Coronary Pressure Measurement to Assess the Hemodynamic Significance of Serial Stenoses Within One Coronary Artery Validation in Humans

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Background—When several stenoses are present within 1 coronary artery, the hemodynamic significance of each stenosis is influenced by the presence of the other(s), and the calculation of coronary and fractional flow reserve (CFR and FFR) for each individual stenosis is confounded. Recently, we developed and experimentally validated a method to determine the true FFR of each stenosis as it would be after the removal of the other stenosis; the true FFR can be reliably predicted by coronary pressures measured before treatment at specific locations within the coronary artery using equations accounting for stenosis interaction. The aim of the present study was to test the validity of these equations in humans.

Methods and Results—In this study of 32 patients with 2 serial stenoses in 1 coronary artery, relevant pressures were measured before the intervention, after the treatment of 1 stenosis, and after the treatment of both stenoses. The true FFR of each stenosis (FFRtrue) was directly measured after the elimination of the other stenosis and compared with the value predicted (FFRpred) from the initial pressure measurements before treatment. Although the hyperemic gradient across 1 stenosis increased significantly (from 10±7 to 19±11 mm Hg after treatment of the other stenosis), FFRpred was close to FFRtrue in all patients (0.78±0.12 versus 0.78±0.11 mm Hg; r=0.92; Δ%≈4±0%). Without accounting for stenosis interaction, the value of FFR for each stenosis would have been significantly overestimated (0.85±0.08; P<0.01).

Conclusions—Coronary pressure measurements made by a pressure wire at maximum hyperemia provide a simple, practical method for assessing the individual hemodynamic significance of multiple stenoses within the same artery.

Key Words: pressure ■ stenosis ■ blood flow

The fluid, dynamic interaction of multiple sequential stenoses in coronary arteries is complex, often unexpected, and cannot be adequately assessed by visual interpretation on the coronary angiogram. Although described by computerized analysis of the entire coronary tree and assessed noninvasively by PET perfusion imaging, these interactions have never been quantified in humans by direct intracoronary pressure or flow measurements.

A well-established method of assessing the hemodynamic severity of single stenosis in coronary arteries uses Doppler wires to measure coronary flow reserve (CFR) or pressure wires to measure fractional flow reserve (FFR). However, diffuse disease or multiple sequential stenoses or plaques are commonly present, and an objective selection of the most appropriate stenosis to be dilated out of several in sequence is an important interventional decision. This is especially true in patients with several intermediate stenoses or those who have diffuse disease present in addition to a segmental stenosis; this disease is often overlooked and may explain the limited improvement in flow reserve often seen after anatomically successful PTCA of a segmental stenosis. Therefore, a method to assess the individual hemodynamic significance of multiple stenoses within the same coronary artery is important.

Recently, we developed and experimentally validated 2 equations for determining the FFR of individual stenoses when each is one of several in sequence; these equations use hyperemic coronary pressure measurements and account for interactions among stenoses. The purpose of the present study was to test the validity of these equations in humans.
The study was to test the validity of these new equations in humans, thereby quantifying the mutual influence of each stenosis on the hemodynamic manifestation of the other.

Methods

Theoretical Basis

FFR is defined as the maximum achievable myocardial blood flow in the presence of a coronary stenosis divided by normal maximum flow. This ratio can be calculated easily using the ratio of the corresponding coronary perfusion pressures (i.e., the ratio of hyperemic distal coronary pressure and mean aortic pressure). In normal coronary arteries, FFR equals 1.0, indicating that no decline of pressure occurs along the length of a normal epicardial coronary artery, even at hyperemia.

For patients with multiple sequential stenoses or diffuse coronary artery disease, a stepwise or more gradual decrease in pressure along the artery is expected during maximum hyperemia; this decrease is proportional to the severity of each stenosis or the diffuse disease. These longitudinal pressure changes can be measured by positioning the pressure wire distal in the coronary artery and pulling it back slowly to the ostium during sustained myocardial hyperemia, as was previously proposed and is illustrated in Figure 1.

On superficial consideration, without accounting for the interaction between stenoses, the FFR of each stenosis would be given by the simple equations \( \frac{P_m}{P_a} \) for a proximal stenosis A and as \( \frac{P_d}{P_m} \) for the distal stenosis B, where \( P_a \), \( P_m \), and \( P_d \) represent mean hyperemic aortic pressure, hyperemic coronary pressure between both stenoses, and hyperemic distal coronary pressure, respectively (Figure 2).

These apparent values, called FFR(A)_{app} and FFR(B)_{app} however, do not account for stenosis interactions, and they are expected to underestimate the true functional significance of each stenosis. This can be illustrated as follows. Suppose that during sustained maximum hyperemia in a stenotic coronary artery, a second stenosis is induced. Consequently, blood flow through that artery will further decrease and, therefore, the pressure gradient across the first stenosis will also decrease. In other words, a second stenosis will decrease the apparent hemodynamic significance of the first stenosis by limiting the maximum flow through it. Conversely, if a second stenosis in the vessel is relieved, blood flow increases, the hyperemic gradient across the first lesion increases, and the true hemodynamic significance of that lesion is unmasked. Thus, although FFR by the summed effect of all lesions is still given by \( \frac{P_m}{P_a} \), the individual true values of FFR(A) and FFR(B) when the other stenosis is physically removed are not obvious beforehand.

We previously developed equations and experimentally validated them for predicting FFR(A) and FFR(B) as if the other stenosis was physically removed. These equations were tested in humans in the present study.
Patient Selection and Angiographic Characteristics
A total of 32 patients were studied (25 men and 7 women aged 61 ± 9 years); each had been referred for PTCA of a native coronary artery that had ≥2 stenoses with ≥50% diameter narrowing by visual estimation, separated by an apparently normal segment of ≥2 cm in length without a large side-branch. The baseline characteristics of these patients and the angiographic characteristics of the lesions are presented in Table 1. The study was approved by the Institutional Review Boards of each institution, and informed consent was obtained from all patients before the study.

Interventional Protocol and Coronary Pressure Measurements
After the administration of 10 000 U of heparin, a 6 or 7-French guiding catheter was introduced into the ostium of the target coronary artery. After this, 300 μg of nitroglycerine was administered intracoronally, and baseline angiograms were made from 2 orthogonal views.

Thereafter, an 0.014-inch pressure guidewire (Pressure Wire, Radi Medical Systems) was advanced to the tip of the guiding catheter, where the pressure measured through the guiding catheter and by the pressure guidewire were verified as being equal. The pressure wire was then advanced into the coronary artery to a position distal to the most distal lesion, and steady-state maximum hyperemia was induced by the continuous administration of 140 μg·kg⁻¹·min⁻¹ adenosine into the femoral vein. This state of maximum hyperemia was maintained for ≈2 minutes to enable reliable coronary pressure measurements.

During maximum hyperemia, the pressure wire was slowly pulled back from the distal coronary artery to the ostium of the coronary artery, thereby recording the pressure drop across each of the individual stenoses, as illustrated in Figure 1. Next, one of the lesions (usually the one with the largest gradient) was dilated and stented using the pressure wire as the primary guidewire, thereby also recording coronary wedge pressure (Pw) during balloon inflation. If a residual hyperemic pressure gradient was present before balloon angioplasty, a stent was placed.

After this initial procedure was completed, another pull-back pressure recording at maximum hyperemia was made to obtain the hyperemic pressures at the same locations as recorded on the initial pull-back. The second stenosis was then dilated and stented if necessary; this was followed by another pull-back pressure recording at maximum hyperemia to obtain the hyperemic pressures at the same locations of interest. Finally, the pressure wire was completely pulled back into the guiding catheter to verify that no drift had occurred during the procedure.

Calculation of FFR
Pd, Pw, and Pm indicate the initially measured mean aortic pressure, mean hyperemic coronary pressure between lesion, mean hyperemic distal coronary pressure distal to the most distal lesion, and coronary wedge pressure, respectively, measured before the intervention. The proximal lesion is called stenosis A, the distal stenosis is B, and the FFR associated with each lesion is indicated by FFR(A) and FFR(B), respectively. After dilating and stenting one of the stenoses, the pressures measured during the pull-back maneuver at hyperemia at the identical locations are called Pdm, Pwm, and Pdm', respectively.

If the proximal lesion was treated first and no residual gradient existed across that stenosis, then Pdm' equaled Pdm. If the distal lesion was treated first without residual hyperemic gradient, then Pwm' equaled Pwm.

Apparent, true, and predicted FFR values were calculated as follows.12 If the distal stenosis (B) was treated first,

\[
(1) \quad FFR(A)_{app} = \frac{P_m}{P_n}
\]

\[
(2) \quad FFR(B)_{app} = \frac{P_d}{P_d'} = \frac{P_m}{P_n}
\]

\[
(3) \quad FFR(A)_{true} = \frac{P_d - \left(\frac{P_m}{P_a}\right) \cdot P_d}{P_d - \left(\frac{P_m}{P_n}\right) \cdot P_d}
\]

If the proximal stenosis A was treated first,

\[
(4) \quad FFR(B)_{app} = \frac{P_m}{P_n}
\]

\[
(5) \quad FFR(B)_{true} = \frac{P_m}{P_m} - \frac{P_m - P_d}{P_m - P_n}
\]

\[
(6) \quad FFR(B)_{pred} = 1 - \frac{P_m - P_d}{P_m - P_n}
\]

In these equations, app indicates the apparent value of FFR of the respective stenoses as it seems to be from the initial measurements on superficial consideration without accounting for stenosis interaction; true indicates the FFR measured after the other stenosis has been completely eliminated physically by PTCA or stenting; and pred indicates the value of FFR predicted from the initial pressure measurements using equations 3 and 6, which account for the interaction of stenoses. The mathematical derivation and experimental validation of these equations, as well as the necessity of including Pw, were recently reported by De Bruyne et al.12

Evaluation of Data and Statistical Analysis
In those patients in whom the proximal lesion was treated first, FFR(B)app and FFR(B)true were compared with FFR(B)true. Conversely, if the distal lesion was treated first, FFR(A)app and FFR(A)true were compared with FFR(A)true. The difference between FFRapp and FFRtrue indicates the confounding effect of one lesion on the hemodynamic significance of the other.

Linear regression analysis was performed between FFRapp as the independent variable and FFRtrue and FFRpred as dependent variables. The percent differences between apparent and true FFR for stenosis A versus B were compared using an unpaired t test. Hemodynamic data are presented as mean ± SD.

Results
Procedural and Angiographic Results
Baseline angiographic data and angiographic results are presented in Table 1. Hemodynamic data throughout the procedure are given in Table 2.

In 19 patients, the proximal stenosis was dilated first, and in 13 patients, the distal stenosis was dilated first. A total of 36 stents were placed: 20 were proximal and 16 were distal. The FFR of the myocardium supplied by the target artery [FFR(A+B)] increased from 0.56 ± 0.15 before the procedure to 0.92 ± 0.05 at the end of the procedure. This latter value has the most important clinical value for the patient. The average hyperemic pressure gradient across the proximal stenosis decreased from 29 ± 13 to 2 ± 2 mm Hg, and the average hyperemic pressure gradient across the distal stenosis decreased from 27 ± 18 to 3 ± 4 mm Hg.

In one patient, a type B dissection occurred proximally in the right coronary artery due to manipulation with the guiding catheter; this did not obstruct flow and it was left untreated. No further complications occurred in any of the patients during the procedure, and angiographically successful intervention was performed on all 64 lesions.

Examples of the angiograms and pressure recordings from 2 patients in whom either the proximal or the distal stenosis was dilated first are presented in Figures 3 and 4.

Apparent and Predicted FFR Versus True FFR
FFRapp was compared with FFRtrue, and the results are presented in Figure 5A. The relation between FFRpred, predicted by equations 3 and 6, and FFRtrue is presented in Figure 5B.
In both the proximal and distal stenosis, FFR$_{pred}$ was significantly closer to FFR$_{true}$ than was FFR$_{app}$ (Table 2). Compared with FFR$_{true}$, the percent differences were $4\pm0\%$ for FFR$_{pred}$ and $11\pm12\%$ for FFR$_{app}$. The differences between FFR$_{app}$ and FFR$_{true}$ were larger for stenosis A than for stenosis B ($14\pm16\%$ versus $9\pm8\%$, respectively; $P<0.01$), which indicates that the influence of a distal stenosis on the hemodynamic appearance of a proximal stenosis is generally larger than that of a proximal stenosis on a distal one (Table 2).

**Figure 3.** Increase of hyperemic gradient across a proximal stenosis after PTCA of the distal stenosis. Panel A shows the right coronary artery of a 65-year-old man with 2 severe stenoses in the mid and distal part of the vessel (stenoses A and B) before PTCA (left), after stenting of the distal lesion (middle), and after stenting of both lesions (right). B, The pressure wire is positioned distal to stenosis B and pulled back slowly to the ostium of the right coronary artery under sustained hyperemia. A large pressure drop, $\Delta P(B)$, is observed when the sensor crosses the distal stenosis, and a much smaller pressure drop, $\Delta P(A)$, is present across stenosis A, which suggests that stenosis A is not very severe from a functional point of view. $P_s$, $P_m$, and $P_d$ in this tracing are 112, 98, and 51 mm Hg, respectively, and $P_w$ equalled 21 mm Hg. Therefore, the apparent value of the FFR related to stenosis A [FFR$_{A(app)}$] is $98/112=0.88$, but equation 3 predicts that its true value must be lower (ie, 0.74 in this case).

C, After PTCA of stenosis B, the distal gradient $\Delta P(B)$ has decreased from 47 to 15 mm Hg, and, as blood flow through the artery has increased, the proximal gradient $\Delta P(A)$ has increased from 14 to 27 mm Hg, unmasking the true severity of stenosis A. The value of FFR(A) derived from this tracing is 0.75 and is very close to its predicted value (0.74). During PTCA, a small dissection occurred in the proximal part of the right coronary artery; this did not obstruct flow. Panel D shows the final pull-back curve after stenting both lesions. Almost no residual gradient is present across stenosis B, and a residual gradient of 11 mm Hg remains present across the proximal stent. Final FFR of the myocardium supplied by the right coronary artery has increased from 0.46 to 0.84 (moderate result).

**Discussion**

In patients with multiple stenoses within the same coronary artery, coronary pressure measurements made using a pressure guidewire can uniquely determine the separate hemodynamic effects of the individual stenoses in sequence. For clinical practice, a pull-back pressure recording at maximum hyperemia provides important information during an interventional procedure, which can help objectively select which of several stenoses is most appropriate for PTCA. This
information will also allow clinicians to avoid performing unnecessary procedures that increase the risk of restenosis without a hemodynamic benefit. The pull-back pressure recording can be repeated during the procedure to evaluate the result of what has been done already and what should still be done.

From a practical point of view, the FFR corresponding to all abnormalities summed together is still given at every step by the simple ratio of hyperemic pressure (measured most distally in the coronary artery) to aortic pressure \( FFR(A + B) \); see Figure 2. As a matter of fact, this ratio is the best one to determine if ischemia may be inducible. However, it is conceptually important to realize that one stenosis influences the hemodynamic effects of another in a sequence that may result in a mutual underestimation of the severity of each unless stenosis interaction is accounted for.

Figure 4. Case of a 68-year-old woman with 2 sequential stenoses in the proximal left anterior descending artery (A). B, The pressure wire is positioned in the distal part of the vessel and slowly pulled back to the ostium of the left anterior descending artery during sustained hyperemia. The locations and respective pressure drops at the sites of the stenoses are easily identified (arrows). After stenting the proximal stenosis, a similar pull-back curve is made (C). The gradient across stenosis A has completely disappeared and, as a result, the gradient across stenosis B has increased from 12 to 17 mm Hg. Panel D shows the pull-back curve after stenting both stenoses. Almost no hyperemic gradient is present, and the FFR has increased to 0.97 (excellent result).
This overestimation of FFR or underestimation of stenosis severity is more pronounced for the proximal lesion than for the distal lesion, as shown in Table 2. Moreover, this underestimation of severity is expected to be more pronounced when the other stenosis in sequence is more severe or when collateral flow is higher, as reflected by a higher wedge pressure in relation to aortic pressure.

This influence of $P_w$ can be explained as follows. Myocardial blood flow is composed of coronary arterial and collateral blood flow. As previously determined, the coronary arterial contribution to maximum myocardial blood flow is determined by coronary FFR, which can be calculated by the ratio $(P_a - P_r)/(P_a - P_w)$. Therefore, in the presence of a particular $P_a$ and a high $P_w$, the given value of $P_d$ indicates a lower coronary FFR than would be the case when $P_w$ is low.

With a high $P_w$, a large component of myocardial FFR is due to fractional collateral flow; with a low $P_w$, a large component is due to coronary arterial flow. Therefore, the relative percent increase in coronary arterial contribution after the elimination of one stenosis is larger with a high $P_w$; this explains the importance of $P_w$ in the equations. This issue was discussed more extensively and derived and quantitated mathematically in the animal validation study.

In a patient with a normal side branch between sequential stenoses (a situation excluded in this study), flow through the distal stenosis could be reduced by diverting flow to the normal, low-resistance branch during hyperemia. This phenomenon has been called “branch steal”; its quantification requires pressure and flow measurement or quantitative arteriographic analysis of the entire coronary tree.

**Clinical Implications**

This study indicates the usefulness of coronary pressure measurement, especially the pull-back pressure recording along the length of a coronary artery during sustained hyperemia, for evaluating the individual hemodynamic effects of each of several sequential stenoses within the same coronary artery. It is important to select the most appropriate lesion for PTCA and to evaluate the results of PTCA or stenting at the different locations. Coronary pressure measurements are unique in this way for assessing the separate hemodynamic effects of different sequential stenoses within 1 vessel.

The study also provides awareness that the presence of one stenosis in a coronary artery influences the hemodynamic appearance of the other and, consequently, that treating one lesion will unmask the true severity of the second. As shown in this study, it is possible to calculate this effect quantitatively by measuring pressures at the relevant sites within the artery and using appropriate equations. This observation also indicates the error in the simple clinical precept that coronary hemodynamics are determined by the most severe lesion in a coronary artery. Not infrequently, after anatomically successful stenting, a considerable hyperemic pressure gradient may remain within the artery. This does not always indicate suboptimum stent deployment; instead, this may be due to more proximal or distal plaques or unrecognized diffuse disease that seemed to be insignificant before the intervention but the effects of which have been unmasked by the increased maximum flow after the successful elimination of one stenosis.

Another important implication is the risk of underestimating functional stenosis severity when large guiding catheters (8 or 9 French) are used. These large guiding catheters often act as an artificial stenosis proximal to the target lesion. In such situations, maximum coronary blood flow will not be as high as it could be without that guiding catheter. Consequently, the severity of the target lesion downstream is underestimated, as reflected by an overestimation of FFR or an underestimation of coronary flow reserve. Therefore, for physiological measurement in coronary arteries, the use of 6 or 7-French guiding catheters without side holes is preferable.

Finally, this study corroborates the fundamental physical principles underlying the concept of FFR, ie, that during maximum vasodilation the distribution of flow in the coronary circulation can be completely determined by coronary pressure measurements. Thus, FFR is a practical tool to guide interventional decisions in the catheterization laboratory.

**Limitations**

This study has also some limitations. First, $P_w$ must be measured; it cannot be estimated because it varies widely in patients with chronic coronary artery disease due to variable collateral development. Therefore, such exact quantifi-
calculation of the mutual influence of one lesion on another can only be applied during coronary interventions. Practically speaking, one must commit to dilating one lesion for complete evaluation of the other; this decision is justified if FFR(A + B) is <0.75. Moreover, in contrast to the simple calculation of FFR in single isolated stenosis, the calculations in this study for sequential stenoses are more complex and depend on obtaining an accurate measurement of all relevant pressures. Therefore, a stable pressure sensor with no drift during the procedure is mandatory, because small mistakes in the pressure recordings can have profound effects on predicted FFR. Finally, as was already discussed, a large side branch between both stenoses may modify the mutual hemodynamic influence of one stenosis on the other.

Despite these limitations, the interventional operator will obtain valuable semiquantitative information on the relative severity of multiple stenoses and/or diffuse disease by recording pull-back pressures along the length of the coronary artery during hyperemia before and after the PTCA of each of several sequential stenoses, as was validated in this clinical study.

**Conclusions**

This study demonstrates that in patients who have multiple stenoses in the same coronary artery, the hemodynamic appearance of each stenosis and the potential benefit of PTCA is influenced by the presence of the second stenosis. These effects can be assessed qualitatively in a simple, practical way by pull-back coronary pressure recordings along the length of a coronary artery during maximum hyperemia before and after the PTCA of each of several sequential stenoses, as was validated in this clinical study.

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