Conclusions—Coronary microcirculatory resistance is independent of functional epicardial stenosis severity when increasing epicardial stenosis. However, the indices used to minimum achievable microcirculatory resistance as a result of severe microcirculatory resistance showed an increase in the epicardial stenosis severity.

There exists over whether microcirculatory resistance is affected by resistance, is an independent predictor of poor outcomes in patients with cardiovascular disease. However, controversy exists over whether microcirculatory resistance, a measure of coronary microcirculatory status, is dependent on epicardial stenosis severity. Previous studies demonstrating that microcirculatory resistance is dependent on epicardial stenosis severity have not accounted for collateral flow in their measurement of microcirculatory resistance. We investigated whether the index of microcirculatory resistance is independent of epicardial stenosis by comparing the index of microcirculatory resistance (IMR) levels in patients before and after percutaneous coronary intervention (PCI).

Methods and Results—Consecutive patients undergoing elective PCI of the left anterior descending artery were recruited. Patients who developed periprocedural myocardial infarction PCI of the left anterior descending artery were excluded. A pressure-temperature sensor wire was used to measure the apparent IMR (IMRapp), which does not adjust for collateral flow, and the true IMR (IMRtrue), which incorporates wedge pressure measurement to account for collateral flow, before and after PCI. In 43 patients, there was no difference between pre- and post-PCI IMRtrue (mean difference = 0.8 ± 11.7, P = 0.675). IMRapp was higher pre-PCI compared with post-PCI (mean difference = 10.0 ± 14.5, P < 0.001). IMRapp was higher than IMRtrue (mean difference = 9.3 ± 14.2, P < 0.001), and the difference between the IMRapp and IMRtrue became greater with decreasing fractional flow reserve and increasing coronary wedge pressure. Pre-PCI fractional flow reserve correlated modestly with IMRapp (r = −0.33, P = 0.03), but not IMRtrue (r = 0.26, P = 0.10).

Conclusions—Coronary microcirculatory resistance is independent of functional epicardial stenosis severity when collateral flow is taken into account. (Circ Cardiovasc Interv. 2012;5:103-108.)

Key Words: index of microcirculatory resistance  ■ microvascular function  ■ percutaneous coronary intervention  ■ stenosis

Recent studies demonstrate that coronary microvascular impairment, as indicated by increased microcirculatory resistance, is an independent predictor of poor outcomes in patients with cardiovascular disease. However, controversy exists over whether microcirculatory resistance is affected by epicardial stenosis severity.

Previous studies using intracoronary Doppler wires to measure microcirculatory resistance showed an increase in the minimum achievable microcirculatory resistance as a result of increasing epicardial stenosis. However, the indices used to measure microcirculatory resistance in these studies were derived from epicardial coronary Doppler velocity measurements to calculate coronary flow, with the assumption that coronary flow is equal to myocardial flow, without accounting for collateral flow. Myocardial flow consists of both coronary flow and collateral flow, and it is important to account for collateral flow in the presence of severe epicardial stenosis for the accurate measurement of microcirculatory resistance.

The index of microcirculatory resistance (IMR) is a pressure temperature sensor guide wire-based measurement of the minimum achievable microcirculatory resistance. In 2 recent studies, IMR was shown to be constant in the presence of varying coronary stenosis, artificially and acutely generated by balloon inflation in a porcine model and in humans, as long as collateral flow was taken into account. The aim of this study is to determine whether chronic and more severe native epicardial stenosis affects microvascular resistance by measuring IMR and accounting for collateral flow.

Methods

Study Sample

Patients from 2 tertiary referral institutions scheduled for elective percutaneous coronary intervention (PCI) of a single target lesion in
WHAT IS KNOWN

- Previous studies showed an increase in the minimum achievable coronary microcirculatory resistance with increasing epicardial stenosis severity.
- However, these studies did not account for collateral flow in the calculation of microcirculatory resistance, despite the presence of significant epicardial stenosis.
- Subsequent studies using artificial balloon dilations to simulate acute epicardial stenoses suggested that microcirculatory resistance is independent of epicardial stenosis when collateral flow is taken into account.

WHAT THE STUDY ADDS

- The results of the current study add further support to the concept that coronary microcirculatory resistance, as assessed by the index of microcirculatory resistance which accounts for collateral flow, is independent of epicardial stenosis severity in native severe coronary lesions.
- Moreover, microvascular resistance may be normal even in patients with severe epicardial coronary artery disease.

The left anterior descending artery were recruited for this study. Consecutive patients who underwent PCI for stable coronary disease and had TIMI 3 grade flow within the target vessel were included. Patients with recent myocardial infarction were excluded because baseline IMR may be elevated in the presence of previous myocardial infarction. Patients who were found to have periprocedural myocardial infarction, defined as having elevated post-PCI troponin levels, were excluded from the analysis, as myocardial infarction will disrupt the microcirculation and may increase the post-PCI IMR level. Baseline clinical and procedural details were recorded. Patients were deemed to have comorbidities, including diabetes, hypertension, and dyslipidemia, if they were diagnosed previously by their physician or if they were on treatment for these conditions. Family history was considered positive if a first degree relative was diagnosed with coronary artery disease ≤60 years of age. Cigarette smokers were defined as subjects who were current smokers or had ceased smoking within 1 year of the day of the study.

Coronary Physiology Measurements

Coronary physiology measurements were performed before and after PCI as described previously. In brief, a 6F angioplasty guiding catheter without side holes first was used to engage the left main coronary artery. A pressure temperature sensor guide wire (Certus Pressure Wire) was used for physiology measurements and PCI. With the sensor positioned at the tip of the catheter, the pressure measurement from the wire first was equalized with that of the guiding catheter. The lesion was then crossed with the wire. The pressure sensor was positioned two thirds of the way down the left anterior descending artery, at least 3 cm beyond the lesion. This first sensor position was noted using the working angiographic view for PCI.

Intracoronary nitroglycerin was administered (100–200 μg). Hyperemia was induced using adenosine infusion (140 μg/kg/min) via the femoral vein. To derive the mean transit time during hyperemia (Tmn), thermodilution curves were obtained by 3 injections of 3 mL of room temperature saline down the coronary artery. Proximal arterial pressure (Pp) and distal arterial pressure (Pd) were recorded during hyperemia (Figure 1). Wedge pressure measurement (Pw) was recorded during first balloon inflation. Patients then underwent PCI. After PCI, care was taken to ensure that the sensor guide wire was positioned identically to the first position before PCI. Hyperemia was induced, and Pp, Pd, and Tmn were measured during hyperemia.

Figure 1. Physiological measurements in a representative case. The panel is divided into 2 windows; the upper window displays the pressure segments recorded during each thermodilution injection, separated from each other by white vertical lines (proximal arterial pressure [Pp] and distal arterial pressure [Pd]). The lower graph displays thermodilution injections at baseline (double arrow) and during hyperemia (single arrow). Between the 2 graphs are mean transit time (Tmn) values at baseline (preceded by “Bas”), and during hyperemia (preceded by “Hyp”). The right side of the figure demonstrates derived fractional flow reserve (FFR) of 0.50. Wedge pressure measurement (Pw) measured as the distal pressure during balloon occlusion was 20 mm Hg (not shown). Calculated apparent index of microcirculatory resistance (IMRapp)=[Pd/Pw]x[Tmn] during hyperemia=40.9. Calculated true microcirculatory resistance (IMRtrue)=[Pp/Pw]x[Tmn] during hyperemia=[Pd−Pw]/[Pp−Pw]=28.4.
again post-PCI. The fractional flow reserve (FFR = Pd/Pa) was derived before and after PCI.

Derivation of the IMR has been described elsewhere and is presented in the appendix (supplemental material; see online-only supplement). In the absence of significant epicardial stenosis, the apparent IMR (IMRapp) can be calculated by a simple formula that does not account for collateral flow. In the presence of significant epicardial stenosis, where collateral flow may be substantial, an expanded formula for the true IMR (IMRtrue) that incorporates coronary Pw to account for collateral flow is needed. For the purposes of the current study, IMRapp (Pd × Tmn) and IMRtrue (Pd × Tmn × [(Pd − Pw)/(Pa − Pw)]) were derived before and after PCI.

Statistical Analysis
In a previous study showing the difference between pre- and post-PCI Doppler-derived microcirculatory resistance, the magnitude of change was 32%. Using a conservative estimate of an expected 25% change in IMR from an assumed baseline of 20 to post-PCI IMR of 15 (absolute difference of 5), with standard deviation of the difference being 10, a total of 43 patients would offer a power of 90% and a 2-sided level of significance of 0.05 to detect a difference between pre- and post-PCI IMR levels.

Results are expressed as mean ± standard deviation unless otherwise stated. Normality of the data were determined using the D’Agostino Pearson test for normality and verified using histogram plots. Because FFR and IMR values were judged to be normally distributed, paired t-tests were used to compare pre- and post-PCI FFR and IMR levels. Bland-Altman analyses were used to assess agreement between pre-PCI and post-PCI IMR levels. Regression analyses were used to obtain straight lines or curves of best fit in describing relationships between 2 variables. Spearman correlation was used to evaluate associations between continuous measures that do not follow a normal distribution. Power calculation was performed using PASS v.11 (NCSS). All formal statistical analyses were performed using SPSS v. 15 (SPSS). Figure and graphs were generated using Prism v. 5.01 (Graphpad). A 2-tailed probability value of <0.05 was considered significant.

Results
Baseline Clinical Characteristics
A total of 43 patients were included in the study. Baseline clinical characteristics of the patient cohort are shown in the Table.

Coronary Physiology Measurements Pre- and Post-Coronary Intervention
The pre-PCI IMRapp values ranged from 5.5 to 81.0, and the IMRtrue values ranged from 3.8 to 47.3. FFR was 0.58 ± 0.17 pre-PCI and 0.84 ± 0.06 post-PCI (mean difference = 0.26 ± 0.17, probability value for difference <0.001).

There was no significant difference between the pre- and post-PCI values for IMRtrue (19.1 ± 11.4 versus 18.4 ± 12.8, mean difference = 0.8 ± 11.7, P = 0.675; Figure 2A), and the difference between these 2 variables had no relationship with FFR (Figure 2B). IMRapp was higher pre-PCI compared with post-PCI (28.4 ± 16.0 versus 19.4 ± 13.1, mean difference = 10.0 ± 14.5, P < 0.001; Figure 2C), and this difference progressively widened with decreasing pre-PCI FFR (Figure 2D).

Pre-FFR correlated modestly with IMRapp (r = −0.33, P = 0.03), but not IMRtrue (r = 0.26, P = 0.10; Figure 3). IMRapp correlated with IMRtrue (r = 0.62, P < 0.001). However, IMRapp was consistently higher compared with IMRtrue (28.4 ± 16.0 versus 19.1 ± 11.4, mean difference = 9.3 ± 14.2, P < 0.001). The difference between the IMRapp and IMRtrue became greater with decreasing FFR and increasing Pw (Figure 4).

Discussion
The main findings of this study are that (1) microvascular resistance as measured by IMRtrue is not affected by native, severe epicardial stenosis, and (2) in patients with documented severe epicardial atherosclerosis, microvascular function is often normal.

There has been increasing awareness about the importance of the coronary microcirculation in determining cardiac outcomes. A recent study showed that impairment in microvascular function was an independent predictor of adverse outcomes in women with suspected coronary disease, and proposed the microcirculation as a potential therapeutic target in these patients. Also, the group of diseases that involve coronary microvascular dysfunction recently has been subclassified into several entities, and this classification is dependent on the presence or absence of epicardial coronary disease.

There are many different techniques to assess the microcirculation, such as positron-emission tomography, nuclear perfusion imaging, magnetic resonance imaging, echocardiographic Doppler imaging, and invasive Doppler or thermodilution based methods. All these methods are dependent on assessing microcirculatory blood flow, which is in turn dependent on the microcirculatory resistance to flow. It is therefore important to ascertain whether microcirculatory resistance is truly independent of epicardial stenosis severity.

Previous clinical studies involving assessment of the coronary microcirculation have employed coronary angiography to determine the extent of epicardial disease. Coronary angiography, however, only provides depiction of the vessel
lumen, and a significant proportion of patients may have angiographically normal-appearing vessels but functionally significant diffuse epicardial disease, as detected by a low FFR. Moreover, the angiographic assessment of stenosis severity correlates poorly with the functional significance of epicardial stenoses. There is, therefore, a need to investigate the relationship between microcirculatory resistance and the functional significance of epicardial disease.

Early studies in this area demonstrated a compensatory decrease in resting microcirculatory resistance, a measure of the microcirculatory status, with increasing epicardial stenosis severity until reaching a minimum achievable microcirculatory resistance, which is unaffected by further increases in stenosis severity. Subsequent studies have claimed that microcirculatory resistance is dependent on epicardial stenosis severity. Human studies demonstrated that a Doppler and pressure derived index of microcirculatory resistance varied in the presence of differing epicardial stenosis severity. In particular, 1 of these studies measured hyperemic microcirculatory resistance before and after PCI in 24 patients, and found that microcirculatory resistance was lower after PCI compared with before PCI. This suggested that the presence of significant epicardial stenosis caused an increase in microcirculatory resistance. However, epicardial coronary flow was assumed to be equivalent to myocardial flow, and the contribution of collateral flow was not accounted for in these studies.

A similar result was obtained when the IMR app was considered in the current study. This is because the IMR app is defined as distal coronary pressure divided by myocardial flow, during maximal hyperemia. As stenosis severity increases, collateral flow contributes to myocardial flow to a greater degree, while coronary flow decreases. Distal coronary pressure also will decrease, but not to as great a degree, given that the augmented collateral flow will contribute some to the distal coronary pressure. Thus, the IMR app, which divides distal coronary pressure by an estimate of coronary flow (not myocardial flow), will be overestimated in the presence of a significant epicardial stenosis, because coronary flow will decrease to a greater degree than distal coronary pressure.

Previous studies using transient balloon dilations in animals and humans to simulate coronary stenoses showed that the IMR true is independent of epicardial stenosis severity.
when collateral flow is accounted for. The present study supports this hypothesis and validates the concept in the presence of severe native chronic coronary stenoses, which might lead to changes in microvascular resistance not detected in the previous acute models. The current study also demonstrates that the difference between IMR_{app} and IMR_{true} becomes greater as FFR decreases or P_w increases (Figure 4). This is consistent with the fact that microcirculatory resistance calculated without incorporation of collateral flow will be increasingly overestimated as epicardial stenosis severity and collateral flow increases.10,11

Animal models have shown that the pressure-flow relationship was no longer linear at low perfusion pressures (approximately <30 mm Hg), and this suggests that microcirculatory resistance will increase out of proportion to decreases in blood flow at low driving pressures.6,21,22 Conditions of ultra-resistance will increase out of proportion to decreases in baseline FFR and IMR_{true}, and that patients with significant epicardial coronary disease,1,2 as well as specifically in coronary microcirculatory disease, despite the presence of significant epicardial coronary stenoses, which might lead to changes in microvascular resistance not detected in the previous acute models. The current study also demonstrates that the difference between IMR_{app} and IMR_{true} becomes greater as FFR decreases or P_w increases (Figure 4). This is consistent with the fact that microcirculatory resistance calculated without incorporation of collateral flow will be increasingly overestimated as epicardial stenosis severity and collateral flow increases.10,11

A previous study showed that IMR was higher in patients with coronary disease compared with control subjects without coronary disease.23 Our results concur with this previous study in showing that there was lack of correlation between baseline FFR and IMR_{true}, and that patients with significant coronary disease may have normal IMR_{true}. Our study extends these findings by providing confirmation that IMR_{true} does not change within an individual, despite treatment of their epicardial coronary disease by PCI. The independence of IMR is interesting, as it implies that the status of the microcirculation is distinct to the severity of epicardial stenosis, and lends evidence to the fact that there may be mutually exclusive pathogenic pathways causing disruption to the epicardial artery and to the coronary microcirculation.1,16

In terms of clinical implications, the current study suggests that the IMR_{true} may be used specifically to interrogate the coronary microcirculation, despite the presence of significant epicardial coronary disease. As existing microcirculatory dysfunction may predict poor outcomes in the general pool of patients with coronary disease,1,2 as well as specifically in patients undergoing percutaneous coronary intervention,24,25 the IMR could be used potentially as a simple clinical tool to identify high risk groups of patients who will benefit from novel therapy in these populations.

**Limitations**
Firstly, to control for variations in size of the microcirculation in different coronary territories, this study was restricted to only left anterior descending arteries. Although absolute IMR values may differ in the other epicardial vessels, we believe that the central concept of unchanging IMR before and after PCI should remain true. Secondly, this study has a small sample size. However, the sample size calculation employed indicates that there was adequate power to detect a difference between the groups. Moreover, there was no detectable trend of difference between pre- and post-PCI IMR_{true}. Lastly, we did not measure central venous pressure, which was assumed to be close to zero in our patients. Theoretically, significantly elevated central venous pressure may affect calculation of the IMR. However, venous pressure is unlikely to change during PCI, and paired IMR calculations before and after PCI should lessen the confounding effect of this variable.

**Conclusions**
Coronary microcirculatory resistance is independent of functional epicardial stenosis severity. The lack of relationship between baseline FFR and IMR suggests that there exist different pathogenic processes for coronary epicardial and microcirculatory disease.

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Supplemental Material

Derived from Aarnoudse et al.1

Resistance in the myocardium = Pressure gradient across the myocardium
Blood flow in the myocardium

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

Adding \( Q_{cor} \) into the equation,

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

Knowing that \( Q_{cor} \equiv 1/T_{mn} \)

\[ R_{myo} = (P_d - P_v) \times T_{mn} \times \frac{Q_{cor}}{Q_{myo}} \]

Adding \( Q_{N_{cor}} \) into the equation,

\[ R_{myo} = (P_d - P_v) \times T_{mn} \times \frac{Q_{cor} \times Q_{N_{cor}}}{Q_{N_{cor}} \times Q_{myo}} \]

Because \( Q_{N_{cor}} = Q_{N_{myo}} \),

\[ R_{myo} = (P_d - P_v) \times T_{mn} \times \frac{Q_{N_{cor}} \times Q_{N_{myo}}}{Q_{N_{cor}} \times Q_{myo}} \]

Where \( Q_{N_{cor}} = FFR_{cor} \) and \( \frac{Q_{myo}}{Q_{N_{myo}}} = FFR_{myo} \),

\[ R_{myo} = (P_d - P_v) \times T_{mn} \times \frac{FFR_{cor}}{FFR_{myo}} \]

\[ = (P_d - P_v) \times T_{mn} \times \frac{(P_d - P_w) \times (P_a - P_v)}{(P_a - P_w) \times (P_a - P_v)} \]

\[ = T_{mn} \times \frac{(P_d - P_w)}{(P_a - P_w)} \times (P_a - P_v) \]

Assuming that \( P_v = 0 \),

\[ IMR_{true} = \frac{P_a \times T_{mn} \times (P_d - P_w)}{(P_a - P_w)} \]
This is the calculation of the true IMR which is corrected for wedge pressure. In the absence of any epicardial disease, collateral flow is assumed to be negligible and $P_w = 0$. The simplified IMR$_{app}$ therefore $= P_d \times T_{mn}$. $R =$ resistance; $Q =$ flow; $P_d =$ mean distal coronary arterial pressure; $P_a =$ mean proximal arterial pressure; $P_v =$ mean central venous pressure; $P_w =$ mean coronary wedge pressure; $T_{mn} =$ mean transit time obtained by thermodilution during hyperemia. The superscript $^N$ refers to the hypothetical normal setting without epicardial stenosis. The subscripts $cor$ refers to coronary and $myo$ refers to myocardial.

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