Epicardial Stenosis Severity Does Not Affect Minimal Microcirculatory Resistance

Wilbert Aarnoudse, MD; William F. Fearon, MD; Ganesh Manoharan, MD; Maartje Geven, MSc; Frans van de Vosse, PhD; Marcel Rutten, PhD; Bernard De Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD

Background—Whether minimal microvascular resistance of the myocardium is affected by the presence of an epicardial stenosis is controversial. Recently, an index of microcirculatory resistance (IMR) was developed that is based on combined measurements of distal coronary pressure and thermodilution-derived mean transit time. In normal coronary arteries, IMR correlates well with true microvascular resistance. However, to be applicable in the case of an epicardial stenosis, IMR should account for collateral flow. We investigated the feasibility of determining IMR in humans and tested the hypothesis that microvascular resistance is independent of epicardial stenosis.

Methods and Results—Thirty patients scheduled for percutaneous coronary intervention were studied. The stenosis was stented with a pressure guidewire, and coronary wedge pressure (Pw) was measured during balloon occlusion. After successful stenting, a short compliant balloon with a diameter 1.0 mm smaller than the stent was placed in the stented segment and inflated with increasing pressures, creating a 10%, 50%, and 75% area stenosis. At each of the 3 degrees of stenosis, fractional flow reserve (FFR) and IMR were measured at steady-state maximum hyperemia induced by intravenous adenosine. A total of 90 measurements were performed in 30 patients. When uncorrected for Pw, an apparent increase in microvascular resistance was observed with increasing stenosis severity (IMR = 24, 27, and 37 U for the 3 different degrees of stenosis; \( P < 0.001 \)). In contrast, when Pw is appropriately accounted for, microvascular resistance did not change with stenosis severity (IMR = 22, 23, and 23 U, respectively; \( P = 0.28 \)).

Conclusions—Minimal microvascular resistance does not change with epicardial stenosis severity, and IMR is a specific index of microvascular resistance when collateral flow is properly taken into account. (Circulation. 2004;110:2137-2142.)

Key Words: coronary disease • microcirculation • pressure

Thirty years ago, Gould et al\(^1\)–\(^3\) postulated that minimum microvascular resistance is independent of epicardial stenosis severity. Confirming this hypothesis in humans has been challenging because of the lack of a reliable invasive methodology to quantify microvascular resistance. Several recent studies using surrogate indexes for calculating microvascular resistance\(^4\)–\(^7\) challenge this postulate by suggesting that epicardial stenoses do affect microvascular resistance. These indexes, however, are based on coronary flow parameters and hampered by the fact that myocardial flow cannot be measured invasively.

Theoretically, combined measurement of myocardial perfusion pressure and absolute myocardial blood flow enables calculation of true microvascular resistance (TMR), defined as myocardial perfusion pressure divided by myocardial blood flow. Although myocardial perfusion pressure, represented by distal coronary pressure (Pd), is easy to measure invasively with a coronary pressure wire, myocardial blood flow can only be estimated by derived indexes in the catheterization laboratory.\(^8\) Of these surrogate flow parameters, coronary flow velocity, measured by a Doppler wire, is the most widely used. Importantly, using Doppler velocity as a surrogate for myocardial flow is correct only in the absence of an epicardial stenosis, when collateral flow can be assumed to be zero and coronary flow equals myocardial flow.\(^9\) In the presence of an epicardial stenosis, myocardial blood flow consists of both coronary and collateral blood flow. Thus, using any parameter for coronary flow most likely underes-
timates myocardial flow and thus overestimates myocardial resistance. Recently, a novel index for invasively assessing the microcirculation has been introduced. It is called the index of microcirculatory resistance (IMR). IMR is calculated from the simultaneous measurement of distal coronary pressure and thermodilution-derived mean transit time (Tmn) of a bolus of saline injected at room temperature into the coronary artery during maximal hyperemia. As demonstrated previously, the inverse of Tmn strongly correlates to absolute coronary blood flow. Therefore, in the absence of an epicardial stenosis and collateral flow, IMR is equal to the product of PW and Tmn at maximum hyperemia and correlates well to TMR both in vitro and in animals. With an epicardial stenosis, however, accurate determination of IMR requires knowledge of coronary wedge pressure. Therefore, IMR should be represented as follows: IMR = PwTmn [(Pd − Pa)/ (Pw − Pa)], where Pw represents aortic pressure measured by the guiding catheter and PW is coronary wedge pressure measured by the pressure wire. The mathematical derivation of this equation is presented in the Appendix.

The aim of the present study was to measure IMR in humans with different degrees of stenosis to test the hypothesis that minimal microvascular resistance is independent of the presence or severity of an epicardial stenosis.

Methods

Patient Population
Thirty patients undergoing elective percutaneous coronary intervention (PCI) of a single stenosis in a coronary artery with a reference diameter of at least 3.0 mm were studied. Patients with an acute coronary syndrome or with total occlusion of the coronary artery were excluded. The study was approved by the institutional review board, and informed consent was obtained from all patients.

Study Protocol
A 7F arterial sheath and a 5F venous sheath were introduced into the femoral artery and vein, respectively. After administration of 5000 U heparin, the guiding catheter was advanced into the coronary ostium. Intracoronary nitroglycerin 0.2 mg was administered, and reference images were made. The pressure wire was advanced across the stenosis, and stenting was performed according to routine practice. Fractional flow reserve (FFR) was measured before and after stenting. During balloon occlusion, PW was recorded. Thereafter, the following protocol was performed to create several degrees of epicardial stenosis and to determine IMR (Figure 1). At first, a PTCA balloon with a diameter 1.0 mm smaller than the deployed stent and a length of 10 mm was placed within the stented segment, thus creating an area stenosis of ~10%. Next, maximal hyperemia was induced by adenosine 140 μg kg⁻¹ min⁻¹ IV administered into the femoral vein. At steady-state hyperemia and with the noninflated balloon in situ, PW, PW, and FFR were measured and 3 consecutive thermodilution curves were obtained by brisk injection of 3 cm³ of room temperature saline into the coronary artery, thereby enabling calculation of Tmn and IMR as described below. With hyperemia maintained, the balloon was then inflated stepwise to 4 and 12 atm, corresponding with area stenoses of ~50% and 75%, respectively.

At every degree of stenosis, PW, PW, and FFR were measured and the sequence of thermodilution curves was repeated to calculate Tmn and IMR. Careful attention was paid to maintaining the same sensor position throughout all measurements.

Pressure/Temperature Guidewire
A 0.014-in floppy pressure wire and modified software (Pressure Wire–4, Radi Medical Systems) were used to measure distal coronary pressure and temperature. This wire has a microsensor at 3 cm from the floppy tip, which enables simultaneous recording of high-fidelity coronary pressure and temperature with an accuracy of 1 mm Hg and 0.02°C, respectively. The shaft of this wire, acting as an additional electric resistance, can be used as a second thermistor, recording the input signal at the coronary ostium of any fluid injection with a temperature different from blood. All signals can be displayed on the regular catheterization laboratory recording system or on a suitable interface (Radi-Analyzer), enabling online analysis of data. Pressure and temperature are sampled with a frequency of 500 Hz. Further details of these thermodilution measurements have been described earlier.

Calculation of IMR
In the absence of a stenosis and collaterals, myocardial flow is equal to coronary flow, and assuming that PW is close to zero, IMR = PWTPmn. In the case of a stenosis with collaterals, however, myocardial flow is not equal to coronary flow but increasingly exceeds coronary flow because of collateral flow. Therefore, Tmn is no longer representative of myocardial flow, and one must account for the increasing contribution of collateral flow as follows: IMR = PWTPmn[(Pd − Pa) (Pw − Pa)]. Details and the mathematical derivation of the equation are presented in the Appendix.

Overestimation of Microcirculatory Resistance in Relation to Collateral Extent
The percentage overestimation of microvascular resistance when collateral flow is neglected is defined for every degree of stenosis by [IMRmn/IMR]−1]. To investigate this percentage for comparable stenosis severity in different patients with different extents of collateral flow, we calculated this value for all patients at an FFR value of 0.53 (the average stenosis severity in our population before stenting) at the actually measured PW. Theoretically, this relation is expected to be hyperbolic, as outlined in the Appendix.

Statistical Analysis
Statistical analysis was performed with GraphPad Prism software. All data are presented as mean±SD. ANOVA was used to compare changes in mean values under the various epicardial settings. Post hoc analysis using Bonferroni multiple-comparisons test was applied to assess statistical significance. Simple regression analysis was used to calculate correlations. A value of P<0.05 was considered significant.

The variability between each set of 3 transit time measurements was defined as Var (ai−ā)/ā = max(i=1,2,3)/(a−ā/ā) according to the earlier studies on thermodilution.
Results

Baseline and Procedural Characteristics

A total of 30 patients were studied without complications. Baseline characteristics are shown in Table 1. Average stenosis severity, measured with quantitative coronary angiography before and after PCI, was 69±14% and 11±6%, respectively. Importantly, in no patients were angiographically visible epicardial collaterals more than grade 1 present before PCI. Average P_d was 22±7 mm Hg (range, 10 to 39 mm Hg), indicating average collateral development. 16,17 FFR values before and after PCI were 0.53±0.19 and 0.90±0.12, respectively. Stent length was 17±5 mm.

Feasibility of IMR Measurements

The study protocol could be performed easily and rapidly in all 30 patients. The variability of T_mn within a set of 3 measurements was 11.0±9.2%, which is in accordance with earlier studies on coronary thermodilution. 12,13 In Table 2, the hemodynamic data for the 3 different degrees of stenosis are summarized.

Minimal Microvascular Resistance With and Without Collateral Flow Neglected

Figure 2 shows all values of IMR for the individual patients and for the different degrees of stenosis quantified by FFR, with and without collateral flow accounted for. When uncorrected for collateral flow, IMR increased significantly with increasing stenosis severity in all patients: IMR=24±17, 27±23, and 37±23 mm Hg · s or units (U), respectively, for 10%, 50%, and 75% stenosis severity (P<0.001; Figure 3). In contrast, when properly corrected for collateral flow, IMR remained unchanged despite increasing stenosis severity: IMR=22±15, 23±14, and 23±14 U, respectively (P=0.28).

Overestimation of Microvascular Resistance in Relation to Collateral Flow

The actual overestimation of microvascular resistance when collateral flow in relation to P_d in the individual patients was

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<tbody>
<tr>
<td>Patients, n</td>
</tr>
<tr>
<td>Male/female, n</td>
</tr>
<tr>
<td>Age±SD, y</td>
</tr>
<tr>
<td>LAD/LCx/RCA, n</td>
</tr>
<tr>
<td>Vessel diameter, mm</td>
</tr>
<tr>
<td>Minimal lumen diameter before stenting, mm</td>
</tr>
<tr>
<td>Stenosis before stenting, %</td>
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<td>Stenosis after stenting, %</td>
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<td>FFR before stenting</td>
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<td>FFR after stenting</td>
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<td>Stent length, mm</td>
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<tr>
<td>Current smoking, n</td>
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<tr>
<td>Diabetes, n</td>
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<tr>
<td>Hypertension, n</td>
</tr>
<tr>
<td>Dyslipidemia, n</td>
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<tr>
<td>Prior infarction in target area, n</td>
</tr>
</tbody>
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LAD indicates left anterior descending artery; LCx, left circumflex artery; and RCA, right coronary artery.

<table>
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<tr>
<th>Table 2. Hemodynamic Data for the Different Degrees of Stenosis</th>
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<tbody>
<tr>
<td>Area Stenosis, %</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>FFR</td>
</tr>
<tr>
<td>P_d, mm Hg</td>
</tr>
<tr>
<td>IMR, mm Hg/s</td>
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<td>IMR, mm Hg/s</td>
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Figure 2. Top, IMR in individual patients at 3 different steps of stenosis calculated as P_d·T_mn and expressed as mm Hg · s or units (U) without correction for collateral flow at increasing stenosis severity quantified by FFR. Bottom, IMR taking into account collateral flow, at increasing stenosis severity as quantified by FFR in the same patients.

Figure 3. Plot of relationship between FFR in mild, moderate, and severe stenoses and IMR when collateral flow is (dots) and is not (squares) taken into account.
neglected is presented in Figure 4 and clearly resembles the predicted hyperbolic relationship.

**Discussion**

Our study indicates that minimal microvascular resistance, when calculated appropriately, is independent of epicardial stenosis severity, as postulated originally and in accordance with a sound physiological point of view. Furthermore, it shows that calculation of IMR through the use of distal coronary pressure and temperature measurement is feasible and easy to perform in humans during PCI but that knowledge of coronary wedge pressure is necessary to calculate IMR in case of a coronary stenosis.

More recent invasive studies substituting coronary flow velocity for myocardial blood flow have suggested that microvascular resistance paradoxically increases with increasing stenosis severity. As will be clear from the present study, such conclusions were based on an incorrect interpretation of data. This can be understood as follows: Myocardial resistance equals myocardial perfusion pressure divided by myocardial blood flow. Myocardial perfusion pressure corresponds to distal coronary pressure, which can be measured accurately. This pressure approaches \( P_w \) if an artery progressively narrows until total occlusion. \( P_w \) varies considerably among patients but has an average value of \( \approx 25\% \) of arterial pressure in large series of patients undergoing PCI. During progressive stenosis, myocardial blood flow does not decrease to zero but approaches collateral flow. On the contrary, coronary blood flow becomes zero in the case of an occlusion. Because previously proposed indexes of microvascular resistance are based on coronary blood flow and not myocardial blood flow, these indexes progressively underestimate myocardial flow with progressive stenosis and consequently overestimate myocardial resistance. Even when collateral development is only moderate or poor, such overestimation will occur with increasing stenosis severity because a finite value (\( P_w \)) is divided by zero. Therefore, it is clear that accounting for collateral flow is mandatory to calculate microvascular resistance reliably in the catheterization laboratory.

Consequently, we derived the theoretical basis for the generally applicable form of IMR (and velocity-based indexes of microvascular resistance), regardless of the status of the epicardial artery or the extent of collateral flow (see the Appendix). We have demonstrated that assessing IMR with this technique is feasible during PCI. Importantly, when calculated properly, minimal microvascular resistance is independent of epicardial stenosis severity.

Therefore, IMR is a specific quantitative measure for minimal microvascular resistance and can be measured invasively during PCI with a pressure wire. Because FFR is also available by the same technique, a better insight into the relative contribution of epicardial and microvascular disease can be achieved, and appropriate management decisions can be made in the catheterization laboratory. This is especially true for those patients in whom both epicardial disease and microvascular abnormalities play an important role.

**Protocol for Inducing Variable Stenosis**

As far as we know, the described method of creating variable coronary artery stenoses in humans is new and provides a unique opportunity to change the epicardial status in a well-controlled manner. A schematic summary of the various steps of this protocol is presented in Figure 1.

In previous studies assessing the effect of an epicardial stenosis on microvascular resistance, patients were studied before and after PCI, thus in the presence and absence of a significant stenosis. There are indications, however, that the myocardial microvasculature can be affected by the invasive procedure itself. Therefore, another confounding factor was introduced, making the conclusions from these studies debatable. In our protocol, such confounding is prevented by performing all measurements after stent placement. Furthermore, with this method, the effect of several degrees of epicardial stenosis, instead of merely the presence or absence of a stenosis, can be studied. Because FFR after stent placement in our study was \( 0.90 \pm 0.12 \), a small but constant resistance was present in the artery after PCI, but because all measurements were performed after stenting, this did not affect the validity of the measurements.

**Study Limitations**

When the concept of IMR is used in humans, several important factors have to be considered. First, the vascular volume of the epicardial coronary artery between the ostium and the location where pressure and temperature are measured should remain constant throughout the study. In clinical practice, this can be obtained by prior administration of 200 \( \mu g \) IC nitroglycerin.

Second, it is of paramount importance to position the sensor at the same distance from the ostium of the coronary artery during subsequent measurements over time in one individual because the more distal the sensor is, the longer the mean transit time will be. Therefore, if follow-up investigations are performed, carefully recording the position of the sensor by angiography is mandatory.

Third, because the vascular volume in itself is unknown, IMR is a relative index and can be used only to measure changes in minimal microvascular resistance within one...
patient and one myocardial territory at different moments in time. Therefore, it can be used to assess changes in microcirculatory function after myocardial infarction or transplantation or for follow-up of medical treatment for conditions affecting microvascular function such as diabetes or hypercholesterolemia. It is unknown so far whether there are circumspect normal and pathological ranges of IMR values that enable comparison of this index between different arteries or different individuals.

Fourth, we did not measure central venous pressure (Pv) and assumed that this value was close to zero in our patients. Theoretically, if Pv is significantly elevated, it might affect the calculation of IMR. But because IMR remained constant even in the presence of a severe stenosis, such a confounding effect was not present in our study.

Finally, our study demonstrates the absence of any change in microvascular resistance during acute changes in stenosis severity in the epicardial artery. Although unlikely, it cannot be predicted whether microvascular resistance is affected by a chronic epicardial stenosis. Such changes cannot be discriminated from changes in microvascular resistance resulting from the progression or regression of atherosclerosis.

Conclusions
This study shows that minimal microvascular resistance, if calculated appropriately, is independent of epicardial stenosis severity, as originally postulated by Gould and coworkers. Furthermore, it shows that the IMR can easily be calculated in conscious humans in the presence of an epicardial stenosis, provided that the coronary wedge pressure is known.

Appendix
According to the principles of indicator dilution theory,14,15

\[ F = \frac{1}{T_{mn}} \]

where F is coronary blood flow, V is the epicardial volume between the injection site and the position of the sensor, and Tmn is the mean transit time of a bolus of indicator.

TMR equals myocardial perfusion pressure divided by myocardial blood flow. In the absence of a stenosis, myocardial flow can be represented by coronary flow and

\[ TMR = \frac{Pd}{F} = \frac{P_d \cdot T_{mn}}{V} \]

And because V is constant,

\[ TMR \approx P_d \cdot T_{mn} \]

(or because without stenosis \( P_d = P_a \).

This product, \( P_d \cdot T_{mn} \), was called the IMR:

\[ \text{IMR} = \frac{P_d}{T_{mn}} \]

Equation 3, however, does not take into account the collateral circulation and is valid only when myocardial flow can be represented by coronary flow, i.e., in the absence of an epicardial stenosis. In case of a stenosis with collaterals, IMR as defined in Equation 3 progressively overestimates TMR, which can be explained as follows. In animals and humans, not coronary flow but myocardial flow should be taken into account, the latter being the sum of coronary flow and collateral flow (Figure 5). Myocardial resistance remains a finite entity because neither distal coronary pressure nor myocardial flow reaches zero. Therefore, at total occlusion, myocardial resistance equals wedge pressure divided by collateral flow. To describe this phenomenon quantitatively and to correct IMR (or any other index) when coronary blood flow parameters are used instead of myocardial flow, the following algorithm can be applied. In the mathematical derivation of that algorithm, standardized nomenclature will be used as in the initial study introducing the concept of FFR.

Let us use the following terminology: \( Q_{cor} \) = myocardial blood flow, \( Q_{cor} \) = coronary artery blood flow (equal to Fc), and \( Q_c \) = collateral blood flow, all measured at maximum vasodilation.

The “normal” values of these indexes at maximal vasodilation are indicated by the superscript N: \( Q_{myo}^N, Q_{cor}^N, Q_c^N \). Equation 1, in this terminology, states that

\[ Q_{cor} = V \cdot T_{mn} \]

which has also been validated both experimentally and clinically.11–13

Rmyo is myocardial resistance at maximum vasodilation.

Myocardial flow equals the sum of coronary artery flow and collateral flow, so:

\[ Q_{myo} = Q_{cor} + Q_c \]

Furthermore, it is assumed that \( Q_{myo}^N = 0 \) and that \( Q_{myo}^N = Q_{cor}^N \).

FFRmyo and FFRcor are defined as follows8: \( FFR_{myo} = \frac{Q_{cor}}{Q_{myo}^N} \) and \( FFR_{cor} = \frac{Q_{cor}}{Q_{cor}^N} \).

The different pressures are defined as follows: \( P_a \) = aortic pressure, \( P_d \) = distal coronary pressure at maximum vasodilation, \( P_v \) = coronary wedge pressure, and \( P_w \) = central venous pressure, all at maximum dilation.

It has been demonstrated that FFRcor and FFRmyo can be expressed in terms of pressures as follows8:

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

and

\[ FFR_{myo} = \frac{P_d - P_v}{P_d - P_v} \]

TMR equals:

\[ R_{myo} = \frac{P_d - P_v}{Q_{myo}} \]

By multiplying the numerator and denominator by \( Q_{cor} \), this can be rewritten as:

\[ R_{myo} = \frac{P_d - P_v}{Q_{myo}} \cdot \frac{Q_{cor}}{Q_{cor}} \]
And by substituting Equation 1a, we obtain
\[
R_{myo} = (P_d - P_a) \cdot T_{mn} \cdot \frac{Q_{cor}}{Q_{myo}}
\]

Because \( Q_{cor} = Q_{myo} \), we obtain
\[
R_{myo} = (P_d - P_a) \cdot T_{mn} \cdot \frac{Q_{cor}}{Q_{myo}} \cdot \frac{Q_{cor}}{Q_{myo}}
\]

Therefore,
\[
IMR = (P_d - P_a) \cdot T_{mn} \cdot \frac{FFR_{cor}}{FFR_{myo}}
\]
or in case \( P_a \) is close to zero,
\[
IMR = P_d \cdot T_{mn} \cdot \frac{FFR_{cor}}{FFR_{myo}}
\]

Note that if there are no collaterals, as in the case of a normal artery, \( FFR_{cor} = FFR_{myo} \) and Equation 6b equals Equation 3, as should be the case.

Equation 6a can be rewritten in terms of measured pressures by substitution of Equations 4 and 5 as follows:
\[
IMR = (P_d - P_a) \cdot T_{mn} \cdot \frac{P_d - P_w}{P_a - P_w} \cdot \frac{P_d - P_a}{P_a - P_w}
\]

And by neglecting \( P_w \), we obtain
\[
IMR = P_d \cdot T_{mn} \cdot \frac{P_d - P_w}{P_a - P_w}
\]
or expressed in a different way,
\[
IMR = P_a \cdot T_{mn} \cdot \frac{P_d - P_w}{P_a - P_w}
\]

In summary, Equation 7a constitutes the general form of IMR, universally applicable in both the presence and absence of a significant stenosis. If studies are performed in patients without significant epicardial stenosis, the simpler Equation 3 can be used for IMR. In addition, when Doppler-derived indexes of microvascular resistance are used, they should be corrected in a similar way as in Equation 6b by multiplying them by \( (FFR_{cor}/FFR_{myo}) \).

Finally, it is clear that overestimation of microvascular resistance when collateral flow is neglected increases with increasing stenosis severity and with increasing recruitable collateral flow. This percentage overestimation can be defined as
\[
\frac{IMR_{meas}}{IMR} - 1 \cdot 100\%
\]

As can be seen, there is no overestimation when \( P_w = 0 \), whereas the overestimation approaches infinity when the stenosis approaches total occlusion and \( P_w = P_a \). To investigate this percentage overestimation specifically in relation to \( P_a \) in the individual patients but for a similar degree of stenosis (FFR = 0.53) and arterial pressure, such a “normalized” percentage overestimation can be calculated by using the values of 100, 53, and \((P_d/P_a \times 100)\) for \( P_d \), \( P_a \), and \( P_w \), respectively. In this way, the actual measurements can be compared with the predicted hyperbolic relation for every degree of stenosis (Figure 4).

**Acknowledgment**

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**References**

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