High prevalence of the thallium-201 reverse redistribution phenomenon in patients with syndrome X


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Objective To evaluate the stress-redistribution myocardial perfusion pattern in patients with angina, positive exercise test and angiographically smooth coronary arteries (syndrome X).

Design Prospective study.

Patients and methods Twenty-five consecutive patients (seven males, mean age 54 ± 8 years) with typical angina, positive exercise test, normal coronary arteries and no inducible spasm, underwent stress-redistribution thallium-201 myocardial perfusion scintigraphy. Thirty-two consecutive patients (14 males, mean age 49 ± 7 years) with atypical chest pain and negative exercise test, undergoing stress-redistribution thallium scan, served as controls.

Results Exercise was discontinued for angina and/or ST-segment depression after 12 ± 3 min. Thallium stress images revealed 40 hypoperfused segments in 27 patients (77%); after 4 h, 16 of these segments had completely normalized, 10 remained unchanged, six exhibited partial reperfusion and eight worsened. Twenty-four patients (69%) exhibited thallium reverse redistribution in 33 segments. Thirty-four patients (97%) had at least one hypoperfused segment in one of the two scintigraphic phases. Of the 24 patients with reverse redistribution, eight also underwent stress-rest 99mTc-MIBI SPECT: six exhibited reduced tracer uptake that was present at rest, but not on stress images, in the same segments showing thallium reverse redistribution. Thallium stress images revealed four hypoperfused segments in three controls (9%); at redistribution, one segment normalized, two remained unchanged and one exhibited partial reperfusion. Additionally, there were four new underperfused segments appearing on redistribution in four patients (13%). Overall, there were seven controls (22%) with at least one hypoperfused myocardial segment in one of the two scintigraphic phases.

Conclusions Our study confirms that perfusion abnormalities are present in most syndrome X patients. Additionally, the data show that reverse redistribution (a perfusion defect that develops or becomes more evident on delayed imaging) is a common finding in these patients. The mechanisms of the phenomenon remain obscure: we suggest that it is due to inhomogeneous perfusion, and the hyperaemic response induced by exercise masks resting underperfusion of certain areas.

Key Words: Thallium myocardial scintigraphy, angina pectoris, normal coronary arteries, syndrome X, reverse redistribution.

Introduction

Syndrome X is a clinical definition that identifies patients with typical angina, positive exercise test and angiographically smooth epicardial coronary arteries. In spite of a considerable number of studies performed in recent years, the pathophysiology of this syndrome remains elusive, although abnormalities of the coronary microcirculation have been said to play a role by the majority of authors. Of the many aspects which have been investigated, those related to left ventricular perfusion have provided conflicting results possibly because of the different inclusion criteria used to select study populations and the different techniques and protocols employed for assessing perfusion.

We report here the results of a study performed in 35 consecutive patients with typical angina,
positive exercise test, angiographically smooth epicardial coronary arteries and no inducible spasm, who underwent stress-redistribution myocardial perfusion scintigraphy with thallium-201.

The study was aimed at investigating the prevalence of regional perfusion abnormalities in a relatively large consecutive cohort of carefully characterized patients with syndrome X undergoing the same scintigraphic protocol.

**Patients and methods**

**Patients**

We prospectively studied 35 consecutive patients (28 females, age 54 ± 8 years, range 38–70 years) with atypical chest pain and a negative exercise test, who underwent a thallium study because of continuing symptoms. Coronary angiography was performed only in patients with perfusion defects at the thallium scan. None of the study patients had diabetes, hypertension, left ventricular hypertrophy, pericardial or valvular disease or overt cardiomyopathy. The presence of regional wall motion abnormalities was excluded by echocardiography and, when performed, by contrast ventriculography.

**Exercise test and perfusion imaging**

Treadmill exercise was performed following the modified Bruce protocol; the 12-lead electrocardiogram and the blood pressure (cuff sphygmomanometer) were recorded at rest and every minute during exercise and recovery. In all patients the test was conducted during pharmacological wash-out.

The following criteria were used for discontinuing the test: (1) achievement of the maximal predicted heart rate; (2) diagnostic (≥1.0 mm rectilinear or downsloping) ST-segment depression on at least one precordial or two peripheral electrocardiogram leads, with or without angina; (3) severe dyspnoea or fatigue; (4) repetitive ventricular arrhythmias; and (5) a greater than 10 mmHg decrease in systolic blood pressure at any exercise step. For all tests, total exercise time and rate–pressure product at peak exercise were analysed.

At peak exercise, 74 MBq of thallium-201 were injected i.v. and the patient was asked to carry on exercising for an additional minute. Standard planar imaging was obtained with a Starcam A 300 General Electric gamma camera; acquisition was started 1 min post-exercise and performed, in the supine position, in three views (45° and 70° left anterior oblique and anterior). For each view, 400 000 counts were obtained. Four hours later, images were again acquired in the same views and with the same counting-statistic.

Eight patients with SX and regional perfusion abnormalities on thallium-201 scintigraphy also underwent myocardial perfusion imaging with 99mTc- MIBI within 10 ± 2 months of the thallium study. The tracer (925 MBq) was given immediately after maximal exercise (same protocol as above) and, after 48 h at rest. SPECT studies were performed 90 min after tracer injection, with a large field of view, single-head rotating gamma camera (General Electric, Starcam 400 AC). Sixty-four angular projections (64 x 64 matrix) were obtained in approximately 40 min over 360°. Transaxial slices, 6.2 cm thick, were reconstructed using a filtered back projection algorithm with a Butterworth filter (cut-off frequency=0.4 cycles/pixel). No correction for attenuation was performed.

**Interpretation for scintigraphic images**

Images were reported independently by two experienced observers unaware of patients' identity and angiographic findings. For both planar and SPECT imaging, the left ventricular myocardium was divided into six segments: anterior, apical, septal, inferior, posterior and lateral. Images were displayed on a colour TV screen in random order and graded using a four-point scale (0=normal, 1=moderate uptake reduction, 2=severe uptake reduction, 3=absent uptake). Disagreement was resolved by consensus.

**Intraobserver and interobserver variability of thallium-201 regional myocardial perfusion**

To assess intra- and interobserver variability, the scans of 40 patients (20 syndrome X and 20 controls) were analysed independently by two independent observers. Each scan was analysed twice by each examiner, in separated sessions. The variability of the results was quantified by the intra- and interobserver correlation coefficients calculated by linear regression analysis.

**Statistics**

The number of hypoperfused segments and the perfusion score were compared using the Student's t-test for unpaired data. A probability (P) value <0.05 represented a significant difference.

**Results**

**Syndrome X patients**

The resting electrocardiogram was normal in 20 patients (57%), but showed T-wave abnormalities in 15 (43%). Exercise was discontinued because of severe angina in...
14 patients, angina and ST-segment depression in 11 patients, and ST-segment depression without angina in six patients. Total exercise time averaged 12 ± 3 min and maximal RPP was 24,500 ± 4,100 bpm x mmHg.

Thallium stress images revealed 40 hypoperfused myocardial segments in 27 patients (77%); after 4 h, 16 of these segments completely normalized, 10 remained unchanged, six exhibited partial reperfusion and eight worsened. At rest, the number of underperfused segments was 49, in 28 patients (80%); of these segments, 10 were seen in seven patients in whom myocardial tracer distribution was apparently homogeneous after stress; 15 occurred in 11 patients in whom perfusion was reduced, after stress, in different segments. Therefore, worsening of the perfusion pattern at rest, relative to that observed during stress (reverse redistribution) was present in 33 myocardial segments (24 patients; 19 females, 5 males, 69%). Of these 33 segments, nine were anterior, seven apical, four septal, three inferior, four posterior and six lateral. Thirty-four patients (97%) exhibited at least one hypoperfused segment in one of the two scintigraphic phases.

The mean number of segments showing underperfusion was greater at rest than after stress (1.57 ± 0.93 vs 1.14 ± 0.84; P<0.05); the underperfusion score was also greater at rest (2.12 ± 1.20 vs 1.35 ± 1.15; P<0.01). Of the 24 patients with reverse redistribution on thallium myocardial scintigraphy, eight underwent a stress-rest 99mTc-MIBI scan 10 ± 2 months later. In six (one male) of them, the study confirmed the reverse redistribution pattern in the same segments (total eight segments; four anterior, two apical, one posterior and one inferior). (Figs 1 and 2).

**Controls**

The resting electrocardiogram was normal in 25 patients (78%), but showed non-specific T-wave abnormalities in seven (22%). Exercise was terminated because of exhaustion in 22 patients; in the remaining 10, the test was discontinued after achievement of the maximal predicted heart rate. None showed diagnostic ST-segment changes. Total exercise time averaged 14 ± 2 min and maximal RPP was 26,300 ± 2,700 bpm x mmHg.

Thallium stress images revealed four hypoperfused myocardial segments in three patients (9%); after 4 h, one of these segments normalized, two remained unchanged and one exhibited partial reperfusion. Additionally, there were four new underperfused segments appearing at redistribution, in four patients (three females) (13%); all these defects, appeared in patients with a normal stress scan. Overall there were seven controls (22%) with at least one hypoperfused myocardial segment in one of the two scintigraphic phases. All seven patients underwent coronary angiography and ergonovine test. In all but one patient, who exhibited a 60% stenosis of the left circumflex coronary artery, angiography showed smooth arteries and absence of inducible coronary spasm.

Figure 1 (a) Stress-redistribution thallium myocardial perfusion images obtained in a patient with angina and angiographically smooth coronary arteries. Stress imaging reveals uniform tracer distribution (b). Delayed (4 h) imaging shows decreased thallium uptake in the anterolateral, septal and apical segments (black arrows).

**Variability of regional myocardial perfusion analysis**

With the use of the method of analysis of thallium-201 myocardial scintigrams described in this study, the intraobserver variability was minimal (r=0.92 for one operator and r=0.89 for the second operator). Likewise, there was a close correlation between the interpretations of the two observers (r=0.90-0.85).
Figure 2  99mTc-MIBI-SPECT scan in the same patient of Fig. 1. Serial slices from the horizontal long axis view are shown. The two upper rows of images refer to the stress study and show, again, uniform tracer distribution. The two lower rows shows images taken at rest: as with thallium, reduced tracer uptake in the antero-apical and septal segments is evident (white arrows).

Discussion

The results of our study confirm the high prevalence of regional perfusion abnormalities in patients with syndrome X. Indeed, when considering stress and rest imaging, 97% of our patients exhibited at least one perfusion defect on thallium myocardial scintigraphy. This figure is considerably higher than that (22%) obtained in our control group.

Impairment of thallium uptake by myocardial cells can be due to both impaired perfusion and metabolic abnormalities affecting potassium transport across the membrane. Previous authors have proposed that the large prevalence of thallium defects observed with exercise in patients with syndrome X, suggests that reduction of regional flow reserve, consistent with microvascular dysfunction, plays a relevant role in this syndrome. However, the presence or persistence of thallium defects on redistribution imaging is difficult to explain, since left ventricular function is generally normal in these patients.

A high proportion of patients included in our series exhibited the so-called reverse redistribution phenomenon. This scintigraphic pattern refers to a perfusion defect that is not present on the initial images acquired immediately after stress, but develops or becomes more evident on delayed imaging. The finding has been sometimes attributed to artefacts or associated with a variety of cardiac conditions such as multivessel coronary disease, previous revascularization, residual tissue viability after myocardial infarction, subendocardial necrosis, cardiomyopathies, post-ischaemic stunning and the Wolff–Parkinson–White Syndrome.

Some authors also found that the reverse redistribution pattern is often present in patients with normal coronary arteries and concluded that this scintigraphic finding is not a specific indicator of coronary artery disease. In fact, the patients included in those studies had undergone thallium scintigraphy and coronary arteriography because of typical chest pain and a presumably positive exercise test. Therefore, they fulfilled the classical diagnostic criteria of syndrome X.

Multiple mechanisms may account for the reverse redistribution phenomenon. Among them, different thallium wash-out rates from different coronary territories could lead to temporal changes in the distribution of thallium activity. Another possible mechanism is the presence of microvascular changes that could alter the rate of thallium wash-out from myocardial tissue. These changes could be due to endothelial dysfunction, smooth muscle cell proliferation, or alterations in the permeability of blood vessels.

In conclusion, the high prevalence of regional perfusion abnormalities in patients with syndrome X is likely to be multifactorial. Further research is needed to better understand the underlying mechanisms and to develop more effective therapeutic strategies.
regions, have been proposed. Although this may apply to some cases, this interpretation does not explain our observation that the reverse redistribution pattern was also present in the majority of patients undergoing myocardial perfusion scintigraphy with 99mTc-MIBI. In fact this tracer predominantly traces flow, has no significant redistribution and negligible myocardial clearance, which is not significantly different in normal and ischaemic regions.

It is interesting to note that the thallium reverse redistribution pattern has been recently associated with non-transmural myocardial infarction and it has been often observed in patients with cardiomyopathy, usually in regions exhibiting less severe wall motion abnormalities. Therefore, it is conceivable that these defects originate from areas in which normal myocardium is mingled with scar tissue. The hyperaemic response to maximal exercise could mask resting underperfusion of these areas, but absolute blood flow measurements would be necessary to prove this hypothesis. It is tempting to speculate that the reverse redistribution phenomenon observed in our patients with syndrome X was caused by inhomogeneous myocardial perfusion, possibly linked to derangements of the coronary microcirculation.

To the best of our knowledge, there are only two previous reports on thallium imaging in carefully characterized patients with syndrome X. In a series of 100 patients, Tweddel et al. did not observe any case of reverse redistribution. Apart from using different selection criteria, these authors did not perform redistribution imaging at 4 h whenever patients had a normal thallium scan after stress. Therefore, by definition, they could not detect reverse redistribution, at least in patients with normal stress imaging. We have no explanation as to why Romeo et al. observed thallium perfusion defects in 33% and reverse redistribution only in a minority (10%) of their 30 patients. The pathophysiological heterogeneity of this clinical syndrome may partly account for the discrepancy between their and our observation.

**Limitations of the study**

In our study scintigrams were assessed only qualitatively and no quantitation was attempted. However, the intra- and interobserver variabilities in the analysis of scintigrams were low and comparable to those reported previously. Furthermore, the prevalence of reverse redistribution observed in our control group was 13%, a figure similar to those reported in the literature. This is considerably lower than the 69% prevalence observed in our syndrome X patients.

In females with large breasts attenuation of radiation may cause apparent defects. In our laboratory this is partly overcome by using adhesive bandages which "lift up" breasts, in a similar fashion after stress and on redistribution. Yet, breast artifacts remain the most frequent cause of false-positive thallium-201 studies. However, in our syndrome X patients the overall number of perfusion defects was similar in the two sexes and, specifically, reverse redistribution was present in 68% of females and in 71% of males included in the study.

We also acknowledge the relatively small number of patients undergoing repeat myocardial perfusion scan with 99mTc-MIBI. However, for ethical reasons this approach was adopted at least 3 months after the thallium scan, only in patients with continuing angina.

**Conclusions**

Our study confirms the heterogeneity of myocardial perfusion in syndrome X. Most of our patients exhibited abnormal perfusion scans and a high percentage exhibited the so-called 'reverse redistribution' phenomenon. We postulate that this scintigraphic pattern results from exercise-induced hyperaemia which masks local inhomogeneous perfusion that becomes apparent only at rest.

Although a precise explanation of its causative mechanisms cannot be provided by the present study, we believe that, in patients with chest pain and normal epicardial coronary arteries, the reverse redistribution phenomenon should not be simply dismissed as an artifact. In fact, this finding could represent the 'undercover spy' of local microcirculation abnormalities or early stage cardiomyopathy. Quantitative assessment of regional perfusion along with careful follow-up will prove useful to define better the pathophysiological and clinical significance of such findings.

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**References**


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