

ABNORMAL SUBENDOCARDIAL PERFUSION IN CARDIAC SYNDROME X DETECTED BY CARDIOVASCULAR MAGNETIC RESONANCE IMAGING

JONATHAN R. PANTING, M.B., M.R.C.P., PETER D. GATEHOUSE, PH.D., GUANG-ZHONG YANG, PH.D., FRANK GROTHUES, M.D., DAVID N. FIRMIN, PH.D., PETER COLLINS, M.D., AND DUDLEY J. PENNELL, M.D.

ABSTRACT

Background In cardiac syndrome X (a syndrome characterized by typical angina, abnormal exercise-test results, and normal coronary arteries), conventional investigations have not found that chest pain is due to myocardial ischemia. Magnetic resonance techniques have higher resolution and therefore may be more sensitive.

Methods We performed myocardial-perfusion cardiovascular magnetic resonance imaging in 20 patients with syndrome X and 10 matched controls, both at rest and during an infusion of adenosine. Quantitative perfusion analysis was performed by using the normalized upslope of myocardial signal enhancement to derive the myocardial perfusion index and the myocardial-perfusion reserve index (defined as the ratio of the myocardial perfusion index during stress to the index at rest).

Results In the controls, the myocardial perfusion index increased in both myocardial layers with adenosine (in the subendocardium, from a mean [\pm SD] of 0.12 ± 0.03 to 0.16 ± 0.03 [$P=0.02$]; in the subepicardium, from 0.11 ± 0.02 to 0.17 ± 0.05 [$P=0.002$]); in patients with syndrome X, the myocardial perfusion index did not change significantly in the subendocardium (0.13 ± 0.02 vs. 0.14 ± 0.03 , $P=0.11$; $P=0.09$ as compared with controls) but increased in the subepicardium (from 0.11 ± 0.02 to 0.20 ± 0.04 , $P<0.001$; $P=0.11$ for the comparison with controls). Adenosine provoked chest pain in 95 percent of patients with syndrome X and 40 percent of controls ($P<0.001$).

Conclusions In patients with syndrome X, cardiovascular magnetic resonance imaging demonstrates subendocardial hypoperfusion during the intravenous administration of adenosine, which is associated with intense chest pain. These data support the notion that the chest pain may have an ischemic cause. (N Engl J Med 2002;346:1948-53.)

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BETWEEN 10 and 20 percent of patients with typical anginal chest pain are found to have normal coronary angiograms.¹ A subgroup of these patients, who also have classic downsloping ST-segment depression on exercise testing, are classified as having cardiac syndrome X.² The exact pathophysiological mechanisms underlying this condition are not well understood, and many mechanisms for the chest pain have been suggested. In some studies, microvascular dysfunction has been proposed as the cause,³⁻⁶ whereas in others, metabolic abnormalities, such as net myocardial lactate production,⁷⁻¹¹ have been demonstrated. However, more recent studies with stricter criteria for the selection of patients suggest that lactate production is normal in patients with syndrome X.¹²

Noninvasive imaging has also been used to determine whether ischemia is present. In the majority of patients, ventricular function under conditions of rest or stress — as assessed by radionuclide ventriculography^{13,14} or echocardiography^{15,16} — has been normal. Thallium-201 myocardial-perfusion studies of patients with syndrome X have found abnormal results in a proportion of patients ranging from a few¹³ to the majority.¹⁷ Some studies in which positron-emission tomography (PET) was used have shown abnormal heterogeneity in perfusion,^{18,19} whereas others have shown no abnormalities.^{20,21}

The lack of consistent findings in previous studies may suggest a predominantly nonischemic origin for the chest pain, but it may also reflect a lack of sensitivity of the tests in detecting limited subendocardial ischemia. Recently, the technique of myocardial-perfusion cardiovascular magnetic resonance imaging has been developed and validated against the use of radioactive microspheres in animal models as a measure of transmural and subendocardial blood flow.^{22,23} When compared with angiography and PET, cardiovascular magnetic resonance imaging has been shown to be accurate for the detection of ischemia in coronary artery disease and has been shown to have higher

From the Cardiovascular Magnetic Resonance Unit (J.R.P., P.D.G., F.G., D.N.F., D.J.P.) and the Department of Cardiovascular Medicine (P.C.), Royal Brompton Hospital and National Heart and Lung Institute, Imperial College, London; and the Department of Computing, Imperial College, London (G.-Z.Y.). Address reprint requests to Dr. Pennell at the Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital, Sydney St., London SW3 6NP, United Kingdom.

resolution than conventional perfusion techniques.²⁴⁻²⁷ We therefore hypothesized that perfusion cardiovascular magnetic resonance imaging would identify non-transmural ischemia in patients with syndrome X.

METHODS

Subjects

We studied 20 patients with syndrome X (16 women and 4 men; mean [\pm SD] age, 55.9 ± 10.5 years) and 10 age- and sex-matched normal control subjects (8 women and 2 men; mean age, 57.9 ± 7.4 years) ($P=0.63$ for both comparisons between the groups). The patients were recruited from the Women's Heart Disease Clinic at Royal Brompton Hospital in London. All had a previously established diagnosis of classic syndrome X, with a typical history of exertional angina, an abnormal exercise electrocardiogram (0.1 mV horizontal or downsloping ST-segment depression of 80 msec after the J point), and completely normal results on coronary angiography, with no inducible spasm on ergonovine-provocation testing.²⁸ The mean time from angiography to the cardiovascular magnetic resonance imaging examination was 18 ± 10 months. No patient had diabetes (defined by a fasting glucose level over 7.8 mmol per liter [141 mg per deciliter] or a random-sample glucose level over 11.1 mmol per liter [200 mg per deciliter]), hypertension (defined as blood pressure over 140/80 mm Hg), left ventricular hypertrophy (defined as a value above 35 mm for the sum of the height of the S wave in lead V₁ and the height of the R wave in lead V₅), or any change in clinical condition between the investigations. Although thallium-perfusion single-photon-emission computed tomography (SPECT) was not performed in this study as part of the protocol, the results of SPECT were available for 14 patients (mean time from thallium SPECT to cardiovascular magnetic resonance imaging, 12 ± 7 months). These results showed normal perfusion in 11 patients and a mild fixed defect in 3. The patients with syndrome X received calcium-channel blockers (11 patients), nitrates (9 patients), hormone-replacement therapy (7 patients), beta-blockers (5 patients), potassium-channel openers (2 patients), or no treatment (1 patient). Some patients received more than one medication.

The controls were all healthy, with no history of chest pain or other cardiovascular symptoms. The profile of the controls with respect to cardiovascular risk factors was as follows: none were smokers; the mean blood pressure was 127/76 mm Hg; the mean total cholesterol level was 5.7 mmol per liter (220 mg per deciliter); the mean high-density lipoprotein (HDL) level was 1.8 mmol per liter (70 mg per deciliter); the mean ratio of total cholesterol to HDL cholesterol was 3.2. No patient had diabetes or left ventricular hypertrophy, and the calculated overall 10-year mean risk of a coronary event was 4.5 percent.²⁹ None of the controls had undergone coronary angiography or thallium SPECT. This study was approved by the institutional ethics committee, and all patients gave written informed consent.

Study Protocol

Cardiovascular magnetic resonance imaging was performed with use of a 1.5-T scanner (Picker Edge) that used a gradient-echo sequence with a 90-degree saturation pulse for T₁ weighting. A cardiac phase-array receiver coil was used with sequence variables as follows: time to echo, 1.2 msec; repetition time, 3 msec; phase matrix, 64; slice thickness, 10 mm; and field of view, 450 by 225 mm, yielding a pixel size of 3.5 by 3.5 mm interpolated to 1.75 by 1.75 mm. The two-slice sequence was started on the R wave for systolic gating and to ensure an adequate acquisition window during any adenosine-induced tachycardia. Studies were performed at rest and during a six-minute infusion of adenosine (140 μ g per kilogram of body weight per minute) to achieve intense coronary hyperemia. The two studies were separated by 20 minutes to allow equilibration of the contrast agent after the first injection. Two

short-axis left ventricular slices were placed one third and two thirds of the distance from base to apex, with acquisition every cardiac cycle for 50 beats. A bolus of gadopentetate dimeglumine (0.05 mmol per kilogram) was injected at a rate of 5 ml per second for each first-pass study by means of a power injector into a 14-gauge cannula in the antecubital vein.

The images were analyzed quantitatively, in a masked fashion, and were presented in random order. Each series of images was analyzed by measuring the signal in regions of interest in the left ventricular blood pool and myocardium. For analysis, the myocardium was divided into two subendocardial and subepicardial regions, which were drawn with the outer borders close to the endocardial and epicardial surfaces and with the inner borders adjacent to each other in the mid-wall. The analysis was performed with software designed in house (CMRtools, Imperial College). The regions of interest were drawn on a single image and propagated automatically throughout the perfusion series; each image was then checked for positioning, and adjustments were made for any respiratory movement. The intervals between images were calculated from the electrocardiographic trace obtained during acquisition, and from these measurements, curves showing signal intensity plotted against time were constructed for each region of interest. An index of myocardial perfusion was then calculated with the use of myocardial slope measurements, as has been previously reported.^{24,26,27} In brief, curve fitting was used to obtain the slope of the first-pass contrast enhancement for each of the myocardial regions of interest and the left ventricular blood-pool region of interest. The myocardial slope was then normalized by dividing it by the left ventricular blood-pool slope. This method compensates for changes in the input function caused by the effects of adenosine on heart rate and systemic circulation. The ratio of the myocardial perfusion index during stress to that with the subject at rest was defined as the myocardial-perfusion reserve index. Subepicardial perfusion and subendocardial perfusion were compared to determine the degree of heterogeneity across the myocardial wall. Transmural perfusion was assessed by combining the subepicardial and subendocardial regions of interest. Heterogeneity within the subendocardial regions of interest was assessed by visual scoring of 6 segments in each slice (total for the two slices, 12 segments). In addition to undergoing magnetic resonance imaging, all subjects graded the level of pain associated with the adenosine infusion on the following scale: 1, no pain; 2, mild discomfort; 3, moderate but bearable pain; 4, severe pain; and 5, the worst pain ever experienced.

Statistical Analysis

Summary values are expressed as means \pm SD. Differences between means of continuous variables were tested by Wilcoxon non-parametric tests because of the small samples. The chi-square test was used to compare categorical data for pain. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Quantitative Analysis

There was no significant difference in the value of the myocardial perfusion index for transmural perfusion between controls and patients with syndrome X either with the subjects at rest (0.12 ± 0.03 vs. 0.12 ± 0.02 , $P=0.63$) or during stress (0.16 ± 0.04 vs. 0.17 ± 0.03 , $P=0.49$). In the controls, the myocardial perfusion index increased significantly during adenosine infusion in both the subendocardium (from 0.12 ± 0.03 to 0.16 ± 0.03 , $P=0.02$) and the subepicardium (from 0.11 ± 0.02 to 0.17 ± 0.05 , $P=0.002$). However,

in the patients with syndrome X, the myocardial perfusion index did not increase significantly in the subendocardium during the adenosine infusion (0.13 ± 0.02 vs. 0.14 ± 0.03 , $P=0.11$; $P=0.09$ as compared with the controls) but did increase in the subepicardium (from 0.11 ± 0.02 to 0.20 ± 0.04 , $P<0.001$; $P=0.11$ as compared with the controls) (Fig. 1A). Subendocardial myocardial perfusion index normalized to heart rate fell in patients with syndrome X (from

$1.7 \pm 0.5 \times 10^{-3}$ to $1.3 \pm 0.4 \times 10^{-3}$ per heartbeat, $P<0.001$), but not in the controls ($1.8 \pm 0.7 \times 10^{-3}$ vs. $1.7 \pm 0.4 \times 10^{-3}$ per heartbeat, $P=0.38$; $P=0.13$ as compared with the patients with syndrome X). Examples of images obtained at the time of maximal contrast uptake in a control subject and in a patient with syndrome X are shown in Figures 2 and 3. The mean number of abnormal myocardial segments in the patients with syndrome X during stress was 5.6, representing 47 percent of the myocardium.

The results of the analysis of the myocardial-perfusion reserve index are shown in Figure 1B. There was no significant difference in the myocardial-perfusion reserve index for the entire transmural extent of myocardium between patients with syndrome X and controls (1.47 ± 0.36 vs. 1.50 ± 0.47 , $P=0.56$). The differences between the myocardial-perfusion reserve index in patients with syndrome X and in controls were of borderline significance for both the subendocardium (1.10 ± 0.23 vs. 1.38 ± 0.4 , $P=0.071$) and the subepicardium (1.84 ± 0.52 vs. 1.63 ± 0.53 , $P=0.11$), but the ratio of subendocardial to subepicardial myocardial-perfusion reserve index was significantly lower in patients with syndrome X (0.61 ± 0.11 vs. 0.85 ± 0.13 , $P=0.002$). According to analysis of the receiver-operating-characteristic curve, the optimal ratio of subendocardial to subepicardial myocardial-perfusion reserve index for distinguishing patients with syndrome X from controls was 0.72, which yielded a sensitivity of 85 percent, a specificity of 100 percent, and an accuracy of 90 percent for the test.

Pain Perception

Among the controls, four (40 percent) had chest pain during adenosine infusion. The mean score for all controls was 1.3, indicating that the pain was mild at the worst. By contrast, 19 of 20 of the patients with syndrome X (95 percent) had chest pain ($\chi^2=26.1$, $P<0.001$), and the majority reported that the pain was either severe or the worst ever experienced (mean score, 4.2; $P<0.001$ for the comparison with the controls).

DISCUSSION

Our results show that patients with syndrome X have significantly different perfusion responses to adenosine than matched controls. Although values for the transmural myocardial perfusion index at base line and under stress were equivalent between the groups, in the patients with syndrome X the subendocardial myocardial perfusion index did not increase with adenosine; in the controls, in contrast, a normal increase was seen. There was also a significant reduction in the subendocardial myocardial perfusion index normalized to heart rate in the patients with syndrome X, which was not seen in the control group.

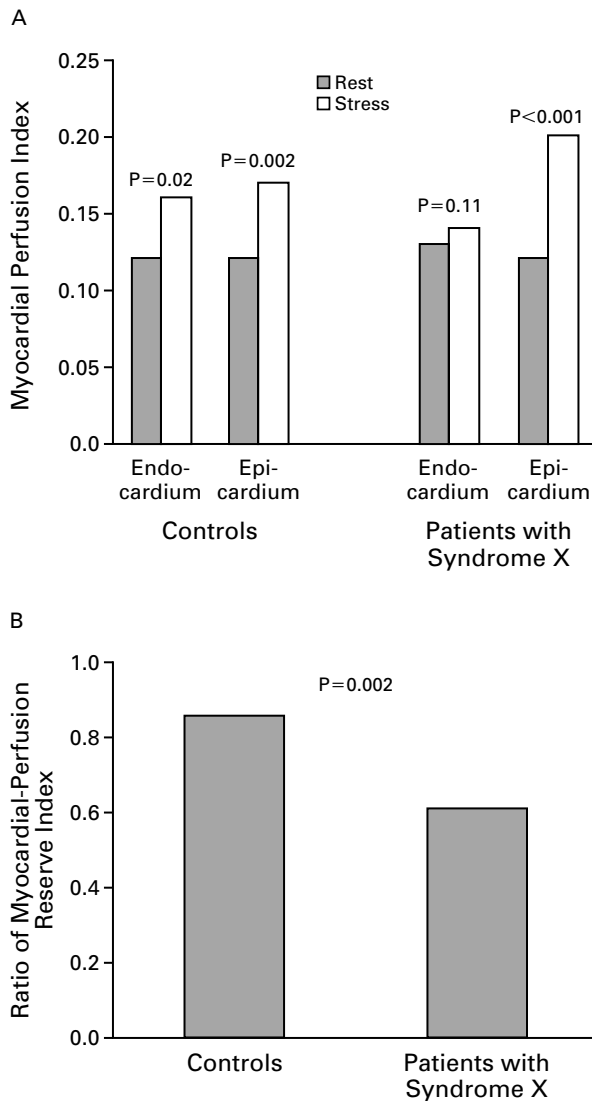


Figure 1. Measurements of Myocardial Perfusion Index in Controls and in Patients with Syndrome X. Panel A shows the myocardial perfusion index at rest and during stress. Panel B shows the ratio of subendocardial to subepicardial myocardial-perfusion reserve index.

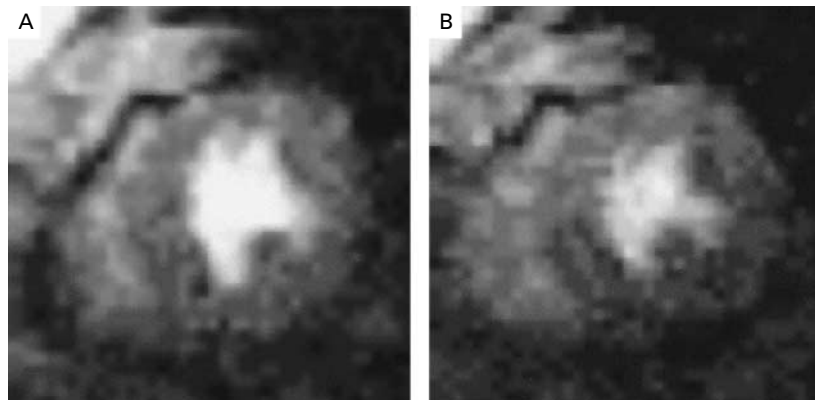


Figure 2. Images of Myocardium at Peak Myocardial Enhancement during the First Pass of Gadolinium in a Control Subject at Rest (Panel A) and during Stress (Panel B), Showing Uniform Myocardial Signal Enhancement.

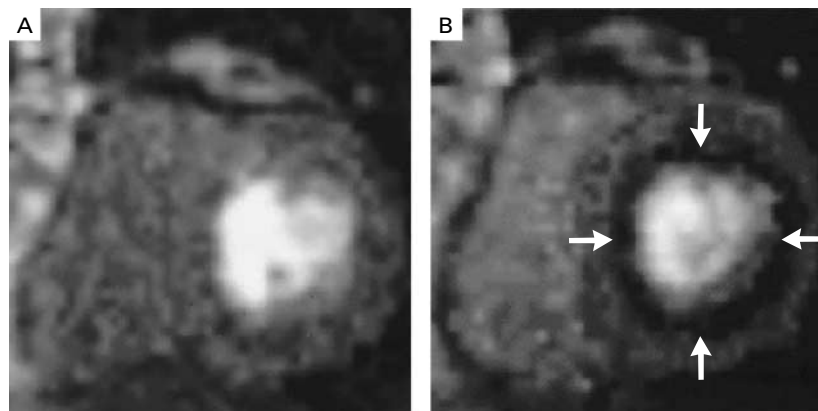


Figure 3. Images of Myocardium at Peak Myocardial Enhancement during the First Pass of Gadolinium in a Patient with Syndrome X at Rest (Panel A) and during Stress (Panel B), Showing a Ring of Delayed Subendocardial Enhancement (Arrows in Panel B).

The responses in the subepicardium were similar in both groups. Thus, the ratio of subendocardial to subepicardial myocardial-perfusion reserve index was significantly lower in patients with syndrome X. We found consistent evidence in patients with syndrome X of an abnormality of myocardial perfusion limited to the subendocardium. These results could be obtained because transmural resolution is higher with cardiovascular magnetic resonance imaging than with other techniques.

Our results show that patients with syndrome X have a reduction in subendocardial myocardial perfusion index normalized to heart rate during stress and a reduction in the ratio of subendocardial to sub-

epicardial myocardial-perfusion reserve index. These findings, combined with the occurrence of chest pain during stress in patients with syndrome X, support the hypothesis that subendocardial ischemia is the cause of the angina symptoms in these patients. However, whether there is an actual absolute reduction in subendocardial perfusion with stress in patients with syndrome X is unresolved, since current techniques for myocardial-perfusion cardiovascular magnetic resonance imaging in humans do not generate reliable absolute measures. This question might be resolved with further developments in quantification with perfusion cardiovascular magnetic resonance imaging, or possibly with the latest generation of high-resolution

PET scanners. However, our findings are consistent with data reported by Buchthal et al.,³⁰ which showed reduced ratios of phosphocreatine to adenosine triphosphate during handgrip exercise in some women with chest pain and normal coronary arteries. This spectroscopic technique may detect cellular ischemia, but because of resolution constraints, it cannot currently determine the distribution of ischemia or identify transmural variations in ischemia. Other data that support our findings come from Buffon et al.,³¹ who demonstrated release of lipoperoxides immediately after pacing-induced tachycardia in all patients with syndrome X, a result consistent with ischemia-reperfusion injury.

In an open-chest dog model, subendocardial and subepicardial perfusion increased with adenosine infusion.³² However, at physiologic perfusion pressures, the ratio of subendocardial to subepicardial perfusion decreased during stress. Our results suggest that in controls, subendocardial and subepicardial perfusion responds to stress in a similar way. In patients with syndrome X, however, the perfusion responses were more similar to those seen in animals with mild coronary-artery stenosis, except that in animals with coronary disease the abnormality was confined to the territory of the stenosed artery, whereas in patients with syndrome X the abnormality was more generalized. Although the perfusion abnormality was confined to the subendocardium, within this region the perfusion was variable, with a mean of 47 percent of segments affected. This result agrees with the findings of Lanza et al.,³³ who showed impaired uptake of [¹²³I]metaiodobenzylguanidine in patients with syndrome X, which was generalized in 4 and regional in 5 of the 12 patients studied.

The patients in our study had well-characterized syndrome X; however, other conditions may lead to microvascular dysfunction, and similar findings might be found in patients with hypertension, hypertrophic conditions, or diabetes. We were therefore careful to exclude patients with these conditions from our study. We have not validated this protocol for perfusion cardiovascular magnetic resonance in our own laboratory, but it has been validated elsewhere.^{22,27} Electrocardiographic evidence of ST-segment depression during adenosine infusion could not be obtained, because of distortion due to the magnetic field, and no attempt was made to interpret the ST segments. Left ventricular function was not measured, but other studies have not found this measurement helpful.^{15,16} Further quantitative work on the heterogeneity of perfusion responses in patients with syndrome X would be useful. Finally, we used only one type of scanner and one contrast protocol in this study; further work is required to test whether these findings can be generalized.

In conclusion, we found that subendocardial perfusion abnormalities occur in patients with syndrome X, with a reduction in subendocardial perfusion normalized to heart rate and a reduction in the ratio of subendocardial to subepicardial perfusion reserve. These results support the concept that the chest pain in these patients may be related to myocardial ischemia, with an unusual nontransmural distribution. Additional research with perfusion cardiovascular magnetic resonance imaging and quantification of absolute subendocardial perfusion is needed in patients with syndrome X; such research may increase understanding of the pathophysiology of this condition and provide new insights into treatments for syndrome X³⁴ and other conditions characterized by microvascular dysfunction.

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