Pressure-Derived Measurement of Coronary Flow Reserve

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OBJECTIVES
We aimed to validate the technique of measuring the coronary flow reserve (CFR) with coronary pressure measurements against an established thermodilution technique.

BACKGROUND
The CFR has traditionally required measurement of coronary blood flow velocity with the Doppler wire and, more recently, using a thermodilution technique with the coronary pressure wire. However, recent work has suggested that the CFR may be derived from pressure measurements alone (the ratio of the square root of the pressure drop across an epicardial stenosis during hyperemia to that value at rest). This depends on the assumption that friction losses across a coronary stenosis are negligible.

METHODS
We compared pressure-derived CFR values with those obtained by the thermodilution technique using the intracoronary pressure wire in 38 stenoses in 34 patients with significant coronary stenoses undergoing percutaneous intervention. We also compared these two techniques of measuring CFR in 25 stenoses (6 vessels) artificially created by inflating small balloons within a stented coronary artery after percutaneous intervention.

RESULTS
There is a close linear relationship between pressure-derived and thermodilution CFR in native (r² = 0.52; p < 0.001) and artificial stenoses (r² = 0.54; p < 0.05), although the pressure-derived technique appears to systematically underestimate CFR values in both situations. This applies to native and artificial stenoses.

CONCLUSIONS
Coronary flow reserve cannot be measured merely with pressure alone, and it cannot be safely assumed that friction losses are negligible across a native coronary stenosis. These data suggest that friction loss is an important determinant of the pressure gradient along an atherosclerotic coronary artery. (J Am Coll Cardiol 2005;45:216–20) © 2005 by the American College of Cardiology Foundation

The coronary flow (velocity) reserve (CFR), defined as the ratio of hyperemic to baseline blood flow, is an established index to gauge the effect of a coronary stenosis on myocardial flow. It is used clinically when investigating the substrate for myocardial ischemia and evaluates resistance in both the epicardial and microvascular compartments (1). Although the CFR can be measured non-invasively using echocardiography (2) and positron emission tomography (3), the traditional clinical technique has been invasive, utilizing the Doppler flow wire (4) and, more recently, coronary thermodilution (5–8).

The latter method takes advantage of the fact that the micromanometer tip of the pressure wire acts as a thermistor, allowing the generation of a thermodilution curve and the derivation of the mean transit time of an intracoronary saline bolus. Thermodilution-derived CFR correlates better with absolute flow reserve in animals (7) and is easier to apply in humans than Doppler-derived flow reserve (8). In addition, it has the major advantage of allowing simultaneous measurement of fractional flow reserve (FFR) and CFR with one single guide wire.

Another recently proposed technique of measuring the CFR uses only pressure data derived from the intracoronary pressure wire during rest and maximal hyperemia, the “pressure-derived CFR.” This technique is derived mathematically and has recently been validated against Doppler flow-derived values of CFR (9).

We undertook this study to compare simultaneously obtained values of thermodilution CFR with pressure-derived CFR using a single intracoronary pressure wire in patients with coronary artery disease.

METHODS
Appropriate approval from the local ethics committee was obtained before commencement of the study, and all patients gave informed consent.

Theory. The general fluid dynamic equation has been proposed to evaluate the pressure gradient induced by an epicardial coronary stenosis (1,10).

\[ \Delta P = fQ + sQ^2 \]  

The two terms of the equation correspond to different mechanisms of pressure (energy) loss across the obstruction. The constant “f” represents viscous friction at the site of the
lesion, the constant “s” represents expansion losses caused by convective acceleration of blood beyond the stenosis, and “Q” is coronary blood flow (10). The relative importance of the various components of this equation, therefore, varies according to the stenosis analyzed. At low flow rates or very long stenosis lengths, friction is the most important determinant of energy loss. However, at higher coronary flow rates (within the physiological range) and short or moderate stenosis lengths, friction loss is generally considered negligible (10). Therefore, assuming, indeed, that this term can be neglected, ΔP is only proportional to Q², i.e.,

\[ \Delta P \propto Q^2 \]  \[2\]

therefore,

\[ \sqrt{\Delta P} \propto Q \]  \[3\]

so if:

\[ \text{CFR} = \frac{Q_{\text{during hyperemia}}}{Q_{\text{at rest}}} \]  \[4\]

then:

\[ \text{CFR} = \frac{\sqrt{\Delta P}_{\text{during hyperemia}}}{\sqrt{\Delta P}_{\text{at rest}}} \]  \[5\]

Values of \( \sqrt{\Delta P} \) (i.e., the square root of the pressure gradient across the coronary lesion) can be obtained easily and accurately from the intracoronary pressure wire. At the same time, thermodilution CFR can be obtained, and the two methods of measuring CFR can be compared.

**Protocol 1—CFR in de novo epicardial stenoses.** We studied 38 coronary arteries in 34 patients. All vessels studied had an angiographically significant epicardial stenosis (>60% luminal diameter stenosis) and a resting pressure gradient of ≥10 mm Hg as measured by the intracoronary pressure wire. It was important to exclude stenoses with low resting gradients because of the potential error this would introduce into Equation 5 in the preceding text. All lesions were assessed with off-line quantitative angiography. After anticoagulation with weight-adjusted unfractionated heparin and treatment with intracoronary nitrates, the study vessel was instrumented with an intracoronary pressure wire (RADI Medical, Uppsala, Sweden). The aortic pressure (Pₐ) was measured from the guiding catheter, and the distal coronary pressure (Pₚ) was measured from the pressure wire positioned distal to the stenosis, as previously described (5,6). The algorithm used to calculate the mean transit time (Tₘₚ) of each thermodilution curve has been slightly altered as recently described (8). After baseline measurements of Pₐ, Pₚ, and mean transit time of a room temperature 3-ml bolus of saline (all acquired in triplicate), maximal hyperemia was induced with either intracoronary papaverine (12-mg bolus in the left coronary artery; 8 mg in the right coronary artery [RCA]) or intravenous adenosine administered into the femoral vein (140 μg/kg/min). Measurements were repeated during maximal hyperemia (5–7).

**Protocol 2—CFR in artificial stenoses.** In order to create a series of “artificial stenoses” of varying severity within the same vessel, six vessels (from six separate patients) were studied after the deployment of an intracoronary stent. These vessels all had a reference diameter of ≥3.0 mm and a stented segment length of ≥15 mm. The “stenoses” were created by the inflation of smaller diameter balloons (1 mm smaller than the final stent diameter) within the stented segment with acquisition of pressure and thermodilution data at rest and during hyperemia at each stage. This allowed the comparison of thermodilution CFR with pressure-derived CFR in a large range of stenosis severities.

**Statistics.** The data are presented as mean values ± SD. Variability between three measurements was defined as:

\[ \text{Var}(a_1, ..., a_n) = \frac{\text{Max}|a_i - \bar{a}|}{\bar{a}} \]

Linear regression analysis was used when appropriate. A Bland-Altman plot is provided. This plot depicts the relationship between the average value between thermodilution CFR and pressure-derived CFR and the absolute difference between thermodilution CFR and pressure-derived CFR (11). A value of p ≥ 0.05 was considered statistically not significant.

**RESULTS**

**Baseline characteristics.** The baseline characteristics of the patients are given in Table 1. The de novo stenoses were located in the left anterior descending coronary artery (LAD) (n = 20 [52.6%]), in the RCA (n = 9 [23.7%]), and in the left circumflex artery (LCx) (n = 9 [23.7%]). The artificial stenoses were created in the LAD (n = 4), in the LCx (n = 1), and in the RCA (n = 1).

### Table 1. Baseline Clinical and Quantitative Angiographic (QCA) Characteristics of Patients in Protocols 1 and 2

<table>
<thead>
<tr>
<th>Protocol 1</th>
<th>Protocol 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 34 Patients; 38 Stenoses)</td>
<td>(n = 6 Patients; 25 Stenoses)</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>67.8 ± 11.1</td>
</tr>
<tr>
<td>% Male</td>
<td>76.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (50%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>17 (50%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (20.6%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>18 (52.9%)</td>
</tr>
<tr>
<td>Family history of IHD</td>
<td>10 (29.4%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>69.7 ± 15.3</td>
</tr>
<tr>
<td><strong>QCA</strong></td>
<td></td>
</tr>
<tr>
<td>% Stenosis</td>
<td>62.4 ± 17.3</td>
</tr>
<tr>
<td>Reference diameter (mm)</td>
<td>3.1 ± 0.7</td>
</tr>
<tr>
<td>MLD (mm)</td>
<td>1.1 ± 0.4</td>
</tr>
</tbody>
</table>

Ejection fraction is calculated from left ventricular angiography.

IHD = ischemic heart disease; MLD = minimal luminal diameter before angioplasty.
De novo epicardial stenoses. The average diameter stenosis of 38 de novo lesions studied was 62.4 ± 17.3% (range 30% to 95%). The average resting pressure gradient was 21.4 ± 15.7 mm Hg, and the average hyperemic pressure gradient was 29.5 ± 14.6 mm Hg. The corresponding FFR values were 0.64 ± 0.13 (range 0.38 to 0.88). There was no relationship between the resting $T_{min}$ and the resting gradient, but a weak correlation was found between the hyperemic $T_{min}$ and the hyperemic pressure gradient. The variability of the $T_{min}$ values at rest and during hyperemia were 11 ± 8% and 12 ± 9%, respectively. The variability of the corresponding pressure gradients were 6 ± 5% and 5 ± 5%. The relationship between thermodilution CFR and pressure-derived CFR is shown in Figure 1a. There is a close linear relationship between CFR values acquired with the two techniques, but this relationship is markedly skewed with the pressure-derived technique significantly underestimating CFR compared with the thermodilution method.

This systematic underestimation is shown in the Bland-Altman plot in Figure 1b, which demonstrates that the degree of discrepancy between the two techniques is proportional to the mean value of CFR.

Artificial stenoses. A total of 25 stenoses were created in six vessels. The mean FFR associated with these stenoses was 0.66 ± 0.09 (range 0.56 to 0.79). All the artificial stenoses created are analyzed together in Figure 2. The relationship between the two techniques of CFR measurement bears a striking similarity to that of the de novo lesions with a systematic underestimation of CFR by the pressure-derived technique when compared with thermodilution, which is proportional to absolute CFR.

DISCUSSION

These studies show that there is a close linear correlation between values of pressure-derived CFR and thermodilution.
CFR in the stenosed human coronary artery. Even though the tightness of the correlation is certainly influenced by the small range of pressure-derived CFR values, this unusually close correlation for measurements in humans is an indirect confirmation of the principle of thermodilution-derived CFR. However, this relationship is markedly skewed with an apparent systematic underestimation of the CFR by the pressure-derived technique (or, indeed, an overestimation by the thermodilution technique). There are a number of possible explanations for this finding. The pressure-derived technique depends on the assumption that the flow in the vessel is proportional to the square root of the pressure drop across the stenosis. This assumption is based on in vitro experiments and mathematical modeling by Shalman et al. (12), whose data suggest that, at flow rates within the normal physiological range, energy losses due to friction and inertial forces can be ignored, converting the general fluid dynamic equation to a simple quadratic relationship. This may not be the case in atheromatous human coronary arteries where flow is likely to be less laminar and, therefore, perhaps friction losses and inertial forces more important. This may explain why the underestimation using this mathematical assumption is proportional to absolute CFR values: friction losses would be higher as flow increases. These friction losses are probably the cause of recently reported, marked, progressive pressure gradients along atherosclerotic arteries without discrete stenosis, while these gradients were absent in strictly normal arteries even during high flow rates (13). Our data also emphasize that there is a large variability in coronary stenoses with respect to the constants f and s in the general fluid dynamic equation. The amount of energy loss due to friction is dependent on lesion morphology, and this has an impact on pressure-derived measurements of CFR. In a short, discrete coronary stenosis, friction will be less important, and the resting pressure gradient may be low (as shown in the examples in Fig. 3A). The quadratic component of the equation(s) will be more important; therefore, the pressure gradient will increase significantly on induction of hyperemia, and the pressure-derived CFR might be overestimated. However, in a long, diffuse, and perhaps less severe stenosis (Fig. 3B), friction will be more important, and there may be a larger resting gradient that does not increase as much on induction of hyperemia. The pressure-derived CFR in this latter case may be underestimated, as the linear component of the equation (f) cannot be ignored in this situation.

In addition, from a purely arithmetic point of view, it is very unlikely that dividing the square roots of any two numbers between 10 (lowest reliable resting pressure gradient) and 60 by each other would give values higher than 2, whereas it is well known that CFR values may reach 5 to 6. An alternative explanation is that the thermodilution technique overestimates CFR. The presence of side branches upstream from the stenosis could conceivably create a “steal” phenomenon during hyperemia, reducing the mean transit time of the saline bolus and increasing the thermo-CFR value. However, this was not observed to any great extent in studies that validated the thermodilution technique against Doppler wire data (6,7). More recently, Barbato et al. (8) have conducted a further “real-world” validation of the thermodilution technique in the form of the “week 25 study.” This study was designed to assess the technique as used in day-to-day clinical practice and involved 86 patients recruited from eight centers. De novo coronary stenoses were interrogated simultaneously with the pressure wire (to obtain thermodilution CFR) and the Doppler flow wire, and a good correlation was obtained,
indicating that thermodilution remained valid in the hands of a wide range of clinical operators and centers.

In addition to the apparent inaccuracy of pressure-derived CFR indicated by this study, another major limitation of the technique is the need for a resting pressure gradient within the vessel. This condition mandates that some degree of epicardial disease is present and prevents the measurement of CFR in the assessment of pure microvascular dysfunction (i.e., in these patients in whom measurements of CFR are most desirable). There is some data to suggest that for vessels with a low resting pressure gradient, the maximum diastolic pressure gradient can be used instead of the mean pressure gradient (12), but this is yet to be formally validated.

Akasaka et al. (9) have compared the assessment of CFR by coronary pressure measurements with flowmeter-derived CFR in dogs with various degrees of artificial stenosis and with velocity-derived CFR in 30 patients with angina. In these patients, the study protocol necessitated instrumentation with both a pressure wire and a Doppler flow wire, and there was a close correlation between the two techniques. As with our data, there seemed to be an underestimation of CFR by the pressure-derived technique, although this was far less marked. The reasons for this correlation being less close than the current study are not clear; the current study utilizes pressure and thermodilution data acquired simultaneously with the same device (rather than with two separate devices), and it is possible that Akasaka et al. (9) studied more proximal stenoses, which may generate larger changes in pressure on induction of hyperemia. Moreover, these investigators included all lesions with a resting gradient of >2 mm Hg (compared with >10 mm Hg in the current study), and this may explain the difference in the results of the two studies. In the current study, by selecting lesions with a resting gradient of >10 mm Hg, we may have introduced a bias toward those stenoses in which friction losses were more important (Fig. 3B), whereas Akasaka et al. (9) may have included more discrete lesions (with a low resting gradient) in which a quadratic relationship to flow was more dominant (Fig. 3A). This inadvertent selection in the current study would have the effect of a systematic underestimation of CFR as seen in our data set. However, there is greater potential for error if a low resting gradient is used, as even a small change in this pressure measurement will translate into a large difference in pressure-derived CFR (see Equation 5 in the preceding text).

**Clinical utility.** The ability to assess CFR and FFR simultaneously with one device is appealing and has a clear clinical utility, offering a comprehensive assessment of coronary flow both at the epicardial and microvascular level. The FFR is increased in the presence of microvascular dysfunction, and although this index remains clinically useful in this setting (indicating as it does the effect of correcting the epicardial obstruction by percutaneous intervention), it tells us nothing about the microvasculature. Use of the pressure wire to give an accurate value of both FFR and CFR would permit the diagnosis of microvascular dysfunction once significant epicardial disease had been excluded. Moreover, the CFR in any particular vessel could be "corrected" for epicardial disease by dividing CFR/FFR. However, current evidence (including the present study) would suggest that thermodilution CFR was the preferred technique.

It is noteworthy that however the CFR is measured, it has limited value for clinical decision-making, as it is influenced by hemodynamic conditions and lacks a reliable/universal normal value. Despite the interesting aspects of the newer, lesion-specific indexes, the FFR remains the most useful index upon which to base revascularization decisions.

**Conclusions.** The conclusions of this study are two-fold. From a practical point of view, the present data indicate that CFR cannot merely be derived by pressure, assuming that only exit (convective) losses are responsible for the coronary pressure gradients in patients with coronary atherosclerosis. From a theoretical point of view, the data suggest that friction loss is an important determinant of the pressure gradient along an atherosclerotic coronary artery.

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**REFERENCES**