE]) are also reported and included in the metaanalysis.

MATERIALS AND METHODS

Systematic Review

Data Sources and Study Selection. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials using predefined search terms (Supplemental Appendix I; supplemental materials are available online only at http://jnm.snmjournals.org). Results were limited by English language.

A broad search strategy was used to identify all studies that are relevant to the use of ^{18}F-FDG PET in the diagnosis of cardiac sarcoidosis in comparison to the MHLW guidelines as the gold standard. For a study to be included, it had to use the MHLW guidelines as the gold standard for diagnosis of cardiac sarcoidosis, it had to use ^{18}F-FDG PET for diagnosis of cardiac sarcoidosis, and it had to perform a diagnostic accuracy assessment of the 2 techniques.

Two independent reviewers masked to the other reviewer's selection reviewed the abstracts with the inclusion criteria.

Quality Evaluation and Data Extraction. Quality Assessment for Diagnostic Accuracy Studies is a tool included in systematic reviews. Whiting et al. described this tool as follows: It "is structured as a list of 14 questions which should each be answered 'yes', 'no', or 'unclear' [Supplemental Table 1]. Items included patient spectrum, reference standard, disease progression bias, verification bias, review bias, clinical review bias, incorporation bias, test execution, study withdrawals, and indeterminate results." (*15*)

Ontario Provincial Registry Study (CADRE)

Patient Selection from CADRE Registry. The CADRE registry is a database for patients referred for ^{18}F-FDG PET in Ontario. This currently comprises more than 300 patients. Most of these patients have been referred for the assessment of ischemic cardiomyopathy and viability imaging (*16*). Such patients were excluded from this study. The current study enrolled only patients who had been referred for assessment of possible cardiac sarcoidosis.

Twenty-four consecutive patients were selected from the CADRE registry from September 2007 to May 2010, who had been referred to 3 centers in Ontario—University of Ottawa Heart Institute, McMaster University Medical Centre, and London Health Sciences Centre—to rule out cardiac sarcoidosis or establish disease activity.

Excluded were patients who had been referred for other reasons, including ^{18}F-FDG PET viability testing, inability to acquire fasting data, known coronary artery disease, age less than 18 y, and refusal to sign the consent form. The registry study was approved by the Human Research Ethics Board of the participating centers.

Protocol. All clinical data (demographics, history, symptoms, electrocardiogram [ECG]) and imaging data (echocardiography, nuclear imaging, and MRI if available) were collected.

The imaging protocol included a rest perfusion (PET or SPECT tracers) and fasting ^{18}F-FDG PET whole-body scan for diagnosis of cardiac sarcoidosis.

Imaging Protocol. Images were obtained using a 64-slice PET/CT scanner (Discovery Rx/VCT or Discovery 690; GE Healthcare) in Ottawa, a 16-slice PET/CT scanner (Discovery ST; GE Healthcare) in London, or an ECAT ART dedicated PET scanner (Siemens) in Hamilton. Scans from all sites were independently reviewed at a single center by both an experienced nuclear cardiologist and a nuclear medicine physician.

Patients underwent a gated cardiac rest perfusion scan using either ^{82}Rb (10 MBq/kg) or ^{13}N-ammonia (5 MBq/kg). Low-dose CT or a ^{137}Cs source transmission scan was used for attenuation correction. In centers where PET perfusion tracers were not available ^{99m}Tc-sestamibi (4 patients) or ^{201}Tl SPECT (2 patients) was used as the perfusion tracer.

For ^{18}F-FDG PET, both whole-body and cardiac acquisitions were performed. All patients fasted for at least 12 h before the examination. Serum glucose level was checked before injection of the tracer. In Ottawa and London, 1 h after intravenous injection of a 5 MBq/kg dose of ^{18}F-FDG (maximum, 550 MBq), an unenhanced low-dose CT scan from the proximal femoral region to the head was acquired for attenuation correction and anatomic localization. (A ^{137}Cs source transmission scan was used for attenuation correction at the Hamilton site, where PET/CT was not available.) Subsequently, emission images of the same region were acquired at 5–7 bed positions. A cardiac scan in static and, where available, ECG-gated modes was obtained. Whole-body ^{18}F-FDG PET was reconstructed and reviewed on standard workstation display software for extracardiac findings. Cardiac PET acquisitions were reconstructed into standard short-axis, horizontal long-axis, and vertical long-axis views. Alignment of cardiac PET and CT images was evaluated using cardiac and extracardiac landmarks to confirm registration between PET and CT images.

Metabolic activity in the left ventricular myocardium was classified into 1 of 3 patterns: no uptake, diffuse uptake, or focal uptake. Only focally increased cardiac uptake was considered positive for active inflammatory sarcoid lesions (Fig. 1 and Supplemental Fig. 1). Diagnostic accuracy was compared with the MHLW guidelines. Based on perfusion and inflammation imaging, normal perfusion and no inflammatory lesion represented normal segments, normal perfusion and an active inflammatory lesion represented an early stage of disease, abnormal perfusion and an active inflammatory lesion represented an advanced stage of disease, and abnormal perfusion and no inflammatory lesion represented end-stage disease (*17*).

Standard for Comparison. We compared the diagnostic accuracy of PET with the modified MHLW guidelines as the reference

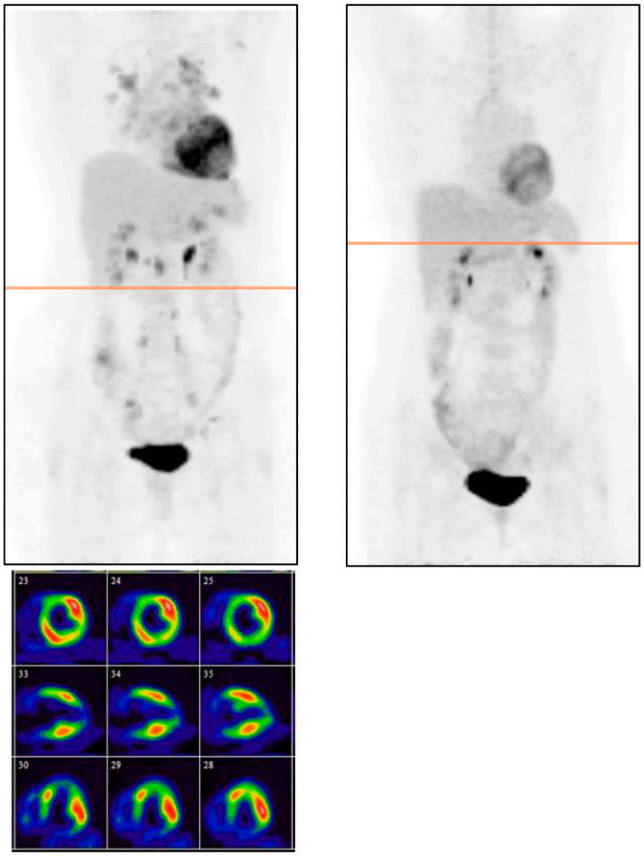

FIGURE 1. A 52-y-old woman who presented with atrial tachycardia and New York Heart Association class III congestive heart failure. High-resolution chest CT revealed pulmonary sarcoidosis. (Left) Extensive multifocal increased cardiac ^{18}F-FDG is seen on short-, horizontal-, and vertical-axis views (bottom) and on whole-body fasting ^{18}F-FDG PET (top), with increased pulmonary and hilar lymph nodes uptake. Findings were interpreted as positive for cardiac sarcoidosis. (Patient was considered positive according to MHLW guidelines.) (Right) Two months after treatment with prednisone (30 mg/d), marked improvement is seen in cardiac and pulmonary ^{18}F-FDG uptake.

(*13,18*). The modified MHLW criteria for clinical diagnosis of cardiac sarcoidosis requires a histologic or clinical (according to the recent guidelines updated in 2006 (*13*)) diagnosis of extracardiac sarcoidosis with a diagnosis of complete right bundle branch block, left-axis deviation, atrioventricular block, ventricular tachycardia, premature ventricular contractions (≥Lown 2), or abnormal Q or ST-T abnormalities on the ECG or ambulatory ECG, plus 1 of the following 3 diagnoses: abnormal regional wall motion, wall thinning, or dilatation of the left ventricle; a perfusion defect (we included any type of nuclear perfusion imaging, e.g., ^{82}Rb, ^{13}N-ammonia PET, ^{201}Tl, or ^{99m}Tc-based tracer SPECT); elevated intracardiac pressures, low cardiac output, or abnormal wall motion or depressed left ventricular ejection fraction on contrast-enhanced left ventriculography.

Statistical Analysis for Specific and Pooled Data

The pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio, with the corresponding 95% confidence intervals (CIs), were calculated (*19,20*). The pooled indices of sensitivity and specificity were calculated using weighted averages according to the sample size of each study. The pooled estimates of likelihood ratios and diagnostic odds ratios were computed by the DerSimonian and Laird method based on a random-effects model (*21*). Forest plots and statistical analysis using the Cochran Q test, and the inconsistency index I^2, were performed to evaluate the threshold effect as an important component of the source of variation of the diagnostic studies used in the different research studies. I^2 describes the percentage of total variance due to heterogeneity rather than to chance across these different studies. A zero percentage index indicates that there is no heterogeneity, whereas 25%, 50%, and 75% indices correspond to low, moderate, and high heterogeneity, respectively (*22*). Given the presence of diagnostic threshold variation in these research studies, the SROC curve is an appropriate summary statistic to assess the overall diagnostic accuracy of ^{18}F-FDG PET across the different threshold definitions. Therefore, the results are described as the area under the SROC curve, with its Q*-point representing the point on the SROC curve that intercepts the anti-diagonal and corresponds to the point where sensitivity and specificity are equal (*23,24*). Furthermore, the shape of the SROC curve (symmetric vs. asymmetric) was determined by assessing the changes in diagnostic odds ratio according to diagnostic thresholds using the method of Moses et al. (*25*). Statistical analyses were performed using Meta-Disk software, version 1.4 (Clinical Biostatistics Unit, Hospital Ramón y Cajal) (*26*).

RESULTS

The search and study selection are depicted in Supplemental Figure 2. In total, 519 titles and abstracts were reviewed by 2 reviewers. Both reviewers agreed that 7 studies met the inclusion criteria. One study by Mehta et al. (*18*) was included in the systematic review yet excluded from the metaanalysis because ^{18}F-FDG PET was used as the gold standard. We incorporated the CADRE registry patients into the database. In total, 7 studies were considered in the analysis.

From the 7 studies, 164 patients had been referred for ^{18}F-FDG PET for diagnosis of cardiac sarcoidosis. Inclusion criteria in most of the studies included patients already diagnosed with systemic sarcoidosis, patients with a diagnosis of cardiac sarcoidosis based on the MHLW guidelines, or strong clinical suspicion. The overall prevalence of cardiac sarcoidosis was 50% in the study population.

Pooling Sensitivities and Specificities

As shown in Supplemental Table 2, the overall range of reported sensitivities and specificities of ^{18}F-FDG PET for diagnosis of cardiac sarcoidosis was 79%–100% and 38%–100%, respectively. The pooled estimate of sensitivity was 89% (95% CI, 79–96), and the pooled estimate of specificity was 78% (95% CI, 68–86).

The data from these ^{18}F-FDG PET studies had statistical heterogeneity, with inconsistency index values of 27.9% (P = 0.22) and 71.7% (P = 0.003) for sensitivity and specificity, respectively (Supplemental Fig. 3). The specificity for the study of Ohira et al (*30*) was substantially lower than that for the other studies, and when this study

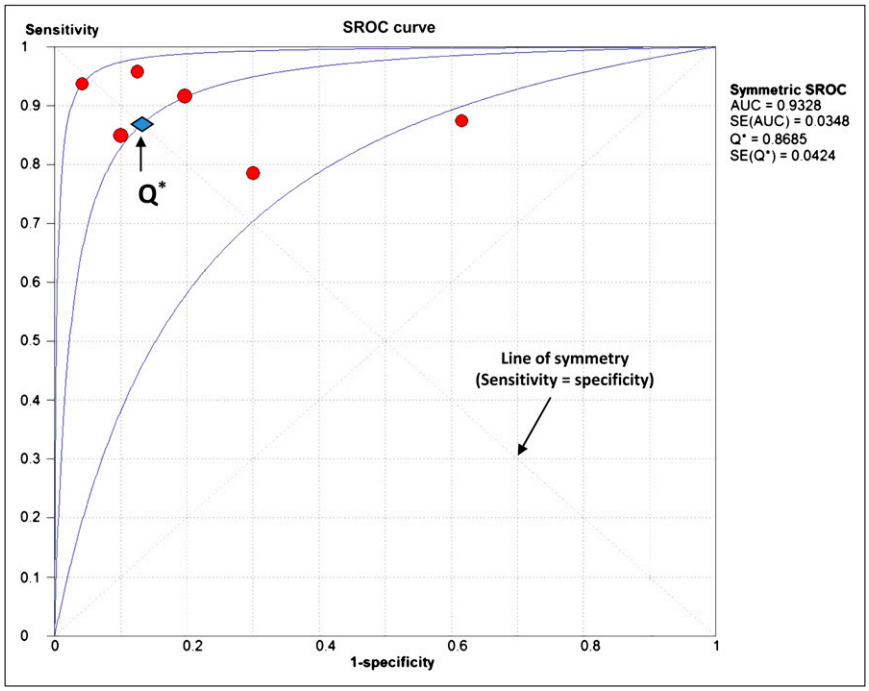

FIGURE 2. SROC curve. Each red circle represents individual study in metaanalysis, with size of circle proportional to sample size of study. Best-fit curve (middle curve) lies between 2 curves that demarcate its 95% CI. Blue diamond denotes Q*-point on SROC curve that intersects line of symmetry. AUC = area under the curve.

was not included in the analysis, the pooled specificity improved to 86% (95% CI, 75–93).

Pooling Likelihood Ratios

The pooled estimate of the positive likelihood ratio was 4.1 (95% CI, 1.7–10), and the positive likelihood ratios of all the studies (except the one by Nishiyama et al. (*27*), which had a positive likelihood ratio of 22) were below 10, with significant heterogeneity (test for heterogeneity, $P = 0.001$). On the other hand, the pooled estimate of the negative likelihood ratio was 0.19 (95% CI, 0.1–0.4). The negative likelihood values showed no evidence of significant heterogeneity ($P = 0.62$) (Supplemental Fig. 4). When the study of Nishiyama et al. was not included in the analysis, the pooled positive likelihood ratio was reduced somewhat to 3.46 (95% CI, 1.5–8.0).

Diagnostic Odds Ratios and SROC Curves

Because of the variability in the data, a random-effects SROC model was used by fitting the pooled accuracy data to a single symmetric SROC curve (Fig. 2). The area under the SROC curve (±SE) and its Q*-point were 93% ± 3.5% and 87% ± 4.0%, respectively. The random-effects model estimated an overall diagnostic odds ratio of 25.6 (95% CI, 7.3–89.5) with insignificant heterogeneity ($P = 0.249$) (Supplemental Fig. 5).

Characteristics of the Ontario Registry Patients

The clinical characteristics of the Ontario registry patients are shown in Table 1. Fourteen of the 24 patients were diagnosed with cardiac sarcoidosis on the basis of MHLW criteria. In the Ontario registry patients, sensitivity was 79% (95% CI, 49–95) and specificity was 70% (95% CI, 35–93). All except one patient were nondiabetic. Eight patients were receiving therapy for sarcoidosis (6 patients, an oral steroid; 1 patient, an inhaled steroid; and 1 patient, methotrexate); only one such patient (who was on an oral steroid) had a negative ^{18}F-FDG PET result. That study was true-negative on the basis of the MHLW criteria.

Role of Perfusion in Ontario Registry Patients

All patients underwent both perfusion and ^{18}F-FDG metabolism studies. None of the patients had perfusion abnormalities without evidence of abnormally increased ^{18}F-FDG uptake. Of the 24 patients, 14 had positive PET

TABLE 1
Clinical Characteristics of Ontario Registry Patients ($n = 24$)

Characteristic	Value
Age (y)	53 ± 6
Men	15 (62.5%)
Diabetes	1 (4.2%)
Fasting blood sugar (mmol/L)	5.59 ± 0.82
Past history of coronary artery disease	0
Left ventricular dysfunction (ejection fraction < 50%)	12 (50%)
New York Heart Association class	2.4 ± 1.03
Left ventricular ejection fraction (%)	42.7 ± 15.5
Heart block	8 (33.3%)
Ventricular tachycardia	6 (25%)
Extracardiac sarcoidosis	19 (79%)
Patients who met the metastatic MHLW criteria	14 (58.3%)

Data are mean ± SD, or number of patients.

findings (1 patient with active inflammation and 13 patients with abnormal perfusion and active inflammation representing an advanced stage of disease).

DISCUSSION

^{18}F-FDG is a glucose analog that is useful for imaging organ involvement in patients with sarcoidosis because of its ability to differentiate between normal and active inflammatory regions. This ability is due to its increased uptake in macrophage-dense regions, where the activated macrophages show a high metabolic rate making them more reliant on external glucose as a source of fuel (*28*).

To our knowledge, this was the first systematic review and metaanalysis of studies that assessed the diagnosis of cardiac sarcoidosis using ^{18}F-FDG PET. Advantages in performing a metaanalysis include improved generalizability to the population, ability to control for study variation, greater statistical power to detect an effect, derivation of pooled estimates of results from different research studies that represent the population studied, and ability to identify gaps in the current knowledge to support further scientific efforts.

From the pooled data, the prevalence of cardiac sarcoidosis is 50%, which is higher than previously reported in a 1978 U.S. autopsy study in which 27% of patients with systemic sarcoidosis had cardiac sarcoidosis (*7*). Regarding this difference, first, this previous series did not count myocardial fibrosis as evidence of cardiac involvement. Although nonspecific, myocardial fibrosis can sometimes be the only manifestation of cardiac sarcoidosis, and this previous study may therefore have underestimated the true prevalence of cardiac sarcoidosis. Second, the higher prevalence in the current study may be due to the specific selection criteria of some of the studies, enrolling patients already diagnosed with cardiac sarcoidosis using the MHLW guidelines or those with strong clinical suspicion. Also, the difference in the incidence of cardiac sarcoidosis in certain populations may affect the reported accuracy of imaging studies. Finally, although all studies used the MHLW guidelines as the gold standard, these may not be appropriate for non-Japanese populations or for studies that used imaging tests, such as PET and MRI, not available at the time that the guidelines were published (*18,29*).

^{18}F-FDG PET was shown to have pooled sensitivity and specificity of 89% and 78%, respectively. However, the specificities had significant heterogeneity ($P = 0.003$), as is evident from the wide range (38%–100%) and the high inconsistency index (71.7%). Regardless of the causes of the heterogeneity, the overall consistency of high sensitivity does suggest that a negative test result has potential clinical use in ruling out cardiac sarcoidosis.

The relatively lower specificity was influenced by the study performed by Ohira et al. (*30*), which reported 38% specificity. The authors hypothesized that ^{18}F-FDG PET might be able to detect early-stage subclinical cardiac sarcoidosis lesions even in patients who do not meet the MHLW criteria. Another explanation may be that ^{18}F-FDG has a variable physiologic myocardial uptake pattern that can add to the false-positive rate. The diffuse myocardial uptake pattern or the focally increased lateral-wall uptake patterns likely represent normal variations rather than active inflammatory states, as was also found in the studies by Ishimaru et al. (*31*) and Ohira et al. (*30*). Supplemental Figure 1 exemplifies the problem: the ^{18}F-FDG PET scan was interpreted as positive, but the case was negative according to the MHLW guidelines. Is this a false-positive result or true cardiac sarcoidosis? Further follow-up studies are needed to better define the true accuracy.

The pooled estimate of the positive likelihood ratio (4.1) was not particularly high and had significant heterogeneity ($P = 0.001$). On the other hand, the pooled estimate of the negative likelihood ratio was 0.19 (95% CI, 0.1–0.4), with no significant heterogeneity ($P = 0.62$). Supplemental Appendix 2 describes how the summary negative likelihood ratio can be applied to estimate the probability of cardiac sarcoidosis in a patient with a negative ^{18}F-FDG PET result.

When the studies by Ohira et al. (*27*) and Nishiyama et al. (*27*) (potential sources of heterogeneity) are excluded from the analysis of specificity and positive likelihood ratio, respectively, the changes in their pooled estimates as compared with the original values are not statistically different.

The SROC model is the most appropriate summary statistic to use in this metaanalysis because of the diagnostic-threshold variation among the research studies. The overall SROC curve demonstrates the high diagnostic accuracy of ^{18}F-FDG PET, with areas under the curve of 93% ± 3.5%.

All studies in this analysis had similar objectives yet showed obvious heterogeneity not only regarding the studied population but also regarding the patients' preparation before the ^{18}F-FDG PET scan, the imaging protocol, the diagnostic schema, and the threshold (Supplemental Table 3).

Methods for inhibition of myocardial uptake include injection of unfractionated heparin before ^{18}F-FDG injection (*27,30,31*), prolonged fasting (*32*), or fatty meal ingestion the day before the study (*33*).

^{67}Ga scintigraphy has been shown to have consistently low sensitivity—as low as 15% in the study by Langah et al. (*32*). Moreover, ^{99m}Tc-sestamibi and ^{201}Tl sensitivities, reported as 40% (*31*) and 35% (*34*), respectively, were also inferior to ^{18}F-FDG PET. Interestingly, in a recent study by Mehta et al. (*18*), ^{18}F-FDG PET was used as the gold standard to test the MHLW guidelines. That study showed a sensitivity of 33% (CI, 1%–55%) and specificity of 97% (CI, 86%–99%), suggesting that either the MHLW criteria underestimate the presence of cardiac sarcoidosis or there is a high rate of false-positive results on ^{18}F-FDG PET.

In patients with an uncertain diagnosis, Mehta et al. (*18*) proposed cardiac MRI and PET because other test results, in particular the ECG, had low sensitivity (8%). Also, sim-

ilar to the findings of the ACCESS (A Case Control Etiologic Study of Sarcoidosis) study group, the severity of pulmonary involvement did not correlate with the presence of cardiac sarcoidosis (*35*).

The combination of perfusion and ^{18}F-FDG data could improve the detection of myocardial sarcoidosis. For example, reduced rest perfusion in the setting of normal ^{18}F-FDG uptake could help decrease false-negative results that may be missed by focusing on ^{18}F-FDG uptake alone, and normal rest perfusion may help increase specificity by helping to clarify apparent increased ^{18}F-FDG uptake that might be due to normal variants of myocardial physiologic uptake. In our ^{18}F-FDG analysis, we took into consideration the available data about other patterns of ^{18}F-FDG uptake that are considered nonspecific, such as diffuse or lateral wall uptake.

This accumulating data, including the current study and metaanalysis, support the role of ^{18}F-FDG PET as an accurate technique likely to aid in diagnosis of cardiac sarcoidosis. Inclusion of ^{18}F-FDG PET in current guidelines as an alternative to the other nuclear techniques or even as a stand-alone investigation may be a consideration, particularly since PET has the advantage of studying both perfusion and metabolism with high diagnostic accuracy.

Limitations

There are some limitations in our metaanalysis. The number of relevant studies was limited, and the numbers of patients were small. The studies were heterogeneous regarding the population studied, preparation protocols, and threshold for diagnosis. The literature search was confined to English publications, though informal searching of the non-English publications did not demonstrate evidence that including them would have significantly changed our results.

The MHLW guidelines were developed by consensus based on the best available autopsy and clinical data. This emphasizes the difficulty in diagnosing cardiac sarcoidosis, the limited standards, and the need for more robust criteria. Developing better criteria may involve imaging with PET or MRI but requires further study (*36*).

The recently proposed promising approach by Tahara et al., using the coefficient of variation of ^{18}F-FDG uptake, was not considered in this metaanalysis as it was outside the dates of the systematic review. In addition, Tahara et al. did not compare ^{18}F-FDG PET with the MHLW guidelines (*37*).

The current study did not assess the role of cardiac MRI. Smedema et al. reported sensitivity and specificity for MRI of 100% and 78%, respectively (*38*). In studies by Ohira and Mehta et al., MRI was shown to have a better specificity but lower sensitivity than ^{18}F-FDG PET (*18,30*). An advantage of MRI is the absence of ionizing radiation. However, a significant limitation of MRI is that it cannot be used to study patients with pacemakers or defibrillators, which are important in the management of many patients with cardiac sarcoidosis. In addition, gadolinium must be used cautiously in patients with renal impairment because of the risk of nephrogenic systemic fibrosis.

Steroids could impair detection of active disease. However, in the Ontario study most of patients on treatment had a positive ^{18}F-FDG PET result. Moreover, similar to our study, all the studies (except that of Nishiyama et al. (*27*)) included patients on steroids or did not report therapy as an exclusion criterion. These data suggest that steroids did not reduce the initial diagnostic power of ^{18}F-FDG PET, but this possibility requires further study.

As ^{18}F-FDG PET emerges as a diagnostic method for sarcoidosis, there will be a need for standardization of preparations, acquisitions (including whole-body), CT data, and diagnostic criteria.

Clinical Relevance and Future Directions

Larger prospective studies with adequate follow-up are needed to identify the role of ^{18}F-FDG PET in the management of cardiac sarcoidosis. Follow-up clinical and imaging data for active cases receiving steroid treatment are needed to highlight the potential prognostic value of ^{18}F-FDG PET, as well as the utility of follow-up scans to assess treatment.

In view of the possibility, though uncommon, that sarcoidosis may affect the heart without clear evidence of other extracardiac organ involvement, further study is warranted. It is interesting to speculate that cardiac sarcoidosis may be more common than previously suspected and may contribute to the pathogenesis of some nonischemic cardiomyopathies causing ventricular tachycardia or to the development of conduction abnormalities. ^{18}F-FDG PET may have a potential role in ruling out cardiac sarcoidosis, but this possibility requires further study.

^{18}F-FDG PET can be an expensive technology. However, its role in diagnosing cardiac sarcoidosis activity and targeting therapy may outweigh the cost of scanning and lower the final individual health-care costs. Future cost-effectiveness studies should be considered.

New Tracers

^{68}Ga is a positron emitter produced by a ^{68}Ge/^{68}Ga generator (half-life, 68 min; $\beta+$, 88%) and is not dependent on a cyclotron. ^{68}Ga-citrate is delivered with increased permeability to the inflammatory lesions through capillaries, where it is taken up by leukocytes. The somatostatin type 2 receptor analog ^{68}Ga-DOTATATE is rapidly excreted from nontarget sites, offers good target-to-nontarget imaging properties, and hence is a potential candidate tracer for imaging granulomatous diseases expressing somatostatin type 2 receptors.

^{111}In-octreotide has been used for imaging of sarcoidosis (*39*), and one may infer that ^{68}Ga-DOTATATE could also be used. At present, there is no literature on the use of ^{68}Ga-citrate PET in sarcoidosis, but if it were to be applied, one may expect that the sensitivity would be far superior to that of conventional ^{67}Ga-citrate. These new approaches will require further exploration.

CONCLUSION

This metaanalysis revealed the following major points: First, the high diagnostic accuracy determined for ^{18}F-FDG PET suggests that it is a potentially valuable technique in patients with suspected cardiac sarcoidosis (at least compared with diagnostic criteria [MHLW guidelines] that represent substantial disease). Second, there were relatively few research studies that met the inclusion criteria for this metaanalysis, highlighting the need for future larger prospective studies. Finally, the heterogeneity in the studies' methodologic quality and interpretation methods demonstrates the importance of adhering to a common validated standard in future studies, thus reducing the study limitations and bias and facilitating comparison between studies. Standardization would also be expected to optimize clinical utility.

It is important to critically evaluate the current evidence to gain knowledge and understanding about the appropriate use of this new technique in clinical practice and to guide future scientific efforts in this field. Awareness of these results has the potential to affect patient care by providing supportive evidence for more effective use of ^{18}F-FDG PET in the diagnosis of cardiac sarcoidosis. ^{18}F-FDG PET may potentially be a useful means to direct therapeutic strategies to improve patient outcome. Prospective outcome studies are needed and are under way.

DISCLOSURE STATEMENT

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