Background—Although increased coronary microvascular resistance (CMR), resulting in coronary microvascular dysfunction, is speculated to be responsible for myocardial ischemia in patients with cardiac syndrome X (CSX), it has never been directly demonstrated, and the correlation between CMR and severity of myocardial ischemia has not been elucidated in this setting. This study aimed to ascertain the increased CMR directly and to explore the relationship between CMR and severity of ischemia in patients with CSX.

Methods and Results—We studied 18 patients with CSX and 18 age- and sex-matched control subjects. Thermodilution-derived coronary flow reserve and index of microvascular resistance were measured using a pressure–temperature sensor-tipped coronary wire. Exercise treadmill test was performed by the Bruce protocol for calculating Duke treadmill score. Coronary flow reserve was significantly lower (2.37±0.81 versus 3.68±0.72; \( P<0.001 \)) and index of microvascular resistance was higher (33.1±7.9 versus 18.8±5.6 U; \( P<0.001 \)) in patients with CSX compared with those in control subjects. The Duke treadmill score was correlated positively to coronary flow reserve (\( r=0.539; P=0.021 \)) and negatively to index of microvascular resistance (\( r=-0.742; P<0.001 \)) in patients with CSX.

Conclusions—Using an intracoronary thermodilution method, we for the first time directly demonstrated an increased microvascular resistance in patients with CSX. Furthermore, severity of ischemia was found to be intimately associated with CMR in this setting.

Key Words: cardiac syndrome X  microvascular angina

Cardiac syndrome X (CSX), defined as typical chest pain, transient myocardial ischemia, and angiographically normal coronary arteries, is an important clinical entity.\(^1\)\(^-\)\(^4\) The likely pathophysiological mechanism for CSX is suggested to be coronary microvascular dysfunction (CMD), presenting with increased coronary microvascular resistance (CMR) and impaired coronary flow reserve (CFR), thus resulting in myocardial ischemia and subsequent angina pectoris.\(^1\)\(^-\)\(^4\) However, although abnormal CFR or myocardial perfusion defects were demonstrated by stress echocardiography,\(^1\)\(^2\)\(^7\) cardiovascular MR,\(^1\)\(^9\) and positron emission tomography,\(^2\) the elevated CMR has never been directly documented, and the correlation between CMR and severity of ischemia has not been elucidated in this setting.

With recent technological advances, it is now possible to measure pressure and estimate coronary artery flow simultaneously with a single pressure–temperature sensor-tipped coronary wire. By this intracoronary thermodilution technique, the status of coronary microcirculation can be invasively assessed using a novel index of microvascular resistance (IMR),\(^9\) which demonstrates less intrinsic variability and better reproducibility than CFR.\(^10\)

Therefore, we conducted the present study to ascertain directly the increased CMR, expressed as IMR, in patients with CSX and to explore the relationship between CMR and Duke treadmill score (DTS), a comprehensive index representing the severity of ischemia.\(^7\)\(^11\)\(^12\)

Methods

Patient Population and Study Protocol

The present prospective study was conducted in the Department of Cardiology, the First Affiliated Hospital of Sun Yat-sen University. We enrolled 18 patients with CSX (CSX group) who fulfilled the diagnostic criteria for CSX in the present study as follows\(^3\)\(^-\)\(^4\): (1) a typical history of exertional angina; (2) a positive exercise treadmill test (ETT); and (3) angiographically normal epicardial coronary arteries without minimal irregularities. With frequency matching method, the control group consisted of 18 age- and sex-matched subjects who were referred for diagnostic coronary angiography because of atypical chest discomfort, with a negative ETT and completely normal coronary arteries at angiography. Subjects with any of the following were excluded from this study: other specific forms of cardiac disease (eg, variant angina, cardiomyopathies, and valvular or congenital heart disease), any regional wall motion abnormalities at rest, any history of exertional angina, uncontrolled hypertension (>160/100 mm Hg), significant renal failure, any significant rhythm disorders, any chronic inflammatory disease, any significant hepatic dysfunction, or any other significant chronic medical illness that may contribute to angina.

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WHAT IS KNOWN

- Coronary microvascular dysfunction has been suggested as the likely pathophysiological mechanism for ischemia in cardiac syndrome X.
- Abnormal coronary microvascular dysfunction or myocardial perfusion defects have been demonstrated by transthoracic Doppler echocardiography, cardiac MR, and positron emission tomography in cardiac syndrome X.

WHAT THE STUDY ADDS

- Using an intracoronary thermodilution-derived coronary flow reserve, we demonstrated direct evidence of coronary microvascular dysfunction as shown by an increased index of myocardial resistance and impaired coronary flow reserve in patients with cardiac syndrome X.
- The severity of myocardial ischemia in patients with cardiac syndrome X was associated with the abnormal coronary microvascular resistance and moderately related to thermodilution-derived coronary flow reserve.

mmHg) or diabetes mellitus (fasting plasma glucose >7.0 mmol/L and postprandial glucose >11.0 mmol/L), systemic disorders, and liver or renal insufficiency.

Within 1 week before or after coronary angiography and thermodilution measurement, ETT was performed by the Bruce protocol for calculating DTS. The hospital Ethics Committee approved the study protocol, and each subject gave written informed consent to the study.

Coronary Angiography

In all study participants, selective coronary angiography was performed using standard Judkins technique. Coronary arteries were visualized in left and right oblique planes with cranial and caudal angulations. Injection of contrast medium (Iopromide, Ultravist-370; Schering AG, Berlin, Germany) was performed by an automatic injector at a speed of 5 mL/s for left coronary artery and 3 mL/s for right coronary artery.

All anti-angina and anti-ischemic medications, except sublingual nitroglycerin, were withheld for ≥1 week before the examination. All coronary angiograms were analyzed by 2 experienced independent investigators, and only angiograms with visually smooth contours and no wall irregularities were accepted as normal.

Intracoronary Thermodilution Measurements

After coronary angiography, an coronary pressure wire (PressureWire-4; Radi Medical Systems, Wilmington, MA) was calibrated outside the body, equalized to the guiding catheter pressure with the sensor positioned at the ostium of the guiding catheter, and then advanced until the wire sensor was located in the distal third of the left anterior descending coronary artery, with the transducer distance at 7 to 10 cm from the guide tip.

With commercially available software (Radi Medical Systems), the shaft of the pressure wire can act as a proximal thermistor by detecting changes in temperature-dependent electric resistance. The sensor near the tip of the wire simultaneously measures pressure and temperature and can thereby act as a distal thermistor. The transit time of room-temperature saline injected down a coronary artery can be determined using a thermodilution technique. Three injections of saline (3 mL, room temperature) were administered down the coronary artery, and the baseline mean transit time was measured. Intravenous adenosine (140 μg/kg per minute) was then administered to induce steady state maximal hyperemia, then 3 more injections of saline (3 mL, room temperature) were given, and the hyperemic mean transit time was measured. Simultaneous measurements of mean aortic pressure (Pa; by guiding catheter) and mean distal coronary pressure (Pd; by pressure wire) were also made in the resting and maximal hyperemic states. CFR was calculated as baseline mean transit time divided by hyperemic mean transit time. IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of hyperemic mean transit time. Fractional flow reserve (FFR) was calculated by the ratio of Pd/Pa at maximal hyperemia.

ETT and DTS

Patients underwent symptom-limited ETT according to the Bruce protocol using Quinton 5000 model after the patients had fasted for >4 hours. If possible, β-blocking agents were discontinued for 24 to 48 hours before the study, and long-acting nitrate agents were stopped for >4 hours. The heart rate, blood pressure, and 12-lead ECG were recorded at a 3-minute interval during and after the exercise.

All the ETT results were assessed by the same independent electrocardiographer who was blinded to the results of angiography and thermodilution measurement of the individual participants. In patients whose baseline 12-lead ECGs had no ST-segment abnormalities, a horizontal or down-sloping ST-segment depression of ≥1 mm or an upsloping ST-segment depression of ≥2 mm 0.08 s after the J point on the exercise ECG was considered positive for myocardial ischemia. The ECG was also considered positive if an additional ≥2 mm ST-segment depression was seen, despite the baseline ST-segment depression, in the absence of left bundle branch block or left ventricular hypertrophy. ETT was considered intermediate if no ST-segment changes were present, but the patient failed to achieve 85% of the maximum predicted heart rate. For the study purpose, intermediate results were considered negative.

In addition, DTS was determined for every patient as described by Mark et al. The score uses 3 prognostic variables from the treadmill test: the amount of net exercise-induced ST-segment deviation in any lead except aVR, the presence and severity of exercise-induced angina, and the duration of exercise on the standard Bruce protocol. These variables are combined into the following equation: DTS=(exercise duration in minutes)−(5×ST deviation in millimeters)−(4×treadmill angina index). The treadmill angina index is equal to 0 for no exercise angina, 1 for exercise-nonlimiting angina, and 2 for exercise-limiting angina. The score typically ranged from −25 to +15.

Statistical Analysis

The statistical analysis was performed using SPSS version 12.0 software. Data were expressed as mean±SD unless otherwise specified. Continuous variables between groups were compared by the Student t test, and paired data (for analysis of reproducibility) were compared by paired t test. Proportions were compared by the Fisher exact test when the expected frequency was <5; otherwise, the χ² test was applied. The Pearson correlation analysis was used to test univariate relationships. Significance was considered to be achieved for 2-tailed P<0.05.

Results

Study Population and Clinical Demographics in Patients With CSX and Controls

Patients’ clinical demographics and characteristics for the use of medications in both groups are indicated in Table 1. The 2 groups were similar for age, sex, cardiovascular risk factors, blood pressure, heart rate, and left ventricular function. There were no differences in characteristics for the use of medications between the 2 groups.
Comparisons of CFR, IMR, FFR, and DTS Between Groups

Thermodilution-derived CFR, IMR, and FFR could be easily measured in all studied cases. To test the reproducibility of CFR, IMR, and FFR values in our catheter laboratory, we conducted 2 sequences, at an interval of 10 to 15 minutes, of these coronary physiology measurements in 15 subjects, with 8 patients with CSX and 7 controls. Between the first and second sequences, the mean values for CFR (3.08±0.94 and 3.01±1.02), IMR (24.8±9.1 and 25.1±8.7 U), and FFR (0.94±0.02 and 0.95±0.02) showed no significant differences (P>0.05 for all comparisons). The mean coefficient of variation between 2 sequences was 4.9±4.7% for IMR and 1.3±1.5% for FFR, both significantly lower than that for CFR (16.8±9.6%; P<0.001 for both comparisons). In those subjects who underwent 2 sequences of coronary physiology measurements, the average value of the 2 measurements was taken as the final corresponding parameters.

The FFR in all subjects was ≥0.90 (range, 0.90–0.98), with no differences between CSX and control groups. CFR and DTS were significantly lower in patients with CSX than in control subjects, whereas IMR was significantly higher in the CSX group (Table 2; Figure 1).

Relationships Among CFR, IMR, and DTS

In patients with CSX, the DTS was correlated positively to CFR (r=0.539; P=0.021) and negatively to IMR (r=-0.742; P<0.001; Figure 2). While assessing correlations of ischemic and nonischemic markers, the DTS was correlated positively to CFR (r=0.94±0.02 and 0.95±0.02) showed no significant differences, with 8 patients with CSX and 7 controls. Between the first and second sequences, the average value of the 2 measurements was taken as the final corresponding parameters. The FFR in all subjects was ≥0.90 (range, 0.90–0.98), with no differences between CSX and control groups. CFR and DTS were significantly lower in patients with CSX than in control subjects, whereas IMR was significantly higher in the CSX group (Table 2; Figure 1).

Discussion

In the present study, we demonstrated the first direct evidence of CMD in patients with CSX, as represented by the increased IMR and the impaired CFR, both of which were measured invasively using intracoronary thermodilution method. This study also showed that severity of myocardial ischemia in these patients is intimately associated with the abnormal CMR and moderately related to thermodilution-derived CFR.

Coronary microvascular abnormalities have already been suggested to be the underlying pathophysiological mechanism for CSX for >2 decades. This was first elucidated by Chilian et al who reported that coronary arterial resistance occurs because of microvessels with a 100 to 500 μm thickness located within the myocardium rather than the epicardial coronary artery. By right ventricular endomyocardial biopsy, Mosseri et al revealed histological evidence for small-vessel coronary artery disease in patients with angina pectoris and patent large coronary arteries. Several studies reported elevated serum or coronary sinus levels of indirect markers of vascular dysfunction in CSX, indicating impaired coronary microvascular function. Furthermore, by transthoracic Doppler echocardiography, single-photon emission computed tomographic myocardial scintigraphy, myocardial contrast echocardiography, and positron emission tomography, many studies were conducted on the impairment of CFR because of anatomic and functional abnormalities of these microvessels participating in symptomatic and ECG changes in patients with CSX or microvascular angina. More recently, Lanza et al concurrently showed dobutamine-induced myocardial perfusion defects on cardiovascular MR and reduced CFR in the left anterior descending coronary artery territory in patients with CSX, thus providing strong evidence that a dysfunction of coronary microcirculation resulting in myocardial perfusion abnormalities is present in these patients.
Figure 1. Representative cases showing relationship between exercise treadmill test (ETT) results and coronary physiology measurements. Case A: a cardiac syndrome X patient showing positive ETT result and abnormal physiological parameters (fractional flow reserve [FFR], 0.96; coronary flow reserve [CFR], 1.9; and index of microvascular resistance [IMR], 48 U); Case B: a control subject showing negative ETT result and approximately normal physiological parameters (FFR, 0.94; CFR, 2.9; and IMR, 15 U).
However, although all these reports strongly suggested that CMD may be the likely pathophysiological mechanism for CSX, direct evidence demonstrating the abnormal CMR is still lacking. Using recently developed intracoronary thermodilution technique, it is now possible to measure pressure and estimate coronary artery flow simultaneously with a single pressure–temperature sensor-tipped coronary wire, and the status of coronary microcirculation can be directly assessed. De Bruyne et al.20 and Pijls et al.21 have developed and validated a simplified thermodilution model where an index rather than quantitative flow is obtained by registration of the mean transit time of the indicator, disregarding absolute temperature changes. Thereafter, a semiquantitative, unit-less index of microcirculatory resistance (IMR) has been introduced by Fearon et al.9 which demonstrates less intrinsic variability and better reproducibility than CFR.10

Using this intracoronary thermodilution method, the present study was undertaken to document CMR directly in patients with CSX, and for the first time, we demonstrated direct evidence of CMD in patients with CSX, as represented by the increased IMR and the impaired CFR. Our results about CFR are in agreement with previous reports as mentioned above,1–3 by noninvasive techniques, indicating impaired CFR in patients with CSX. Our findings that severity of myocardial ischemia in these patients is related to thermodilution-derived CFR endorse the results of previous clinical studies7,19 that DTS can reflect transthoracic CFR in patients with CSX. IMR measurement may provide a simple, quantitative, intermediately with CFR, also suggesting that IMR may be a more superior and reliable index reflecting coronary microcirculatory function in patients with CSX.

Study Limitations
This is a prospective, observational study designed to demonstrate CMD invasively in patients with CSX. The primary limitation was the comparatively small number of patients, but the diagnostic criteria we adopted were well characterized, including only patients with completely normal coronary angiograms, effort-induced angina pectoris, and positive exercise stress test, which resulted in a relatively low incidence of CSX.22 Second, we did not exclude subjects with traditional cardiovascular risk factors, such as hypertension, diabetes mellitus, hypercholesterolemia, or smoking, which can also influence vascular function and lead to CMD.3,23 However, the patients with CSX were strictly matched to a control group, with no differences between groups in clinical demographics and cardiovascular risk factors, which gives strength to our findings. Third, we did not measure absolute coronary blood flow. Using the thermodilution system, we can only measure flow velocity, which is expressed as the inverse of the mean transit time and has been shown to closely correlate with absolute flow.20,21

Conclusions
Using an intracoronary thermodilution method, we demonstrated the first direct evidence of CMD in patients with CSX, as represented by the increased IMR and the impaired CFR. Furthermore, severity of myocardial ischemia in patients with CSX is intimately associated with abnormal CMR and moderately related to thermodilution-derived CFR, suggesting that IMR may be a more superior and reliable index reflecting coronary microcirculatory function.

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Disclosures
None.

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