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

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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\textsubscript{pred}) of each stenosis separately (ie, as if the other one were removed) from arterial pressure (P\textsubscript{a}), pressure between the 2 stenoses (P\textsubscript{m}), distal coronary pressure (P\textsubscript{d}), and coronary occlusive pressure (P\textsubscript{w}). In 5 dogs with 2 stenoses of varying severity in the left circumflex coronary artery, FFR\textsubscript{pred} was compared with FFR\textsubscript{app} (ratio of the pressure just distal to that just proximal to each stenoses) and to FFR\textsubscript{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\textsubscript{true} by FFR\textsubscript{app} was larger than that of FFR\textsubscript{true} by FFR\textsubscript{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\textsubscript{true} by FFR\textsubscript{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\textsubscript{d}/P\textsubscript{a} during hyperemia) applied to each separately but can be predicted by more complete equations taking into account P\textsubscript{a}, P\textsubscript{m}, P\textsubscript{d}, and P\textsubscript{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\textsubscript{d}) to mean aortic pressure (P\textsubscript{a}) recorded simultaneously under conditions of maximum hyperemia.\textsuperscript{1,2} FFR has been shown to be valid in patients with stable angina pectoris under widely varying hemodynamic conditions\textsuperscript{3,4} and to be clinically useful for diagnostic and interventional purposes.\textsuperscript{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\textsubscript{d}/P\textsubscript{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.
Methods

Mathematical Model

As illustrated in Figure 1, \(P_e\) is the pressure proximal to the first stenosis, \(P_i\) 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 (\(P_v\)) 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:

\[
(1) \quad FFR(A)_{app} = \frac{P_d}{P_i}
\]

and

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

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:

\[
(3) \quad FFR(A)_{pred} = \frac{P_e - P_m}{P_e - P_m + P_e - P_i}
\]

and

\[
(4) \quad FFR(B)_{pred} = \frac{1 - (P_e - P_m)/(P_m - P_i)}{P_e - P_i}
\]

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:

\[
(5) \quad FFR(A)_{true} = \frac{P_d}{P_i}
\]

and

\[
(6) \quad FFR(B)_{true} = \frac{P_d}{P_e}
\]

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 (Drager Spiromat 650). General anesthesia was sustained with isofluorane 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 coronary 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 left 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 guide-wires (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 (\(P_s\)), and phasic and mean coronary pressures recorded by both pressure guide-wires (\(P_m\) and \(P_i\), 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 130 to 300 \(\mu g \cdot kg^{-1} \cdot min^{-1}\). 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, postocclusional hyperemia could be elicited. In 1 dog, no maximum hyperemia could be achieved by adenosine, and an additional infusion of dobutamine 20 \(\mu g \cdot kg^{-1} \cdot min^{-1}\) 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 (\(P_e\) and \(P_i\)) and by both pressure guidewires (\(P_m\), coronary pressure between both occluders, and \(P_i\), coronary pressure distal to the distal occluder). Thereafter, different degrees of proximal and distal stenoses 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 transtenotic 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 \(< 5 \text{ mm Hg}\) 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, \(P_e\) 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. Paired \(t\) tests and \(\chi^2\) tests were used when appropriate. Values of \(P > 0.05\) were considered nonsignificant.

Results

Baseline Hemodynamics

Mean aortic pressure was \(88\pm 21\text{ mm Hg}\) (range 71 to 125 mm Hg), and heart rate was \(71\pm 14\text{ bpm}\) (range 64 to 129 bpm) at rest. Mean blood pressure decreased significantly to \(78\pm 19\text{ mm Hg}\) (range 63 to 118 mm Hg) and heart rate increased significantly to \(125\pm 26\text{ bpm}\) (range 76 to 158 bpm) during postocclusion hyperemia. Yet, during pharmacologi-
estimates $\text{FFR}(A)$ true and that there is an inverse correlation of $\text{FFR}(B)$ app of the same lesion $B$ when a progressively increasing level of stenosis $B$ is created upstream. A large scatter is observed in the plot of the relationship between $\text{FFR}(B)$ true and $\text{FFR}(B)$ pred ($r^2=0.39$, $P<0.01$). Similarly, a total of 20 proximal stenoses (stenoses $A$) were created. For each of those, 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 [$\text{FFR}(B)_{\text{true}}$] versus the apparent value of FFR [$\text{FFR}(B)_{\text{app}}$] 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 $\text{FFR}(B)_{\text{true}}$ and $\text{FFR}(B)_{\text{app}}$. As expected from the theory, the corresponding Bland-Altman plot (Figure 3B) shows that $\text{FFR}(B)_{\text{app}}$ systematically overestimates $\text{FFR}(B)_{\text{true}}$ and that there is an inverse correlation between this overestimation and $\text{FFR}(B)_{\text{true}}$ ($r=-0.39$, $P<0.01$).

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 [$\text{FFR}(A)_{\text{true}}$] versus the apparent value of FFR [$\text{FFR}(A)_{\text{app}}$] 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 $\text{FFR}(A)_{\text{app}}$ significantly overestimates $\text{FFR}(A)_{\text{true}}$ and that there is an inverse correlation between this overestimation and $\text{FFR}(A)_{\text{true}}$ ($r=-0.62$, $P<0.01$).

Relation Between $\text{FFR}_{\text{true}}$ and $\text{FFR}_{\text{pred}}$

In investigating the influence of a varying stenosis $A$ on a given, fixed, stenosis $B$, a close correlation was found between $\text{FFR}(B)_{\text{true}}$ and $\text{FFR}(B)_{\text{pred}}$ ($r^2=0.95$, Figure 4A). The Bland-Altman plot (Figure 4B) shows a small mean difference (+0.03±0.04) without systematic overestimation or underestimation of $\text{FFR}(B)_{\text{true}}$ by $\text{FFR}(B)_{\text{pred}}$. 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 $\text{FFR}(A)_{\text{true}}$ and $\text{FFR}(A)_{\text{pred}}$ (Figure 4C). The Bland-Altman plot (Figure 4D) indicates a small overestimation (+0.04±0.066).

Relation Between $\text{P}_w$ and $\text{FFR}_{\text{app}}$ Versus $\text{FFR}_{\text{pred}}$

No relationship was found between the level of coronary occlusive pressure (wedge pressure, $\text{P}_w$) and the accuracy of $\text{FFR}_{\text{app}}$ versus $\text{FFR}_{\text{pred}}$ in determining $\text{FFR}_{\text{true}}$.

Accuracy of $\text{FFR}_{\text{app}}$ and $\text{FFR}_{\text{pred}}$ in Determining $\text{FFR}_{\text{true}}$

Figure 5 depicts the absolute difference between $\text{FFR}_{\text{app}}$ and $\text{FFR}_{\text{true}}$ and between $\text{FFR}_{\text{pred}}$ and $\text{FFR}_{\text{true}}$ 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 $\text{FFR}_{\text{true}}$ by $\text{FFR}_{\text{pred}}$ is significantly smaller than the corresponding overestimation or underestimation of $\text{FFR}_{\text{true}}$ by $\text{FFR}_{\text{app}}$. For a fixed stenosis $B$, the absolute error in FFR was >0.1 in 22% of measurements for $\text{FFR}(B)_{\text{app}}$ and in 5% of measurements for $\text{FFR}(B)_{\text{pred}}$ ($P<0.01$). For a fixed stenosis $A$, the absolute error in FFR was >0.1 in 45% of the measurements of $\text{FFR}(A)_{\text{app}}$ and 9% of measurements for $\text{FFR}(A)_{\text{pred}}$ ($P<0.01$). The error in calculating FFR for a stenosis by use of the simple $\text{P}_d/\text{P}_a$ ratio ($\text{FFR}_{\text{app}}$) was significantly larger in the presence of a second more proximal stenosis than for a second more distal stenosis. The greatest errors in $\text{FFR}_{\text{app}}$ 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 ($\text{P}_d/\text{P}_a$, 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 $\text{P}_a$, pressure between the 2 stenoses ($\text{P}_d$), $\text{P}_w$, and recorded during maximum hyperemia. The data also suggest that FFR calculated as the $\text{P}_d/\text{P}_a$ ratio for the stenosis has a greater error in the presence of a second more proximal 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...
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. 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. In case of multiple stenoses along the same coronary artery, collateral flow will influence both $P_a$ 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 $P_m$ cannot be neglected and was incorporated into the equations derived in the Appendix.

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**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.
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, 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 can be applied to each stenosis rather than the simple ratio P/P, being applied to each stenosis to determine the severity of each. In clinical practice, the measurements of P, P, and P 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 may be more pronounced than in the present study and must be included in the equations for FFR in case of serial stenoses.

Second, P 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, very small inaccuracies in measuring P might induce large errors in FFR. 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” 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. 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.
Respectively, before any intervention, and indicate the hyperemic pressure gradients across stenoses A and B, \( \text{FFR}_{\text{app}} \) and \( \text{FFR}_{\text{pred}} \) in case of fixed distal stenosis and variable distal stenosis (B).

Proximal stenosis (A) and in case of fixed proximal stenosis and variable distal stenosis (C) and corresponding Bland-Altman plot (D).

Plots of values of FFR\(_{\text{pred}}\) vs FFR\(_{\text{true}}\) in case of fixed proximal stenosis and variable distal stenosis (A) and corresponding Bland-Altman plot (B). Plots of values of FFR\(_{\text{pred}}\) vs FFR\(_{\text{true}}\) in case of fixed distal stenosis and variable proximal stenosis (B).

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Figure 4. Plots of values of FFR\(_{\text{pred}}\) vs FFR\(_{\text{true}}\) in case of fixed distal stenosis and variable proximal stenosis (A) and corresponding Bland-Altman plot (B). Plots of values of FFR\(_{\text{pred}}\) vs FFR\(_{\text{true}}\) 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 \( \text{FFR}_{\text{A\_app}} \) and \( \text{FFR}_{\text{B\_app}} \) 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\(_{a}’\) equals P\(_{a}\), and after the distal stenosis B has been removed, P\(_{w}’\) equals P\(_{w}\). True measured FFR of 1 stenosis after physical removal of the other stenosis in the animal model is indicated by \( \text{FFR}_{\text{A\_app}} \) and \( \text{FFR}_{\text{B\_app}} \), and is equal to P\(_{a}’\)/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\(_{\text{cor}}\) and Q\(_{\text{N}}\) indicate maximum coronary blood flow before and after elimination of 1 or both stenoses, and Q\(_{\text{cor}}’\) and Q\(_{\text{N}}’\) indicate the normal values of Q\(_{\text{cor}}\) and Q\(_{\text{N}}\), respectively (ie, those values if no stenoses were present). FFR\(_{\text{app}}\) and FFR\(_{\text{cor}}\) 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\(_{a}’\)=P\(_{a}\) and FFR(A)\(_{\text{app}}\) equals P\(_{a}’\)/P\(_{a}\) or P\(_{a}’\)/P\(_{w}’\).

How to predict FFR(A)\(_{\text{app}}\) from P\(_{a}\), P\(_{m}\), P\(_{d}\), and P\(_{w}\)?

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

\[
\begin{align*}
\frac{Q_{\text{cor}}'}{Q_{\text{cor}}} & = \frac{Q_{\text{cor}}^N}{Q_{\text{cor}}} \\
\frac{Q_{\text{N}}'}{Q_{\text{N}}} & = \frac{Q_{\text{N}}^N}{Q_{\text{N}}} \\
& = \text{FFR'}_{\text{cor}} = \frac{Q_{\text{cor}}^N}{Q_{\text{cor}}}, \\
& = \frac{1}{\text{FFR}_{\text{cor}}}, \\
& = \frac{P_{a}}{P_{m}} - \frac{P_{d}}{P_{w}} \\
& = \frac{P_{a}'}{P_{m}'} - \frac{P_{d}'}{P_{w}'} \\
& = \frac{P_{a}'}{P_{m}'} - \frac{P_{d}}{P_{w}} \\
& = \frac{P_{a}'}{P_{w}}.
\end{align*}
\]

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

\[
\begin{align*}
\Delta P(A) \frac{Q_{\text{cor}}}{Q_{\text{cor}}} & = \frac{P_{a}'}{P_{a}} - \frac{P_{d}}{P_{w}} \\
\Delta P(A) \frac{Q_{\text{cor}}}{Q_{\text{cor}}} & = \frac{P_{a}'}{P_{m}'} - \frac{P_{d}'}{P_{w}'} \\
\text{or } \quad \frac{P_{a}'}{P_{m}'} & = \frac{P_{a}'}{P_{m}} \frac{P_{a}}{P_{m}} \\
\text{or } \quad \frac{(P_{a}'} - P_{a})}{(P_{a} - P_{a})}, \frac{(P_{m}'} - P_{m})}{(P_{m} - P_{m})} \\
\text{or } \quad \frac{P_{a}'}{P_{m}'} \frac{P_{m}'}{P_{m}} - \frac{P_{d}'}{P_{w}'} \frac{P_{d}'}{P_{w}}
\end{align*}
\]

It has been proved theoretically and validated experimentally\(^1\) that P\(_{a}’\)/P\(_{m}’\)=P\(_{a}’\)/P\(_{w}’\). Therefore, P\(_{m}’\)=P\(_{m}\)/P\(_{w}\), and those terms can be cancelled in the expression above.

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

\[
\frac{P_{a}'}{P_{m}'} \left( P_{a} - P_{a} + P_{a} - P_{w} \right) = P_{a} - P_{a} + P_{a} - P_{w} - P_{a} - P_{w}
\]

Division of both the right and left terms by P\(_{a}’\) gives

\[
\frac{P_{a}'}{P_{a}} \left( P_{a} - P_{a} + P_{a} - P_{w} \right) = P_{a} - \left( \frac{P_{m}}{P_{m}'} \right) P_{a} - \left( \frac{P_{w}}{P_{w}'} \right) P_{a}
\]

and therefore,

\[
\text{FFR}(A)_{\text{app}} = \frac{P_{a}'}{(P_{m}/P_{w}) P_{a}} - P_{m} + P_{a} - P_{w}
\]

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\(_{a}=P_{a}\).

In that case, FFR(A)\(_{\text{app}}\) = P\(_{a}’\)/P\(_{w}’\) = 1 - FFR(A),

(b) No distal stenosis: P\(_{w}=P_{w}\).

In that case, FFR(A)\(_{\text{app}}\) = P\(_{a}’\)/P\(_{m}’\)P\(_{a}\) - P\(_{m}’\) + P\(_{a}’\) - P\(_{w}’\).
\[
\frac{P_m - P_a}{P_m} = \frac{P_m}{P_m - P_d} = FFR(A).
\]

(c) No collaterals: \( P_m = 0 \).

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

This latter equation has been erroneously claimed to represent \( FFR(A) \), 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: \( P_m = P_d = P_a \).

In that case, \( FFR(A)_{\text{pred}} = \frac{P_d}{P_a} = FFR(A) \) 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, \( P_m = P_d = P_a \) and \( FFR(B)_{\text{true}} = \frac{P_d}{P_a} \), which simplifies to \( FFR(B)_{\text{true}} = P_d/P_a \). Therefore, \( (P_m - P_a) = (P_d - P_a) \), and as a consequence, \( P_m = P_d = P_a \).

Therefore, \( (P_m - P_a) = (P_d - P_a) \), and as a consequence, \( P_m = P_d = P_a \).

Substitution of this latter expression by \( * \) gives

\[
\frac{P_m - P_a}{P_m - P_d} = \frac{P_m}{P_m - P_d} = FFR(A).
\]

or

\[
\frac{P_m - P_a}{P_m - P_d} = \frac{P_m}{P_m - P_d} = FFR(A).
\]

and because the hyperemic gradient across B is assumed to be proportional to blood flow and because \( P_m = P_d \), this means that

\[
\Delta P'(B) = \frac{P_m - P_d}{P_m - P_a} \quad (**) \]

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, \( P_m = P_d = P_a \). Therefore, \( (P_m - P_a) = (P_d - P_a) \), and as a consequence, \( P_m = P_d = P_a \).

So, \( P_m = P_d = P_a \).

Substitution of this latter expression by \( * \) gives

\[
\frac{P_m - P_a}{P_m - P_d} = \frac{P_m}{P_m - P_d} = FFR(A).
\]

or

\[
\frac{P_m - P_a}{P_m - P_d} = \frac{P_m}{P_m - P_d} = FFR(A).
\]

and because \( P_m = P_d = P_a \), as indicated in the first part of this Appendix, one obtains

\[
FFR(B)_{\text{true}} = 1 - \frac{(P_m - P_a)(P_m - P_d)}{P_m - P_d}.
\]

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

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

In that case,

\[
FFR(B)_{\text{true}} = \frac{P_m}{P_m} = FFR(B).
\]

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

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

(c) No collaterals: \( P_m = 0 \).

In that case,

\[
FFR(B)_{\text{true}} = \frac{P_m}{P_m} = FFR(B).
\]

Note: This emphasizes that only in the theoretical case that \( P_m = 0 \) does the proximal stenosis not influence the hemodynamics of the distal lesion.

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

In that case,

\[
FFR(B)_{\text{true}} = \frac{P_m}{P_m} = FFR(B).
\]

for a total occlusion of B. 1

**Acknowledgments**

The secretarial expertise of Josefa Cano is warmly acknowledged.

**References**


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

_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
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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:
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