Influence of hemodynamic conditions on fractional flow reserve: parametric analysis of underlying model

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Siebes, Maria, Steven A. J. Chamuleau, Martijn Meuwissen, Jan J. Piek, and Jos A. E. Spaan. Influence of hemodynamic conditions on fractional flow reserve: parametric analysis of underlying model. Am J Physiol Heart Circ Physiol 283: H1462–H1470, 2002. First published May 23, 2002; 10.1152/ajpheart.00165.2002.—Pressure-based fractional flow reserve (FFR) is used clinically to evaluate the functional severity of a coronary stenosis, by predicting relative maximal coronary flow (Qs/Qn). It is considered to be independent of hemodynamic conditions, which seems unlikely because stenosis resistance is flow dependent. Using a resistive model of an epicardial stenosis (0–80% diameter reduction) in series with the coronary microcirculation at maximal vasodilation, we evaluated FFR for changes in coronary microvascular resistance (R_cor = 0.2–0.6 mmHg·ml⁻¹·min⁻¹), aortic pressure (P_a = 70–130 mmHg), and coronary outflow pressure (P_cor = 0–15 mmHg). For a given stenosis, FFR increased with decreasing P_a or increasing R_cor. The sensitivity of FFR to these hemodynamic changes was highest for stenoses of intermediate severity. For P_cor > 0, FFR progressively exceeded Qs/Qn with increasing stenosis severity unless P_cor was included in the calculation of FFR. Although the P_cor-corrected FFR equaled Qs/Qn for a given stenosis, both parameters remained equally dependent on hemodynamic conditions, through their direct relationship to both stenosis and coronary resistance.

coronary artery stenosis; coronary circulation; coronary stenosis evaluation; coronary flow reserve

WITH THE INTRODUCTION of sensor-tipped guide wires, physiological parameters are increasingly used to assess coronary stenosis severity in functional terms. Pressure-based fractional flow reserve (FFR) has rapidly developed into a frequently used parameter to identify clinically relevant stenoses and to serve as a basis for evaluating the success of coronary interventions (6, 35). The established cutoff value for FFR is 0.75, which implies that the stenosis is considered significant when distal pressure during maximum hyperemia is <75% of aortic pressure and otherwise is not significant (33). FFR is considered to be independent of hemodynamic conditions (8, 15, 32–34), although it has been pointed out that the flow dependence of stenosis resistance is hardly compatible with such a conclusion (13).

Conceptually, FFR derives from pressure-flow relations of the stenosed epicardial vessel and of the coronary circulation at full vasodilation. A number of physiological studies have demonstrated that external hemodynamic conditions affect coronary pressure-flow relations at maximum vasodilation (21). Similarly, it is well known that stenosis resistance depends on flow because of the quadratic relation between pressure loss and flow rate due to the Bernoulli effect (49). Hence, extrapolation of these findings would predict a dependence of FFR on physiological conditions that alter coronary flow, such as aortic pressure or coronary vascular bed resistance (17).

To systematically assess the individual impact of different hemodynamic circumstances on the value of FFR as derived from intracoronary pressure signals, we carried out this parametric study based on the model underlying the concept of FFR.

METHODS

Description of model. The coronary circulation was modeled as a flow-dependent stenosis resistance in series with a lumped downstream coronary resistance (Fig. 1A). At maximum vasodilation and in the absence of a stenosis, the coronary pressure-flow relation can be approximated, within limits, by a straight line with a positive intercept on the pressure axis, denoted here as P_cor, which is a few millimeters of mercury higher than venous pressure (P_v) (3, 21). Hence, a change in flow (Q) is proportional to a change in perfusion pressure (P_a) (Fig. 1B). In this model we defined the inverse of this slope as coronary microvascular resistance during maximal vasodilation (R_cor), in accordance with the model originally presented by Pijls et al. (36). This model resistance, together with P_cor, correctly describes the physiological pressure-flow line over a wide range of pressures. Because of the incremental-linear nature of the coronary pressure-flow line, a model with coronary resistance equal to the inverse of the slope of this line is allowed only if P_cor is subtracted from the perfusion pressure, whereas coronary resistance defined as P/Q or (P – P_cor)/Q is pressure dependent (Fig. 1B; Refs. 22, 45).

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Although flow rate was varied as the independent variable for 
FFR calculated with Eq. 5 were compared with the actual 
maximal flow ratio, Q/Qn, to quantify the effect of disregard-
ning flow pressure Pb.

Model parameters. The stenosis was modeled as a blunt-
shaped, rigid obstruction in a noncompliant vessel with a 
3-mm diameter. Stenosis severity was varied between 0% 
and 80% diameter reduction with a length of 6 mm. The 
hemodynamic parameters were chosen in variations about a 
normal value. Coronary resistance at maximum vasodilation 
was varied from 0.2 to 0.6 mmHg·ml⁻¹·min⁻¹, with 0.4 
mmHg·ml⁻¹·min⁻¹ representing control conditions. Outflow 
pressure Pb was used at values of 0, 10 (control), and 15 
mmHg. To illustrate the potential effect of advanced diseased 
states, we also modeled pathophysiological examples with a 
threelfold increase in Rcor (1.8 mmHg·ml⁻¹·min⁻¹) and Pb (45 
mmHg). Flow rate was varied as the independent variable 
from 0.1 to 600 ml/min, resulting in perfusion pressures P2 
between Pb and 200 mmHg. The resulting values for FFR 
were then interpolated to obtain data at aortic pressures of 
70 and 130 mmHg for each combination of Pb and Rcor. All 
dimensionless variables are presented without indication of 
units of measurement.

RESULTS

Table 1 lists the calculated pressure loss coefficients 
A2 and B that were used to determine the pressure drop 
for each stenosis model according to Eq. 3. The 
resulting curvilinear pressure drop-flow relationships 
are shown in Fig. 2A. Stenosis resistance increased 
with increasing flow rate (Eq. 4), as reflected by the 

<table>
<thead>
<tr>
<th>%DS</th>
<th>Dmin, mm</th>
<th>A2, mmHg/ml/min</th>
<th>B2, mmHg/ml/min²</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>2.40</td>
<td>0.003598</td>
<td>9.5794 x 10⁻⁶</td>
</tr>
<tr>
<td>40</td>
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<td>0.011370</td>
<td>9.5686 x 10⁻⁵</td>
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<tr>
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<td>2.7248 x 10⁻⁴</td>
</tr>
<tr>
<td>60</td>
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<td>8.3447 x 10⁻⁴</td>
</tr>
<tr>
<td>65</td>
<td>1.05</td>
<td>0.098197</td>
<td>1.5535 x 10⁻³</td>
</tr>
<tr>
<td>70</td>
<td>0.90</td>
<td>0.18192</td>
<td>3.0852 x 10⁻³</td>
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<tr>
<td>75</td>
<td>0.75</td>
<td>0.37723</td>
<td>6.8120 x 10⁻³</td>
</tr>
<tr>
<td>80</td>
<td>0.60</td>
<td>0.92098</td>
<td>1.7439 x 10⁻²</td>
</tr>
</tbody>
</table>

Values were calculated (20,43) for a normal vessel diameter 
D0 = 3 mm, stenosis length L = 6 mm, blood viscosity µ = 3.6 cP, blood 
density ρ = 1.06 g/cm³. A2, coefficient for viscous pressure loss along 
stenosis; B2, coefficient for inertial pressure loss at exit of stenosis; 
Dmin = minimum stenosis diameter; %DS = percent diameter 
stenosis.
increasing slope of the curve for each stenosis. Corresponding coronary pressure-flow lines of the stenosed coronary circulation represented by 2 resistances in series ($R_s$ and $R_{cor}$ in Fig. 1). Calculations were done at control conditions ($R_{cor} = 0.4 \text{ mmHg}\cdot\text{ml}^{-1}\cdot\text{min}$, $P_b = 10 \text{ mmHg}$). Vertical lines are drawn at aortic pressures of 70 mmHg and 130 mmHg. %DS, percent diameter stenosis.

Fig. 2. A: pressure-drop-flow lines (Eq. 3) of the stenosis models represented by $R_s$ in Fig. 1. B: pressure-flow lines of the stenosed coronary circulation represented by 2 resistances in series ($R_s$ and $R_{cor}$ in Fig. 1). Calculations were done at control conditions ($R_{cor} = 0.4 \text{ mmHg}\cdot\text{ml}^{-1}\cdot\text{min}$ and $P_b = 10 \text{ mmHg}$). Vertical lines are drawn at aortic pressures of 70 mmHg and 130 mmHg. %DS, percent diameter stenosis.

Fig. 3. A: relationship of fractional flow reserve (FFR) = $P_d/P_a$ to aortic pressure (control conditions). For a given stenosis, $P_d/P_a$ decreases hyperbolically with increasing perfusion pressure. The dashed line indicates the clinical cutoff value of 0.75 for FFR. B: relationship of FFR = $P_d/P_a$ to flow (control conditions). $P_d/P_a$ decreases with increasing flow caused by increasing $P_a$. Symbols are drawn at flow rates corresponding to aortic pressures of 70 and 130 mmHg.

The sensitivity of $P_d/P_a$ to changes in hemodynamic conditions in terms of coronary resistance, coronary outflow pressure, and aortic pressure is shown in Fig. 4 as a function of stenosis severity. Results are shown for the total range of hemodynamic changes modeled in this study.
Figure 4A depicts the nonlinear decrease of $P_d/P_a$ with increasing stenosis severity at $P_b = 0$ mmHg. For a specific stenosis, however, $P_d/P_a$ was a function of the modeled hemodynamic conditions. An increase in $R_{cor}$ from 0.2 to 0.6 mmHg·ml⁻¹·min caused a substantial increase in $P_d/P_a$ for stenosis severities of greater than 20% diameter reduction. This trend continued at a lower rate for a further increase of $R_{cor}$ to 1.8 mmHg·ml⁻¹·min. Absolute differences (left) are highest for stenoses of intermediate severity, whereas percent differences (right) increase with stenosis severity. The sensitivity shifts toward more severe stenosis severities with increasing $R_{cor}$. Dashed lines depict changes due to an increase in $R_{cor}$ from 0.6 to 1.8 mmHg·ml⁻¹·min at $P_a = 130$ mmHg.

The magnitudes of changes induced by these altered hemodynamic conditions are illustrated in Fig. 4B in absolute (Fig. 4B, left) and relative (Fig. 4B, right) terms. For $R_{cor}$ between 0.2 and 0.6 mmHg·ml⁻¹·min, absolute changes in $P_d/P_a$ were largest for intermediate lesions between 40% and 70% diameter reduction, reaching a maximal value of 0.34. With $R_{cor}$ increasing even further, the maximum sensitivity to hemodynamic changes shifted to higher stenosis severities (Fig. 4B, dashed lines). The maximum absolute change in $P_d/P_a$ was on the order of 0.08 for a decrease in $P_a$ from 130 to 70 mmHg. Because the FFR for intermediate lesions is close to the clinical threshold of 0.75 (Fig. 4A), prevailing hemodynamic conditions can introduce a significant margin of error in clinical decision-making.
Figure 4C illustrates that an increase in P_b to 15 mmHg caused an increase in P_d/P_a compared with the corresponding values at P_b = 0 mmHg. The sensitivity to a change in P_b increased with stenosis severity and was higher when R_cor was low, reaching maximal values on the order of 0.2 (Fig. 4C, left). Compared with the data obtained at P_l = 0 mmHg (Fig. 4B, left), the modeled response to lowering P_a increased by ~62% for intermediate stenoses, reaching values on the order of 0.13, whereas the response to changing R_cor was slightly reduced by 12%. A further rise in P_b to a pathophysiological value of 45 mmHg amplified the increase in P_d/P_a by approximately a factor of 3 as shown by the dashed curve in Fig. 4C for the example of R_cor = 0.2 mmHg·ml⁻¹·min at P_a = 130 mmHg. Relative differences from values at P_b = 0 mmHg rose rapidly for stenoses greater than 40% diameter reduction (Fig. 4C, right).

Figure 5A illustrates the effect of changes in hemodynamic parameters on the relationship between FFR and Q_s/Q_n, for the case of R_cor = 0.2 mmHg·ml⁻¹·min. When P_b > 0 (15 mmHg in this example) and FFR was not corrected for P_b (FFR = P_d/P_a; Eq. 6), the relative maximal flow, Q_s/Q_n, was progressively overestimated with increasing stenosis severity (Fig. 5A, top 2 regression lines). In that case, the relationship between FFR and Q_s/Q_n became dependent on P_a, with a larger overestimation at lower perfusion pressures. An increase of P_b to 45 mmHg aggravated the overestimation by a factor of 3, with the data points and corresponding regression lines rotating clockwise around the upper right point representing no stenosis (not shown here). The relationships were independent of coronary resistance, but for higher values of R_cor both FFR and Q_s/Q_n increased (see Fig. 4A) and corresponding data points for a given stenosis shifted to higher values on their respective regression lines (not shown here for clarity). Consequently, the percent overestimation for a given stenosis became lower, as shown in Fig. 5B for the case of P_a = 130 mmHg.

With P_b = 0 mmHg (Fig. 5A), the relationships became equal to the line of identity and P_d/P_a matched Q_s/Q_n. Similarly, when FFR was calculated by including a nonzero P_b (Eq. 5), the data were also brought to the line of identity and FFR was equal to Q_s/Q_n (Fig. 5A). However, equivalence between FFR and Q_s/Q_n did not imply that P_a or P_b no longer had an influence. Changes in hemodynamic conditions affected both FFR and Q_s/Q_n to the same degree, shifting individual data points for a given stenosis along the line of identity. Note that the values at P_a = 0 and P_l = 15 mmHg (Eq. 5) are different because of differences in flow through the stenosis. Boxes around the data for a specific stenosis in Fig. 5A indicate the range of changes in corresponding values of FFR and Q_s/Q_n obtained for the hemodynamic conditions shown here.

**DISCUSSION**

This parametric model study demonstrates, based on realistic pressure-flow relations of a fixed stenosis in an epicardial artery and of the coronary circulation at maximum vasodilation, that the FFR for a given stenosis is influenced by arterial input pressure, the slope of the coronary pressure-flow line at maximal vasodilation.
lation, and coronary outflow pressure. These parameters change flow through the stenosed artery, which has a nonlinear effect on the pressure distal to the stenosis and, therefore, on the ratio of distal to proximal pressure, commonly used to represent FFR.

Equivalence of FFR and relative maximal flow \( Q_s/Q_n \).
In 1977 Young et al. (50) proposed the stenosis-induced relative reduction of maximally possible flow to a vascular bed, \( Q_s/Q_n \), as a useful index for characterizing the effect of a stenosis. The concept of myocardial FFR was developed with the purpose of quantifying this index for the myocardial vascular bed on the basis of pressure measurements proximal and distal to the stenosis. The equivalence of the pressure-based and flow-based ratios has been demonstrated on the basis of a theoretical model in which stenosis resistance was assumed to be constant (32, 34). However, pragmatically, the pressure-flow relation can be approximated over the range of physically and clinically relevant pressures by a straight line, intercepting the pressure axis at a pressure denoted as \( P_b \) in this study. In this context, it is important to note that, irrespective of the constant slope of the pressure-flow line, coronary microvascular resistance calculated as distal perfusion pressure divided by flow is indeed pressure dependent, leading to higher values at lower distal pressures downstream of severe stenoses (see Fig. 1B; Ref. 37).

The initial slope of our coronary pressure-flow relation without a stenosis follows from a realistic coronary blood flow of 224 ml/min under conditions of maximum vasodilation. This value compares well with maximal regional myocardial blood flow for 80–100 g of tissue measured in healthy volunteers or in regions supplied by minimally stenosed arteries (10, 47, 48). The range we evaluated (±0.2 mmHg·ml⁻¹·min, or ±50%) reflects the variation found for normal hearts and patients with coronary artery disease (28, 48) but also the variation between different perfusion areas of the same heart (7). Left ventricular hypertrophy, ischemia, infarction, microvascular disease (5, 12, 25, 47), and acute changes in contractility or heart rate (11, 37) also affect minimum coronary resistance to a degree comparable to the range modeled in this study. The resulting range of values for FFR compares well to that obtained in an unselected patient cohort (2) and to data obtained in dogs (15) for similar stenosis degrees. The highest value of 1.8 mmHg·ml⁻¹·min was chosen to illustrate the direction of outcomes for a large decrease in coronary conductance, e.g., caused by severe microvascular dysfunction.

The in vivo value of \( P_b \) at maximum vasodilation exceeds coronary venous pressure by a few millimeters of mercury (18, 21). From physiological studies in dogs and swine one finds values on the order of 10–15 mmHg in normal beating hearts (4, 31) but as high as 40 mmHg in hypertrophy (11, 12). Moreover, it has been demonstrated that \( P_b \) depends on factors such as left ventricular filling pressure, heart rate, and contractility (11, 19). Hence, the normal range we studied, 0–15 mmHg, is quite realistic, with an extreme value of 45 mmHg chosen to elucidate the potential effect of severe left ventricular hypertrophy.

Comparison with experimental studies. Our findings on the pressure dependence of FFR appear to be at odds with earlier reports, which suggest that FFR is rather independent of hemodynamic conditions (8, 15, 36, 38). Gould et al. (15) critically demonstrated the importance of using relative maximal flow \( Q_s/Q_n \), denoted as relative flow reserve, over absolute coronary...
flow reserve in that the latter was more dependent on aortic pressure. However, their results of relative maximal flow for the intermediate stenosis range demonstrated sufficient variability (e.g., Qs/Qn = 0.42 ± 0.18, or 43% change for a 61% diameter stenosis) with a change in aortic pressure from 70 to 150 mmHg to be consistent with our model predictions.

Pijls et al. (36) compared FFR, calculated by including Pb (Eq. 5), with the relative maximal flow velocity (Qs/Qn), measured directly by a Doppler transducer proximal to the stenosis, in dogs at three different levels of aortic pressure, ranging from an average of 56 to 113 mmHg. They found an excellent correlation of Qs/Qn with the pressure-derived values of relative maximal flow, which confirmed the validity of the underlying equations (36) and is consistent with our results shown in Fig. 5A. However, the stenosis degrees in their study were not the same at different pressures and, therefore, the data did not allow inferences about pressure dependence of FFR for a given stenosis. As discussed above, a change in aortic pressure affects both the relative maximal flow for a given stenosis and the corresponding pressure ratio representing FFR and all points fall on one line. As shown in the study by Pijls and coworkers (36), this is the line of identity when collateral flow is absent and a line with a positive intercept when collateral flow is present.

These important studies solidly established the principles of the applicability of FFR to predict relative maximal flow but did not conclusively demonstrate an independence of FFR from hemodynamic conditions for a given stenosis. Others also based their conclusion of FFR being independent of aortic pressure on the relationship between FFR and Qs/Qn, using data obtained in a mock circulation system (38) or misinterpreting results obtained in the earlier animal studies (32, 33, 35). However, as discussed above, the FFR vs. Qs/Qn relationship is not suited for drawing conclusions on the hemodynamic independence of FFR for a specific stenosis.

In a clinical study, De Bruyne et al. (8) focused on the dependence of FFR on hemodynamic conditions for a given stenosis by comparing data before and after a change in heart rate, aortic pressure, or contractility. Stenosis severities ranged from 21% to 66% diameter reduction. A change in heart rate or contractility did not result in a significant change in mean aortic pressure, blood flow velocity, or pressure gradient during maximal vasodilation, and, consequently, average Pa/Pd did not change either. When aortic pressure was lowered by an average of 20 mmHg, Pa/Pd also did not change significantly, despite a significant reduction in maximal blood flow velocity. However, as noted by the authors, interaction of hemodynamic effects could not be avoided in this patient study. A reflex tachycardia was induced, which most likely reduced left ventricular end-diastolic pressure, thereby decreasing Pb. Because FFR in this study was calculated assuming Pb = 0 mmHg (FFR = Pa/Pd, Eq. 6), an undetected decrease in Pb could have masked the effect of lowering arterial pressure on Pa/Pd. In our study, values of Pa/Pd at Pb = 15 mmHg and Pb = 130 mmHg differed <5% from those at Pb = 0 mmHg and Pb = 70 mmHg for stenoses less than 70% in diameter reduction. Hence, if Pb and Pb both change in the same direction, Pa/Pd may stay almost constant. The same is true for an appropriate combination of changes in perfusion pressure and coronary resistance.

Why is FFR dependent on hemodynamic conditions?

The interpretation of the experimental studies and our model results may be simplified by expressing the maximal flow ratio (Eq. 5) as

\[ \text{FFR} = \frac{Q_s}{Q_n} = \frac{R_{\text{cor}}}{R_\text{cor} + R_{\text{cor}}} \]

This equation states in a straightforward manner that the hemodynamic effect of a stenosis in terms of fractional reduction of normal maximal flow depends on the relative proportion between the stenosis resistance Rs and the coronary microvascular resistance R_cor. This fundamental relationship was demonstrated several decades ago in peripheral arteries (41) and more recently, in coronary vessels of dogs (44). R_cor depends on factors such as microvascular disease and on the hemodynamic conditions at the time of measurement. In addition, R_c depends on flow through the stenosis (Eq. 4), which in turn is altered by changes in R_cor or total driving pressure (Pa − Pb). Maximal flow in the presence of an epicardial stenosis therefore increases nonlinearly with increasing perfusion pressure (Fig. 2B), and Qs/Qn is no longer independent of aortic pressure. This flow-dependent behavior of FFR has been demonstrated both in vivo (50) and in vitro (27). It follows from Eq. 7 that FFR crosses the threshold value of 0.75 when stenosis resistance becomes greater than 33% of coronary microvascular resistance. The combined influence of hemodynamic changes on FFR depends on their relative effect on Rs and R_cor.

Critique of model.

In the development of this model, we have used fundamental fluid dynamic and physiological principles to describe the pressure-flow relations of the diseased coronary circulation. Our study aimed to quantify the hemodynamic dependence of FFR on a theoretical basis by independent variation of individual physiological parameters. However, hemodynamic changes in vivo rarely occur in isolation and may combine to amplify or reduce the overall effect. As discussed above and consistent with our model, FFR may appear constant in vivo despite altered hemodynamic conditions (8, 44), depending on the combination and magnitude of hemodynamic changes.

Because we wanted to focus on the effect of hemodynamic changes on relative maximal flow in a stenosed vessel, we did not include collateral flow in our model. The presence of a collateral circulation has two related effects: total flow to the myocardium is higher than flow through the stenosed vessel alone, and myocardial FFR (Eq. 5) is therefore higher than the relative maximal flow Qs/Qn through the stenosed vessel alone. The addition of collateral flow to our model would affect our results only insofar as the effect of a flow-dependent
stenosis resistance on myocardial FFR is diminished by the relative contribution of collateral flow to total coronary flow at maximal vasodilation. With the linear inverse relation between fractional collateral flow and \( Q_c/Q_n \), data for intermediate lesions (FFR = 0.75) can be derived from the animal study by Pijls et al. (36) and an average 12.6% of total myocardial flow. Even for severe lesions (mean diameter reduction = 74–84%), mean FFR = 0.53–0.64), collateral flow was shown to contribute only between 13% and 33% of total coronary flow at maximal vasodilation in humans (39), depending on the degree of collateral development. Assuming that the collateral contribution is not influenced by hemodynamic changes, the effect of collateral flow on the hemodynamic dependencies related to stenosis resistance would thus be rather small.

Consideration of \( P_b \) is also important for the interpretation of FFR measurements regarding collateral flow. In the presence of collateral flow, myocardial FFR (Eq. 5) progressively exceeds \( Q_c/Q_n \) with increasing stenosis severity (36), thus correctly reflecting the addition of collateral flow to total flow to the myocardium. As shown in this study, an elevated \( P_b \) has the same effect, when FFR is calculated assuming that \( P_b \) is zero (Eq. 6). In that case, however, it represents an overestimation of total myocardial perfusion and of the collateral flow contribution.

Finally, it should be considered that by crossing the stenosis, the pressure-monitoring catheter or guide wire contributes to the measured pressure gradient (9, 23). This contribution was shown to be dependent on the ratio of catheter-to-lumen diameter and to be relatively small for the ultrathin guide wires used today, especially if the wire is located eccentrically within the lumen (1). The analysis of our model would still hold because an increased stenosis resistance caused by the presence of a catheter would decrease both FFR and \( Q_c/Q_n \) to the same degree, as was shown by the excellent correlations obtained in animals with a pressure wire crossing the stenosis (36). However, one should realize that the hemodynamic effect of a stenosis may be markedly overestimated in clinical practice once the ratio of catheter-to-lumen diameter exceeds 0.4 (23), which translates into a 70% diameter stenosis for a 0.035-mm guide wire in a 3-mm vessel.

**Clinical implications.** FFR has been shown repeatedly to identify functionally relevant stenoses based on a cutoff value of 0.75, in both patients with normal ventricular function and patients with prior myocardial infarction, and our results do not refute its clinical usefulness. However, stenosis and coronary microvascular resistances are critical determinants of the value of FFR at the time of measurement. Limits of agreement between FFR and coronary flow velocity reserve caused by variability of microvascular resistance and the important role of stenosis resistance have been demonstrated by recent studies by our group (28–30). A gray zone around the cutoff value of 0.75 for clinical decision-making should therefore be appreciated, which is determined by the acute hemodynamic status of the patient (17). Moreover, our data demonstrate the risk of underestimating the contribution of a stenosis to a reduction in maximal blood flow, or of overestimating the fractional contribution of collateral flow, when \( P_b \) is assumed to be zero.

In conclusion, although FFR correctly represents the maximal flow ratio \( Q_c/Q_n \), if \( P_b \) is included in the calculation, its absolute value depends on hemodynamic conditions at the time of measurement, and FFR therefore cannot be considered a specific index for the epicardial stenosis alone. For intermediate lesions, which are not only close to the clinically used cutoff value but also more affected by hemodynamic changes than mild or severe lesions, the same stenosis can have an FFR above or below the cutoff value at different hemodynamic conditions. It is important to realize that both pressure- and flow-based indexes of flow reserve are a function of stenosis resistance and myocardial bed resistance, which vary as a consequence of variable hemodynamic conditions.

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