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

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Background. Severity of coronary artery stenosis has been defined in terms of geometric dimensions, pressure gradient-flow relations, resistance to flow and coronary flow reserve, or maximum flow capacity after maximum arteriolar vasodilation. A direct relation between coronary pressure and flow, however, may only be presumed if the resistances in the coronary circulation are constant (and minimal) as theoretically is the case during maximum arteriolar vasodilation. In that case, pressure measurements theoretically can be used to predict maximum flow and assess functional stenosis severity.

Methods and Results. A theoretical model was developed for the different components of the coronary circulation, and a set of equations was derived by which the relative maximum flow or fractional flow reserve in both the stenotic epicardial artery and the myocardial vascular bed and the proportional contribution of coronary arterial and collateral flow to myocardial blood flow are calculated from measurements of arterial, distal coronary, and central venous pressures during maximum arteriolar vasodilation. To test this model, five dogs were acutely instrumented with an epicardial, coronary Doppler flow velocity transducer. Distal coronary pressures were measured by an ultrathin pressure-monitoring guide wire (0.015 in.) with minimal influence on transstenotic pressure gradient. Fractional flow reserve was calculated from the pressure measurements and compared with relative maximum coronary artery flow measured directly by the Doppler flowmeter at three different levels of arterial pressure for each of 12 different severities of stenosis at each pressure level. Relative maximum blood flow through the stenotic artery (Qf) measured directly by the Doppler flowmeter showed an excellent correlation with the pressure-derived values of Qf (r=0.98±0.01, intercept=0.02±0.03, slope=0.98±0.04), of the relative maximum myocardial flow (r=0.98±0.02, intercept=0.26±0.07, slope=0.73±0.08), and of the collateral blood flow (r=0.96±0.04, intercept=0.24±0.07, slope=−0.24±0.06). Moreover, the theoretically predicted constant relation between mean arterial pressure and coronary wedge pressure, both corrected for venous pressure, was confirmed experimentally (r=0.97±0.03, intercept=9.5±13.3, slope=4.4±1.2).

Conclusions. These results provide the experimental basis for determining relative maximum flow or fractional flow reserve of both the epicardial coronary artery and the myocardium, including collateral flow, from pressure measurements during maximum arteriolar vasodilation. With a suitable guide wire for reliably measuring distal coronary pressure clinically, this method may have potential applications during percutaneous transluminal coronary angioplasty for assessing changes in the functional severity of coronary artery stenoses and for estimating collateral flow achievable during occlusion of the coronary artery. (Circulation 1993;86:1354–1367)

Keywords: • blood flow, collateral • coronary wedge pressure • coronary flow reserve, fractional • percutaneous transluminal coronary angioplasty

Severity of coronary artery stenosis can be quantified by all of its geometric dimensions or by gradient-flow relations reflecting its fluid dynamic effects. Coronary flow reserve has been related to or derived from geometric anatomy of a stenosis and its fluid dynamic characteristics.1–4 Thus, under conditions of maximum coronary vasodilatation, flow measurements

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alone expressed as coronary flow reserve without knowledge of stenosis geometry or pressure gradient is a simplified but theoretically accurate and complete descriptor of functional severity that has been validated experimentally as equivalent to geometric or fluid dynamic analysis and shown to be applicable clinically.\textsuperscript{1-6}

A direct relation between coronary pressure and flow or flow reserve, however, may be presumed only if coronary resistances remain constant (and minimal) as theoretically is the case during maximum arteriolar vasodilation. In that case, pressure measurements alone theoretically can be used to predict flow and thereby functional stenosis severity. Under those circumstances, coronary pressure measurements in principle also should be able to quantify collateral flow without using radiolabeled micropherses suitable only for experimental preparations. The concept of coronary pressure measurements alone during maximum vasodilation to assess stenosis severity, flow reserve, and collateral flow has not been reported previously, although it is important to our understanding of the fluid dynamics of the stenotic coronary artery.

Therefore, the purpose of this study was to describe systematically the theoretical basis for calculation of flow in the different components of the coronary circulation, including collateral flow, with pressure measurements during maximum coronary vasodilation; to validate experimentally this theoretical model; and to show its potential clinical applications for assessing changes in functional stenosis severity before and after percutaneous transluminal coronary angioplasty (PTCA). For this study, the maximally achievable coronary and myocardial flows in the presence of a stenosis are expressed as a fraction of their normal maximum values expected in the absence of a stenosis, defined as zero pressure gradient. Therefore, a normal coronary artery or normal reference distribution elsewhere in the heart is not necessary in this approach. Furthermore, the separate contributions of coronary arterial and collateral flow to myocardial perfusion can be quantitated. The basic theory is developed by the use of hemodynamic equations and validated experimentally in this report with potentially practical applications through PTCA.

**Methods**

**Theoretical Background**

Previous attempts to relate transstenotic pressure gradient $\Delta P$ to the functional significance of a stenosis have been disappointing such that at present only a few centers still routinely perform these measurements.\textsuperscript{7-13} Although decrease of $\Delta P$ after PTCA has been used to assess the success of the procedure, the correlation is poor and has little additional value over morphological assessment of results.\textsuperscript{7-13}

There are three reasons why pressure measurements have not been useful for assessment of flow. First, the instrument used for pressure measurement in previous studies (in most cases, the balloon catheter) is unsuitable because its size is too large compared with the size of the coronary artery. The cross-sectional area of an 80% area stenosis in a vessel with a diameter of 3.0 mm is almost completely obstructed by a 3F balloon catheter, which is the thinnest catheter available. Thus, with standard PTCA catheters, severe overestimation of $\Delta P$ may occur.\textsuperscript{7,14}

Second, most previous measurements have been made in the basal state,\textsuperscript{8-11,15,16} in which $\Delta P$ is determined primarily by flow as affected by distal coronary autoregulation. Flow and pressure are related to each other by epicardial and myocardial vascular resistances. These resistances are continuously changing under the influence of myocardial oxygen demand, arterial pressure, contrast injections, and coronary vasomotion. Therefore, theoretically, the relation between flow and pressure cannot be related to stenosis severity unless these resistances are known or at least remain constant. This condition can be met by obtaining pressure measurements during maximum vasodilation of the vascular bed when all resistances in the coronary circulation are close to minimal and presumably constant.\textsuperscript{1,2} As is true for coronary flow reserve, making functional measurements of stenosis severity from pressure measurements after maximum vasodilation is intuitively reasonable because the functional capacity of patients with ischemic heart disease is determined by the maximally achievable blood flow through the stenosis and its dependent myocardium.\textsuperscript{1,2,12,16,17} Although the necessity of maximum vasodilation generally is recognized at present, it has not been applied to measurements of pressure gradients in a number of previous studies.\textsuperscript{8-11,14,15}

Third, in previous studies for assessing stenosis severity by pressure measurements, coronary flow or improvement of flow has been related to transstenotic pressure gradient or decrease of that gradient or to transstenotic pressure gradient expressed as a percent of proximal arterial pressure.\textsuperscript{7-11,15} This approach is fundamentally limited because it fails to recognize that the stenosis is only one part of a complex hydrodynamic system of which other parts may also affect the influence of the stenosis on blood flow.

Gould and Kirkeeide\textsuperscript{3,4} first described a systematic analysis of flow-pressure relations that considered the coronary circulation as a system of serial resistances with the stenosis of the epicardial artery being one component. Their description, however, did not take into account the collateral circulation and as a result could not explain a number of experimental data. Therefore, we modeled the coronary circulation in flow-pressure terms after maximum vasodilation, including the contribution of flow through the epicardial coronary artery and the collateral flow to the total myocardial blood flow. In this specific restricted model of maximum vasodilation, measurements of pressures alone enable calculation of relative maximum flow in the epicardial coronary artery and the myocardium and the relative contribution of collateral flow. Therefore, this model theoretically provides a good measure of the functional significance of a coronary artery stenosis. Furthermore, changes in maximum coronary flow, myocardial flow, and collateral flow as a result of an intervention can be readily determined in this model through simple pressure measurements under the conditions of maximum vasodilation.

**Description of the Model**

The purpose of this model was to derive equations relating pressures to the regional distribution of maximal perfusion. Maximum flow through a stenotic ar-
tery is compared with what maximum flow would be in that same artery in the absence of that stenosis. Consequently, we express coronary flow reserve for a stenotic artery as a fraction of its normal expected value in that same artery in the absence of a stenosis. We therefore use the term “fractional flow reserve” (FFR). In the literature, the term “relative flow reserve” is used in the sense of a flow reserve relative to an adjacent normal coronary artery. However, a unique strength of the model described here is the theoretical capacity to determine FFR even in the presence of three-vessel disease when no normal adjacent coronary artery is present. FFR of the coronary artery defined in this way therefore represents the maximally achievable flow in the artery in the presence of a stenosis divided by maximum flow expected in the same artery in the absence of that stenosis. This parameter exactly indicates the degree to which the vessel’s function is affected by the stenosis. FFR of the myocardium supplied by the corresponding artery is defined in a similar way.

In Figure 1, modified from Gould, the coronary circulation is schematically represented as an arrangement of variable resistances in parallel and in series. For maximum vasodilation obtained by intracoronary administration of papaverine or adenosine, the resistances of the myocardial capillary bed (R) and the collateral circulation (Rc) are minimal and constant, and in that case the flow-dependent resistance (Rf) is maximal and therefore also constant. Rf may be changed by an intervention, such as PTCA. Mean arterial pressure (Pma), central venous pressure (Pcv), and coronary pressure distal to the stenosis (Pp) are defined in the usual way, whereas the coronary wedge pressure (Pw) is defined as the pressure distal to the stenosis during coronary artery occlusion. ΔP is defined as Pp - Pp. The total blood flow through the myocardial bed (Q) is the sum of the blood flow through the supplying, stenotic artery (Qs, also called coronary artery flow) and collateral flow (Qc). If no stenosis is present, Q and Qs are equal. Qs represents maximum myocardial and coronary blood flows in the case that the supplying coronary artery would be completely normal.

As stated before, FFR is defined as the maximally achievable flow in the presence of a stenosis divided by the maximum flow expected in the same distribution in the absence of a stenosis. In analogy to Qs and Q, fractional coronary artery flow reserve (FFRcor) and fractional myocardial flow reserve (FFRmyo) are defined as Qs/Qs and Q/Qs, respectively.

By using this model of the coronary circulation, the relation among Qs, Qs, and Qc can be elucidated, and both FFRcor and FFRmyo can be calculated by performing pressure measurements under maximum vasodilated conditions using Equations 2, 3, and 4. Different degrees of stenosis are indicated by the suffix (1) or (2), where the (1) can be considered a future equivalent to the condition before PTCA and the (2) thereafter.

As derived in the Appendix, the relation among Q1, Q2, Q1(Q2), Q2(Q1), and Q2(Q1) can be completely described by Equations 2–7, which theoretically means that maximum myocardial, coronary, and collateral flows can be compared before and after PTCA; that the contributions of coronary and collateral flows to myocardial flow can be quantified both before and after PTCA; and that all of these parameters can be expressed as a percentage of normal maximally achievable myocardial blood flow. The respective formulas are listed below. Their derivations, as well as examples of how to use them, are described in detail in the Appendix.

Equations for FFR and collateral blood flow. Equation 1, also derived in the Appendix, states the fundamental observation that the ratio of (Pp - Pp) to (Pp - Pp) is constant under conditions of maximum vasodilation:

\[
\frac{P_p - P_v}{P_p - P_v} = \frac{R_c}{R} = \text{constant}
\]

As explained later, Equation 1 is used in connection with Equation 2 in case P is not constant.

\[
\text{FFR}_{\text{cor}} = \frac{Q_{\text{s}}}{Q_{\text{s}}} = \frac{P_{\text{d}} - P_{\text{w}}}{P_{\text{d}} - P_{\text{w}}} = 1 - \frac{\Delta P}{P_{\text{d}} - P_{\text{w}}}
\]

\[
\text{FFR}_{\text{myo}} = \frac{Q}{Q} = \frac{P_{\text{d}} - P_{\text{v}}}{P_{\text{d}} - P_{\text{v}}} = 1 - \frac{\Delta P}{P_{\text{d}} - P_{\text{v}}}
\]

or

\[
Q = Q_s + Q_c
\]

\[
Q_c = (\text{FFR}_{\text{myo}} - \text{FFR}_{\text{cor}}) \cdot Q_s
\]
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\[
\frac{Q_s^{(2)}}{Q_s^{(1)}} = \frac{P_d^{(2)} - P_w^{(2)}}{P_d^{(1)} - P_w^{(1)}} 
\]

or

\[
\frac{\text{FFR}_{\text{myo}}^{(2)}}{\text{FFR}_{\text{myo}}^{(1)}} = \left(1 - \frac{\Delta (2) P}{P_d^{(2)} - P_w^{(2)}}\right) \left(1 - \frac{\Delta (1) P}{P_d^{(1)} - P_w^{(1)}}\right) 
\]

or

\[
\frac{\text{FFR}_{\text{myo}}^{(2)}}{\text{FFR}_{\text{myo}}^{(1)}} = \frac{\Delta (2) P}{\Delta (1) P} 
\]

Animal Instrumentation

After premedication with 0.1 mg fentanyl, 5.0 mg droperidol, and 0.5 mg atropine i.m., five mongrel dogs (weight, 24–36 kg) were anesthetized with 25 mg/kg sodium pentobarbital i.v. and ethrane. A left thoracotomy was performed, and the proximal left circumflex artery was dissected free. A perivascular ring-mounted 20-MHz pulsed Doppler transducer (Crystal Biotech Inc., Holliston, Mass.) was placed around the artery, and a circular balloon occluder (R.E. Jones, Silver Spring, Md.) was placed just distal to the Doppler probe. A femoral vein and two femoral arteries were dissected free. An 8F Millar manometer catheter (Millar microtipped-catheter transducer SPC-780 C) was introduced into the femoral vein and positioned into the right atrium for measurement of central venous pressure. Another 8F Millar manometer catheter was introduced into the left femoral artery and positioned into the ascending aorta, just above the aortic valve, for measurement of arterial pressure. A 6F left Judkins coronary arteriography catheter was introduced into the right femoral artery and advanced into the ostium of the left main coronary artery. Finally, a pressure-monitoring device was advanced through the Judkins catheter into the left circumflex artery and positioned with its tip 3–5 cm distal to the balloon occluder (Figure 2). This pressure-monitoring device consisted of a flexible synthetic tube with a length of 75 cm and an outer diameter of 0.028 in., connected to the distal 15 cm of an 0.015-in. pressure-monitoring guide wire (Advanced Cardiovascular System, Santa Clara, Calif.). Only the distal part of this device (i.e., the guide wire) was allowed to enter the coronary artery. The time constant of this device was determined in advance according to a protocol described earlier, and it never exceeded 1 second. ECG, venous pressure \( (P_v) \), aortic pressure \( (P_a) \), and phasic and mean coronary blood flow velocities in the left circumflex artery were continuously recorded on an eight-channel recorder (Hewlett-Packard).

Experimental Protocol

In all dogs, experiments were performed at three different levels of mean arterial pressure called the normotensive, hypertensive, and hypotensive states. After stabilization of all hemodynamic parameters, maximum coronary blood flow velocity in the left circumflex artery was measured after intracoronary (i.c.) administration of 8 mg papaverine through the guiding catheter into the left main coronary artery. This value was compared with maximum hyperemic blood flow velocity after a 20-second occlusion period to confirm that maximum arteriolar vasodilation was obtained by that dose of papaverine. Also, \( P_w \) was recorded at the end of that 20-second occlusion of the left circumflex artery. Thereafter, 12 different degrees of stenosis were induced in the left circumflex artery by partial inflation of the balloon occluder. Each stenosis was applied after an 8 mg papaverine i.c. injection through the guiding catheter. Next, \( P_w \), \( P_r \), and \( P_a \), were measured at the moment of maximum transtenotic pressure gradient, corresponding to peak coronary hyperemia (Figure 3). Measurement of \( P_a \) during occlusion of the coronary artery was repeated halfway through and at the end of the series of stenoses.

Intravenous infusion of phentolamine (0.05 mg/mL) then was started to achieve a steady-state arterial pressure of approximately 25–50% above the normotensive state. After the desired steady hypertensive state was achieved, another series of 12 measurements at 12 different degrees of stenosis was performed, preceded and followed by registration of \( P_a \) during total occlusion in a way identical to that described before.

Finally, intravenous administration of sodium nitroprusside (1 mg/mL) was started to create hypotension at an arterial pressure of approximately 25–50% below the initial value, and another series of measurements at 12 different degrees of stenosis was performed, again preceded and followed by determination of \( P_a \), respectively.
Figure 3. Example of hemodynamic recordings in one series of one dog. Central venous pressure (Pv), distal coronary pressure (Pd), mean aortic pressure (Pa), and phasic and mean blood flow velocity (Qs) in the left circumflex artery are recorded before vasodilation (first column), after intracoronary papaverine administration (second column), in the presence of a moderate (third column) and a severe stenosis (fourth column) induced at papaverine-induced maximum hyperemia, and at coronary artery occlusion (fifth column). O, occlusion of the coronary artery; P, intracoronary administration of 8 mg papaverine; R, release of stenosis; S, induction of stenosis.
TABLE 1. Mean Arterial Blood Pressure in the Five Experiments Without Medication, During Infusion of Phenylephrine and Nitroprusside, Respectively, as Well as Individual Correlation Coefficients, Slope, and Intercepts of Regression Lines of Relations Investigated in This Study

<table>
<thead>
<tr>
<th>Experiment</th>
<th>$P_a$ (mm Hg)</th>
<th>$FFR_{cor}$ vs. $Q_s/Q_s^N$</th>
<th>$FFR_{myo}$ vs. $Q_s/Q_s^N$</th>
<th>$(P_a-P_v)$ vs. $(P_w-P_v)$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P_a$</td>
<td>$r$</td>
<td>sl</td>
<td>int</td>
</tr>
<tr>
<td>1</td>
<td>77</td>
<td>97</td>
<td>59</td>
<td>0.99</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>115</td>
<td>40</td>
<td>0.97</td>
</tr>
<tr>
<td>3</td>
<td>67</td>
<td>98</td>
<td>50</td>
<td>0.99</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
<td>131</td>
<td>55</td>
<td>0.99</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>125</td>
<td>77</td>
<td>0.98</td>
</tr>
</tbody>
</table>

$P_a$, mean arterial blood pressure; 0, no medication; Ph, infusion of phenylephrine; N, nitroprusside; sl, slope; int, intercept; $P_a$, venous pressure; $P_a$, coronary wedge pressure; $FFR_{myo}$, fractional coronary flow reserve calculated from pressure measurements; $FFR_{myo}$, fractional myocardial flow reserve calculated from pressure measurements; $Q_s$, blood flow through the coronary artery at maximum vasodilation in the presence of a stenosis; $Q_s^N$, blood flow through the coronary artery at maximum vasodilation in the absence of a stenosis. The ratios $Q_s/Q_s^N$ were measured directly by perivascular Doppler.

Data Processing and Statistical Analysis

With this experimental protocol, in each dog values for $P_a$, $P_e$, and $P_v$ during maximum vasodilation were determined for 36 different stenoses at three different pressure states. At first, $P_a$, $P_e$, and $P_v$ as measured during the different coronary artery occlusions were substituted in Equation 1 to test the constancy of this expression. Thereafter, $FFR_{cor}$ and $FFR_{myo}$ were calculated according to Equations 2a and 3a, and these calculated values were compared with fractional coronary flow reserve ($Q_s/Q_s^N$) as measured directly by the epicardial Doppler probe. Correlation coefficients were calculated for each dog. Finally, at every degree of stenosis and at every pressure state, contribution of collateral blood flow was calculated according to Equation 4b. All hemodynamic data are expressed as mean±SD.

Results

Hemodynamic Observations and the Relation Between Mean Arterial Pressure and Coronary Wedge Pressure

No serious complications and no technical problems occurred in performing the pressure measurements. In every dog, maximum coronary blood flow in the presence of the different degrees of stenosis ranged from near 0% to 100% of the initial control value in the absence of a stenosis, thereby indicating that the complete spectrum of stenosis severities was represented. The ratio between maximum blood flow velocity after intracoronary papaverine injection (8 mg) and postocclusional maximum blood flow velocity at the start of each series was 0.99±0.03 (range, 0.95–1.03), confirming that the presence of maximum arteriolar vasodilation was obtained by this dose of papaverine. In Figure 3, examples of hemodynamic recordings at a number of steps in one series of stenoses for one dog are demonstrated. In all dogs, the three levels of arterial blood pressure were achieved (Table 1). In one dog, at the end of the hypertensive series, diffuse intrathoracic bleeding occurred and led spontaneously to arterial hypotension, which was controlled thereafter by fluid infusion to obtain a steady-state hypotensive level for completion of the third series of stenoses. No sodium nitroprusside was administered in this case.

The relation between $(P_a-P_v)$ and $(P_w-P_v)$ is shown for the individual dogs in Figure 4. As expected from theory (Equation 1), the experimentally observed relation is constant. The correlation coefficient is 0.97±0.03 with a slope of 4.4±1.2 and an intercept of 9.5±13.3 mm Hg (Table 1). This intercept is not significantly different from 0 (Student's t test). The slope of the regression line equals 1+$R_e/R$ and therefore can be considered to be a measure of the extent of collateral circulation. The resistance of the collateral circulation as a percentage of the resistance of the myocardial bed can be calculated directly from this slope.

Calculated Versus Measured FFR and Contribution of Collateral Flow to Total Flow

$FFR_{cor}$ as directly measured by the Doppler transducer ($Q_s/Q_s^N$) was compared with $FFR_{cor}$ as calculated from

![Figure 4. Plots of relation between (Pa-Pv) and (Pw-Pv) in the five dogs. The solid line indicates the least squares best fit of the data. Pa, mean aortic pressure; Pw, central venous pressure; Pw, coronary wedge pressure.](image-url)
pressure measurements by \((P_d-P_w)/(P_a-P_w)\) at maximum hyperemia according to Equation 2a. This relation is shown in Figure 5, with excellent correlation in all dogs and a correlation coefficient of 0.98±0.01, a slope of 0.98±0.04, and an intercept of almost 0 (0.02±0.03; Table 1). If these data of all dogs and all pressure levels are combined, the correlation coefficient is 0.98, the slope 0.97, and the intercept is 0.03. These data validate the basic, essential Equations 2 and 5 and prove the correctness of this part of the theoretical model experimentally.

The major goal of this study was to validate the basic concepts expressed in Equations 1 and 2 using multiple Doppler and pressure measurements over a wide range of flows and pressures as shown in Figures 4 and 5. We did not use radiolabeled microspheres for myocardial perfusion because large numbers of flow measurements could not be made with that technique. Consequently, we could not validate directly the prediction of FFRmno from pressure measurements (i.e., Equation 3). However, we obtained indirect support for the validity of Equation 3 by comparing FFRmno, predicted from pressure measurements by the expression \((P_d-P_w)/(P_a-P_w)\) according to Equation 3a, with \(Q_s/Q_s^N\) measured directly by Doppler. This relation is shown in Figure 6. For mild or no stenosis, \(Q_s/Q_s^N\) is equal to the calculated value \((P_d-P_w)/(P_a-P_w)\) because collateral flow is negligible in that case. With more severe stenoses, FFRmno and FFRmno are both reduced, and \((P_d-P_w)/(P_a-P_w)\), representing calculated FFRmno, is related to but larger than \(Q_s/Q_s^N\), representing measured FFRmno to the extent that collateral flow contributes to myocardial perfusion. As shown in Figure 6, a good correlation is present between \(Q_s/Q_s^N\), measured by Doppler, and \((P_d-P_w)/(P_a-P_w)\), representing FFRmno from pressure measurements \((r=0.98±0.02, slope=0.73±0.08, intercept=0.26±0.07)\). With total occlusion, \(Q_s/Q_s^N\) is 0, and the y intercept theoretically indicates the relative contribution of collateral flow to the myocardium, achievable during total occlusion.
Discussion

In our model of a stenotic arterial system at maximum arteriolar vasodilation, the flow expressed as a fraction of normal maximum flow in the absence of a stenosis can be calculated from measurements of the relevant pressures, provided that vascular resistances are constant as theoretically is the case at maximum vasodilation. These calculated values of FFR correspond closely to those directly measured by Doppler velocity meter, thereby confirming the validity of the concept that pressures alone under conditions of maximum vasodilation are related to maximum flow.

The basis for coronary flow reserve or maximum flow as a functional measure of stenosis severity has been well established.1-5,12,17 Since the concept of flow reserve was first introduced as a measure of stenosis severity, absolute coronary flow reserve, defined as maximum flow divided by resting flow, has been considered the standard for the functional status of a coronary artery for many years.22 In clinical practice, however, measuring absolute coronary flow reserve has limited applications largely due to methodological limitations.1,16,23-26 In addition, because coronary flow reserve is defined as a ratio, diminished coronary flow reserve can reflect decreased maximum flow, increased resting...
The functional significance of a stenosis or the improvement by PTCA. In a recent study, we demonstrated an excellent correlation between increase in maximum blood flow after PTCA measured by videodensitometry and improved exercise test result, emphasizing the value of maximum flow as a clinically relevant end point.

For assessing functional significance of coronary artery disease by pressure measurements, most previous studies have measured transstenotic pressure gradient or this gradient in relation to arterial pressure.\(^1\)\(^,\)\(^9\)\(^,\)\(^11\)\(^,\)\(^15\)\(^,\)\(^27\) Equations 1–7 indicate that measuring gradients only is an incomplete approach. Our model and results show that with increasing severity of stenosis, the contribution of collateral flow increases considerably, even in acutely studied dogs. Corresponding FFR of the coronary artery is overestimated when based on Equation 3 or 6 instead of the more complete Equations 2 and 5. Thus, coronary FFR should be calculated using Equation 2 or 5 rather than Equation 3 or 6, as initially proposed by Gould et al.\(^5\) but incomplete in failing to account for collateral flow. Myocardial FFR, on the other hand, can be correctly addressed by Equations 3 and 6.

In the present study, the separate contributions of flow through the supplying coronary artery and collateral flow to myocardial blood flow can be differentially quantified. According to our calculations, the maximum recruitable collateral flow, as encountered during coronary artery occlusion, ranged from 18% to 36% of normal maximum myocardial blood flow. These data are compatible with a former study by Schaper in chronic instrumented dogs.\(^28\) In that study, maximum collateral flow was approximately 30% of maximum myocardial blood flow.

Our model also shows that reduction of a transstenotic pressure gradient (e.g., from 40 to 10 mm Hg) by PTCA does not carry the same meaning in different patients, even when arterial pressure is identical in both patients. The extent of collateral flow represents a significant associated variable, where the effects of collaterals are not represented exclusively by \(P_c\) at coronary occlusion but also significantly depend on simultaneously measured \(P_c\) and \(P_r\). From Equation 4b, applied during complete coronary artery occlusion (in which case FFR\(_{\infty}\) equals 0), it can be shown that the collateral flow expressed as a fraction of normal maximum myocardial flow equals \(Q_c/Q^0 = (P_r - P_c)/(P_r - P_c)\). Therefore, according to our theory, \(P_r = 20\) mm Hg in an individual with \(P_c = 90\) mm Hg and \(P_r = 10\) mm Hg indicates a collateral contribution of only 12.5% of maximum myocardial perfusion, whereas the same \(P_r\) in another individual with a simultaneously measured \(P_r = 70\) mm Hg and \(P_c = 0\) mm Hg results in a collateral contribution of 29% of maximum myocardial perfusion. This example illustrates why \(P_c\) alone does not reliably reflect the extent of collateral circulation, as assumed in previous studies.\(^8\)\(^,\)\(^13\)

**Limitations of the Model**

Our model applies only to maximally dilated conditions when all resistances are constant and the derivation of flow reserve from pressure is possible. In this study, maximum arteriolar vasodilation and the resulting constant resistances were achieved by intracoronary administration of papaverine. Papaverine has been

**FIGURE 7.** Diagram from one of the experiments, illustrating how at every arbitrary degree of stenosis the contribution of coronary \((Q_c)\) and collateral blood flow \((Q_s)\) to myocardial blood flow \((Q)\) can be estimated from the regression lines of FFR\(_{\text{cor}}\) [fractional coronary artery flow reserve] and FFR\(_{\text{myo}}\) [fractional myocardial flow reserve] (top panel). Pressure-derived collateral blood flow, according to Equation 4b, is presented in bottom panel. In the absence of a stenosis, \(Q_c = Q_s\) whereas \(Q_s = 0\). At total occlusion, \(Q_c = 0\) and \(Q_s = Q_s\). In bottom panel, the intercept of the regression line with the \(y\) axis represents the collateral flow achievable at total occlusion, expressed as a fraction of normal maximum myocardial flow \((Q^0)\).
shown to induce maximum coronary and myocardial hyperemia within 30 seconds after intracoronary administration. The duration of maximum vasodilation, approximately 30 seconds, is long enough to permit reliable pressure measurements after which the effect completely vanishes within minutes so that repeated measurements may be made.19,21 Although polymorphous ventricular tachycardia associated with prolongation of the QT interval has been described,29 in our experience with more than 600 patients, serious dysrhythmias occurred in only two cases. Theoretically, other pharmacological stimuli such as intravenous or intracoronary adenosine also may be used.20 However, the plateau phase after an intracoronary bolus of adenosine in a recommended dose of 16 µg is quite short (approximately 10 seconds), and no steady-state distal coronary pressure may be reached, whereas very high doses of intracoronary adenosine of >60 µg will give longer-lasting maximum hyperemia but often are accompanied by pronounced bradycardia. Intracoronary infusion of adenosine at a sufficient rate induces steady-state maximum hyperemia, but this method of administration prevents recording of arterial pressure by the guiding catheter. Finally, intravenous adenosine will achieve maximum hyperemia in only 84% of the patients and sometimes is accompanied by various side effects.20 Therefore, in our view papaverine remains the best coronary vasodilation for this kind of study in the human coronary circulation and is used routinely for this purpose in our laboratory.

In the present study, flow ratios were assessed by a Doppler velocity meter, which could have been influenced by changes in luminal diameter of the coronary artery associated with the arteriolar vasodilation. However, as shown by Wilson and White21 in a previous study, no significant changes in epicardial luminal diameter occur after intracoronary papaverine injection. Therefore, it is assumed that ratios of flow were accurately represented by ratios of flow velocity.

A prerequisite for correct pressure measurements is a sufficiently small catheter or guide wire that has a negligible effect on the transstenotic pressure gradient. Standard PTCA catheters do not meet this criterion, and severe overestimation of ΔP may have occurred in former studies. Recently, we demonstrated that for a wide range of stenosis severity, ΔP decreased significantly if pressure was measured by a small pressure-monitoring guide wire with a cross-sectional area of only 0.11 mm² compared with measurements by a standard balloon catheter with a cross-sectional area of 0.72–1.0 mm².7 The device used for measuring distal coronary pressure in this study is of comparable small size and occupies only 25% of the area of a 90% area stenosis in a moderate-sized coronary artery with a diameter of 2.5 mm. It consists of a main proximal part with a length of 75 cm and diameter of 0.71 mm (0.028 in.) connected to the distal 15 cm of the hollow pressure-monitoring guide wire with a diameter of 0.38 mm (0.015 in.) in. Advanced Cardiovascular Systems, Santa Clara, Calif.). Only the distal part of this device—the guide wire—entered the coronary artery in this study. The guide wire–tipped device is a prototype to test our concept as a basis for developing the complete wire.

Our model is not intended to address or separately account for a number of phenomenon affecting pressure and flow, such as extravascular compression and critical closing pressure, because the model deals with flow and pressure as end points affected by net accumulation of these phenomenon lumped together.30–35 Our results give only some indirect support to former observations that in maximally vasodilated beds, critical closing pressure exceeds coronary venous pressure by only a few millimeters of mercury.32 To whatever extent these factors affect pressure and flow, they are accounted for through the pressure measurements at maximal vasodilation.

The capacitance characteristics of the coronary vascular bed may affect its instantaneous, phasic pressure flow patterns.36,37 In this study, however, the end points measured are mean pressures at steady-state maximum flow or at steady-state levels after coronary occlusion. Therefore, because capacitance effects cancel out over diastole and systole, mean pressure measurements theoretically are not affected. Furthermore, because pressures at coronary occlusion were measured only after reaching a steady state, venous capacitance effects also are avoided in our study. Consequently, we believe that potential effects of capacitance are not germane and do not have to be accounted for in our model or in its potential clinical applications.

Our model assumes that maximally recruitable flow in collaterals remains constant throughout the procedure of a number of brief total occlusions for measuring P.. The literature indicates different and sometimes variable time constants for opening collateral channels compared with our measurement period,37,38–42 subject to further experimental validation. Therefore, it should be emphasized that changes in recruitable collateral flow during the procedure would invalidate the conceptual interpretation of our model. The excellent correlation between pressure-derived FFR and directly measured FFR provide strong indirect evidence for the correctness of our equations for measuring collateral flow. However, further confirmation of the details of our model for collateral flow is warranted and requires a different animal model in which arterial flow and separate collateral and myocardial perfusion are measured by radiolabeled microspheres. Because large numbers of flow measurements could not be made with that technique and because proof of Equations 2 and 5 was most essential to our concept, we used the simpler animal model described here to compare FFR calculated from pressure measurements to direct measurements of relative maximum coronary flow, thereby validating the essential concept and the most complex Equations 2 and 5 directly.

Our results raise some conceptual questions that need further investigations in carefully controlled animal and human studies. Strictly speaking, we have validated the model in Figure 1 by experimental one-vessel disease with collateral flow that enters at the prearteriolar level. Although theoretically our equations are also true with repetitive units of the model in Figure 1 that would be the equivalent of multivessel disease, further validation studies are warranted.

Assessment of relative flow reserve by imaging techniques becomes problematic in diffuse or balanced three-vessel disease where relative flow reserve may erroneously appear normal despite extensive coronary artery disease.1 Pressure, however, is a universal measure of the
function of the coronary vascular system for different sizes of regional coronary vascular beds with and without coronary artery disease. Therefore, theoretically, our approach should predict FFR accurately even in the presence of balanced three-vessel disease. This hypothesis, however, remains to be tested experimentally.

Another important qualification is necessary in the presence of small vessel disease distal of the location where $P_d$ and $P_r$ are measured, as occurs in diabetes. In that case, Equations 2a and 3a represent maximum flow in the presence of an epicardial stenosis, expressed as a fraction of maximum flow in the absence of that epicardial stenosis, but still not normal because of the distal small vessel disease. The value of this method for assessing the increase of maximum flow by PTCA would not be affected by that limitation. However, in that case, ambiguity would remain about normal reference flow due to presence of small vessel disease.

A final issue that should be addressed in this context is coronary steal, a clearly recognized, well-documented phenomenon occurring in a number of patients with collateral circulation during maximum vasodilatation. In our opinion, however, this phenomenon is already accounted for in our model because any decrease in $Q_e$ caused by increased conductance of the artery supplying the collaterals is reflected by a lower coronary wedge pressure ($P_w$).

**Clinical Implications**

The methods used in this animal study are applicable in humans during PTCA provided that a pressure-monitoring guide wire is used with a small size similar to that of the distal part of our device. No simplifications, adaptations, or additional hypotheses are necessary. The guide wire should be positioned across the stenosis as usual. Before the lesion is crossed with the PTCA balloon, a maximum vasodilatory stimulus such as papaverine is administered through the guiding catheter, and $P_d$ and $P_r$ can be measured by the guiding catheter and the pressure-sensitive guide wire tip, respectively. During balloon inflation, $P_a$ and $P_r$ again are recorded. After the last balloon inflation, when the balloon has been pulled back but the guide wire remains in situ, $P_a$ and $P_r$ are measured again after intracoronary administration of papaverine. $P_r$ after papaverine can be measured directly with a Swan-Ganz catheter or estimated from the neck veins. If venous pressure is not elevated and one is only interested in increase of $\text{FFR}_{\text{cor}}$, after the PTCA (which is most important from the view of the interventional cardiologist), the venous pressure may be neglected because its influence on Equation 2 or 5 is minimal in that case. The complete pressure-measuring sequence can be implemented during routine PTCA with prolongation of the procedure by only a few minutes. Other than a pressure-monitoring guide wire, no special equipment is needed. No special instructions to the patient or extra contrast injections or other manipulations are necessary. Therefore, coronary FFR of the instrumented artery and its dependent myocardium as well as the contribution of collateral flow would be readily obtainable before and after the intervention. Due to the necessity of determining $P_a$ at balloon inflation, this approach is not suitable for diagnostic cardiac catheterization.

Despite its importance for understanding coronary artery disease, a clinically feasible method for quantitative assessment of collateral blood flow has not been described previously. Our study provides the theory and experimental bases for a potential clinical method for assessing FFR and collateral flow during PTCA.

Thus, despite some limitations, this model, based on pressure measurements at maximum vasodilation, provides a functional measure of stenosis severity and important insights into maximum coronary, collateral, and myocardial blood flows before and after PTCA with potential clinical application.

**Appendix**

It should be kept in mind that all of the theoretical considerations in this appendix apply to a system at maximum vasodilation. Therefore, the resistances $R$ and $R_c$ are minimal and constant.

First, it will be proved that the ratio between mean arterial pressure ($P_a$) and coronary wedge pressure ($P_r$), both after subtraction of venous pressure ($P_v$), is constant. For that purpose, suppose in Figure 1, at any arbitrary pressures $P_a$ and $P_r$, that $R_c=\pi$ and $Q=0$, as with total occlusion; then, $Q=Q_c$ and $P_a=P_r$, by definition. In that case:

$$P_a-P_r=Q(R+R_c)$$

and

$$P_a-P_r=QR$$

Therefore

$$P_a-P_r=QR$$

$$P_a-P_r=QR$$

Equation A1a can also be rearranged into the following two forms, which will be helpful in later considerations:

$$P_a-P_r=QR$$

and

$$P_a-P_r=QR$$

where $C_1$, $C_2$, and $C_3$ are all different constants characterizing collateral resistance relative to the resistance of the myocardial bed supplied by the collaterals at maximum vasodilation.

The second step is the calculation of fractional flow reserve of the stenotic coronary artery ($\text{FFR}_{\text{cor}}$). By definition,

$$\text{FFR}_{\text{cor}}=\frac{Q/Q_c}{Q/Q_c}$$

Because $Q^c=0$:

$$\text{FFR}_{\text{cor}}=\frac{Q/Q_c}{Q^c}$$

Substitution of the constant value $C_1$, obtained from Equation A1b, gives the following:
Flow Assessment by Pressure Measurements at PTCA

\[ FFR_{cor} = \frac{(P_d - P_w)(P_a - P_d) - (P_a - P_w)(P_d - P_w)}{(P_a - P_w)(P_a - P_d)} \]

\[ = \frac{P_d - P_w}{P_a - P_w} \]

\[ = 1 - \frac{\Delta P}{P_a - P_w} \]  

(A2a)

Equation A2 has been derived previously by Gould.\(^{1,5}\)

The contribution of collateral flow to total flow now is calculated as follows:

\[ FFR_{myo} = \frac{Q}{Q_N} = \frac{Q}{Q_{N}} \]

and because \(Q_N = Q_N^c\), this can be written as the following:

\[ Q_c = (FFR_{myo} - FFR_{cor}) \cdot Q_N \]  

(A4b)

Next, fractional flow reserve of the myocardium (FFR\(_{myo}\)) is calculated as follows:

\[ FFR_{myo} = \frac{Q}{Q_N} = \frac{Q}{Q_{N}} \]

Equation A3 has been derived previously by Gould.\(^{1,5}\)

The contribution of collateral flow to total flow now is calculated as follows. By definition,

\[ Q = Q_c + Q_s \]  

(A4a)

Therefore:

\[ Q_c = \frac{Q}{Q_N} \cdot Q_N \]

and because \(Q_N = Q_N^c\), this can be written as the following:

\[ Q_c = (FFR_{myo} - FFR_{cor}) \cdot Q_N \]  

(A4b)

In case of interventions, it should be realized that flow at maximum vasodilation is directly proportional to the driving pressure \(P_d - P_w\). Therefore, the ratio between maximum flow through the coronary artery before (situation 1) and after the intervention (situation 2) can be written as the following:

\[ \frac{Q_1}{Q_2} = \frac{Q_2}{Q_2^N} \cdot \frac{Q_1^N}{Q_1} \]

\[ = FFR_{cor} \cdot \frac{P_{2a} - P_{2w}}{P_{1a} - P_{1w}} \cdot \frac{1}{FFR_{cor}^{(1)}} \]

\[ = FFR_{cor} \cdot \frac{P_{2a} - P_{2w}}{P_{1a} - P_{1w}} \cdot \frac{1}{FFR_{cor}^{(1)}} \]

By substitution of Equations A1c and A2a:

\[ \frac{Q_1}{Q_2} = \frac{Q_2}{Q_2^N} \cdot \frac{Q_1^N}{Q_1} \]

Note that for evaluation of the functional improvement of a stenotic artery after PTCA, \(FFR_{cor}^{(2)} / FFR_{cor}^{(1)}\) theoretically is a better measure than \(Q_2 / Q_1\) because the first expression is independent of arterial pressure. From Equation A2b it is clear that

\[ FFR_{cor}^{(2)} / FFR_{cor}^{(1)} = \frac{P_{2a} - P_{2w}}{P_{1a} - P_{1w}} \]

and by substituting Equation A1a.

Theoretically, maximum blood flow through the myocardium can be compared before and after the intervention by:

\[ \frac{Q_2}{Q_1} = \frac{Q_2}{Q_1} \cdot \frac{Q_1}{Q_1^N} \cdot \frac{Q_1^N}{Q_1} \]

or, if correction for pressure changes is made, by:

\[ \frac{Q_2}{Q_1} = \frac{Q_2}{Q_1} \cdot \frac{Q_1}{Q_1^N} \cdot \frac{Q_1^N}{Q_1} \]

Finally, the theoretical relation between collateral flow at different degrees of stenosis can be obtained. From Figure 1, it is clear that \(Q_c = (P_d - P_w)/Rc\). Therefore:

\[ \frac{Q_2}{Q_1} = \frac{Q_2}{Q_1} \cdot \frac{Q_1}{Q_1^N} \cdot \frac{Q_1^N}{Q_1} \]

or, if correction for pressure changes is made:

\[ \frac{Q_2}{Q_1} = \frac{Q_2}{Q_1} \cdot \frac{Q_1}{Q_1^N} \cdot \frac{Q_1^N}{Q_1} \]

In fact, Equation A7 states that decrease of \(\Delta P\) by improved stenosis geometry after PTCA induces a proportional decrease of the relative contribution of collateral flow to total myocardial flow, which will be further clarified in the following examples.

Application of these equations in clinical practice also will be demonstrated.

Example 1

The first example is based on the simple hemodynamic case in which systemic pressures (\(P_s\) and \(P_i\)) are unchanged during PTCA. Therefore, according to Equation A1a, wedge pressure (\(P_w\)) is constant.

Before and after PTCA of one of the coronary arteries, pressure measurements are performed by the pressure-monitoring guide wire at maximum coronary hyperemia induced by intracoronary administration of papaverine or adenosine. Mean arterial pressure (\(P_a\)) is 90 mm Hg both before and after the procedure; transstenotic pressure gradient \(\Delta P\) is reduced from 50 mm Hg before to 10 mm Hg after the procedure; and venous pressure (\(P_v\)) is 0 both before and after the procedure. \(P_a\) measured during balloon inflation, is 20 mm Hg. Therefore, \(P_a^{(1)} = 90\) mm Hg, \(P_a^{(2)} = 40\) mm Hg, \(P_a^{(2)} = 80\) mm Hg, \(P_a^{(1)} = 20\) mm Hg, and \(P_v^{(1)} = P_v^{(2)} = 0\) mm Hg.

With Equations A6b, A5b, and A7b, the following is obtained:

\[ FFR_{myo}^{(2)} / FFR_{myo}^{(1)} = (1 - 10/90):(1 - 50/90) = 2.0 \]

\[ FFR_{cor}^{(2)} / FFR_{cor}^{(1)} = (1 - 10/70):(1 - 50/70) = 3.0 \]

\[ Q_2 / Q_1 = (10/90):50/90 = 1.5 \]
In other words, maximally achievable blood flow through the myocardium increased by a factor 2; maximally achievable blood flow through the dilated artery increased by a factor 3; and collateral blood flow decreased by a factor 5.

By using Equations A2b, A3b, and A4b (both before and after PTCA), one obtains the values of all flow parameters expressed as a fraction of normal maximum myocardial blood flow expected in the absence of a stenosis and normalized for pressure changes:

\[
\begin{align*}
    FFR(1)_{max} &= 4/9 = 28/63 = 0.44 \\
    FFR(2)_{max} &= 8/9 = 56/63 = 0.89 \\
    FFR(1)_{coll} &= 2/7 = 18/63 = 0.29 \\
    FFR(2)_{coll} &= 6/7 = 54/63 = 0.86
\end{align*}
\]

\[
Q(1)_{max} = 4/9 - 2/7 = 10/63 = 0.15 \\
Q(2)_{max} = 8/9 - 6/7 = 2/63 = 0.03
\]

or, in summary:

<table>
<thead>
<tr>
<th></th>
<th>Before PTCA</th>
<th>After PTCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractional myocardial flow</td>
<td>0.44</td>
<td>0.89</td>
</tr>
<tr>
<td>Fractional coronary flow</td>
<td>0.29</td>
<td>0.86</td>
</tr>
<tr>
<td>Fractional collateral flow</td>
<td>0.15</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Such a matrix completely describes the distribution of flow in the coronary circulation both before and after PTCA.

Example 2

The second example demonstrates the calculations when mean arterial and venous pressure do change during PTCA.

PTCA is performed of one of the coronary arteries. At maximum coronary hyperemia, mean arterial pressure is 96 mm Hg before and 80 mm Hg after PTCA. \( \Delta P \) is 45 mm Hg before and 15 mm Hg after the procedure; and venous pressure is 6 mm Hg before and 5 mm Hg after the procedure. \( P_c \) is 23 mm Hg during balloon inflation. Mean arterial pressure during balloon inflation is 92 mm Hg, and mean venous pressure during balloon inflation is 6 mm Hg.

In this case, with changing \( P_a \) and \( P_r \), at first \( P(1)_{max} \) and \( P(2)_{max} \) have to be calculated because \( (P \times P)/P \) is constant according to Equation A1a: Because \( P(1)_{max} = 24 \) mm Hg, and \( P(2)_{max} = 20 \) mm Hg, in an identical way as in example 1, Equations A6b, A5b, and A7b are used to calculate the following:

\[
\begin{align*}
    FFR(2)_{max}/FFR(1)_{max} &= (1 - 15/75):(1 - 45/90) = 1.6 \\
    FFR(2)_{coll}/FFR(1)_{coll} &= (1 - 15/60):(1 - 45/72) = 2.0 \\
    Q(2)/Q(1)_{max} &= 15/75:45/90 = 1.25
\end{align*}
\]

In other words, maximally achievable blood flow through the myocardium increased by a factor 1.6, maximally achievable blood flow through the dilated artery increased by a factor 2, and collateral flow decreased by a factor 2.5.

By using Equations A2b, A3b, and A4b (both before and after PTCA), one obtains the values of all flow parameters, expressed as a fraction of normal maximum myocardial blood flow expected in the absence of a stenosis and normalized for pressure changes:

\[
\begin{align*}
    FFR(1)_{max} &= 0.50 \\
    FFR(2)_{max} &= 0.375 \\
    FFR(1)_{coll} &= 0.125
\]

\[
\begin{align*}
    FFR(2)_{coll} &= 0.40 \\
    Q(1)_{max} &= 0.03 \\
    Q(2)_{max} &= 0.06
\end{align*}
\]

References

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.

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