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Estimation of Coronary Flow Reserve by Transesophageal Coronary Sinus Doppler Measurements in Patients With Syndrome X and Patients With Significant Left Coronary Artery Disease

MANFRED ZEHETGRUBER, MD, GERALD MUNDIGLER, MD, GÜNTER CHRIST, MD, DEDDO MÖRTL, CM, PETER PROBST, MD, FACC, HELMUT BAUMGARTNER, MD, GERALD MAURER, MD, FACC, PETER SIOSTRZONEK, MD

Vienna, Austria

Objectives. **This study sought to determine the feasibility of coronary sinus flow velocity analysis by transesophageal Doppler echocardiography for estimation of coronary flow reserve in patients with syndrome X and patients with coronary artery disease.**

Background. **Coronary flow reserve provides useful information in patients with coronary artery disease and patients with syndrome X. Current methods of measuring coronary flow reserve are invasive or require extensive laboratory equipment, or both. Transesophageal Doppler recordings of coronary sinus flow velocity before and after vasodilator application may allow noninvasive determination of coronary flow reserve.**

Methods. **We obtained coronary sinus flow velocity recordings before and after dipyridamole administration (0.6 mg/kg body weight per 5 min) in 9 patients with syndrome X, 14 with significant left coronary artery disease and 22 age-matched control patients. We used the formula anterograde minus retrograde flow velocity time integral times heart rate as an index of coronary sinus flow. Coronary flow reserve was calculated by dividing coronary sinus flow variables after dipyridamole administration by the respective baseline values.**

Results. **Technically adequate recordings were obtained in 44 (98%) of 45 patients. Compared with that in the control group (2.78 ± 0.95 [mean ± SD]), coronary flow reserve was significantly lower in patients with syndrome X (1.21 ± 0.23, $p \leq 0.001$) as well as in those with coronary artery disease (1.47 ± 0.7, $p \leq 0.001$). Using a cutoff coronary flow reserve value of 1.8, sensitivity, specificity and overall predictive value of coronary flow reserve determinations were, respectively, 100%, 91% and 94% for syndrome X and 86%, 91% and 89% for coronary artery disease.**

Conclusions. **Coronary flow reserve calculation by transesophageal coronary sinus flow velocity recordings is feasible in a large proportion of patients and might be useful for the noninvasive evaluation of patients with syndrome X and patients with severe left coronary artery disease.**

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Assessment of coronary flow reserve from myocardial blood flow measurements before and after administration of coronary vasodilators has been shown to provide important diagnostic information in a variety of cardiac diseases (1,2). There is particular interest in this variable in patients with syndrome X in whom coronary flow reserve is typically impaired. Unfortunately, methods used for estimation of coronary flow reserve are either invasive, time-consuming or require extensive laboratory staff and equipment (3–7). Therefore, a noninvasive widely available method would be desirable.

We recently proposed the measurement of coronary sinus flow velocity by transesophageal Doppler echocardiography before and after dipyridamole for the assessment of coronary flow reserve in normal subjects and in patients with dilated cardiomyopathy (8). However, the feasibility and diagnostic value of this method in patients with syndrome X and in those with coronary artery disease has not yet been evaluated. Thus, the present study was performed to address the hypothesis that the analysis of coronary sinus flow velocity by transesophageal Doppler echocardiography before and after dipyridamole provides a feasible method for coronary flow reserve estimation in patients with syndrome X and in those with extensive left coronary artery disease.

Methods

Patients. Demographic data of the three study groups are presented in Table 1. All patients had normal transthoracic echocardiographic results without evidence of valvular disease, left ventricular hypertrophy and regional or diffuse wall motion abnormalities.

Group A (syndrome X). Patients meeting the following criteria were considered to have syndrome X (9): 1) history of typical effort angina, promptly relieved at cessation of activity

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Address for correspondence: Dr. Manfred Zehetgruber, Department of Cardiology, University of Vienna, Währinger Gürtel 18-20, Vienna, A-1090, Austria.

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Table 1. Demographic Data for Three Patient Groups

	Patients With Syndrome X (n = 9)	Patients With CAD (n = 14)	Control Patients (n = 22)
Age (yr)	60 ± 8	54 ± 8	53 ± 14
Women/men	5/4	3/11	11/11
LV mass (g)	170 ± 55	214 ± 17	175 ± 51
LV EF (%)	74 ± 8	68 ± 12	74 ± 12
LV EDD (mm)	46.2 ± 6.7	53.2 ± 6.2	50.2 ± 4.3

Data presented are mean ± SD or number of patients. CAD = coronary artery disease; EDD = end-diastolic diameter; EF = ejection fraction; LV = left ventricular.

or sublingual administration of nitroglycerin, or both; 2) normal 12-lead rest electrocardiographic (ECG) findings; 3) positive symptom-limited supine bicycle ergometric stress test results, with transient horizontal or downsloping ST segment depression ≥0.1 mV 0.08 s after the J point, with occurrence of typical angina was defined as a positive result; and 4) normal coronary angiographic findings and a negative response to ergonovine administration. Multiple views of the left and right coronary artery were reevaluated independently by two experienced observers. Absence of coronary artery stenosis as well as wall irregularities was unequivocally reconfirmed in all patients. Furthermore, patients with a history of smoking, hypertension or hypercholesterolemia were excluded. Overall, nine patients fulfilled the inclusion criteria. Mean achieved work load in these nine patients was (mean ± SD) 112.5 ± 23W (63.5 ± 24% of the predicted gender-, age- and body surface area–corrected physical working capacity). ST segment depression (0.1 mV in seven and 0.2 mV in two patients) occurred at a mean work load of 87.5 ± 29.8 W (49.6 ± 22% of the corrected working capacity). Two patients were receiving beta-adrenergic blocking agents, three calcium antagonists and two long-acting nitrates; two patients had no antianginal treatment.

Group B (coronary artery disease). Group B comprised 14 consecutive patients with significant (>70%) stenosis of the left coronary artery. Patients with left main coronary artery stenosis and unstable angina, with occlusion of a major coronary vessel, or patients with an extensive myocardial infarction were excluded. According to severity and location of the lesion, patients were classified into two subgroups: group B1 included patients with severe (>90%) stenosis of the left anterior descending artery proximal to the first septal branch (n = 7) with or without additional lesions of the left anterior descending coronary artery or of the left circumflex coronary artery. Group B2 included patients with less severe (70% to 90%) or more distal stenosis, or both, of the left anterior descending coronary artery or left circumflex coronary artery (n = 7). Using the modified Gensini index (10) for estimating severity and extent of coronary artery disease, group B1 had a significantly higher index than group B2 (127.8 ± 33 vs. 54.7 ± 13, $p < 0.0001$). Overall, five patients had a history of previous myocardial infarction (Q wave infarction in three, non Q wave infarction in two). Four patients had intravenous thrombolysis. Coronary angiography revealed patency of the infarct-related vessel in all cases. Antianginal medication included nitrates in 11 patients, beta-blockers in 9 and calcium antagonists in 3.

Group C (control patients). Twenty-two age- and gender-matched neurosurgical patients with intended posterior cranial fossa surgery and no cardiac disease formed the control group. These patients were preoperatively referred for transesophageal echocardiography to exclude patency of the foramen ovale. All patients were free of cardiac symptoms, had a normal 12-lead rest ECG as well as normal echocardiographic findings. Moreover, patients with cardiovascular risk factors were excluded.

Echocardiography. The study protocol was in accordance to the guidelines of the local human subjects committee. Informed consent was obtained from all patients. In patients with syndrome X, all antiangial medication was withheld for >24 hours before the examination. In patients with severe symptomatic coronary artery disease, antianginal medication was interrupted on the day of the study only.

The study was performed with a Vingmed 800 system (Diasonics) using a 3.25-MHz transthoracic and a single-plane 5-MHz transesophageal probe. Transthoracic echocardiography comprised all standard views, including a parasternal M-mode study of the left ventricle. Measurements of left ventricular dimensions, function and mass were performed according to standard criteria (11,12). Transesophageal echocardiography was performed without sedation using topical anesthesia to the oropharynx. Continuous ECG recording was performed, and arterial blood pressure was measured noninvasively at baseline and after dipyridamole administration.

Recording of coronary sinus flow velocity. A modified four-chamber view with dorsal angulation of the transducer was used to visualize the ostium of the coronary sinus. The position of the probe was optimized until the coronary sinus with its ostium into the right atrium could be visualized throughout the cardiac cycle. Coronary sinus flow velocity recordings were performed with the Doppler sample volume placed in the coronary sinus within a distance of no more than 10 mm from its ostium (Fig. 1). In all patients the angle between the Doppler beam and the long axis of the coronary sinus was <30°. Flow signals were recorded during prolonged expiration and were repeated until constant flow signals of acceptable quality were obtained. Maximal coronary sinus diameter was measured at baseline and after dipyridamole.

After baseline recordings, the transducer was maintained in the identical position. Dipyridamole was administered intravenously at a constant infusion rate of 0.6 mg/kg body weight per 5 min (13). Two minutes after cessation of dipyridamole infusion, coronary sinus flow velocity recordings were repeated. In case of anginal pain occurring during dipyridamole infusion, a bolus of aminophylline (0.12 to 0.24 g) was administered intravenously.

Coronary sinus flow velocity analysis and assessment of coronary flow reserve. Videotape recordings of three cardiac cycles with optimal examination quality before and after

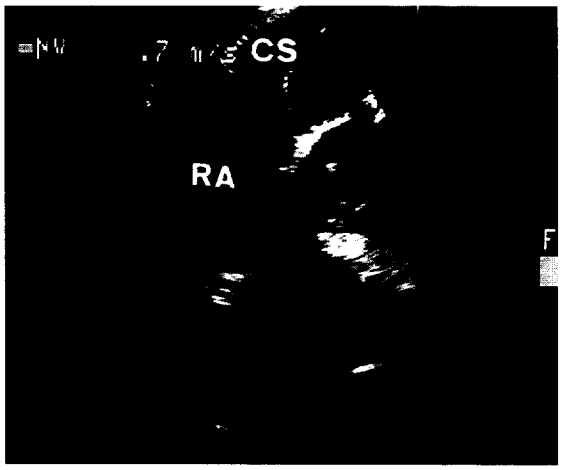

Figure 1. Modified transesophageal four-chamber view visualizing the coronary sinus (CS) draining into the right atrium (RA) with the Doppler sample volume placed in the position used for measurements.

dipyridamole were analyzed. Measurements included maximal systolic and diastolic anterograde flow velocity, maximal retrograde flow velocity and respective flow velocity time integrals. Net forward flow velocity time integral (VTInet) was calculated by subtracting the retrograde from the anterograde flow velocity time integral, and VTInet × Heart rate was calculated as index of coronary sinus forward flow. Coronary flow reserve was defined as (VTInet × Heart rate) dipyridamole/(VTInet × Heart rate) baseline. On the basis of previously defined cutoff value, a coronary flow reserve >1.8 was considered normal (8). Coronary flow reserve was additionally calculated from the anterograde flow velocity time integral and maximal anterograde flow velocitity, using the respective dipyridamole/rest ratios.

Statistical analysis. Data are expressed as mean value ± SD. To compare data of various patient groups, analysis of variance with a subsequent Scheffé *F* test for multiple comparisons was performed. Analysis of variance for repeated measures was used to compare data before and after dipyridamole infusion. Statistical significance was considered at $p < 0.05$. The coronary flow reserve cutoff value of 1.8 was tested for sensitivity and specificity in patients with syndrome X and those with coronary artery disease.

Results

Clinical and hemodynamic data before and after dipyridamole infusion. Hemodynamic data before and after dipyridamole administration are presented in Table 2. Dipyridamole provoked chest pain in 4 of 9 patients with syndrome X and 3 of 14 patients with coronary artery disease. In one patient with syndrome X and two with coronary artery disease, aminophylline had to be administered for prompt relief of symptoms.

Coronary sinus Doppler measurements before and after dipyridamole. Overall, adequate coronary sinus flow velocity tracings could be obtained in 44 (97.7%) of 45 consecutive patients. Alignment of the Doppler beam and coronary sinus long axis could not be achieved in one control patient. An example of a coronary sinus Doppler recording is shown in Figure 2. Typically, a biphasic anterograde flow pattern and short mid- or end-diastolic periods of retrograde flow, or both, were observed. An example of a marked flow velocity increase after dipyridamole infusion in a healthy control patient is presented in Figure 3. By contrast, Figure 4 shows only a minor change in the coronary sinus flow velocity pattern in a patient with syndrome X.

Table 3 presents various Doppler variables in the three patient groups at rest and after dipyridamole infusion. After dipyridamole infusion, variables of coronary sinus forward flow increased in most patients. However, changes from baseline markedly differed in the three patient groups: Increase in anterograde flow variables was significantly lower in patients with syndrome X and those with coronary artery disease compared with control patients. Retrograde flow variables as well as coronary sinus diameter remained unchanged in all patient groups after dipyridamole administration.

Coronary flow reserve. Coronary flow reserve as calculated from net forward flow velocity time integral measurements before and after dipyidamole was 1.21 ± 0.23 in patients with syndrome X and 1.47 ± 0.7 in those with coronary artery disease (Fig. 5). This was significantly lower than the coronary flow reserve of 2.78 ± 0.95 found in the control group ($p < 0.001$ for both patient groups). Coronary flow reserve tended to be lower in patients with more severe coronary artery disease (group B1) than in group B2 with less severe disease (1.43 ± 0.26 vs. 1.76 ± 0.94, p = NS).

Table 2. Hemodynamic Data Before and After Dipyridamole Administration for the Three Patient Groups

	Patients With Syndrome X		Patients With CAD		Control Patients	
	Rest	DPM	Rest	DPM	Rest	DPM
HR (beats/min)	91 ± 15	96 ± 16	74 ± 18*	87 ± 19†	81 ± 13	97 ± 17†
Blood pressure (mm Hg)						
Systolic	147 ± 13	153 ± 20	155 ± 23	148 ± 23	147 ± 2	142 ± 22‡
Diastolic	83 ± 10	87 ± 8	82 ± 9	81 ± 10	83 ± 13	79 ± 11‡
Mean	104 ± 10	109 ± 11	106 ± 12	103 ± 13	104 ± 15	100 ± 13§

*$p \leq 0.05$, syndrome X versus coronary artery disease (CAD). †$p \leq 0.001$, ‡$p \leq 0.05$, §$p < 0.005$, rest versus dipyridamole (DPM). Data presented are mean value ± SD. HR = heart rate.

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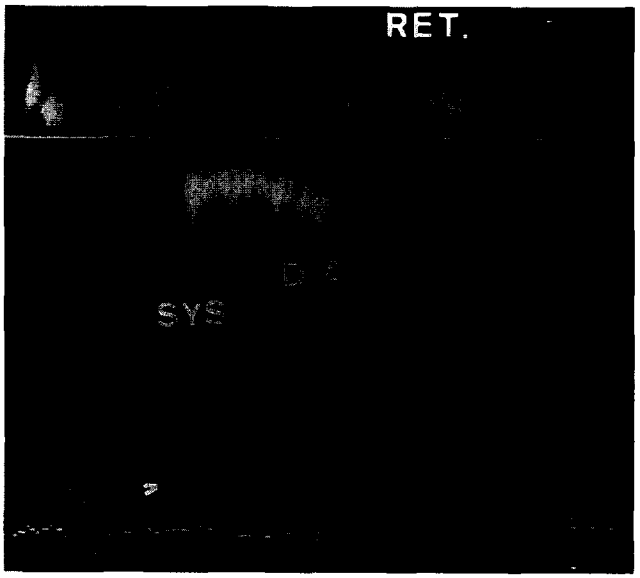

Figure 2. Transesophageal Doppler flow velocity tracing of coronary sinus flow, characterized by biphasic systolic (SYS.) and diastolic (DIA.) anterograde flow and a short period of end-diastolic retrograde (RET.) flow. ECG = electrocardiogram.

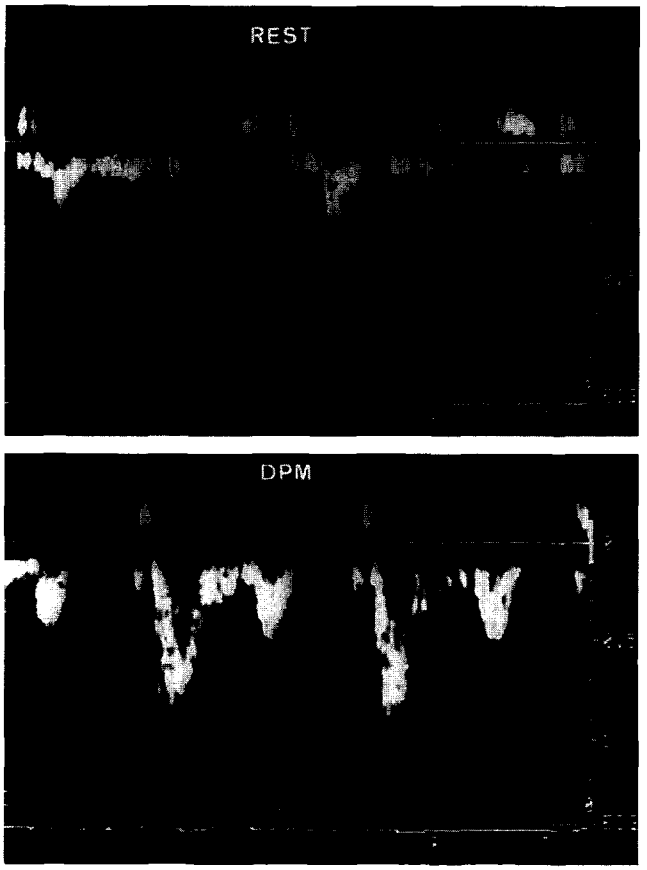

Figure 3. Coronary sinus flow velocity recording in a control patient with normal coronary flow reserve. After dipyridamole (DPM) administration, a marked increase in flow velocity occurs. ECG = electrocardiogram.

The predefined coronary flow reserve value of 1.8 allowed excellent differentiation of patients with syndrome X and with significant coronary artery disease from control patients (Table 4). All patients with syndrome X had a coronary flow reserve <1.8 (sensitivity 100%), whereas 20 of 22 patients without cardiac disease were found to have a flow reserve >1.8 (specificity 91%). In patients with coronary artery disease, 12 of 14 presented with a coronary flow reserve <1.8 (sensitivity 86%). Coronary flow reserve was <1.8 in seven of seven patients in group B1 and five of seven patients in group B2. Coronary flow reserve was 1.35 ± 0.24 in patients with chest pain after dipyridamole infusion (four with syndrome X and three with coronary artery disease) and was 1.52 ± 0.68 in asymptomatic patients in groups A and B (p = NS).

Using the anterograde flow velocity time integral for coronary flow reserve calculation, coronary flow reserve was 2.28 ± 0.74 in control patients, 1.23 ± 0.22 in patients with syndrome X ($p < 0.001$ vs. control patients), and 1.40 ± 0.66 in patients with coronary artery disease ($p < 0.001$ vs. control patients), yielding a sensitivity and specificity of 100% and 77% and 91% and 77% in patients with syndrome X and those with coronary artery disease, respectively. Using the maximal anterograde flow velocity, coronary flow reserve was 1.82 ± 0.76 in control patients, 1.17 ± 0.20 in syndrome X ($p < 0.001$ vs. control patients) and 1.35 ± 0.25 in those with coronary artery disease, yielding a sensitivity of 100% in patients with syndrome X and those with coronary artery disease at a lower specificity of 50%.

Discussion

Transesophageal Doppler recordings of coronary sinus flow velocity before and after dipyridamole administration may offer noninvasive assessment of coronary flow reserve. Initial results demonstrated the feasibility and reproducibility of this method in a large proportion of patients (8). The present study extends these preliminary findings by evaluating the diagnostic accuracy of the method in patients with syndrome X and those with significant left coronary artery disease.

Various coronary sinus Doppler variables were evaluated for calculation of coronary flow reserve: Among the variables tested, net forward flow velocity time integral (i.e., anterograde–retrograde flow velocity time integral) times heart rate may best represent coronary sinus forward flow per time unit. However, the retrograde Doppler signal may not only represent left coronary artery drainage but also may result from reflux of right atrial blood into the compliant coronary sinus due to increasing right atrial pressure during the cardiac cycle (14). Accordingly, in the present study retrograde flow variables remained unchanged after dipyridamole administration. Assessment of coronary flow reserve by less complex anterograde flow variables, such as the anterograde flow velocity time integral or the maximal anterograde flow velocity, also enabled classification of different patient groups, but diagnostic accuracy was lower.

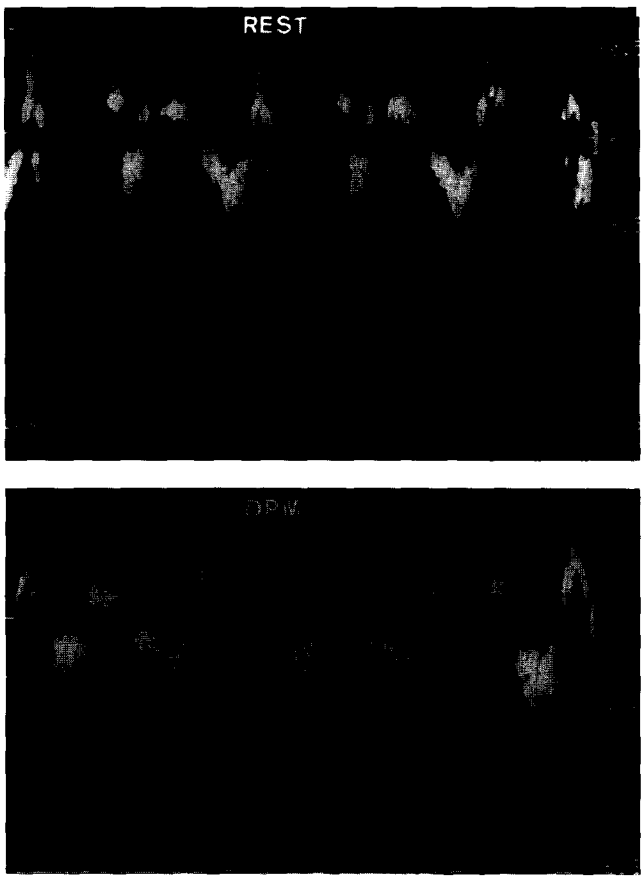

Figure 4. Coronary sinus flow velocity recording in a patient with syndrome X. Flow velocity is not significantly altered by dipyridamole (DPM) administration. ECG = electrocardiogram.

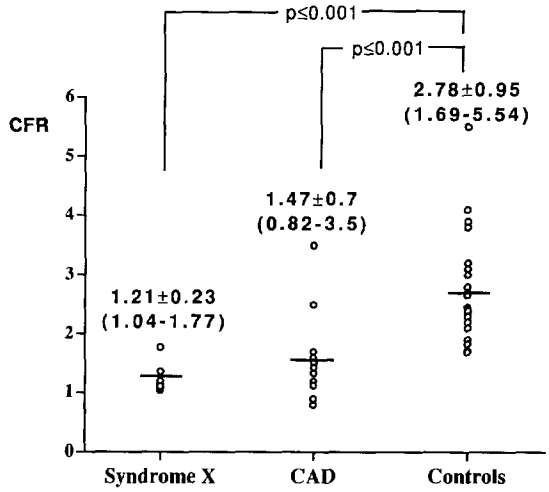

Figure 5. Coronary flow reserve (CFR) in control patients and those with syndrome X and coronary artery disease (CAD).

Determination of coronary flow reserve in syndrome X. A reduced coronary flow reserve in patients with typical angina and a normal coronary angiogram constitutes an essential clue for the diagnosis of syndrome X (15,16). Previous studies using the coronary sinus thermodilution technique reported mean coronary flow reserve values of 1.5 (range 1.2 to 2.1) in patients with syndrome X and 2.4 (range 2.0 to 2.9) in control patients (17–21). Slightly higher values were achieved using positron emission tomography (22,23) or intracoronary Doppler catheters (4,13). Transesophageal Doppler recordings of proximal left anterior descending coronary artery flow velocity may also be applied for assessment of coronary flow reserve, but as a result of cardiac motion and the small diameter of the vessel examined, adequate flow signals could be achieved by this method in only 70% of patients (24).

In the present study, transesophageal coronary sinus Doppler recordings enabled assessment of coronary flow reserve in >90% of patients. Patients with syndrome X were found to

Table 3. Doppler Echocardiographic Data Before and After Dipyridamole Administration for the Three Patient Groups

	Patients With Syndrome X		Patients With CAD		Control Patients	
	Rest	DPM	Rest	DPM	Rest	DPM
Max flow velocity (cm/s)						
Systolic	44 ± 21	55 ± 24*	32 ± 15	52 ± 31*	38 ± 19	66 ± 27†
Diastolic	42 ± 17	48 ± 16	39 ± 16	40 ± 14‡	30 ± 9	53 ± 17§
Retrograde	31 ± 15	31 ± 14	21 ± 13	23 ± 15	23 ± 10	25 ± 15
Flow VTI						
Systolic	54 ± 29	68 ± 31	48 ± 23	65 ± 49	48 ± 24	93 ± 47§
Diastolic	75 ± 35	83 ± 42	69 ± 29	78 ± 31	52 ± 23	87 ± 32§
Retrograde	31 ± 20	34 ± 21	29 ± 21	25 ± 23	27 ± 19	33 ± 31
Anterograde	135 ± 19‖	157 ± 35	116 ± 27	144 ± 77	100 ± 32	187 ± 51§
Net	104 ± 26‖	123 ± 40	87 ± 28	118 ± 82	73 ± 26	154 ± 45§
Net VTI × HR	975 ± 298¶	1,175 ± 392*	629 ± 209#	1,001 ± 623*	581 ± 210	1,483 ± 416§
CSdiam (mm)	9 ± 3	9 ± 4	10 ± 2	11 ± 4	9 ± 3	9 ± 2

*$p \leq 0.05$, †$p < 0.01$, §$p \leq 0.001$, rest versus dipyridamole (DPM) administration. ‡$p \leq 0.05$, control patients versus those with coronary artery disease (CAD). ‖$p \leq 0.05$, ¶$p < 0.001$, control patients versus those with syndrome X. #$p \leq 0.005$, patients with syndrome X versus those with coronary artery disease. Data presented are mean value ± SD. CSdiam = coronary sinus diameter; HR = heart rate; Max = maximal; VTI = flow velocity time integral.

Table 4. Sensitivity and Specificity of Coronary Flow Reserve Determinations

Variable	Syndrome X	CAD
Sensitivity	9/9 (100%)	12/14 (86%)
Specificity	20/22 (91%)	20/22 (91%)
PPV	9/11 (82%)	12/14 (86%)
NPV	20/20 (100%)	20/22 (91%)
OPV	29/31 (94%)	32/36 (89%)

Data presented are number of patients (sensitivity). Results are calculated for a cutoff coronary flow reserve of 1.8. CAD = coronary artery disease; NPV (OPV, PPV) = negative (overall, positive) predictive value.

have a significantly reduced coronary flow reserve compared with that in the control group (1.21 ± 0.23 vs. 2.78 ± 0.95, $p < 0.001$) (Fig. 5). Applying a previously defined cutoff value for a normal coronary flow reserve >1.8 (8), all patients with syndrome X had a reduced coronary flow reserve. Conversely, coronary flow reserve was >1.8 in 20 of 22 control patients.

Determination of coronary flow reserve in coronary artery disease. In the present group of patients with significant left coronary artery disease, coronary flow reserve was significantly attenuated compared with that in the control group (1.47 ± 0.7 vs. 2.78 ± 0.95, $p \leq 0.001$). However, coronary flow reserve ranged considerably from 0.82 to 3.5, which may be explained by the variable degrees of stenoses as well as by the inability of coronary angiography to adequately assess the physiologic severity of stenosis (25–27). In addition, coronary sinus flow results from drainage of both the left anterior and circumflex coronary artery territory. Therefore, coronary flow reserve calculation based on coronary sinus flow constitutes the average flow reserve of the left coronary system. Presence of an isolated or more distal stenosis within the left coronary artery may therefore have only a limited effect on coronary flow reserve calculation based on coronary sinus flow (28). Nevertheless, 12 of 14 patients with coronary artery disease had a coronary flow reserve <1.8. Moreover, all patients with severe proximal stenosis of the left anterior descending coronary artery had a reduced coronary flow reserve <1.8; only two patients with less severe stenosis had a coronary flow reserve >1.8.

Study limitations. Although transesophageal echocardiography is generally considered a noninvasive technique, it is associated with minimal discomfort and risk to the patient (29). Hyperkinetic cardiac motion, malalignment of the ultrasound beam with the coronary sinus long axis or a patient's inability to hold their breath may eventually prevent adequate Doppler recordings.

Regional coronary flow reserve cannot be determined by transesophageal coronary sinus flow velocity recordings. Therefore, this method may be insensitive for the detection of distal or side branch stenoses and will not provide information about the location of a stenosis. Because of the physiology of coronary venous drainage, coronary flow reserve calculations are limited to the territory of the left coronary artery. These limitations are shared by other techniques using coronary sinus flow measurements for the calculation of coronary flow reserve. However, in cardiac disease with diffuse reduction of coronary flow reserve, evaluation of global flow reserve by coronary sinus techniques may be even more appropriate.

Quantitative flow measurements cannot be achieved by Doppler techniques without the additional measurement of the cross-sectional area of the interrogated vessel. We did not incorporate coronary sinus diameter measurements into the present method because the diameter of the coronary sinus may change considerably throughout the cardiac cycle. Therefore, coronary flow reserve was derived from the comparison of flow velocity recordings before and after dipyridamole administration, which is based on the presence of a constant diameter of the coronary sinus during vasodilator application. To minimize potential errors resulting from different angulations between the ultrasound beam and the coronary sinus, the transducer probe was kept in identical position throughout the study period. Nevertheless, adherence to a strict examination protocol as well as a learning curve experience are required to obtain reproducible results.

The present control group was formed by otherwise healthy neurosurgical patients in whom preoperative transesophageal echocardiography was indicated to exclude the presence of a patent foramen ovale. These patients had normal ECG and echocardiographic findings, and major cardiovascular risk factors were absent. However, coronary angiography was not performed in this group because it was not considered appropriate in patients without cardiac symptoms.

Clinical implications. Evaluation of coronary sinus flow velocity by transesophageal Doppler echocardiography before and after dipyridamole administration appears to be a feasible method for assessment of coronary flow reserve. Although the transesophageal examination presents some discomfort to the patient and is associated with a minimal risk, it is less invasive, less time-consuming, and less expensive and requires less laboratory equipment and personnel than most previously used techniques. It can be performed on an ambulatory basis within reasonable time using routine echocardiographic equipment and can be applied in the majority of patients.

The results of the present study suggest that evaluation of coronary sinus flow velocity by transesophageal Doppler echocardiography can be used to identify patients with syndrome X with high sensitivity once coronary artery disease has been excluded.

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