Improved assessment of functional severity of coronary artery stenosis by analysis of combined intracoronary pressure and flow velocity signals

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Chapter 4

Effect of axial location on intracoronary hemodynamic measurements and derived clinical indices of stenosis severity and microvascular resistance

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Submitted
Abstract

Background
Only limited data are available on the effect of axial measurement location on concomitantly measured coronary flow velocity and pressure and on derived physiological indices of epicardial and microvascular flow impairment.

Methods
In 26 patients, intracoronary flow velocity and pressure were recorded at two different axial locations in reference vessels and distal to a stenosis in diseased vessels. Basal and hyperemic pressure and velocity, coronary flow velocity reserve (CFVR), fractional flow reserve (FFR), and hyperemic stenosis (HSR) and microvascular (HMR) resistance were compared between measurement locations. Two scaling laws were tested in relation to vessel diameter: Murray’s law (velocity varies linearly with diameter) and Square law (constant velocity).

Results
In diseased vessels, basal and hyperemic pressure were reduced by less than 7% (p<0.05) at the more distal location. A small, but clinically not relevant effect on FFR and HSR was only observed in reference vessels, with no difference in HMR. Group averages of flow velocity and CFVR were location-independent in both reference and diseased vessels (p>0.22). However, more distal measurements were associated with a lower inter-patient variability. Flow velocity generally did not follow Murray’s law but supported the Square law.

Conclusions
Functional indices of stenosis severity and microvascular resistance were not affected by measurement location. The inter-patient variability between flow velocities at different locations in reference vessels suggests a stronger influence of patient-specific vascular network morphology at proximal measurement locations. More distal locations are therefore advised for obtaining velocity or velocity-derived indices to assess epicardial obstructions.
Background

Detection of functionally significant stenosis is advised for adequate patient selection prior to percutaneous coronary intervention (PCI) (1). During cardiac catheterization, intracoronary hemodynamic signals can be obtained downstream of a stenosis using a sensor-equipped guide wire (2). Presently adopted clinical indices of functional stenosis severity include the pressure-based fractional flow reserve (FFR) and the Doppler-based coronary flow velocity reserve (CFVR). If pressure and flow velocity are measured simultaneously, epicardial and microvascular contributions to decreased coronary perfusion can be separated in terms of the hyperemic stenosis resistance (HSR) and the hyperemic microvascular resistance (HMR) (3).

Current practice guidelines specify that the pressure or Doppler sensor should be positioned at least 2–3 cm beyond the stenosis to avoid effects of disturbed flow emerging from the throat of the lesion (4). However, there are other factors to consider with respect to wire tip positioning as well. In diffuse disease without a focal narrowing, pressure has been shown to gradually decline along the vessel (5). In stenosed vessels, pullback curves have proven useful in identifying serial lesions by distinguishing abrupt from gradual pressure patterns along the vessel. Coronary pressure distal to the lesion is a function of sensor position and indeed, FFR is lower more distal to a stenosis compared to FFR directly beyond the lesion (6). Similar results were reported post PCI, where FFR was significantly reduced with increasing distance from the stent (7).

The factors determining flow velocity along coronary arteries are more complicated than those determining pressure and only few studies investigated the relation between coronary flow velocity and lumen diameter in humans (8–10). The flow carried by a vascular segment is determined by the vascular network and the amount of tissue that is dependent on it (11, 12). Flow velocity in a given vascular segment was shown to depend on lumen diameter and mass of perfused tissue even in diseased coronary arteries (8). Moreover, vessel diameter adapts in response to several biochemical and biophysical factors, a process denoted as remodeling. Although a potential location effect on flow velocity has been assessed previously in unstenosed coronary vessels (13), an assessment in diseased vessels is lacking.

The aim of this study was to establish the dependency of concomitantly measured flow velocity and pressure on axial location in human coronary arteries and its effect on physiological indices of stenosis severity incorporating one of these signals, such as CFVR and FFR, or a combination of both signals, such as HSR. Also the location effect on HMR to assess minimal microvascular resistance was evaluated.

Methods

Patient population
The study population consisted of 26 patients with stable angina pectoris, scheduled for elective PCI. Patients were included based on the presence of a single discrete
stenosis (40–70% diameter stenosis at visual assessment) in the target vessel. Exclusion criteria were age (<18 or >80 years), subtotal or serial lesions, diffuse or 3-vessel disease, significant left main coronary artery stenosis (>50% diameter reduction), hypertrophic cardiomyopathy, recent myocardial infarction (<6 weeks prior to screening), cardiac arrhythmia, severe aortic valve disease, severe heart failure or prior cardiac surgery. Anti-anginal medication was continued as clinically indicated. The institutional ethics committee approved the study procedure, and all patients gave written informed consent.

Cardiac catheterization and intracoronary measurements
Cardiac catheterization was performed using a percutaneous femoral or radial artery approach. Heparin was administered at the beginning of the procedure (5000–7500 IU, intravenous bolus) followed by an intracoronary bolus of nitroglycerin (0.1 mg) in order to minimize vascular tone in the large epicardial vessels. Diagnostic coronary angiography was performed according to standard protocol. A 12-lead surface ECG was recorded continuously.

Aortic pressure (Pa) was measured via a 5 or 6F guiding catheter advanced into the coronary ostium. Intracoronary distal pressure (Pd) and peak cross-sectional blood flow velocity were measured simultaneously using a 0.014-inch dual-sensor guide wire (ComboWire XT®, model 9500, Volcano Corp., San Diego, USA) equipped with both a Doppler and pressure sensor at the tip. The pressure at the wire tip was normalized to the proximal pressure prior to advancing the guide wire and care was taken to obtain an optimal and stable flow velocity signal. Hemodynamic signals were digitally stored at a sampling rate of 200 Hz for offline analysis.

Protocol
Measurements were obtained in angiographically normal reference and diseased vessels at two axial locations, denoted as location 1 and location 2, where location 2 is more distal. There was at least one side branch between the measurement sites. In the diseased vessels, both locations were distal to the stenosis. All data were obtained prior to PCI. Hemodynamic signals were recorded starting at baseline until the end of the hyperemic response to an intracoronary bolus of 40 µg of adenosine (14). Measurements were repeated in a subgroup of patients for reproducibility analysis. Coronary angiograms were taken under basal conditions for offline quantitative coronary angiography (QCA) analysis of vessel dimensions and the axial position of the wire tip at each measurement site was recorded by short contrast injections in the same angiographic view.

Data analysis
Coronary angiograms were quantitatively analyzed using a validated automated contour detection algorithm (QAngio XA 7.2, Medis Medical Imaging Systems, Leiden, The Netherlands) to determine stenosis diameter reduction, lumen diameter at the measurement site as well as distance and number of side branches between the two axial measurement sites. Hemodynamic data were processed using custom software (written in Delphi vs. 2010, Embarcadero, CA, USA). In case repeat measurements were obtained, the one with the best quality pulsatile flow velocity signal and the
The highest hyperemic response was selected for the location effect and the second best was additionally used to assess reproducibility. Cycle averages of heart rate, Pa, Pd, pressure gradient (ΔP = Pa-Pd) and flow velocity were determined over at least 7 consecutive heart beats at baseline and 3 consecutive heart beats during peak hyperemia. CFVR (= hyperemic/baseline flow velocity), FFR (= Pd/Pa, at peak hyperemia), HSR (= ΔP/flow velocity, at peak hyperemia) and HMR (= Pd/flow velocity, at peak hyperemia) were derived from these averages.

**Relationship between flow velocity and branch diameter**

Based on physical principles the relationship between blood flow and branch diameter can be expressed as a power equation of the general form \( Q = a \cdot D^b \), where \( Q \) represents coronary flow and \( D \) the branch diameter (12). The exponent \( b \) varies with the assumed underlying principle. For the principle of minimum energy, equivalent to constant wall shear stress based on Murray’s law (15), \( b=3 \). In the second model, \( b=2 \), and this model will be denoted as the “Square law” in this paper. Assuming a parabolic blood flow profile and circular vessel area, these relations can be converted to a relationship between flow velocity and branch diameter. The Square law then results in a constant mean flow velocity throughout the coronary vasculature, while Murray’s law predicts a linear relationship between flow velocity and branch diameter. The data of the present study will be compared to these two models.

**Statistical analysis**

Continuous variables are expressed as mean±standard deviation (SD) or median (interquartile range (IQR)). Baseline and hyperemic hemodynamic parameters and derived indices between the two axial measurement locations were compared using Student’s t-test or Wilcoxon signed rank test where appropriate. Pearson’s correlation coefficient was used to assess the association between the baseline and hyperemic flow velocity and CFVR at the two axial measurement locations, as well as to assess the relationships between the distance between the two measurement locations and the difference in FFR and HSR between the two measurement locations. Linear regression was performed to assess the relationship between branch diameter and flow velocity. Reproducibility of hemodynamic parameters and derived indices was assessed by the coefficient of variance (COV), 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. A two-sided alpha-level of 0.05 was considered statistically significant.

**Results**

The study population consisted of 19 males and 7 females (mean age 58±8 years). Patient demographics are presented in Table 1. Pairs of adenosine responses at the two distal measurement sites were collected in 12 diseased and 17 reference vessels. QCA yielded a diameter reduction of 47±13% in the diseased vessels and 20±12% in the reference vessels. Duplicate measurements were collected in 17 diseased and 19 reference vessels.
Angiographic dimensions at the measurement sites
Table 2 summarizes the morphologic characteristics at the two measurement sites, which were on average 21.6±10.7 mm apart in the diseased and 29.2±13.2 mm in the reference vessels (p=0.17), with 1 to 4 side branches in between. In the diseased vessels, distal branch diameter varied between 1.17 and 3.02 mm at location 1 and was 13±33% smaller at location 2 (p=0.08). In the reference vessels, branch diameter ranged from 1.29 to 3.93 mm at location 1 and was 32±22% smaller at location 2 (p<0.001). Branch diameter at location 1 was 23% smaller for the diseased vessels compared to the reference vessels (p<0.05), with no difference at location 2 (p=0.56).

Table 1: Patient characteristics (n=26).

| Age (yrs) | 58±8 |
| Male sex | 19 (73) |
| Coronary risk factors | |
| Cigarette smoking | 7 (27) |
| Hypertension | 11 (42) |
| Positive family history of CAD | 15 (58) |
| Hypercholesterolemia | 14 (54) |
| Diabetes mellitus | 4 (15) |
| Prior myocardial infarction | 2 (8) |
| Prior PCI | 3 (12) |
| Medication | |
| Beta-blockers | 22 (85) |
| Nitrates | 11 (42) |
| Calcium antagonists | 7 (27) |
| ACE-inhibitors | 5 (19) |
| Lipid lowering drugs | 23 (89) |
| Aspirin | 26 (100) |
| Diseased vessels (n=12) | |
| Left anterior descending | 2 (17) |
| Left circumflex | 2 (17) |
| Right coronary artery | 8 (67) |
| Percent stenosis (%) (n=11) | 47±13 |
| Reference vessels (n=17) | |
| Left anterior descending | 9 (53) |
| Left circumflex | 1 (6) |
| Right coronary artery | 7 (41) |
| Percent stenosis (%) (n=16) | 20±12 |

Values are mean±SD or frequency (%). ACE, angiotensin-converting enzyme; CAD, coronary artery disease; PCI, percutaneous coronary intervention.
Table 2: Angiographic characteristics at measurement sites.

<table>
<thead>
<tr>
<th></th>
<th>Diameter at location 1 (mm)</th>
<th>Diameter at location 2 (mm)</th>
<th>Distance between location 1 and 2 (mm)</th>
<th>Side branches between location 1 and 2 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease vessels</td>
<td>2.1 ±0.6</td>
<td>1.7 ±0.5</td>
<td>21.6 ±10.7</td>
<td>1.5 (1.0–2.75)</td>
</tr>
<tr>
<td>(n=11)</td>
<td>(n=10)</td>
<td>(n=10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessels</td>
<td>2.8 ±0.8</td>
<td>1.9 ±0.6 ‡</td>
<td>29.2 ±13.2</td>
<td>1.0 (1.0–2.0)</td>
</tr>
<tr>
<td>(n=13)</td>
<td>(n=13)</td>
<td>(n=13)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or median (IQR). ‡ p<0.001 compared to location 1. Due to insufficient contrast to perform QCA analyses, diameters could not be determined for location 1 in one patient and for location 2 in two patients in the diseased vessels, and for both locations in four patients in the reference vessels.

Table 3: Reproducibility of hemodynamic and derived parameters for reference and diseased vessels combined (n=36).

<table>
<thead>
<tr>
<th></th>
<th>Coefficient of variance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>Pa (mmHg)</td>
<td>3.2</td>
</tr>
<tr>
<td>Pd (mmHg)</td>
<td>3.0</td>
</tr>
<tr>
<td>ΔP (mmHg)</td>
<td>26.6</td>
</tr>
<tr>
<td>Velocity (cm/s)</td>
<td>12.4</td>
</tr>
<tr>
<td>FFR</td>
<td>1.1</td>
</tr>
<tr>
<td>CFVR</td>
<td>10.9</td>
</tr>
<tr>
<td>HSR (mmHg/cm/s)</td>
<td>13.9</td>
</tr>
<tr>
<td>HMR (mmHg/cm/s)</td>
<td>8.8</td>
</tr>
</tbody>
</table>

CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; HMR, hyperemic microvascular resistance; HSR, hyperemic stenosis resistance; ΔP, pressure gradient; Pa, aortic pressure; Pd, distal coronary pressure.

Figure 1: (A) Angiogram showing a 60% diameter stenosis in the left anterior descending artery in which the two measurement locations are indicated with the guide wire tip at location 2. (B) Corresponding hemodynamic recordings at location 2 throughout the hyperemic response to an intracoronary bolus of adenosine. Flow velocity rises, while coronary distal pressure (Pd) decreases resulting in a pressure gradient (ΔP) over the stenosis during hyperemia. Pa, aortic pressure.
Chapter 4

Reproducibility

The COV for all hemodynamic and derived parameters is listed in Table 3. The variability in Pd and ΔP was in part due to variations in Pa, for which the COV equaled 3.2% at baseline and 3.4% at hyperemia. Normalizing the hyperemic Pd with respect to hyperemic Pa reduced the variability to 1.1%. Note that hyperemic Pd/Pa equals FFR.

One may expect that variation in repeat hyperemic velocity is to some degree related to variations in Pa. The ratio between coronary flow velocity and Pa can be considered as a measure of coronary conductance. However, the conductance during hyperemia was slightly less reproducible (COV=7.1%) than hyperemic flow velocity (COV=5.8%).

Hemodynamic characteristics

Figure 1 shows a typical angiographic image (panel A) with the two measurement locations in the left anterior descending artery with a proximal 60% diameter stenosis and the corresponding hemodynamic recording at location 2 (panel B) following an intracoronary bolus injection of adenosine. In this example flow velocity rises
Figure 2: Location effect on baseline and hyperemic coronary distal pressure (Pd), the ratio of baseline coronary distal pressure to baseline aortic pressure (Pd/Pa) and fractional flow reserve (FFR) for reference vessels (top panels) and diseased vessels (bottom panels). * p<0.05 and ‡ p<0.001 compared to location 1.

Figure 3: Relationship between the distance between location 1 and location 2 and the difference in fractional flow reserve between location 1 (FFR₁) and location 2 (FFR₂) for the reference vessels (triangles) and diseased vessels (circles). In both conditions the difference in fractional flow reserve tended to increase with increasing distance between the two measurement sites.
2.5 times above the baseline value, with a concomitant decrease in Pd resulting in a pressure gradient of 39.2 mmHg across the stenosis during hyperemia. Table 4 provides an overview of all hemodynamic and derived parameters obtained at the two locations.

**Location effects on pressure and FFR**

As depicted in Figure 2, both baseline and hyperemic Pd in the reference vessels were similar at both locations, whereas in the diseased vessels, Pd was 6.1±7.4 mmHg lower at the more distal location (p<0.05) at baseline and 4.1±6.4 mmHg lower during hyperemia (p<0.05). For the reference vessels, hyperemic ΔP increased by 4.6±4.1 mmHg (p<0.001) and FFR was 0.01±0.05 lower (p<0.001) at location 2 compared to location 1. This reduction in FFR tended to increase with increasing distance between the two measurement sites (p=0.09, Figure 3). However, in the diseased vessels, no significant difference in either hyperemic ΔP or FFR was found between the two measurement locations (p>0.20). Again, FFR tended to increase with increasing distance between the two measurement sites (Figure 3), but this relationship did not reach statistical significance (p=0.12).

**Location effects on flow velocity and CFVR**

No differences due to location were found for average baseline and hyperemic flow velocity or CFVR in either the reference or diseased vessels (Figure 4). However, flow velocities at the two locations were linearly related (Figure 5A) for the reference vessels at baseline (r=0.78, p<0.001) and hyperemia (r=0.66, p<0.01). These relationships crossed the identity line with slopes less than unity, i.e. a given range of velocities at the proximal location corresponds to a smaller predicted range of more distally measured velocities. In other words, the inter-patient dispersion of flow velocity was less at the distal locations. Moreover, for low values, flow velocity was higher at the distal than at the more proximal location and vice versa for high values. For the diseased vessels (Figure 5B), flow velocities at the two locations were only poorly related, both at baseline (r=0.01, p=0.97) and hyperemia (r=0.43, p=0.16). In 76% of the reference vessels and 83% of the diseased vessels we found that when the ratio of distal to proximal velocities was <1 at baseline, this was also the case at hyperemia, and likewise for velocity ratios >1. Consequently, the relation between proximal and distal CFVR was stronger (r=0.77, p<0.05) for the diseased vessels (Figure 5C) than for the reference vessels (r=0.47, p=0.06).

Relationships between flow velocity and branch diameter are shown in Figure 6. The expected dependencies as predicted by the Square and Murray’s laws are depicted only for location 1, since the predictions are rather similar for both locations. Only baseline velocity at the more proximal location in reference vessels had a moderate inverse relationship to branch diameter (p<0.05), with a slope of -5.5 cm/s/mm (95% confidence interval: -10.9—-0.05). During hyperemia or in diseased vessels, flow velocities were rather independent of branch diameter (p>0.14).
Figure 4: Location effect on baseline and hyperemic flow velocity and coronary flow velocity reserve (CFVR) for reference vessels (top panels) and diseased vessels (bottom panels).

Figure 5: Relationship between more proximally (location 1) and more distally (location 2) obtained flow velocity and coronary flow velocity reserve (CFVR). (A) Flow velocity obtained at baseline (triangles) and hyperemia (circles) at location 1 ($\text{Velocity}_{1}$) and location 2 ($\text{Velocity}_{2}$) in the reference vessels and (B) in diseased vessels. (C) CFVR obtained at location 1 ($\text{CFVR}_{1}$) and location 2 ($\text{CFVR}_{2}$) in the reference vessels (open symbols) and diseased vessels (closed symbols).
Location effects on hyperemic indices combining flow velocity and pressure

Hyperemic stenosis and microvascular resistance were generally not influenced by measurement location (Figure 7). Only HSR in the reference vessels slightly increased from 0.07±0.06 at location 1 to 0.18±0.12 mmHg/cm/s (p<0.001) at location 2, but this was hemodynamically not significant. Differences in HSR values were not related to the distance between the two measurement sites in the diseased (r=-0.47, p=0.17) or the reference (r=-0.32, p=0.29) vessels (Figure 8).

Discussion

In this study we addressed the influence of axial measurement location for several indices of stenosis severity and microvascular resistance based on distal pressure and/or distal velocity. The main finding of this study is that inter-patient range of flow velocities in reference vessels is less at distal than more proximal locations. The velocity ratio between proximal and distal location depended on velocity magnitude both at baseline and in hyperemia. These findings point to yet not well understood morphometric dissimilarities between hearts, which may in part be due to structural adaptation of the epicardial vessel diameter. In particular, the lower inter-patient variation of distally measured flow velocity in reference vessels suggests better adaptation of vessel diameter to flow velocity at this position. Location dependency of flow velocity was not established in diseased vessels and did not affect assessment of stenosis or microvascular resistance. Overall our findings indicate that branching epicardial vessels mostly follow a “constant velocity” law rather than Murray’s law which predicts velocity and diameter to be proportional.

Reproducibility of pressure and flow velocity measurements and derived indices

The repeated pressure measurements demonstrated that variations in Pd were mostly due to variations in Pa. The COV for hyperemic flow velocity and distal pressure was 5.8% and 3.3%, respectively, which tallies well with the earlier reported value of 6.4% and 3.5% (2). This COV was not reduced by compensation for variations in Pa, which may be due to physiological variations in oxygen consumption and extravascular resistance (16, 17). Such variability contains physiological information and should not be attributed to noise or measurement inaccuracy. This is underlined by the higher COV found for the stenosis pressure drop compared to that of Pd, which is in part due to variations in flow velocity. Obviously, variability in flow velocity also contributed to the variability of around 10% for dependent derived indices.

Interpretation of location and branch diameter dependency of flow velocity

Several studies proposed allometric scaling laws for the branching network of the coronary circulation, which can be roughly categorized into two different models (12). The first model is the Square law (18), derived from the observation that the sum of the square of the daughter vessel diameters is equal to the square of the mother vessel diameter, which implies that flow velocity remains constant throughout the coronary vasculature. The second model is Murray’s law, which postulates that the
Figure 6: Relationship between branch segment diameter and flow velocity for the reference (A, B) and diseased (C, D) vessels obtained at location 1 (closed symbols) and location 2 (open symbols). Baseline results are shown on the left, hyperemic results on the right. In each graph, the expected dependency of flow velocity on diameter as predicted by the Square law (gray dotted line) and Murray’s law (gray dashed line) are indicated. For clarity, these predictions are only displayed for location 1.
Figure 7: Location effect on hyperemic stenosis resistance (HSR) and hyperemic microvascular resistance (HMR) for reference vessels (top) and diseased vessels (bottom). ‡ p<0.001 compared to location 1.
The relation between coronary blood flow and vascular diameter results from a minimum energy hypothesis (15), corresponding to a constant wall shear stress (19, 20). In this law, the sum of the cubes of the daughter vessel diameters is equal to the cube of the mother vessel diameter, which entails that flow velocity is proportional to diameter and hence location-dependent. Our data are in accordance with a morphological study by VanBavel and Spaan (18) on healthy pigs, where the Square law was found to hold in the epicardial arteries, whereas Murray’s law was applicable to the smaller arteries down to the precapillary arterioles.

In agreement with findings in reference vessels by Ofili et al. (13), the group means of flow velocity were independent of location both in the reference vessels and in segments downstream of a stenosis. Such location independence of flow velocity matches with the Square law and justifies the use of flow velocity as surrogate for flow in computation of resistance indices. However, inter-patient analyses revealed a location dependency for the minimally diseased reference vessels. Although flow velocities at the two locations were significantly related, proximal velocities exceeded distal ones at more elevated flow velocities while the opposite was true at low velocity values (Figure 5A). This was found for both baseline and hyperemic conditions. It is difficult to relate these findings to a consistent relationship between diameter and velocity as a general principle throughout the epicardial tree since location dependence differs for higher and lower velocities.

Murray’s law predicts a positive linear relationship between flow velocity and diameter for branching networks. Hence, since distal diameters are smaller than...
proximal diameters, flow velocity should be lower at the distal location. This does not correspond to the location independence of means of flow velocity and contradicts the higher distal flow velocity at location 2 for those patients with a low flow velocity (Figure 5A). Murray’s law is also not supported by the flow velocity data as a function of diameter (Figure 6.) The only significant slope found was in the reference vessels for location 1 at baseline, and this slope was negative rather than positive. Except for this specific condition, the present data supported the Square law. However, neither of the two laws provides sufficient explanation for the observed transition in proximal-to-distal velocity ratio with increasing velocity and the lower inter-patient variation at the more distal location. Hence, there is an effect of patient-specific vascular morphology and adaptation that is not yet well understood.

**Location dependency of functional indices of stenosis severity**

Obviously, the location dependency of FFR strongly depends on the anatomy of the interrogated vessels. FFR in vessels with a well-defined single stenosis in an otherwise smooth segment is expected to vary less over some distance downstream of the stenosis than in vessels with diffuse disease. In the present study, FFR tended to decline with increasing distance both in the diseased and reference vessels, which corresponds to findings reported earlier (6, 7).

On average, we observed no significant difference in CFVR measured at the two locations for both the reference and diseased vessels. The strong correlation between proximally and distally measured CFVR for the diseased vessels was not present for the reference vessels. Two reference vessels had a CFVR below the diagnostic threshold of 2.0 at both locations, while the corresponding FFR and HSR values indicated that these lesions were not functionally significant. These low CFVR values must be related to microvascular factors, which corresponds with discordance between FFR and CFVR observed in about 30% of patients with an intermediate stenosis (21). When excluding these 2 below threshold data points, the inter-patient variation of CFVR at location 2 was less than at location 1.

Combined pressure and velocity measurements allow differentiation between epicardial and microvascular resistance. In diffusely diseased vessels one would expect a higher stenosis resistance index at the distal position. Although all values remained far below the clinical cut-off of 0.8 mmHg/cm/s, HSR at location 2 was indeed higher compared to location 1 in the reference vessels. Furthermore, an added contribution due to vessel tapering distal to a stenosis is offset by the pressure gradient along the downstream segment. In the present study, HSR did not increase with increasing distance from the stenosis and no significant relation was found between the change in HSR and the distance between the measurement locations. Similarly, no location effect was detected for HMR for either the reference or diseased vessels, despite a small decrease in Pd at the more distal measurement site in diseased vessels. Hence, the differential effect of flow velocities on CFVR was not present for HMR.
Study limitations
An important limitation is the relatively small patient group. Especially the relationship between flow velocity and branch diameter may have been more conclusive with a larger group and warrants future studies.

Neither distance nor number of side branches between the sites of measurements were controlled in this study. The number of side branches was at least one but varied between 1 and 4. Standardizing the distance between measurement sites may well have resulted in a better correlation between flow velocities at different locations, but would be difficult to realize in practice.

The present study adhered to the amount of adenosine used in clinical validation studies of FFR, which is considered to provide a hyperemic response equivalent to that induced by the intravenous administration of adenosine (22).

Clinical implications
For clinical decision making it is best when the assessed hemodynamic parameters do not depend on axial measurement location. Although current practice guidelines recommend a minimum distance of about 2–3 cm beyond the stenosis to avoid effects of disturbed flow (4), no upper limit is specified. A distal location difference of 3 cm, representing the range of distances reported in this study, can theoretically affect all indices studied.

It seems attractive to choose the index that demonstrates the lowest COV in repeat measurements and the lowest location dependence, but accuracy of measurement and physiological information content are two separate issues. FFR is certainly the index with lowest variability but it lacks specific information related to morphological and physiological factors. It appears therefore plausible that the positive clinical impact of FFR on clinical decision making can be further improved by flow velocity-related information such as CFVR (22, 23).

The lower inter-patient variation in flow velocity demonstrated in the present study is in favor of a more distal measurement position. This may seem at odds with the assessment of proximal stenosis resistance. However, downstream of a focal stenosis the measurement location had no consistent effect on velocity and in case of serial lesions or in the presence of additional diffuse disease, it is important to assess the total epicardial resistance versus the microvascular resistance. Although a close correlation was found for CFVR between proximal and distal locations for the diseased vessels, the inter-patient variability in reference vessels with a CFVR>2 was more pronounced at the more proximal location. To avoid interference of variability related to patient-specific vascular network morphology or adaptation in clinical decision making, it may be advisable to obtain intracoronary hemodynamic measurements at a more distal location.
References


