

Noninvasive Assessment of Microvascular Function in Arterial Hypertension by Transthoracic Doppler Harmonic Echocardiography

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OBJECTIVES	The present study sought to investigate the use of transthoracic Doppler harmonic echocardiography (TTDHE) to evaluate changes in coronary flow dynamics due to microvascular dysfunction.
BACKGROUND	Coronary flow velocity reserve (CFVR) measurements by TTDHE are useful for assessing epicardial coronary artery stenoses. It remains unclear, however, if microvascular disease can be detected.
METHODS	In 54 patients with chest pain, intracoronary Doppler (ICD) and TTDHE were used to measure average peak velocity at baseline and hyperemia. Significant coronary lesions had been ruled out by both angiography and intravascular ultrasound. Comparative measurements were performed in the distal left anterior descending coronary artery after intracoronary and intravenous administration of adenosine, and CFVR was calculated. Hypertensive patients (n = 25) were studied and compared to a control group (26 normotensive individuals).
RESULTS	Three patients (5%) had to be excluded because of insufficient image quality or side effects. In both groups, TTDHE-derived CFVR data correlated closely with ICD measurements (group 1: $y = 0.67x + 0.076$, standard error of estimate [SEE] = 0.25, $r = 0.87$, $p < 0.001$; group 2: $y = 0.64x + 1.11$, SEE = 0.26, $r = 0.87$, $p < 0.001$). CFVR was lower in hypertensives than in normotensive controls (2.44 ± 0.49 vs. 3.33 ± 0.40 , $p < 0.001$, cut point = 2.84).
CONCLUSIONS	The newly described echocardiographic method is suitable for assessing microvascular dysfunction noninvasively and corresponds well to invasive measurements. (J Am Coll Cardiol 2002;39:2012–8) © 2002 by the American College of Cardiology Foundation

The abnormal coronary microcirculation in left ventricular hypertrophy due to arterial hypertension is known to reduce cardiac oxygen supply, even in the absence of coronary artery stenoses (1). Impaired coronary flow reserve has been reported in patients with hypertension and diabetes mellitus and in smokers (2–4). In addition to evaluating coronary artery disease, intracoronary Doppler (ICD) assessment of coronary flow velocity reserve (CFVR) is gaining importance in the detection of suspected microvascular disorders (5,6). Transthoracic Doppler harmonic echocardiography (TTDHE) is an ultrasound approach for the assessment of CFVR. The technique uses contrast Doppler enhancement to measure flows at baseline and during adenosine infusion (7). In the majority of patients, peripheral left anterior descending coronary artery flow can be detected and flow velocity adequately determined (8). But it is unknown if the method can detect microvascular dysfunction due to arterial hypertension (9).

The present study sought to evaluate coronary flow velocities and CFVR in arterial hypertension as assessed by TTDHE. For this purpose, both intracoronary readings and

TTDHE were performed in hypertensive patients without epicardial stenoses and in normotensive controls.

METHODS

Patients. From September 2000 to June 2001, 175 patients were prospectively studied. Among these, 54 patients had no epicardial stenoses on diagnostic coronary angiography and intravascular ultrasound examination. A minimal luminal cross-sectional area $>4 \text{ mm}^2$ and a lumen area stenosis $<50\%$ were required for inclusion in the study. The remaining 121 individuals had significant coronary artery disease. Patients were enrolled prospectively. Patients with hypertrophic cardiomyopathy, dilated cardiomyopathy, valvular heart disease, endocarditis, myocarditis and cardiac decompensation were excluded from the study. Informed consent was obtained from all patients at least 24 h before the examinations. In one patient, transthoracic Doppler flow was not detectable. Two patients did not tolerate intravenous administration of adenosine because of flush, dyspnea and chest discomfort. Eventually, comparative measurements of coronary flow velocity were successfully carried out in 51 patients (Table 1). Twenty-five patients had arterial hypertension (group 1), whereas 26 patients were normotensive (group 2). Patients with blood pressures of $>160/90 \text{ mm Hg}$ on repeated measurements were included in group 1. Group 2 had no documented arterial hyperten-

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Abbreviations and Acronyms

APV	= average peak velocity
bAPV	= baseline average peak velocity
bMDV	= baseline mean diastolic velocity
bMSV	= baseline mean systolic velocity
bPSV	= baseline peak systolic velocity
CFVR	= coronary flow velocity reserve
hAPV	= hyperemic average peak velocity
ICD	= intracoronary Doppler
MDV	= mean diastolic velocity
MSV	= mean systolic velocity
PDV	= peak diastolic velocity
PSV	= peak systolic velocity
TTDHE	= transthoracic Doppler harmonic echocardiography

sion and a baseline blood pressure <140/85 mm Hg. Left ventricular mass was determined according to the Penn convention (10). The study protocol was approved by the institutional review board (00-26-1381).

Intracoronary ultrasound measurements. Intravascular ultrasound examination was performed with a mechanical intravascular ultrasound system (Insight, CVIS, Boston Scientific Scimed Inc., Maple Grove, Minnesota) using a Microrail-catheter and motorized pullback at 0.5 mm/s. Doppler flow data were obtained with a 0.014 in. Doppler wire (FloWire, Jomed Inc., Helsingborg, Sweden) advanced into the distal segments of the left anterior descending coronary artery (5). Under baseline conditions and after stable readings were achieved, Doppler signals were recorded as gray-scale spectral Doppler. Next, an intracoronary bolus of 18 µg adenosine was injected into the left coronary artery over a guiding catheter, and peak hyperemic flow was recorded at the maximal change of blood flow velocity. Average peak velocity (APV) was determined and CFVR calculated online from hyperemic average peak velocity (hAPV) and baseline average peak velocity (bAPV) as described (4).

Table 1. Patient Characteristics

Total number of patients	51
Women	21 (41.2%)
Men	30 (58.8%)
Age (yrs)	55 ± 11* (range 20-75)
Hemodynamic parameters†	
HR (beats/min)	64 ± 13*
sBP (mm Hg)	136 ± 23*
dBP (mm Hg)	77 ± 11*
mBP (mm Hg)	93 ± 13*
Stress ECG	
Number of patients	51
Adequate exercise and end points	44
Positive	18
Negative	26

*Mean ± standard deviation; †at baseline conditions during echocardiographic Doppler examination.

BP = blood pressure; d = diastolic; ECG = electrocardiogram; HR = heart rate; m = mean; s = systolic.

Echocardiographic coronary flow measurement. Transthoracic Doppler harmonic echocardiography examinations were done with an ultrasonographic unit (Sequoia C256, Acuson Corp., Mountain View, California) equipped with a broadband transducer with second harmonic capability (3V2c). In a short-axis view of the left ventricle, the anterior groove was examined for diastolic blood flow under guidance by color Doppler flow mapping to identify the distal left anterior descending coronary artery (7). Two-dimensional and contrast-enhanced color Doppler imaging was routinely performed in the second-harmonic mode using 1.7 MHz for transmitting and 3.5 MHz for receiving ultrasound waves. In contrast, spectral Doppler data were obtained with the fundamental imaging mode at 2.5 MHz. If the angle between Doppler beam and coronary flow exceeded 30°, the standard software package of the ultrasound unit was used for angular correction. During continuous peripheral intravenous infusion of 200 mg/ml Levovist (Schering AG, Berlin, Germany) at 0.5 to 2.0 ml/min, significant portions of the studies were captured at end-expiration and digitally stored in cine-loop format and as spectral Doppler still frames for offline analysis. Peak systolic velocity (PSV), peak diastolic velocity (PDV), mean systolic velocity (MSV), mean diastolic velocity (MDV), and APV were measured at baseline and under hyperemic conditions from at least two cardiac cycles, and CFVR was calculated (Fig. 1). After coronary flow measurement under baseline conditions, adenosine was intravenously infused at a rate of 50 µg/kg/min and increased in steps of 1 min to doses of 75 and 100 µg/kg/min, and finally to a dose of 140 µg/kg/min, which was maintained for another 2 min.

Statistical analysis. Parametric data are expressed as mean ± SD and were tested by use of the unpaired two-tailed Student *t* test for group distinction. The paired two-tailed Student *t* test with Bonferroni correction was employed to analyze changes of flow velocities due to increasing doses of adenosine. Nonparametric data were tested employing the chi-square test with one degree of freedom. The optimal cutoff points were determined by receiver operating characteristic curves (ROC analysis) using SPSS for Windows (release 10.0.1, SPSS Inc., Chicago, Illinois), and the sensitivity and specificity of TTDHE measurements for group distinction were determined according to:

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{False negatives}} \cdot 100\%$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{False positives}} \cdot 100\%$$

Linear correlation analysis was used to compare TTDHE with intracoronary data on APV and CFVR. Analyses included the determination of regression equations, correlation coefficients, and standard error of the estimate. The statistics program StatView for Macintosh (release 5, Abacus Concepts Inc., Berkeley, California) was employed for

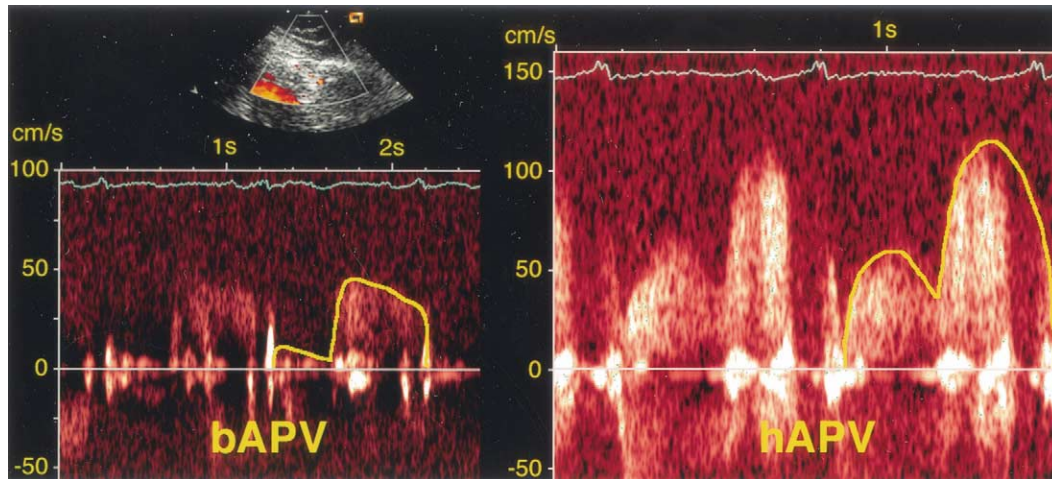


Figure 1. Echocardiographic readings of coronary flow velocity. bAPV = baseline average peak velocity; hAPV = hyperemic average peak velocity.

these analyses. Differences between TTDHE and intracoronary measurements and limits of agreement were displayed according to Bland-Altman (11). Statistical significance was defined as a $p < 0.05$.

RESULTS

Group characteristics. Between groups 1 and 2, there were no differences in age, gender, men-women ratio and heart rate. Patients were also categorized according to risk factors for microvascular dysfunction (12). Group 1 had significantly higher values of rate-pressure product, systolic, diastolic and mean blood pressure than group 2. In contrast, the proportions of smokers and diabetics were not significantly different. Left ventricular mass was higher in group 1 than in group 2, but not to a significant degree (Table 2).

Table 2. Group Characteristics Including Results of Intracoronary Doppler Measurements

Variable	Group 1 (n = 25)	Group 2 (n = 26)	Difference
Men/women ratio	14/11	16/10	$\chi^2 = 0.16$, NS
Age (yrs)	58 ± 9	53 ± 12	NS
Diabetes mellitus*	2	2	$\chi^2 = 0.0013$, NS
Smoking	7	6	$\chi^2 = 0.16$, NS
HR (beats/min)	63 ± 10	66 ± 16	NS
sBP (mm Hg)	154 ± 16	118 ± 13	$p < 0.0001$
dBp (mm Hg)	85 ± 6	68 ± 8	$p < 0.0001$
mBP (mm Hg)	100 ± 14	86 ± 8	$p < 0.0001$
Rate-pressure product	9,665 ± 1,469	7,837 ± 2,357	$p = 0.008$
LV mass	153 ± 51	134 ± 32	NS
bAPV (cm/s)	20.0 ± 9.40	15.2 ± 4.68	$p = 0.0239$
hAPV (cm/s)	48.0 ± 16.9	51.4 ± 14.5	NS
CFVR	2.50 ± 0.63	3.49 ± 0.54	$p < 0.0001$

Parametric data are expressed as mean ± SD. Left ventricular mass is determined according to the American Society of Echocardiography convention. *Noninsulin-dependent diabetes mellitus in all cases.

APV = average peak velocity; b = baseline; BP = blood pressure; d = diastolic; CFVR = coronary flow velocity reserve; h = hyperemic; HR = heart rate; LV = left ventricle; m = mean; NS = not significant; s = systolic.

Linear correlation analyses and accuracy. Separate analyses for both groups revealed close correlation between ICD and TTDHE measurements of bAPV (Fig. 2A). In group 1, intracoronary and echocardiographic readings were in agreement with respect to the partly increased bAPV values. In contrast to group 2, flow velocity measured by TTDHE was slightly underestimated in group 1 (Fig. 2A). This underestimation occurred exclusively in those patients of group 1 who presented with increased bAPV. Thus, the mean differences between ICD and TTDHE measurements were higher in group 1 than in group 2. As shown for comparative measurements of bAPV, correlation coefficients and differences indicated good agreement between ICD and TTDHE measurements of hAPV, although the correlation was better in group 1 than in group 2 (Fig. 2B). In contrast to bAPV, measurements of hAPV revealed lower values in group 1 than in group 2. The differences between ICD and TTDHE readings were comparable in both groups. The highest correlation coefficients between ICD and TTDHE data acquisition were found for CFVR (Fig. 2C), also showing the smallest differences between both approaches. TTDHE underestimated CFVR slightly (Table 2).

Doppler flow measurements in hypertensives. In group 1, bPSV, bMSV and bAPV were significantly higher than in group 2. The same was evident at the lowest adenosine infusion rate. Neither in group 1 nor in group 2 was a significant APV increase over baseline conditions detectable at an adenosine infusion rate of 50 $\mu\text{g}/\text{kg}/\text{min}$. But with adenosine infusion rates above 50 $\mu\text{g}/\text{kg}/\text{min}$, APV increased more slowly in group 1 than in group 2. Finally, hAPV was lower in group 1 than in group 2, although the mean differences of all hyperemic flow parameters were not significantly different between both groups. Nevertheless, TTDHE-derived CFVR was significantly lower in group 1 than in group 2 (Table 3). Coronary flow velocity reserve was the most distinctive echocardiographic parameter, discriminating both groups with the highest sensitivity and

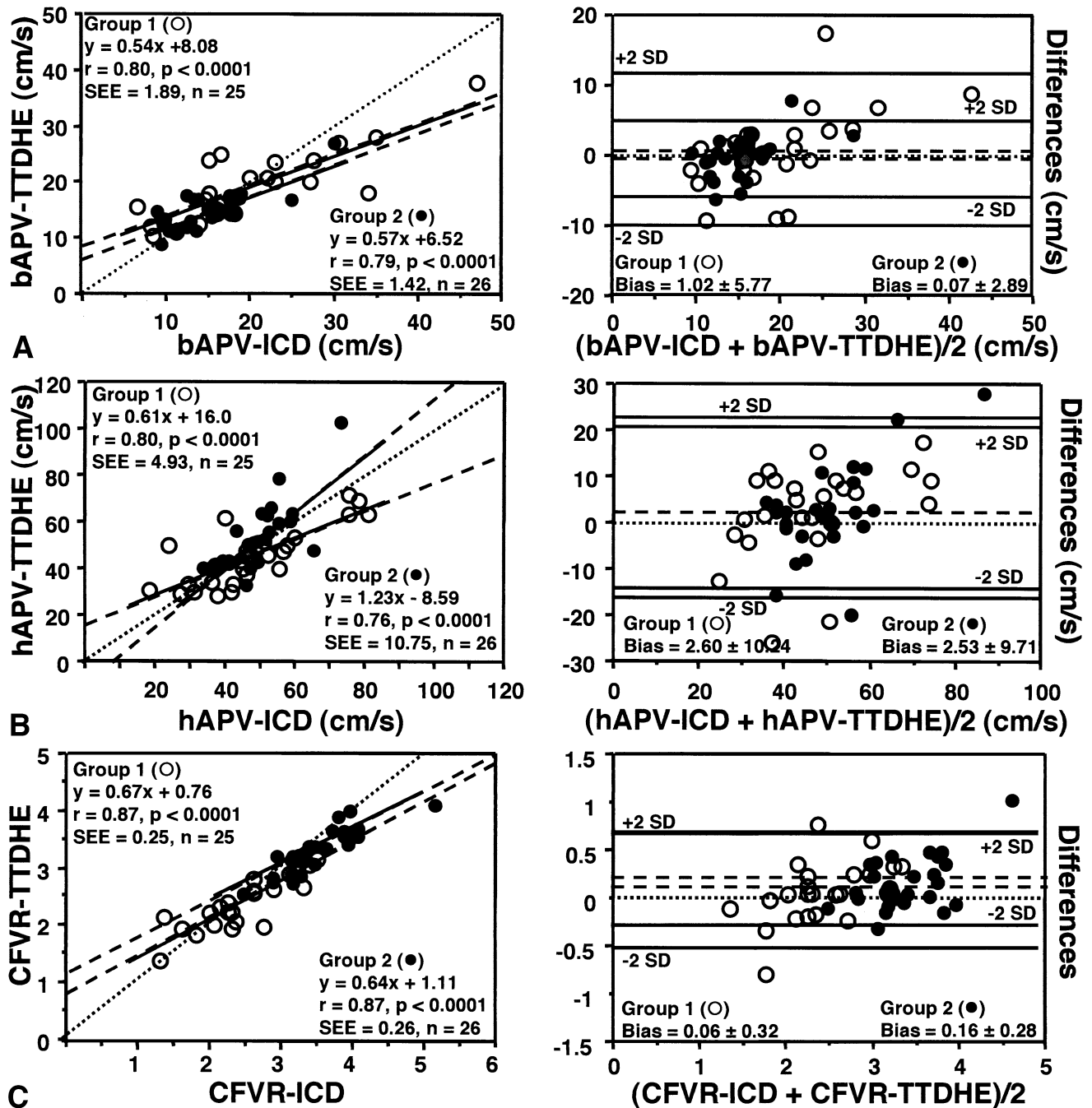


Figure 2. Linear regression analyses including Bland-Altman plots of differences (11) between intracoronary and Doppler echocardiographic measurements. Some symbols represent more than one pair of data. (A) Comparison of intracoronary vs. echocardiographic baseline average peak velocity (bAPV) in group 1 and group 2; (B) comparison of intracoronary vs. echocardiographic hyperemic average peak velocity (hAPV) in both groups; (C) comparison of intracoronary vs. echocardiographic coronary flow velocity reserve (CFVR) in both groups. Open circle = group 1; filled circle = group 2. ICD = intracoronary Doppler; SD = standard deviation; SEE = standard error of estimate; TTDHE = transthoracic Doppler harmonic echocardiography.

specificity at its optimal cut point (Fig. 3). Other indices, especially bMDV and bAPV, as well as PSV and MSV at an infusion rate of 50 $\mu\text{g}/\text{kg}/\text{min}$, showed partly higher specificity but markedly lower sensitivity at their particular optimal cutoff points than CFVR (Table 4).

DISCUSSION

This is the first study to show that TTDHE is capable of measuring CFVR with similar results as intracoronary Doppler in patients with and without arterial hypertension,

Table 3. Transthoracic Doppler Harmonic Echocardiography Results in Both Groups

Adenosine	Group	PSV (cm/s)	MSV (cm/s)	PDV (cm/s)	MDV (cm/s)	APV (cm/s)	CFVR
Baseline	1	13.4 ± 4.96	11.9 ± 4.54	28.6 ± 9.22	23.9 ± 8.11	19.0 ± 6.41	—
	2	10.3 ± 2.78	9.15 ± 2.60	25.1 ± 7.76	19.7 ± 4.75	15.1 ± 3.35	—
	Difference	p = 0.0082	p = 0.0117	NS	p = 0.0273	p = 0.0091	—
50 U	1	15.5 ± 6.87*	14.0 ± 6.19*	29.8 ± 0.79	25.0 ± 8.46	20.6 ± 6.73	—
	2	10.8 ± 2.17	10.1 ± 2.49	25.4 ± 7.51	20.6 ± 5.22	16.1 ± 3.33	—
	Difference	p = 0.0017	p = 0.0040	NS	p = 0.0285	p = 0.0035	—
75 U	1	21.5 ± 11.3*	18.8 ± 9.06*	37.5 ± 12.6*	32.0 ± 10.9*	27.0 ± 9.67*	—
	2	17.2 ± 8.23*	15.9 ± 7.73*	34.8 ± 17.1*	29.4 ± 13.8*	23.4 ± 11.3*	—
	Difference	NS	NS	NS	NS	NS	—
100 U	1	29.4 ± 13.9*	26.1 ± 11.3*	52.6 ± 20.4*	44.8 ± 18.0*	36.3 ± 13.6*	—
	2	26.9 ± 13.1*	24.3 ± 11.4*	51.3 ± 20.3*	43.6 ± 17.0*	35.3 ± 13.7*	—
	Difference	NS	NS	NS	NS	NS	—
140 U (Hyperemia)	1	36.1 ± 11.8*	33.2 ± 10.9*	63.4 ± 20.1*	55.0 ± 16.2*	45.4 ± 13.0*	2.44 ± 0.49
	2	37.8 ± 11.3*	34.5 ± 9.19*	70.6 ± 16.8*	59.6 ± 11.7*	48.8 ± 8.95*	3.33 ± 0.40
	Difference	NS	NS	NS	NS	NS	p < 0.0001

Data are expressed as mean ± SD. *Significant increase compared to next lower dosage of adenosine (p < 0.05 after alpha-adjustment according to Bonferroni). APV = average peak velocity; CFVR = coronary flow velocity reserve; MDV = mean diastolic velocity; MSV = mean systolic velocity; NS = not significant; PDV = peak diastolic velocity; PSV = peak systolic velocity; U = μg/kg/min.

and that TTDHE is suitable to assess microvascular function and dysfunction. Promising new technical developments allow CFVR measurements with transthoracic Doppler echocardiographic methods, as demonstrated in recently published investigations (7,13). Moreover, TTDHE has already been extensively validated as a useful method to assess coronary artery disease (14,15).

Alterations of coronary flow dynamics in arterial hypertension. Significant coronary lesions were ruled out with intravascular ultrasound, which allows to reliably assess difficult anatomic situations including angiographic superimposition of side branches. The results of our investigation clearly indicate that two independent functional abnormalities impair CFVR in arterial hypertension, that is, increase in basal flow velocity and decrease in vasodilative response to adenosine. This particular finding is in agreement with

early results by Hoffman (16). Especially at higher adenosine doses, APV increased less when arterial hypertension was present. Arterial hypertension is well known to lead to pathologic left ventricular hypertrophy and structural and functional alterations of intramyocardial coronary arterioles, usually resulting in impaired coronary flow dynamics and lowered CFVR in particular (9). Structural remodeling of intramyocardial arterioles and the accumulation of fibrillar collagen seem to be decisive factors for a reduced coronary dilatory reserve (17). The increased CFVR that can be demonstrated by transthoracic Doppler echocardiography after aortic valve replacement for aortic stenosis, and that parallels the regression of left ventricular hypertrophy, shows that hypertrophy plays another important role in this respect (18).

Value of TTDHE. The present results clearly demonstrate that echocardiographic readings of CFVR are in good agreement with intracoronary data, no matter what the microvascular function is. As previously reported, echocardiography tends to slightly underestimate APV (8). This

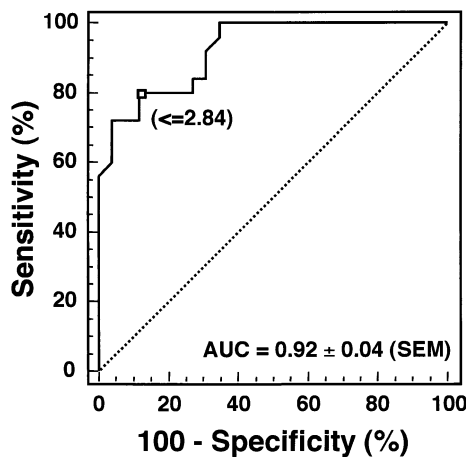


Figure 3. Calculation of the optimal cutoff point between group 1 and group 2 by use of receiver operating characteristic curve with respect to coronary flow velocity reserve. Dotted line shows a random distribution. AUC = area under the receiver operating characteristic curve; SEM = standard error of the mean.

Table 4. Sensitivity and Specificity of Echocardiographic Measurements with Respect to Group Distinction

Variable	Sensitivity (%)	Specificity (%)	Optimal cutoff point (cm/s)
bPSV	68	58	11.3
bMSV	56	77	10.7
bMDV	48	85	23.3
bAPV	68	66	15.5
PSV (50 μg/kg/min)	56	100	14.7
MSV (50 μg/kg/min)	56	96	13.7
MDV (50 μg/kg/min)	64	69	21.0
APV (50 μg/kg/min)	72	54	16.3
CFVR	80	88	2.84

APV = average peak velocity; b = baseline; CFVR = coronary flow velocity reserve; MDV = mean diastolic velocity; MSV = mean systolic velocity; PSV = peak systolic velocity.

report also demonstrates that hypertensives can be clearly distinguished from nonhypertensives on the basis of APV, PSV, MSV and MDV at baseline and at a low dose of adenosine. The capability of a detailed systolic and diastolic coronary flow velocity analysis during gradual increase of hyperemia, represents an advantage of TTDHE in comparison with the invasive approach. As determined by this technique, CFVR was found to be even more distinctive than the other flow velocity parameters. It is interesting to note that the sensitivity and specificity we found for echocardiographic CFVR match the sensitivity and specificity of CFVR for the detection of coronary artery disease (19). The cutoff point for distinguishing normal from coronary flow dynamics impaired by microvascular disease is very close to the 3.0 value previously reported, and it exceeds the cutoff value recently proposed for microvascular dysfunction in women by only a very small amount (12,20). The established invasive flow measurement techniques provide comprehensive information on the functional significance of epicardial coronary stenoses and on microvascular dysfunction (20).

Clinical implications. As previously shown, TTDHE is suitable for assessing functional disorders of coronary flow dynamics noninvasively when following patients (18). Therefore, TTDHE can be considered capable of assessing microvascular function and may also become a valuable noninvasive tool for evaluating drug effects on the coronary microcirculation. As an extension of this work, it would be also interesting to evaluate the relation between the results of stress testing and CFVR in hypertensive patients with normal coronary arteries. Obviously, coronary stenosis and microvascular dysfunction have the same effect on CFVR, but increased baseline flow may be more related to dysfunctional microcirculation (21).

Study limitations. A small number of noninsulin-dependent diabetics and smokers were included in the study (2,3,20). Nevertheless, comparison of coronary flow dynamics was not markedly altered, because both groups had similar proportions of patients. The fact that echocardiographic coronary flow velocity data were obtained from the very distal coronary arteries and that intracoronary measurements were performed more proximally can lead to small differences between both methods (8,12). The different routes of adenosine administration for the intracoronary and echocardiographic measurements may cause TTDHE to slightly underestimate APV in comparison with invasive readings (8). These dissimilarities appear to affect hAPV measurements in the two groups differently. In addition, we are now aware that in some patients higher doses of intracoronary adenosine are needed for maximum hyperemia. The doses used are nevertheless in agreement with standard doses used in international multicenter trials, such as the DEBATE trial (22). Because of the inability of TTDHE to measure CFVR in other vessels than in the left anterior descending coronary artery, reference measure-

ments in patients with abnormal CFVR in the left anterior descending coronary artery were not carried out.

Conclusions. In arterial hypertension, microvascular function and dysfunction can be reliably assessed noninvasively by coronary flow measurement using TTDHE. Specific changes of coronary flow dynamics detectable by incremental induction of hyperemic conditions seem to be characteristic for hypertensives. These results promise that TTDHE might also be valuable for assessing the microcirculation in other clinical conditions.

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