Intracoronary Pressure and Flow Velocity with Sensor-Tip Guidewires: A New Methodologic Approach for Assessment of Coronary Hemodynamics Before and After Coronary Interventions

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The use of miniaturized pressure and velocity sensors mounted on angioplasty guidewires allows the simultaneous measurement of coronary blood flow velocity and transstenotic pressure gradient, 2 parameters that, combined, should perfectly characterize stenosis hemodynamics. The aim of this article is assessment of the changes in coronary blood flow velocity observed with a Doppler-tipped angioplasty guidewire in 35 patients undergoing balloon angioplasty. We also report our initial experience in 16 patients with the combined use of sensor-tip pressure and Doppler guidewires, and we discuss the application of new methodologic approaches for the study of the coronary circulation allowed by these techniques, such as the instantaneous assessment of the flow velocity/pressure and pressure gradient/flow velocity relations. Before and after angioplasty, flow velocity measurements were obtained distal to the stenosis, both in baseline conditions and after intracoronary injection of 8–12.5 mg of papaverine. The Doppler guidewire was left in place during the dilation procedure and the Doppler signal was continuously recorded during balloon inflation and after deflation to monitor the development of collateral flow, the restoration of flow after balloon deflation, the phase of postocclusive reactive hyperemia, and, incidently, the development of flow-limiting complications. Merits and pitfalls of several flow velocity parameters (average peak velocity, coronary flow velocity reserve, diastolic/systolic velocity ratio), as well as of parameters derived from the combination of pressure and velocity measurements (transstenotic pressure gradient/flow velocity relation and instantaneous diastolic hyperemic flow velocity/pressure relation) were evaluated in 35 patients with, and 37 without, significant coronary stenoses. Miniaturization of flow velocity and pressure sensors has made these methodologic approaches applicable in the interventional suite, yielding reproducible and accurate assessments of parameters previously measured only in experimental animal models.

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Since the advent of coronary angioplasty, assessment of the acute results of interventions has been a source of debate and discussion. Several methodologic approaches have been considered and explored in the past.[1] Andreas Grüntzig, the inventor of the technique, made use of the transstenotic pressure gradient to guide the progression of the balloon catheter in the coronary tree beyond the targeted stenotic lesion and to demonstrate the severity of the stenosis.[2] Following dilation, the transstenotic gradient was used to assess the hemodynamic change brought about by the dilating process, but no attempt in those early days was made to assess the pressure drop across the lesion during hyperemia. Subsequently, pressure recording was progressively disregarded because it was demonstrated that the measurement was not always reliable.[3]

The physiologic value of these measurements, even those obtained with the smallest catheters, must be questioned, since the catheter impedes flow by its presence. Experimental data obtained in

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dog femoral arteries suggest that the "true" stenosis gradient is overestimated in a predictable manner, dependent on the ratio of the catheter diameter over the stenosis diameter.[4] In addition, further miniaturization of the balloon catheter and introduction of the movable guidewire and of the monorail technique soon rendered measurement of pressure gradient less applicable.

In recent years, major efforts were made to obtain accurate measurements of the lumen area of the stenotic lesion, before and after coronary angioplasty, using quantitative angiography with computer-based automatic edge detection.[5] However, for the evaluation of the angioplasty results, this technique has inherent limitations. The disruption of the internal wall of the vessel following the barotrauma of angioplasty cannot be easily delineated by contour detection of the shadowgram obtained with coronary angiography.[6] Videodensitometry was a possible promising alternative, but this method did not fulfill the expectations and critical methodologic problems remained unresolved.[7,8] These limitations have prompted investigators to use blood flow measurement for the functional assessment of angioplasty results. Various digital angiographic techniques and Doppler catheters were introduced and tested.[9–12] The recent miniaturization of pressure and velocity sensors[13,14] has allowed the simultaneous measurement of intracoronary flow velocity and transstenotic pressure gradient, the 2 parameters that characterize the stenosis hemodynamics.

In this article we report the results obtained in 35 patients with a Doppler guidewire during coronary interventions, as well as our initial experience in 16 patients with the combined use of sensor-tip pressure and Doppler guidewires. New methodologic approaches allowed by these techniques include the instantaneous assessment of the flow velocity/pressure and pressure gradient/flow velocity relations.

METHODS

Doppler guidewire during coronary interventions: In 35 patients (31 men, 4 women, mean age 57 ± 10 years) undergoing coronary angioplasty because of symptomatic coronary artery disease, a Doppler angioplasty guidewire was used. Patients who had acute myocardial infarction, arterial occlusion or subocclusion (Thrombolysis in Myocardial Infarction [TIMI] flow class 0–1), valvular heart disease, extreme tortuosity of the vessel to be dilated, and the presence of an open aortocoronary bypass graft on the vessel to be treated were not included for study. Systemic arterial hypertension was present in 9 cases (26%). Seven patients (20%) had a previous myocardial infarction in the territory of distribution of the dilated vessel (Q wave in 2 patients, nontransmural in 5 patients). Antianginal treatment, including in 21 patients (60%) β-adrenergic blocking agents, calcium antagonists, long-acting nitrates, or a combination of these 3 drugs, was not withheld. In 1 patient the Doppler guidewire was used for a 2-vessel angioplasty procedure. The left anterior descending artery was the treated artery in 20 cases (56%), the left circumflex in 4 cases (11%), and the right coronary artery in 8 cases (22%). Four stenoses of a saphenous vein bypass graft were treated using the Doppler guidewire as the angioplasty guidewire (11%).

Catheterization procedure: After intravenous administration of 10,000 IU of heparin and 250 mg of acetylsalicylic acid, an 8 F guiding catheter was advanced up to the coronary ostium. After isosorbide dinitrate (2–3 mg intracoronary), cineangiograms suitable for quantitative assessment were obtained in 1–3 angiographic views.

The Doppler guidewire was advanced into the artery to be dilated and a flow velocity recording was obtained distal to the stenosis, both in baseline conditions and after intracoronary bolus injection of papaverine (8 mg, right coronary; 12.5 mg, left coronary, saphenous vein bypass graft).[15] Intracoronary nitrates were used before the injection of papaverine in order to induce a maximal coronary vasodilation and avoid changes in cross-sectional area between baseline and post-papaverine assessment.[16] Care was taken to avoid the presence of impairment of flow during maximal hyperemia due to the presence of the guiding catheter in the coronary ostium. If damping occurred (Figure 1), the guiding catheter was withdrawn from the coronary ostium immediately after the injection of papaverine. An appropriately sized balloon catheter (2–4 mm) was then introduced, using a monorail technique in most cases. The Doppler guidewire was left in place distal to the lesion during the dilation procedure. The Doppler signal was continuously acquired during balloon inflation and after deflation to monitor the development of collateral flow, the restoration of flow after balloon deflation, the phase of postocclusive reactive hyperemia, and, incidently, the development of flow-limiting complications. Immediately after the end of the inflation, the balloon was withdrawn in the guiding catheter in order to avoid the residual obstruction of flow due to the presence of the deflated balloon across

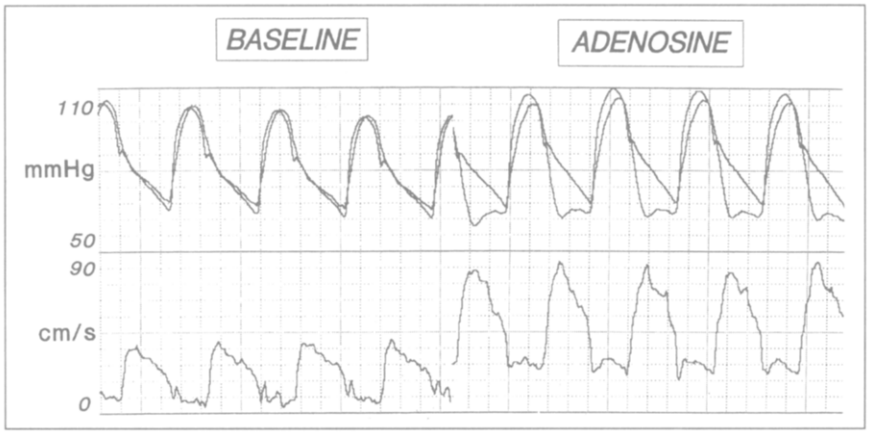


FIGURE 1. ***Top,*** **simultaneous recordings of the pressure in the ascending aorta (tip manometry) and of the aortic pressure recorded with a fluid-filled 8 F guiding catheter at the ostium of the left coronary artery. At baseline the 2 tracings are superimposed, indicating that the voluminous guiding catheter does not impede the flow in the main stem. The intracoronary administration of 18 μg of adenosine induces the development of a pressure gradient between aorta and left main coronary artery, generated by the presence of the guiding catheter. Note the ventricularization of the proximal coronary pressure.** ***Bottom,*** **the simultaneous changes in flow velocity are recorded using a Doppler guidewire positioned in the proximal left anterior descending artery.**

the lesion. When the dilation was judged successful (angiographic percent diameter stenosis <50%), new baseline and post-papaverine flow velocity measurements were obtained distal and proximal to the lesion, taking care that flow velocity measurements were repeated in the same positions as before angioplasty.

Doppler guidewire and flow velocity measurements: The Doppler angioplasty guidewire, a 0.018-in (diameter = 0.46 mm), 175-cm long flexible and steerable guidewire with a floppy shapable distal end mounting a 12 MHz piezoelectric transducer at the tip (Flowire; Cardiometrics, Mountain View, CA), has been described previously.[17] The flow velocity measurements obtained with this system have been validated in vitro and in an animal model using simultaneous electromagnetic flow measurements for comparison.[17] The Doppler system performs a real-time spectral analysis of the Doppler signal[18] and calculates and displays on-line several spectral variables, including the instantaneous peak velocity and the time-averaged (mean of 2 beats) peak velocity. The time-averaged systolic and diastolic flow velocity components were analyzed off-line based on the flow pattern and on the simultaneous recordings of electrocardiogram and aortic pressure (Figure 2). Coronary flow reserve was defined as the ratio between maximal flow velocity at the peak effect of the papaverine injection and in baseline conditions.

Quantitative angiographic measurements: The guiding catheter, filmed without contrast medium, was used as a scaling device.[19] A previously validated on-line analysis system operating on digital images (ACA-DCI; Philips, Eindhoven, The Netherlands[20]; n = 24) and a cinefilm-based off-line system (CAAS System; Pie Medical Data, Maastricht, The Netherlands[21]; n = 11) were used. After automatic detection of the vessel centerline, a weighted first and second derivative function with predetermined continuity constraints was applied to the brightness profile on each scan line perpendicular to the vessel centerline.[22] From the measured minimal luminal diameter (MLD), the minimal luminal cross-sectional area was calculated, assuming a circular cross-section (average of the measurements if multiple views were acquired). An interpolated technique was used to define the reference diameter. Percent diameter and cross-sectional area stenosis were also calculated. A user-defined reference diameter was measured at the site of the Doppler sample volume in order to detect changes of the position of the transducer before and after angioplasty and to calculate the maximal and mean coronary flow.[18,23]

Combination with transstenotic pressure measurements: A total of 16 patients undergoing

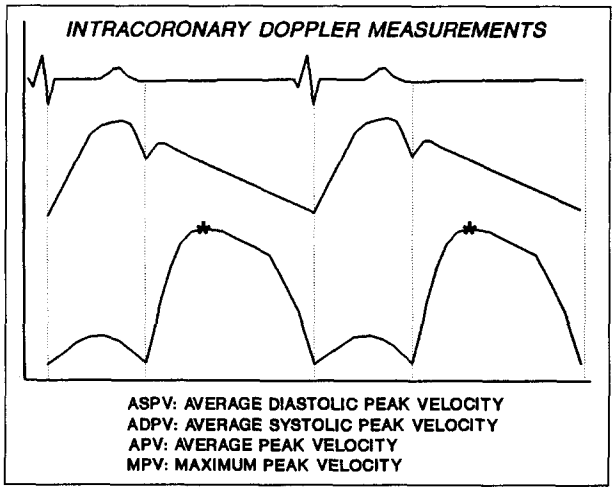


FIGURE 2. Diagram of a simultaneous recording of electrocardiogram, aortic pressure, and flow velocity. The systolic and diastolic phases of the cardiac cycle are identified by vertical bars on the diagram. The R wave of the electrocardiogram and the dicrotic notch of the aortic pressure serve as landmarks of the systolic and diastolic phases. The asterisks indicate the maximum peak flow velocity.

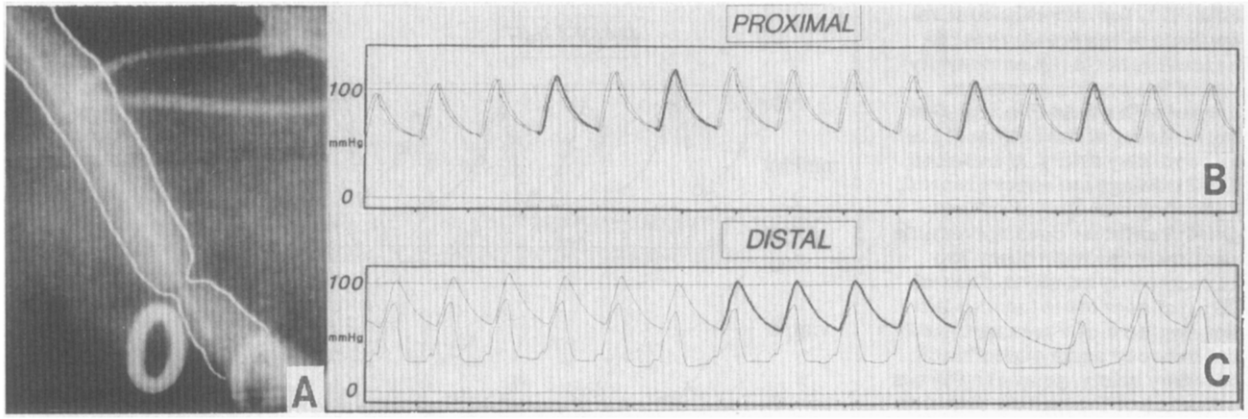


FIGURE 3. *A*, cineangiogram of a saphenous vein bypass graft; automatic edge detection of the contours delineates the stenotic lesion while the radiopaque structure of the pressure guidewire (diameter: 0.46 mm) is seen inside the lumen of the vessel. *B*, pressure recording with the pressure sensor located immediately proximal to the stenotic lesion. Note the almost complete superimposition of the 2 pressure curves. *C*, a significant transstenotic gradient is recorded with the sensor advanced distal to the stenotic lesion.

elective coronary angioplasty (n = 9) or scheduled for a possible angioplasty procedure but with a stenosis angiographically of intermediate severity (>40% and <60% diameter stenosis; n = 7) were studied with a simultaneous measurement of flow velocity and poststenotic coronary pressure. The measurements were obtained in baseline conditions and after papaverine using the Doppler guidewire positioned *proximal* to the stenosis and a fiberoptic pressure microsensor advanced *distal* to the stenosis. This pressure sensor is incorporated in the flexible distal segment of a 0.018-in guidewire (diameter 0.45 mm, cross-sectional area 0.17 mm^2; Radi Medical Systems, Uppsala, Sweden). This system has already been validated in vitro with regard to signal transfer characteristics, linearity, and frequency response.[13] 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 guidewire and the proximal coronary pressure measured with the guiding catheter (Figure 3). A correction of a 5/15 mm Hg drift of the 0 pressure was necessary in 4 cases (25%). The mean transstenotic gradient was calculated as the difference of mean proximal and mean distal coronary pressure over 8 consecutive beats in baseline conditions and at peak papaverine effect (Figure 4). In order to facilitate the comparison of patients with different hemodynamic characteristics at the time of the study, the transstenotic pressure gradient was normalized for the corresponding coronary proximal pressure. The coronary flow measurements derived from the quantitative angiographic and Doppler measurements were used to calculate a flow/gradient index, defined as the ratio between the difference of the peak papaverine and baseline measurements of coronary flow and transstenotic gradient.

Instantaneous assessment of the flow velocity/pressure relation: Feasibility and reproducibility of the assessment of the relationship between coronary blood flow velocity and aortic pressure were evaluated in 31 patients with significant coronary artery disease in a nontreated coronary artery without diameter stenosis >30% and in 6

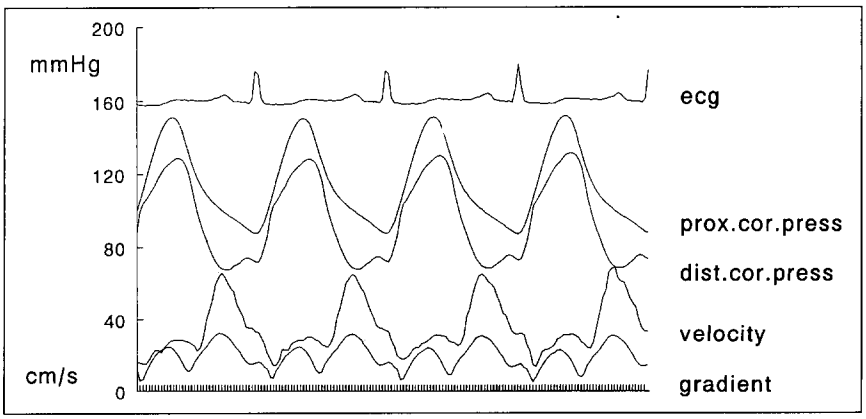


FIGURE 4. From top to bottom: electrocardiogram (ecg), proximal coronary pressure (prox. cor. press) recorded through the guiding catheter (mm Hg), distal coronary pressure (dist. cor. press) recorded with a tip-mounted pressure guidewire (mm Hg), coronary flow velocity recorded with a Doppler guidewire (cm/sec), and transstenotic pressure gradient (mm Hg). Note that the systolic/diastolic changes in flow velocity correspond to the phasic variations of the transstenotic gradient, with the maximal velocity and gradient in proto-mid-diastole.

patients (8 angiographically normal arteries) 1–5 years after cardiac transplantation. The measurement was performed in a proximal–middle segment of the studied artery (left anterior descending in 18 cases [46%], left circumflex in 9 [23%], right coronary artery in 12 [31%] cases) in baseline condition and after papaverine-induced hyperemia. The proximal coronary pressure, measured through the guiding catheter, and the instantaneous peak velocity were continuously acquired using a 12-bit analog-to-digital converter at a sampling frequency of 125 Hz (Data-Q Instruments, Akron, OH). Linear regression analysis was used to assess the slope of the velocity/pressure relation ($cm \cdot s^{-1} \cdot mm\ Hg^{-1}$) in 4 consecutive cardiac cycles during maximal coronary vasodilation. The analyzed mid-to-late diastolic intervals were defined using as start- and endpoints the maximal diastolic peak velocity and the acceleration of the slope of the velocity decrease induced by the myocardial contraction (Figure 5). In 6 cardiac transplant recipients left ventricular and aortic high fidelity pressures were measured simultaneously using a double-sensor pigtail catheter (Sentron, Roden, The Netherlands). In these cases the analysis was performed using the digitized pressure and flow velocity data obtained in the time interval originally proposed by Mancini et al[24,25] (20 msec after the peak negative left ventricular dP/dt-upstroke of the positive left ventricular dP/dt). In the 8 arteries studied in cardiac transplant recipients a bolus of 3 mg of adenosine was also rapidly injected intracoronary during the maximal papaverine effect so that the velocity/pressure relation could be studied also during a series of long diastolic pauses (up to 11 seconds). Right ventricular pacing was used to restore a normal cardiac contraction when necessary.

Statistical analysis: The differences between flow velocity measurements and derived indexes before and after angioplasty were compared using a paired Student's t test. The differences between diastolic/systolic flow velocity ratio in the angioplasty patients and in the control group without significant coronary stenosis of the studied vessel were compared using an unpaired Student's t test. The beat-to-beat variability of the slope of the velocity/pressure relation was defined as the ratio between the standard deviation and the average of the slopes measured over 4 consecutive cardiac cycles. In the 8 arteries of cardiac transplant recipients studied during a normal sinus beat and during pharmacologically induced cardiac arrest, the difference between the slopes of the velocity/pressure relation in normal cardiac cycles and prolonged diastolic pauses was compared using a

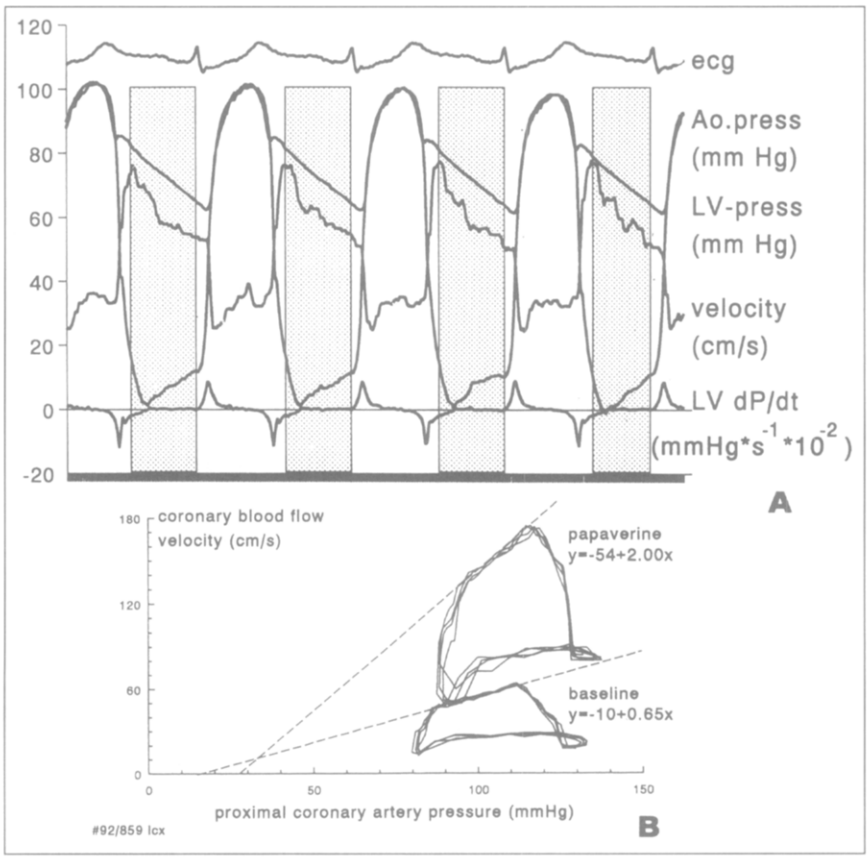


FIGURE 5. *A*, from top to bottom: electrocardiogram (ecg), aortic pressure (Ao. press; tip manometry), left ventricular pressure (LV-press; tip manometry), coronary blood flow velocity (Doppler guidewire), and first derivative of the left ventricular pressure (*dP/dt*). The *dotted areas* indicate the intervals used for the analysis of the pressure/flow velocity relation from the digitized pressure and flow velocity (starting point, 20 msec after peak negative *dP/dt*, endpoint: left ventricular end-diastolic pressure/upstroke of the positive left ventricular *dP/dt*). *B*, Velocity/pressure loops of 4 consecutive cardiac cycles superimposed (clockwise rotation) in baseline conditions and at the peak effect of papaverine. The regression lines calculated in the mid–late diastolic phases are displayed and extrapolated up to the zero-flow pressure.

nonparametric (Wilcoxon) test. Statistical significance was defined as $p < 0.05$. All data were expressed as mean ± SD.

RESULTS

Monitoring of the angioplasty procedure with the Doppler guidewire: The angioplasty guidewire was successfully used to cross the stenosis in 32 of 36 arteries (89%). Stable Doppler recordings distal to the lesion were acquired in all these cases. During balloon inflation, a complete disappearance of flow was observed in 26 arteries (81%). In the remaining 6 cases (19%) the flow velocity progressively increased during inflation (in 5 cases with inverted flow velocity signal), presumably indicating recruitment of collateral coronary flow. The restoration of anterograde flow could be immediately detected during the deflation of the balloon, before the disappearance of the electrocardiographic changes or of the symptoms. In 3 cases (9%) a sudden decrease of blood flow velocity was the first warning signal of the development of a flow-limiting wall dissection after angioplasty (Figure 6). Two of these cases were successfully treated with stent implantation and 1 patient required emergency bypass surgery. Coronary angioplasty was judged angiographically successful in all the 29 remaining cases. Minimal luminal diameter increased from 1.02 ± 0.72 mm before coronary angioplasty to 2.12 ± 1.69 mm after angioplasty ($p < 0.001$). Minimal luminal cross-sectional area stenosis increased after percutaneous transluminal coronary angioplasty (PTCA) from 0.84 ± 0.41 to 3.45 ± 2.25 mm^2 ($p < 0.001$). Percent cross-sectional area stenosis decreased from 80 ± 9% to 46 ± 19% after PTCA ($p < 0.001$).

Baseline and hyperemic average peak velocity changes after angioplasty: Baseline and post-papaverine flow velocity signals were obtained before and after dilation in 29 coronary arteries (81%; Figure 7). Baseline average peak velocity increased from 16 ± 9 to 27 ± 14 cm/sec post-PTCA ($p < 0.001$). A >2-fold increase was observed for the average peak velocity recorded at the maximal effect of papaverine (27 ± 17 and 60 ± 28 cm/sec before and after PTCA, respectively; $p < 0.001$). The cross-sectional area at the site of the Doppler recording showed a nonsignificant change before and after PTCA (from 6.08 ± 3.73 to 5.74 ± 3.68 mm^2, difference not significant), suggesting that the velocity changes reflect a true flow increase after PTCA in baseline and hyperemic conditions. Coronary flow reserve, as a ratio of the hyperemic/baseline flow velocity measurements, showed a moderate but significant increase after PTCA (from 1.75 ± 0.55 to

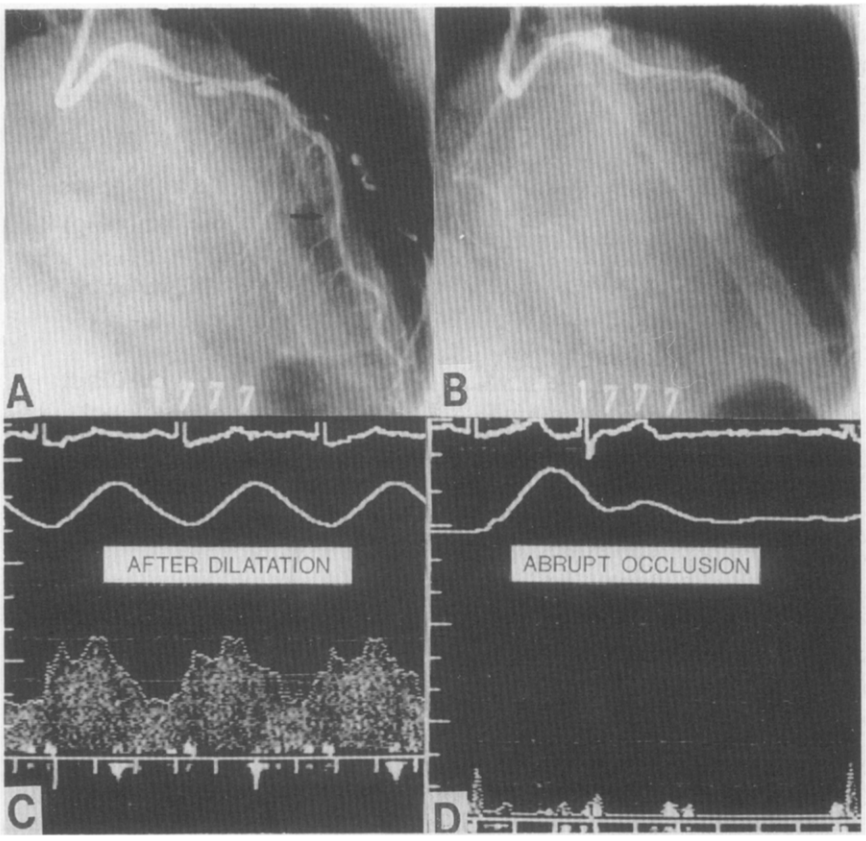


FIGURE 6. Coronary angiogram before *(A)* and after *(B)* abrupt occlusion following balloon dilation. The position of the Doppler guidewire is indicated by an arrow. *C*, simultaneous recordings of the flow velocity signals. *D*, the disappearance of the flow velocity signal consequent to the flow-limiting dissection, a warning signal preceding the electrocardiographic changes and the development of symptoms.

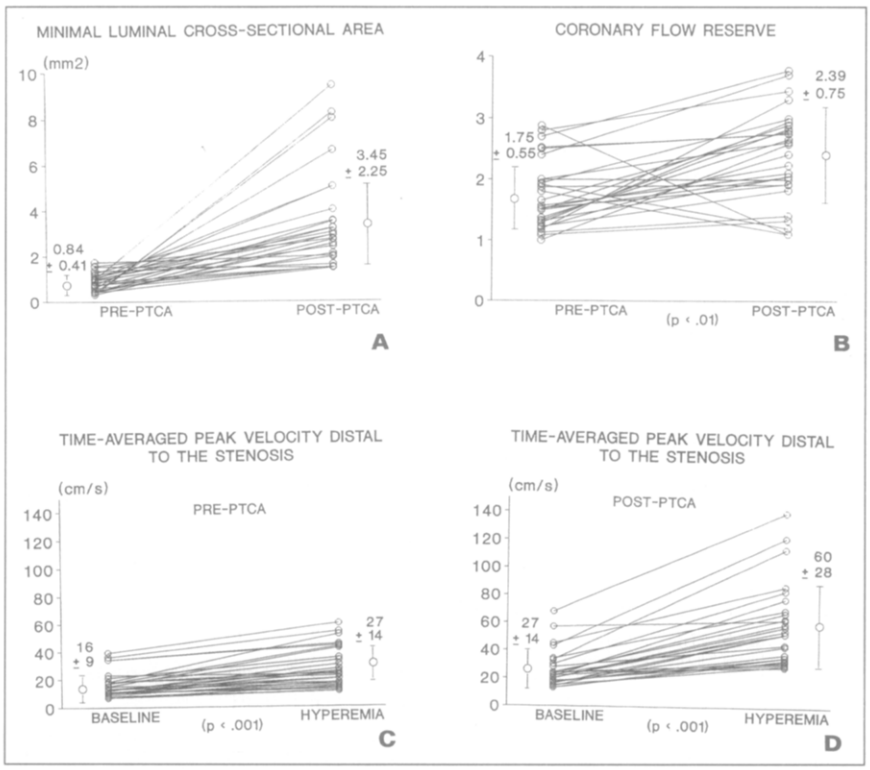


FIGURE 7. *A, B*, Individual changes in minimal luminal cross-sectional area *(A)* and coronary flow reserve *(B)* are shown before and after percutaneous transluminal coronary angioplasty (PTCA). Individual changes in time-averaged peak velocity distal to the stenosis PTCA *(C)* and post-PTCA *(D)*. Both the baseline and the maximal hyperemic flow velocity showed a significant increase post-PTCA ($p < 0.001$).

2.39 ± 0.75; $p < 0.005$). Comparable flow velocity increases were observed after PTCA at the peak effect of the papaverine injection and in the phase of the maximal reactive hyperemia recorded following balloon dilation in 14 patients (45 ± 22 cm/sec peak reactive hyperemia vs 47 ± 20 cm/sec after papaverine, difference not significant). Figure 8 illustrates the relation observed between minimal luminal diameter, before and after PTCA, and maximal hyperemic flow velocity.

Changes in the diastolic/systolic flow velocity ratio after angioplasty: The ratio between mean diastolic and mean systolic flow velocity measured in baseline conditions distal to the stenosis was 1.51 ± 0.58 before PTCA, significantly lower than the ratio measured in the 39 normal or near-normal arteries (2.09 ± 0.90; $p < 0.001$). After angioplasty, the diastolic/systolic flow velocity ratio increased from 1.51 ± 0.58 to 2.16 ± 0.98 ($p < 0.001$) and did not differ from the control group.

Flow velocity/transstenotic pressure gradient measurements: The quantitative angiographic, flow velocity, and pressure measurements of the 16 patients studied with the combined use of Doppler and pressure guidewires are reported in Table I. The maximal (post-papaverine) transstenotic pressure gradient showed a significant inverse correlation with the minimal luminal cross-sectional area ($y = -8.4x + 45$; $r = -0.62$; $p < 0.01$). Coronary flow reserve had only a borderline significant correlation with the minimal cross-sectional area ($y = 0.36x + 1.55$; $r = 0.46$; $p < 0.1$). A parameter derived from the integration of flow and pressure gradient changes from baseline to hyperemia (flow/gradient index) showed a more strict correlation with the minimal cross-sectional area ($y = 5.6x + 0.6$; $r = 0.70$; $p < 0.002$). In particular, a flow/gradient index <3 mL/min/mm Hg was able to identify 10 of 14 cases with a minimal cross-sectional area <1.5 mm^2 (Figure 9B). When the normalized transstenotic gradients were plotted against the coronary flow reserve (Figure 9A),

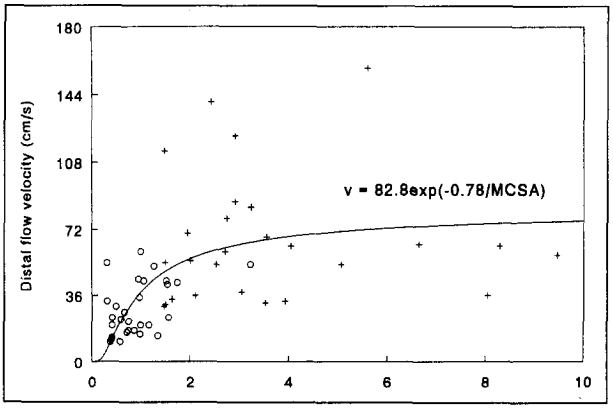


FIGURE 8. Relation between minimal cross-sectional area (MCSA, mm^2) and hyperemic distal flow velocity. The data points obtained before and after percutaneous transluminal coronary angioplasty are indicated with open circles and crosses, respectively. A curvilinear relation was observed between these 2 parameters, with a plateau above the value of cross-sectional area of 2.5 mm^2.

TABLE I Clinical and Hemodynamic Characteristics of the Patients Studied by a Simultaneous Recording of Transstenotic Pressure Gradient and Flow Velocity

Pt	Age (yr)	Sex	MI	Vessel	MLCSA (mm^2)	CSA (%)	BAPV (cm/sec)	HAPV (cm/sec)	CFR	BAS Grad (mm Hg)	HYP Grad (mm Hg)	Norm BASG (%)	Norm HYPG (%)	BAS Flow (mL/min)	HYP Flow (mL/min)	ΔFlow/Δ Grad (mL/min/mm Hg)
WA	60	M	No	RCA	0.49	0.92	10	27	2.70	21	43	23	51	20	53	1.53
BJL	73	M	No	SVBG	0.21	0.98	7	11	1.57	42	46	53	58	20	31	2.85
FB	70	F	No	RCA	2.26	0.74	31	62	2.00	4	17	3	15	84	167	6.44
BKJ	59	M	No	RCA	0.82	0.95	10	15	1.50	12	35	14	41	50	74	1.08
BJ	62	M	No	LAD	0.78	0.87	34	45	1.32	38	46	43	47	65	86	2.61
RTR	69	M	No	RCA	0.33	0.97	8	11	1.37	38	39	46	49	24	33	9.00
SA	73	M	No	SVBG	4.78	0.68	18	56	3.11	5	11	6	14	81	252	28.50
WC	59	M	No	LAD	1.14	0.84	19	83	4.37	5	14	6	19	41	181	15.53
BJ	55	M	No	LAD	1.1	0.86	66	141	2.14	5	18	5	19	157	336	13.74
DHTA	80	M	Yes	RCA	0.30	0.97	8	10	1.25	44	49	49	57	23	28	1.13
SEA	74	M	No	RCA	0.23	0.95	11	12	1.09	49	50	52	54	17	18	1.60
OMV	81	F	No	RCA	1.39	0.85	48	131	2.73	28	37	28	39	132	361	25.39
EC	57	M	Non Q	RCA	0.80	0.92	30	45	1.50	15	42	13	39	97	146	1.80
BW	67	M	Yes	SVBG	1.16	0.87	8	11	1.37	35	39	42	45	21	29	1.99
JB	63	F	Yes	RCA	1.00	0.82	13	20	1.54	13	29	13	29	23	35	0.77
LTW	50	M	No	LAD	1.19	0.71	21	39	1.86	28	65	28	63	33	56	2.05
Mean	66				1.12	0.87	21	45	1.96	23	36	27	40	55	118	7.24
± SD	9				1.07	0.09	16	40	0.84	15	14	18	16	42	109	8.67

BAPV = baseline time-averaged peak blood flow velocity; BAS = baseline; CSA = cross-sectional area; CFR = coronary flow reserve; ΔFLOW/ΔGRAD = (hyperemic flow—baseline flow)/(hyperemic gradient—baseline gradient); HAPV = hyperemic time-averaged peak blood flow velocity; HYP = hyperemic; LAD = left anterior descending; MI = myocardial infarction; MLCSA = minimal luminal cross-sectional area; NORM BASG = normalized baseline gradient; NORM HYPG = normalized hyperemic gradient; RCA = right coronary artery; SVBG = saphenous vein bypass graft.

3 subgroups of patients were identified. At one extreme, the presence of large transstenotic gradients in baseline conditions and during hyperemia (>40% of the corresponding aortic pressure), associated with a minimal increase of flow during hyperemia (<2 times baseline), identified the most severe stenoses. At the other extreme, normalized hyperemic transstenotic pressure gradients <20% with an increase of 2–4 times the baseline flow after papaverine characterized a group with non-flow-limiting lesions. The intermediate group of hemodynamically significant stenoses exhibited variable pressure gradient/flow responses. Coronary flow reserve and maximal (post-papaverine) transstenotic pressure gradient showed a significant inverse correlation ($p < 0.02$; $r = -0.56$).

Instantaneous assessment of the hyperemic flow velocity/coronary pressure relation: A clear Doppler envelope allowing a reliable automatic detection of the hyperemic diastolic peak velocity during 4 consecutive beats was obtained in 31 of 39 cases (79%). The slope of the regression line was 1.86 ± 0.84 mm Hg $\cdot$ $cm^{-1} \cdot s^{-1}$. Negative intercepts on the y-axis were calculated in 27 cases so that a positive pressure at zero flow was estimated in most cases, with a mean value of 34 ± 16 mm Hg. The applicability of linear regression analysis to the study of the flow velocity/pressure relation in the range of measurements obtained during a diastolic interval of a normal cardiac cycle is confirmed by the high correlation coefficients observed ($r = 0.95 \pm 0.03$).

Table II reports the zero-flow pressure and the slope of the hyperemic diastolic flow velocity/pressure relation during sinus beats and during long diastolic pauses induced by the injection of adenosine in 8 angiographically normal arteries of cardiac transplant recipients. The lower slope and x-intercept of the long diastolic pauses as well as the shape of individual curves (Figure 10) suggest that the linearity of the pressure/flow velocity relation observed during normal sinus beats cannot be extrapolated over a larger range of pressures and flow velocity, and cannot be used for an accurate estimation of the zero-flow pressure.

DISCUSSION

Practical and theoretical concerns of using coronary flow reserve: Since the original work of Gould et al,[26] the assessment of coronary flow reserve has been viewed as a method of establishing indirectly the severity of a coronary stenosis. It is assumed that the reduction in flow reserve through the stenotic lesion would be an indicator of stenosis severity. In fact, this simple assumption is derived from the complex hemodynamic principles regulating the coronary circulation. In the schematic description by Klocke[27] (Figure 11A),

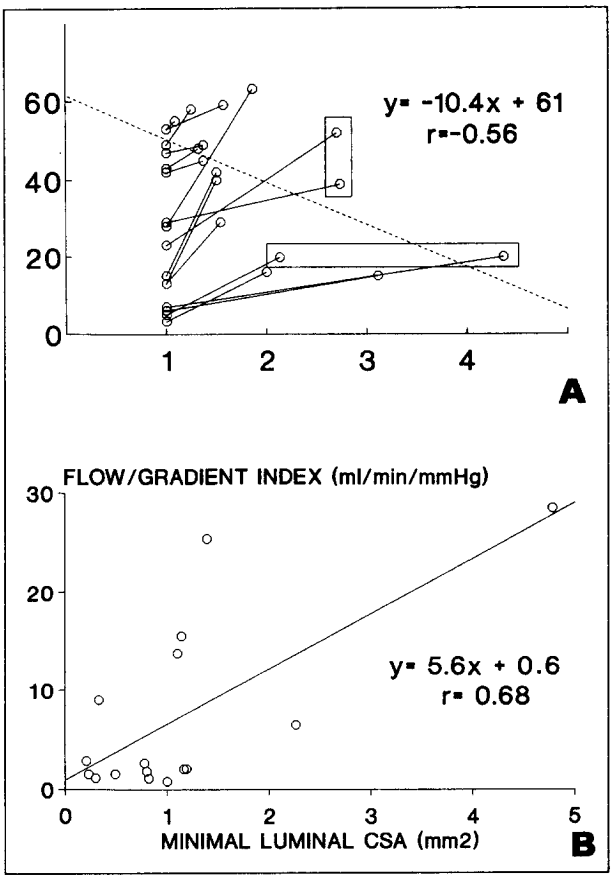


FIGURE 9. *A*, relation between normalized transstenotic pressure gradient and coronary flow reserve as described in the text. Three subgroups of patients can be identified, each of them with specific pressure gradient flow response. The framed data points indicate either stenotic lesions having similar transstenotic gradients during hyperemia in the presence of different increases in flow reserve or stenotic lesions having similar increases in coronary flow reserve with different increases in transstenotic gradient during maximal hyperemia. *B*, relation between minimal cross-sectional area (CSA) and the flow/gradient index, defined as the ratio between the difference of the hyperemic versus baseline flow and the difference of the corresponding transstenotic pressure gradients. Transstenotic flow/gradient indexes of <10 mL/min/mm Hg identify the majority of the lesions with minimal cross-sectional area of <1.5 mm².

flow reserve at a certain level of pressure is defined by the ratio between flow measured during maximal hyperemia and flow in baseline conditions. At rest, flow is independent of the driving pressure over a wide range of physiologic pressures (60–180 mm Hg), a phenomenon classically described as autoregulation of the coronary circulation. During maximal vasodilation, flow becomes linearly related to the driving pressure. The presence of a flow-limiting stenosis in a major epicardial vessel generates a pressure drop across the stenotic lesion, which is the result of viscous and turbulent resistances, so that the driving pressure distal to the stenosis decreases exponentially with the velocity of blood.[28]

TABLE II Instantaneous Hyperemic Diastolic Flow Velocity/Pressure Relation in Normal Sinus Beats Versus Prolonged Diastolic Pauses

	Sinus Beats	Pauses
Analyzed time interval (msec)	266 ± 187	1,852 ± 1,100
Minimal aortic pressure (mm Hg)	64 ± 4	38 ± 9
Minimal blood flow velocity ($cm \cdot sec^{-1}$)	41 ± 14	14 ± 8
Zero-flow pressure (mm Hg)	38 ± 9	20 ± 9
Slope ($cm \cdot sec^{-1} \cdot mm\ Hg^{-1}$)	1.9 ± 0.9	1.2 ± 0.6

The coronary flow reserve concept is mainly appealing to the clinician because it constitutes a functional surrogate to the anatomic description of the lesions located in the epicardial vessels, and many authors have shown that a decrease in flow reserve may discriminantly detect a lesion of increasing severity.[28,29] Although the concept may be easily and accurately applied in an optimal physiologic situation,[30,31] it must be recognized that coronary flow reserve is influenced by factors independent of the hydrodynamic characteristics of the stenotic lesion. Since flow reserve is by definition a ratio, similar ratios may be obtained at very different levels of resting and hyperemic flow. Changes in basal resting flow without changes in hyperemic flow will considerably affect the ratio so that knowledge of the absolute flow values is a prerequisite to the interpretation of a relative measurement such as coronary flow reserve. Any factors affecting the hyperemic pressure flow relation would likewise modify the flow reserve and thereby change the assessment of the severity of the coronary lesion under study. The hyperemic flow/pressure relation is influenced by factors such as heart rate,

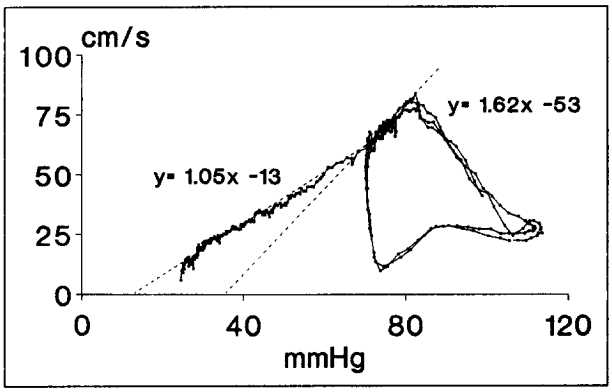
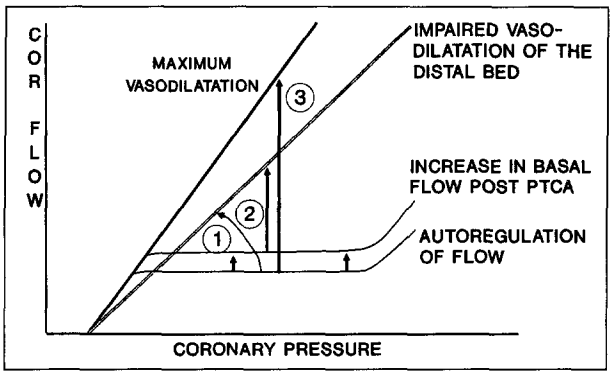


FIGURE 10. Flow velocity/pressure loops during maximal hyperemia in 3 consecutive sinus beats. During mid–late diastole, a linear relation is observed, with an extrapolated zero-flow pressure of 37 mm Hg. However, during a long diastolic pause (cardiac arrest induced by the intracoronary injection of 3 mg of adenosine), the pressure/flow velocity/pressure relation deviates considerably from the extrapolated curve.

preload, myocardial hypertrophy, or disease of the microvasculature.[27,32] Following coronary intervention, acute changes in resting blood flow together with changes in the anatomy of the stenotic lesion and concomitant persistent modifications of the hyperemic flow/pressure relation considerably hamper the clinical usefulness of coronary flow reserve for the assessment of the functional results. The aforementioned considerations are schematically illustrated in Figure 11. Our present results confirmed the observations made by other investigators,[9,11,12,33] namely that an increase in resting and hyperemic flow velocity occurs following angioplasty so that the usefulness of coronary flow reserve is limited in this clinical setting. Similar observations have been made by our group in the past, using Doppler tip balloon angioplasty catheters.[10]



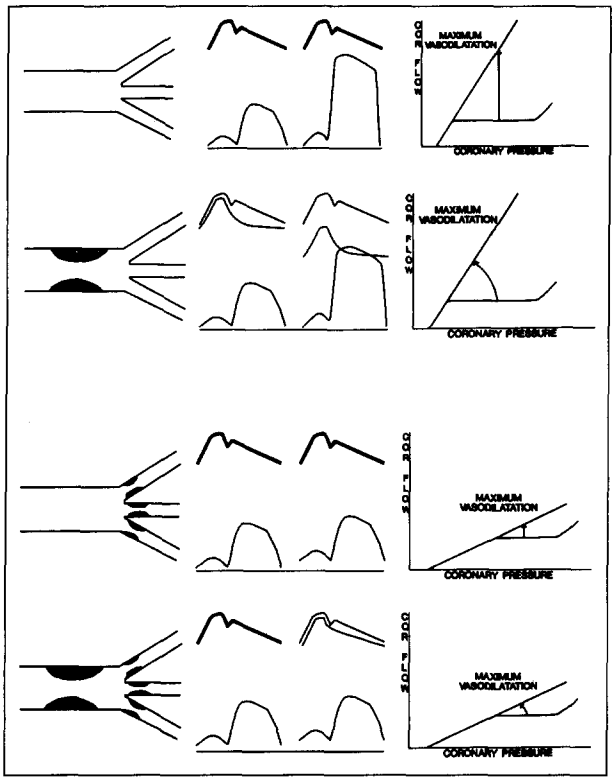


FIGURE 11. ***Upper part*****, flow/pressure relation in resting and hyperemic conditions according to the description of Klocke.[27] Three confounding factors may obscure the interpretation of the change in coronary flow reserve following a PTCA procedure: (1) an increase in resting blood flow; (2) acute or chronic changes in the flow/pressure relation during hyperemia; (3) alteration of the severity of the stenotic lesion treated by balloon angioplasty.** ***Lower part*****, from** ***top*** **to** ***bottom*****, an example of normal epicardial artery with normal distal vascular response and of a significant epicardial stenosis inducing a pressure gradient in baseline and hyperemic conditions and an impaired coronary (COR) flow reserve. The presence of an abnormal distal vascular response (last 2 series of diagrams) minimizes the changes in the transstenotic pressure gradient and in maximal flow observed with and without an epicardial stenosis.**

Flow velocity/pressure relation: As previously demonstrated, the determination in absolute terms (cm/sec) of the maximal hyperemic velocity may be more indicative of the increase in coronary conductance achieved with balloon angioplasty. It must be realized, however, that the interpretation of this change in hyperemic response remains ambiguous, since the limiting factor to its increase may be either the persistence of a residual stenosis or an impaired distal vasodilatory response. The simultaneous measurement of a pressure gradient across a stenotic lesion may clarify the situation and indicate the reason why flow does not increase or increases abnormally (see algorithm in Figure 11B). Conversely, the sole measurement of the pressure gradient during hyperemia has also inherent limitations. The absence of a significant transstenotic gradient, for instance, may be related either to the absence of a flow-limiting stenosis or to the presence of a low flow across the stenosis due to either an impaired distal vasodilation or a well-developed collateral circulation.

A more accurate characterization of the severity of a stenotic lesion may be defined by the slope of the relation between mean gradient and coronary flow.[34] The slope of this relation is inversely correlated with the resistance of the stenotic lesion. However, this simplified assessment is only a limited estimation of the true physiologic phenomenon because mean gradient and flow velocities instead of instantaneous values are employed and because only 2 points (baseline and maximal hyperemia) are analyzed. A more complex but more complete and accurate analysis of the pressure gradient/flow velocity relation requires a continuous assessment of the instantaneous pressure gradient/flow velocity changes during the cardiac cycle in a beat-to-beat analysis.[34–36] The combined measurement of transstenotic gradient and flow velocity may provide a comprehensive interpretation of the fluid dynamics across the stenotic lesion, as well as of the myocardial capillary circulation. The

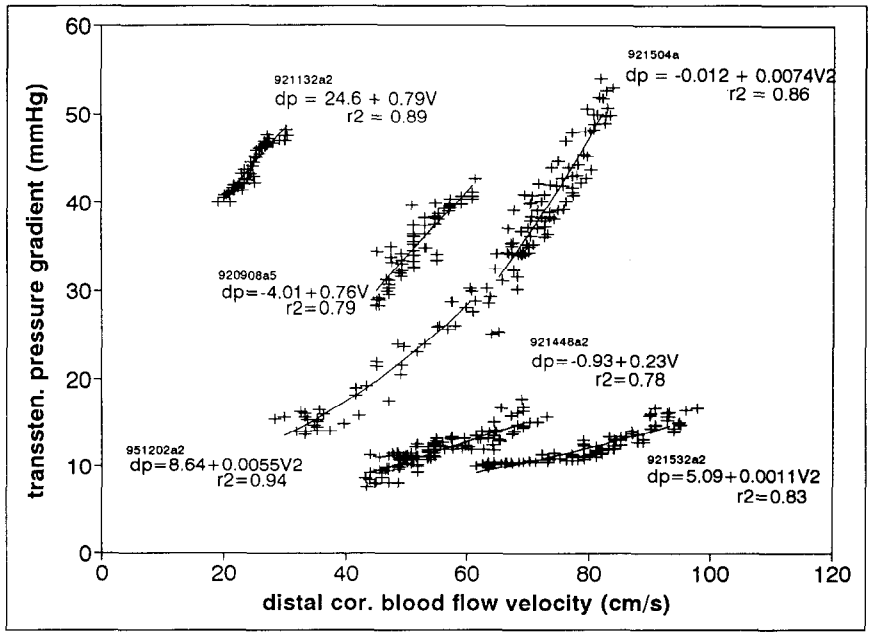


FIGURE 12. Instantaneous hyperemic diastolic pressure gradient/flow velocity relation for 6 stenoses of increasing hemodynamic severity (from *left* to *right* and from *bottom* to *top*). The corresponding best fit equation and curve are also indicated for each set of data. cor = coronary; transsten. = transstenotic.

simultaneous measurement of the instantaneous pressure gradient and flow velocity yields a unique relation that characterizes the hemodynamic properties of the stenosis (Figure 12). On the other hand, the instantaneous hyperemic flow velocity/driving pressure relation allows the analysis of the characteristics and functional integrity of the microcirculation, the other determinant of coronary flow resistance (Figure 13). A prerequisite for a widespread clinical application of these indexes is the assessment of the reproducibility and the identification of the normal and pathologic range in a large patient population.[35] Our preliminary results indicate that measurement of the slope of the flow velocity/pressure relation extrapolated from measurements obtained during normal sinus beats is feasible and reproducible. The slope measurement during a prolonged diastole, however, shows a curvilinear profile deviating substantially from the slope extrapolated during a normal cardiac cycle, an observation previously reported in the experimental literature.[37,38] The necessity to induce a short asystole to obtain a complete assessment of the instantaneous hyperemic flow velocity/pressure relation is a condition that may considerably hamper its clinical applicability. However, for practical purposes, the relation determined only in the physiologic range of pressure and flow velocity appears sufficient to characterize the conductance of the studied vessel.

Phasic alterations of flow velocity after interventions: An alternative approach to the assessment of the acute change after coronary intervention is measurement of the diastolic/systolic flow

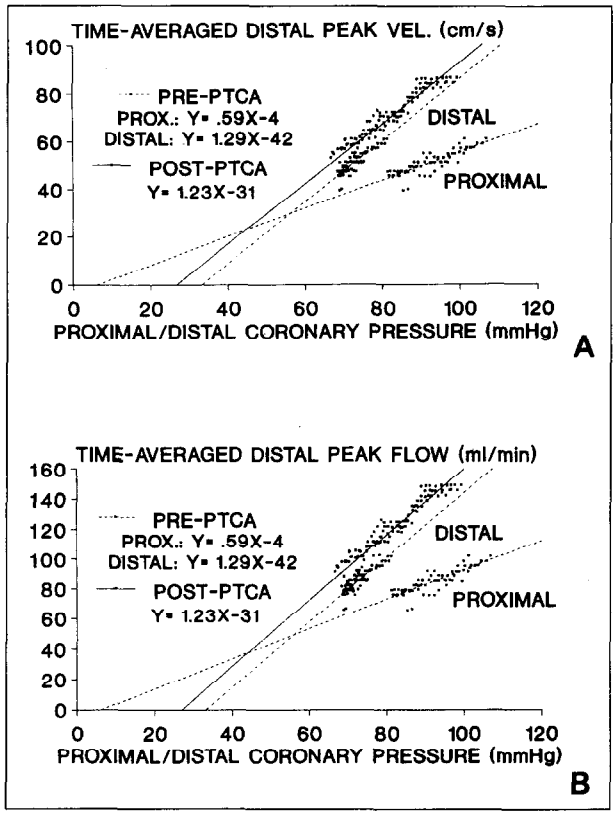


FIGURE 13. Instantaneous hyperemic diastolic flow velocity/pressure relation (*A*) and flow/pressure relation (*B*) before and after coronary angioplasty. The dashed lines indicate the relation observed before percutaneous transluminal coronary angioplasty (PTCA) using the proximal coronary pressure (*lower line*) and the true driving pressure (poststenotic coronary pressure measured with the pressure microsensor, *upper dashed line*). After PTCA (*continuous line*), despite the increase in flow velocity and the absence of transstenotic gradient, the slope of the instantaneous flow velocity/pressure relation was similar to the slope observed before PTCA (*upper dashed line*).

velocity ratio.[11] As previously reported,[12] a normalization of this index occurs in the minutes following a successful angioplasty. The physiologic explanation of this phenomenon remains controversial. The normalization of the diastolic/systolic flow velocity ratio after angioplasty may be intimately related to a rapid modification of the vasodilatory capacity of the capillary bed after angioplasty, possibly reflected by the slope of the instantaneous hyperemic flow velocity/pressure relation. Nevertheless, the clinical applicability of the diastolic/systolic flow velocity ratio, as an index capable of describing the results of coronary angioplasty in individual patients, requires a complete investigation of the factors that can modify this index independently of the stenosis severity (heart rate, contractility, type of studied vessel, etc.).

CONCLUSION

Miniaturization of flow velocity and pressure sensors with guidewire technology now permits the application in conscious humans of methodologic approaches previously limited to the experimental animal laboratory. The initial results based on the slope of the instantaneous hyperemic flow velocity/pressure relation and of the pressure gradient/velocity relation suggest that these techniques can yield a reproducible and accurate assessment of parameters that more precisely characterize the physiologic significance of coronary stenoses before and after interventions.

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