Relation Between Stress-Induced Myocardial Perfusion Defects on Cardiovascular Magnetic Resonance and Coronary Microvascular Dysfunction in Patients With Cardiac Syndrome X

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Objectives: The purpose of this study was to investigate whether a direct relation can be demonstrated between myocardial perfusion defects detected during dobutamine stress test (DST) by cardiovascular magnetic resonance (CMR) and impairment of coronary microvascular dilatory function in patients with cardiac syndrome X (CSX).

Background: Despite the fact that coronary microvascular dysfunction has been shown in most patients with CSX, the ischemic origin of CSX remains debated. No previous study assessed whether a strict relation exists between abnormalities in myocardial perfusion and coronary microvascular dysfunction in CSX patients.

Methods: Eighteen CSX patients (mean age 58 ± 7 years, 7 men) and 10 healthy control subjects (mean age 54 ± 8 years, 4 men) underwent myocardial perfusion study by gadolinium-enhanced CMR at rest and at peak DST (maximal dose 40 μg/kg/min). Coronary flow response (CFR) to adenosine (140 μg/kg/min in 90 s) in the left anterior descending (LAD) coronary artery was assessed by high-resolution transthoracic echo-Doppler and expressed as the ratio between coronary flow velocity at peak adenosine and at rest.

Results: At peak DST, reversible perfusion defects on CMR were found in 10 CSX patients (56%) but in none of the control subjects (p = 0.004). The CFR to adenosine in the LAD coronary artery was lower in CSX patients than in control subjects (2.03 ± 0.63 vs. 3.29 ± 1.0, p = 0.0004). The CSX patients with DST-induced myocardial perfusion defects in the LAD territory on CMR had a lower CFR to adenosine compared with those without perfusion defects in the LAD territory (1.69 ± 0.5 vs. 2.31 ± 0.6, p = 0.01). A significant correlation was found in CSX patients between CFR to adenosine and a DST perfusion defect score on CMR in the LAD territory (r = −0.45, p = 0.019).

Conclusions: Our data concurrently show DST-induced myocardial perfusion defects on CMR and reduced CFR in the LAD coronary artery territory in CSX patients, thus giving strong evidence that a dysfunction of coronary microcirculation resulting in myocardial perfusion abnormalities is present in these patients. (J Am Coll Cardiol 2008;51:466–72) © 2008 by the American College of Cardiology Foundation

In patients with cardiac syndrome X (CSX), typical ST-segment depression on the electrocardiogram during exercise stress test suggests myocardial ischemia caused by coronary microvascular dysfunction (1). The presence of coronary microvascular abnormalities in these patients has been supported by the detection of reversible myocardial perfusion defects during stress myocardial scintigraphy (2,3) and, even more, by the evidence of an impaired response to vasodilator stimuli of coronary blood flow and/or resistance, assessed with several different methods (4–10). In particular, a blunted increase in subendocardial flow in response to intravenous administration of adenosine (11) was shown by cardiovascular magnetic resonance (CMR), a high-resolution technique that allows the assessment of transmural myocardial perfusion homogeneity with gadolinium as contrast medium (12).

Yet, the ischemic origin of CSX remains still debated (13), mainly because of the usual lack—during stress tests—of regional myocardial wall motion abnormalities,
which are considered the most reliable finding of myocardial ischemia (14,15). Furthermore, some studies failed to confirm the impaired response to vasodilator stimuli of coronary microcirculation (16,17). A recent study in particular, in contrast with a previous one (11), did not find any apparent impairment of subendocardial blood flow in response to adenosine on gadolinium CMR imaging (18).

Together with these challenging data, doubts about the microvascular origin of CSX can also be fostered by the fact that in previous studies the documentation of coronary blood flow alterations was always obtained with single diagnostic techniques and without any clear demonstration of a relationship between abnormalities in coronary blood flow regulation in a myocardial region and inducibility of findings compatible with myocardial ischemia in the same territory. Also, no previous study in CSX patients assessed whether abnormalities in coronary blood flow, attributable to microvascular dysfunction, could be detected concurrently by different, independent methods in the same patients, which would give considerable strength to the notion of a coronary microvascular origin of the syndrome.

Accordingly, in this study we investigated, in a group of CSX patients, whether a direct relation could be demonstrated between the induction of myocardial perfusion defects on gadolinium CMR images during dobutamine stress test (DST) and the presence of abnormalities in coronary microvascular vasodilator function, as assessed by the response to adenosine of coronary blood flow with an independent method (i.e., transthoracic echocardiographic Doppler recording of the left anterior descending [LAD] coronary artery).

Methods

Subjects. We enrolled 19 CSX patients. However, a 60-year-old male patient did not complete the CMR study (see following text) owing to severe chest pain during DST, associated with peaking of T waves and mild ST-segment depression in precordial leads, which required intravenous metoprolol administration and precluded assessment of myocardial perfusion at peak DST.

Thus, 18 patients (mean age 58 ± 7 years, 7 men) formed the CSX study group. All patients had a history of effort angina, ST-segment depression associated with angina during at least 1 previous exercise stress test, and angiographically normal epicardial coronary arteries. Mild hypertension was present in 6 patients, but left ventricular hypertrophy was excluded by echocardiography in all of them. Other cardiac or systemic diseases were carefully excluded according to clinical history, physical examination, routine laboratory tests, and 2-dimensional Doppler echocardiography.

A group of 10 volunteers (mean age 54 ± 8 years, 4 men) served as control subjects. These subjects were enrolled from the non-medical staff of our hospital and were selected to be comparable to CSX patients as to age and gender. Control subjects did not have any cardiac symptom or clinically relevant disease, and they all had normal standard 12-lead electrocardiography (ECG), exercise stress test, and 2-dimensional Doppler echocardiography.

All cardiologic drugs were withdrawn for 72 h before the study protocol. The study complies with the Declaration of Helsinki and was approved by the institutional review board of the Università Cattolica del Sacro Cuore. All subjects enrolled gave their informed consent for participation in the study.

DST. All patients and control subjects underwent DST at least 45 min after a basal CMR study (see the following text). Intravenous infusion of dobutamine was started at a dose of 5 mg/kg/min and was increased after 5 min to 10 mg/kg/min; it was then increased thereafter at 3-min intervals to 20, 30, and 40 mg/kg/min, if tolerated. If heart rate did not reach 85% of its maximal theoretical value, intravenous atropine 0.5 mg was administrated and repeated after 5 min, if necessary. Standard 12-lead ECG was continuously monitored throughout the test. Furthermore, ECG was printed and blood pressure recorded at baseline and at the end of each DST stage until the patient was brought to the CMR room for image acquisition. The ECG and blood pressure were recorded as soon as possible after CMR recording. The occurrence of angina, ST-segment depression, or any other clinically significant abnormality was recorded.

Dobutamine infusion was stopped in cases of intolerable angina, hypertensive response (blood pressure ≥240/140 mm Hg), complex ventricular arrhythmias, or any other potentially dangerous clinical condition. The ST-segment changes did not constitute a criterion to stop dobutamine infusion.

CMR. All participants underwent gadolinium-enhanced CMR study at rest and at peak DST. The stress study was performed at least 45 min after the rest study, to permit clearance of gadolinium after the first injection.

The CMR was performed with a 1.5-T scanner (Signa Excite2, General Electrics Medical Systems, Buc, Paris, France), with a cardiac 8-channel phased array dedicated receiver coil and following a standardized protocol (19). All sequences were obtained with ECG-gating and during breath-holding by the patient.

After a tri-plane localizer, vertical long-axis (2-chamber view) and horizontal long-axis (4-chamber view) steady state free precession (FIESTA) sequences were acquired. The scan parameters for long-axis cine sequences were: repetition time/echo time/flip angle (TR/TE/FA) 4.0 ms/1.4 ms/45°, slice thickness 8 mm, matrix 224 × 288, number of excitations (NEX) 1, bandwidth 125 kHz.

Contrast medium (gadolinium-DTPA, Magnevist AG, Berlin, Germany) was injected through a 14-gauge cannula in an antecubital vein, at a dose of 0.1 mmol/kg, with a flow rate of 3 to 4 ml/s. Perfusion first-pass imaging was obtained through 3 short-axis views (basal,
mid-ventricular, and apical), with a fast gradient echo train sequence. Different frames of the chosen planes were acquired during 1 min. Owing to this long acquisition time, patients were instructed to hold their breath at end-expiration as long as possible and then to breath superficially and slowly thereafter. The scan parameters for first-pass imaging were: TR/TE/FA 6.9 ms/1.6 ms/25°, slice thickness 8 mm, gap 12 to 15 mm, matrix 128 × 128, NEX 1, bandwidth 125 kHz.

After first-pass imaging, global systolic function assessment was obtained employing a modified short-axis very fast FIESTA sequence (FIESTA-SP), encompassing the whole left ventricle. Total scan time was approximately 30 s, divided in 2 to 3 breath-holds. The scan parameters for this image acquisition were: TR/TE/FA 3.2 ms/1.3 ms/45°, slice thickness 8 mm, gap 0 mm, matrix 192 × 184, NEX 0.5, bandwidth 125 kHz.

The same study protocol was applied at rest and at peak dobutamine infusion. Approximately 15 min after stress imaging, delayed enhancement sequence was obtained in short-axis, with a conventional inversion recovery-fast gradient echo technique in the same orientation of the 3 slices of the first-pass study and of the functional study. Parameters of the sequence were: TR/TE/FA 6.6 ms/3.1 ms/20° every heartbeat, slice thickness 8 mm, gap 0 mm, matrix 256 × 192, NEX 1 to 2.

The first-pass study was analyzed both in qualitative and semi-quantitative ways, with a 16-segment left ventricle model. On qualitative assessment, perfusion defects were defined as subendocardial or transmural visually dark myocardial areas, respecting coronary distribution, with a delay of at least 2 s compared with remote healthy myocardium, and persisting for at least 10 frames (19).

Semi-quantitative analysis was performed by signal intensity (SI)/time curves, with a commercially available software (Mass plus, Medis, Leiden, the Netherlands); endocardial and epicardial borders of the 3 slices were traced manually, and curves and bull’s eye plots were obtained by 2 independent skilled operators, with divergences being resolved by consensus.

A score was assigned for each left ventricular segment, according to the following scale: 0 = no perfusion defect; 1 = subendocardial perfusion defect with transmural extension <25%; 2 = subendocardial perfusion defect with transmural extension between >25% and 50%; 3 = subendocardial perfusion defect with transmural extension between >50% and 75%; and 4 = subendocardial perfusion defect with transmural extension >75%.

For each patient a total score was obtained as the sum of the individual scores of each segment. If a perfusion defect was also present at rest, the stress-related (ischemic) score was calculated as the difference between the score after stress minus the score at rest.

**Coronary flow response to adenosine.** The tests were all performed in the morning by the same expert echocardiographer within ± 2 days of CMR study, following a well-standardized protocol (20). Subjects were positioned in the left lateral decubitus position in a quiet, temperature-controlled room (22°C). The LAD coronary artery was imaged by a 7-MHz transducer connected to an Acuson Sequoia C512 ultrasound system (Siemens S.p.A., Milano, Italy), and flow in its mid-distal portion of the vessel was interrogated with color Doppler mapping. Color gain was adjusted to provide optimal images. A 2-mm-wide sample volume was then positioned on the color signal of the LAD coronary artery, and when an anterograde monophasic decrescendo diastolic flow was confirmed, Doppler spectral tracing of LAD coronary flow velocity was recorded.

Coronary microcirculatory dilation and consequent increase in coronary blood flow velocity was induced by infusion of adenosine (140 μg/kg/min in 90 s) under constant ECG and blood pressure monitoring. Peak coronary blood flow velocity was measured at baseline and during adenosine infusion. For each phase, the 3 highest Doppler velocities were averaged. The CFR to adenosine was expressed as the ratio of hyperemic to basal peak diastolic coronary blood flow velocity.

**Statistics.** Continuous variables showed a normal distribution according to the Kolmogorov-Smirnov test and were compared by the Student t test. Covariance analysis was applied to adjust average differences for potentially confounding variables. Bonferroni’s rule for 2 comparisons was applied to compare CFR to adenosine in the subgroups of CSX patients with and without DST-induced reversible perfusion defects on gadolinium CMR imaging in the LAD artery territory with CFR to adenosine in healthy control subjects. Proportions were compared by the Fisher exact test. Correlation analyses were performed by the Spearman rank test.

Data are reported as mean ± SD. A 2-sided p value <0.05 was always required for statistical significance. The software SPSS version 12.0.2 (SPSS Inc., Florence, Italy) was used for statistical analyses.

**Results**

**Clinical data.** The main clinical characteristics of CSX patients and healthy subjects who completed the study are summarized in Table 1. Overall, CSX patients tended to have more cardiovascular risk factors and were taking more medications, although differences did not achieve statistical significance.

**CMR study.** The main DST results are summarized in Table 2. Heart rate and blood pressure at rest and at peak DST did not differ between CSX patients and control subjects. Angina was induced by DST in 9 CSX patients (50%) and in none of the control subjects (p = 0.01). ST-segment depression also occurred in 9 CSX patients but in no healthy control subjects (p = 0.01). Both angina and ST-segment depression occurred in 7 patients. No left
ventricular wall motion abnormalities were detected on CMR during DST.

No perfusion defects during gadolinium-enhanced first-pass CMR were found at rest in any of the CSX patients and control subjects. In contrast, at peak DST, perfusion defects were found in 10 CSX patients (56%, Fig. 1) but in none of the control subjects (p = 0.004).

The perfusion defects were limited to 1, 2, 3, and 4 segments in 3, 3, 3, and 1 CSX patients, respectively. In 6 patients the perfusion defect was limited to the subendocardial layer (transmural myocardial perfusion <25% of myocardial thickness), whereas in 4 patients the perfusion defect extended between 25% and 50% of myocardial thickness, whereas in 2 patients they were shown in the right coronary artery territory. In 8 of 10 CSX patients, myocardial perfusion defects were localized in the LAD coronary artery territory, whereas in 2 patients they were shown in the right coronary artery territory.

Angina during DST was referred by 6 (60%) and by 3 (37%) of CSX patients with and without perfusion defects on CMR, respectively (p = 0.64). Also, ST-segment depression during DST was observed in 6 and 3 CSX patients with or without perfusion defects on CMR, respectively (p = 0.64).

Coronary flow response to adenosine. No relevant side effects were observed during intravenous adenosine infusion, although some patients experienced transient minor side effects, including dyspnea and headache. Heart rate and blood pressure were similar, both at rest and at peak adenosine, in the 2 groups (Table 3). Among CSX patients,
5 (27.8%) developed anginal pain and 6 (33%) developed ST-segment depression. No healthy control subjects developed either angina or ST-segment changes during adenosine infusion.

In CSX patients, compared with control subjects, LAD coronary blood flow velocity tended to be higher at rest (226.8 ± 94 cm/s vs. 179.2 ± 46 cm/s, p = 0.25) but lower at peak adenosine (452.5 ± 170 cm/s vs. 576.3 ± 85 cm/s, p = 0.11). As a result, CFR to adenosine was significantly lower in CSX patients than in control subjects (2.03 ± 0.6 vs. 3.29 ± 1.0, p = 0.0004). The difference in CFR to adenosine in the LAD coronary artery between the 2 groups persisted unchanged after adjustment for basal LAD coronary flow velocity (p < 0.01).

The CSX patients with a perfusion defect in at least 1 myocardial segment in the LAD coronary artery territory on DST-CMR had a significantly lower CFR to adenosine in the LAD artery compared with those with no DST-induced myocardial perfusion defects in the LAD coronary artery territory on CMR (1.69 ± 0.5 vs. 2.31 ± 0.6, p = 0.037).

The latter group, however, still showed a significantly lower CFR to adenosine in the LAD artery compared with control subjects (p < 0.05) (Fig. 2).

Interestingly, in the 2 patients with DST-induced perfusion defects in the right coronary artery territory, CFR to adenosine in the LAD artery was clearly reduced in 1 (1.6) and at the bottom of the range of values of healthy control subjects (2.1) in the other patient, thus suggesting a more generalized microvascular dysfunction. Notably, CFR to adenosine in the LAD artery was still lower in the 8 CSX patients without any appreciable reversible perfusion defects on CMR images, as compared with control subjects (2.42 ± 0.6 vs. 3.29 ± 1.0, p < 0.05).

A significant correlation was found in CSX patients between CFR to adenosine in the LAD artery and CMR perfusion defect score during DST in the LAD territory (r = −0.45, p = 0.019).

Discussion

In this study, for the first time, we give evidence in CSX patients of a strict relation between impairment of coronary microvascular vasodilation in the LAD coronary artery (as assessed by CFR to adenosine) and induction of reversible perfusion defects by DST on CMR images in the same myocardial territory. The concordance between these abnormal findings, obtained by independent operators with 2 independent techniques and methods, lend strong support to the notion that coronary microvascular dysfunction is a major cause of CSX.

Microvascular dysfunction in CSX. Although suggested since the early descriptions of the syndrome, the coronary microvascular origin of syndrome X has long been debated.

The ST-segment depression during stress-induced angina is a landmark of CSX and suggests myocardial ischemia caused by microvascular dysfunction (1), which is also suggested by reversible perfusion defects detectable by stress myocardial scintigraphy in several patients (2,3). More direct evidence of a coronary microvascular dysfunction comes from studies showing an impaired response of coronary blood flow/resistance to primarily endothelium-independent stimuli, including dipyridamole, adenosine, and papaverine, with several different diagnostic techniques (thermodilution, intracoronary Doppler recording, positron...
emission tomography, CMR) (4–11). Furthermore, an impairment of endothelium-dependent coronary microvascular dilation has been shown by several studies (6–8), and other data also support an increased vasoconstrictor reactivity of small coronary artery vessels in these patients (5,21).

Despite this evidence, some authors have questioned the microvascular/ischemic origin of CSX, objecting that the demonstration of myocardial ischemia would require the evidence of more specific and convincing alterations, including typical metabolic changes and left ventricular wall motion abnormalities (14,15). In fact, some studies failed to find stress-induced metabolic abnormalities (22) or left ventricular dysfunction indicative of myocardial ischemia (3,23). Yet, a metabolic evidence of stress-induced myocardial ischemia, including myocardial lactate production (24), coronary sinus oxygen desaturation (25), and myocardial phosphorus–31 metabolism by CMR spectroscopy (26), has been obtained in at least a subgroup of CSX patients. Furthermore, Buffon et al. (27), in a group of these patients, found a high myocardial release of lipoperoxide products in the coronary circulation after atrial pacing, similar to that found in patients after coronary occlusion by balloon inflation during percutaneous coronary intervention.

In a previous study, Panting et al. (11), with gadolinium CMR imaging, supported the presence of coronary microvascular dysfunction in CSX patients by showing an impairment of myocardial perfusion in subendocardial layers in response to adenosine. This finding has recently been challenged by Vermeltfoort et al. (18), who with an analogous protocol found a similar, apparently normal, increase in subendocardial and subepicardial blood flow in response to adenosine in a group of patients with angina and normal coronary arteries, although 2 patients (10%) showed reversible perfusion defects. The population of this study, however, seems quite heterogeneous and no control group was included (18).

In the present study, we provide novel evidence of coronary microvascular dysfunction in CSX patients. Indeed, with dobutamine as a pharmacological stressor, we showed reversible perfusion defects on CMR images in more than one-half of patients but in none of the healthy control subjects. Perfusion defects were localized in subendocardial layers, in keeping with the findings of Panting et al. (11). Most important, in our study we found a strict relation between the DST-induced reversible perfusion defects on CMR and the reduced CFR to adenosine, as assessed by transthoracic Doppler coronary flow recording, in the LAD territory, thus confirming by an independent method the microvascular origin of the CMR perfusion defects. Most regional perfusion defects were observed in the LAD territory, but they were detectable in the right coronary artery territory in 2 patients, thus suggesting the importance of the assessment of the whole coronary circulation in these patients.

Perfusion defects and reduced CFR to adenosine were not associated with left ventricular wall motion abnormalities, which could be explained with a patchy distribution of microvascular dysfunction and/or with a limited extension and severity of ischemia (28).

Also, only a minority (27.8%) of our patients developed angina pain during adenosine infusion, in contrast with the 95% rate of chest pain reported by CSX patients in Panting’s study (11). The reasons for this difference are not completely clear, but it might be explained, at least in part, by the shorter duration of adenosine infusion in our study (1.5 min vs. 6 min) and by the possible inclusion of a different proportion of patients with increased painful perception of cardiac stimuli, a distinctive finding that can be present and contribute to the symptomatic burden in a variable number of CSX patients (29,30).

Interestingly, our data suggest that coronary microvascular dysfunction in most CSX patients can be more diffuse than that indicated by the evidence of reversible regional perfusion defects on stress CMR and can also be present in patients who do not exhibit reversible perfusion defects at all. Indeed, CFR to adenosine in the LAD coronary artery seemed low in the 2 patients who displayed reversible perfusion defects only in the right coronary artery territory and was also reduced, on average, compared with healthy control subjects, in the group of CSX patients in whom no apparent regional perfusion defects could be detected. A patchy diffuse form of mild coronary microvascular dysfunction, not sufficiently confluent to result in detectable regional perfusion defects (27), might be involved in these cases, in agreement with our recent data showing diffuse reduction of CFR to adenosine in a group of CSX patients on contrast echocardiography (31).

However, in the few patients showing both adequate CFR to adenosine and normal CMR imaging on DST, chest pain episodes might be caused by mechanisms different from coronary microvascular dysfunction, including pure enhanced cardiac pain sensitivity (29,30), or even noncardiac causes. Yet, it cannot be excluded that, at least in some patients, the lack of demonstration of coronary microvascular alterations in our study might have been related to variability over time of the mechanisms responsible for the coronary microvascular dysfunction or to inadequacy of stress stimuli used to reveal coronary microvascular abnormalities.

Conclusions

Our data show a correlation between myocardial perfusion abnormalities on CMR during pharmacological stress test and reduced coronary microvascular vasodilator response to adenosine in patients with CSX. The concordance between these abnormal findings, obtained by independent methods, strongly supports the notion that coronary microvascular dysfunction is a key pathogenetic component of this syndrome.

These findings also suggest that transthoracic echodoppler study of the LAD coronary artery could represent a useful screening modality to assess coronary microvascular function in patients with chest pain and normal coronary
REFERENCES