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Coronary Doppler Intensity Changes During Handgrip: A New Method to Detect Coronary Vasomotor Tone in Coronary Artery Disease

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OBJECTIVES This study evaluates whether a quantitative measurement of Doppler intensity during handgrip may disclose coronary vasomotor dysfunction in patients with coronary artery disease (CAD).

BACKGROUND Atherosclerotic coronary segments show an exaggerated constrictive response to handgrip. The intensity of the scattered Doppler signal is proportional to the number of blood cells flowing through the vessel, and should be reduced during vasoconstriction. Therefore, changes in coronary flow during handgrip may be detected by measuring Doppler intensity rather than velocities.

METHODS The distal left anterior descending coronary artery (LAD) was imaged by high-resolution transthoracic color Doppler echocardiography during handgrip in 47 patients: 15 with normal coronary arteries and 32 with significant CAD involving the LAD. The Doppler signal was acquired at 70 dB dynamic range at baseline, 30-s handgrip and 5 min recovery. Peak and mean flow velocity, pressure half-time, deceleration time (ms), deceleration rate (cm/s^2) and mean gray level intensity (intensity units [IU]) of the Doppler spectrum were measured in diastole.

RESULTS The velocity parameters did not change significantly during handgrip both in normal and CAD patients. The Doppler intensity significantly decreased during handgrip (from 87.0 ± 32.8 to 57.7 ± 35.3 IU; $p < 0.001$) in patients with CAD, and it increased or remained unchanged in normals (from 74.1 ± 27.3 to 85.1 ± 31.2 IU; p = NS). The sensitivity of Doppler intensity in detecting CAD was 84.4%, specificity 93.3%, negative predictive value 73.7% and positive predictive value 96.4%.

CONCLUSIONS Doppler intensity measured by transthoracic echocardiography during handgrip allows the detection of CAD and coronary vasomotor dysfunction. (J Am Coll Cardiol 1999;34: 428–34) © 1999 by the American College of Cardiology

Coronary vasomotor tone in response to neurohumoral stress is an important factor influencing the symptoms and probably the prognosis of patients with coronary artery disease (CAD) (1–14). Handgrip elicits coronary vasoconstriction in patients with CAD that is probably mediated by a paradoxical response of the diseased endothelium to the adrenergic drive (15–18).

Recent improvements in ultrasound imaging design allowed us to image by color Doppler the middle-distal tract of the left anterior descending coronary artery (LAD) by specially designed, high-frequency transthoracic probes, and to measure by pulsed Doppler coronary flow velocity (19–24). Significant LAD stenosis can be detected by assessing velocity flow reserve during adenosine infusion (22,23).

A new and relatively unexplored Doppler parameter is the intensity of the signal, which is relatively independent from flow velocity (25–27) and may provide a measure of blood volume changes, secondary to coronary vasomotion. Doppler intensity is proportional to the amount of scatterers (blood cells) flowing in the vessel, and if the entire vessel is included in the sample volume, changes in blood volume should translate into changes in Doppler intensity. During coronary vasoconstriction, the number of scatterers crossing the sample volume per ultrasound pulse is reduced and the intensity of the reflected Doppler signal is decreased. Conversely, during vasodilation, the number of scatterers increases and Doppler intensity increases. The aim of this study was to evaluate whether a quantitative measurement of Doppler intensity during handgrip may disclose coronary vasomotor dysfunction in patients with CAD.

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Abbreviations and Acronyms

CAD = coronary artery disease
IU = intensity units
LAD = left anterior descending coronary artery

METHODS

Eighty-three consecutive patients (45 with CAD and 38 with normal coronary arteries) were screened and included if the distal LAD could be adequately imaged by transthoracic color Doppler echocardiography and the characteristic diastolic Doppler signal was clear and constantly recordable (Fig. 1).

Patients with CAD. Thirty-two out of 45 CAD patients (71%, 29 men, 3 women, aged 61 ± 8 years) had adequate LAD imaging. All had angiographically assessed CAD involving the proximal or middle tract of the LAD and chronic, effort angina pectoris. Eleven had three-vessel, 9 had two-vessel and 12 had isolated LAD disease. The stenosis of the LAD was >60% in all patients, and was expressed as diameter stenosis. Quantitative angiography was not performed. Ten patients had old myocardial infarction (two lateral and eight inferior). Three had non-insulin-dependent diabetes mellitus, 2 emphysema, 3 obesity and 8 mild hypertension. Fifteen patients were ex smokers, and 4 were active smokers. Twelve patients had hypercholesterolemia with total cholesterol level >230 mg/dl. All patients were in sinus rhythm, and the echocardiographically assessed ejection fraction was >45%. No patient received alpha- or beta-blockers within 48 h, or vasodilators (as calcium antagonists, ACE, inhibitors or long-acting nitrates) 24 h before the study. No patient received allopurinol, estrogen therapy or antioxidant drugs. Lipid-lowering drugs and ascorbic acid, which may normalize endothelial vasodilator response in epicardial conductance vessels (11,12), were withdrawn.

Normal subjects. Fifteen out of 38 normal subjects (40%, 10 men and 5 women, aged 48 ± 18 years) had adequate LAD imaging. Eleven of them underwent coronary angiography, which showed normal, smooth coronary arteries, without luminal irregularities; four patients under 25 years did not undergo coronary angiography. The ejection fraction was >60%, and there were no wall motion abnormalities. None of these patients had hypertension (blood pressure 150/90 mm Hg or higher), diabetes mellitus or hypercholesterolemia (total cholesterol >230 mg%).

Transthoracic echocardiography. Echocardiography was performed in the left lateral decubitus, by a multihertz transducer allowing independent change of frequency between two-dimensional (3.5–7.0 MHz) and color Doppler (3.5 to 6.0 MHz) imaging. The transducer was connected to an ultrasound system (Sequoia C256; Acuson, Mountain View, California), which utilizes multiple image formers and coherent image formation preserving both phase and amplitude data. This system provides a high spatial and temporal resolution (>130 to 160 frames/s for imaging at 5 to 7 MHz and >40 frames/s for color Doppler at 3.5 to 6.0 MHz) and up to 70 dB dynamic range for pulsed Doppler. To image the distal LAD, the transducer was placed either at the cardiac apex or one intercostal space above, and focused on the proximal field. Once an optimal two-dimensional image of the apex or distal anteroseptal wall had been obtained, the transducer was rotated and tilted until one coronary segment or perforating branches could be visualized by color Doppler. Color Doppler imag-

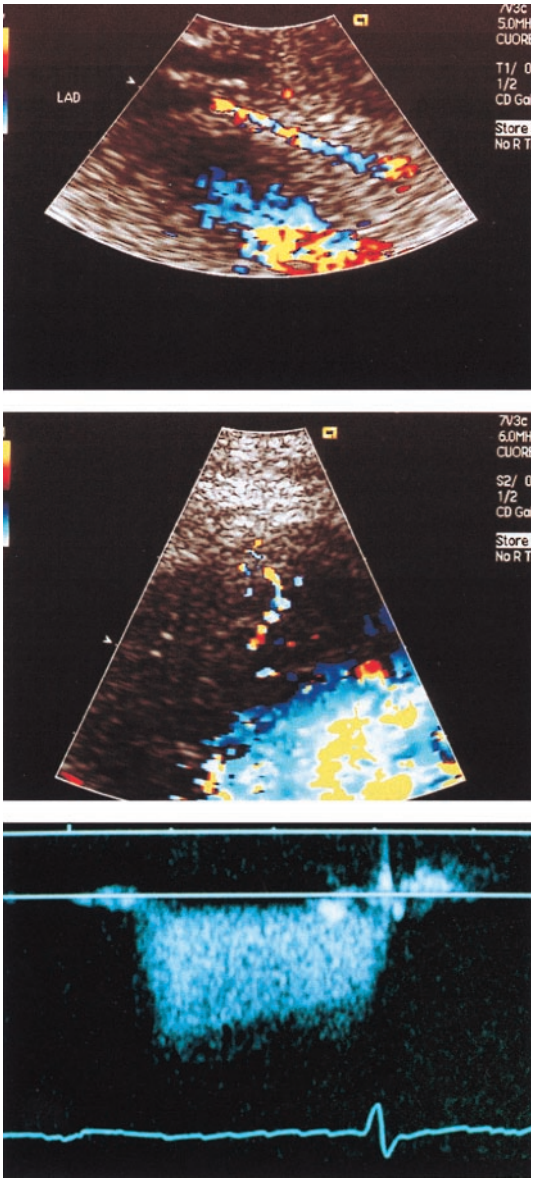

Figure 1. Transthoracic color Doppler echocardiography showing the distal left anterior descending coronary artery **(top),** a periapical perforating branch **(middle)** and the characteristic diastolic pattern of coronary flow velocity **(bottom).**

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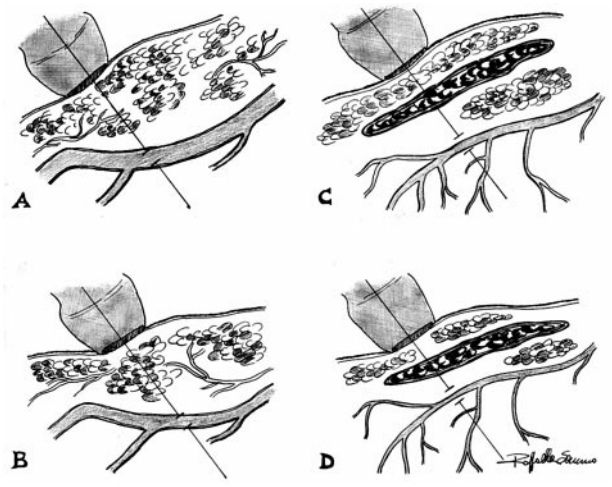

Figure 2. Conventional vascular pulsed Doppler **(A** and **B)** is performed by positioning the sample volume within the vessel. Vasoconstriction **(B)** may not affect the amount of red blood cells crossing the sample volume and Doppler intensity may remain unchanged. Conversely, in coronary imaging **(C** and **D),** the sample volume exceeds the diameter of the vessel. Coronary vasoconstriction **(D)** reduces the amount of red blood cells flowing through the sample volume and Doppler intensity is decreased.

ing was performed by reducing the Nyquist limit to 110–170 mm/s for 3.5 MHz, 120 to 190 mm/s for 5 MHz and 130 to 200 mm/s for 6 MHz. As an alternative, a special preset coronary program, displaying only one color (yellow-red) to denote flows both towards and away from the transducer (nondirectional Doppler) can be used. Adequate filtering was used to minimize low frequency wall motion artifacts. The highest pulsed Doppler dynamic range (70 dB) was used to detect subtle changes in Doppler intensity during handgrip. The baseline Doppler intensity was maintained low by gain adjustments to prevent signal compression at high intensities.

Pulsed Doppler parameters were measured using a sample volume of 24 to 35 mm, always exceeding the diameter of the coronary artery under investigation (Fig. 2). The angle between the blood flow and ultrasound beam was optimized and adequately corrected, when necessary. Images were acquired at baseline, peak handgrip and recovery, and stored on hard disk for off-line analysis.

Handgrip. Patients were monitored by electrocardiogram. After a stable imaging of the distal LAD had been obtained and baseline blood flow velocity had been recorded, bilateral maximal 30-s handgrip was performed using a Vigorimeter dynamometer (Martin Vigorimeter, Berlin, Germany). Patients were instructed to avoid Valsalva maneuver and to hold breathing during data acquisition. Images were acquired on hard disk at baseline, 30-s handgrip and 5-min recovery. Blood pressure and heart rate were measured at baseline, 30-s handgrip and 5-min recovery.

Doppler analysis. Two independent blinded observers reviewed the Doppler echocardiographic recordings. Peak and mean blood flow velocity, pressure half-time, deceleration time (ms) and deceleration rate (cm/s^2) were measured on the diastolic phase of the Doppler tracing using an in-built program. Doppler intensity was derived by tracing a region of interest on the diastolic phase of the Doppler spectrum and measuring mean pixel intensity. Any noise, eventually generated by movements of the heart muscle, was excluded from the tracing. All velocity and video-intensity measurements were repeated three times and averaged. Intra- and interobserver variability was calculated by repeating in all subjects measurements of velocity and video-intensity parameters.

Statistical analysis. Quantitative measurements are expressed as mean ± SD. The interobserver variability was assessed by the intraclass correlation coefficient. Intraclass correlation coefficient was computed in order to evaluate the concordance level between the two readers. Doppler data were analyzed by the analysis of variance with repeated measures according to the coronary status (normal or CAD) as between-subject factors and time of echocardiographic evaluation (baseline, handgrip and recovery) as repeated measures factor. Multiple comparisons were performed by applying the appropriate test with Bonferroni's correction. A p value of <0.05 was considered statistically significant. Sensitivity, specificity, negative predictive value and positive predictive value for the differences in baseline-handgrip of the gray level were also computed considering normal a decrement $\leq$mean $-$ $t_{0.975}(df)$*SD, where $t_{0.975}(df)$ is t value at the 0.975 percentile with degree of freedom (df) = n $-$ 1. The analysis was performed using a BMDP (Biomathematics Department Statistical Software, Berkeley, California) package.

RESULTS

Handgrip. All patients tolerated the test well and none had angina. Blood pressure, heart rate and rate × pressure product were not significantly different in CAD versus normals either at baseline or after handgrip, but significantly increased in both groups after handgrip compared with baseline (Table 1).

Feasibility. The middle-distal tract of the LAD was visualized by color Doppler in 71% of CAD patients but only in 40% normal subjects. Periapical perforating branches were visualized in 19 of 32 (59%) of CAD patients and 2 of 15 (13%) normal subjects (Fig. 1). In all patients with adequate color Doppler imaging of the LAD, measurement of blood flow velocity by pulsed Doppler was feasible.

Pulsed Doppler data. The velocity pattern was characterized by a prevalent diastolic component (Fig. 1). The systolic component was less pronounced compared with the diastolic and could not be obtained in all patients, probably because the rotational and translational movements of the heart in systole prevent sampling of systolic flow once an

Table 1. Blood Pressure, Heart Rate and Rate-Pressure Product Changes During Handgrip

	Normal Subjects		Ischemic	
	Base	Handgrip	Base	Handgrip
BP	130.0 ± 6.8/74.3 ± 6.5	150.3 ± 9.8/93.7 ± 7.2	127.2 ± 6.8/76.1 ± 7.8	153.1 ± 6.6/89.8 ± 8.7
HR	70.0 ± 9.8	94.0 ± 10.9	74.7 ± 9.2	98.9 ± 10.1
HR × BP	9125.0 ± 1553.2	14138.7 ± 1943.8	9483.6 ± 1152.3	15135.9 ± 1621.0

P = NS (normal subjects vs. ischemic).
BP = blood pressure; HR = heart rate; HR × BP = rate-pressure product.

optimal projection for diastolic flow has been obtained. Peak and mean diastolic flow velocities, pressure half-time, deceleration time and rate and mean gray level intensity of the Doppler spectrum at baseline during handgrip and after recovery are given in Table 1. Peak and mean diastolic flow velocities did not change significantly throughout the test. The only parameter discriminating normal subjects and CAD patients was the video-intensity of the Doppler signal. In normal subjects, the Doppler intensity increased slightly or remained unchanged during handgrip (Fig. 3), and in CAD it significantly decreased, reflecting coronary vasoconstriction and returned to baseline at recovery (Fig. 4). In some patients, Doppler intensity decreased as early as 5 s after starting handgrip, confirming the role of a reflex

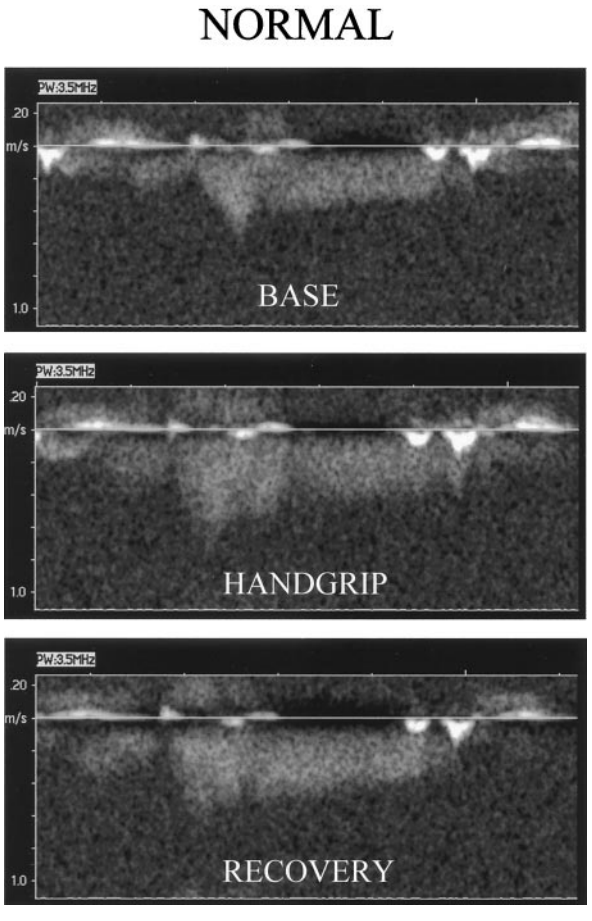

Figure 3. Coronary Doppler tracing during 30-s handgrip in a subject with normal coronary arteries. The Doppler intensity and flow velocities remain unchanged throughout the test.

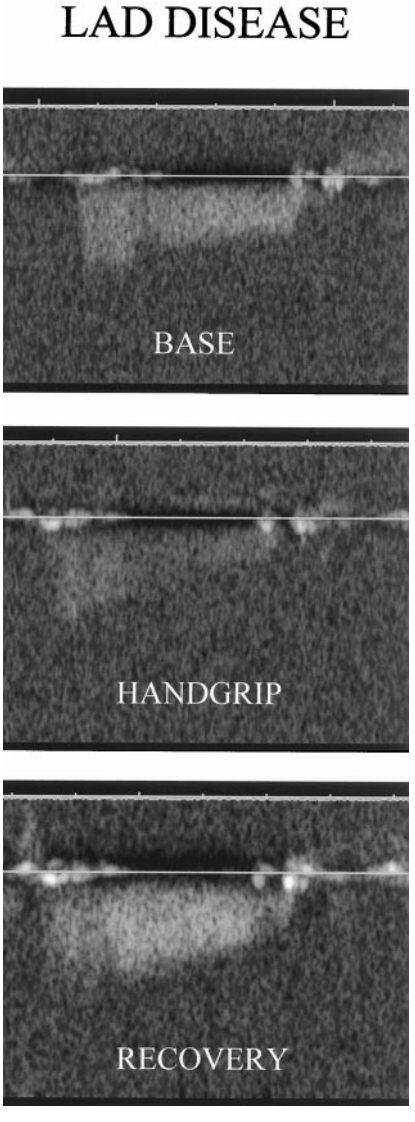

Figure 4. Coronary Doppler tracing during 30-s handgrip in a patient with significant LAD disease. The Doppler intensity is reduced during handgrip, probably due to coronary vasoconstriction, and is slightly increased at recovery, probably due to reactive hyperemia. Flow velocities remain unchanged during handgrip, but there is a slight increase at recovery.

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Table 2. Results of Analysis of Variance With Repeated Measures

Variables	Group		p Values		
	Normal Subjects (n = 15) Mean ± SD	Ischemic (n = 32) Mean ± SD	Main Effect Grouping Factor	Main Effect Repeated Measures	Interaction
Peak velocity (cm/s)			NS	NS	NS
Baseline	44.8 ± 19.1	58.6 ± 37.6			
Handgrip	47.5 ± 18.4	59.4 ± 37.3			
Recovery	45.6 ± 21.2	56.1 ± 34.4			
Mean velocity (cm/s)			NS	NS	NS
Baseline	31.3 ± 11.6	41.2 ± 26.1			
Handgrip	33.0 ± 13.2	43.0 ± 28.3			
Recovery	31.9 ± 14.5	40.9 ± 26.3			
P 1/2 (ms)			NS	NS	NS
Baseline	251.5 ± 107.3	258.1 ± 77.2			
Handgrip	209.5 ± 80.1	258.6 ± 116.9			
Recovery	214.7 ± 75.8	280.9 ± 123.2			
Deceleration time (ms)			NS	NS	NS
Baseline	901.5 ± 440.0	888.3 ± 295.4			
Handgrip	696.7 ± 272.2	879.0 ± 412.9			
Recovery	744.1 ± 253.9	917.0 ± 384.5			
Deceleration rate (cm/s^2)			NS	0.0444	NS
Baseline	83.0 ± 97.5	79.1 ± 69.0			
Handgrip	111.6 ± 162.7	83.7 ± 66.8			
Recovery	92.7 ± 124.1	69.1 ± 54.1			
Gray level (IU)			NS	< 0.0001	< 0.0001
Baseline	74.1 ± 27.3	87.0 ± 32.8			
Handgrip	85.1 ± 31.2	57.7 ± 35.3			
Recovery	78.9 ± 26.8	90.5 ± 34.9			

Interaction refers to comparison between effect of grouping factor (normal vs. ischemic) and repeated measures.

coronary constriction, but in others, it started to decline later. There was a trend for deceleration rate to change during handgrip, but the standard deviation was too high to draw any conclusion (Table 2). Furthermore, multiple comparison analysis with Bonferroni's correction did not confirm the weak statistical significance obtained with the analysis of variance (Table 3).

Diagnostic value. In normal subjects, the difference in Doppler intensity at handgrip compared with baseline was 11.1 ± 15.1 IU (mean ± SD). According to the described formula, five CAD patients showing a reduction in Doppler intensity >15.6 were classified as false negative. Only one normal subject was classified as false positive. Therefore, the sensitivity of the method in predicting the presence of CAD was 84.4%, the specificity 93.3%, the negative predictive value 73.7% and the positive predictive value 96.4%.

Repeatability. The interobserver variability as assessed by the intraclass correlation coefficient for mean and peak diastolic flow velocities and Doppler video-intensity was extremely high (>0.97), but was lower for pressure half-time, deceleration time and deceleration rate, probably reflecting some uncertainty in recognizing the early slope of the curve (Table 4).

Table 3. p Values of the Multiple Comparisons in the Two Groups of Patients

Parameters	HG vs. Baseline		Recovery vs. Baseline	
	Normal Subjects	Ischemic	Normal Subjects	Ischemic
Peak velocity	NS	NS	NS	NS
Mean velocity	NS	NS	NS	NS
P 1/2	NS	NS	NS	NS
Deceleration time	NS	NS	NS	NS
Deceleration rate	NS	NS	NS	NS
Gray level	NS	< 0.001	NS	NS

Paired *t* test with Bonferroni's correction.
HG = handgrip.

Table 4. Interobserver Variability Assessed by the Intraclass Correlation Coefficient

Peak velocity	
Baseline	0.986
Handgrip	0.979
Mean velocity	
Baseline	0.988
Handgrip	0.967
P 1/2	
Baseline	0.762
Handgrip	0.865
Deceleration time	
Baseline	0.708
Handgrip	0.811
Deceleration rate	
Baseline	0.867
Handgrip	0.804
Gray level	
Baseline	0.980
Handgrip	0.990

Duration and logistics of the test. The described test is very fast and completely noninvasive: it requires only one doctor or technician and one nurse, and it can be completed in 5 to 10 min.

DISCUSSION

The introduction of the new Sequoia technology allows for the first time the ability to study, by transthoracic echocardiography, coronary blood flow in the middle-distal tract of the LAD. We have utilized the periapical window to detect LAD flow for three reasons: 1) the LAD is the most important artery of the heart and has a strong prognostic effect in patients with CAD; 2) it surrounds the apex in most cases, and therefore flow alterations at any point of the LAD should be detected at the apex; and 3) at the apex, the LAD is best detectable, because it is more superficial than in the proximal and middle segments, and chest wall attenuation is lower.

Feasibility. Our success rate in coronary imaging is lower (71% CAD patients and 40% normal subjects) than that recently reported by Hozumi et al. (22). These authors used two commercially available ultrasound systems (ATL HDI-3000CV and Toshiba SSA-380A [Tokyo, Japan]) and reported an overall success rate of 94%, in a population of 12 patients with significant LAD and 24 with nonsignificant LAD disease. This difference may be due to the higher prevalence of subjects with normal, smooth coronary arteries in our study, but also to a difference in chest conformation between the white and Japanese populations.

Three factors may explain why the coronary arteries are better imaged in CAD than in normals: 1) ventricular contraction interferes with color Doppler imaging of the coronary arteries, and is more efficient in normals than CAD patients. At one extreme, when the apex is still as after acute infarction, reperfusion imaging is very easily obtained (24); 2) compensatory vasodilation of distal and intramyocardial branches may occur in CAD, thus facilitating detection of coronary flow; and 3) turbulent flow, produced by coronary stenoses, may be better detected than laminar flow of a normal coronary artery.

Interestingly, the LAD, and in particular its perforating branches, may not be constantly visualized from day to day, probably reflecting a circadian variation in coronary vasomotor tone.

The coronary vasomotor effect of handgrip. Handgrip has no significant vasomotor effect in normal vessels, but produces a 20% to 25% lumen reduction in atherosclerotic segments (16,17) that may compete with local metabolic control (15).

In CAD, the altered endothelium and smooth muscle response may mediate a paradoxical response of the coronary artery to physiologic stimuli. Endothelin is one of the most potent endothelium-derived contracting factors that potentiates the effects of other vasoconstrictors such as norepinephrine even at subthreshold concentrations (5). The indirect potentiating effect of endothelin is due to an increased calcium sensitivity of vascular smooth muscle cells and can be prevented by pretreatment with dihydropyridine calcium antagonists (5).

The false-negative tests (15.6%) in our CAD patients may be explained with an already increased vasomotor tone at rest, probably influenced by drug withdrawal. In this setting, further vasoconstriction during handgrip may be too little to be detected by Doppler intensitometry.

Why Doppler intensity is decreased during handgrip. The ultrasonic energy received by the transducer depends on the intensity of the transmitted wave, the efficiency and number of scatterers and attenuation of the signal as it travels from the transducer to the scatterers and back (25,26). During handgrip, the transmitted ultrasound intensity and the attenuation of the chest are constant, but the number of scattering elements crossing the sample volume changes. In patients with CAD, the number of scatterers is reduced due to uniform coronary vasoconstriction, while in normal subjects, it remains relatively constant.

Why the velocity pattern is not altered during handgrip. In both CAD patients and normal controls, the velocity parameters were not significantly altered during 30-s handgrip, probably because of a parallel increase in blood pressure and coronary resistance (14). Others have found an increase in coronary blood flow velocity by intracoronary Doppler, but only after 60-s cold pressor test (6). This late increase in velocity is probably the result of metabolic autoregulation secondary to increased oxygen demand.

Comparison with previous studies. Hozumi et al. (22) measured coronary flow reserve in the LAD obtaining high sensitivity and specificity (92% and 86%, respectively). Our study investigates the converse, i.e., the vascular reactivity to sympathetic stimulation, using a new Doppler parameter.

Potential clinical applications. This method may allow the evaluation of coronary vasomotor tone and the effect of

therapeutic interventions, which may have a prognostic effect on CAD. The diagnosis of isolated LAD disease, which may be missed by other noninvasive tests, also may be improved by this method.

Future developments. The introduction in clinical practice of ultrasound contrast agents, which increase the signal-to-noise ratio in the vascular bed after venous injection, may improve the feasibility of the technique and may allow a more complete imaging of the coronary arteries. The new contrast agents not only may improve coronary vessel detection (19), but also produce myocardial opacification, providing additional information on microvascular flow.

New methods of analysis, including direct measurements in decibels of the reflected Doppler beam and frequency analysis, may improve the diagnostic value of the proposed method.

Study limitations. The detection of coronary artery flow by transthoracic echocardiography requires a learning curve, and even experienced physicians may find it difficult to maintain a constant projection throughout a simple stress test such as handgrip. Movements of the chest wall and contraction of the pectoral muscles should be avoided to prevent probe dislocation during the stress test.

Videodensitometry is an indirect method to assess Doppler intensity, and at high intensities the signal undergoes a logarithmic compression. In our study, only two CAD patients showed baseline Doppler intensity over 130 IU (154 and 161 IU, respectively), therefore, compression probably did not occur. A quantitative evaluation in decibels, of the native audio Doppler signal, that is linear and uncompressed was not performed in this study, but may be used in the future to improve the accuracy of the results.

The test may be positive in nonsignificant CAD, which may also present vasomotor dysfunction. Rather than being a limitation, this may turn to be an advantage, if the method allows early detection of atherosclerosis or endothelial dysfunction.

Last, despite the fact that the periapical area is usually perfused by the LAD, confirmation of the anatomic identity of the vascular structure is not possible. The operator should be aware that the apex may rarely be perfused by the right coronary artery and that proximal segments of the anterior wall may be perfused by a diagonal branch.

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