

Interventional Physiology

Utilization of Translesional Hemodynamics: Comparison of Pressure and Flow Methods in Stenosis Assessment in Patients With Coronary Artery Disease

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Aim of this study is the assessment of feasibility and clinical usefulness of a new index of stenosis severity, the slope of the instantaneous transstenotic pressure gradient/velocity relationship. Twenty-one patients scheduled for percutaneous revascularization procedures were studied with simultaneous measurement of poststenotic coronary pressure and flow velocity, in basal condition and during maximal hyperemia induced with intracoronary papaverine. Reliable measurements of the transstenotic pressure gradient/velocity relationship could be obtained in 11 patients. In 64% of the cases, a quadratic equation showed the best fit for the data. Steeper increases of the transstenotic pressure gradient at any given velocity increase were observed in the lesions with the smallest cross-sectional area measured with quantitative angiography. A comparison of this new index with coronary flow reserve, maximal hyperemic velocity, stenosis flow reserve derived from quantitative angiography, basal and hyperemic transstenotic pressure gradient and fractional flow reserve is presented and the relative merits of all these parameters are discussed. This pilot experience suggests that the instantaneous relationship between pressure gradient and flow velocity changes during the cardiac cycle can accurately characterize the stenosis hemodynamics in the catheterization laboratory.

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Key words: coronary stenosis, hemodynamics, intracoronary Doppler

INTRODUCTION

Assessment of functional severity of coronary stenoses is traditionally limited to noninvasive techniques such as stress electrocardiography, echocardiography, or myocardial scintigraphy. The results of these examinations, however, are not always sufficient to determine severity of individual stenoses visualized with coronary angiography, precluding immediate application of coronary interventions in the same session of the diagnostic procedure, and requiring additional investigations which prolong hospital stay and increase treatment cost. Noninvasive techniques cannot be used for immediate assessment of results of coronary interventions, when haziness of contours and wall disruption further impair the accuracy of conventional angiographic evaluation. A major technical development facilitating a functional evaluation in the catheterization laboratory was the introduction of miniaturized pressure and Doppler sensors with guide wire technology, allowing the measurement of poststenotic flow velocity and pressure [1,2]. The aim of this

study was the assessment of feasibility and clinical usefulness of indices of stenosis severity based on simultaneous measurements of transstenotic pressure gradient and flow velocity.

METHODS

Patient Population

Twenty-one patients (age: 62 ± 10 years, 17 males and 4 females) were studied with a simultaneous measurement of flow velocity and poststenotic coronary

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TABLE I. Clinical and Hemodynamic Characteristics of Patients Studied With Simultaneous Recording of Transstenotic Pressure Gradient and Flow Velocity*

Initials	Age (years)	Sex	VES	MLCSA (mm ²)	CSA sten (%)	BAPV (cm/sec)	HAPV (cm/sec)	CFR	SFR	Bas. grad. (mmHg)	Hyp. grad. (mmHg)	Bas. flow (ml/min)	Hyp flow (ml/min)	FFR _{myo}
WA	60	m	rca	0.49	0.92	10	27	2.70	1.25	21	43	20	53	0.48
BJL	73	m	svbg	0.21	0.98	7	11	1.57	0.30	42	46	20	31	0.41
FB	70	f	rca	2.26	0.74	31	62	2.00	3.13	4	17	84	167	0.85
BKJ	59	m	rca	0.82	0.95	10	15	1.50	1.0	12	35	50	74	0.58
BJ	62	m	lad	0.78	0.87	34	45	1.32	2.21	38	46	65	86	0.52
RTR	69	m	rca	0.33	0.97	8	11	1.37	0.49	38	39	24	33	0.51
SA	73	m	svbg	4.78	0.68	18	56	3.11	3.14	5	11	81	252	0.85
WC	59	m	lad	1.14	0.84	19	83	4.37		5	14	41	181	0.80
BJ	55	m	lad	1.10	0.86	66	141	2.14	2.66	5	18	157	336	0.80
DHTA	80	m	rca	0.30	0.97	8	10	1.25	0.46	44	49	23	28	0.42
SEA	74	m	rca	0.23	0.95	11	12	1.09	0.66	49	50	17	18	0.45
OMV	81	f	rca	1.39	0.85	48	131	2.73	2.89	28	37	132	361	0.61
EC	57	m	rca	0.80	0.92	30	45	1.50	1.92	15	42	97	146	0.60
BW	67	m	svbg	1.16	0.87	8	11	1.37	2.31	35	39	21	29	0.54
JB	63	f	rca	1.00	0.82	13	20	1.54	2.87	13	29	23	35	0.71
LTW	50	m	lad	1.19	0.71	21	39	1.86	4.24	28	65	33	56	0.36
WHP	41	m	lcx	1.89	0.77	14	37	2.64	3.92	1	23	34	89	0.76
DAG	52	m	rca	1.00	0.81	10	28	2.80	2.87	5	17	25	70	0.83
JKF	52	m	lcx	1.33	0.88	13	17	1.31	2.50	17	31	27	36	0.66
GMJP	60	f	lad	2.32	0.80	61	148	2.43	3.99	2	41	102	247	0.86
JAK	52	m	rca	0.36	0.93	15	33	2.20	1.31	12	33	21	46	0.68
Mean	62			1.18	0.86	22	47	2.04	2.21	20	33	52	113	0.63
± SD	10			1.02	0.09	17	44	0.81	1.20	16	15	41	105	0.16

*BAPV, baseline time-averaged peak blood flow velocity; CSA, cross-sectional area; CFR, coronary flow reserve; FFR_{myo}, fractional flow reserve myocardium; HAPV, hyperemic time-averaged peak blood flow velocity; lad, left anterior descending; LCX, left circumflex; MLCSA, minimal luminal cross-sectional area (angiographic measurement minus cross-sectional area of the pressure and (5 cases) Doppler guide wire); rca, right coronary artery; SFR, stenosis flow reserve; svbg, saphenous vein bypass graft.

pressure, before an intervention of percutaneous revascularization.

Patients with acute myocardial infarction, arterial occlusion/subocclusion (thrombolysis in myocardial infarction (TIMI) flow class 0–1), valvular heart disease, extreme tortuosity of the vessel to be dilated, or presence of an open aortocoronary bypass graft on the vessel to be treated were not included in the study. Systemic arterial hypertension was present in 5 cases (23%). Previous myocardial infarction in the territory of distribution of the studied artery was present in 7 cases (33%) (Table I). All patients were under antianginal treatment at the time of the study.

Catheterization Procedure

After intravenous administration of 10,000 IU of heparin and 250 mg of acetylsalicylic acid, an 8 French guiding catheter was advanced up to the coronary ostium. After isosorbide-dinitrate (2–3 mg intracoronary), cineangiograms suitable for quantitative assessment were obtained in multiple angiographic views.

The pressure guide wire was advanced into the artery to be dilated, and the pressure sensor was positioned 3–4 cm distal to the stenosis (Fig. 1). The Doppler guide wire

was maintained proximal to the stenosis, avoiding the presence of major side-branches between the site of the measurement and the stenosis and the segment of pre-stenotic acceleration of flow. In 5 patients, due to presence of side-branches immediately proximal to the stenosis, only flow velocity recordings distal to the stenosis were used for analysis. Proximal coronary pressure, poststenotic pressure, and proximal flow velocity were recorded both in baseline conditions and after an intracoronary bolus injection of papaverine (8 mg, right coronary; 12.5 mg, left coronary, saphenous vein bypass graft) [3]. Intracoronary nitrates (isosorbide dinitrate, 2–3 mg) were used before the injection of papaverine in order to induce maximal coronary vasodilatation and to prevent changes in cross-sectional area between baseline and postpapaverine assessment [4]. Care was taken to avoid impairment of flow during maximal hyperemia due to the presence of the guiding catheter in the coronary ostium. If damping occurred, the guiding catheter was withdrawn from the coronary ostium immediately after injection of papaverine. The Doppler guide wire was then advanced distal to the stenosis, and a new basal and postpapaverine acquisition of pressure and velocity measurements was obtained (Fig. 2).

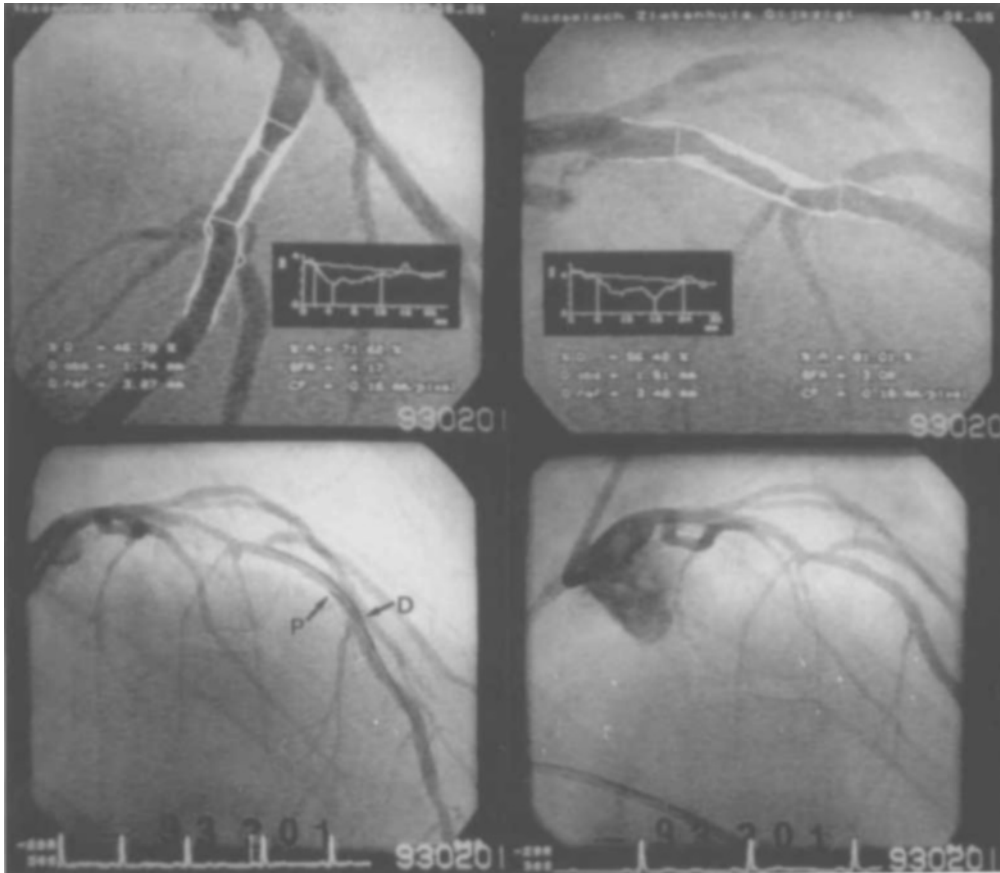


Fig. 1. Upper: Biplane orthogonal digital angiograms (left, LSO; right, RSO) of a left anterior descending coronary artery showing presence of a significant concentric stenosis of the mid-segment. Diagrams show diameter function of the examined segment after automatic contour detection. Lower: Positions of tip-mounted Doppler sensor (D) and of sensor of the pressure guide wire (P), both advanced distal to stenosis, as indicated by arrows.

Quantitative Angiographic Measurements

The guiding catheter, filmed empty of contrast medium, was used as a scaling device. A previously validated [5] on-line analysis system operating on digital images (ACA-DCI, Philips, Eindhoven, the Netherlands) was used during the catheterization procedure. From the measured minimal luminal diameter (MLD), the minimal luminal cross-sectional area was calculated assuming a circular cross section (in 15 patients (71%) as the average of measurements in multiple views). An interpolated technique was used to define the reference diameter, and percent diameter and cross-sectional area stenosis were calculated. A user-defined diameter was also measured at the site of the Doppler sample volume in order to calculate coronary blood flow as the product of mean blood-flow velocity and cross-sectional area.

Doppler Flow Velocity Measurements

A 0.018" (diameter, 0.45 mm; cross-sectional area, 0.17 mm²) 12-MHz Doppler guide wire (Cardiometrics

Inc., Mountain View, CA) [1] was used in this study. After real-time processing of the quadrature audio signal using a fast-Fourier transform algorithm [6], the Doppler system calculates and displays on-line several spectral variables, including time-averaged (mean of two beats) peak velocity. The instantaneous peak velocity is calculated after spectral analysis of the Doppler signal [6] and is also available as a calibrated analog signal for continuous recording [7]. Mean flow velocity was calculated as time-averaged peak velocity/2, assuming a fully developed flow velocity profile [8]. Coronary flow reserve was defined as the ratio between maximal flow velocity at the peak effect of the papaverine injection and at baseline conditions.

Pressure Guide Wire and Transstenotic Pressure Gradient Measurements

A pressure sensor, located 2 cm proximal to the flexible tip of a 0.018" guide wire (Radi Medical Systems, Uppsala, Sweden), was used in this study. The system

PRESSURE-VELOCITY RECORDING 4 HEART BEATS

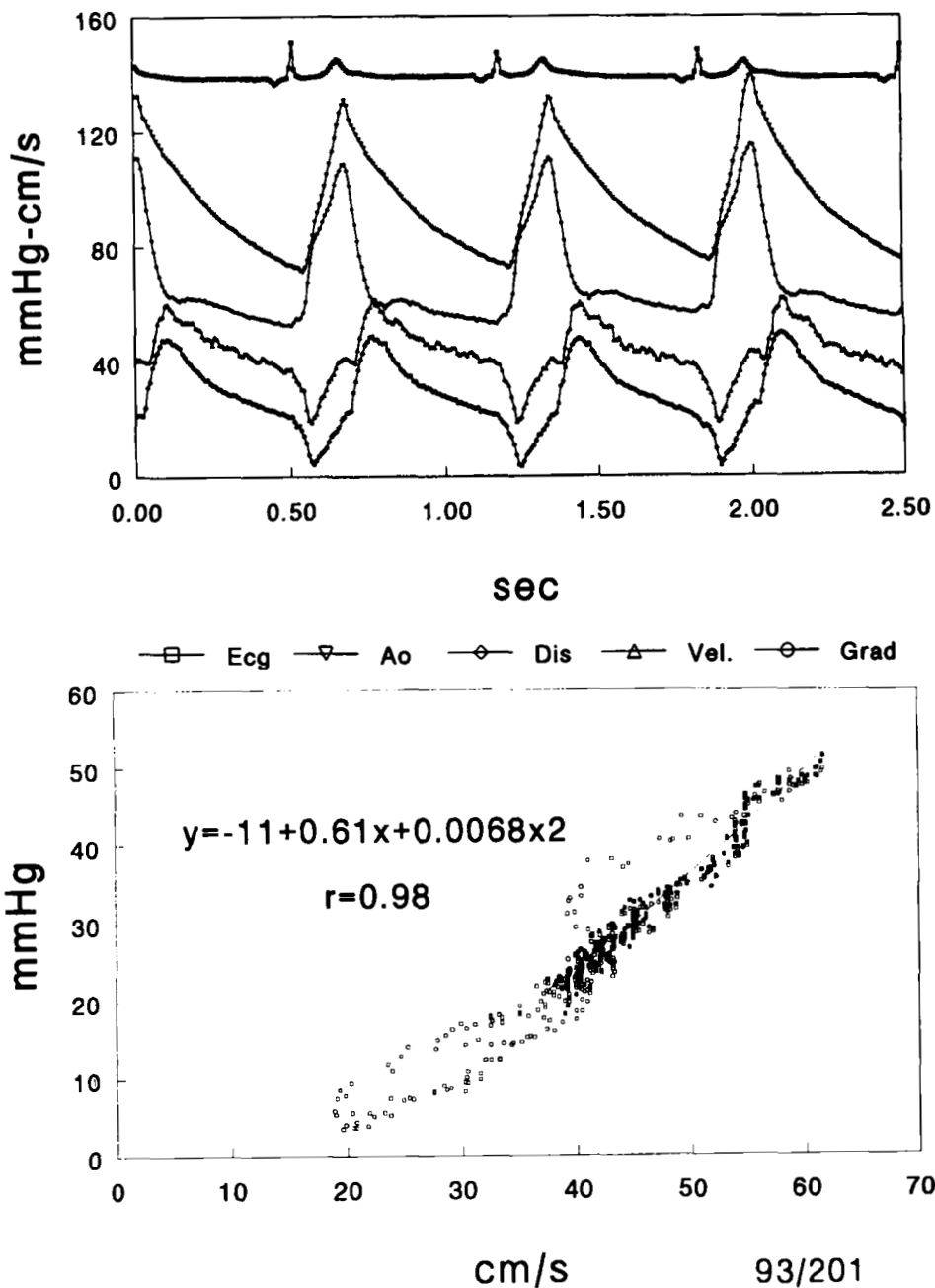


Fig. 2. Upper: Simultaneous recording of electrocardiogram, proximal and distal (post-stenotic) coronary pressures, instantaneous peak flow velocity, and transstenotic pressure gradient during four consecutive cardiac cycles at the peak effect of papaverine. Lower: Pressure gradient and flow velocity relationship of same four cardiac cycles. Data points corresponding to phases of early diastolic relaxation and of early systolic contraction, and the remaining systolic data points (empty squares), are not considered in the analysis. Dashed line is drawn from exponential equation showing best fit for mid-late diastolic data points (black squares).

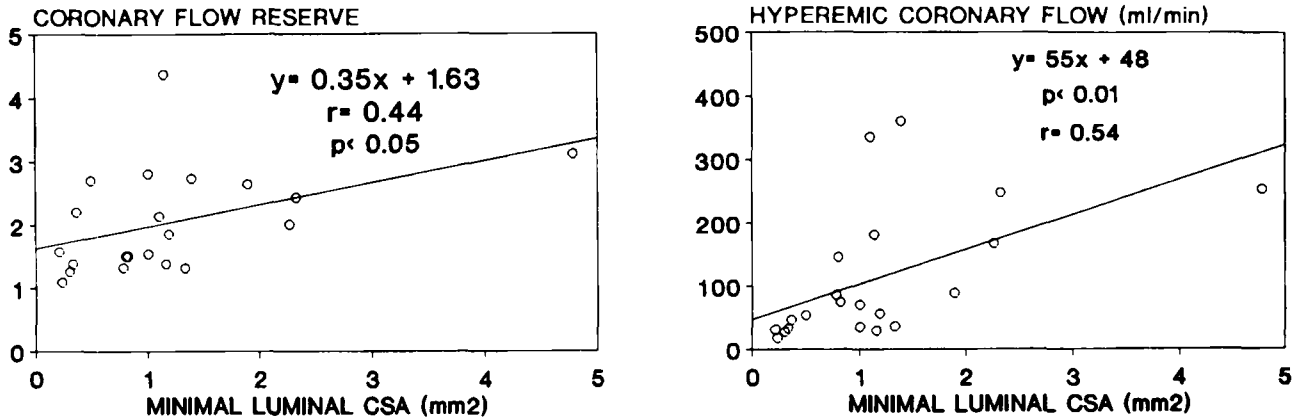


Fig. 3. Linear regression analysis of coronary flow reserve (left) and hyperemic coronary flow (right) vs. minimal luminal cross-sectional area (MLCSA).

has already been described and validated in vitro with regard to signal transfer characteristics, linearity, and frequency response [2]. The pressure signal was calibrated immediately before insertion, and the accuracy of the measurement was checked by superimposing the prestenotic coronary pressure measured with the pressure guide wire, and the proximal coronary pressure measured with the guiding catheter.

The mean transstenotic gradient was calculated as the difference of mean proximal and mean distal coronary pressure over four consecutive beats in baseline conditions and at peak effect of papaverine (Fig. 2). The simultaneous maximal hyperemic measurements of aortic pressure (P_{ao}) poststenotic coronary pressure (P_d) were used to calculate the fractional flow reserve of the myocardium (FFR_{myo}), defined as the ratio between actual maximal hyperemic flow and maximal theoretical flow in the absence of a coronary stenosis. Fractional flow reserve was calculated, according to the formula proposed by Pijls et al. [9], as:

$$FFR_{myo} = \frac{P_d - P_v}{P_{ao} - P_v}$$

Since no patients had signs of right ventricular failure, right atrial pressure (P_v) was neglected for the calculation.

Comparison With Physiological Parameters Derived From QCA Measurements

Stenosis flow reserve has been described by Kirkeeide et al. [10] as a single integrated index of stenosis severity, based on measurements of stenosis geometry, of transstenotic maximal pressure gradient, and of maximal flow increase under standardized conditions. These authors validated in vivo [11] flow dynamic equations de-

veloped in in vitro models by Young and Tsai [12] and Young et al. [13], and adapted for tapering stenoses and X-ray analysis by Brown et al. [14]. The algorithm, also implemented in the software package of the Philips DCI analysis system, uses the formula:

$$\Delta P = \frac{8\pi\mu L}{1.33A_s^2} Q + \frac{k_e \rho}{0.266} \left(\frac{1}{A_s} - \frac{1}{A_n} \right)^2 Q^2 \quad (1)$$

where ΔP is the transstenotic pressure gradient in mmHg, μ is dynamic blood viscosity in Poise (assumed equal to 0.03), L is the length of the stenosis in mm, A_n is the cross-sectional area of the reference normal segment in mm², A_s is the minimal cross-sectional area of the stenotic segment in mm², Q is the mean coronary blood flow in ml/sec, ρ is blood density in g/ml (assumed equal to 1.05), and k_e is the expansion coefficient used to correct for entrance effect in order to apply the above equation in short stenoses as:

$$K_e = 1.21 + 0.08 \frac{L_{prox}}{REF - D} \quad (2)$$

where L_{prox} is the length of the entrance segment, approximated as lesion length divided by 2, and $REF-D$ is the diameter of the reference segment [15,16]. Based on the poststenotic pressure calculated from the above equations and the measurements of stenosis geometry, stenosis flow reserve was calculated assuming a maximal increase in coronary flow of five times at a mean aortic pressure of 100 mmHg [17], a coronary venous pressure of 10 mmHg, and a mean blood flow velocity of 15 cm/sec [10,11].

Stenosis flow reserve was compared both with the measured coronary flow reserve and, to allow a compar-

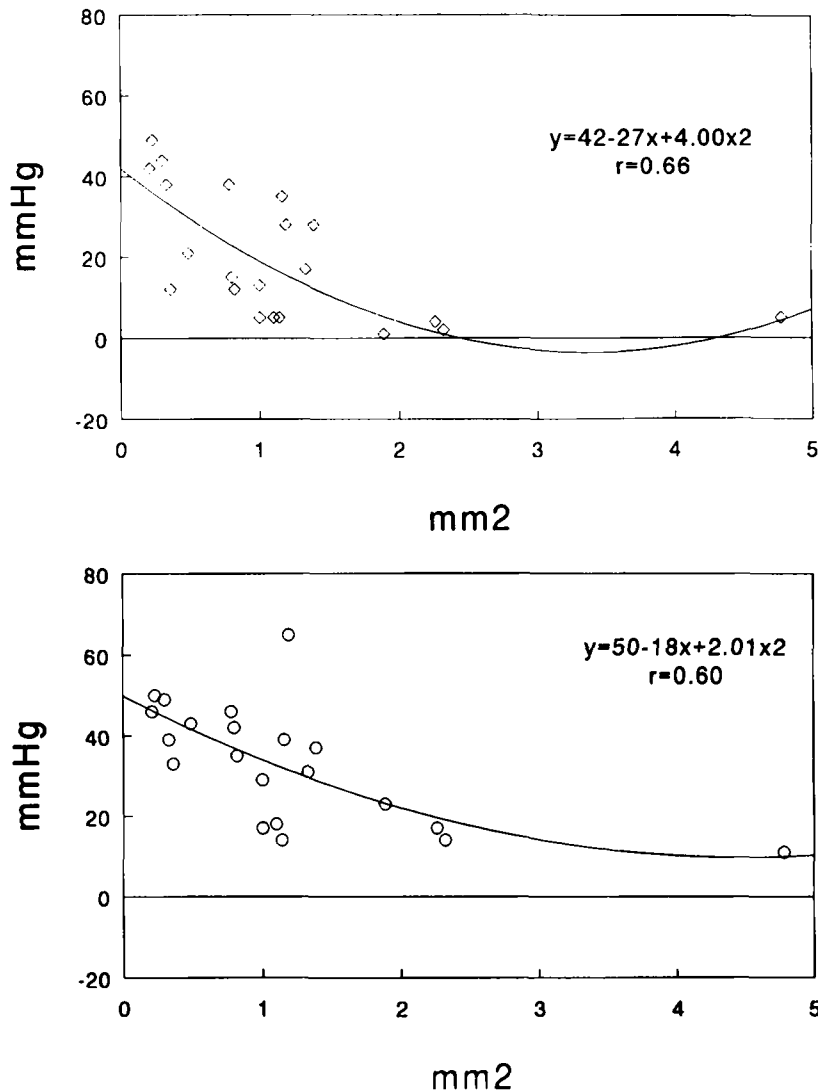


Fig. 4. Baseline (above) and hyperemic (below) transstenotic pressure gradient plotted vs. minimal luminal cross-sectional area (MLCSA). An exponential increase in pressure gradient was observed with decrease in cross-sectional area.

ison under more standardized conditions, with the ratio between measured hyperemic mean velocity and the basal mean velocity assumed in the above equation (15 cm/sec).

Equation 1 was used to calculate baseline and maximal hyperemic transstenotic pressure gradient, using the real baseline and hyperemic flow velocities to calculate the corresponding coronary flow so that estimated and measured pressure gradients could be compared at the same level of flow.

Instantaneous Assessment of Pressure Gradient/Flow Velocity Relationship

In 15 patients (71%) a continuous acquisition of data was performed with a 12-bit analog-to-digital converter

connected to a PC. Electrocardiogram, pre- and post-stenotic coronary pressure, and peak coronary blood-flow velocity were continuously sampled at 125 Hz per channel and stored on hard disk for off-line analysis (Fig. 2). Positive or negative drifts of the zero-pressure of the pressure sensor, present in 7 patients (33%), and the phase delay of the pressure signal recorded through the fluid-filled guiding catheter were corrected by superimposing the pressure recorded through the guiding catheter and the prestenotic coronary pressure recorded with the pressure guide wire. Afterwards, the instantaneous transstenotic pressure gradient was calculated and plotted against the corresponding coronary flow velocity, using dedicated software (AdvCodas, DataQ, Akron, OH), (Fig. 2). The transstenotic pressure gradient/flow veloc-

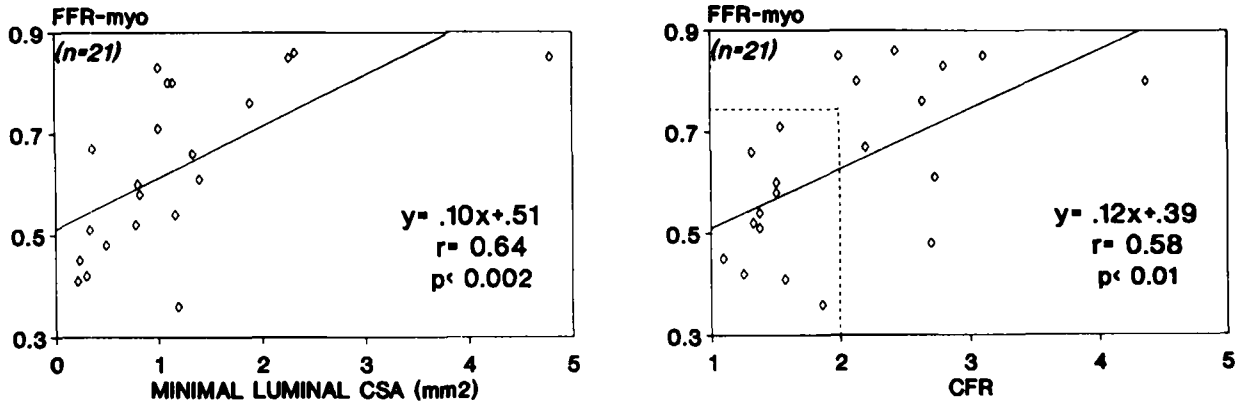


Fig. 5. Left: Relationship between fractional flow reserve (FFR_{myo}) and minimal luminal cross-sectional area (MLCSA). Right: Relationship between fractional flow reserve (FFR_{myo}) and coronary flow reserve (CFR). Note that all patients with coronary flow reserve smaller than 2.0 also had pathologic measurements of fractional flow reserve (dashed area in left lower corner).

ity relationship was analyzed from the digitized pressure and flow velocity during middiastole (start point, maximal diastolic flow velocity; end point, rapid deceleration of flow due to beginning of myocardial contraction). Phases of rapid acceleration/deceleration of flow were not considered for analysis, as suggested by Gould [18], because the flow changes in these phases are influenced by factors not related to severity of lesion (capacitance effects, myocardial contractility, heart rate, etc.). The systolic phase of the cardiac cycle was not considered, in order to avoid possible artifacts of the flow velocity signal, frequent during cardiac contraction (wall thumps, motion artifacts). Four consecutive beats were analyzed at the peak effect of the injection of papaverine.

Statistical Analysis

Regression analysis was used to compare measurements of pressure gradient and coronary flow and derived indices with the minimal luminal cross-sectional area of the explored stenosis and with transstenotic pressure gradients and stenosis flow reserve. A best-fit analysis was used to assess the relationship between instantaneous pressure gradient and flow velocity (BmDP statistical package). Statistical significance was defined as $P < 0.05$. All data were expressed as mean \pm SD.

RESULTS

Flow Velocity and Transstenotic Pressure Gradient Measurements

The quantitative angiographic, flow velocity, pressure gradient, and flow measurements of the 21 patients studied are reported in Table I. Coronary flow reserve

showed a partial but statistically significant correlation with minimal luminal cross-sectional area (Fig. 3, $r = 0.44$, $P < 0.05$). Coronary flow during maximal hyperemia, but not baseline flow ($r = 0.37$, NS), was significantly correlated with minimal luminal cross-sectional area ($r = 0.54$, $P < 0.01$) (Fig. 3). Baseline and hyperemic transstenotic pressure gradients showed a significant inverse correlation with minimal luminal cross-sectional area ($r = -0.66$ and $r = -0.60$, respectively) (Fig. 4). An exponential increase in pressure gradient with decrease in minimal luminal cross-sectional area was observed. Fractional flow reserve showed a significant correlation with minimal luminal cross-sectional area (Fig. 5).

Measured (Doppler) and Estimated (QCA) Flow Reserve and Transstenotic Pressure Gradients

Fractional flow reserve was correlated with coronary flow reserve and, in particular, pathologic values of coronary flow reserve (< 2.0) were associated with an impairment of fractional flow reserve (< 0.75) (Fig. 5). No correlation was present between coronary flow reserve and stenosis flow reserve (Fig. 6). Despite a statistically significant correlation, measured and estimated stenosis flow reserve showed a large dispersion of the individual measurements ($r = 0.52$, Fig. 6). A better correlation was observed between estimated and measured transstenotic pressure gradient in baseline condition ($r = 0.65$, $P < 0.002$, Fig. 7). During maximal hyperemia, however, no significant correlation was observed between estimated and measured transstenotic pressure gradients ($r = 0.13$, Fig. 7). Table II summarizes the correlation observed between different measurements and indices of stenosis severity (absolute correlation coefficients are reported).

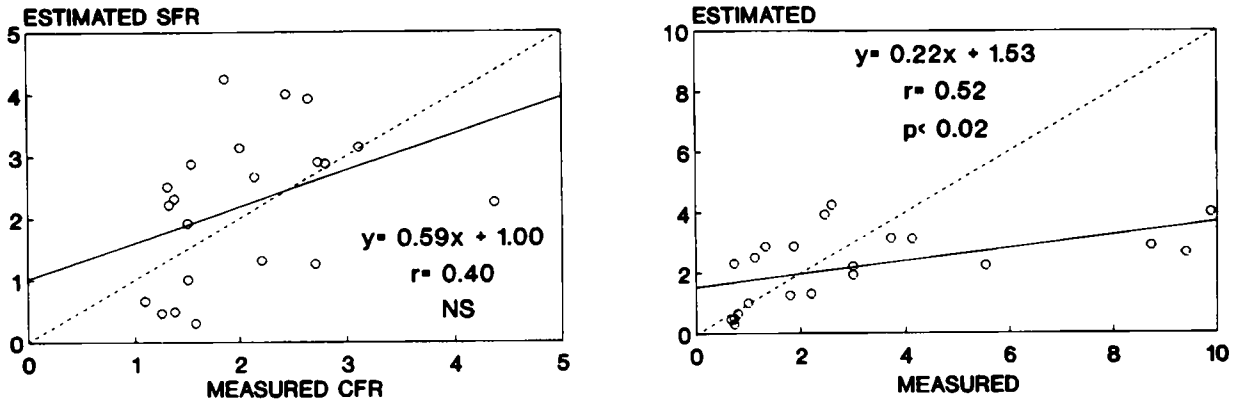


Fig. 6. Stenosis flow reserve estimated from angiographic stenosis geometry is plotted against measured coronary flow reserve (left) and against the ratio between measured maximal hyperemic flow velocity and mean velocity assumed for calculation of stenosis flow reserve (15 mmHg) (right). Dashed lines indicate identity lines. Solid lines indicate regression lines.

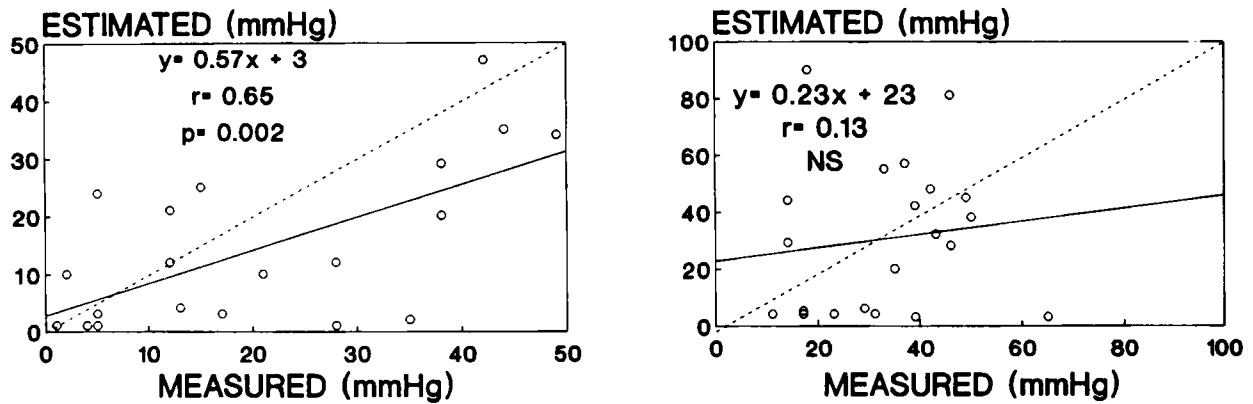


Fig. 7. Estimated and measured transstenotic pressure gradients in baseline conditions (left) and at peak hyperemia (right). Dashed lines, identity lines; solid lines, regression lines.

Instantaneous Assessment of Hyperemic Coronary Pressure/Flow Velocity Relationship

A clear Doppler envelope allowing reliable automatic detection of the hyperemic diastolic peak velocity during four consecutive beats was obtained in 11/15 cases (73%) (Fig. 8). A linear relationship between transstenotic gradient and flow velocity was observed in 4/11 patients (36%). In the remaining patients a quadratic equation had the best fit for the data obtained (7/11, 64%). In all but one case an intercept close to 0 (± 10 mmHg) was observed. Steeper increases of the transstenotic pressure gradient at a given flow velocity increase were measured in the arteries with the most severe reduction in luminal cross-sectional area and with the most severe impairment in fractional flow reserve.

DISCUSSION

The interest in new indices for characterizing the functional severity of coronary stenoses is justified by the

limitations of the currently used velocity and pressure parameters, evident also in our limited study group.

Coronary Flow Reserve

Theoretically, measurement of impairment in maximal coronary flow is the ideal method to determine functional severity of a stenosis, as shown in animal experiments [19]. Coronary flow reserve is well correlated with the results of myocardial scintigraphy, with values <2.0 highly associated with presence of a normal radioisotopic uptake [20–22]. Coronary flow reserve, however, is influenced by hemodynamic conditions at time of assessment (heart rate, aortic pressure) [23–25]. The discrepancy between angiography and Doppler following coronary interventions may reflect the inability of a silhouette technique such as angiography to detect incomplete dilatations in the presence of a diffuse wall disruption. In other cases, however, an alternative explanation may be found in the development of acute

TABLE II. Correlation Coefficients of Multiple Measurements and Indices of Stenosis Severity*

	MLCSA	SFR-QCA	FFR-myocardium
ΔP rest	0.66	0.62	0.88
ΔP hyper	0.60	0.28	0.87
Hyp flow	0.54	0.46	0.56
CFR	0.44	0.40	0.58

* ΔP rest/Hyper, basal and hyperemic pressure gradient; FFR-myocardium, fractional flow reserve (myocardium); MLCSA, minimal luminal cross-sectional area (mm^2); SFR-QCA, stenosis flow reserve, based on quantitative angiographic measurements; Hyp flow, hyperemic coronary flow; CFR, coronary flow velocity reserve.

changes in resting flow and of transient modifications of the vasodilatory capacity of the distal coronary vasculature induced by microemboli or by the release of powerful vasoconstrictors [26–31]. Furthermore, several pathologic conditions (cardiac hypertrophy, myocardial scarring, diabetes, hypercholesterolemia, systemic hypertension, etc.) induce more permanent changes of the hyperemic pressure-velocity relationship. In these conditions, stenosis severity is overestimated if the low flow during maximal vasodilatation is attributed to high resistance across the stenosis.

Stenosis Flow Reserve

Stenosis flow reserve is an alternative approach, based only on quantitative angiographic measurements, to evaluate the severity of a coronary stenosis assuming standardized hemodynamic conditions and a normal pressure-velocity relationship [10,11]. As clearly pointed out by the proposers of this index [10,11], stenosis flow reserve cannot be considered an estimate of real coronary flow reserve, determined also by hemodynamic conditions at time of assessment, presence of collateral flow, and properties of microcirculation. In this respect, the use of standardized conditions assumed in the calculation of this index has the advantage that only flow limitations induced by the studied stenosis are considered. The difference between actual and assumed hemodynamic conditions, and the coexistence of alterations of the arteriolar vasodilatory capacity, are sufficient to explain the poor correlation between estimated stenosis flow reserve and measured coronary flow reserve, observed in this study and in a recent study by Tron et al. [32]. A more consistent methodology for testing whether hemodynamic parameters derived from quantitative angiographic measurements reflect real measurements is the comparison with the transstenotic pressure gradients calculated, assuming a coronary flow velocity and an aortic pressure equal to the measured velocity and pressure. This comparison, however, also showed large individual differences between measured and estimated transstenotic pressure gradients, possibly as a consequence of the unavoidable

inaccuracies in the measurement of the multiple geometric factors which determine stenosis severity, and in the application of equations derived from simplified in vitro hydraulic models to stenoses of complex geometry.

Transstenotic Pressure Gradient and Fractional Flow Reserve

The importance of the dimensions of the pressure sensor used for measurement of the transstenotic pressure gradient has been extensively studied in the years following the introduction of coronary angioplasty, when the pressure gradient recorded through the central lumen of the balloon catheter was used for immediate assessment of the results of the procedure [33–35]. More recently, using a fluid-filled pressure guide wire as the angioplasty guide wire, the large increase in pressure gradient observed with the balloon catheter positioned in the lesion has been confirmed [36]. The correlation observed in this study between basal and hyperemic transstenotic pressure gradients and angiographic indices of stenosis severity has been confirmed in a larger series of patients by Emanuelsson et al. [37]. Donohue et al. [38] studied the correlation of basal measurements of transstenotic pressure gradient and myocardial scintigraphy and velocity indices of stenosis severity. The dependency of myocardial flow on the driving pressure over the myocardium may explain why measurements of pressure gradient alone may be deceptive when not corrected for the corresponding aortic and venous pressures. The revolutionary concept of fractional flow reserve, introduced by Pijls et al. [9] and validated in man by de Bruyne et al. using positron emission tomography [39], can greatly simplify and increase the accuracy of the methods of assessment of stenosis severity. The ultimate goal of these methods is to establish in what proportion the maximal hyperemic flow of a given myocardial area is reduced by the presence of a stenosis, and this information is provided by fractional flow reserve, an index independent of hemodynamic conditions during assessment, of baseline flow, and of the integrity of peripheral resistance vessels.

Simultaneous Measurement of Pressure Gradient and Flow Velocity

The simultaneous measurement of transstenotic pressure gradient and flow velocity avoids any possible misinterpretation of the changes of both these indices during maximal vasodilatation. When a low maximal flow is present due to factors not dependent on stenosis resistance, the measurement of a low transstenotic pressure gradient can be misleading, falsely suggesting the presence of a nonsignificant stenosis. Conversely, only the simultaneous measurement of pressure gradient can discriminate between a low flow increase during maximal

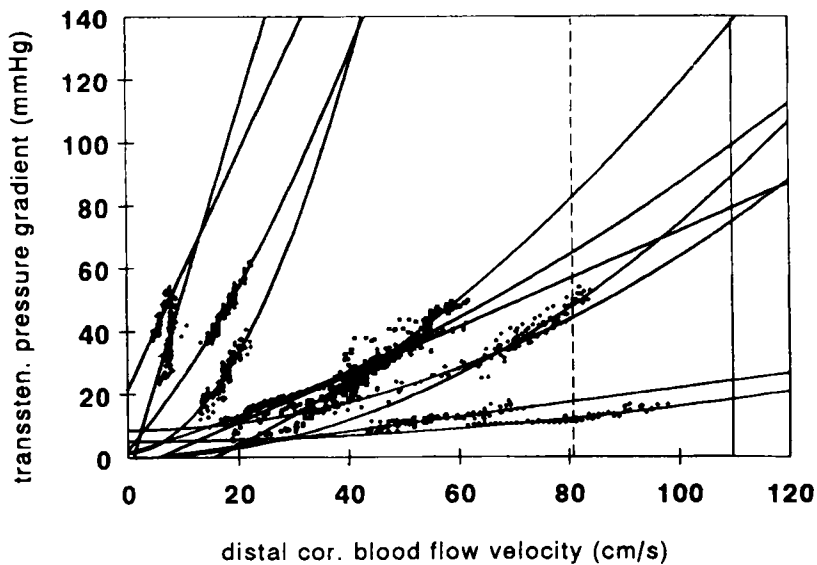
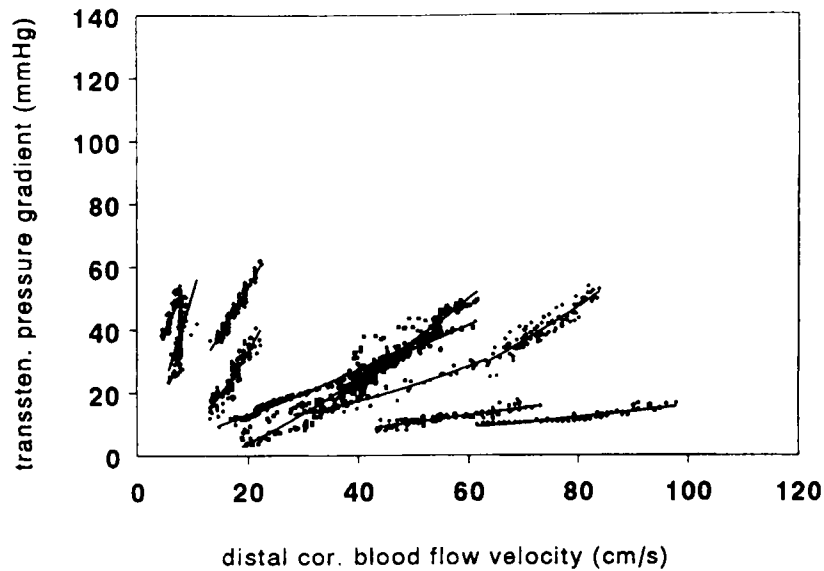


Fig. 8. Upper: Instantaneous hyperemic diastolic pressure gradient/flow velocity relationship for 11 stenoses of decreasing hemodynamic severity (from left to right, and from top to bottom). Corresponding fractional flow reserve (FFR_{myo}) and minimal luminal cross-sectional area (MLCSA) are reported after subtraction of cross-sectional areas of pressure and Doppler guide wires (1 = left upper curve, 11 = right lower curve).

Nb/Init.	MLCSA (mm ²)	FFR_{myo}	Equation
1 BJL	0.21	0.41	$y = 21 + 3.72x$
2 RTR	0.33	0.51	$y = -6 + 5.76x$
3 JKF	1.16	0.65	$y = 2 + 2.01x + 0.0275x^2$
4 BKJ	0.82	0.58	$y = 2 + 0.11x + 0.073x^2$
5 DAG	0.83	0.83	$y = 1.6 + 0.50x + 0.0035x^2$
6 WHP	1.72	0.76	$y = -4 + 0.28x + 0.009x^2$
7 JB	0.83	0.71	$y = -4 + 0.76x$
8 JAK	0.36	0.68	$y = 9 + 0.0055x^2$
9 LTW	1.19	0.36	$y = -0.1 + 0.0074x^2$
10 SA	4.61	0.71	$y = -1 + 0.23x$
11 FB	2.09	0.84	$y = 5 + 0.0011x^2$

Lower: Same plots of pressure gradient/flow velocity relationship after extrapolation of curves to the average of the maximal instantaneous hyperemic peak velocity in 34 normal coronary arteries indicated by solid line; dotted line indicates average minus standard deviation [25].

vasodilatation due to a hemodynamically severe stenosis (high-pressure gradient) and a low flow increase due to an impairment of the distal vasodilatory mechanisms or to competition of flow through a well-developed collateral circulation (low-pressure gradient). Although maximal flow and, consequently, maximal transstenotic gradient are determined also by factors independent of stenosis resistance, the relationship between transstenotic pressure gradient and flow is intimately correlated with stenosis hemodynamics. When the slope of this relationship is calculated, the actual maximal measurements of flow velocity and transstenotic pressure gradient are irrelevant, and the hemodynamic severity of a stenosis can also be determined when an impairment of the peripheral vasodilatory reserve is the factor limiting maximal flow response. The extrapolation of the calculated pressure gradient/velocity relationship to a maximal theoretical instantaneous flow velocity is a possible method for comparing different stenoses. The only limitation to this approach is the large range of maximal hyperemic instantaneous peak velocities observed in arteries without significant stenoses, caused by physiologic differences in arterial diameter and increased by atherosclerotic changes of lumen diameter not detected angiographically but producing diffuse arterial narrowing or ectasia. It must be noted that the pressure gradient/flow velocity relationship shows a steeper increase in smaller arteries than in larger arteries for a given severity of the coronary stenosis [40]. The use of velocity instead of flow can be considered a correction of this limitation, because the characteristics of the coronary branching system result in a moderate reduction of flow velocity from proximal to distal coronary segments, despite the presence of large changes in coronary flow [41].

The precise characterization of stenosis hemodynamics obtained with the measurement of the pressure gradient-velocity relationship does not provide direct elements to confirm or rule out myocardial ischemia in the territory of distribution of the examined artery. In particular, in the presence of stenoses of similar hemodynamic severity, the development of myocardial ischemia is influenced by the amount of recruitable collateral flow and by the mass of viable myocardium perfused. These limitations can explain the presence of the same normal myocardial fractional flow reserve in two arteries with a completely different slope of transstenotic gradient/velocity relationship (n. 7 and n. 10 in the legend to Fig. 8). With these conflicting results, the first impression is that the fractional flow reserve is giving the right answer, since this index appears to completely meet the expectations of the clinician for a measurement predicting the potential of a given stenosis to induce myocardial ischemia. Consequently, it seems irrelevant whether a stenosis has a steep or a flat pressure gradient/flow velocity relationship, as

long as the myocardium supplied by the vessel under investigation receives sufficient perfusion for its metabolic and contractile needs. A more thorough investigation, however, would reveal that fractional flow reserve also has pitfalls. After coronary interventions or in patients with acute syndromes or after myocardial infarction, transient changes in maximal hyperemic flow (microemboli, release of vasoconstrictors), or a reduction of oxygen demand due to a temporary impairment of regional ventricular function (stunning), would lead to an underestimation of stenosis severity using fractional flow reserve, but not using the gradient/velocity relationship which is independent of the maximal velocity increase.

The most important limitation of the proposed approach, remains the complexity of the instrumentation required for measurements. The ingenious system used in this study to record a high-fidelity pressure signal still has practical limitations because of the rigidity of the segment mounting the sensor, and because of the possibility that a shift of the zero-pressure occurs when this segment is positioned in a sharp vascular bend. The passage of two separate guide wires, both with a cross-sectional area of 0.17 mm^2 , can induce a significant additional obstruction in the presence of severe coronary stenoses [35], and was the main cause of failure in this series. Smaller Doppler guide wires (0.014") and a prototype of a 0.014" pressure guide wire are now available, but a real solution can only be the combination of the two sensors in the same guide wire system. Although these preliminary observations demonstrate that assessment of the instantaneous relationship between pressure gradient and velocity is feasible, this study is unable to demonstrate the potential clinical advantages of this new index because of the small number of patients assessed, and because of the heterogeneity of the population studied. In particular, it should be mentioned that, despite their limitations, the currently available indices based only on velocity or pressure measurements are able to characterize the functional severity of intermediate stenoses and the results of coronary interventions more precisely than angiography [20–22,38,42].

CONCLUSIONS

Miniaturization of flow velocity and pressure sensors with guide wire technology now permits the application in conscious humans of a methodological approach to the assessment of stenosis severity previously limited to the animal laboratory. This initial experience suggests that the simultaneous measurement of the instantaneous pressure gradient and flow velocity changes during the cardiac cycle can reproducibly and accurately characterize stenosis hemodynamics.

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REFERENCES

- Doucette JW, Douglas Corl P, Payne HP, Flynn AE, Goto M, Nassi M, Segal J: Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 85:1899–1911, 1992.
- Emanuelsson H, Dohnal M, Lamm C, Tenerz L: Initial experiences with a miniaturized pressure transducer during coronary angioplasty. *Cathet Cardiovasc Diagn* 24:137–143, 1991.
- Zijlstra F, Serruys PW, Hugenholtz PG: Papaverine: The ideal coronary vasodilator for investigating coronary flow reserve? A study of timing, magnitude, reproducibility, and safety of the coronary hyperemic response after intracoronary papaverine. *Cathet Cardiovasc Diagn* 12:298–303, 1986.
- Zijlstra F, Reiber JHC, Serruys PW: Does intracoronary papaverine dilate epicardial coronary arteries? Implications for the assessment of coronary flow reserve. *Cathet Cardiovasc Diagn* 4:1–6, 1986.
- Keane D, Haase J, Slager C, van Swijndregt WJ, Ozaki Y, Di Mario C, Serruys PW: Comparative validation of quantitative coronary angiographic systems: Results and implications from a multicenter study using standardized approach. *Circulation* 91:2174–2183, 1995.
- Di Mario C, Roelandt JRTC, de Jaegere P, Linker DT, Oomen J, Serruys PW: Limitations of the zero-crossing detector in the analysis of intracoronary Doppler. A comparison with fast Fourier transform of basal, hyperemic, and transstenotic blood flow velocity measurements in patients with coronary artery disease. *Cathet Cardiovasc Diagn* 28:56–64, 1993.
- Di Mario C, Krams R, Gil R, Serruys PW: Slope of the instantaneous hyperemic diastolic coronary flow-velocity pressure relation. A new index for assessment of the physiological significance of coronary stenosis in humans. *Circulation* 90:1215–1222, 1994.
- Di Mario C, de Feyter PJ, Slager CJ, de Jaegere P, Roelandt JRTC, Serruys PW: Intracoronary blood flow velocity and transstenotic pressure gradient using sensor-tip pressure and Doppler guidewires. *Cathet Cardiovasc Diagn* 29:311–319, 1993.
- Pijls N, van Son JAM, Kirkeeide RL, de Bruyne B, Gould KL: Experimental basis of determining maximum coronary myocardial and collateral blood flow from pressure measurements for assessing functional severity before and after coronary angioplasty. *Circulation* 86:1354–1361, 1993.
- Kirkeeide RL, Gould KL, Parsel L: Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilatation. Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. *J Am Coll Cardiol* 7:103–113, 1986.
- Gould KL, Kirkeeide RL, Buchi M: Coronary flow reserve as a physiologic measure of stenosis severity. *J Am Coll Cardiol* 15:459–74, 1990.
- Young DF, Tsai FY: Flow characteristics in models of arterial stenoses—II. Unsteady flow. *J Biomech* 6:547–559, 1973.
- Young DF, Cholvin NR, Roth AC: Pressure drop across artificially induced stenoses in the femoral arteries of dogs. *Circ Res* 36:735–743, 1975.
- Brown GB, Bolson E, Frimer M, Dodge HT: Quantitative coronary arteriography. Estimation of dimensions, hemodynamic resistance and atheroma mass of coronary artery lesions using the arteriogram and digital computation. *Circulation* 55:329–337, 1977.
- Kern MJ, Aguirre FV, Bach RG, Caracciolo EA, Donohue TJ, Labovitz AJ: Fundamentals of translesional pressure-flow velocity measurements. Part II. *Cathet Cardiovasc Diagn* 31:137–143, 1994.
- Siebes M, Gottwik M, Schleppe M: Quantitative and qualitative experimental studies in the evaluation of model coronary arteries from angiograms. *Comput Cardiol* 211–214, 1984.
- Bache RJ, Schwartz JS: Effect of perfusion pressure distal to a coronary stenosis on transmural myocardial blood flow. *Circulation* 65:928–935, 1982.
- Gould KL: Phasic pressure-flow and fluid-dynamic analysis. In Gould LD (ed): “Coronary Artery Stenosis.” New York, Amsterdam, London: Elsevier, 1991, pp 40–52.
- Gould KL, Lipscomb K, Hamilton GW: Physiologic basis for assessing critical coronary stenosis: Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol* 33:87–94, 1974.
- Miller DD, Donohue TJ, Younis LT, Bach RG, Aguirre FV, Witty MD, Goodgold HM, Chaitman BR, Kern MJ: Correlation of pharmacological ^{99m}Tc-SestaMIBI myocardial perfusion imaging with post-stenotic coronary flow reserve in patients with angiographically intermediate artery stenoses. *Circulation* 89:2150–2160, 1994.
- Deychak YA, Segal J, Reiner SR, Rohrbeck SC, Thompson MA, Lundergan CF, Ross AM, Wasserman AG: Doppler guide wire flow velocity indexes measured distal to coronary stenoses associated with reversible thallium perfusion defects. *Am Heart J* 129:219–227, 1995.
- Joye JD, Schulman DS, Lasorda D, Farah T, Donouhe BC, Reichel N: Intracoronary Doppler guide wire versus stress single photon emission computed tomographic thallium-201 imaging in assessment of intermediate coronary stenoses. *J Am Coll Cardiol* 24:940–947, 1994.
- Klocke FJ: Measurements of coronary flow reserve: Defining pathophysiology versus making decisions about patient care. *Circulation* 76:245–253, 1987.
- McGinn AL, White CW, Wilson RF: Interstudy variability of coronary flow reserve: Influence of heart rate, arterial pressure and ventricular preload. *Circulation* 81:1319–1330, 1990.
- Di Mario C, Gil R, Serruys PW: Long-term reproducibility of coronary flow velocity measurements in patients with coronary artery disease. *Am J Cardiol* 75:1177–1180, 1995.
- Serruys PW, Di Mario C, Meneveau N, de Jaegere P, Strikwerda S, de Feyter PJ, Emanuelsson H: Intracoronary pressure and flow velocity from sensor tip guidewires. A new methodological comprehensive approach for the assessment of coronary hemodynamics before and after interventions. *Am J Cardiol* 71:41–53, 1993.
- Wilson RF, Johnson MR, Marcus ML, Aylward PEG, Skorton DJ, Collins S, White CW: The effect of coronary angioplasty on coronary blood flow reserve. *Circulation* 71:873–885, 1988.
- Kern MJ, Deligonul U, Vandormael M, Labovitz A, Gudipati CV, Gabliani G, Bodet J, Shah Y, Kennedy HL: Impaired coronary vasodilator reserve in the immediate postcoronary angioplasty period: Analysis of coronary artery flow velocity indexes and regional cardiac venous efflux. *J Am Coll Cardiol* 13:860–872, 1989.
- Segal J, Kern MJ, Scott NA, King SB, Doucette JW, Heuser RR, Ofili E, Siegel R: Alterations of phasic coronary artery flow ve-

- locity in humans during percutaneous coronary angioplasty. *J Am Coll Cardiol* 20:276-286, 1992.
30. Ofili EO, Kern MJ, Labovitz AJ, Vrain J, Segal J, Aguirre FV, Castello R: Analysis of coronary blood flow velocity dynamics in angiographically normal and stenosed arteries before and after endolumen enlargement by angioplasty. *J Am Coll Cardiol* 21:308-316, 1993.
 31. Stewart RE, Bowers TR, Reddy VM, O'Neill WW, Safian RD: Coronary flow reserve does not improve after successful rotablator atherectomy and adjunctive angioplasty (abstract). *J Am Coll Cardiol* 322, 1994.
 32. Tron C, Kern MJ, Donohue TJ, Bach RG, Aguirre FV, Caracciolo EA, Moore JA: Comparison of quantitative angiographically derived and measured translesion pressure and flow velocity in coronary artery disease. *Am J Cardiol* 75:111-117, 1995.
 33. Grüntzig AR, Senning A, Slegenthaler WE: Nonoperative dilatation of coronary-artery stenosis: Percutaneous transluminal coronary angioplasty. *N Engl J Med* 301:61-68, 1977.
 34. Serruys PW, Wijns W, Reiber JHC, de Feyter PJ, van den Brand M, Piscione F, Hugenholtz PG: Values and limitations of transstenotic pressure gradients measured during percutaneous coronary angioplasty. *Herz* 10:337-342, 1985.
 35. Leiboff R, Bren G, Katz R, Korhegi R, Katzen B, Ross A: Determinants of transstenotic gradients observed during angioplasty: An experimental model. *Am J Cardiol* 52:1311-1317, 1983.
 36. De Bruyne B, Pijls NHJ, Paulus WJ, van Trimpont PJ, Sys SU, Heyndrickx GR: Transstenotic coronary pressure gradient measurement in man: In vitro and in vivo evaluation of a new pressure monitoring PTCA guide-wire. *J Am Coll Cardiol* 22:119-126, 1993.
 37. Emanuelsson H, Lamm C, Di Mario C, Serruys PW: Measurements of coronary artery pressure and stenosis gradients. Clinical applications and comparison with quantitative angiography. In Serruys PW, Foley DL, de Feyter PJ (eds): "QCA in Clinical Practice." Dordrecht: Kluwer Academic Publishers, 1993, pp 167-173.
 38. Donohue TJ, Kern MJ, Aguirre FV, Ofili EO: Assessing the hemodynamic significance of coronary artery stenosis: Analysis of translesional pressure-flow velocity relationship in patients. *J Am Coll Cardiol* 22:449-458, 1993.
 39. De Bruyne B, Baudhuin T, Melin JA, Pijls NHJ, Sys SU, Boll A, Paulus WJ, Heyndrickx GR, Wijns W: Coronary flow reserve calculated from pressure measurements in humans: Validation with positron emission tomography. *Circulation* 89:1013-1022, 1994.
 40. Gould KL: Interactions with the distal coronary vascular bed. In Gould KL (ed): "Coronary Artery Stenosis." New York, Amsterdam, London: Elsevier, 1991, pp 31-39.
 41. Seiler C, Kirkeeide RL, Gould KL: Basic structure-function relations of the epicardial coronary vascular tree. *Circulation* 85:1987-2001, 1992.
 42. Sunamura M, Vrints CH, Probst P, Piek JJ, Schroeder E, Heyndrickx GR, Muhlberger VA, Di Mario C, Serruys PW, DEBATE Study Group: Do angiographic measurements of stenosis severity correlate with Doppler flow reserve? Effect of balloon angioplasty (abstract). *J Am Coll Cardiol* 153, 1995.