The diastolic flow velocity-pressure gradient relation and \( dpv_{50} \) to assess the hemodynamic significance of coronary stenoses

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**METHODS**

*Patients.* The study population consisted of patients with stable angina pectoris (Canadian Cardiovascular Society class I through III) scheduled to undergo coronary angiography. Before coronary angiography, patients underwent noninvasive ischemia detection either by dobutamine stress echocardiography or by stress technetium-99m sestamibi single photon emission computed tomography (SPECT). Furthermore, a mild to severe stenosis in the proximal part of at least one major coronary artery had to be found at coronary angiography. Exclusion criteria were previous coronary artery bypass grafting, multiple consecutive stenoses in a coronary artery, a very tight stenosis prohibiting simultaneous passage of a Doppler and pressure guide wire, aneurysmatic morphology, or coronary occlusion. Anti-ischemic medication was continued during catheterization as clinically indicated. The study was approved by the institutional review and ethical committee, and the procedures were in accordance with institutional guidelines. Written informed consent was obtained from all patients.

*Myocardial perfusion scintigraphy.* SPECT was performed according to a 2-day stress/rest protocol. Exercise or adenosine was used for the stress images. Technetium-99m-labeled sestamibi was injected at maximal exercise or after intravenous infusion of adenosine (0.14 mg·kg\(^{-1}\)·min\(^{-1}\)). SPECT was performed by using a two-headed gamma camera equipped with low-energy high-resolution collimators.

**THE FRACTIONAL FLOW RESERVE (FFR) and coronary flow velocity reserve (CFVR) are indexes used during catheterization to assess the hemodynamic effect of a coronary stenosis. The FFR is considered to be a specific index of the epicardial stenosis severity and is defined as the ratio of mean distal \( P_d \) to proximal \( P_{\text{prox}} \) coronary pressure at maximal hyperemia (22). The CFVR is the ratio of mean maximal hyperemic to baseline coronary flow velocity and is measured with a Doppler guide wire. The CFVR accounts both for the epicardial and microvascular resistance but does not allow discrimination between these two (5). A good agreement with noninvasive stress tests has been shown for these indexes at cutoff values varying between 1.7 and 2.0 for CFVR and 0.75 for FFR (1, 2, 18, 20, 25).

The combination of both flow velocity and pressure measurements and, more specifically, the diastolic flow velocity-pressure gradient \( v-dp \) relation gives a comprehensive description of the coronary stenosis severity as has been shown in animal experiments by Gould (7). Recently, we reported on the feasibility and reproducibility of the \( v-dp \) relation in humans and found distinct \( v-dp \) relations in normal arteries versus intermediate and severe coronary stenoses (16).

We propose a new index, the \( dpv_{50} \), which is derived from the \( v-dp \) relation. \( dpv_{50} \) is the instantaneous pressure gradient at a middiastolic coronary flow velocity of 50 cm/s.

The aim of the present study is to compare the diagnostic performance of the \( dpv_{50} \) with the CFVR and FFR in the assessment of the coronary stenosis severity.
Acquisition was performed using a 360-degree circular orbit. The scintigraphic images were analyzed using a 13-segment model (24). Stress and rest segments were semiquantitatively scored as normal (grade 0) or having a mild, moderate, or severe (grade 3) perfusion defect. Perfusion defects were allocated to the territory of a coronary artery. Defects located in the anterior and anteroseptal region were allocated to the left anterior descending coronary artery (LAD); defects in the posterolateral wall were allocated to the left circumflex coronary artery (LCx) and inferior and basal inferoseptal defects were allocated to the right coronary artery (RCA). Apical defects were considered to be located in the LAD region unless the defect extended to the posterolateral (LCx) or inferior (RCA) wall. Reversible perfusion defects were present when the rest perfusion score improved one grade or more and were considered as positive for the presence of ischemia. Segments with irreversible perfusion defects or normal perfusion were considered negative for the presence of ischemia. The technetium-99m-methoxyisobutylisonitrile (MIBI) scintigrams were scored by two experienced cardiologists; in case of disagreement, a majority decision was achieved by a third cardiologist.

**Dobutamine stress echocardiography.** An intravenous infusion of dobutamine was started at a rate of 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) and was increased by 10 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) every 3 min until either wall motion abnormalities were observed or a maximal rate of 40 \( \mu g \cdot kg^{-1} \cdot min^{-1} \) was reached. In patients who did not reach 90% of their age-adjusted maximal heart rate and who had no objective signs of ischemia, 0.25 mg of atropine was given every minute up to a maximum of 1 mg while the dobutamine infusion was continued. End points for stopping the infusion were the same as mentioned in the guidelines (23).

Two-dimensional echocardiography was performed obtaining parasternal long- and short-axis views and apical four- and two-chamber views. Imaging was performed throughout the study and during recovery until resolution of new wall motion abnormalities. On-line digital images in quadscreen format were analyzed for the presence, extent, severity, and location of segmental wall motion abnormalities. Myocardial contractile function was graded as normal, hypokinetic, akinetic, or dyskinetic in each segment. An echocardiographic stress test was considered positive when new or worsening stress-induced wall motion abnormalities were observed. The standard algorithm was used to assign ventricular segments to coronary territories: LAD (basal and midanteroseptal segments; basal, mid, and apical anterior segments; mid and apical septal and apical lateral segments); LCx (basal and midlateral segments; basal and midposterior segments); and RCA (basal, mid, and apical inferior segments and basal septal segments) (6). The dobutamine stress echocardiograms were scored by two experienced cardiologists; in case of disagreement, a majority decision was achieved by a third cardiologist.

**Cardiac catheterization procedure.** All patients received 5,000 IU heparin at the beginning of the procedure. After intracoronary administration of 0.2 mg nitroglycerine, coronary angiography of the left and right coronary artery was performed according to standard procedures. At least two, preferably orthogonal, views were obtained displaying each coronary lesion with minimal foreshortening and no vessel overlap. Quantitative coronary angiography (QCA) was performed off-line using the CAAS II system (CAAS System; Pie Medical Data, Maastricht, The Netherlands). Percentage diameter stenosis and minimal lumen diameter were measured in a standard manner.

**FFR, CFVR, and simultaneous flow velocity and pressure measurements.** First, the sensor of the pressure wire (WaveWire, Volcano Therapeutics or Radi pressure wire, Radi Medical Systems, Upplands, Sweden) was advanced close to the tip of the guiding catheter. If a pressure difference was found, the measurement of the pressure wire was electronically adjusted to obtain equalization of pressures. The pressure wire was then advanced distal to the coronary stenosis. The FFR was calculated as the ratio of \( P_d \) and \( P_{prox} \) at maximal hyperemia, induced by intracoronary administration of 40 \( \mu g \) adenosine. Subsequently, the Doppler guide wire (FlowWire, Volcano Therapeutics) was advanced distal to the stenosis with the Doppler crystal near the sensor of the pressure wire. The Doppler wire was manipulated until an optimal and stable flow velocity signal was obtained. Hyperemia was induced again. Finally, the pressure wire was withdrawn and the CFVR was measured with the Doppler wire as the ratio of mean maximal hyperemic to baseline flow velocity, averaged over two heartbeats.

**Assessment of the v-dp relation and dpv50.** 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 ECG were recorded on a data acquisition unit (Cardiodynamics, Zoetermeer, The Netherlands) connected to a personal computer. Data acquisition (sample frequency 100 Hz) was started before administration of adenosine to disappearance of the hyperemic response (Fig. 1).

The v-dp relation and dpv50 were determined after the following three steps. First, the instantaneous flow velocity values from middiastole to atrial activation and from peak hyperemia to return of baseline condition (on average 20 to 30 cardiac cycles) were plotted against the instantaneous pressure gradient data (aortic minus distal coronary pressure). Second, the v-dp relation was calculated; all data were fitted using a quadratic equation: \( \Delta P = 0 + k \cdot v + S \cdot v^2 \), where \( \Delta P \) is the pressure gradient (mmHg), \( v \) is the coronary flow velocity (cm/s), \( k \) is \( (\text{mmHg} \cdot \text{s}^2 / \text{cm}) \) the coefficient of pressure loss due to viscous friction, and \( S \) (mmHg \cdot s^2/cm^2) is the coefficient of pressure loss due to flow separation or localized turbulence (26). The \( k \) and \( S \) coefficients were determined by using the least squares curve-fitting algorithm in the SPSS 9.0 for Windows software package (SPSS, Arlingon, VA). In the search for the single instantaneous flow velocity value yielding the highest diagnostic accuracy for all patients and all measurements, we assessed the flow velocities from 10 to 150 cm/s, with incremental steps of 10 cm/s. The highest accuracy was

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Fig. 1. Simultaneous, instantaneous, and mean aortic, distal coronary pressure, and flow velocity recordings before and after intracoronary administration of adenosine (indicated by downward arrow). During a fourfold increase in the mean coronary flow velocity, a mean pressure gradient of 13 mmHg is recorded. For each cardiac cycle after adenosine administration, the middiastolic time window is indicated.

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found at a flow velocity of 50 cm/s. Third, based on the $k$ and $S$ coefficients, the dpv50 was calculated. An example is given in Fig. 2.

*Diagnostic performance of FFR, CFVR, and dpv50.* With the use of the results of the noninvasive stress tests (absence or presence of ischemia during myocardial perfusion scintigraphy or dobutamine stress echocardiography) and ROC analysis, the cutoff value for the dpv50 to discriminate hemodynamic significant and insignificant stenoses was established at 22.4 mmHg. To assess and compare the diagnostic performance of the three indexes, the sensitivity, specificity, and accuracy were determined based on the results of the noninvasive stress tests. For FFR and CFVR the generally recommended cutoff values (FFR 0.75 and CFVR 2.0) were used. We also determined the cutoff values for FFR and CFVR based on this study population.

**dpv50 and submaximal hyperemia.** To investigate the influence of submaximal hyperemia on the assessment of the dpv50, the following procedure was undertaken. As described in the section on the assessment of the dpv50, all middiastolic flow velocity and corresponding pressure gradient data were plotted. We determined the range of instantaneous flow velocity values for each individual measurement, with the lowest flow velocity value representing 0% and the highest value representing 100% of the range. Then, all data with a flow velocity higher than 75% of the maximal flow velocity were disregarded. The dpv50 was again determined after regression analysis of the remaining data.

**Statistical analysis.** Continuous variables are presented as mean value (SD). Sensitivity was defined as the number of true positive tests divided by the total number of myocardial territories with ischemia by noninvasive stress testing. Specificity was defined as the number of true negative tests divided by the total number of myocardial territories without ischemia by noninvasive stress testing. Accuracy was defined as the total number of true positive and true negative tests divided by the total number of myocardial territories. The McNemar test was used to compare the sensitivity, specificity, and accuracy of FFR, CFVR, and dpv50. A value of $P < 0.05$ was considered statistically significant.

**RESULTS**

**Patients characteristics.** The study included 77 patients [51 male, 26 female, mean age 60 yr (SD 10)]. Patients demographics and medication are given in Table 1. Four patients had chronic atrial fibrillation. A history of myocardial infarction was present in 44% of patients. Hypertension was present in 40% of patients, diabetes mellitus in 29%, smoking in 45%, and hypercholesterolemia in 52%.

**Results of noninvasive stress testing, quantitative coronary angiographic, and hemodynamic data.** Successful measurements were performed in 124 coronary vessels. In 37 patients 1 stenosis, in 33 patients a stenosis in 2 coronary vessels and in 7 patients stenoses in 3 coronary vessels were assessed. Measurements were performed 64 times in the LAD, 39 times in the LCx, and 21 times in the RCA. In 20 patients a stenosis in an infarct-related artery was analyzed. Dobutamine stress echocardiography was performed in 28 (36%) patients. New wall motion abnormalities during dobutamine infusion were found 15 times in the LAD perfusion territory, once in the LCx, and three times in the RCA. In 20 patients a stenosis in an infarct-related artery was analyzed. Dobutamine stress echocardiography was performed in 28 (36%) patients. New wall motion abnormalities during dobutamine infusion were found 15 times in the LAD perfusion territory, once in the LCx, and three times in the RCA perfusion territory. In these patients, 41 (24 LAD, 11 LCx, and 6 RCA) coronary arteries were analyzed. MIBI scintigraphy was performed in 49 (64%) patients. Reversible perfusion defects were found 18 times in the LAD perfusion territory, 2 times in the LCx, and 4 times in the RCA perfusion territory. In these patients, 83 (40 LAD, 28 LCx, and

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**Table 1. Patient demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>60 (SD 10)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>51/26</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 (5)</td>
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<tr>
<td>History of myocardial infarction</td>
<td>34 (44)</td>
</tr>
<tr>
<td>Coronary risk factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31 (40)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (29)</td>
</tr>
<tr>
<td>History of smoking</td>
<td>35 (45)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>40 (52)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>70 (91)</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>65 (84)</td>
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<tr>
<td>Nitrates</td>
<td>36 (47)</td>
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<tr>
<td>Calcium antagonists</td>
<td>27 (35)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>30 (39)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Oral antiaggregants</td>
<td>13 (17)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>52 (68)</td>
</tr>
</tbody>
</table>

Except for age, values in parentheses indicate percentages; $n = 77$ patients.

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Fig. 2. A: flow velocity-pressure gradient relation of coronary stenoses A and B (v-dp). For both coronary arteries, all middiastolic data are shown of all cardiac cycles after administration of adenosine. B: regression line, representing the v-dp relation for both stenoses, is displayed. The pressure gradient at a flow velocity of 50 cm/s (dpv50) of stenosis A is 56 mmHg and of stenosis B is 9 mmHg.
15 RCA) coronary arteries were evaluated. When compared with patients who underwent stress echocardiography, diabetes mellitus was significantly more present in patients who underwent MIBI scintigraphy; other patient characteristics did not differ between the two groups (data not shown).

The quantitative coronary angiographic and hemodynamic data are displayed in Table 2. Results are given for all measurements; furthermore, a distinction is made between stenoses with corresponding abnormal and normal noninvasive stress tests. The coronary stenoses with abnormal stress tests had a smaller minimal luminal diameter and higher percentage diameter stenosis, a lower FFR and CFVR, and a higher dpv50. All these differences were statistically significant.

**Diagnosis performance of dpv50, FFR, and CFVR.** As shown in Table 3, the sensitivity of dpv50 (95%) was significantly higher than FFR (77%) and CFVR (56%). The specificity of dpv50 (95%) was comparable to FFR (99%). The accuracy of dpv50 (95%) and FFR (91%) and dpv50 (91%) were significantly higher than CFVR (76%). In this study population the best cutoff value for CFVR and FFR was found at 1.9 and 0.75. For a CFVR of 1.9, the sensitivity, specificity, and accuracy, respectively, were 53%, 91%, and 78%.

As described in Methods, we also assessed the dpv50 after omitting the upper quartile highest instantaneous flow velocity data. We found a 3% difference between the dpv50 based on all data compared with the dpv50 based on the submaximal measurements. This resulted in one additional false-positive result, decreasing the specificity of the dpv50 from 95% to 94%. The relation between FFR or CFVR and dpv50 for all measurements is graphically represented in Fig. 3A and B. The cutoff values for the three indexes are displayed. The data in the lower right and upper left quadrant represent discordant data. In the upper right quadrant of Fig. 3A, discordant measurements (normal FFR and abnormal dpv50) can be found; there were no measurements with an abnormal FFR and normal dpv50 (lower left quadrant). Overall, concordance between dpv50 and FFR was found in 90% of all measurements. From Fig. 3B, it can be appreciated there were more discordant results between CFVR and dpv50 (upper right and lower left quadrant). For the dpv50 and CFVR, concordant results were found in 76% of all measurements.

**Discussion**

In the present study we compared the diagnostic performance of two commonly used invasive indexes, the CFVR and...
FFR, with a new index, the dpv50, to detect hemodynamic significant coronary stenoses. We found that the dpv50 yielded the highest accuracy. Compared with the FFR, the dpv50 had a significantly higher sensitivity and a similar specificity and accuracy. Furthermore, the dpv50 had a significantly higher sensitivity and accuracy compared with the CFVR. We also demonstrated that maximum hyperemia is not required to reliably assess the dpv50.

Diastolic v-dp and dpv50 to assess the hemodynamic effect of coronary stenoses. Fluid dynamics of coronary artery stenoses are complex (17). The pioneering work of Gould et al. (7–9) and Young et al. (27) has demonstrated that the relation between pressure gradient and flow velocity in stenoses can be described by \( \Delta P = 0 + kv + Sv^2 \). We have previously shown the feasibility to measure the diastolic coronary flow velocity-pressure gradient relation in humans in a reproducible way (16).

To compare the v-dp relation of a stenosis with the FFR or CFVR, it has to be described by a single index. For this purpose the use of the \( k \) and \( S \) coefficients, which are both required to adequately describe the nonlinear v-dp relation, is not adequate. Therefore, we defined a new index, which is directly derived from the v-dp relation. In the search for the single instantaneous flow velocity value yielding the highest diagnostic accuracy for all patients and all measurements, we assessed the flow velocities from 10 to 150 cm/s, with incremental steps of 10 cm/s. From 30 to 80 cm/s, we found an identical sensitivity of 95%. The specificity ranged from 93% to 95% for the flow velocities from 30 to 60 cm/s. This indicates that within the flow velocity range of 30–60 cm/s, the corresponding instantaneous pressure gradient most reliably characterizes the hemodynamic significance of a stenosis. Within this range, the highest accuracy was found at a flow velocity of 50 cm/s; therefore this value was chosen to use in the present study.

The dpv50 of a coronary stenosis is calculated after regression analysis by using the \( k \) and \( S \) coefficients. This has three advantages. First, as can be seen in Fig. 2, we found scattering of the data due to noise in the flow velocity (despite a sharply defined flow velocity contour) and pressure data. With the use of all data instead of the average data only with a flow velocity of 50 cm/s, a more reliable assessment of the dpv50 is obtained. Second, in 43 of 124 measurements, a peak instantaneous middiastolic coronary flow velocity lower than 50 cm/s was recorded; 13 of these stenoses did not cause ischemia. In these measurements, the dpv50 could only be assessed after regression analysis and extrapolation. Therefore, in most hemodynamic insignificant stenoses and in some hemodynamic significant stenoses, the dpv50 is a physiological measure. Third, it can be postulated that missing the data at the highest flow velocities will not dramatically alter the course of the regression line and that maximal hyperemia thus is not a prerequisite to reliably assess the dpv50. To test the latter, we omitted for each stenosis the data in the upper quartile of the flow velocities and then reassessed the dpv50. A difference of 3% was found between the dpv50 based on the complete and incomplete data, resulting in one measurement to be reclassified from true negative to false positive. In contrast, assessment of CFVR and FFR by definition requires achievement of maximal hyperemia. In this study, we always gave 40 \( \mu \)g adenosine ic; it has been shown that this dose evokes an equipotent hyperemic response as intravenous adenosine (4). In the literature it has been suggested that for technical and pharmacokinetic reasons, intracoronary administration of adenosine may induce only submaximal hyperemia, resulting in underestimation of a coronary stenosis when FFR and overestimation when CFVR is used (4, 14, 19, 21). Furthermore, it remains uncertain whether adenosine can elicit maximal hyperemia. It has been shown that the addition of \( \alpha_1- \) and \( \alpha_2- \) adrenergic blocking agents to adenosine induces a stronger hyperemic stimulus after PCI, in patients with coronary atherosclerosis and in normal humans (10–12, 15). Coronary occlusion also can induce a stronger hyperemic response than adenosine (13).

Spatial resolution of dpv50. In this study we took care to determine the dpv50 distal to the most distal stenosis visible at angiography. However, flow velocity and coronary pressure can be measured simultaneously at any location in a coronary artery. If flow and pressure data are obtained at the same spot, the dpv50 gives information on the epicardial resistance from the coronary ostium to the location where measurements are obtained. By the virtue not to be dependent on maximal hyperemia, the dpv50 of a coronary segment thus can be assessed irrespective of any additional epicardial or microcirculatory resistance distal to the point of measurement. Therefore, in case of diffuse atherosclerosis or serial epicardial stenoses, by determining the dpv50 at different spots, the location with the largest resistance can be identified.

Study limitations. In six measurements it was not possible to obtain optimal Doppler flow velocity recordings, and in these cases no reliable v-dp relation could be computed. The cutoff value of the dpv50 in this study is derived from measurements with two wires through a coronary stenosis, probably increasing its severity. Very recently, a single 0.014” wire (Combowire, Volcano Therapeutics, Rancho Cordova, CA) allowing combined flow velocity and pressure measurements has become available for clinical use. The diagnostic performance of the dpv50 was assessed based on the cutoff value established in the same study population; this might lead to a bias toward better test results. To properly determine the accuracy of the dpv50 in the assessment of coronary stenoses, a prospective study is needed to establish the predictive value of this cutoff value. It can be assumed on theoretical grounds that the v-dp relation and dpv50 are independent of hemodynamic conditions (heart rate, aortic pressure, and contractility) (3). This has not been thoroughly evaluated yet. However, in patients with atrial fibrillation we found that the data of each cardiac cycle fitted the same v-dp curve, despite widely varying cardiac cycle lengths and aortic pressure. To further investigate the effect of heart rate and changes of preload on the dpv50, measurements at different pacing rates should be done. Measurements in a poststenotic aneurysmatic part of a coronary artery modify the v-dp relation. Therefore, we always have measured in the distal, normally sized part of the coronary artery. Coronary arteries with a very diffuse, ectatic appearance were excluded from this study. At the present time, computation of the dpv50 has to be done off-line.

In conclusion, we found a very high sensitivity and specificity for the dpv50 in the assessment of the hemodynamic significance of coronary stenoses. In contrast to the CFVR and FFR, calculation of the dpv50 is not critically dependent on the induction of maximal hyperemia.
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REFERENCES


