The Diastolic Flow-Pressure Gradient Relation in Coronary Stenoses in Humans

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OBJECTIVES

We assessed the feasibility and reproducibility of the instantaneous diastolic coronary flow velocity-pressure gradient relation to characterize different degrees of coronary stenoses.

BACKGROUND

Assessment of the hemodynamic significance of coronary stenoses can be difficult. Using sensor-tipped guidewires, various physiologic indexes can be determined in the catheterization laboratory. Each of the current methods, however, has limitations.

METHODS

After positioning a Doppler flow wire and a pressure wire distal of a coronary stenosis, the flow velocity signals and the proximal and distal pressure were sampled simultaneously, at baseline and after intracoronary administration of adenosine. The instantaneous diastolic flow velocity and pressure gradient of single cardiac cycles at baseline, at maximal and intermediate hyperemia were plotted. Data were fitted with a regression line using the equation: \( \Delta P = \frac{\Delta \Delta P}{\Delta \Delta t} + \frac{\Delta V}{\Delta \Delta t} \). Measurements were performed in 11 normal coronary arteries, 20 intermediate stenoses and in 7 severe stenoses before and after percutaneous transluminal coronary angioplasty plus stenting.

RESULTS

We found significant differences between normal coronary arteries, intermediate and severe stenoses. Percutaneous transluminal coronary angioplasty nearly normalized the highly abnormal flow-pressure gradient relation in the severe stenoses. A high degree of reproducibility was observed. In 3% of the measurements, analysis was not possible due to the occurrence of pressure drift or bad flow velocity signals.

CONCLUSIONS

It is feasible to assess the diastolic flow-velocity-pressure gradient relation over a wide range of stenoses. It characterizes the hemodynamics of epicardial coronary stenoses and allows discrimination between normal coronary arteries, intermediate and severe stenoses. (J Am Coll Cardiol 2002;39:1630–6) © 2002 by the American College of Cardiology Foundation

Presently several techniques are available in the catheterization laboratory to assess the physiological significance of coronary stenoses, including measurement of the coronary flow velocity reserve (CFVR) (1,2), the instantaneous hyperemic flow versus pressure slope index (3–5) and the fractional flow reserve (FFR) (6–8). Each of these methods, however, has limitations (6,9).

In his fundamental work, Gould (10) correlated the severity of experimentally induced coronary stenoses in dogs with the relation between the flow velocity and the transstenotic pressure gradient. This quantitative description of a stenosis has, mainly for technical reasons, hardly been applied in the clinical setting. Thus, at this time only limited data are available on the instantaneous diastolic flow velocity-pressure gradient (v-dp) relation. The availability of miniaturized pressure sensors and Doppler guidewires now has made it feasible to perform this measurement in humans.

Therefore, the aim of this study was to: 1) assess the feasibility of measuring the v-dp relation over a wide range of coronary stenoses in patients, 2) assess the reproducibility of these measurements, and 3) study the acute effects of coronary angioplasty on the v-dp relation.

METHODS

Patient population. The study population consisted of 23 patients scheduled for diagnostic cardiac catheterization or percutaneous transluminal coronary angioplasty (PTCA). Patients with coronary occlusion, diffuse multivessel disease, diabetes mellitus, left ventricular hypertrophy as assessed by echocardiography (wall thickness >11 mm by M-mode), recent myocardial infarction (<4 weeks) or previous coronary artery bypass grafting were excluded. Infarct-related coronary arteries were not studied. Anti-ischemic and anti-platelet medication were continued during catheterization as clinically indicated.

Oral informed consent was obtained in each patient. The study was approved by the institutional review and ethical committee, and the procedures followed were in accordance with institutional guidelines.

Cardiac catheterization procedure. Measurements were made in the left anterior descending (LAD) or circumflex artery (LCX) only. A guiding catheter was advanced up to the left main stem. After administration of 0.2 mg isosorbide dinitrate, control angiograms were made. First, the sensor of the pressure wire (Wavewire, Endosonics, Rancho

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Abbreviations and Acronyms

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CFVR</td>
<td>coronary flow velocity reserve</td>
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<td>FFR</td>
<td>fractional flow reserve</td>
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<td>LAD</td>
<td>left anterior descending artery</td>
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<tr>
<td>LCX</td>
<td>left circumflex artery</td>
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<tr>
<td>PTCA</td>
<td>percutaneous transluminal coronary angioplasty</td>
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<tr>
<td>QCA</td>
<td>quantitative coronary angiography</td>
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<tr>
<td>rCFVR</td>
<td>relative coronary flow velocity reserve</td>
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<tr>
<td>v-dp</td>
<td>the instantaneous diastolic flow velocity-pressure gradient</td>
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Cordova, California, or Radi pressure wire, Radi Medical Systems, Uppsala, Sweden) was advanced close to the tip of the guiding catheter. If a pressure difference was found, the level of the pressure transducer of the guiding catheter was adjusted until equalization was obtained. Then the pressure wire was advanced to the distal part of the artery or distal of the epicardial stenosis. Subsequently, the Doppler guidewire (Cardiomedi Inc., Mountain View, California) was advanced distally of the stenosis with the Doppler crystal near the pressure sensor. Hyperemia was induced by intracoronary administration of 20 μg to 40 μg adenosine.

**Instantaneous measurement of flow velocity and pressure gradient.** The pressure measured at the tip of the guiding catheter (aortic pressure), the distal coronary pressure measured by the pressure wire, the instantaneous coronary flow velocity and the electrocardiogram were recorded on a data acquisition unit (Cardidynamics, Zoetermeer, the Netherlands) connected to a personal computer. Data acquisition (sample frequency 100 Hz) was started before administration of adenosine and ended at complete disappearance of hyperemia. Coronary stenting was performed in all patients who underwent PTCA; in these patients the measurements were done before PTCA and repeated after an optimal angiographic result had been obtained. Neither the flow velocity nor the pressure measurements in these patients were used to do additional balloon inflations after stent implantation.

Duplicate measurements were obtained in each coronary artery. The data of the first measurement were used for data analysis; the data of the second measurement were solely used to assess the reproducibility.

**Quantitative angiographic measurements.** Quantitative coronary angiography (QCA) was performed off-line using the CAAS II system (CAAS System, Pie Medical Data, Maastricht, the Netherlands). The percent diameter stenosis and minimal lumen diameter were measured in a standard manner. In this study, we defined a coronary artery without any visible angiographic abnormality as normal. Severe stenoses were defined as coronary lesions with unequivocal proof of ischemia by noninvasive testing. All patients with a severe stenosis were scheduled for PTCA. Any angiographic narrowing with undefined or unclear hemodynamic significance was defined as an intermediate stenosis.

**Data analysis.** After completion of all recordings, the digital data were further processed. A correction was made for the time delay between the two pressure measurement systems. The mean delay of the electronic signal was 22 ± 12 ms. From each hyperemic response to adenosine, three single cardiac cycles were chosen for analysis: one cycle at baseline, one cycle at maximal hyperemia (maximal flow velocity) and one cycle with flow velocities intermediate to maximum and baseline. Of these three cardiac cycles, the flow velocity values from middiastole to atrial contraction were plotted against the instantaneous pressure gradient (aortic pressure – distal coronary pressure). An example is given in Figure 1. These data were fitted using a quadratic equation: \( \Delta P = 0 + kv + Sv^2 \), where \( \Delta P \) is the pressure gradient in mm Hg, \( v \) is the coronary flow velocity in cm/s, \( k \) (mm Hg s/cm) is the coefficient of pressure loss due to viscous friction and \( S \) (mm Hg s²/cm²) is the coefficient of pressure loss due to flow separation or localized turbulence.

The coefficients \( k \) and \( S \) and their SD were determined using the least squares curve-fitting algorithm in the SPSS 9.0 for Windows software package (SPSS Inc., Arlington, Virginia). An example is given in Figure 2.

**Statistical analysis.** Continuous variables are presented as mean value ± 1 SD and compared using the Student \( t \) test. A \( p \) value <0.05 was considered significant. The variables in severe stenoses and post-stenting were compared using the paired \( t \) test.

In order to assess the interobserver variability, a second person independently fitted the data. To assess the reproducibility of two measurements in one coronary artery, the calculated coefficients \( k \) and \( S \) from the first measurement were compared with those of the second measurement. When they were found to be within 2 SD, we concluded there was no statistical difference. In order to quantify the degree of agreement between two measurements in one coronary artery or between two observers for the same measurement, the highest and lowest common flow velocity value of both measurements were determined. In this common flow range, the area delineated by the highest and lowest 2 SD pressure gradient of the first and second measurements was calculated. The overlapping part of both areas was defined as the common flow velocity-pressure gradient area. The degree of agreement was defined as the ratio of the common area and the averaged flow velocity-pressure gradient area of the first and second measurement.

A graphical example is given in Figure 3.

**RESULTS**

**Patient characteristics.** The study population included 23 patients (Table 1). In most patients, measurements were performed in two coronary arteries. Eleven angiographic normal coronaries (two LAD, nine LCX) were studied. In 20 coronary arteries with an intermediate stenosis (four left main, seven LAD, one diagonal, six LCX, one intermediate branch, one marginal branch), the mean diameter stenosis...
was 33 ± 8%. Balloon angioplasty and stent implantation decreased the diameter stenosis in seven severely narrowed arteries (six LAD, one LCX) from 70 ± 8% to 5 ± 4%.

v-dp relation: feasibility. In one patient, it was not possible to cross a severe lesion with the two wires; this patient was excluded from the study. None of the patients had angina pectoris after introduction of the wires. On a total of 90 measurements (two measurements in 45 coronary arteries), three were unsuitable for analysis. In two measurements, pressure drift occurred, and in one measurement the digital flow signals were not analyzable.

Hemodynamic data. The maximal diastolic flow velocities in the normal coronaries and in the intermediate, severe and post-stenting stenoses were, respectively, 76 ± 26 cm/s,
67 ± 17 cm/s, 26 ± 15 cm/s and 93 ± 27 cm/s as shown in Table 2. Severe stenoses had a significantly lower maximal diastolic flow velocity compared with the other three groups. The maximal diastolic pressure gradients in these vessels were 6 ± 3 mm Hg, 19 ± 9 mm Hg, 63 ± 14 mm Hg and 17 ± 10 mm Hg, respectively. The maximal diastolic pressure gradient was highly significantly different between normal arteries and intermediate stenoses, between intermediate and severe stenoses and between severe and post-stenting stenoses. The post-stenting gradient was significantly higher than in normal arteries, but not significantly lower than in intermediate stenoses.

Significant differences in the k and S coefficients were found between normal arteries and intermediate, between intermediate and severe and between severe and post-stenting stenoses. Between post-stenting and intermediate stenoses, these coefficients were not statistically different. The k coefficient, but not the S coefficient, was significantly lower in normal arteries compared with post-stenting stenoses. The v-dp relations (mean value ± 1 SD) in normal coronary arteries, intermediate and severe stenoses are displayed in Figure 4A; the immediate effect of PTCA and stenting is displayed in Figure 4B.

Reproducibility. The mean degree of agreement (overlapping area) between two independent observers for repeated curve fitting of the same data was 91 ± 4% for all measurements.

In three of 45 coronary arteries, no good second measurement was obtained. In 29 of 42 coronary arteries (69%), both the k and S coefficient of the first measurement was within 2 SD of the second measurement. In 10 measurements (24%) one coefficient and in three measurements (7%) both coefficients were significantly different between the two measurements. No significant difference for both coefficients was found in 7 of 9 (77%) normal coronary arteries, in 12 of 19 (63%) intermediate stenoses and in 5 of 7 (71%) severe or post-stenting stenoses.

The mean degree of agreement (overlapping area) was 78 ± 10% for duplicate measurements. In the normal coronary arteries, the intermediate, severe and post-stenting stenoses, the mean degree of agreement between two measurements was 88 ± 8%, 75 ± 9%, 77 ± 13% and 77 ± 7% (Table 2). The overlapping area was significantly larger for the normal arteries. There was no significant difference between the other groups.

The degree of agreement for measurements without

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**Table 1. Clinical Characteristics of 23 Study Patients**

<table>
<thead>
<tr>
<th>Features</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean ± SD</td>
<td>64 ± 8</td>
<td></td>
</tr>
<tr>
<td>Gender, male/female</td>
<td>14/9</td>
<td></td>
</tr>
<tr>
<td>History of MI</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>Previous PTCA</td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Cardiovascular risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>26</td>
</tr>
<tr>
<td>History of smoking</td>
<td>11</td>
<td>48</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>9</td>
<td>39</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>16</td>
<td>70</td>
</tr>
<tr>
<td>Nitrates</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>Ca-blockers</td>
<td>13</td>
<td>57</td>
</tr>
<tr>
<td>LVEF</td>
<td>23</td>
<td>54 ± 6</td>
</tr>
<tr>
<td>% Diameter stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal artery</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Intermediate stenosis</td>
<td>20</td>
<td>33 ± 8</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>7</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>Stenosis poststenting</td>
<td>7</td>
<td>5 ± 4</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.
significant difference in the degree of agreement between measurements with one or two significantly different coefficients was 75 ± 10%. This difference was not significant.

**DISCUSSION**

We assessed the feasibility and reproducibility of the instantaneous diastolic flow velocity-pressure gradient relation over a wide range of coronary stenoses. Significant differences in this relation were found between normal coronary arteries, intermediate and severe coronary stenoses. Immediately after PTCA and stenting, an impressive improvement in the v-dp relation was found compared with the measurements before PTCA, with near normalization of the v-dp relation. The fluid dynamic coefficients of the flow velocity-pressure gradient relations in these patients were similar to the experimental coefficients previously reported, thereby demonstrating the universality of the basic concepts demonstrated initially in animals.

**The v-dp relation.** More than 25 years ago, Gould (10) described the hemodynamic properties of coronary stenoses in dogs by the instantaneous and simultaneous assessment of the flow velocity and pressure gradient changes during the middiastolic part of the cardiac cycle in baseline and maximal hyperemic conditions. Only the middiastolic part of the heart cycle was analyzed because at this interval the compressive forces of the contracting ventricle are minimal and coronary flow-pressure relation is exclusively related to the severity of the epicardial lesion, the microcirculatory resistance and the driving pressure. Thus, this combined measurement provides a comprehensive description of the fluid dynamics across the stenotic epicardial lesion.

Until present, two reports on the v-dp relation in humans have been published (11,12). The authors normalized the trans-stenotic pressure gradient to the proximal pressure. No uniform equation was used to describe the regression; also, equations not crossing the zero intercept were used, which is not logical from a physiological point of view. No data on the reproducibility were given.

**Interpretation.** As shown in Figure 4A, overlap was found between the mean v-dp in normal arteries and intermediate lesions. Intravascular ultrasound studies have demonstrated that a considerable amount of atherosclerosis can be present in coronary arteries without any clue in the angiogram (13,14). At high flow velocities, this obstruction can generate a pressure gradient. On the other hand, it is known that the hemodynamic impact of intermediate stenoses (as defined by QCA) is difficult to predict (15,16). Those factors may explain the partial overlap of normal coronary arteries and intermediate stenoses.

In this study, the mean post-stenting v-dp relation and k coefficient overlap with the lower range of the intermediate stenoses and the higher range of the normal coronary arteries. The angiographic post-stenting result closely approached normal coronary arteries. Here also, most likely the residual amount of atherosclerosis in the nontreated segments accounts for the hemodynamic alterations at higher flow velocities.

**Methodological considerations.** It is essential to obtain the most intense spectral flow velocity tracing with the Doppler wire, in order to avoid underestimation of maximal distal flow velocities. In some measurements, we did not maintain a good flow velocity signal during hyperemia. After repositioning or reshaping the angle of the tip of the flow wire, this always could be corrected. A few times we noticed cross-talk between the Doppler flow wire and the Radi pressure wire resulting in noise; this could be avoided by positioning the Doppler crystal of the flow wire distal of the tip of the pressure wire. Pressure drift occurred a few times. By regularly comparing the pressure measured by the wire and guiding catheter, drift could easily be detected and corrected.

In order to validate this method, we assessed the reproducibility of repetitive measurements. In 69% of the measurements, the k and S coefficients were not different between both measurements. Sometimes we noticed that, despite a close resemblance of the regression lines, the coefficients were statistically different. Therefore, we assessed the degree of agreement between the two-flow velocity-pressure gradient areas. Even in case of difference of both coefficients, we found that the degree of agreement was not worse compared with measurements with no difference in the k or S coefficient.

**Study limitations.** A total of 3% of all measurements were unsuitable for analysis due to bad flow tracking or unnoticed

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**Table 2. Characteristics of the Instantaneous Flow Velocity-Pressure Gradient Relation**

<table>
<thead>
<tr>
<th></th>
<th>k</th>
<th>S</th>
<th>Max Diast Flow Vel</th>
<th>Max Diast Peak Grad</th>
<th>Degree of Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal artery</td>
<td>0.032±0.018††</td>
<td>0.00060±0.00049*</td>
<td>76±26</td>
<td>6±3††</td>
<td>88±8††</td>
</tr>
<tr>
<td>Int stenosis</td>
<td>0.15±0.11</td>
<td>0.0021±0.0014†</td>
<td>67±17††</td>
<td>19±9†</td>
<td>75±9</td>
</tr>
<tr>
<td>Severe stenosis</td>
<td>2.67±1.58††</td>
<td>0.014±0.010††</td>
<td>26±15††</td>
<td>63±14††</td>
<td>77±13</td>
</tr>
<tr>
<td>Poststenting</td>
<td>0.11±0.06**</td>
<td>0.00096±0.00066††</td>
<td>93±27**</td>
<td>17±10**</td>
<td>77±7</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. k and S are the coefficients in the equation Δ P = kv + Sv2. *p < 0.005 vs. intermediate stenosis; †p < 0.05 vs. intermediate stenosis; ‡p < 0.01 vs. poststenting; §p < 0.001 vs. poststenting; ††p < 0.001 vs. severe stenosis; ‡‡p < 0.05 vs. poststenting; †††p < 0.01 vs. severe stenosis; ‡‡‡p < 0.01 vs. severe stenosis; ‡‡‡‡p < 0.001 vs. normal artery.

Int stenosis = intermediate stenosis; Max Diast Flow Vel = maximal diastolic flow velocity; Max Diast Peak Grad = maximal diastolic peak gradient.
pressure drift. Nevertheless, in all coronary arteries at least one good measurement was obtained.

At this time, the assessment of the v-dp relation requires the use of two separate guidewires. The flow velocity-pressure gradient relation certainly is affected by the obstructive effect of the two wires (each 0.1 mm²), especially in
severe lesions. The degree of overestimation needs to be established in an experimental setting. In clinical practice, however, questions usually arise about the hemodynamic impact of intermediate lesions. For the intermediate lesions in this study, the cross-sectional area of both guidewires made up less than 10% of the minimal luminal cross-sectional area and, therefore, overestimated the hemodynamic effect only slightly. A combined 0.014-in. pressure section and Doppler flow wire, which will be available soon, will reduce this problem.

This study did not address the correlation of the v-dp relation with other estimates of myocardial ischemia. Further work has to be done to determine the cutoff points between significant and nonsignificant stenoses using this index.

Although one can speculate that this index is independent of hemodynamic conditions, this has to be established. Clinical implications. The v-dp relation has the potential to become a new standard to determine the hemodynamic characteristics of an epicardial stenosis because it contains all parameters affecting its significance. This might be an advantage compared with the currently available techniques at the catheterization laboratory. The major concern in interpreting the CFVR or relative CFVR (rCFVR) and the FFR is the impact of the microcirculatory flow resistance. Coronary flow velocity reserve is not lesion-specific, and rCFVR is only applicable if the microcirculatory resistance is uniform and if a suitable reference vessel is available. In case of severe microcirculatory flow impairment, the FFR underestimates the significance of an epicardial stenosis (17).

At this time, due to the complex instrumentation and the need for laborious postmeasurement analysis, the v-dp index is not yet ready for general implementation in the catheterization laboratory. Improvements in wire technology, signal processing and automatization of analysis have to be performed.

Acknowledgment
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