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Single-Wire Pressure and Flow Velocity Measurement to Quantify Coronary Stenosis Hemodynamics and Effects of Percutaneous Interventions

Maria Siebes, PhD; Bart-Jan Verhoeff, MSc; Martijn Meuwissen, MD; Robbert J. de Winter, MD; Jos A.E. Spaan, PhD; Jan J. Piek, MD

Background—Lack of high-fidelity simultaneous measurements of pressure and flow velocity distal to a coronary artery stenosis has hampered the study of stenosis pressure drop–velocity (ΔP -v) relationships in patients.

Methods and Results—A novel 0.014-inch dual-sensor (pressure and Doppler velocity) guidewire was used in 15 coronary lesions to obtain per-beat averages of pressure drop and velocity after an intracoronary bolus of adenosine. ΔP -v relations from resting to maximal hyperemic velocity were constructed before and after stepwise executed percutaneous coronary intervention (PCI). Before PCI, half of the ΔP -v relations revealed the presence of a compliant stenosis, which was stabilized by angioplasty. Fractional flow reserve (FFR), coronary flow reserve (CFVR), and velocity-based indices of stenosis resistance (h-SRv) and microvascular resistance (h-MRv) at maximal hyperemia were compared. Stepwise PCI significantly lowered h-SRv, with an initial marked reduction in hyperemic pressure drop followed by further gains in velocity. A concomitant significant reduction of h-MRv accounted for half of the gain in velocity after PCI. The average magnitude of absolute incremental hemodynamic changes was highest for h-SRv ($56.8 \pm 39.2\%$) compared with CFVR ($35.3 \pm 34.5\%$, $P < 0.005$) or FFR ($19.5 \pm 25.2\%$, $P < 0.0001$).

Conclusions— ΔP -v relations comprehensively visualize improvements in coronary hemodynamics after PCI. h-SRv is a powerful and sensitive descriptor of the functional gain achieved by PCI, combining information about both pressure gradient and velocity, which are oppositely affected by PCI. Simultaneous assessment of stenosis and microvascular resistance may provide a valuable tool for guidance of PCI. (*Circulation*. 2004;109:756-762.)

Key Words: coronary disease ■ hemodynamics ■ stenosis ■ angioplasty ■ microcirculation

Both pressure-derived myocardial fractional flow reserve (FFR) and coronary flow velocity reserve (CFVR) have been evaluated as powerful predictors of inducible ischemia, as measured by noninvasive stress tests, and of adverse events after stent placement.^{1,2} However, as the underlying models of these traditional indices demonstrate, their values depend not only on stenosis resistance but also on microvascular resistance at full dilation, which may vary as a result of heart rate, metabolic demand, or microvascular disease^{3–5} and which affects FFR and CFVR in opposite directions.^{6,7} The combination of pressure and flow velocity into an index of hyperemic stenosis resistance significantly improved diagnostic accuracy as assessed by noninvasive ischemic testing,⁸ especially in cases with discordant outcomes between the traditional parameters.⁶

The relationship between distal coronary velocity and transstenotic pressure gradient is almost entirely determined by the coronary stenosis and is thus by definition well suited to evaluate its hemodynamic severity.^{9,10} Diastolic pressure

gradient–velocity (ΔP -v) relationships have been obtained in humans with 2 single-sensor–equipped guidewires.^{11–13} Recently, the simultaneous measurement of phasic distal pressure and velocity by a single dual-sensor–equipped guidewire has become possible.

In the present study, we report on the first group of patients in whom this novel device was used to quantify changes in stenosis hemodynamics and its alterations due to stepwise executed percutaneous coronary intervention (PCI) by the assessment of complete ΔP -v curves obtained from per-beat averages throughout the response to a vasodilator stimulus. We hypothesized that evaluation of stenosis hemodynamics and effects of PCI benefits from combined distal pressure and velocity measurements, because they reveal information not attainable with single-variable measurements and uncover mechanisms of action on the epicardial (stenosis) and microvascular compartments of the coronary circulation through quantitative assessment of the functional gain after PCI in terms of stenosis and microvascular resistance.

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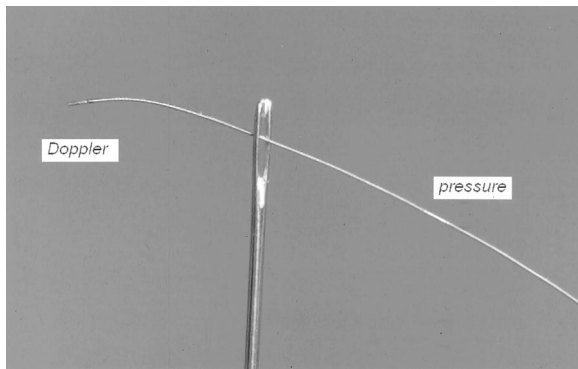


Figure 1. Dual-sensor guidewire (JOMED Inc; now Volcano Therapeutics Inc).

Methods

Patient Population

The study population consisted of 19 patients (15 males, mean age 56 ± 8 years) with stable angina pectoris scheduled for elective PTCA. Exclusion criteria were diffuse or 3-vessel disease, significant left main coronary artery stenosis, or a subtotal lesion in the target vessel; recent myocardial infarction (< 6 weeks); prior cardiac surgery; or hypertrophic cardiomyopathy. The procedures were in accordance with institutional guidelines. All patients gave written informed consent, and the institutional Medical Ethics Committee approved the study protocol.

Cardiac Catheterization Procedure

All antianginal and antiplatelet medication was continued until cardiac catheterization. After oral administration of lorazepam (1 mg), cardiac catheterization was performed by percutaneous femoral approach. All patients received a bolus of heparin (7500 IU IV) at the beginning of the procedure. Additional heparin was administered if the procedure lasted more than 90 minutes. Nitroglycerin (0.1 mg IC) was given before coronary angiography and every 30 minutes throughout the procedure.

Hemodynamic Measurements

Aortic pressure was measured through a 5F or 6F guiding catheter. In an angiographically normal reference vessel and distal to the stenosis in the target vessel, intracoronary pressure and flow velocity were measured with a novel 0.014-inch-diameter guidewire (JOMED Inc; now Volcano Therapeutics Inc) that combines a standard Doppler sensor at the tip and a standard pressure sensor 3 cm proximal to the tip (Figure 1). The signals were processed by standard hardware (FloMap and WaveMap, JOMED Inc; now Volcano Therapeutics, Inc). Benchtop testing before the patient study verified high-quality measurements similar to those of established single-sensor guidewires. The position of the Doppler sensor was manipulated until an optimal and stable blood flow velocity signal was obtained distal to the lesion. The sensors were positioned at the same location for all measurements obtained throughout the procedure. Aortic pressure (Pa), coronary pressure (Pd) and instantaneous peak velocity (v) distal to the stenosis, and the ECG were recorded on a personal computer after 12-bit analog-to-digital conversion at 120 Hz. All signals were continuously recorded at rest and throughout induction and decline of maximum hyperemia after an intracoronary bolus of 20 to 40 μ g of adenosine.¹⁴

Protocol

After baseline hemodynamic measurements were taken in an angiographically normal reference vessel and in the target vessel, all patients underwent balloon angioplasty, with the balloon size based on angiographic dimensions, followed by placement of a single slotted-tube stent. The stent was upsized according to the CLOUT (Clinical Outcomes with Ultrasound Trial) criteria by intravascular

ultrasound guidance.¹⁵ Immediately after PTCA and stent placement, hemodynamic and angiographic recordings were obtained.

Coronary Angiography

Coronary angiograms were obtained before and after each step of the percutaneous intervention. Several views were obtained before PCI, and the one that showed the most severe stenosis without overlap or foreshortening was maintained for comparison with the posttreatment situation. Biplane views were obtained when possible, and the results were averaged.

Data Analysis

Percent diameter stenosis, reference diameter, and minimal lumen diameter were obtained by quantitative analysis of the coronary angiograms with a validated computer-assisted analysis system (QCA-CMS version 5.0, MEDIS). For each heart cycle throughout the complete hyperemic response to administration of adenosine, the per-beat average of stenosis pressure gradient (in mm Hg; $\Delta P = P_a - P_d$) was plotted versus the mean flow velocity v (in cm/s). These data were fitted with the equation describing the underlying fluid dynamic model.^{9,10}

$$(1) \quad \Delta P = A v + B v^2$$

Parameters of functional stenosis severity were calculated as myocardial FFR (P_d/P_a), CFVR ($v_{\text{hyp}}/v_{\text{baseline}}$), relative CFVR ($\text{CFVR}_{\text{target}}/\text{CFVR}_{\text{reference}}$), and velocity-based indices of stenosis resistance ($\text{h-SRv} = \Delta P/v$) and distal microvascular resistance ($\text{h-MRv} = P_d/v$) at maximal hyperemia.⁶ Because stenosis resistance is flow dependent,^{8,16} it should be determined at maximum hyperemia. Signed and unsigned (absolute) incremental changes in these parameters were compared per PCI step.

The separate contribution of changes in each of these 2 resistance indices to the velocity gain achieved by PCI was assessed with a lumped model of 2 resistances in series representing the coronary circulation. With venous pressure assumed to be zero and the vessel diameter at the site of measurement constant, velocity can be expressed as

$$(2) \quad v = \frac{P_a}{(\text{SRv} + \text{MRv})}$$

By substituting the hyperemic MRv measured before PCI (MRv_{pre}), the relative gain in velocity exclusively due to a decrease in h-SRv after each PCI step was then calculated with the maximal hyperemic velocity achieved after PCI (v_{SRv}) as

$$(3) \quad v_{\text{SRv}} = \frac{P_a}{(\text{SRv} + \text{MRv}_{\text{pre}})}$$

Statistical Analysis

Continuous variables were expressed as mean \pm SD and compared by paired Student's t test or ANOVA with repeated measures followed by contrast analysis as appropriate (SPSS version 11.5). Reproducibility of hyperemic measurements before PCI was assessed by coefficient of variation, calculated as the square root of the within-subject variance component obtained with the use of a 1-way random-effect model ANOVA divided by the group mean. Values of $P < 0.05$ were considered statistically significant.

Results

Clinical and Angiographic Characteristics

The protocol could not be completed in 5 patients (in 3 because of initial technical problems related to drift or electromagnetic interference between the 2 sensors and in 2 for clinical reasons). The clinical profile of the remaining 14 patients is summarized in Table 1. Most patients had moderate to severe anginal complaints (72% Canadian Cardiovascular Society [CCS] class 3, 14% CCS class 2, and 14% CCS

TABLE 1. Patient Clinical Characteristics

Age, y, mean \pm SD	55.2 \pm 5.7
Male gender, n (%)	11 (79)
Coronary risk factors, n (%)	
Cigarette smoking	7 (50)
Hypertension	3 (21)
Positive family history	7 (50)
Hyperlipidemia	11 (79)
Insulin-dependent diabetes mellitus	1 (7)
Prior myocardial infarction (>6 wk)	3* (21)
Prior coronary angioplasty	3† (21)
Medication, n (%)	
β -Blockers	13 (93)
Nitrates	9 (64)
Calcium antagonists	3 (21)
ACE inhibitors	2 (14)
Lipid-lowering drugs	13 (93)
Aspirin	14 (100)

*Two in the area perfused by the target vessel.

†One in the target vessel.

class 1). In 3 patients, direct stenting needed to be performed without hemodynamic measurements after balloon angioplasty. These patients are included in the “balloon” group for stepwise comparison. In 2 patients, the reference vessel was not instrumented for clinical reasons. One patient required 2 stents in the same vessel in different procedures. Hemodynamic baseline characteristics of the treated lesions (11 left anterior descending coronary arteries, 2 right coronary arteries, 1 left circumflex artery, and 1 marginal branch) and reference vessels (2 left anterior descending coronary arteries, 9 left circumflex arteries, and 2 marginal branches) are listed in Table 2.

Balloon angioplasty and stent implantation reduced diameter stenosis from $52.2\pm 8.6\%$ (range 33.3% to 65.5%) to $2.5\pm 8.9\%$ (range -14.6% to 19.3%). Minimum stenosis diameter increased from 1.33 ± 0.30 to 3.33 ± 0.48 mm. Average diameter stenosis in the reference vessels was $24.3\pm 8.8\%$.

Hemodynamic Data

Reproducibility of repeated hyperemic measurements obtained in the reference vessel and in the target vessel before PCI (n=46) was excellent. The coefficient of variation was 6.4% for velocity, 3.2% for aortic pressure, and 3.5% for distal pressure. Corresponding values for derived data were 5.7% for h- Δ P, 4.6% for h-SRv, and 6.2% for h-MRv.

A typical example of phasic signals is shown in Figure 2. The left panel was obtained before treatment and shows that injection of adenosine caused a transient decrease in MRv, accompanied by only a small increase in flow velocity and a marked drop in distal pressure. These characteristics improved after completion of PCI, as shown in the right panel.

Figure 3 illustrates PCI-induced hemodynamic changes in terms of Δ P-v relations obtained in 1 patient before treatment and after balloon angioplasty, stenting, and upsized stenting. Each data point represents the average over 1 beat, from baseline in the lower left to maximal hyperemia at the upper right of each curve. These curves provide a comprehensive overview of the progressive hemodynamic improvement achieved by stepwise PCI. With reduction in stenosis severity by PCI, the relationships became less steep, and maximal flow velocity increased, thereby approaching the Δ P-v relation of the reference vessel.

Before treatment, 7 of the 15 lesions exhibited a “looped” Δ P-v relation, which disappeared after PTCA or stenting (Figure 4). This hysteresis-like behavior is characteristic for a compliant, often flow-limiting lesion (ie, a lesion in which further reduction in downstream resistance will not increase flow). This special hemodynamic behavior was not obvious from the continuous pressure and flow-velocity tracings obtained during catheterization, nor could it be discerned from angiographic, clinical, or descriptive hemodynamic parameters.

Figure 5 illustrates that the initial PCI step (balloon angioplasty) caused a significant decrease in hyperemic pressure gradient ($P<0.005$) followed by progressively smaller changes for further treatment steps (stenting and upsized stenting). In contrast, maximal velocity continued to increase significantly ($P<0.025$), with both signals approaching the values obtained in the reference vessel. The relative

TABLE 2. Hemodynamic Characteristics of the Stenoses

	Pretreatment (n=15)	Balloon (n=12)	Stent (n=15)	Upsized Stent (n=10)	Reference (n=13)
b-v, cm/s	16.4 \pm 6.8	20.6 \pm 2.2*	20.4 \pm 7.63	24.3 \pm 11.5	20.7 \pm 6.5
h-v, cm/s	30.4 \pm 17.6	44.6 \pm 9.5*	55.4 \pm 15.7*	64.0 \pm 20.0	55.1 \pm 13.8
h-Pa, mm Hg	100.3 \pm 17.9	90.0 \pm 13.8	91.5 \pm 15.5	90.7 \pm 16.1	95.8 \pm 15.4
h- Δ P, mm Hg	36.9 \pm 17.3	21.2 \pm 9.7*	13.8 \pm 11.6*	14.0 \pm 10.7	2.8 \pm 2.6†
CFVR	1.80 \pm 0.64	2.16 \pm 0.36*	2.86 \pm 0.59*	2.82 \pm 0.53	2.8 \pm 0.74
Relative CFVR	0.67 \pm 0.3	0.81 \pm 0.24*	1.05 \pm 0.23*	1.07 \pm 0.32	1.0 \pm 0.0
FFR	0.62 \pm 0.16	0.77 \pm 0.09*	0.85 \pm 0.11*	0.85 \pm 0.10	0.97 \pm 0.03†
h-SRv, mm Hg \cdot cm ⁻¹ \cdot s ⁻¹	2.09 \pm 2.15	0.50 \pm 0.30*	0.26 \pm 0.23*	0.26 \pm 0.25	0.05 \pm 0.05
h-MRv, mm Hg \cdot cm ⁻¹ \cdot s ⁻¹	2.51 \pm 1.39	1.59 \pm 0.38*	1.49 \pm 0.41	1.29 \pm 0.40	1.75 \pm 0.37†

b indicates baseline; h, hyperemic.

* $P<0.02$ vs prior step.† $P<0.05$ vs upsized stent.

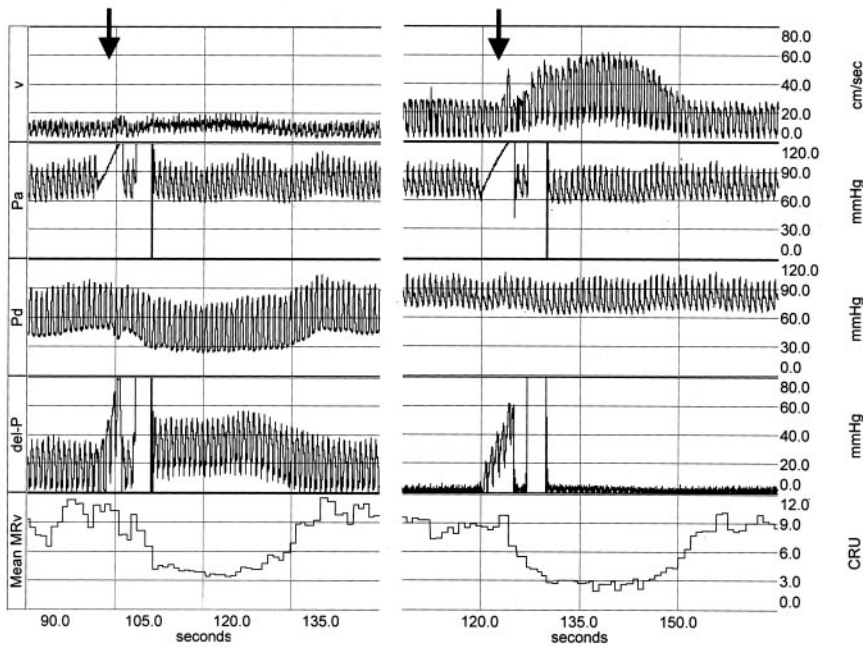


Figure 2. Hemodynamic tracings before (left) and after (right) intervention. Arrows indicate adenosine injection.

unsigned incremental change in h-SRv averaged over all PCI steps was therefore significantly higher than that of FFR ($P<0.0001$), CFVR ($P<0.01$), or relative CFVR ($P<0.005$), as shown in Figure 6.

Heart rate did not change. In addition to the expected increase in FFR and CFVR and the anticipated large decrease in h-SRv compared with pretreatment values (Table 2), there was a significant reduction in h-MRv after PCI ($P<0.005$). The vertical arrows in Figures 3 and 4 indicate the calculated maximally achievable hyperemic flow velocity (Equation 3) if h-MRv had remained unchanged at the pretreatment level. Averaged over all steps, the relative contribution of the decrease in h-SRv and h-MRv to the gain in maximal velocity after PCI was approximately equal ($52.4\pm 63.6\%$ versus $47.6\pm 63.6\%$, $P=0.82$).

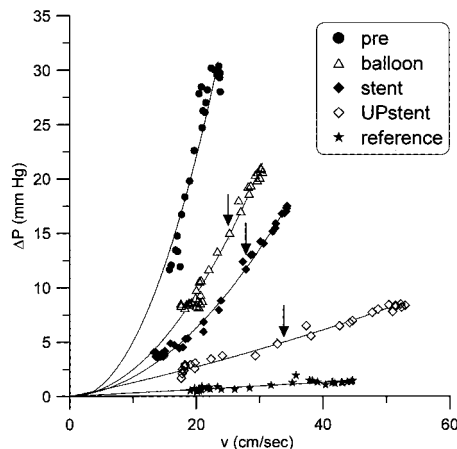


Figure 3. Pressure drop-velocity relationships obtained before (pre) and after successive treatment steps in 1 patient. UPstent indicates upsized stent; arrows indicate maximum flow achievable if microvascular resistance had remained at pretreatment level.

Discussion

We assessed the effect of PCI on stenosis and coronary microvascular hemodynamics in terms of ΔP -v relations obtained throughout the hyperemic response to adenosine. PCI-induced changes in stenosis geometry resulted in characteristic hemodynamic changes that were comprehensively visualized by ΔP -v relations. Compared with traditional measures of functional stenosis severity such as FFR, CFVR, and relative CFVR, a velocity-based index of stenosis resistance during maximal hyperemia (h-SRv) was the most sensitive hemodynamic measure of PCI-induced improvements in stenosis severity, by combining opposite changes in ΔP and velocity. A concomitant decrease in microvascular resistance (h-MRv) accounted for approximately half of the increase in maximal flow velocity after PCI.

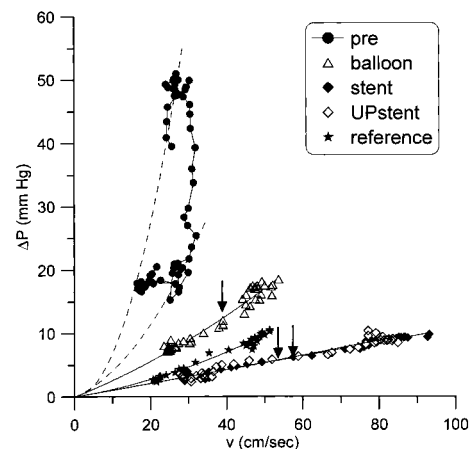


Figure 4. Example of pressure drop-velocity relationship demonstrating a loop before treatment (pre), which indicates a compliant stenosis. Arrows indicate maximum flow achievable if microvascular resistance had remained at pretreatment level.

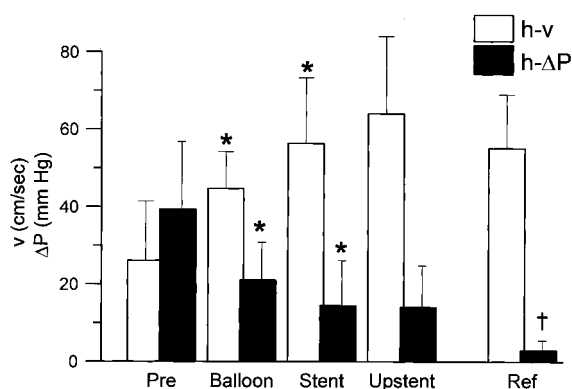


Figure 5. Average hyperemic pressure gradient (h- ΔP) and distal velocity (h-v). * $P < 0.02$ vs previous step, † $P < 0.05$ vs upsized stent. pre indicates before treatment; Upstent, upsized stent; and Ref, reference.

Interpretation of the Pressure-Gradient-Flow-Velocity Relationship

The hemodynamic behavior of an arterial stenosis is uniquely characterized by its pressure drop-velocity relation, a concept put forward by Young⁹ and extensively validated by in vitro and in vivo studies.^{10,17,18} For a given coronary stenosis, ΔP -v relations start at resting values of ΔP and v and increase curvilinear to hyperemic values in response to microvascular dilation after adenosine injection. Alterations in stenosis geometry (eg, by PCI) will result in a different curve. The composite of curves thus obtained per patient after stepwise PCI provides a clear and comprehensive overview of the hemodynamic improvement in both stenosis and distal coronary hemodynamics achieved by the interventions.

Instantaneous ΔP -v relationships obtained in artificially created coronary artery stenoses in dogs were first reported by Gould¹⁸ for the diastolic part of the cardiac cycle. Fifteen years later, the first ΔP -v relationships of coronary stenoses in humans were obtained after placement of both a pressure and Doppler guidewire distal to the lesion.^{11,12} Marques and coworkers¹³ demonstrated the feasibility and reproducibility of this diastolic relationship and its ability to discriminate between normal and diseased coronary arteries.

We used a single dual-sensor-equipped wire, thereby minimizing potential overestimation of stenosis severity, especially before treatment.¹⁹ In addition, instead of diastolic

portions of selected cycles during the hyperemic response, we used successive per-beat averages to generate the pressure-drop-flow relationship of a coronary stenosis from baseline throughout maximal hyperemia.^{10,17} The main advantages are easier postprocessing with less user interaction, which circumvents problems related to phase delays between the pressure transducers, the characterization of stenosis hemodynamics over the entire range of possible flow velocities, and the ability to identify partially compliant lesions. The present results support previous findings that coronary flow can be considered as quasi-steady,^{10,17} because the mean pressure drop-velocity data were nicely fit with the quadratic equation when a fixed stenosis was present. Rapid changes in the flow waveform are confined to brief periods during the cardiac cycle, and flow pulsatility declines with increasing stenosis severity, thus only minimally affecting means of pressure and flow.

Flow-mediated dilation of the normal reference diameter can worsen stenosis severity, which results in an upward shift of the instantaneous diastolic ΔP -v relation between baseline and maximal hyperemia.²⁰ However, patients in the present study received intracoronary nitroglycerin every 30 minutes throughout the procedure to vasodilate the epicardial vessels before hyperemia was induced. In contrast, coronary artery stenoses are frequently at least partially compliant, and stenosis dimensions then depend on intrastenotic pressure.^{16,21–24} As intrastenotic pressure falls with increasing flow during the hyperemic response, the stenosis becomes more severe, which results in a deviation from the quadratic ΔP -v relation. Although we did not obtain angiograms during maximal hyperemia to document possible changes in stenosis dimensions, this explanation can be inferred from the nature of the pressure drop-flow relationship of partially compliant stenoses.^{25,26} In severe cases, the stenosis may behave as a Starling resistor, where flow becomes disassociated from the pressure gradient.²⁴

At minimum MRv after adenosine injection, partial collapse of a compliant stenosis produces maximal pressure gradient at submaximal flow. Flow reaches a maximum at a considerably lower pressure gradient (dashed lines in Figure 4). This behavior represents an additional mechanism for the existence of discordant measurements between FFR and CFVR at the epicardial level, besides the role of h-MRv.^{6,7} The frequent occurrence of this phenomenon in the patient group in the present study suggests that stenosis compliance may be a contributing factor to anginal complaints, especially during periods of low microvascular resistance.

Changes in Hemodynamic Parameters by PCI

Quantitative analysis of the data obtained at rest and during maximal hyperemia revealed h-SRv to be a powerful and sensitive indicator of the functional gain achieved after PCI. Generally, a large initial decline in pressure gradient was followed by further gains in hyperemic flow velocity with treatment. The combination of pressure gradient and flow velocity is therefore well suited to assess changes in hemodynamic stenosis severity and avoids pitfalls due to variations in baseline velocity affecting CFVR,²⁷ the declining sensitivity of pressure-based methods (FFR) with improvement in

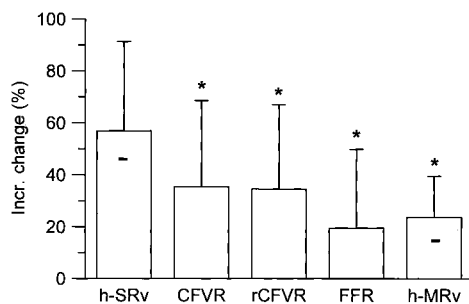


Figure 6. Average unsigned incremental (Incr.) changes in hemodynamic parameters. Minus sign indicates actual direction of changes was negative for h-SRv and h-MRv. * $P < 0.005$. rCFVR indicates relative CFVR.

stenosis geometry, or nonmaximal hyperemia (CFVR and FFR).³

The simultaneous assessment of distal pressure and flow velocity furthermore permits the separate assessment of changes in both the proximal epicardial and distal myocardial resistance index with PCI. The initial results obtained in the present study indicate that flow restoration after PCI is not only due to the primary effect of treating the epicardial lesion but also to a significant accessory reduction in hyperemic microvascular resistance. Additional studies should be performed in a larger patient group to elucidate this phenomenon, which has been described previously.²⁸

Methodological Considerations

Current prototypes of the dual-sensor guidewire were designed with a distance of 3 cm between the Doppler flow sensor at the tip and the pressure sensor. Ideally, pressure and velocity should be measured at the same location to avoid time delays between the signals. However, this is only relevant for the instantaneous (diastolic) ΔP -v relation and not for relationships between means as in the present study. Another disadvantage of this design is the inability to measure between lesions that are <3 cm apart. Future designs could result in a more practical compromise between sensor distance and wire-tip flexibility.

The use of velocity-based parameters is potentially limited by their diameter dependence and thus by the axial position of the Doppler sensor and possible diameter variations at that location. However, velocity normalizes flow for differences in coronary arterial diameter due to branching and is preserved between proximal and distal segments.²⁹ An increase in distal diameter due to pressure restoration after PCI attenuates the rise in hyperemic velocity that would be seen if vessel diameters remained at pre-PCI levels. Hence, the observed decrease in the velocity-based resistance indices after PCI may have been underestimated compared with the pre-PCI situation. Although the principles of stenosis ΔP -v relationships to assess the presence of a compliant stenosis and treatment success have been established in the present study, the small sample size limits extension of our quantitative findings to a larger patient group.

Clinical Implications

Combined measurement of distal pressure and flow velocity, made possible by recent advancements in wire fabrication technology, not only yields a high diagnostic accuracy⁸ but also holds great potential for improved guidance of coronary interventions in the catheterization laboratory. The ΔP -v relationship does not depend on the level of vasodilation achieved by adenosine but only on the severity of the stenosis. It can identify compliant lesions, the severity of which changes as a function of intrastenotic pressure, which may be an additional mechanism responsible for anginal complaints. The frequent occurrence of this phenomenon illustrates potential pitfalls in the analysis of coronary hemodynamics based on traditional hemodynamic parameters. The effect of interventions on the hemodynamics of the stenosed artery and distal microcirculation can be separately quanti-

fied, thereby providing insight into mechanisms for nonoptimized FFR or CFVR after PCI that have been associated with a worse outcome.^{1,2} Further studies are needed to establish the potential prognostic value of h-SRv and h-MRv after coronary interventions.

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