Scintigraphic Detection of Regional Disruption of the Adrenergic Nervous System in Sarcoid Heart Disease

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The presence of defects on resting thallium (^{201}Tl) myocardial scintigraphy has been previously demonstrated in myocardial sarcoidosis. To examine cardiac sympathetic nerve activity in patients with cardiac sarcoidosis, we performed ^{201}Tl and I-123 MIBG (meta-iodobenzylguanidine) myocardial scintigraphy in patients with sarcoidosis.

Sixteen patients with sarcoidosis were classified into 2 groups according to the presence or absence of defects on ^{201}Tl scintigraphy. Myocardial images by both ^{201}Tl and I-123 MIBG were then divided into 20 segments and scored using a 6-point scoring system. Defect Score was defined as the sum of significant scores in each image. The mean Defect Score in I-123 MIBG images was higher in the ^{201}Tl defect group (44.3 ± 13.3) than in both the normal ^{201}Tl group (25.1 ± 10.5) and the control group (22.7 ± 11.4). Moreover, the locations of defects on I-123 MIBG scans were consistent with those on ^{201}Tl scans. This study suggests that cardiac adrenergic function may be impaired in cardiac sarcoidosis, and I-123 MIBG scintigraphy may be more sensitive in detecting cardiac sarcoidosis than ^{201}Tl scintigraphy, although the clinical significance of these findings requires further study.

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SARCOIDOSIS, a systemic granulomatous disease of undetermined etiology and pathogenesis, most often involves the lymph nodes, lungs, liver, spleen, skin, eyes, phalangeal bones and parotid glands, although any organ may be affected. Cardiac involvement is significant because it may induce arrhythmias, atrioventricular block, congestive heart failure, and sudden death^{1–3}

A positive finding by endomyocardial biopsy is diagnostic. However, due to the patchy distribution of the disease, a negative result is often obtained, and a negative result

is therefore of no value. Although echocardiography and systolic time intervals are also relatively insensitive, radionuclide methods offer great promise for the diagnosis of this disease. Defects in thallium (^{201}Tl) myocardial perfusion scan have been shown to be associated with sarcoid heart disease^{4,5} even in patients without overt cardiac symptoms. Although the reason for this finding is presently unclear, it may be highly specific for sarcoidosis in the appropriate clinical setting.

Radiolabelled meta-iodobenzylguanidine (MIBG), an analog of norepinephrine, was recently developed⁶. The kinetics of MIBG accumulation in the myocardium can serve as an indicator of cardiac adrenergic neuron

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TABLE I CLINICAL CHARACTERISTICS OF PATIENTS WITH SARCOIDOSIS

No.	case	sex/age	BAL fluid		CXR staging	ST-T change		
			Ly(%)	CD4/8		Holter	Master	
<i>²⁰¹Tl defect group</i>								
1	I.K.	M	42	17	1	2	N	N
2	S.M.	F	40	36	3	2	N	—
3	Y.N.	M	39	25	2	3	N	N
4	J.T.	F	51	43	10	2	N	N
5	S.T.	M	68	17	4	3	N	—
6	I.K.	M	65	26	4	2	N	—
mean			50.8	27.3	3.8			
SE			5.3	4.2	1.3			
<i>²⁰¹Tl normal group</i>								
7	A.M.	F	73	47	3	2	N	—
8	C.K.	F	57	56	2	2	N	N
9	H.Y.	F	69	17	5	2	N	N
10	K.Y.	F	74	38	2	3	N	N
11	Y.I.	M	66	17	2	1	N	N
12	M.I.	F	61	42	3	2	—	N
13	H.M.	M	39	48	3	2	—	—
14	A.K.	F	81	43	10	2	N	N
15	K.S.	F	58	23	2	2	N	N
16	K.M.	M	58	63	2	2	N	—
mean			63.6	39.3	3.4			
SE			3.7	5.0	0.8			

BAL: bronchoalveolar, Ly(%): Percentage of lymphocyte, CXR: chest roentgenogram, Holter: Holter ECG, Master: Master's double 2 step test, N: negative for ischemia
 —: not performed.

injury and function? In some cardiac disorders, there have been reports that interdictions of adrenergic innervation in different regions of the heart may suggest left ventricular dysfunction^{8,9} or may predispose the patient to arrhythmias^{10,11}.

In this study, we performed I-123 MIBG scintigraphy in patients with sarcoidosis who had abnormal ²⁰¹Tl findings and examined whether cardiac adrenergic neuron activity might be impaired in these subjects.

METHODS

Patient Population

Sixteen patients (7 males and 9 females, mean age 58.8 years) who had been diagnosed as sarcoidosis by biopsy from skin, scalene node, or transbronchial lung biopsy (TBLB) were studied. None of them had a history of diabetes mellitus or ischemic heart disease, or showed any ischemic ST-T changes in Holter electrocardiogram (ECG)

or in Master's two step test (Table I).

Patients were classified into 2 groups according to the presence or absence of defects on myocardial ²⁰¹Tl scintigraphy. Six patients showed ²⁰¹Tl defects (group A) and the other 10 patients showed no defects (group B). There were no significant differences between the 2 groups with respect to mean age, 12-lead ECG findings, chest roentgenographic findings, mean lymphocyte counts, or mean CD4/8 ratio in bronchoalveolar fluid (Table I). Eleven control subjects without sarcoidosis or any cardiac disorders (7 males and 4 females, mean age 63.4 years) who were matched for age and gender with the patients with sarcoidosis were also studied (group C).

The study protocol conformed to the guidelines established by the Ethics Committee at our institution. Informed consent was obtained from each patient.

²⁰¹Tl Imaging Protocol

Fig 1. Diagrammatic representation of SPECT images, showing the assignment of anatomic left ventricular segments and ventricular territories. The images were scored using a 6-point scoring system (0=normal, 1=equivocal defect, 2=mild defect, 3=moderate defect, 4=severe defect, 5=no uptake). The Defect Score was defined as the sum of significant (greater than 2) scores in each image.

Fifteen minutes after the intravenous injection of 3 mCi of ionic ^{201}Tl chloride, myocardial perfusion scans were performed in a routine manner with a high-resolution scintigraphy camera. Scintillation counts of peak energy were 71 keV, with a window of 20%.

I-123 MIBG Imaging Protocol

I-123 MIBG (Daiichi Radioisotope Laboratory) had a chemical purity of 100%. Four hours after the injection of 3 mCi of I-123 MIBG, myocardial images were recorded as with ^{201}Tl . Scintillation counts of peak energy were 159 ± 10 keV, with a window of 20%. For SPECT images, all short-axis and vertical long-axis tomograms were displayed on transparency film, with the intensity of each image normalized to the maximal pixel value in that image. Separate films were obtained for aligning slices of the initial thallium and 4 h I-123 MIBG images. For ^{201}Tl and I-123 MIBG imagings, tomograms were divided into 20 segments (Fig 1).¹² These segments were assigned to 6 evenly spaced regions in the representative apical, mid-ventricular, and basal cuts of the short-axis views and anteroapical and inferoapical segments of the mid-vertical long-axis cut. The images were scored independently by two experienced observers (IM and KN) using a 6-point scoring system (0=normal, 1=equivocal, defect,

Fig 2. Differences between mean Defect Scores by I-123 MIBG scintigraphy among groups A, B, and C. The mean Defect Score in I-123 MIBG scans was higher in group A than in both groups B and C.

2=mild defect, 3=moderate defect, 4=severe defect, 5=no uptake). Disagreements were resolved by consensus. The Defect Score was defined as the sum of significant (greater than 2) scores in each image. Intra-observer reliabilities¹³ were 0.96 and 0.97. Inter observer reliability was expressed as a correlation coefficient of 0.95.

Statistical Analysis

Values for Defect Scores on I-123 MIBG and ^{201}Tl images are expressed as the mean $\pm$ SD. Two groups were compared by the paired t-test. Three groups were compared by a one-way analysis of variance. Duncan's multiple range test was performed if a significant difference was found. Probability values <0.05 were considered statistically significant.

RESULTS

Differences in Mean Defect Scores by I-123 MIBG Scintigraphy Among the 3 Groups (Fig 2)

The mean Defect Scores by I-123 MIBG scintigraphy were 44.3 ± 13.3 in group A, 25.1 ± 10.5 in group B, and 22.7 ± 11.4 in group C. The mean Defect Score by I-123 MIBG was higher in group A than in groups B and C ($p < 0.01$).

Comparison of Defects in ^{201}Tl and I-123 MIBG Images in Group A (Table II)

The locations of the defects in ^{201}Tl scans

Fig 3. ^{201}Tl (left) and I-123 MIBG scintigrams in a patient (case 5) in group A. In the ^{201}Tl image, a defect was seen only in the inferior segment (left). However, in the I-123 MIBG image (right), defects were seen in the anterior, inferior, and posterior segments.

TABLE II REGIONS OF DEFECTS IN ^{201}Tl AND I-123 MIBG IN GROUP A

Case No.	^{201}Tl segment	I-123 MIBG segment
1	inferior	inferior
2	septum, inferior	septum, inferior
3	inferior, posterior	inferior, posterior
4	anterior, inferior	anterior, inferior
5	inferior	anterior, inferior, posterior
6	inferior, posterior	inferior, posterior

were, in order of frequency, inferior ($n=6$, all patients), posterior ($n=2$), septal ($n=1$), and anterior ($n=1$). Two patients had 1 defect (inferior) and 4 patients had 2 defects each (4 inferior, 2 posterior, 1 anterior and 1 septum). The lateral wall exhibited the best uptake. I-123 MIBG scans revealed all of the defects in ^{201}Tl images, as well as 2 additional defects (anterior and posterior) in 1 patient (case 5) (Fig 3). Moreover, the Defect Scores were higher on I-123 MIBG images than on ^{201}Tl images in 5 of the 6 patients, but this difference was not significant (Fig 4).

DISCUSSION

The value of myocardial ^{201}Tl imaging in detecting myocardial involvement has been previously demonstrated in patients with suspected cardiac sarcoidosis^{4,5}. In this study,

Fig 4. Differences in the mean Defect Scores between I-123 MIBG and ^{201}Tl images in group A. Although there was no significant difference, the Defect Scores on I-123 MIBG images were greater than those on ^{201}Tl images in 5 of the 6 patients.

we classified patients on the basis of myocardial ^{201}Tl scintigraphy. ^{201}Tl defects in the myocardium are not specific to sarcoidosis, and may also be found with ischemic heart disease or other cardiomyopathies. However, none of our patients had any history of these diseases or showed any ischemic ST-T changes by Holter ECG or Master's two step exercise test, and the sites of ^{201}Tl defects did not always correspond to the anatomic structure of coronary arteries (not shown). Therefore, the probability that diseases

other than cardiac sarcoidosis may have produced these defects is very low. We regarded the patients in the ^{201}Tl defect group as patients with cardiac sarcoidosis.

There have been no reports on the relationship between ^{201}Tl and I-123 MIBG images in sarcoidosis. In this study, we found that the mean Defect Score in I-123 MIBG images was higher in the ^{201}Tl defect group (group A) than in both the normal ^{201}Tl group (group B) and the control group (group C). Since MIBG is an analog of noradrenaline⁶ and scintigraphically measured I-123 MIBG activity is positively correlated with the activity in biopsy samples taken from the same region,¹⁴ myocardial scintigraphy with I-123 MIBG is thought to reflect the status of myocardial adrenergic innervation. Thus, our results may suggest that cardiac adrenergic function is impaired in patients with cardiac sarcoidosis.

In the ^{201}Tl defect group, there was a good correlation between the locations of defects on ^{201}Tl scans and those on I-123 MIBG scans. The defects on I-123 MIBG scans were in the same locations as those on ^{201}Tl scans, as well as in some ^{201}Tl -normal areas, and the Defect Scores on I-123 MIBG scans were higher than those on ^{201}Tl scans in 5 patients and similar in 1 patient. These results suggest that I-123 MIBG scintigraphy may be more sensitive for detecting cardiac sarcoidosis.

Although there is no information available regarding the clinical significance of myocardial I-123 MIBG imaging in patients with sarcoidosis, there have been reports of I-123 MIBG imaging in some cardiac disorders. It is possible that arrhythmias in cardiac sarcoidosis may also be related to the adrenergic nervous system and I-123 MIBG findings.^{10,11} Moreover, findings in I-123 MIBG scintigraphy have been demonstrated to be correlated with left ventricular function and heart failure in idiopathic cardiomyopathy and doxorubicin cardiomyopathy.^{8,9} Thus, findings in I-123 MIBG imaging may also be indicative of cardiac dysfunction in cardiac sarcoidosis.

In conclusion, this study suggests that cardiac adrenergic function may be impaired in patients with cardiac sarcoidosis, although the clinical significance of these findings requires further study.

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