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Variations in Normal Coronary Vasodilatory Reserve Stratified by Artery, Gender, Heart Transplantation and Coronary Artery Disease

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Objectives. **The purpose of the study was to assess the spectrum of coronary vasodilatory reserve values in patients with angiographically normal arteries who had atypical chest pain syndromes or remote coronary artery disease or were heart transplant recipients.**

Background. **The measurement of post-stenotic coronary vasodilatory reserve, now possible in a large number of patients in the cardiac catheterization laboratory, is increasingly used for decision making. Controversy exists regarding the range of normal values obtained in angiographically normal coronary arteries in patients with different clinical presentations.**

Methods. **Quantitative coronary arteriography was performed in 214 patients classified into three groups: 85 patients with chest pain syndromes and angiographically normal arteries (group 1); 21 patients with one normal vessel and at least one vessel with >50% diameter lumen narrowing (group 2); and 108 heart transplant recipients (group 3). Coronary vasodilatory reserve (the ratio of maximal to basal average coronary flow velocity) was measured in 416 arteries using a 0.018-in. (0.04 cm) Doppler-tipped angioplasty guide wire. Intracoronary adenosine (8 to 18 μg) was used to produce maximal hyperemia.**

Results. **Coronary vasodilatory reserve was higher in angiographically normal arteries in patients with chest pain syndromes (group 1: 2.80 ± 0.6 [group mean ± SD]) than in normal vessels in patients with remote coronary artery disease (group 2: 2.5 ± 0.95, p = 0.04); both values were significantly higher than those in the post-stenotic segment of the diseased artery (1.8 ± 0.6, p < 0.007). Coronary vasodilatory reserve in transplant recipients (group 3) was higher than that in the other groups (3.1 ± 0.9, p < 0.05 vs. groups 1 and 2) as a group and for individual arteries. When stratified by vessel, coronary vasodilatory reserve was similar among the left anterior descending, left circumflex and right coronary arteries. There were no differences between coronary vasodilatory reserve values on the basis of gender for patients with coronary artery disease and transplant recipients. In group 1 (chest pain), there was a trend toward higher coronary vasodilatory reserve in men than in women (2.9 ± 0.6 vs 2.7 ± 0.6, p = 0.07).**

Conclusions. **These findings identify a normal reference range for studies assessing the coronary circulation and post-stenotic coronary vasodilatory reserve in patients with and without coronary artery disease encountered in the cardiac catheterization laboratory.**

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The normal range of coronary vasodilatory reserve measured in the catheterization laboratory in awake patients remains controversial because variation can be observed, depending on the technique of measurement, clinical features, myocardial function and extracardiac factors. Studies in experimental animals and in patients using a variety of blood flow measuring techniques (1–6) have indicated that normal coronary blood flow or flow velocity reserve should exceed 3.5 × basal flow values. However, lower vasodilatory coronary reserve values observed using a Doppler-tipped guide wire have been reported by our and other cardiac catheterization laboratories (7–10), especially in patients with atypical chest pain and angiographically normal coronary arteries (10). The technique of intracoronary flow velocity measurement has been simplified by use of a Doppler-tipped angioplasty guide wire and spectral analysis (11–14). This method permits rapid, reproducible measurements in multiple coronary arteries and within arterial locations more distal than previously studied using larger 3F Doppler-tipped catheters. Because coronary vasodilatory reserve measurements are being increasingly used for clinical decision making (1,12,14,15), establishment of the range of coronary vasodilatory reserve values expected in angiographically normal vessels would be helpful for interpretation of coronary flow responses in various clinical circumstances. Thus, the purpose of this study was to determine coronary vasodilatory reserve values encountered in a large number of patients with angiographically normal arteries during cardiac catheterization for chest pain syndromes and during annual surveillance of heart transplant recipients.

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Abbreviations and Acronyms
ECG = electrocardiogram, electrocardiographic
PET = positron emission tomographic

The hypotheses tested were that 1) variability in coronary vasodilatory reserve would be minimal among patients with angiographically normal arteries so studied, and that 2) coronary vasodilatory reserve would fall within the normal range in angiographically nondiseased arteries in patients with obstructive coronary artery disease in another vessel. We further questioned whether coronary vasodilatory reserve in cardiac allograft arteries would also be in the normal range in the absence of clinical allograft rejection. These findings would provide a reference range for studies assessing the coronary circulation using a Doppler guide wire in a variety of patients typically encountered in the cardiac catheterization laboratory.

Methods

Patient groups. All patients undergoing routine diagnostic angiography were considered eligible for the study. Two hundred fourteen patients were prospectively enrolled to enable study of coronary vasodilatory reserve responses. A total of 416 arteries were studied. Eighty-five patients (group 1) underwent diagnostic coronary angiography for chest pain syndromes and were found to have angiographically normal coronary arteries and normal left ventricular function. One hundred fourteen arteries were studied. Twenty-one patients (group 2) had coronary artery disease (≥50% lumen diameter narrowing) in at least one vessel with coronary vasodilatory reserve measured in both the post-stenotic region of the obstructed artery and in an angiographically normal adjacent vessel (42 vessels in total). These patients were not excluded on the basis of previous myocardial infarction in the territory of the diseased vessel, but had no myocardial contractile abnormalities in the territory subtended by the angiographically normal vessel. One hundred eight patients (group 3) underwent diagnostic cardiac catheterization as part of their annual surveillance after heart transplantation. Two hundred sixty arteries were studied. Patients were clinically excluded for recent acute myocardial infarction, unstable angina, valvular disease, severe congestive heart failure or renal insufficiency. Angiographic exclusions were >20% lumen diameter narrowing in the target epicardial vessel (except in the diseased vessel in group 2), histologic evidence of acute allograft rejection (16) or unsuitable anatomy or guide catheter engagement.

Informed consent for the determination of coronary vasodilatory reserve was approved by the Institutional Review Board and obtained in writing before the procedure. All medications were continued as clinically indicated. All patients received diazepam (2 mg intravenously), diphenhydramine (25 mg intravenously) and sublingual (0.4 mg) or intracoronary (200 μg) nitroglycerin before coronary angiography and had uncomplicated diagnostic catheterization studies performed from the femoral arterial approach using preformed Judkins-shaped 6F or 8F angiographic catheters.

Flow velocity measurements. Coronary flow velocity measurements were obtained ~10 min after the administration of sublingual or intracoronary nitroglycerin after routine diagnostic angiography. All patients received a 5,000- to 10,000-U bolus of intravenous heparin. A 0.018-in. (0.04 cm) Doppler-tipped angioplasty guide wire (FloWire, Cardiometrics, Inc.) was inserted through a standard angioplasty-type Y-connector attached to the angiographic catheter and advanced to the proximal portion of the study vessel. After satisfactory baseline flow velocity signals were obtained, hyperemic flow velocity data were continuously acquired after intracoronary adenosine (12 μg for the right and 18 μg for the left main coronary artery) through the guiding catheter, as previously reported (17,18). Intracoronary adenosine at the doses given uniformly produces maximal hyperemia within 25 to 40 s (17).

Quantitative angiography. Quantitative angiography of the normal vessel diameter at the site of the flow velocity measurements was performed using the automated Philips DCI-ACA system. When the automated analysis was unavailable, computer-assisted hand planimetry using digitized calipers was performed. The vessel cross-sectional area was calculated assuming a circular geometry using the following formula: $\pi(d/2)^2$, d = diameter. For angiographically normal reference vessel caliber in our laboratory, the intraobserver differences for quantitative coronary angiography and caliper measurements were (mean ± SD) 0.21 ± 0.19 mm (6.8 ± 6.9%) and 0.25 ± 0.25 mm (7.3 ± 6.9%), respectively.

Flow velocity data analysis. The coronary flow velocity Doppler spectral envelope was automatically identified by the commercially available software within the signal analyzer. Spectral peak velocity waveforms from two cardiac cycles were averaged to yield the average peak velocity. The peak velocity integral was computed as the area under the curve defined by the combined systolic and diastolic velocity spectra. Previous validation by manual planimetry in our laboratory (19) demonstrated that the automatic computation of the flow velocity indexes were accurate and reproducible when the spectral signal envelope was satisfactorily maintained. Satisfactory flow velocity signals were analyzable in 95% of patients with angiographically normal coronary arteries.

Coronary vasodilatory reserve was calculated as the ratio of maximal hyperemic to basal average peak velocity. In 50 patients in group 1, coronary flow velocity was corrected for vessel dimensions computing volumetric flow as quantitative coronary angiographic area at rest times average velocity. Measurements were performed in duplicate in 20 normal patients with an average variation of 15 ± 9%. Variation between duplicate basal average peak velocity was 14 ± 10%.

Hemodynamic data. Heart rate was measured from the electrocardiogram (ECG), and arterial blood pressure was measured through the angiographic guiding catheter using fluid-filled transducers (Merit Medical, Inc.). The calibrated

Table 1. Clinical Characteristics

	Angiographically Normal Group (n = 85)	Coronary Artery Disease Group (n = 21)	Transplant Recipients (n = 108)
Age (yr)			
Mean ± SD	54 ± 13	57 ± 13	49 ± 12
Range	26–83	30–78	19–69
Male	43 (51)	12 (57)	86 (80)
Hypertension	45 (53)	9 (43)	46 (43)
Diabetes mellitus	4 (5)*	6 (29)*	14 (13)
Cholesterol	26 (31)	11 (52)	29 (27)
Smoke			
Current	21 (25)†‡	7 (33)†	4 (4)‡
Previous	7 (8)	6 (29)	14 (13)
Myocardial infarction	0 (0)	9 (43)	2 (2)
Coronary angioplasty	0 (0)	9 (43)	1 (1)

*p = 0.0008. †p = 0.0258. ‡p = 0.0001. Data present are number (%) of patients, unless otherwise indicated.

physiologic signals were simultaneously input to the flow velocimeter.

Statistical analysis. Analysis of variance was used with the Scheffé test for multiple comparisons of group mean values. Comparison from baseline to hyperemic conditions for each individual artery or between two specific subsets was performed with the Student paired *t* test. Comparison between groups for individual arteries was performed with the Student nonpaired *t* test. Categoric variables were compared using chi-square analysis. A p value < 0.05 was considered statistically significant. Results are presented as mean value ± SD.

Results

Clinical findings. Clinical characteristics of the 214 study patients are shown in Table 1. A majority (80% [86 of 108]) of the transplant recipients were male compared with a nearly even gender distribution in the normal and coronary artery disease groups. There were similar ranges in age and prevalence of hypertension and hypercholesterolemia. More patients with coronary artery disease (group 2) had diabetes than in the normal group (group 1), and there was a higher percentage of cigarette smokers in group 1 than in groups 2 or 3. Mean time after transplantation (group 3) was 3.0 ± 2.6 years (range 1 to 9).

Coronary vasodilatory reserve by artery. Coronary vasodilatory reserve by artery (Table 2) for the normal group overall was 2.8 ± 0.6 and, for individual arteries, 2.88 ± 0.6 for the right, 2.81 ± 0.6 for the left anterior descending and 2.68 ± 0.5 for the left circumflex coronary arteries. The relation between left coronary artery branches (left anterior descending and left circumflex) was variable in this group (n = 15, r = 0.1, p = 0.345, SEE = 0.14, 95% confidence limits [CL] 2.65 and 2.89).

In patients with coronary artery disease (group 2), the normal vessel coronary vasodilatory reserves were lower than those in the same branch in group 1 (Table 2). There were no right to left coronary artery comparisons for group 2.

Coronary vasodilatory reserve by transplant status. In the transplant recipients, all arteries had significantly higher mean coronary vasodilatory reserves than the angiographically normal arteries in the other patient groups. Coronary vasodilatory reserve for the group was 3.1 ± 0.01 and, in individual arteries, 3.3 ± 0.9, 3.1 ± 0.9 and 3.0 ± 0.1 for the right, left anterior descending and circumflex coronary arteries, respectively. There was no difference among arteries in transplant recipients, where the left anterior descending and circumflex coronary vasodilatory reserves were related (n = 7, r = 0.66, p = 0.0001, SE 0.09, 95% CL 2.92 and 3.25). There were no statistically significant differences for absolute basal flow velocity values among the vessels within transplant recipients or compared with the other groups (Table 3). The distribution frequency of coronary vasodilatory reserve values for normal patients (group 1) and transplant recipients (group 3) is shown in Figure 1.

Coronary vasodilatory reserve and clinical variables. For all groups, there was no correlation between age and coronary vasodilatory reserve (Fig. 2). In group 2 patients with diabetes mellitus, there was a trend toward lower coronary vasodilatory reserves (Table 4). This effect was not observed in group 1 or in the transplant recipients. Cholesterol levels and tobacco use did not influence the coronary vasodilatory reserve in any group. Hypertension did not lower the coronary vasodilatory reserve in any group and paradoxically was associated with a

Table 2. Coronary Vasodilatory Reserve Data

	Coronary Vasodilatory Reserve					
	LAD		LCx		RCA	
Group	No. of Vessels	Mean ± SD (range)	No. of Vessels	Mean ± SD (range)	No. of Vessels	Mean ± SD (range)
Angiographically normal	60	2.81 ± 0.6 (1.87–4.74)*	27	2.68 ± 0.5 (1.65–3.58)*	27	2.88 ± 0.6 (2.18–4.56)
CAD						
Normal vessel	7	2.66 ± 1.2 (1.8–5.2)*	13	2.34 ± 0.8 (1.8–5.2)*	1	3.4
Abnormal vessel	15	1.77 ± 0.7 (1.0–3.3)†	5	1.78 ± 0.3 (1.5–2.1)†	1	2.1
Transplant recipients	104	3.1 ± 0.9 (1.6–5.8)‡	83	3.0 ± 0.9 (1.8–6.9)‡	73	3.3 ± 0.9 (1.7–5.9)‡

*p < 0.05 versus angiographically normal group. †p < 0.05 versus normal vessel. ‡p < 0.05 versus other groups. CAD = coronary artery disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery.

Table 3. Average Peak Velocity Data

Group	Average Peak Velocity (cm/s)					
	LAD		LCx		RCA	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
Angiographically normal						
Rest	21.6 ± 7.8	9.5–49.1	18.9 ± 6.6	9.2–36.7	18.1 ± 5.2	9.6–26.5
Hyperemia*	58.2 ± 16.3	29–99.4	48.7 ± 13.3	28–84.2	51.3 ± 14.7	24.0–86.1
CAD						
Normal vessel						
Rest	40.6 ± 22.1	16.2–82.1	28.8 ± 12.5	8.8–57.1	—	—
Hyperemia*	94.8 ± 33.7	63.3–150.0	59.5 ± 16.1	35.0–92.3	—	—
Abnormal vessel						
Rest	25.4 ± 9.8	10.6–42.8	18.8 ± 7.6	8.4–26.9	—	—
Hyperemia*	44.2 ± 23.9	13–109	31.6 ± 12.8	17.7–48.2	—	—
Transplant recipients						
Rest	22.0 ± 8.3	9.8–53.2	18.7 ± 7.5	6.8–51.4	16.1 ± 5.9	6.3–40.3
Hyperemia*	63.3 ± 18.8	21.4–119.0	53.8 ± 16.6	23.8–113.0	50.2 ± 16.0	13.8–88.0

*$p < 0.01$ versus rest. — = not measured; abbreviations as in Table 2.

slightly higher coronary vasodilatory reserve in the transplant group. There was no correlation between heart rate, mean arterial pressure or rate-pressure product and coronary vasodilatory reserve in any of the patient groups.

There were 12 patients with a coronary vasodilatory reserve <2.0 (2 in group 1, 10 in group 3). These patient subsets could not be differentiated after stratification of coronary vasodilatory reserve by clinical data on stress testing or by left ventricular hypertrophy using ECG or echocardiographic criteria. Table 5 shows comparisons of functional testing and symptomatic presentation versus coronary vasodilatory reserve.

Coronary vasodilatory reserve by gender. When men and women were compared, there was a trend toward a lower coronary vasodilatory reserve among women in group 1 (2.91 ± 0.58 vs. 2.7 ± 0.58, p = 0.068) but not in group 2 (normal vessels) (2.52 ± 1.18 vs. 2.48 ± 0.58, p = 0.93) or group 3 (3.1 ± 0.9 vs. 3.1 ± 0.7, p = 0.968), respectively.

In 50 group 1 patients, basal volumetric blood flow increased from 102 ± 43, 84 ± 38 and 79 ± 36 ml/min to 267 ± 122, 214 ± 97 and 198 ± 83 ml/min during hyperemia, respectively, in the left anterior descending, right and circumflex coronary arteries.

Discussion

The results of the present study indicate that in unselected adult patients undergoing study for chest pain syndromes with

Figure 1. Histogram showing distribution frequency of coronary vasodilatory reserve (CVR) values for the transplant **(top)** and angiographically normal groups **(bottom)**. Each **block** represents coronary vasodilatory reserve greater than or equal to the value indicated.

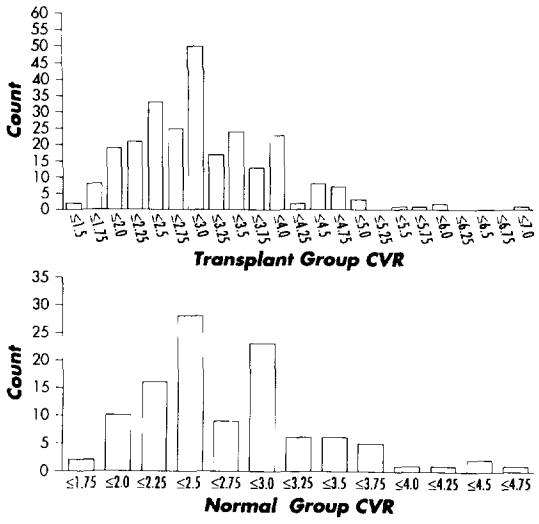

Figure 2. Correlation of coronary (vasodilatory) flow reserve (CFR) with age of patient for normal patients **(top)** and transplant recipients **(bottom)**.

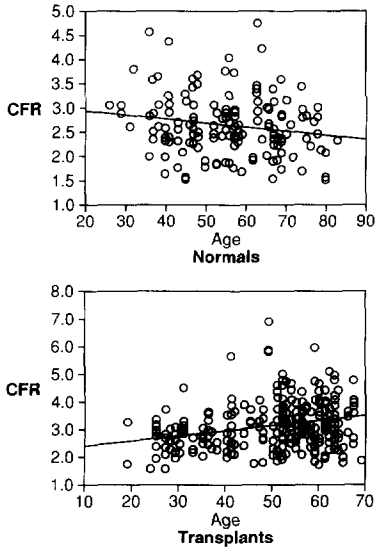

Table 4. Cardiovascular Risk Factors and Coronary Vasodilatory Reserve

	Coronary Vasodilatory Reserve							
			CAD Group					
	Angiographically Normal Group		Abnormal Vessel		Normal Vessel		Transplant Recipients	
Risk Factor	No. of Arteries	Mean ± SD	No. of Arteries	Mean ± SD	No. of Arteries	Mean ± SD	No. of Arteries	Mean ± SD
Hypertension								
Present	57	2.79 ± 0.58	9	1.98 ± 0.53	10	2.19 ± 0.60	116	3.29 ± 0.84*
Absent	57	2.79 ± 0.60	12	1.64 ± 0.61	11	2.78 ± 1.14	144	2.96 ± 0.86
Diabetes mellitus								
Present	5	2.53 ± 0.6	6	1.42 ± 0.29*	5	1.87 ± 0.46	36	3.21 ± 0.79
Absent	109	2.81 ± 0.58	15	1.93 ± 0.62	16	2.70 ± 0.99	224	3.08 ± 0.87
Hypercholesterolemia								
Present	35	2.83 ± 0.57	11	1.85 ± 0.49	10	2.23 ± 0.37	69	3.25 ± 0.82
Absent (>200 mg/dl)	79	2.77 ± 0.60	10	1.77 ± 0.71	11	2.75 ± 1.24	191	3.05 ± 0.88
Smoking								
Present	40	2.92 ± 0.63	13	1.72 ± 0.58	10	2.41 ± 0.73	42	2.94 ± 0.87
Absent	74	2.74 ± 0.55	8	1.89 ± 0.63	11	2.58 ± 1.14	218	3.13 ± 0.86

*$p < 0.05$ versus absent risk factor.

angiographically normal coronary arteries, the average coronary vasodilatory reserve measured using an intracoronary Doppler guide wire was 2.8 ± 0.6 (range 1.7 to 4.7). This value is lower than both historical control subjects measured using Doppler catheters and current values in the same study in orthotopic heart transplant recipients. Although transplant recipients had higher coronary vasodilatory reserves (>3.0 × basal flow), they also did not achieve the levels commonly reported for patients with normal coronary arteries using the zero-crossing Doppler catheter technique (>4.5 × basal flow) (1–5,17).

Experimental studies often report coronary volumetric flow reserve, which may be higher than flow velocity reserve. The discrepancy is potentially related to the alteration of epicardial vessel cross-sectional area at the measurement site. As shown in a subset of our transplant recipients (20), cross-sectional vessel area measured by intracoronary ultrasound imaging was constant during intracoronary bolus adenosine-induced hyperemia. Coronary vasodilatory reserve values using this technique may be systematically underestimated but are generally accepted as an accurate surrogate for volumetric blood flow reserve.

Table 5. Functional Testing and Symptomatic Presentation Versus Coronary Vasodilatory Reserve

	Functional Tests		
	Positive	Negative	Indeterminate/ Not Done
No. of vessels	36	16	33
CVR (mean ± SD)	2.8 ± 0.51*	3.07 ± 0.8*	2.72 ± 0.58*
	Anginal Symptoms		
	Typical	Atypical	None
No. of vessels	33	45	7
CVR (mean ± SD)	2.71 ± 0.6	2.91 ± 0.59	2.72 ± 073†

*$p < 0.151$. †$p < 0.144$. CVR = coronary vasodilatory reserve.

Coronary vasodilatory reserve values among different coronary arteries. In the current study in patients with chest pain syndromes, the average coronary vasodilatory reserve was similar among the left circumflex, left anterior descending and right coronary arteries. An earlier study using the subselective Doppler catheters and zero-crossing technique (7) also showed a nonsignificant trend for coronary vasodilatory reserve measured in the left main, left anterior descending and circumflex coronary arteries (3.04 ± 1.07, 3.25 ± 1.29 and 2.85 ± 1.1, respectively). Left anterior descending coronary vasodilatory reserve demonstrated slightly higher values obtained with the Doppler catheter than with the guide wire (19). This difference may have been partly due to the sampling locations of the two systems and spectral signal analysis of the Doppler guide wire method (21). The differences among vessels may also be due to variations in vessel and myocardial bed size. A smaller myocardial mass would most likely result in a lower coronary vasodilatory reserve relative to a larger nearby myocardial territory.

Coronary vasodilatory reserve and coronary artery disease. As noted previously (22) and confirmed in the present study, coronary blood flow reserve differs between regions supplied by angiographically normal vessels and those supplied by vessels with significant epicardial artery narrowing. Coronary vasodilatory reserve measured by positron emission tomographic (PET) scanning (22) also demonstrated similar values in both the post-stenotic (1.80 ± 0.82 and 1.78 ± 0.26 for PET and Doppler techniques, respectively) and normal regions (2.73 ± 0.89 and 2.76 ± 1.42, respectively). Coronary vasodilatory reserve was lower in the normal vessel in patients with coronary artery disease than those with chest pain. We specu-

late that risk factors for coronary artery disease and angiographically inapparent coronary artery disease influenced flow in the apparently uninvolved artery.

In contrast to the current Doppler-derived flow velocity reserve, control subjects in the PET studies have a higher coronary vasodilatory reserve (4.07 ± 0.98) (22). The PET control group included mostly young healthy normal volunteers, subjects not often undergoing cardiac catheterization. In the current study the normal group included middle-aged patients with chest pain syndromes or transplant recipients with normal results on coronary angiography. Although whether these groups constitute truly normal subjects can be questioned, such patients are frequently used as a control group in catheterization laboratory studies. Reduced coronary vasodilatory reserve due to syndrome X in some group 1 patients may be present. Characterization of responses by associated left ventricular hypertrophy or positive stress test results did not identify a distinct subgroup of patients with a lower coronary vasodilatory reserve.

Coronary vasodilatory reserve and risk factors for coronary artery disease. Coronary artery disease risk factors, such as hypertension, diabetes and hypercholesterolemia, are often associated with an impaired coronary vasodilatory reserve (6,23–25). In the current study, only diabetes appeared to have an adverse effect on coronary vasodilatory reserve values in nontransplant recipients, whereas hypertensive patients with angiographically normal arteries did not have statistically lower coronary vasodilatory reserve values than those in patients without hypertension. Paradoxically, transplant recipients with hypertension (secondary to antirejection medications) had a higher coronary vasodilatory reserve. Sudden elevations of blood pressure in the catheterization laboratory did not affect coronary vasodilatory reserve with proportional increases in both rest and hyperemic blood flow (4). In patients with hypertension, the difference in coronary vasodilatory reserve may be due to the degree of left ventricular hypertrophy (24). Houghton et al. (24) reported that coronary vasodilatory reserve in black and white Americans without left ventricular hypertrophy was 4.4 ± 2.3 and 4.1 ± 2.0 versus 3.2 ± 1.34 and 3.6 ± 1.5 for patients with moderate hypertrophy and 2.7 ± 1.1 and 3.0 ± 1.5, for patients with severe left ventricular hypertrophy, respectively. The degree of left ventricular hypertrophy was not systematically identified in the current study design.

Influence of hemodynamic factors on coronary vasodilatory reserve. Changes in heart rate and left ventricular filling pressures affect serial coronary vasodilatory reserve measurements (4,5). Increasing the heart rate from 76 to 120 beats/min significantly reduced coronary vasodilatory reserve from 4.5 ± 0.2 to 3.2 ± 0.1. Volume loading also decreased the coronary reserve from 3.8 to 2.9 ± 0.2 (4). In the current study with single time point measurements, there was no relation between coronary vasodilatory reserve and heart rate or mean arterial pressure. For serial coronary vasodilatory reserve determinations, standardization of heart rate and filling pressures (if possible) would reduce the deviation from the reference coronary vasodilatory reserve value.

In patients with coronary artery disease, a post-stenotic coronary vasodilatory reserve value >2.0 has an excellent concordance with negative myocardial perfusion imaging studies (15,26,27). In some of these patients, translesional pressures gradients were <15 mm Hg, indicating that the predominant lesion may be small-vessel flow impairment rather than the epicardial stenosis. Caution is indicated in the interpretation of a post-stenotic coronary vasodilatory reserve value <2.0, especially in patients in whom microvascular disease may be a concomitant factor.

Coronary vasodilatory reserve in heart transplant recipients. Angiographically inapparent coronary atherosclerosis may be a contributing factor to decreased coronary vasodilatory reserve. Most transplant recipients with angiographically normal coronary arteries have evidence of intimal thickening by two-dimensional ultrasound imaging (28,29). Early angiographic signs of atherosclerosis do not appear to influence coronary vasodilatory reserve in transplant recipients (29). It was notable that the coronary vasodilatory reserve for each vessel was higher than the corresponding value in the other patient groups. This result may be due to the younger age of the donors with less longstanding conditions related to coronary artery disease risk factors. This postulated mechanism might also explain why diabetes mellitus in the transplant recipient does not appear to be a significant negative factor for coronary vasodilatory reserve in this group.

Acute cardiac allograft rejection is a condition that may diminish coronary vasodilatory reserve. Nitenberg et al. (30) showed that coronary vasodilatory reserve (Doppler catheter) was 2.3 ± 0.5 in patients with acute allograft rejection compared with 5.4 ± 0.8 in normal patients. After treatment of rejection, coronary vasodilatory reserve increased to 4.7 ± 0.8. Although the mean coronary vasodilatory reserve (3.0 ± 0.11) in the current study was intermediate between that of the acute rejection and normal groups, no patient in the current study was examined during a period of acute cardiac rejection.

Study limitations. The current results differ from earlier invasive studies of coronary vasodilatory reserve, in part due to the Doppler signal location and analysis. Spectral flow velocity signal analysis avoids having to accept poor quality, low velocity signals as a basal value, which, compared with hyperemic values, would give a relatively high coronary vasodilatory reserve. Spectral velocity analysis has been demonstrated (21) to be more accurate, reproducible and less operator dependent for obtaining reliable velocity signals than the zero-crossing technique. Other technical limitations related to achieving maximal coronary vasodilatory reserve, such as obstruction of blood flow by the guiding catheter, selective delivery of hyperemic drug and concomitant medical therapy, have been addressed previously (3,4,11) and were not considered substantial limiting factors.

Pharmacologic or flow-mediated vasodilation may be responsible in part for the lower coronary vasodilatory reserve using flow velocity data, although the brief period of adenosine

hyperemia does not appear to increase vessel cross-sectional area in transplant recipients (20). However, this effect was not examined in normal patients with chest pain syndromes. The use of nitroglycerin before coronary vasodilatory reserve data collection should limit artifactual responses due to vasodilation. Cardioactive agents were continued as clinically indicated. Heart transplant recipients were studied during standard triple-drug immunosuppressive therapy, medications that do not appear to have a significant effect on coronary vasodilatory reserve (29,30–32).

Conclusions. Coronary vasodilatory reserve values measured by Doppler guide wire flow velocity technique in angiographically normal vessels have a lower normal range than previously reported. Coronary vasodilatory reserve may differ depending on the patients studied (chest pain syndromes, heart transplantation) but is generally similar in men and women. Because post-stenotic coronary vasodilatory reserve is being increasingly used for clinical decision making, these data have practical relevance for various types of patients in the cardiac catheterization laboratory undergoing study of the coronary circulation.

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