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Anginal chest pain in sarcoidosis

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ABSTRACT Of 43 consecutive black patients (42 male) with sarcoidosis, 12 (28%) complained of chest pain that met the clinical criteria for typical (four patients) or atypical (eight patients) angina pectoris. These patients underwent cardiopulmonary assessment, which included exercise and redistribution thallium-201 scans and, if indicated, coronary angiography. Nine control patients with sarcoidosis matched for age and duration of disease, but without chest pain, were also studied by thallium-201 scintigraphy. Six of the 12 patients with chest pain had thallium scans indicative of myocardial ischaemia, but all had normal coronary angiograms; no patient from the control group had evidence of ischaemia on the thallium scan. Four additional patients with chest pain and one from the control group had other (non-specific) abnormalities on the thallium scan, so that scans were abnormal in 10 of the 12 patients with sarcoidosis who had chest pain. Most patients with anginal chest pain reported partial or complete relief of symptoms with nitrates. Anginal chest pain appears to be common in black male patients with sarcoidosis, is associated with abnormal myocardial perfusion scans, and may result from myocardial sarcoidosis.

Introduction

Sarcoid disease of the myocardium is a serious complication that frequently presents as sudden death.[1 2] Although necropsy series report that as many as 27% of patients with sarcoidosis have myocardial disease,[2] fewer than 5% of patients are diagnosed clinically, usually when they develop arrhythmias or syncope.[2] Chest pain suggestive of angina pectoris or myocardial infarction is well recognised in sarcoidosis,[3] though many studies on sarcoid disease of the myocardium either did not address this symptom or excluded patients with a history of chest pain so that a "pure" population with sarcoidosis could be studied.[4–6]

We selected patients with precordial chest pain and performed exercise testing with thallium-201 myocardial perfusion scintigraphy to exclude ischaemic heart disease. The patients had symptoms strongly suggesting angina pectoris or important symptoms to warrant further evaluation. On the basis of Baysian analysis, we suspected that chest pain in our relatively young male clinic population was less likely to result from coronary artery disease than from sarcoidosis.[7] An age matched control population of patients with sarcoidosis who had no chest pain was studied for comparison.

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Methods

PATIENT POPULATION

A detailed cardiac history was obtained from 43 consecutive patients seen in the sarcoid clinic over 14 months. All had had sarcoid lung disease at some time, though it was not necessarily active at the time of the study. Patients reporting a classic history of anginal chest pain—that is, pain that was substernal, exertional, and relieved by rest or nitroglycerin or both—were included. Patients reporting chest pain that lasted from one to 20 minutes that was not induced by exercise, that occurred and resolved spontaneously, and that often occurred early in the morning were also included. The quality of the pain was usually described as "dull, aching" or a "pressure" sensation. Patients who had chest pain that was fleeting, lasting less than 30 seconds, and associated with a single movement of the torso or arms were excluded. The patients were selected on history alone. Studies to exclude oeso-

phageal or gastroenterological origins of the chest pain were not performed routinely.

Eight patients seen in the sarcoid clinic during the same period who did not have chest pain were matched with the study patients for age and approximate extent of disease on the basis of pulmonary function, and served as a control group. The patients were not matched for smoking or blood pressure. The remaining patients in the clinic either did not match any individual in the study group or declined to participate in the study.

In all patients sarcoidosis had been diagnosed by tissue biopsy with cultures negative for fungi and *Mycobacterium tuberculosis*. The two groups of patients included those with inactive as well as active disease. Exercise data from eight normal male volunteers studied in our laboratory were also used for comparison.

Written, informed consent was obtained from all patients. Patients without chest pain who received thallium signed consent forms approved by our institutional review board.

EXERCISE STUDIES

All exercise studies were performed with the subjects fasting. The studies included exercise and redistribution thallium-201 (^{201}Tl) myocardial imaging, 12 lead electrocardiography, blood gas analysis or ear oximetry, and measurement of oxygen consumption and carbon dioxide production. Determination of pulmonary gas exchange data was made with a Beckman Horizon Metabolic Cart. Exercise was performed on a Quinton treadmill according to a modified Bruce protocol, the ECG being recorded every 60 seconds. The exercise study was terminated when the subject reached maximal heart rate, experienced significant chest pain, or stopped because of fatigue or shortness of breath.

When the patient signalled that he could walk only one more minute, 2 mCi of ^{201}Tl was injected through an indwelling catheter in the antecubital vein and exercise was continued for one more minute. Exercise images of the myocardium were obtained within 10 minutes of injection. Delayed images were obtained four hours after injection. Images were obtained with the patient supine and in the anterior, the 40° and 60° left anterior oblique, and the left lateral projections. All images were recorded for 10 minutes, with at least 300 000 counts collected on a Technicare 420 mobile gamma camera.

Blood samples for estimation of arterial blood gases were drawn from all patients with sarcoidosis while they were at rest and, when an arterial line was in place, at peak exercise. Arterial lines were placed with a 20 gauge plastic cannula into a radial artery by standard techniques. When an arterial line was not used, arterial oxygen saturation was determined by a Biox II ear oximeter.

Spirometry and estimation of transfer factor for carbon monoxide (TLCO) by the single breath technique were performed with a Jaeger Transferscreen pneumotach apparatus and compared with predicted normal values.[8 9]

INTERPRETATION OF THALLIUM SCANS

Interpretation of the myocardial perfursion scans was performed by one of us (AM). Repeat interpretations were performed in a blinded fashion on two further occasions with a random mixture of scans from patients not suffering from sarcoidosis. All interpretations from the two blinded readings of patients with sarcoidosis agreed with one another and were used for the analyses.

Thallium scans that showed defects or diffuse, severely inhomogeneous uptake were interpreted as being abnormal. A segment with initially decreased activity that showed partial or complete reperfusion on the delayed image was interpreted as having a reversible defect or redistribution. Lung thallium activity was calculated visually by comparing the initial (10 minutes after exercise) and delayed (four hours after injection) unprocessed anterior projection scintiphotographs.

DATA ANALYSIS

The results of the thallium scans were analysed by means of Fisher's exact test. Pulmonary function data from the two groups of patients were compared by Student's t test. Data from the exercise studies were analysed by using one way analysis of variance and the Bonferroni multiple comparison test, $p < 0{\cdot}025$ being regarded as significant.

Results

PATIENT PROFILES

The control group did not differ from the study population in age, FVC, TLCO, or duration of disease. Two patients with chest pain were having high dose steroids at the time of the study; one had a negative result in the thallium study. All of the patients were veterans, all but one were male, and all were black. The mean time since diagnosis for the patients with sarcoidosis was 7 (SD 0·5) years. Of the 43 patients seen, 17 had some form of chest pain and the 12 with symptoms suggesting angina were studied. The patients with chest pain were more likely to be smokers than non-smokers (8 *v* 4), whereas the reverse was true of the control group without chest pain (2 *v* 7; $p = 0{\cdot}056$, Fisher's exact text).

Exercise data (mean (SD) values): comparison of patients having no chest pain with those having chest pain and with normal subjects

	Chest pain (n = 12)	*Significance*	*No chest pain (n = 9)*	*Significance*	*Normal subjects (n = 8)*
Age (y)	35 (9)	NS	37 (9)	NS	36 (2)
FVC*	87 (17)	NS	80 (21)	—	ND
TLCO*	77 (18)	NS	85 (33)	—	ND
$\dot{V}_E$max*	75 (23)	NS	67 (15)	NS	73 (13)
$\dot{V}O_2$/kg max (ml min^{-1} kg^{-1})	23 (6)	NS	25 (7)	$p < 0{\cdot}001$	42 (4)
Anaerobic threshold: $\dot{V}O_2$/kg (ml min^{-1} kg^{-1})	14 (4)	NS	15 (4)	$p < {\cdot}01$	22 (4)
Max HR*	75 (12)	$p < 0{\cdot}01$	92 (9)	NS	100 (4)
DP	26 059 (5 602)	$p < 0{\cdot}02$	32 542 (5 279)	NS	33 096 (3 000)

*Percentage of predicted value.
FVC—forced vital capacity; TLCO—transfer factor for carbon monoxide; $\dot{V}_E$ max—maximum minute ventilation; $\dot{V}O_2$/kg max—maximun oxygen consumption; Max HR—maximum achieved heart rate; DP—double product (max HR × systolic blood pressure); ND—not done.
To convert $\dot{V}O_2$ from ml min^{-1} kg^{-1} to mmol min^{-1} kg^{-1} multiply by 0·0446.

EXERCISE STUDIES

All patients exercised to maximal tolerance or until they developed chest pain. Those limited by chest pain exceeded the anaerobic threshold determined by pulmonary gas exchange data as described by Wasserman.[10]

There were no significant differences between the two groups of patients in the maximum attained minute ventilation ($\dot{V}O_2$ max), in the level of $\dot{V}O_2$ at anaerobic threshold, or oxygen desaturation (table). No patient from either group had ECG evidence of ischaemia with exercise, abnormalities of rhythm or conduction, or cardiac arrhythmias.

The patients with angina had lower maximum heart rates and double products than those without chest pain. The double product of the normal subjects was not significantly different from that of the patients without chest pain. Both groups of patients, however, though not different from each other, had significantly lower anaerobic thresholds than the normal subjects (see table). Eight subjects either had clinical hypertension (diastolic blood pressure repeatedly >90 mm Hg) or had a hypertensive response to exercise (diastolic blood pressure >100 mm Hg), five in the chest pain group and three in the control group ($p = 0{\cdot}392$). The two patients with resting hypertension were in the chest pain group, though one was having treatment and his blood pressure was well controlled.

THALLIUM SCANS

Ten patients with chest pain had abnormal thallium scans, of whom six had transient perfusion defects suggesting coronary artery disease. One patient in the control group had a small, fixed defect. The difference between patients with and without chest pain was significant ($p < 0{\cdot}001$). There was no difference between groups in the number of patients with arterial desaturation during exercise, and none of the patients with redistribution on thallium imaging showed arterial desaturation with exercise. Two of the patients with chest pain and an abnormal thallium scan showed increased pulmonary uptake of thallium during exercise, suggesting an exercise induced rise in pulmonary capillary wedge pressure.[11] None of the studies showed abnormal right ventricular uptake.

Smoking did not appear to be an important factor as normal and abnormal thallium scans were seen in both smokers (4 *v* 6) and non-smokers (6 *v* 5; $p = 0{\cdot}41$). Hypertension was also unrelated to the outcome, as normal and abnormal thallium scans were seen respectively in three and five subjects with hypertension and in seven and six subjects who were normotensive ($p = 0{\cdot}392$).

The six patients with changes on thallium imaging suggestive of ischaemia had coronary angiography but none had more than minimal evidence of coronary atherosclerosis (less than 50% narrowing). All had normal pulmonary artery pressure, left ventricular ejection fraction, and valvular function at catheterisation. Two patients had intracoronary injection of ergometrine without evidence of coronary artery spasm.

Discussion

Defects on thallium scans in patients with myocardial sarcoidosis were first reported by Bulkey *et al* in 1977.[12] The five patients in their series all had clinical evidence of myocardial disease, verified by necropsy in one patient. Subsequently, Kinney *et al* studied 44 symptomless patients with sarcoidosis and found 14 had perfusion defects suggesting myocardial sarcoidosis.[4] Although Kinney's patients did not have evidence of cardiac disease, chest pain was noted to be a frequent complaint, two of their patients having had a normal coronary angiogram.[4] Other studies examining patients for cardiac sarcoidosis have either excluded patients with chest pain intentionally or have

found no association between this symptom and other evidence of cardiac manifestations.[6 13] Both chest pain and abnormal thallium perfusion scans have been noted in sarcoidosis, but previous studies have not described an association between the two.

In our predominately male veterans, 12 of the 43 patients with biopsy proved sarcoidosis had typical or atypical angina. Ten of the 12 had abnormalities on thallium perfusion scans compared with only one of the nine patients without chest pain, suggesting that chest pain may be an important early clinical indicator of myocardial sarcoidosis. There is good histological evidence based on necropsy and biopsy studies in sarcoidosis that defects on thallium scans are due to infiltrative myocardial disease or scarring.[12-14]

Six patients had ischaemic defects on thallium scans, which are usually associated with obstructive coronary artery disease or coronary artery spasm. Significant coronary artery disease was excluded, however, in those patients by angiography. Extramural coronary artery spasm is not a likely cause of these findings in our patients as none had a history of Prinzmetal's variant angina, none had ST segment elevation with exercise, and two had ergometrine administration at catheterisation without detectable spasm.

Complete resolution of thallium myocardial perfusion defects associated with an increase in coronary sinus blood flow has been found in a patient with sarcoidosis after infusion of a potent vasodilator, dipyridamole, suggesting that the perfusion defects may be due to microvascular spasm.[15] This may also be a cause of atypical angina in sarcoidosis, and chronic sustained microvascular spasm could add to the necrosis and scarring caused by the infiltrative granulomas. This theory was first proposed by Makler *et al,* who observed an ischaemic pattern in resting thallium scans in patients with sarcoidosis.[5] The same pathophysiology has also been suspected in myocardial scleroderma, where exercise thallium perfusion scans are similar to those in this study.[16] The possible presence of microvascular spasm in myocardial sarcoidosis has obvious implications for the early use of vasodilator agents to treat this potentially fatal complication. Most of our patients with chest pain reported either complete or partial improvement in their symptoms with administration of nitrates. Steroids have remained the main treatment for myocardial sarcoidosis but they have undesirable side effects and do not seem to prevent the development of myocardial fibrosis.[1]

Although there appeared to be a slight predominance of smoking and hypertensive patients in the patients with chest pain, neither condition was independently associated with abnormal thallium scans in those patients. The possible contribution of hypertension or smoking to these findings could be defined only by a much larger study.

Exercise heart rates of patients with abnormal thallium scans and chest pain were inappropriately low by comparison with the control sarcoid group, though they did not meet the strict criteria for chronotropic incompetence as seen in patients with significant coronary artery disease.[17] There was no difference between the two groups of patients in other indicators of fitness, such as maximal oxygen consumption or level of anaerobic threshold; and the cause of the relatively slower heart rates in our angina patients is not clear.

In summary, we found a substantial incidence of anginal type chest pain in patients with chronic sarcoidosis, and most of these patients showed myocardial perfusion abnormalities with exercise thallium imaging. None of the patients with ischaemia on thallium imaging had angiographic evidence of significant coronary artery disease, suggesting that microvascular spasm may be concerned in the pathophysiology of myocardial sarcoidosis.

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