New concepts for interpretation of intracoronary velocity and pressure tracings

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Abstract
The development of quantitative angiography and the introduction of new imaging techniques cannot replace functional methods of assessing the severity of stenosis. Measurement of transstenotic pressure gradient and poststenotic flow velocity using miniaturised sensors with guidewire technology offers an alternative to the conventional non-invasive methods that is immediately applicable in the catheterisation laboratory during interventional procedures. The complexity of the coronary circulation, however, makes it difficult to establish simple cut-off criteria to identify the presence of a flow-limiting stenosis. For intermediate lesions or in the presence of variable haemodynamic conditions, the accuracy of the assessment can be improved by the application of more complex indices proposed and validated in the laboratory animals. Two of these indices are myocardial fractional flow reserve and the slope of the instantaneous relation between pressure or pressure gradient and flow velocity.

Keywords: coronary circulation; intracoronary Doppler echocardiography

Coronary angiography, which provides a rapid overview and effective road-map during diagnostic and interventional procedures, is not expensive and is widely available. Computer-assisted quantitative coronary angiography can be used during interventional procedures to measure absolute and relative dimensions of the stenotic segment, giving precise and reproducible results. Methods of assessment of the functional severity of a coronary stenosis based on the integration of multiple anatomical characteristics of the stenotic segment measured with quantitative angiography (minimum luminal cross sectional area and percentage cross sectional area stenosis, length, entrance and exit angles) are cumbersome and correlate poorly with direct measurements of poststenotic flow velocity and pressure (fig 1). Measurement of the transstenotic pressure gradient and of coronary flow velocity is not a new approach to the

Figure 1 (A) On-line quantitative angiographic measurements of an intermediate stenosis of the mid left anterior descending coronary artery (Philips, DCI AQA analysis program). In the two projections considered, left cranial 30° (on the left) and right superior oblique 30°-30° (on the right), minimum lumen diameter (D ob) and percentage diameter stenosis (%D) are 1.4 mm and 1.30 mm, and 56% and 53% respectively. In the lower panels the angiographic measurements are integrated to calculate stenosis flow reserve (SFR) as proposed by Kirkeeide et al. (B) Flow velocity is measured proximal (upper panels) and distal (lower panels) to the stenosis with an 0.014 inch Doppler guidewire in baseline and conditions and after maximal hyperaemia induced by an intracoronary bolus of 18 μg of adenosine. Note that when coronary flow reserve is measured proximal to the stenosis the true flow increase distal to the stenosis is overestimated. The maximal flow increase distal to the stenosis is half the flow increase predicted by angiography and confirms the functional severity of the stenosis. APV, time-averaged peak flow velocity; CFR, coronary flow reserve; SFR, stenotic flow reserve.
assessment of stenosis severity. Lately, however, pressure and Doppler transducers mounted at the tip of a guidewire have become available. These can be used to make recordings distal to the stenosis with a minimum obstruction to flow and they give more accurate and reliable measurements.

We review the role and limitations of the measurement of the poststenotic pressure gradient and flow velocity in the functional assessment of stenosis severity and discuss the possibilities offered by the combination of velocity and pressure signals recorded with high-fidelity miniaturised transducers.

**Transstenotic pressure gradient measured with pressure microsensors**

Andreas Grünzig, the inventor of coronary angioplasty, used the transstenotic pressure gradient to guide progress of the balloon catheter in the coronary tree up to the targeted stenotic lesion, to demonstrate the severity of the stenotic lesion, and to assess the results of the intervention. The physiological value of measurements performed through the lumen of the balloon catheter has always been questioned because the catheter impedes flow. A recent comparison with measurements obtained using a pressure guidewire suggests that the true transstenotic gradient cannot be measured with sufficient accuracy with a balloon catheter during percutaneous coronary angioplasty. The further miniaturisation of the balloon catheter and the introduction of the movable guidewire, and of the monorail technique soon precluded measuring pressure gradient during balloon angioplasty.

Interest in the use of poststenotic pressure measurements in the catheterisation laboratory revived when ultraminiaturised transducers were developed. These transducers can measure poststenotic pressure without causing an appreciable additional reduction in cross sectional area.

**TECHNIQUE**

The pressure microsensor is located 3 cm back from the flexible tip of a 0.018 inch or 0.014 inch guidewire (Radi Medical Systems, Uppsala, Sweden). Light is emitted from a control unit through a beam splitter and is transmitted to the sensor element along an optical fibre integrated in the guidewire. The sensor element consists of a silicon cantilever with a mirror integrated into its free end. Deflection of the mirror induced by the elastic movement of the sensor in response to changes in the external pressure modulates the reflected light. The signal is then transmitted back through the same optical fibre and is detected by a photodiode in the control unit. The signal transfer characteristics, linearity, and frequency response of the system has been validated in vitro and in vivo. Fluid-filled guidewire systems have also been designed and successfully tested in vitro and in vivo. These transducers cost less and are easier to use but cannot provide a phasic pressure recording because of the small diameter of the internal lumen.

**APPLICATION FOR THE ASSESSMENT OF STENOSIS SEVERITY**

Baseline and hyperaemic pressure gradients could be measured with a pressure guidewire in 48 patients scheduled for a possible coronary angioplasty and both gradients showed a curvilinear relation with angiographic measurements of minimum luminal cross sectional area stenosis and with percentage area stenosis. Concepts developed and validated by Pijs et al. stimulated a new interest in the application of the measurements of poststenotic pressure to the assessment of stenosis severity. Pijs et al. used a set of hydrodynamic equations based on poststenotic coronary pressure measurements during maximal coronary vasodilatation, corrected for aortic and right atrial pressure, to measure separately the contributions of anterograde flow and coronary collateral circulation to poststenotic flow. In particular, the ratio of poststenotic pressure to aortic pressure (both pressures corrected for coronary venous pressure) reflects the fractional flow reserve of the myocardium, defined as the ratio between normal hyperaemic flow in the absence of epicardial stenoses and maximal anterograde and collateral flow supplied to the myocardium distal to the stenosis under assessment. This index is independent of the haemodynamic conditions at the time of assessment and, because in the absence of cardiac failure right atrial pressure is of negligible importance, the fractional flow reserve of the myocardium can be easily calculated in the catheterisation laboratory because it requires only the measurement of a mean poststenotic coronary pressure during maximal hyperaemia.

Measurements of regional myocardial perfusion using positron emission tomography have been used in humans to validate the myocardial fractional flow reserve calculated from pressure measurements. Reserves of less than 0.7 correlate with abnormal measurements of myocardial perfusion and are associated with evidence of reversible ischaemia during exercise. These preliminary results have not yet been confirmed in large studies because current pressure guidewires are not sufficiently steerable and flexible. The two components of myocardial fractional flow reserve (anterograde flow and collateral flow) can also be distinguished using the proposed set of equations. These last measurements, however, have the practical drawback that they require a poststenotic pressure during balloon occlusion (wedge pressure), which limits the application of this technique for diagnostic purposes.

**Poststenotic flow velocity measured with a Doppler transducer mounted on the tip of an angioplasty guidewire**

**TECHNIQUE**

The Doppler angioplasty guidewire is a 0.018 inch or 0.014 inch 175 cm long flexible and steerable guidewire with a floppy shapable distal end with a 12–15 MHz piezoelectric transducer mounted at the tip (Cardiometrics, Mountain View, California). The sample
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Figure 2 (A) Long diastolic pause induced by the intracoronary infusion of adenosine (3 mg). From top to bottom peak flow velocity, instantaneous transstenotic pressure gradient and proximal and poststenotic coronary pressure. (B) Instantaneous hyperaemic diastolic pressure gradient/flow velocity relation of the diastolic pause shown in (A).

APPLICATION DURING CORONARY INTERVENTIONS

The Doppler guidewire had similar handling characteristics to an angioplasty guidewire and crossed the lesion in most patients (98% of instances in 297 patients) examined in the multicentre study DEBATE (Doppler Endpoints Balloon Angioplasty Trial Europe; personal communication).

Before angioplasty the Doppler guidewire can be used to confirm the severity of the lesion to be treated, and during dilatation it can be left in place distal to the lesion to detect collateral flow. The restoration of anterograde flow can be immediately detected during the deflation of the balloon, before the electrocardiographic changes or symptoms disappear. After the angioplasty balloon is withdrawn into the guiding catheter, to avoid residual obstruction of flow, the rapid increase in flow velocity during post-occlusion reactive hyperaemia can be used immediately to assess the adequacy of lumen enlargement after angioplasty. In a study of 34 patients Serruys et al found that coronary flow reserve, expressed as the ratio of hyperaemic/baseline flow velocity, showed a moderate but significant increase after angioplasty (from a mean (SD) of 1.75 (0.55) to 2.39 (0.75), P < 0.005) (fig 3).\textsuperscript{17} There were comparable increases in flow velocity after angioplasty in the phase of maximal reactive hyperaemia recorded after balloon dilatation and when the effect of a papaverine injection was greatest (45 (22) cm/s peak reactive hyperaemia v 47 (20) cm/s after papaverine, NS). The ratio between mean diastolic and mean systolic flow velocity measured during baseline conditions distal to the stenosis was 1.51 (0.98) before angioplasty, significantly lower than the ratio measured in 39 normal or nearly normal arteries (2.09 (0.90), P < 0.001). After angioplasty, the diastolic to systolic flow velocity ratio increased to 2.16 (0.98) (P < 0.001) and was not significantly different from that in the control group.

Segal et al have also recently reported their

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Volume is positioned 5.2 mm from the transducer and is about 2.25 mm wide because of the divergent ultrasound beam. This means that a large part of the flow velocity profile is included in the sample volume, even when the Doppler guidewire is positioned eccentrically. After real-time processing of the quadrature audio signal a fast-Fourier transform algorithm is used to increase the reliability of the analysis\textsuperscript{14} (fig 1). The Doppler system calculates and displays on-line several spectral variables including the instantaneous peak velocity and the time-averaged (mean of two beats) peak velocity. The flow velocity measurements obtained with this system have been validated in vitro and in an animal model in which a comparison was made with simultaneous measurements with an electromagnetic flowmeter.\textsuperscript{13,15} Mean flow velocity is calculated as time-averaged peak velocity divided by two, assuming a fully developed parabolic flow velocity profile.\textsuperscript{16}
results after balloon angioplasty in 38 patients. Twelve patients without significant coronary artery disease served as a control group. After angioplasty, the time-averaged peak velocity in the distal vessel increased from 19 (12) to 35 (16) cm/s mean (SD) (P < 0.01), whereas the velocity in the proximal vessel increased to a lesser extent (from 34 (18) to 41 (14) cm/s, P = 0.04). Coronary flow reserve did not increase significantly after angioplasty in either the distal or proximal part of the coronary artery (P < 0.10). When measured distal to significant stenoses before angioplasty, the diastolic to systolic flow velocity pattern was abnormal, with a low ratio of diastolic to systolic flow (1·3 (0·5) compared with the ratio recorded in patients without significant stenoses (1·8 (0·5), P < 0.01). Normal phasic velocity patterns with a significant increase in diastolic to systolic flow velocity ratio (1·9 (0·6), P < 0.01), were seen within 10–15 minutes of successful balloon angioplasty. In the proximal vessel, the phasic diastolic to systolic flow pattern was not significantly different from the pattern seen in normal vessels (diastolic to systolic flow velocity ratio 1·8 (0·8) proximal to stenosis v 1·8 (0·5) in normal vessels, NS) and the diastolic to systolic flow velocity ratio did not increase significantly after angioplasty (NS).

Similar findings were reported by Ofili et al who found a significant increase in the total velocity integral and the peak diastolic velocity during hyperaemia in the distal velocity measurements after angioplasty. The mean and peak diastolic velocities during hyperaemia were also significantly higher in the proximal and distal stenotic regions than before angioplasty. An additional indicator of a satisfactory result was the improvement in the ratio of proximal to distal mean velocity which correlated with the angiographic success of the procedure. The distal mean velocity increased 200% compared with 90% for proximal mean velocity (P < 0.05), which resulted in near equalisation and normalisation of proximal and distal velocities and significant reduction in the proximal to distal velocity ratio. Systolic velocity integrals were also significantly lower after angioplasty (2·1 (1·2) v 1·2 (0·3), P < 0.02). A significant increase in coronary flow reserve and diastolic to systolic velocity ratio after balloon angioplasty was confirmed by the initial results (108 patients examined) of the DEBATE study, a multicentre trial designed to identify symptoms or restenosis after angioplasty. More interestingly, the results of the clinical examination of the exercise test 1 month after angioplasty, available in 75 patients, indicate a significantly lower coronary flow reserve and for the left coronary system diastolic to systolic flow velocity ratio distal to the stenosis after angioplasty in the patients with recurrence of ischaemia (fig 3). Flow velocity monitoring after PTCA can also contribute to the identification of the patients at risk of immediate complications. Cyclic variations in flow in the first 30 min after balloon angioplasty were seen in 5/27 (19%) patients and this feature correlated with a higher incidence of abrupt closure or early recurrence of symptoms. The gradual decline in flow velocity followed by an abrupt increase was similar to the flow changes reported in experimental models of obstructed vessels after intimal damage. Also the mechanism of these changes seems to be the same, because aspirin and the monoclonal antibody to the platelet surface membrane GPIIb/IIIa receptor (c7E3) eliminated this phenomenon.

**Figure 3** Correlation between quantitative angiography and measurements of poststenotic flow velocity after PTCA and recurrence of angina or evidence of ischaemia in non-invasive tests (stress test) 1 month after PTCA in the second interim analysis of the DEBATE trial (75 patients). Measurements of MLD (minimal lumen diameter) were similar in the groups with and without recurrent ischaemia but the distal coronary flow reserve (CFR) and diastolic-to-systolic velocity ratio (DSVR) was significantly lower in the group with recurrence. LCA, left coronary artery.
selected subsets of patients.37-39 This index could not be applied to a large population of patients with coronary artery disease. Furthermore, after coronary interventions the increase in baseline flow and/or the persistence of an impaired vasodilatory response of the distal vasculature explains the unsuccessful results obtained using coronary flow reserve for the immediate assessment of the effects of interventional procedures.17-19 30-32 Despite these conceptual limitations, distal coronary flow reserve is highly correlated with the results of myocardial perfusion scintigraphy with 99mTc SestaMIBI. In 33 patients with stenoses of intermediate severity on coronary angiography, Miller et al found that MIBI-SPECT was abnormal in all the patients with distal coronary flow reserve smaller than 2:0.33

Diastolic to systolic flow velocity ratio

In contrast to the flow characteristics of most arterial beds, coronary arterial blood flow has a distinctive and unique phasic pattern. Blood flow is higher in diastole and lower in systole. The classic experiments of Sabiston and Gregg confirmed that the systolic reduction of arterial coronary flow is caused by constriction of the heart.34 Squeezing the capillary network was regarded as the cause of the flow changes during the cardiac cycle and was attributed to the increase in tissue pressure caused by myocardial compression in the presence of a high systolic intraventricular pressure. More recently, increased systolic stiffness of the cardiac myocytes has been proposed as an alternative mechanism.35 36

Experimental and intraoperative human studies have shown that the contribution of the systolic components is increased distal to a stenosis.37-40 The ratio of distal diastolic to systolic velocity was significantly different in normal arteries and arteries with significant stenosis17 41 42 and in arteries examined before and after coronary angioplasty.17-19 The application of this index to the assessment of the haemodynamic severity of individual stenoses is limited by the different patterns seen in the right and left coronary arteries (fig 4) and the variability of the diastolic to systolic flow velocity ratio and of the changes in this ratio caused by changes in cardiac contractility.

Proximal to distal velocity ratio

There is a moderate decrease in mean velocity, inversely proportional to the moderate increase in total cross sectional area, from the proximal to the distal segments in the epicardial coronary arteries43 (fig 5). This uniform pattern of velocity decrease in normal epicardial arteries is drastically modified in the presence of significant coronary stenoses, which reduce the poststenotic velocity by redistributing flow in the lower resistance branches proximal to the stenosis. The ratio of proximal to distal mean velocity was significantly lower in normal arteries than in arteries with significant stenoses (1:1 (0-2) v 2:4 (0-7), P < 0-001).43 A trend towards a normalisation of the proximal to distal velocity ratio has also been observed after coronary angioplasty.18-19 Despite these significant differences in the total population studied, there was considerable overlap between patients with flow-limiting coronary stenoses and those without. Furthermore, if there are no important side branches between site of proximal measurement and the stenosis (for example, with very proximal stenosis or stenosis of the middle segment of the right coronary artery or with bypass grafts) flow cannot be redistributed and, according to the principle of continuity of flow, proximal and distal flow will be constant.

Instantaneous hyperaemic velocity-pressure or pressure gradient relation

To overcome the limitations of the above mentioned indices, Mancini et al proposed assessing the instantaneous relation between aortic pressure and coronary flow during maximal hyperaemia in the phase of progressive
flow decrease (mid and end diastole). In their experimental preparation, Mancini et al used electromagnetic flowmeters to measure coronary flow. Changes in left ventricular pressure during the cardiac cycle were used to define the start and end points for the measurement: this avoids the diastolic phase which is influenced by the rapid cardiac relaxation, and the phase of isovolumetric myocardial contraction. In a separate series of experiments, the slope of the instantaneous hyperaemic diastolic flow-pressure relation (IHDFPS) was shown to be independent of changes in heart rate, preload, aortic pressure, and cardiac contractility. The IHDFPS correlated better than the conventional CFR with the severity of coronary stenoses induced by epicardial constrictors. The measurement of coronary conductance obtained with this index was highly correlated with the measurement obtained with microspheres. In humans, selective measurements of instantaneous coronary flow cannot be easily performed in the cardiac catheterisation laboratory. Intracoronary
Doppler, however, can accurately measure instantaneous flow velocities during the cardiac cycle.\textsuperscript{13} 14 Doppler-tipped guidewires can be used to measure velocity distal to the stenosis, so that the flow changes will certainly reflect the severity of the lesion under study.

We have studied the feasibility, reproducibility, and independence from haemodynamic indices at the time of the assessment of the instantaneous hyperaemic diastolic velocity-pressure slope (IHDVPS) in 52 arteries with $< 30\%$ diameter stenosis.\textsuperscript{46} The sensitivity and specificity of the IHDVPS for the assessment of a flow-limiting stenosis was established by comparing the measurements of IHDVPS in the control group with the measurements obtained in 24 arteries with $\geq 30\%$ diameter stenosis (fig 6). With a cut-off value of $\leq 0.8 \text{ cm}^2\text{s}^{-1}.\text{mm Hg}^{-1}$, the sensitivity and specificity of this index for detecting the absence of a $\geq 30\%$ diameter stenosis were 95% and 91%, respectively, with a sensitivity slightly greater than that of coronary flow reserve. The assessment of a larger group of patients with flow limiting stenoses is required to establish the potential advantage of IHDVPS over CFR in the assessment of an impairment of coronary conductance. Other studies are needed to determine the value of this index for the assessment of changes of coronary conductance after coronary interventions. Compared with CFR the IHDVPS has the advantage of being independent of haemodynamic changes and changes in baseline velocity.

The measurement of the relation between proximal coronary pressure and flow velocity distal to the stenosis explores both the changes in coronary conductance caused by the presence of a stenosis and the vasodilatory capacity of the distal coronary circulation. An independent assessment of these two components can be obtained if the pressure distal to the stenosis can be measured simultaneously. In a series of animal experiments performed by Gould the relation between transstenotic pressure and flow velocity showed an excellent correlation with the severity of experimentally induced coronary stenoses.\textsuperscript{15} The simultaneous measurement of the transstenotic pressure gradient and flow velocity has several practical advantages. The possible misinterpretation of a low flow increase during maximal vasodilatation is avoided because the simultaneous recording of the transstenotic pressure gradient discriminates between a low flow increase caused by haemodynamically severe stenosis (high pressure gradient) and a low flow increase caused by an impairment of the distal vasodilatory mechanisms or by competition of flow through a well-developed collateral circulation (low pressure gradient). Conversely, when maximum flow is low because of factors not dependent on the stenosis resistance, the measurement of a low transstenotic pressure gradient can be misleading by suggesting the presence of a non-significant stenosis.

Though the maximum flow and consequently the maximal transstenotic gradient are also determined by factors that are independent of the stenosis resistance, the pressure gradient/flow relation is intimately correlated with stenosis haemodynamics. A high-fidelity pressure transducer mounted on an angioplasty guidewire has been used in combination with a separate Doppler guidewire in humans\textsuperscript{57} 46-49 (fig 2). The initial results of the analysis of the instantaneous pressure gradient/velocity relation suggest that this technique can reproduce and accurately assess indices that more precisely characterise the physiological significance of coronary stenoses.

**Conclusions**

Miniaturisation of Doppler and high-fidelity pressure sensors has permitted the application in the human catheterisation laboratory of sophisticated methods of functional assessment of stenosis severity previously confined to the experimental animal laboratory. These techniques could add a new dimension, the functional assessment, to the morphological evaluation of coronary stenosis with angiography or intracoronary ultrasound. Indices derived from poststenotic pressure and/or velocity measurements correlate well with the results of non-invasive provocative tests of myocardial ischaemia and can be used to predict the recurrence of ischaemia after coronary interventions.

\begin{enumerate}
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