

METABOLISM-PERFUSION IMAGING TO PREDICT DISEASE ACTIVITY IN CARDIAC SARCOIDOSIS

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ABSTRACT. FDG-PET is a sensitive but not specific test for myocardial sarcoidosis and its ability to define prognosis remains unclear. Combination with perfusion scanning may improve accuracy by differentiating scar from inflammation. We conducted this retrospective chart review to ascertain the utility of a rubidium -FDG PET scan for assessment of disease activity in patients with cardiac sarcoidosis. The presence of any perfusion-metabolism mismatch or a mismatch of > 6% of the myocardium on the scan were compared with the clinical course. Among 18 subjects, mismatched segments were present in 11 scans, whereas 7 demonstrated mismatch > 6%. There was a suggestion of association between PET scan and active disease using the threshold of any mismatch ($p=0.09$), with sensitivity of 80% and specificity of 62.5%. The threshold of >6% mismatch improved the specificity to 100% with 70% sensitivity, and the association between PET findings and clinically active disease was highly significant ($p=0.0002$). Eight patients had follow-up Rb-FDG PET scans, all of which were concordant with the clinical course. The positive predictive value of Rb-FDG PET scan showing >6% mismatch for detecting clinically active cardiac sarcoidosis was 100%. However, the finding of any mismatch still portends a high chance of clinical activity. Further studies to define the utility of Rb-FDG PET scan for management of cardiac sarcoidosis are warranted. (*Sarcoidosis Vasc Diffuse Lung Dis* 2011; 28: 50-55)

KEY WORDS: FDG-PET scan, cardiac sarcoidosis, mismatched

Abbreviation list

FDG:	Fluoro-deoxyglucose
MRI:	Magnetic Resonance Imaging
NYHA:	New York Heart Association
PET:	Positron Emission Tomography
Rb:	Rubidium
ICD:	Implantable Cardioverter Defibrillator

INTRODUCTION

Myocardial involvement has been reported in up to 25% of patients with sarcoidosis in the U.S. and remains a substantial cause of mortality (1). Although most cases are clinically silent, cardiac involvement can lead to congestive heart failure and life-threatening cardiac dysrhythmias in 2-7% of patients. Corticosteroid therapy has been shown to improve outcomes when started before the occurrence of systolic dysfunction (2), probably by prevention of malignant arrhythmias (3) and preservation of LV function; however, it may not be as effective in the later stages, where the response is variable (4).

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Given the toxicities associated with corticosteroids and other immunosuppressive medications, differentiating active granulomatous inflammation from myocardial scar is a major clinical dilemma in the management of cardiac sarcoidosis. However, there is currently no validated tool to reliably determine which patients have active disease. An imaging modality that identifies disease activity in cardiac sarcoidosis may predict response to therapy and help guide management.

Various imaging tools such as thallium-201 scintigraphy, gallium-67 scintigraphy, magnetic resonance imaging (MRI) and FDG-PET have been used to identify cardiac involvement in sarcoidosis. Both thallium and gallium scintigraphy have poor sensitivity and are not reliable for identifying cardiac sarcoidosis (5). MRI has high sensitivity (78-100%) and good specificity (78%) for diagnosing the presence of cardiac sarcoidosis (6), but cannot distinguish between active inflammation and scar tissue. It is additionally limited as a follow-up tool since it cannot be used in patients with indwelling cardiac devices. Recently, some studies have suggested that FDG-PET findings may be a promising tool for diagnosis and assessment of cardiac sarcoidosis (7-10). In these studies, localized uptake of ^{18}F -FDG PET appeared to be a hallmark of active inflammatory change.

Since the myocardium has high obligate glucose metabolism, FDG-PET metabolism scan without perfusion imaging can be difficult to interpret (11) and may overestimate the presence of active inflammation. Thus, FDG-PET in isolation exhibits modest specificity for the diagnosis of cardiac sarcoidosis (11). However, combination with perfusion scanning allows characterization of the relative metabolism-perfusion ratio and provides more precise anatomic definition, which may improve specificity significantly compared with the prior reports.

METHODS

We identified consecutive patients with a diagnosis of cardiac sarcoidosis who had Rubidium (Rb)-FDG PET testing at our institution from 2004-2008. The presence of cardiac sarcoidosis was defined according to the criteria used in A Case Control Etiologic Study of Sarcoidosis (ACCESS) (12).

ACCESS investigators defined "definite" cardiac involvement in patients with biopsy-proven extracardiac sarcoidosis as one of: a) treatment-responsive cardiomyopathy; b) conduction defects or atrioventricular nodal block; c) positive cardiac gallium scans that improve with therapy; or, d) myocardial granulomas. Probable cardiac sarcoidosis includes patients with a) ventricular dysrhythmias without other causes; b) cardiomyopathy; or c) positive imaging study (thallium-201, sestamibi or MRI) compatible with cardiac sarcoidosis. Patients were excluded if they had coronary artery disease or other co-morbidities that could also explain the cardiac disease or if adequate follow-up data were not available. This research was approved by our institutional review board.

Imaging was performed on all the patients following an overnight fast. Forty mCi of rubidium-82 chloride was infused intravenously two minutes prior to myocardial perfusion image acquisition. FDG metabolic images were obtained 45 minutes after infusion of 7-15 mCi of ^{18}F FDG. PET perfusion and metabolic images were interpreted using the standard 17 segment model (13). In this model, the apex is considered to represent 4% of LV mass, while each of the other segments is considered to represent 6% of LV mass. Perfusion defects were defined by a relative segmental tracer concentration of 70% or less of maximal myocardial activity on the rubidium-82 images. Perfusion-metabolism mismatches were defined by a relative FDG concentration exceeding that in normally perfused myocardium by 15% or more on background subtracted images. Perfusion-metabolism matches were defined by concordant reductions in FDG uptake in hypoperfused myocardial areas.

Predefined thresholds for accuracy analysis included the presence of any perfusion-metabolism mismatch or the presence of a perfusion-metabolism mismatch of >6% (corresponding to more than one cardiac segment). Clinically active disease was defined as either improvement or progression of the index cardiac variable during the course of follow-up, regardless of treatment. We defined active disease as a change in ejection fraction of $\geq 10\%$, a 50% change in the number of ventricular events on Holter/ICD checks, or development of new clinically-important dysrhythmias in patients (3) for whom Holter data were not available.

RESULTS

Patient Characteristics and Demographic Data

We identified 18 patients with cardiac sarcoidosis who had Rb-FDG PET testing at our institution between 2004-2008 and who had adequate follow-up for at least six months after the PET imaging. The mean length of follow-up was 12 months (6-22 months). Baseline demographic data did not differ significantly between the patients with or without metabolism-perfusion mismatches (Table 1).

Ten (56%) of the 18 patients were noted to have clinically active disease (nine due to dysrhythmias and one on the basis of cardiomyopathy). Of the nine patients with disease activity defined on the basis of dysrhythmias, four patients showed a mean decrease in the number of ventricular events of 67% (52%-71%) when immunosuppression was augmented or initiated. Two patients exhibited a mean increase of 63% in the number of ventricular events during the follow-up period. The remaining three patients were felt to have significant clinically active disease as well: one patient reported marked worsening of palpitations, but no data were available from ICD interrogations; the second patient required an ablation procedure for worsening ventricular dysrhythmias; the last patient had an outside hospital Holter monitor recording that showed increased ventricular events that prompted a change in anti-arrhythmic therapy.

During the follow-up period, none of the patients had a change in dysrhythmias that was attrib-

utable to a change in the anti-dysrhythmic medications. All cases where anti-dysrhythmic medications were added were among patients who demonstrated deterioration; all four patients who improved their electrical activity did so with augmentation of immunosuppression alone. The patient defined as active on the basis of cardiomyopathy showed an improvement in the left ventricular ejection fraction from 20% to 35% after initiation of corticosteroids. This patient was on an angiotensin converting enzyme inhibitor and a beta blocker for the cardiomyopathy. However from the time of initiation of corticosteroids to the 15 month follow-up echocardiogram showing improvement in the ejection fraction, no significant change in the dose of either medication had been made.

Eleven (61%) of the scans showed the presence of any mismatch, whereas only seven (39%) demonstrated mismatch >6%. Eight of the 11 patients with a scan showing any degree of perfusion-metabolism mismatch had evidence of clinically active disease, while two of the remaining seven patients with a negative scan were noted to have clinically active disease. Thus, using the threshold of any mismatch, the sensitivity and specificity of Rb-FDG PET scan for detection of clinically active disease was 80% and 62.5%, respectively ($p=0.09$ Fisher's exact test).

Using a threshold of >6% mismatch, seven of the 18 scans were positive. All seven of these patients had clinically active disease, while three of the 11 patients with a negative scan had active disease. Two of these three patients with a negative scan had a completely normal scan while the third patient had a combination of matched defects as well as a 6% area of mismatch. Using the threshold of >6% mismatch, sensitivity decreased to 70% while specificity was 100% ($p=0.0002$ Fisher's exact test). Of the two patients with active disease but a completely normal Rb-FDG PET scan, one was on treatment with azathioprine at a dose of 100 mg/day at the time of the PET scan. The patient had progressive dysrhythmias which were attributed to cardiac sarcoid. He was subsequently treated with infliximab infusions with marked improvement in the dysrhythmias. The other patient with a normal scan but active disease also had dysrhythmias as the major manifestation of cardiac sarcoid. This patient had an MRI, done around the same time as the normal Rb-FDG PET which showed changes suggestive of cardiac sarcoid. Omission

Table 1.

	Mismatched segments N=11 (61%)	No mismatched Segments N=7(39%)
Age	53.53±18.32	55.40±17.73
Female (%)	6 (55%)	4 (57%)
Race		
Caucasian	5 (45%)	2 (29%)
African-American	6 (55%)	5 (71%)
Therapy at baseline	8 (73%)	6 (86%)
Prednisone	8	5
[mean dose/day (mg)]	14 (5-35)	10 (5-20)
Azathioprine	1	2
Methotrexate	1	
Mean length of follow-up (months)		
Active disease	12.8 (6-22)	12 (9-15)
Inactive disease	13 (9-15)	10 (6-18)

sion of the three patients with solely clinical evidence of active disease from the analysis did not change the results significantly ($p=0.08$ for any mismatch, $p=0.001$ for $>6\%$ mismatch).

Eight of the 18 patients had follow-up Rb-FDG PET scans during their follow-up course. All of these scans showed findings concordant with the patient's clinical course. Six of the repeat scans showed a persistence, decrease or resolution of perfusion-mismatch consistent with patient's clinical course (Figure 1). Two scans repeated in patients with clinically inactive disease showed persistence of matched defects. None of the perfusion-metabolism mismatched defects transitioned to matched defects.

DISCUSSION

The promise of newer imaging modalities like cardiac MRI and PET imaging to diagnose cardiac sarcoidosis has been emphasized in several recent re-

ports (6-11). However, the clinical role of these emerging technologies remains undefined, and will challenge clinicians caring for these patients, since the significance of isolated imaging abnormalities is uncertain. For example, a recent study by Mehta et al suggested abnormalities revealed by cardiac MRI or cardiac PET scanning do not predict arrhythmias in patients with preserved cardiac function (11). Even more difficult is the question of how to interpret discrepant information when tests identify divergent abnormalities (9, 14).

It is possible that risk-stratification is a more relevant goal than diagnosis of subtle involvement in cardiac sarcoidosis. Clinically available risk factors for adverse outcomes in cardiac sarcoidosis include NYHA functional class (2), sustained ventricular dysrhythmias (2), left ventricular end-diastolic volume (2) and the presence of atrioventricular conduction block (15). Yazaki et al emphasized that ejection fraction $<35\%$ is associated with a lower likelihood of response to corticosteroids (2). Nonetheless, some

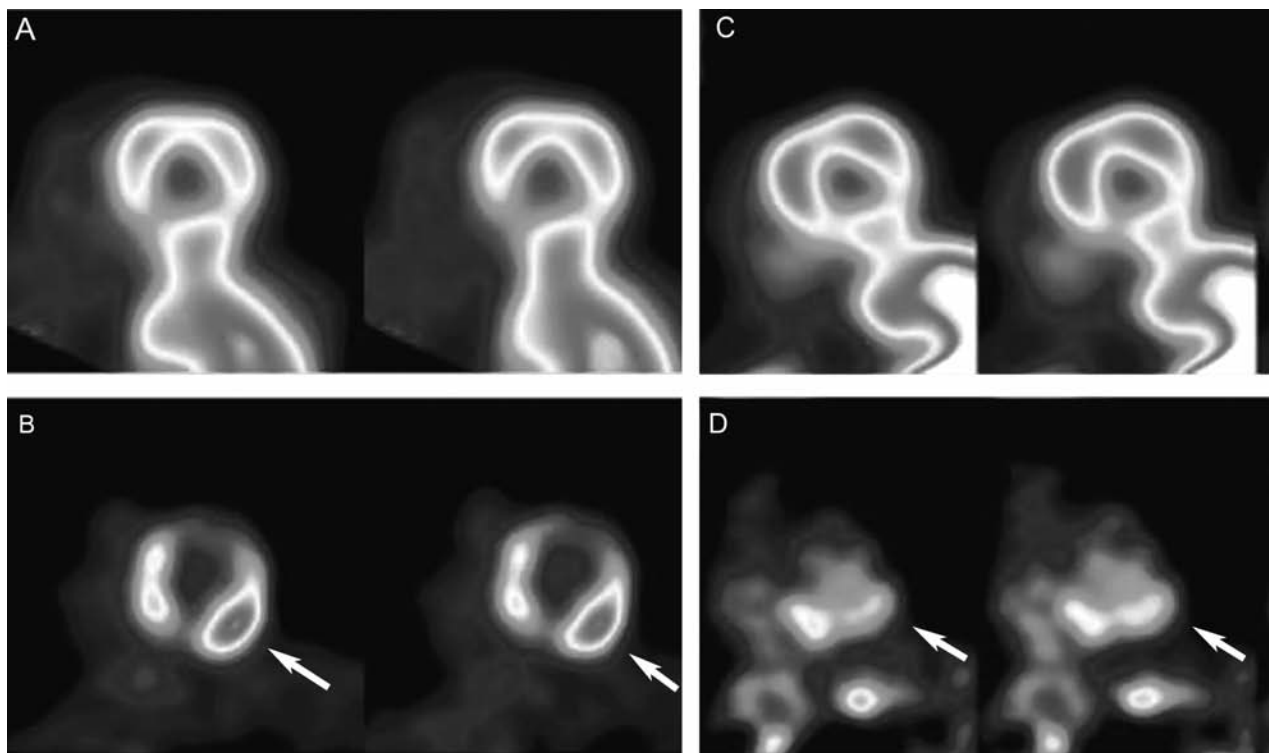


Fig. 1. A) Initial Rubidium perfusion scan. B) Initial FDG metabolism images. C) Rubidium perfusion scan 6 months later. D) FDG metabolism images 6 months later. Areas of increased FDG uptake on the initial scan with resolution (white arrows) on repeat scan done 6 months later

patients with low ejection fractions do respond to immunosuppressives. In patients with pre-existing use of immunosuppressives and deteriorating ejection fraction or worsening dysrhythmias, the clinical issue of whether to intensify immunosuppressives is a difficult one.

One report from the Netherlands emphasized that the extent of delayed enhancement on cardiac MRI correlates with the severity of cardiac dysfunction⁶. However, whether this metric can also be used to predict treatment efficacy is unclear. Similarly, Vignaux et al reported progression of imaging findings at 12 month follow-up MRI in three of five untreated patients with baseline abnormal cardiac MRIs, compared with none of the seven patients treated with corticosteroids (16). These data were recently corroborated in a larger cohort of 81 North American patients, where evidence of delayed enhancement on screening cardiac MRI predicted adverse cardiac events twice as often as clinical criteria for cardiac involvement (10).

Complementary use of FDG-PET and perfusion scanning with ¹³N-NH₃ was reported by Yamagashi et al. (17) in a series of 17 patients with cardiac sarcoidosis. In these patients, the perfusion defects demonstrated little change following steroid treatment, while the FDG abnormalities largely resolved with steroid treatment. However, the report does not describe the clinical course of cardiac disease in the patients. We previously described a patient whose clinical course paralleled the findings on serial Rb-FDG PET. In that situation, steroid dose reduction in the setting of persistent metabolism-perfusion mismatch led to worsening of both the dysrhythmias and the mismatch (9).

In our retrospective analysis of 18 patients, the positive predictive value of Rb-FDG PET scan showing >6% perfusion-metabolism mismatch for detecting clinically active cardiac sarcoidosis was 100%. However, using this criterion, the sensitivity was low at 70%. Using the criterion of any mismatch, sensitivity was higher at 80%; however the test had much lower specificity (62.5%). This suggests that although the finding of a >6% mismatch is highly indicative of clinically active disease, the finding of any mismatch still portends some chance of clinical activity. Major limitations of this report include that it is retrospective and uncontrolled, that the sample size is small, and that the majority of

clinically-active disease occurred in patients with dysrhythmias. Also, we cannot extrapolate these results to patients who do not meet ACCESS criteria for definite or probable cardiac involvement. Larger, prospective studies would be necessary to elucidate the marginal utility of this expensive modality compared with standard tests. The data here do not provide guidance about the accuracy of Rb-FDG PET for the diagnosis of cardiac sarcoidosis, or for its long-term prognosis. However, to the extent it is important to control active inflammation in cardiac sarcoidosis, these data do support the potential usefulness of this modality.

Eight of the 18 patients had follow-up Rb-FDG-PET scans, all of which showed results concordant with the patient's clinical course. This suggests that besides initial identification of disease activity in cardiac sarcoid, Rb-FDG PET scans may be beneficial as a follow-up tool to guide immunosuppressive therapy. A worsening/persistence of clinical symptoms associated with perfusion-metabolism mismatches on Rb-FDG PET scans would warrant more aggressive therapy, while development of a matched defect would suggest formation of scar tissue and lack of benefit from escalation of immunosuppressive therapy.

CONCLUSION

Given the guarded prognosis of patients with active cardiac disease, the implication of this preliminary report is that any evidence of metabolism-perfusion mismatch constitutes a reasonable indication to treat the patient as if active granulomatous inflammation is present. Larger, prospective trials are needed.

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