

Pressure-Derived Fractional Flow Reserve to Assess Serial Epicardial Stenoses

Theoretical Basis and Animal Validation

Bernard De Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD; Guy R. Heyndrickx, MD, PhD; Dominique Hodeige, MD; Richard Kirkeeide, PhD; K. Lance Gould, MD

Background—Fractional flow reserve (FFR) is an index of stenosis severity validated for isolated stenoses. This study develops the theoretical basis and experimentally validates equations for predicting FFR of sequential stenoses separately.

Methods and Results—For 2 stenoses in series, equations were derived to predict FFR (FFR_{pred}) of each stenosis separately (ie, as if the other one were removed) from arterial pressure (P_a), pressure between the 2 stenoses (P_m), distal coronary pressure (P_d), and coronary occlusive pressure (P_w). In 5 dogs with 2 stenoses of varying severity in the left circumflex coronary artery, FFR_{pred} was compared with FFR_{app} (ratio of the pressure just distal to that just proximal to each stenoses) and to FFR_{true} (ratio of the pressures distal to proximal to each stenosis but after removal of the other one) in case of fixed distal and varying proximal stenoses ($n=15$) and in case of fixed proximal and varying distal stenoses ($n=20$). The overestimation of FFR_{true} by FFR_{app} was larger than that of FFR_{true} by FFR_{pred} (0.070 ± 0.007 versus 0.029 ± 0.004 , $P<0.01$ for fixed distal stenoses, and 0.114 ± 0.01 versus 0.036 ± 0.004 , $P<0.01$ for fixed proximal stenoses). This overestimation of FFR_{true} by FFR_{app} was larger for fixed proximal than for fixed distal stenoses.

Conclusions—The interaction between 2 stenoses is such that FFR of each lesion separately cannot be calculated by the equation for isolated stenoses (P_d/P_a during hyperemia) applied to each separately but can be predicted by more complete equations taking into account P_a , P_m , P_d , and P_w . (*Circulation*. 2000;101:1840-1847.)

Key Words: flow reserve ■ stenosis

Coronary pressure-derived fractional flow reserve (FFR) is a measure of coronary stenosis severity. FFR is the ratio of hyperemic myocardial blood flow in the presence of a stenosis to hyperemic flow in the absence of stenosis. Stated another way, FFR is the fraction of hyperemic flow that is preserved despite the presence of a stenosis in the epicardial coronary artery. This ratio of hyperemic flows with and without a single stenosis can be derived from the ratio of mean distal coronary pressure (P_d) to mean aortic pressure (P_a) recorded simultaneously under conditions of maximum hyperemia.^{1,2} FFR has been shown to be valid in patients with stable angina pectoris under widely varying hemodynamic conditions^{3,4} and to be clinically useful for diagnostic and interventional purposes.⁵⁻¹⁴

In humans, however, coronary atherosclerosis is diffuse, and coronary arteriograms frequently demonstrate several consecutive stenoses along the same epicardial artery, the

severities of which need to be determined separately. In case of 2 consecutive stenoses, the fluid dynamic interaction between the stenoses alters their relative severity and complicates determination of FFR for each stenosis separately from the simple ratio of P_d/P_a for a single stenosis. Consequently, for stenoses in series, FFR determined by this simple ratio for a single stenosis may not predict to what extent a proximal lesion will influence myocardial flow after complete relief of the distal stenosis, and vice versa.

Therefore, in the present study, theoretical equations were developed for 2 serial stenoses to predict the FFR of each stenosis separately as if the other stenosis were absent. In addition, an animal model of sequential stenoses was used to validate these theoretical equations for determining FFR of each of 2 serial stenoses with direct clinical applicability.

Received June 10, 1999; revision received November 5, 1999; accepted November 15, 1999.

From the Cardiovascular Center, Aalst, Belgium; Department of Cardiology, Catharina Hospital and Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands; Department of Physiology, University of Louvain, Brussels, Belgium; and the Weatherhead PET Center for Preventing and Reversing Atherosclerosis, Department of Medicine, University of Texas Medical School, Houston.

Dr K. Lance Gould is the Martin Bucksbaum Distinguished Professor and Director of the Weatherhead PET Center for Preventing and Reversing Atherosclerosis.

Guest Editor for this article was Morton J. Kern, MD, St Louis University Health Sciences Center, St Louis, Mo.

Correspondence to Bernard De Bruyne, MD, PhD, O.L.V.-Hospital, Cardiovascular Center, 164, Moorselbaan, 9300 Aalst, Belgium. E-mail bernard.de.bruyne@olvz-aalst.be

© 2000 American Heart Association, Inc.

Circulation is available at <http://www.circulationaha.org>

Methods

Mathematical Model

As illustrated in Figure 1, P_a is the pressure proximal to the first stenosis, P_m is the pressure between the two stenoses, and P_d is the pressure distal to the second stenosis. For simplicity, it is assumed that the resistances of the microvasculature are minimal and that the central venous pressure (P_c) is close to zero.

Superficially, the apparent FFR of A and B (FFR_{app}) can be calculated by dividing the pressure distal to stenosis A or B by the pressure proximal to stenosis A or B, respectively, as follows:

$$(1) \quad FFR(A)_{app} = P_m / P_a$$

and

$$(2) \quad FFR(B)_{app} = P_d / P_m.$$

However, fluid dynamics theory suggests that the FFR of proximal stenosis A is influenced by the presence of stenosis B and vice versa. In that case, the FFR of stenosis B is influenced by the presence of stenosis A, because hyperemic flow through 1 stenosis is limited by the presence of the other stenosis. As described in the Appendix, the predicted FFR of the proximal stenosis (A) and of the distal lesion (B) as if the other stenosis were hypothetically absent can be calculated by the following equations:

$$(3) \quad FFR(A)_{pred} = \frac{P_d - (P_m / P_a) P_w}{P_a - P_m + P_d - P_w}$$

and

$$(4) \quad FFR(B)_{pred} = 1 - \frac{(P_a - P_w)(P_m - P_d)}{P_a(P_m - P_w)}.$$

These predicted values of FFR (FFR_{pred}) as if the other stenosis were hypothetically absent can then be compared with the true FFR (FFR_{true}) determined for each stenosis when the other one was actually physically removed in the animal model.

When stenosis B is actually physically absent, the actual FFR of stenosis A [$FFR(A)_{true}$], and when stenosis A is actually physically absent, the actual FFR of stenosis B [$FFR(B)_{true}$] can be calculated as follows:

$$(5) \quad FFR(A)_{true} = P_d / P_a$$

and

$$(6) \quad FFR(B)_{true} = P_d / P_a.$$

Animal Instrumentation

After premedication with 0.1 mg fentanyl, 5.0 mg droperidol, and 0.5 mg atropine IM, 5 mongrel dogs (weight 38 to 43 kg) were anesthetized with 7 mg/kg IV sodium thiopental, intubated, and ventilated with oxygen-enriched air with a respirator (Dräger Spiromat 650). General anesthesia was sustained with isoflurane gas (1.5% to 2 vol%). A left thoracotomy was carried out in the fifth intercostal space, and the pericardium was incised. The proximal left circumflex artery was dissected free. A perivascular ring-mounted 20-MHz pulsed-Doppler transducer (Triton) was placed around the artery, and 2 circular hydraulic cuff occluders (In Vivo Metric) were implanted just distal to the Doppler probe and 2 to 3 cm more distal, respectively. The occluders were placed so that there was no arterial branch between the stenoses. A femoral artery was dissected free, and a 6F Amplatz coronary guiding catheter was introduced into the right femoral artery and advanced under fluoroscopy into the ostium of the left main coronary artery. Through this guiding catheter, two 0.014-in sensor-tipped high-fidelity pressure guidewires (Pressure Wire, Radi Medical System) were advanced and positioned distal to the locations of the first and second balloon occluder, respectively. ECG, phasic and mean coronary flow velocity signal, phasic and mean arterial pressure (P_a), and phasic and mean coronary pressures recorded by both pressure guidewires (P_m and P_d , respectively) were recorded continuously on an 8-channel

recorder (Gould ES 1000) and stored digitally on a computer system (Notocord), which allowed offline analysis of all signals. After completion of the surgical preparation, the animals were allowed to stabilize for 30 minutes before the study protocol was begun. The investigations conformed to the guidelines of the committee for animal research of the Belgian Fonds de la Recherche Scientifique Médicale.

Experimental Protocol

At first, maximum hyperemia was induced by continuous intravenous infusion of adenosine, from 150 to 300 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After a steady-state hyperemia had been achieved, a 20-second occlusion of the coronary artery was performed by inflation of the proximal occluder to determine coronary wedge pressure (P_w) and to verify that no additional, postocclusion hyperemia could be elicited. In 1 dog, no maximum hyperemia could be achieved by adenosine, and an additional infusion of dobutamine 20 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ was started to further increase blood flow until the presence of a steady-state maximum hyperemia was confirmed as described above. Next, phasic and mean pressures were recorded by the guiding catheter (P_a) and by both pressure guidewires (P_m , coronary pressure between both occluders, and P_d , coronary pressure distal to the distal occluder). Thereafter, different degrees of proximal and distal stenosis were induced, as follows: at first, a mild stenosis was induced by the proximal occluder (stenosis A in Figure 1), guided by the pressure signal. Whereas this proximal stenosis remained constant, the distal occluder was inflated to create mild, moderate, severe, and very severe stenoses, respectively, guided by the pressure signals. It was aimed at inducing the stenosis in such a way that the classifications mild, moderate, severe, and very severe corresponded to transstenotic hyperemic gradients of $\approx 25\%$, 50%, 75%, and 90% of the pressure gradient as observed at total coronary occlusion. Stenoses with a pressure gradient of < 5 mm Hg were avoided. Next, all stenoses were relieved, and after all signals had stabilized again, a moderate stenosis was induced in the proximal occluder, followed by the same sequence of distal stenoses as described above. This sequence of induction of different distal stenoses was repeated for a severe and finally for a very severe proximal stenosis. After this first series, P_w as well as the presence of ongoing maximum hyperemia was checked again, and the second series of the sequences was started. This time, at first a mild stenosis was induced by the distal occluder (stenosis B in Figure 1), after which the proximal lesion was varied stepwise from mild to moderate to severe and to very severe. After release of all stenoses, this was repeated for a fixed moderate, severe, and very severe proximal lesion, respectively. Figure 2 illustrates these pressure tracings.

Data Processing and Statistical Analysis

To investigate the influence of a stenosis B on a given stenosis A, 71 combinations of a fixed stenosis A and a variable stenosis B were obtained. For each of these combinations, $FFR(A)_{app}$ and $FFR(A)_{pred}$ were compared with $FFR(A)_{true}$ by linear regression analysis. To investigate the influence of a stenosis A on a given stenosis B, 84 combinations of a fixed stenosis B and a variable stenosis A were created. For each of these combinations, $FFR(B)_{app}$ and $FFR(B)_{pred}$ were compared with $FFR(B)_{true}$ by linear regression analysis. For each comparison, a Bland-Altman plot was given.¹⁵ Paired t tests and χ^2 tests were used when appropriate. Values of $P > 0.05$ were considered nonsignificant.

Results

Baseline Hemodynamics

Mean aortic pressure was 88 ± 21 mm Hg (range 71 to 125 mm Hg), and heart rate was 71 ± 14 bpm (range 64 to 129 bpm) at rest. Mean blood pressure decreased significantly to 78 ± 19 mm Hg (range 63 to 118 mm Hg) and heart rate increased significantly to 125 ± 26 bpm (range 76 to 158 bpm) during postocclusion hyperemia. Yet, during pharmacologi-

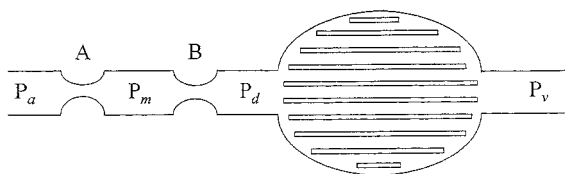


Figure 1. Schematic of experimental setting. Epicardial vessel (with 2 stenoses, A and B, induced by pneumatic occluders) and its depending myocardial bed. P_a indicates arterial pressure, ie, pressure recorded proximal to stenosis A by guiding catheter; P_m , pressure between stenosis A and stenosis B recorded by pressure-monitoring 0.014-in guidewire; P_d , pressure distal to stenosis B measured by a second pressure-monitoring guidewire; and P_v , central venous pressure.

cally induced hyperemia, mean pressure and heart rate remained unchanged throughout the experiments in each dog. The ratio of postocclusion to pharmacologically induced hyperemic blood flow velocities was 1.12 ± 0.14 (range 0.98 to 1.25), suggesting that the dosages of adenosine used in each animal induced maximum arteriolar vasodilation.

Relation Between FFR_{true} and FFR_{app}

A total of 15 distal stenoses (stenoses B) were created. For each of them, a mean of 4.7 proximal stenoses (stenoses A) were superimposed to test their influence on the calculation of FFR on stenosis B. Figure 3A shows, in the 71 combinations of stenoses (variable stenosis A and fixed stenosis B) analyzed in all animals, the plots of the relation between the FFR of lesion B alone [$FFR(B)_{true}$] versus the apparent value of FFR [$FFR(B)_{app}$] of the same lesion B when a progressively increasing level of stenosis A is created upstream. A large scatter is observed in the plot of the relationship between $FFR(B)_{true}$ and $FFR(B)_{app}$. As expected from the theory, the corresponding Bland-Altman plot (Figure 3B) shows that $FFR(B)_{app}$ systematically overestimates $FFR(B)_{true}$ and that there is an inverse correlation between this overestimation and $FFR(B)_{true}$ ($r = -0.39$, $P < 0.01$).

Similarly, a total of 20 proximal stenoses (stenoses A) were created. For each of those, a mean of 4.2 distal stenoses (stenoses B) were created to test their influence on the calculation of FFR on stenosis A. Figure 3C shows, in the 84 combinations of stenoses (fixed stenosis A and variable stenosis B) analyzed in all animals, the plots of the relation between the FFR of lesion A alone [$FFR(A)_{true}$] versus the apparent value of FFR [$FFR(A)_{app}$] of the same lesion A when a progressively increasing level of stenosis B is created downstream. The corresponding Bland-Altman plot (Figure 3D) shows that $FFR(A)_{app}$ significantly overestimates $FFR(A)_{true}$ and that there is an inverse correlation between this overestimation and $FFR(A)_{true}$ ($r = -0.62$, $P < 0.01$).

Relation Between FFR_{true} and FFR_{pred}

In investigating the influence of a varying stenosis A on a given, fixed, stenosis B, a close correlation was found between $FFR(B)_{true}$ and $FFR(B)_{pred}$ ($r^2 = 0.95$, Figure 4A). The Bland-Altman plot (Figure 4B) shows a small mean difference ($+0.03 \pm 0.04$) without systematic overestimation or underestimation of $FFR(B)_{true}$ by $FFR(B)_{pred}$. In investigation of the influence of a varying stenosis B on a given fixed

stenosis A, a close correlation ($r^2 = 0.95$) was found between $FFR(A)_{true}$ and $FFR(A)_{pred}$ (Figure 4C). The Bland-Altman plot (Figure 4D) indicates a small overestimation ($+0.040 \pm 0.066$).

Relation Between P_w and FFR_{app} Versus FFR_{pred}

No relationship was found between the level of coronary occlusive pressure (wedge pressure, P_w) and the accuracy of FFR_{app} versus FFR_{pred} in determining FFR_{true} .

Accuracy of FFR_{app} and FFR_{pred} in Determining FFR_{true}

Figure 5 depicts the absolute difference between FFR_{app} and FFR_{true} and between FFR_{pred} and FFR_{true} in the 2 experimental settings as described above, ie, fixed stenosis B and varying stenosis A (left) and fixed stenosis A and varying stenosis B (right). In both settings, the overestimation or underestimation of FFR_{true} by FFR_{pred} is significantly smaller than the corresponding overestimation or underestimation of FFR_{true} by FFR_{app} . For a fixed stenosis B, the absolute error in FFR was >0.1 in 22% of measurements for $FFR(B)_{app}$ and in 5% of measurements for $FFR(B)_{pred}$ ($P < 0.01$). For a fixed stenosis A, the absolute error in FFR was >0.1 in 45% of the measurements of $FFR(A)_{app}$ and 9% of measurements for $FFR(A)_{pred}$ ($P < 0.01$). The error in calculating FFR for a stenosis by use of the simple P_d/P_a ratio (FFR_{app}) was significantly larger in the presence of a second more proximal stenosis than for a second more distal stenosis. The greatest errors in FFR_{app} were found for milder downstream stenoses when the upstream stenosis was more severe.

Discussion

For serial epicardial stenoses without intervening arterial branches, the equation of FFR (P_d/P_a , when central venous pressure is neglected) remains valid for determining the hemodynamic consequences of both stenoses together. However, the present study confirms that this simple ratio cannot be applied to predict the FFR of each stenosis separately as if the other were removed. In contrast, the individual FFR of each stenosis separately can be predicted by different equations from P_a , pressure between the 2 stenoses (P_m), P_d , and P_w recorded during maximum hyperemia. The data also suggest that FFR calculated as the P_d/P_a ratio for the stenosis has a greater error in the presence of a second distal stenosis than in the presence of a second proximal lesion.

Importance of Maximum Transstenotic Flow

Pressure-derived FFR is defined as the ratio of hyperemic flow in a stenotic territory expressed as a fraction of what it would be in the hypothetical case that the epicardial stenosis were absent. This ratio of 2 flows can be derived, during maximum hyperemia, from the ratio of their respective driving pressures. An essential prerequisite for the calculation of pressure-derived FFR is the achievement of maximum transstenotic flow. When only 1 discrete stenosis is present, pharmacologically induced microvascular vasodilation will lead to maximum transstenotic flow for a given lesion in a given patient. For that reason, FFR tells us exactly to what extent hyperemic flow is limited by the presence of an

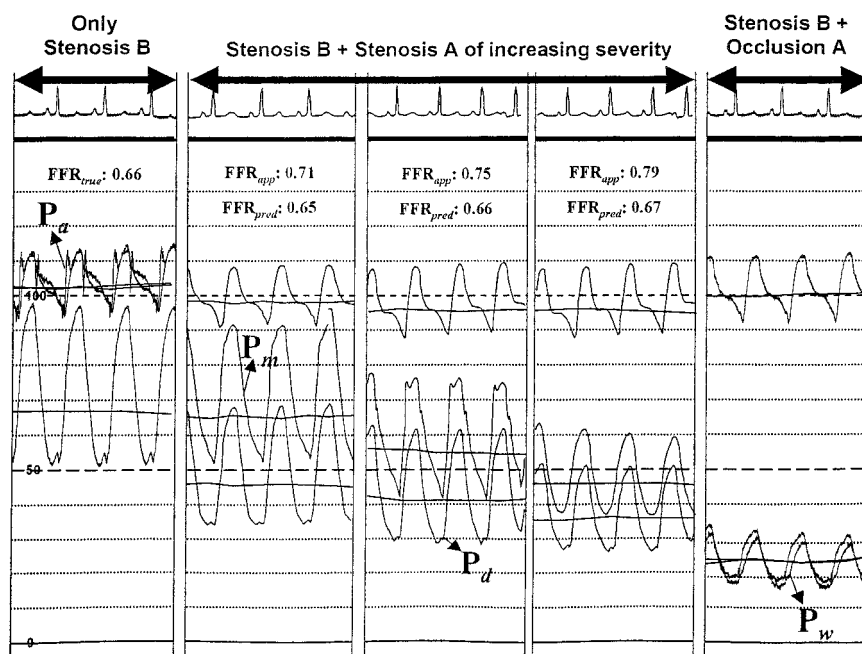
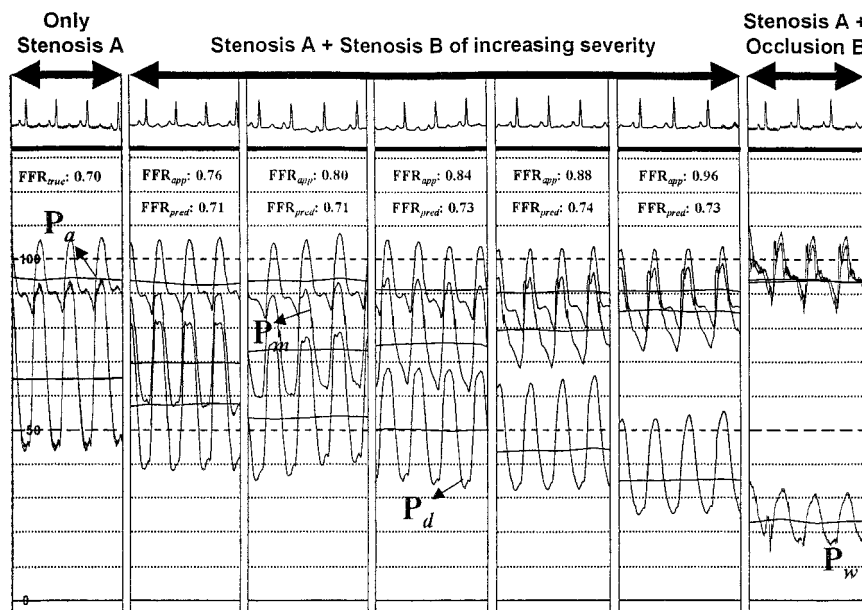


Figure 2. Example of hyperemic pressure tracings obtained in dog 4. Top, Influence of a varying distal stenosis B on a fixed proximal stenosis A. Bottom, Influence of a varying proximal stenosis A on a fixed distal stenosis B. In both examples, FFR_{pred} remains very close to FFR_{true} , whereas FFR_{app} progressively diverges from FFR_{true} as other stenosis tightens.

epicardial stenosis and, conversely, to what extent hyperemic flow will increase after the conductance of the epicardial vessel is restored.

In contrast, when a second stenosis is present along the same epicardial vessel, flow through 1 stenosis will be submaximal because of the second stenosis, even during vasodilation of the microvasculature. The extent to which both stenoses influence each other is unpredictable from the simple ratio of the pressures distal and proximal to each individual stenosis.

Importance of Collateral Flow

In patients with severe coronary artery disease, myocardial perfusion depends both on antegrade flow through the stenotic epicardial artery and on collateral flow. A >2-fold

increase of myocardial perfusion can be provided solely by collaterals.¹⁶ Myocardial FFR takes into account the contribution of collateral circulation to hyperemic myocardial flow, because the distal coronary pressure is determined by aortic pressure and by the extent of collateral circulation in case of isolated epicardial stenosis. Measurements of P_w obtained during coronary occlusion determine the separate contributions of antegrade flow and of collateral flow to total hyperemic myocardial perfusion.¹ In case of multiple stenoses along the same coronary artery, collateral flow will influence both P_w and P_m . The extent to which collateral flow will influence P_m depends on the severity of the second stenosis. Therefore, the value of P_w cannot be neglected and was incorporated into the equations derived in the Appendix.

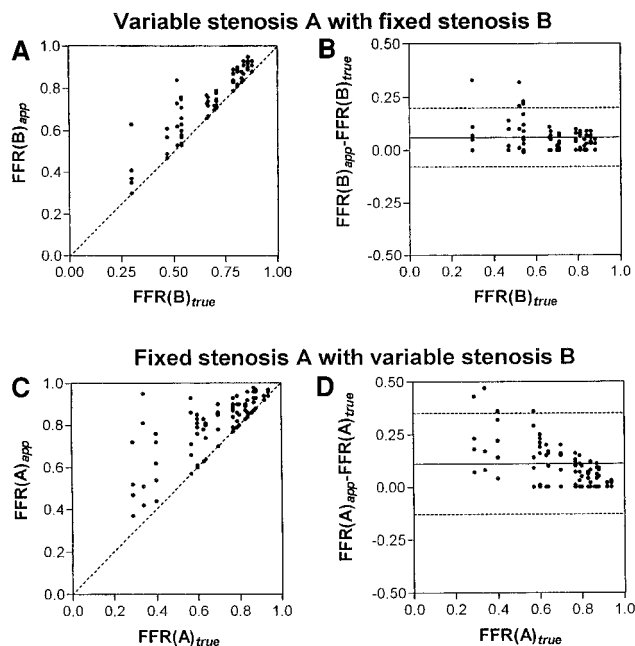


Figure 3. Plots of values of FFR_{app} vs FFR_{true} in cases of fixed distal stenosis and variable proximal stenosis (A) and corresponding Bland-Altman plot (B). Plots of values of FFR_{app} vs FFR_{true} in case of fixed proximal stenosis and variable distal stenosis (C) and corresponding Bland-Altman plot (D).

Clinical Implications

Because coronary atherosclerosis is commonly diffuse, the occurrence of ≥ 2 stenoses in 1 epicardial vessel is frequent. Determining the independent contribution of each stenosis to the total decrease in conductance of the epicardial vessel may be useful for clinical decision-making. With the pressure-measuring guidewire,^{17,18} it is common to measure a significant residual hyperemic pressure gradient after optimal stenting of a stenosis. This residual pressure gradient is commonly a result of another proximal or distal stenosis, the severity of which was unmasked by elimination of the resistance of the stented segment. Objective quantification of the functional significance of a stenosis of undetermined severity at angiography may help in guiding the intervention. In investigation of 1 stenosis out of several in series by pressure measurements before an intervention, the worst stenosis, as indicated by the largest pressure drop during hyperemia, may not occur where it would have been expected from angiography. In that case, the equations for FFR_{pred} can be applied to each stenosis rather than the simple ratio P_d/P_a being applied to each stenosis to determine the severity of each. In clinical practice, the measurements of P_a , P_m , and P_d can be obtained during a simple pullback of the pressure sensor from the distal to the proximal part of the vessel under maximum hyperemia.

Limitations

These experimental data should be extrapolated to humans with caution. First, the collateral circulation in humans with chronic coronary artery disease is most likely more developed than in a canine model. Therefore, in humans, the influence of P_w is probably more pronounced than in the present study and

must be included in the equations for FFR in case of serial stenoses.

Second, P_w can be obtained only during balloon coronary occlusion, which constitutes a practical limitation.

Third, when 1 stenosis is very tight, so that the pressure distal to that stenosis is very close to P_w , very small inaccuracies in measuring P_w might induce large errors in FFR_{pred} . However, this limitation is somewhat academic, because a very tight stenosis will be dilated anyway, and the second stenosis will be evaluated after treatment of the first stenosis.

Finally, for the 2 stenosis equations to be applicable, there should be no major arterial branch between the 2 stenoses being investigated. If there is an arterial branch between the 2 stenoses, the nonstenotic low-resistance branch increases flow through the first stenosis, thereby causing a greater pressure drop across the first stenosis than would occur without the intervening arterial branch. With a lower pressure between the stenoses, flow through the distal stenosis would be reduced in the presence of an arterial branch compared with that without the side branch. Thus, the side branch between the stenoses would divert a "steal" flow away from the second stenosis, so that the flow through the second stenosis would not be maximal. The pressure gradient across the second stenosis would therefore be less than it would have been in the absence of the side branch. Because the flow through the second stenosis would be reduced in the presence of a side branch, removal of the distal stenosis would result in only limited increased flow capacity through the first stenosis.

With several serial stenoses and intervening branches, this phenomenon of "branch steal"¹⁹ cumulatively along the length of a branching coronary artery may cause a fall in flow at the apex to below normal resting flow after dipyridamole, with resulting ischemia. In diffuse coronary artery disease, this phenomenon is seen as a longitudinal base-to-apex perfusion gradient on dipyridamole PET perfusion imaging.¹⁹ For multiple stenoses or diffuse disease with intervening arterial branches, calculation of flow reserve (or FFR) at each branch point becomes complex and requires fully developed fluid dynamics equations accounting for the myocardial mass supplied by each branch as described previously. For these complex branch-stenosis interactions, both pressure and flow velocity measurements may be necessary for assessing the functional severity of multiple stenoses and/or diffuse disease.

Conclusions

The present study demonstrates for interventionalists that for multiple stenoses in the same vessel, the hemodynamic assessment of 1 stenosis and the potential benefit of angioplasty is significantly influenced by the presence of the second stenosis. The practical clinical application of these new concepts for interventional decisions in patients with multiple stenoses and diffuse disease are now being studied.

Appendix

In this Appendix, the equations for predicting myocardial FFR of each of 2 sequential stenoses as if the other stenosis were removed will be derived mathematically from the initially measured pressures

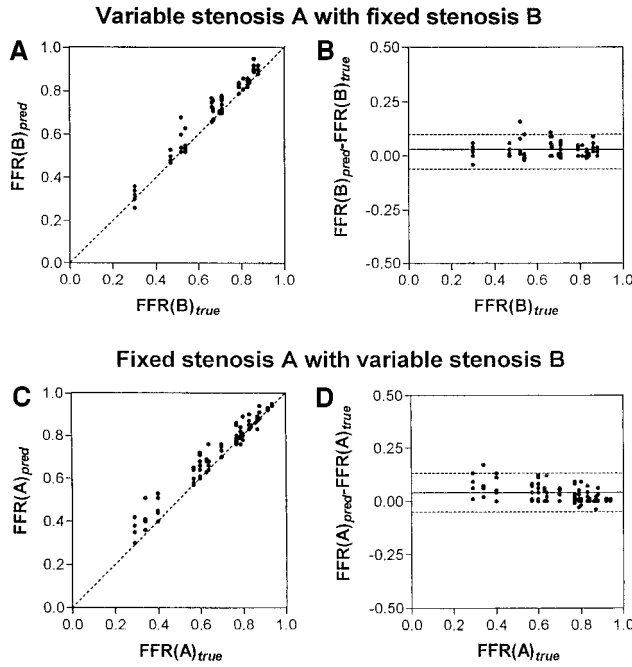


Figure 4. Plots of values of FFR_{pred} vs FFR_{true} in case of fixed distal stenosis and variable proximal stenosis (A) and corresponding Bland-Altman plot (B). Plots of values of FFR_{pred} vs FFR_{true} in case of fixed proximal stenosis and variable distal stenosis (C) and corresponding Bland-Altman plot (D).

P_a , P_m , P_d , and P_w . These predicted values of myocardial FFR are called $FFR(A)_{pred}$ and $FFR(B)_{pred}$ for the proximal (A) and distal (B) stenoses, respectively. The terminology is consistent with the original article on the concept of FFR^1 and is further clarified in Figure 1: P_a , P_m , P_d , and P_w indicate mean aortic pressure, coronary pressure between the 2 stenoses, coronary pressure distal to the second stenosis, and coronary wedge pressure (distal coronary pressure during total coronary occlusion) at that particular P_a , all measured at maximum coronary hyperemia before any intervention. P'_a , P'_m , P'_d , and P'_w indicate the corresponding pressures after 1 of the 2 lesions has been completely removed.

After the proximal stenosis A has been removed, P'_m equals P'_a , and after the distal stenosis B has been removed, P'_m equals P'_d . True measured FFR of 1 stenosis after physical removal of the other stenosis in the animal model is indicated by $FFR(A)_{true}$ and $FFR(B)_{true}$, respectively, and is equal to P'_d/P'_a . $\Delta P(A)$ and $\Delta P(B)$ indicate the hyperemic pressure gradients across stenoses A and B, respectively, before any intervention, and $\Delta P'(A)$ and $\Delta P'(B)$ represent the same gradients after elimination of stenoses B and A, respectively.

Q_{cor} and Q'_{cor} indicate maximum coronary blood flow before and after elimination of 1 or both stenoses, and Q^N_{cor} and $Q^{N'}_{cor}$ indicate

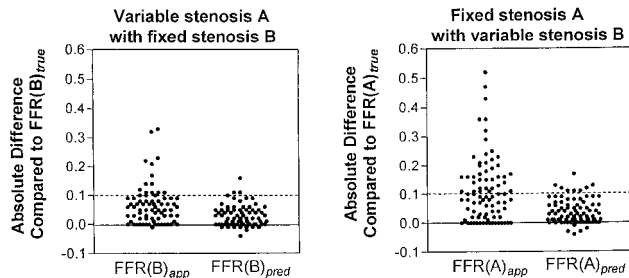


Figure 5. Column scatter of differences between FFR_{true} vs FFR_{app} and FFR_{pred} in case of fixed distal stenosis and variable proximal stenosis (A) and in case of fixed proximal stenosis and variable distal stenosis (B).

the normal values of Q_{cor} and Q'_{cor} , respectively (ie, those values if no stenosis were present). FFR_{cor} and FFR'_{cor} indicate FFR of the coronary artery before and after elimination of 1 of the 2 stenoses.

Influence of Removal of Distal Stenosis B on Hemodynamics of Proximal Stenosis A

Suppose that stenosis B is eliminated. In that case, $P'_m = P'_d$ and $FFR(A)_{true}$ equals P'_m/P'_a or P'_d/P'_a .

How to predict $FFR(A)_{true}$ from P_a , P_m , P_d , and P_w ?

Because all measurements are performed at maximum vasodilation of the coronary circulation, the resistances are constant, and therefore

$$\begin{aligned} \frac{Q'_{cor}}{Q_{cor}} &= \frac{Q'_{cor}}{Q^N_{cor}} \cdot \frac{Q^N_{cor}}{Q_{cor}} \\ &= FFR'_{cor} \cdot \frac{Q^N_{cor}}{Q_{cor}} \cdot \frac{1}{FFR_{cor}} \\ &= \frac{P'_d - P'_w}{P'_a - P'_w} \cdot \frac{P_a - P'_w}{P_a - P_w} \cdot \frac{P_a - P_w}{P_d - P_w} \\ &= \frac{P'_d - P'_w}{P_d - P_w} \\ &= \frac{P'_m - P'_w}{P_d - P_w} \end{aligned}$$

Because the hyperemic gradient across stenosis A is assumed to be proportional to blood flow, this also means that

$$\frac{\Delta P'(A)}{\Delta P(A)} = \frac{Q'_{cor}}{Q_{cor}} = \frac{P'_m - P'_w}{P_d - P_w},$$

$$\text{or} \quad \frac{P'_a - P'_m}{P_a - P_m} = \frac{P'_m - P'_w}{P_d - P_w},$$

$$\text{or} \quad (P'_a - P'_m) \cdot (P_d - P_w) = (P_a - P_m) \cdot (P'_m - P'_w),$$

$$\text{or} \quad P'_a P_d - P'_a P_w - P'_m P_d + P'_m P_w = P_a P'_m - P_a P'_w - P_m P'_m + P_m P'_w.$$

It has been proved theoretically and validated experimentally¹ that $P_w/P_a = P'_w/P'_a$. Therefore, $P_w P'_a = P'_w P_a$, and those terms can be cancelled in the expression above.

By rearrangement of the remaining terms, the following equation is obtained:

$$P'_m(P_a - P_m + P_d - P_w) = P'_a P_d - P_m P'_w.$$

Division of both the right and left terms by P'_a gives

$$\frac{P'_m}{P'_a} \cdot (P_a - P_m + P_d - P_w) = P_d - \left(\frac{P_m}{P'_a}\right) P'_w = P_d - \left(\frac{P_m}{P_a}\right) P_w,$$

and therefore,

$$FFR(A)_{pred} = \frac{P_d - (P_m/P_a) P_w}{P_a - P_m + P_d - P_w}.$$

The correctness of this equation can be verified by substitution of the boundary values of the respective pressures and verification if $FFR(A)$ is obtained:

(a) No proximal stenosis: $P_a = P_m$.

$$\text{In that case, } FFR(A)_{pred} = \frac{P_d - P_w}{P_d - P_w} = 1 = FFR(A),$$

(b) No distal stenosis: $P_m = P_d$.

$$\text{In that case, } FFR(A)_{pred} = \frac{P_m - \left(\frac{P_m}{P_a}\right) P_w}{P_a - P_w}$$

$$\begin{aligned} &= \frac{P_a P_m - P_w P_m}{P_a (P_a - P_w)} \\ &= \frac{P_m (P_a - P_w)}{P_a (P_a - P_w)} \\ &= \frac{P_m}{P_a} = \frac{P_d}{P_a} = \text{FFR}(A). \end{aligned}$$

(c) No collaterals: $P_w=0$.

In that case, $\text{FFR}(A)_{\text{pred}} = \frac{P_d}{P_a - P_m + P_d}$.

This latter equation has been erroneously claimed to represent $\text{FFR}(A)$, but it holds true only in the simplified case that collateral flow is neglected.

Note: This emphasizes that even in the absence of collaterals, the distal lesion influences the hemodynamics of the proximal lesion.

(d) Total occlusion of A: $P_m=P_d=P_w$.

In that case, $\text{FFR}(A)_{\text{pred}} = \frac{P_w}{P_a} = \text{FFR}(A)$ for a total occlusion.¹

Influence of Removal of Proximal Stenosis A on Hemodynamics of Distal Stenosis B

Suppose again that stenosis A will be completely eliminated. In that case, $P_m'=P_a'$ and $\text{FFR}(B)_{\text{true}}$ equals $P_d'/P_m' = P_d'/P_a'$.

How to predict $\text{FFR}(B)_{\text{true}}$ from P_a , P_m , P_d , and P_w ?

As above, it is proved that

$$\frac{Q_{\text{cor}}'}{Q_{\text{cor}}} = \frac{P_d' - P_w'}{P_d - P_w},$$

and because the hyperemic gradient across B is assumed to be proportional to blood flow and because $P_m' = P_a'$, this means that

$$\frac{\Delta P'(B)}{\Delta P(B)} = \frac{P_d' - P_w'}{P_d - P_w}$$

or

$$\frac{P_a' - P_d'}{P_m - P_d} = \frac{P_d' - P_w'}{P_d - P_w} \quad (*)$$

In case of coronary stenosis, arterial pressure P_a is proportional to distal coronary pressure P_d and to coronary wedge pressure P_w (so-called pressure independence of FFR) during maximal hyperemia,^{1,3} and therefore, in case of 2 stenoses, $P_a \approx P_m \approx P_d \approx P_w$.

Therefore, $(P_m - P_w) \approx (P_d - P_w)$, and as a consequence,

$$\frac{P_m' - P_w'}{P_m - P_w} = \frac{P_d' - P_w'}{P_d - P_w}$$

Substitution of this latter expression by (*) gives

$$\frac{P_a' - P_d'}{P_m - P_d} = \frac{P_d' - P_w'}{P_d - P_w} = \frac{P_m' - P_w'}{P_m - P_w} = \frac{P_a' - P_w'}{P_m - P_w}$$

or

$$P_a' - P_d' = \frac{(P_m - P_d)(P_a' - P_w')}{(P_m - P_w)} \quad (**)$$

Because

$$\text{FFR}(B)_{\text{pred}} = \frac{P_d'}{P_a'} = \frac{P_a' - (P_a' - P_d')}{P_a'} = 1 - \frac{(P_a' - P_d')}{P_a'}$$

it is obtained by substitution of expression (**) that

$$\text{FFR}(B)_{\text{pred}} = 1 - \frac{(P_m - P_d)(P_a' - P_w')}{P_a'(P_m - P_w)}$$

Multiplication of both the numerator and denominator of the right term in the last expression by P_a'/P_a' gives

$$\text{FFR}(B)_{\text{pred}} = 1 - \frac{(P_m - P_d) \left(P_a' - \frac{P_a'}{P_a'} \cdot P_w' \right)}{P_a'(P_m - P_w)},$$

and because $P_w'/P_a' = P_w/P_a$, as indicated in the first part of this Appendix, one obtains

$$\text{FFR}(B)_{\text{pred}} = 1 - \frac{(P_a - P_w)(P_m - P_d)}{P_a(P_m - P_w)}$$

The correctness of this equation can be verified by substitution of the boundary values of the respective pressures and verification if $\text{FFR}(B)$ is obtained:

(a) No proximal stenosis: $P_a=P_m$.

In that case,

$$\text{FFR}(B)_{\text{pred}} = \frac{P_d}{P_a} = \text{FFR}(B).$$

(b) No distal stenosis: $P_m=P_d$.

In that case, $\text{FFR}(B)_{\text{pred}} = 1 = \text{FFR}(B)$.

(c) No collaterals: $P_w=0$.

In that case,

$$\text{FFR}(B)_{\text{pred}} = \frac{P_d}{P_m} = \text{FFR}(B).$$

Note: This emphasizes that only in the theoretical case that $P_w=0$ does the proximal stenosis not influence the hemodynamics of the distal lesion.

(d) Total occlusion at B: $P_a=P_m$ and $P_d=P_w$.

In that case,

$$\text{FFR}(B)_{\text{pred}} = \frac{P_w}{P_a} = \text{FFR}(B)$$

for a total occlusion of B.¹

Acknowledgments

The secretarial expertise of Josefa Cano is warmly acknowledged.

References

- Pijls NHJ, van Son AM, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354-1367.
- De Bruyne B, Baudhuin T, Melin JA, Pijls NHJ, Sys SU, Bol A, Paulus WJ, Heyndrickx GR. Coronary flow reserve calculations from pressure measurements in humans: validation with positron emission tomography. *Circulation*. 1994;89:1013-1022.
- De Bruyne B, Bartunek J, Sys SU, Pijls NHJ, Heyndrickx GR, Wijns W. Simultaneous coronary pressure and flow velocity measurements in humans: feasibility, reproducibility, and hemodynamic dependence of coronary flow velocity reserve, hyperemic flow versus pressure slope index, and fractional flow reserve. *Circulation*. 1996;94:1842-1849.
- Segers P, Fostier G, Neckebroek J, Verdonck P. Assessing coronary stenosis severity: in vitro validation of the concept of fractional flow reserve. *Catheter Cardiovasc Interv*. 1999;46:375-379.
- De Bruyne B, Bartunek J, Sys SU, Heyndrickx GR. Relation between myocardial fractional flow reserve calculated from coronary pressure measurements and exercise-induced myocardial ischemia. *Circulation*. 1995;92:39-46.
- Pijls NHJ, Van Gelder B, Van der Voort P, Peels K, Bracke FALE, Bonnier JJRM, El Gamal MIH. Fractional flow reserve: a useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation*. 1995;92:3183-3193.
- Pijls NHJ, De Bruyne B, Peels K, Van der Voort P, Bonnier JJRM, Bartunek J, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary artery stenoses. *N Engl J Med*. 1996; 334:1703-1708.

8. Pijls NHJ, Bech GJW, El Gamal MIH, Bonnier JJRM, De Bruyne B, Van Gelder B, Michels HR, Koolen JJ. Quantification of recruitable coronary collateral blood flow in conscious humans and its potential to predict future ischemic events. *J Am Coll Cardiol*. 1995;25:1522–1528.
9. Bartunek J, Marwick TH, Rodrigues AT, Vincent M, Van Schuerbeeck E, Sys SU, De Bruyne B. Dobutamine-induced wall motion abnormalities: correlations with myocardial fractional flow reserve and quantitative coronary angiography. *J Am Coll Cardiol*. 1996;27:1429–1436.
10. Bartunek J, Van Schuerbeeck E, De Bruyne B. Comparison of exercise electrocardiography and dobutamine echocardiography with invasively assessed myocardial fractional flow reserve in evaluation of severity of coronary arterial narrowing. *Am J Cardiol*. 1997;79:478–481.
11. Bartunek J, Sys SU, Heyndrickx GR, Pijls NHJ, De Bruyne B. Quantitative coronary angiography in predicting functional significance of stenoses in an unselected patient cohort. *J Am Coll Cardiol*. 1995;26:328–334.
12. Bech GJW, De Bruyne B, Bonnier HJRM, Bartunek J, Wijns W, Peels K, Heyndrickx GR, Koolen JK, Pijls NHJ. Long-term follow-up after deferral of percutaneous transluminal coronary angioplasty of intermediate stenosis on the basis of coronary pressure measurement. *J Am Coll Cardiol*. 1998;31:841–847.
13. Bech GJW, Pijls NHJ, De Bruyne B, Peels KH, Michels RH, Bonnier HJRM, Koolen JJ. Usefulness of fractional flow reserve to predict clinical outcome after balloon angioplasty. *Circulation*. 1999;99:883–888.
14. Hanekamp CEE, Koolen JJ, Pijls NHJ, Michels RH, Bonnier HJRM. Comparison of quantitative coronary angiography, intravascular ultrasound, and coronary pressure measurement to assess optimum stent deployment. *Circulation*. 1999;99:1015–1021.
15. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet*. 1986;1:307–310.
16. Vanoverschelde JL, Wijns W, Depre C, Essamri B, Heyndrickx GR, Borgers M, Bol A, Melin JA. Mechanisms of chronic regional posts ischemic dysfunction in humans: new insights from the study of noninfarcted collateral-dependent myocardium. *Circulation*. 1993;87:1513–1523.
17. De Bruyne B, Pijls NHJ, Paulus WJ, Vantrimpont PJ, Sys SU, Heyndrickx GR. Transstenotic coronary pressure gradient measurement in humans: in vitro and in vivo evaluation of a new pressure monitoring angioplasty guide wire. *J Am Coll Cardiol*. 1993;22:119–126.
18. De Bruyne B, Sys SU, Heyndrickx GR. Percutaneous transluminal coronary angioplasty catheters versus fluid-filled pressure monitoring guidewires for coronary pressure measurements and correlation with quantitative coronary angiography. *Am J Cardiol*. 1993;72:1101–1106.
19. Gould KL. *Coronary Atherosclerosis and Reversing Atherosclerosis*. 2nd ed. London, UK: Arnold Publishers; 1999. Distributed by Oxford University Press.

**Pressure-Derived Fractional Flow Reserve to Assess Serial Epicardial Stenoses:
Theoretical Basis and Animal Validation**

Bernard De Bruyne, Nico H. J. Pijls, Guy R. Heyndrickx, Dominique Hodeige, Richard Kirkeeide and K. Lance Gould

Circulation. 2000;101:1840-1847
doi: 10.1161/01.CIR.101.15.1840

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:

<http://circ.ahajournals.org/content/101/15/1840>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>