Patients With Syndrome X Have Normal Transmural Myocardial Perfusion and Oxygenation
A 3-T Cardiovascular Magnetic Resonance Imaging Study

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Background—The pathophysiology of chest pain in patients with cardiac syndrome X remains controversial. Advances in perfusion imaging with cardiovascular magnetic resonance (CMR) now enable absolute quantification of regional myocardial blood flow (MBF). Furthermore, blood oxygen level-dependent (BOLD) or oxygenation-sensitive CMR provides the unprecedented capability to assess regional myocardial oxygenation. We hypothesized that the combined assessment of regional perfusion and oxygenation with CMR could clarify whether patients with syndrome X show evidence of myocardial ischemia (reduced perfusion and oxygenation) during vasodilator stress compared with normal volunteers.

Methods and Results—Eighteen patients with syndrome X (chest pain, abnormal exercise treadmill test, normal coronary angiogram without other causes of microvascular dysfunction) and 14 controls underwent CMR scanning at 3 T. Myocardial function, scar, perfusion (2–3 short-axis slices), and oxygenation were assessed. Absolute MBF was measured during adenosine stress (140 μg/kg per minute) and at rest by model-independent deconvolution. For oxygenation, using a T2-prepared BOLD sequence, signal intensity was measured at adenosine stress and rest in the slice matched to the midventricular slice of the perfusion scan. There were no significant differences in MBF at stress (2.35 versus 2.37 mL/min per gram; \( P = 0.91 \)), BOLD signal change (17.3% versus 17.09%; \( P = 0.91 \)), and coronary flow reserve measurements (2.63 versus 2.53; \( P = 0.60 \)) in patients with syndrome X and controls, respectively. Oxygenation and perfusion measurements per coronary territory were also similar between the 2 groups. More patients with syndrome X (17/18 [94%]) developed chest pain during adenosine stress than controls (6/14 [43%]); \( P = 0.004 \).

Conclusions—Patients with syndrome X show greater sensitivity to chest pain compared with controls but no evidence of deoxygenation or hypoperfusion during vasodilatory stress. (Circ Cardiovasc Imaging. 2012;5:201.)

Key Words: ischemia ■ chest pain ■ microvascular angina ■ blood flow ■ oxygen

Cardiac syndrome X is the presence of predominantly effort-induced angina and ST-segment depression on stress electrocardiography despite angiographically normal coronary arteries.\(^1\) There has been substantial controversy about whether myocardial ischemia is widely prevalent in syndrome X.\(^1\) Some studies, using both invasive and noninvasive testing, have shown that both endothelium-dependent and -independent coronary vasodilatation is reduced in some patients with syndrome X, and up to 20% of patients have metabolic evidence of myocardial ischemia.\(^2\)–\(^4\) In contrast, other studies, especially those using stress echocardiography, have shown normal global or regional contractile reserve despite the provocation of typical symptoms.\(^5\)–\(^7\) Moreover, the observation that patients with syndrome X commonly experience their typical chest pain during cardiac catheterization maneuvers (simple catheter movements or saline injection in the heart) has led several investigators to believe that enhanced cardiac pain perception is a central component of the pathophysiology of the syndrome.\(^8\)–\(^9\)

Clinical Perspective on p 200

Cardiovascular magnetic resonance (CMR) imaging permits assessment of both myocardial scar and myocardial perfusion concurrently with high spatial resolution.\(^10\)–\(^11\) CMR during the first pass of an injected tracer permits assessment of myocardial perfusion both at rest and during pharmacological stress and gives superior spatial resolution compared with nuclear imaging methods.\(^11\) CMR perfusion results from animal experiments have shown a strong correlation with
microspheres for the assessment of blood flow,\textsuperscript{12} and we have previously used this technique to report resting myocardial blood flow (MBF) in patients with hibernating myocardium.\textsuperscript{13} Over the past decade, several investigators have reported on CMR perfusion in cardiac syndrome X with conflicting results. Panting et al.\textsuperscript{14} using semiquantitative perfusion analysis, showed global subendocardial ischemia in patients with syndrome X; Lanza et al.\textsuperscript{15} demonstrated regional perfusion defects only in the left anterior descending coronary territory; and Vemelfoort et al\textsuperscript{16} found no differences between subendocardial and subepicardial perfusion. It should be noted, though, that all 3 studies used visual or semiquantitative assessment of myocardial perfusion. No study has yet used CMR to quantify MBF in absolute terms in patients with syndrome X.\textsuperscript{17} Furthermore, the addition of blood oxygenation level-dependent (BOLD) or oxygenation-sensitive CMR allows for the unprecedented capability to assess regional myocardial oxygenation,\textsuperscript{18–20} providing a more direct measure of microvascular dysfunction and ischemia than perfusion.

Using these novel and complementary techniques, the aim of the present study was to quantify regional MBF and oxygenation using CMR in patients with syndrome X and to compare them with age-matched healthy volunteers. We hypothesized that patients with syndrome X would demonstrate myocardial ischemia by impairment in both regional perfusion and oxygenation as assessed by perfusion and BOLD CMR, respectively.

Methods

Study Population

We recruited 18 patients with cardiac syndrome X and 14 controls. The controls were healthy individuals with no history of chest pain or other cardiovascular symptoms, had a normal 12-lead ECG and no cardiovascular risk factors, and were not taking any medications. All patients with cardiac syndrome X had a typical history of effort-induced angina and abnormal exercise electrocardiography, suggesting ischemia (≥0.1 mV horizontal or downsloping ST-segment depression 80 ms after the J point with chest pain during exercise). All patients had undergone invasive x-ray coronary angiography, showing angiographically smooth normal epicardial coronary arteries. The mean time from coronary angiography to CMR scan was 6.3 months. Despite the reassurance of a normal angiogram, all patients continued to experience chest pain on exertion in the period between the angiogram and the CMR scan. We excluded patients with coronary spasm during the coronary angiography, diabetes (defined as a fasting glucose level >7.0 mmol/L), hypertension (defined as blood pressure >140/90 mm Hg), and left ventricular (LV) hypertrophy (septum >12 mm on CMR or echocardiography). Other cardiac or systemic diseases were excluded based on clinical history, physical examination, and routine laboratory tests. The study protocol was approved by the Oxfordshire Research Ethics Committee, and all participants gave written informed consent.

CMR Scanning Protocol

CMR was performed on a 3-T system (TIM Trio; Siemens Healthcare). All participants were instructed to refrain from caffeine-containing drinks and food in the 24 hours preceding the study. Images were acquired with the patient supine, using anterior and posterior phased-array surface coils. For cine CMR, from standard pilot images, short-axis cine images covering the entire LV were acquired using a retrospectively ECG-gated steady-state free precession sequence (echo time, 1.5 ms; repetition time, 3 ms; flip angle, 50°). For BOLD-sensitive CMR, a single midventricular slice was acquired at mid-diastole using a T2-prepared ECG-gated steady-state free precession sequence (repetition time, 2.86 ms; echo time, 1.43 ms; T2 preparation time, 40 ms; matrix, 168×192; field of view, 340×340 mm; slice thickness, 8 mm; flip angle, 44°). Each BOLD image was obtained during a single breath-hold over 6 heart beats. A set of 4 to 6 images was acquired at rest and during peak adenosine stress (140 μg/kg per minute). If necessary, shimming and center frequency adjustments were performed before oxygenation imaging to minimize off-resonance artifacts.

Immediately following stress BOLD-sensitive imaging (4–5 minutes after commencing the adenosine infusion), a 0.04-mmol/kg bolus of gadolinium-based contrast (gadodiamide; Omniscan; GE Healthcare) was injected followed by 15 mL of normal saline at a rate of 6 mL/s for first-pass perfusion imaging. During the first pass of contrast, 2 to 3 short-axis images were acquired every cardiac cycle using an ECG-gated 1T-weighted fast gradient echo sequence with generalized autocalibrating partially parallel acquisitions reconstruction (echo time, 0.36 ms; repetition time, 2 ms; saturation recovery time, 95 ms; voxel size, 2.1×2.6×8 mm3; flip angle, 17°; slice thickness, 8 mm; acceleration factor, 2; reference lines, 20; temporal acquisition, 157 ms/slice for a typical 400×333-mm field of view). The adenosine infusion was then discontinued, and after a break of at least 20 minutes, the same sequence was repeated for resting perfusion. Patients were instructed to hold their breath for as long as possible in end expiration during perfusion imaging. For late gadolinium enhancement CMR, a top-up bolus of 0.05 mmol/kg of gadodiamide followed by a 15-mL saline flush was administered. After a 5-minute delay, ECG-gated images were acquired in long- and short-axis planes identical to those of the cine images by using a breath-hold 1T-weighted segmented inversion-recovery turbo fast low-angle shot sequence as previously described.\textsuperscript{21} Heart rate and blood pressure were recorded by a vital signs monitoring machine at baseline and at 1-minute intervals during stress.

Each participant was questioned during and immediately after termination of adenosine infusion about the occurrence of the following adverse events: chest pain or tightness, shortness of breath, and other minor symptoms (flushing, nausea, headache). Additionally, those participants who experienced chest pain or tightness during the infusion of adenosine were asked to grade the severity of pain on a scale from 1 (minimal pain) to 10 (maximum pain).

CMR Data Analysis

For each patient, LV volumes, ejection fraction, and mass were calculated using Argus version VA60C software (Siemens AG) by manually tracing the endocardial and epicardial contours in end-diastolic and end-systolic images as previously described.\textsuperscript{22} The BOLD analysis has been previously published.\textsuperscript{18} Briefly, myocardial signal intensity was measured after manually tracing the endocardial and epicardial contours using QMass version 6.2.3 software (Medis Medical Quantification Software). Each midventricular short-axis BOLD image was divided into 6 segments (inferior septum, anterior septum, anterior, anterolateral, inferolateral, and inferior) according to the middle slice 6 segments of the American Heart Association 17-segment model.\textsuperscript{23} Mean signal intensities were calculated for resting and stress conditions by averaging signal measurements from images during rest and adenosine stress, respectively. BOLD signal intensity measurements were corrected for variations in heart rate between resting and stress as previously described.\textsuperscript{18}

For analysis of myocardial perfusion, signal intensity curves were generated by tracing endocardial and epicardial contours (QMass version 6.2.3 software) as previously described.\textsuperscript{24} Based on the American Heart Association segment model, the myocardium was divided into equiangular segments (6 for basal and midventricular slices and 4 for apical slices), and a region of interest was placed at the center of the LV cavity to measure the arterial input of contrast. The 3 contours (epicardial, endocardial, LV blood pool) were drawn on a single image and propagated automatically through-out the perfusion series. Each image was then checked for positioning, and if necessary, contours were manually corrected for respiratory movement.

Absolute MBF (in milliliters per minute per gram) was calculated for each myocardial segment by model-independent deconvolution...
of myocardial and arterial input signal intensity curves. Each myocardial segment was ascribed a coronary territory according to the previously described standard criteria. To account for cardiac workload, we corrected resting MBF for the rate pressure product (RPP), an index of myocardial oxygen consumption, as follows: MBF=(MBF/RPP)×104. Coronary flow reserve was calculated as the ratio of MBF during adenosine-induced hyperemia to MBF at rest corrected for RPP. In addition to quantitative analysis, perfusion images were analyzed qualitatively. If an endocardial dark band appeared at the arrival of the contrast in the LV cavity and before contrast arrival in the myocardium, this was considered an artifact. By definition, these artifacts were present during both rest and stress studies. Regions with reduced contrast uptake during stress were defined as perfusion defects only if they persisted for more than 5 frames and were absent at rest; otherwise, they were considered to be artifacts. For late gadolinium enhancement images, qualitative (visual) analysis was performed.

Statistical Analysis
Data analysis was performed with commercially available software packages (SPSS, version 17.0 for Windows, STATA version 10.0, and MedCalc version 11.5). All continuous variables were normally distributed (Kolmogorov-Smirnov test). The χ² test or Fisher exact test was used to compare discrete data, as appropriate. Linear mixed models were used to analyze perfusion and oxygenation CMR measurements, taking into account the correlation between measurements on the same participant. Unpaired t tests were used to compare the hemodynamic response of controls and patients with syndrome X during the CMR scans. Statistical tests were 2 tailed, and P<0.05 was considered to indicate statistical significance.

Results
All 14 controls and 18 patients with syndrome X completed the study protocol. The 2 groups were similar in age and sex distribution. With respect to LV function, patients with syndrome X had a slightly increased ejection fraction (72% versus 67%, P=0.014), most likely reflecting a mildly increased sympathetic state. LV mass and wall thickness measurements were similar in the 2 groups and within normal limits. There were no statistical differences in lipid and glucose levels between patients and controls. All patients with syndrome X received were taking at least 1 medication; some patients were taking >1 medication. Table 1 presents participant baseline characteristics.

Hemodynamic Response to Adenosine
The duration of adenosine infusion was similar for patients with syndrome X and controls (297 versus 278 s, P=0.09). Patients and controls demonstrated a similar rise in heart rate and RPP during adenosine stress. Specifically, the heart rate increased by an average of 30 beats/min in controls versus 29 beats/min in patients (P=0.68). The mean change in RPP between stress and rest was 3576 in controls and 4352 in patients with syndrome X (P=0.26). Table 2 summarizes participant hemodynamic parameters.

Pain Perception
Seventeen of the 18 (94%) patients with syndrome X developed chest pain during the infusion of adenosine, whereas only 6 (43%) controls experienced chest pain (P=0.004). The mean chest pain score was 5.4 for patients with syndrome X, indicating that the pain was at least of moderate severity. By contrast, the mean score for controls was 1.7, indicating that the pain was only mild.

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients With Syndrome X (n=18)</th>
<th>Healthy Controls (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>15 (83)</td>
<td>11 (79)</td>
<td>1.00</td>
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<tr>
<td>Age, y</td>
<td>62±6</td>
<td>58±6</td>
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<tr>
<td>Weight, kg</td>
<td>73±8</td>
<td>71±9</td>
<td>0.44</td>
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<td>Height, cm</td>
<td>167±7</td>
<td>170±7</td>
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</tr>
<tr>
<td>BSA, m²</td>
<td>1.84±0.13</td>
<td>1.82±0.13</td>
<td>0.75</td>
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<td>BMI, kg/m²</td>
<td>26±2</td>
<td>24±3</td>
<td>0.064</td>
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<td>Left ventricular analysis</td>
<td></td>
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<tr>
<td>End-diastolic volume, mL</td>
<td>121±24</td>
<td>136±24</td>
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<tr>
<td>End-systolic volume, mL</td>
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<td>Ejection fraction, %</td>
<td>72±5</td>
<td>67±5</td>
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<td>Maximum wall thickness, mm</td>
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<td>8.8±1.0</td>
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<tr>
<td>Mass, g</td>
<td>79±20</td>
<td>91±25</td>
<td>0.14</td>
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<td>Blood tests</td>
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<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.89±0.61</td>
<td>5.03±0.49</td>
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<tr>
<td>HDL, mmol/L</td>
<td>1.39±0.37</td>
<td>1.46±0.28</td>
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<td>LDL, mmol/L</td>
<td>3.08±0.85</td>
<td>3.13±0.50</td>
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<tr>
<td>Triglycerides, mmol/L</td>
<td>1.13±0.36</td>
<td>0.98±0.49</td>
<td>0.34</td>
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<tr>
<td>Glucose, mmol/L</td>
<td>5.22±0.56</td>
<td>5.05±0.54</td>
<td>0.41</td>
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<td>Medications</td>
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<tr>
<td>Calcium channel blocker</td>
<td>8 (44)</td>
<td>0 (0)</td>
<td></td>
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<tr>
<td>Nitrate</td>
<td>8 (44)</td>
<td>0 (0)</td>
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<tr>
<td>ACE inhibitor</td>
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<tr>
<td>Statin</td>
<td>7 (39)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Hormone replacement</td>
<td>2 (11)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as n (%) or mean±SD. One patient received no treatment, and some patients received >1 medication.

BSA indicates body surface area; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ACE, angiotensin-converting enzyme.

Qualitative Perfusion and Late Gadolinium Enhancement Analysis
Only 1 patient with syndrome X (7 frames) and 1 control (6 frames) had regional or circumferential areas of hypoenhancement lasting >5 frames on visual analysis of stress perfusion images, but similar areas of hypoenhancement were seen on their resting scans and, therefore, considered to be artifacts. Overall, 10 (55%) patients with syndrome X and 4 (29%) controls showed areas of short-lived regional or circumferential hypoenhancement (P=0.54), which were considered to be artifacts. None of the patients and controls had evidence of late gadolinium enhancement in any myocardial segment.

Absolute Myocardial Perfusion and Oxygenation Measurements
The variance of MBF measurements at stress was not equal between the 2 groups (variance ratio, 1.68; P<0.001 with F test). This was taken into account on the comparison of mean MBF, which revealed no significant differences in mean resting MBF or hyperemic MBF postadenosine stress between controls and patients with syndrome X (Table 3). Similarly, there were no differences in coronary flow reserve values between the 2 groups (P=0.60). The variance of
BOLD-sensitive signal intensity measurements were similar for patients and controls (variance ratio, 1.10; \( P = 0.65 \) with \( F \) test). There were no differences in global oxygenation measurements between controls and patients (\( P = 0.91 \)). Figure 1 shows a representative example (midventricular short-axis slice) of perfusion and oxygenation in 1 patient with syndrome X.

**Analysis per Coronary Artery Territory**

To explore whether patients with syndrome X demonstrate perfusion abnormalities in specific coronary artery territories, as some previous studies suggested for the left anterior descending coronary artery, we analyzed MBF and BOLD signal intensity change measurements on a per-coronary artery basis. These demonstrated that resting MBF, stress MBF, and coronary flow reserve measurements showed no differences between controls and patients with syndrome X on any of the 3 major coronary artery territories. Similarly, oxygenation measurements per coronary artery were similar in controls and patients. This analysis is shown in Table 3 and Figure 2.

**Discussion**

Using quantitative perfusion and oxygenation-sensitive CMR imaging, the present study shows that although patients with syndrome X demonstrate a higher variance of perfusion measurements, this is not translated into deoxygenation and myocardial ischemia during vasodilatory stress. Furthermore, visual assessment of CMR perfusion images revealed no convincing regional or circumferential perfusion defects. The study findings may have important implications for understanding the pathophysiology of chest pain in patients with cardiac syndrome X and for understanding the relationship between MBF and oxygenation in this condition.

To the best of our knowledge, this study is the first to use a validated quantitative CMR technique to concurrently examine myocardial perfusion and oxygenation in patients with syndrome X; the only study to date to report quantitative MBF in syndrome X using CMR (either at 1.5 or 3 T); and the first CMR perfusion study of any description in this condition at the higher field of 3 T, which is considered superior to 1.5 T for perfusion assessment.\(^{29,30}\) A major strength of the present study is that we quantitatively assessed not only regional myocardial perfusion, but also oxygenation in patients with syndrome X using the BOLD technique at 3 T. As we recently showed in patients with coronary artery disease, oxygenation-sensitive CMR at 3 T can identify not only deoxygenated myocardial segments subtended by stenosed vessels, but also segments with microvascular dysfunction and intermediate signal intensity changes to adenosine stress compared to controls.\(^{18}\) In the present study, we found that the stress oxygenation response seen in the patients was entirely within the normal range of the age-matched controls and that there was no impairment in myocardial oxygenation during vasodilatory stress either in the ischemic range or in the microvascular dysfunction range. This finding gives weight to our perfusion findings that substantial myocardial ischemia, microvascular dysfunction, or both is not occurring in these patients, at least during vasodilatory stress.

Previous CMR studies using semiquantitative perfusion assessment at 1.5 T have given conflicting results. Panting and colleagues\(^{14}\) found that although transmural myocardial perfusion reserve index was similar between patients with
syndrome X and controls, in patients, the subendocardial myocardial perfusion index did not increase with adenosine. Therefore, Panth et al concluded that patients with syndrome X have subendocardial hypoperfusion. In contrast, Vermeltfoort and colleagues, using the same technique of semiquantitative perfusion assessment, found that patients with syndrome X show similar response to adenosine in both the subendocardium and subepicardium. Finally, Lanza and colleagues, using dobutamine stress perfusion CMR with semiquantitative analysis and coronary Doppler during adenosine, found myocardial hypoperfusion with significantly reduced coronary flow reserve in only the left anterior descending coronary artery territory. One reason for the discrepant findings is the different inclusion and exclusion criteria, which resulted in different study populations. For example, Lanza et al included patients with hypertension, hypercholesterolemia, and active smoking history, all of which are well-known causes of microvascular dysfunction. However, the classic definition of syndrome X excludes patients with cardiac or systemic diseases that adversely affect microcirculation. Additionally, the classic definition of syndrome X calls for an abnormal exercise test with at least 0.1-mV horizontal or downsloping ST-segment depression at 80 ms after the J point. Recently, a modified definition of syndrome X that includes evidence of ischemia in any diagnostic testing (exercise stress test, single-photon emission CT, CMR, PET, or Doppler ultrasound) has been proposed.

On the basis of this definition, the majority (80%) of patients with syndrome X in the study by Vermeltfoort et al had reversible perfusion defects in single-photon emission CT and not an abnormal exercise ECG.

In the present study, we used strict inclusion and exclusion criteria based on the classical definition of syndrome X, including only patients with effort-induced chest pain and

Figure 1. Example of perfusion and oxygenation in a patient with syndrome X. A, Blood oxygen level-dependent-sensitive image at rest. B, Blood oxygen level-dependent-sensitive image at stress. After correction for heart rate differences between stress and rest, the signal intensity change ranged from 12% to 19% for all myocardial segments. C, Corresponding late gadolinium enhancement image showing no evidence of scarring or fibrosis. D, Still image of the stress perfusion scan showing circumferential subendocardial hypoenhancement. This could be mistakenly regarded as evidence of subendocardial ischemia. E, Still image of the same scan 5 frames later without evidence of hypoenhancement, indicating that this was an artifact. Regional hyperemic blood flow measurements were normal and ranged from 2.4 to 3.4 mL/min per gram. F, Still image of the rest perfusion scan.

Figure 2. Stress perfusion and oxygenation measurements per coronary artery. Error bars are ±SE. BOLD indicates blood oxygen level-dependent; MBF, myocardial blood flow.
abnormal exercise ECG in the absence of any cardiac or systemic diseases that can potentially cause microvascular dysfunction. Importantly, almost all the patients continued to have anginal symptoms even after the reassurance of a normal angiogram. Another possible reason for the discrepant results between our study and previous CMR studies is the different stress agent used. For example, Lanza and colleagues used dobutamine and not adenosine stress to assess myocardial perfusion. It is well-known that dobutamine stress is associated with increased heart rate response (compared to adenosine) and greater cardiac motion, which exacerbates artifacts in regions perpendicular to the phase-encoding direction (eg, septum). This is one likely explanation of why Lanza et al found a high incidence of perfusion defects in the left anterior descending coronary artery territory. In contrast, Vermeltfoort et al used adenosine stress as we did and did not find evidence of hypoperfusion.

The present results agree with previous PET studies that quantitatively assessed myocardial perfusion and found no evidence of hypoperfusion during vasodilator stress in patients with syndrome X compared with controls. Although the CMR perfusion sequence we used resulted in greatly improved spatial resolution (2.6 versus ~8.4 mm with PET), transmural hypoperfusion was not evidenced. Previous PET studies reported a wide dispersion of MBF values after dipyridamole stress in patients with syndrome X. Interestingly, although we also found a dispersion of stress perfusion measurements in patients with syndrome X, there was no corresponding variation of deoxygenation at stress, indicating that true myocardial ischemia was not present. Another rather universal finding in studies of patients with syndrome X and vasodilator stress is that the perception of pain is enhanced in patients compared with healthy controls, a finding that we also confirm in the present cohort. Several studies reproduced typical chest pain in patients with syndrome X with stimulus to the right side of the heart, including right atrial saline infusion and right ventricular pacing. In these studies, chest pain may have resulted from mechanical distortion of mechanoreceptors to catheter stimulation. Rosen and colleagues showed that altered ventral neural handling of afferent signals may contribute to the abnormal pain perception in these patients. Autonomic nervous system imbalance with increased adrenergic activity and impaired parasympathetic tone could explain both increased pain sensitivity and endothelial dysfunction. More recently, Valeriani et al investigated abnormalities in electric cerebral signals to pain stimuli and found decreased habituation to repetitive noxious stimuli in patients with cardiac syndrome X. In the present study, the majority of patients with syndrome X reported chest pain of moderate extent during adenosine stress. In contrast, the frequency and extent of chest pain was much reduced in controls.

**Limitations**

The present study has some limitations. First, we measured only transmural perfusion and not subendocardial versus subepicardial MBF. Therefore, subendocardial hypoperfusion may have been missed. However, the resolution of the technique in conjunction with the relatively low-normal myocardial wall thickness in the predominantly female patients precluded performing separate analyses for subendocardial versus other myocardial layers. Recently, high-resolution CMR perfusion techniques have been developed at 3 T with ~1-mm in-plane resolution that will likely enable reliable assessment of subendocardial versus subepicardial perfusion. However, even if subtle differences in subendocardial perfusion existed in our cohort, these did not result in myocardial deoxygenation, and therefore, true tissue ischemia was not present. Second, the sample size was small; however, as previously described, we applied strict inclusion and exclusion criteria and made every possible effort to recruit only patients with true syndrome X. None of the patients had cardiac or systemic diseases associated with microvascular dysfunction. Finally, the majority of the patients were women; therefore, the findings may not apply to male patients with syndrome X, who are rather rare.

**Conclusions**

Using CMR imaging with absolute quantification of MBF and oxygenation measurements with the BOLD technique, patients with syndrome X have no evidence of transmural hypoperfusion or deoxygenation during vasodilatory stress but show greater sensitivity to chest pain compared with healthy controls. Further confirmation of our findings in larger-scale studies is needed.

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**Disclosures**

None.

**References**

The pathophysiology of chest pain in patients with syndrome X (chest pain, abnormal exercise treadmill test, normal coronary angiogram) remains controversial. Previous studies using nuclear techniques or cardiovascular magnetic resonance to assess myocardial perfusion have shown conflicting results. Other studies suggest that abnormal pain perception may be a central component of this enigmatic syndrome. We used cardiovascular magnetic resonance to quantitatively assess regional myocardial blood flow and oxygenation during vasodilatory stress (adenosine) in patients with syndrome X and healthy controls. The findings indicate that patients with syndrome X have no evidence of transmural hyperperfusion or deoxygenation but a greater incidence of chest pain during vasodilatory stress compared with controls. Studies using high-resolution perfusion cardiovascular magnetic resonance (>1-mm in-plane resolution) are needed to further investigate subendocardial and subepicardial perfusion in these patients.
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/content/5/4/e56.full.pdf

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In the article by Karamitsos et al, “Patients With Syndrome X Have Normal Transmural Myocardial Perfusion and Oxygenation: A 3-T Cardiovascular Magnetic Resonance Imaging Study,” which appeared in the March 2012 issue of the journal (Circ Cardiovasc Imaging. 2012;5:194–200), there is an error in Figure 2. The y axis of the graph on the left should be labeled “Stress MBF (mL/min per g)”.

This error has been corrected in the current online version of the article, which is available at: http://circimaging.ahajournals.org/content/5/2/194.full.