When Collateral Supply is Accounted For Epicardial Stenosis Does Not Increase Microvascular Resistance

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Background—The relationship between epicardial stenosis and microvascular resistance remains controversial. Exploring the relationship is critical, as many tools used in interventional cardiology imply minimal and constant resistance. However, variable collateralization may impact well on these measures. We hypothesized that when collateral supply was accounted for, microvascular resistance would be independent of epicardial stenosis.

Methods and Results—Forty patients with stable angina were studied before and following percutaneous intervention. A temperature and pressure sensing guide wire was used to derive microvascular resistance using the index of microcirculatory resistance (IMR), defined as the hyperemic distal pressure multiplied by the hyperemic mean transit time. Lesion severity was assessed using fractional flow reserve. For comparison, evaluation of an angiographically normal reference vessel from the same subject also was undertaken. Both simple IMR (sIMR) and IMR corrected for collateral flow (cIMR) were calculated. When collateral supply was not accounted for, there was a significant difference in IMR values between the culprit, the post PCI, and nonculprit values (culprit sIMR 26.68±2.06, nonculprit sIMR 18.37±1.89, \(P=0.002\); post percutaneous intervention sIMR 18.5±1.94 versus culprit sIMR 26.68±2.06, \(P<0.0001\)). However, when collateral supply was accounted for there was no difference observed (cIMR 16.96±1.78 versus nonculprit sIMR 18.37±1.89, \(P=0.52\); post percutaneous intervention sIMR 18.5±1.94 versus cIMR 16.96±1.78, \(P=0.42\)).

Conclusions—When collateral supply is accounted for, epicardial stenosis does not increase microvascular resistance in patients with stable angina. (Circ Cardiovasc Interv. 2012;5:97-102.)

Key Words: microcirculation ■ epicardial stenosis ■ FFR ■ PCI

There is increasing interest in the importance of microcirculation in patients with ischemic heart disease. Novel invasive techniques allow assessment of microcirculation at the time of coronary angiography.1 Recently, the index of microvascular resistance (IMR) has been described and validated as a tool to assess the coronary microcirculation.2 It involves the use of a temperature and pressure sensing guide wire (TPSG) that now is used routinely for the assessment of fractional flow reserve (FFR), and can be used for the assessment of microvascular resistance in patients with coronary artery disease using a validated algorithm.3

Whether an epicardial stenosis has an impact on microvascular resistance remains controversial. Recent studies examining the relationship using different methodologies and techniques to assess microvascular resistance have produced conflicting results.4,5 Severe coronary stenosis may lead to a reduction in perfusion pressure, resulting in conformational changes within the resistance arteriolar vessels to maintain myocardial blood flow.6 The pressure dependence of the distal arterioles is such that at very low perfusion pressures they possess a capacity to collapse, a fact that may explain the curvilinear pattern of the diastolic pressure flow relationship at lower perfusion pressures.7 Evidence for this originates from animal models, whereby a severe stenosis led to a reduction in diameter of arterioles greater than 100 \(\mu\)m.8 This may account for the observed increase in microvascular resistance produced by an epicardial stenosis.

However, other investigators have shown that even in the presence of epicardial vessel occlusion, microvessels remain open with continued antegrade flow, possibly a result of collateral flow.9 It also has been demonstrated that collateral flow results in a shift of the pressure intercept of the pressure flow relationship above venous pressure, but only at lower perfusion pressures (<40 mm Hg).10 This would have the effect of maintaining antegrade flow at lower perfusion pressures. Thus collateral flow could minimize the impact of an epicardial stenosis on microvascular resistance by maintaining the patency of the resistance vessels.
Knowing the effect of a stenosis on microvascular resistance is critical, as many techniques used in interventional cardiology assume minimal and constant resistance.\(^7\)\(^1\)\(^1\) Also of interest is whether microvascular resistance is homogeneously distributed across coronary beds within the same patient.\(^12\) We hypothesized that microvascular resistance would be independent of epicardial stenosis, and that collateral supply would reduce the downstream impact an epicardial stenosis has on the microvasculature.

### WHAT IS KNOWN
- The relationship between epicardial stenosis and microvascular resistance remains uncertain.

### WHAT THE STUDY ADDS
- When compared with an angiographically normal control vessel, epicardial stenosis does not increase microvascular resistance.
- Collateral supply reduces the impact of an epicardial stenosis on microvascular resistance.

### Methods

#### Patient Selection
The study population consisted of patients undergoing elective percutaneous coronary intervention for stable angina, with single vessel disease angiographically and a positive noninvasive functional test. Patients were excluded if they had a recent myocardial infarction (within 7 days) or any history of myocardial infarction in the culprit/nonculprit territory, severe renal impairment (estimated glomerular filtration rate $<$30 ml/min), left ventricular dysfunction (ejection fraction $<$35%), previous coronary artery bypass surgery, significant valvular heart disease, or if the lesion involved a major side branch ($>$2.0 mm). The Human Research Ethics Committee at St Vincent’s Hospital Melbourne approved the study protocol.

For the procedure, all patients received an initial bolus of 5000 U of intravenous heparin, with additional bolus dosing to maintain an activated clotting time of 250 seconds, and were receiving aspirin and clopidogrel. A 6F coronary guidance catheter was used to engage the selected coronary artery. A 5F sheath was placed within the right femoral vein for measurement of right atrial pressure and drug delivery. All patients received 200 micrograms of intracoronary nitroglycerin in each study artery. A 0.014 coronary TPSG was calibrated, and then equalized to the guiding catheter pressure, with aortic pressure during hyperemia. Care was taken to ensure that the distal sensor was in the same position between measurements to avoid errors in transit time acquisition.

As a reference, the procedure was repeated in a major epicardial nonculprit vessel free of epicardial stenosis. Only simplified IMR, CFR, and FFR were calculated in the nonculprit vessel.

#### Study Protocol
IMR, CFR, and FFR were measured in an angiographically normal reference vessel and then in the culprit artery at baseline. Stenting of the culprit vessel then was performed and physiological measures were repeated. The decision to intervene was at the operators’ discretion.

#### Statistical Analysis
Statistical analysis was performed using a SPSS (SPSS Inc.) statistical software package. Normality of data were assessed with the Kolmogorov-Smirnov statistic. Continuous variables are summarized as mean±SEM. Physiological values obtained in the nonculprit vessel were compared with the culprit vessel pre PCI and post PCI using paired T tests. \(P<0.05\) was considered statistically significant. Strength of relationships was assessed using the Pearson correlation coefficient.

Based on previous human data that demonstrated an absolute difference of 14 U of IMR in patients with significant epicardial stenosis if collateral flow was not accounted for,\(^4\) we hypothesized a mean difference of 14 U of IMR in vessels with and without correction for collateral flow. With an alpha error of 0.05 and a power of 90%, and a standard deviation of 14, we estimated that a minimal sample size of 23 subjects would be required to demonstrate the true effect of epicardial stenosis on microvascular resistance. With 40 patients in the study population we anticipated that a type II error would be less likely.

### Results
One hundred forty-nine patients were potentially eligible for inclusion in the study. However, a significant number of patients were excluded following either coronary angiography or PCI. Figure 1 provides information on the reasons for patient exclusion. The total study population consisted of 40 patients with stable angina. Patient demographic and procedural data are shown in Table 1 and 2. Physiological data are shown in Table 3, and the distribution of IMR across territories with and without correction for collateral supply is shown in Figure 2. FFR and CFR were lower in the culprit artery compared with the nonculprit values (FFR culprit 0.65±0.03 versus FFR nonculprit 0.93±0.05, \(P<0.0001\),...
CFR culprit 1.97 ± 0.18 versus CFR nonculprit 2.81 ± 0.18, P = 0.01. There was a significant difference in sIMR values between the culprit territory and nonculprit vessels (culprit sIMR 26.68 ± 2.06, nonculprit sIMR 18.37 ± 1.89, P = 0.002).

However, when collateral supply was accounted for by correcting for coronary wedge pressure, there was no difference between the nonculprit microvascular resistance and culprit microvascular resistance (cIMR 16.96 ± 1.78 versus nonculprit sIMR 18.37 ± 1.89, P = 0.52).

Mean TmnHyp was increased (coronary blood flow was reduced) in the culprit territory compared with the nonculprit vessel (TmnHyp culprit 0.57 ± 0.06 versus TmnHyp nonculprit 0.24 ± 0.02, P < 0.001), and also when compared with mean post PCI values (TmnHyp post PCI 0.25 ± 0.02, P < 0.001). Furthermore, baseline and hyperemic transit time were inversely correlated with FFR (r = −0.44, P = 0.004, r = −0.73, P < 0.0001, respectively; Figures 3 and 4, respectively). However, lesion severity as assessed by quantitative coronary angiography did not correlate with baseline transit time, yet there was a significant relationship between stenosis severity and hyperemic transit time (r = 0.56, P = 0.01). There also was a significant negative correlation between FFR in the culprit territory and coronary wedge pressure (r = −0.44, P = 0.005; Figure 5), and a positive correlation between TmnHyp in the culprit vessel and the coronary wedge pressure (r = 0.46, P = 0.033).

Changes in Coronary Physiology Following PCI

FFR and CFR were higher following PCI when compared with pre PCI values (FFR pre PCI 0.65 ± 0.03 versus FFR post PCI 0.92 ± 0.01, P < 0.0001; pre PCI CFR 1.97 ± 0.18 versus post PCI CFR 2.41 ± 0.17, P = 0.007).

Microvascular resistance decreased following PCI (culprit cIMR 16.96 ± 1.78 versus nonculprit cIMR 26.68 ± 2.06 versus post PCI cIMR 18.51 ± 1.94, P < 0.0001). However, when collateral supply was accounted for using the corrected IMR equation, no effect of PCI on microvascular resistance was observed (culprit cIMR 16.96 ± 1.78 versus post PCI cIMR 18.51 ± 1.94, P = 0.424). There was a similar relationship observed with post PCI cIMR (culprit cIMR 16.96 ± 1.78 versus post PCI cIMR 17.06 ± 1.88, P = 0.91).

There also was no difference between post PCI IMR and the nonculprit IMR (nonculprit sIMR 18.37 ± 1.89 versus post PCI sIMR 18.51 ± 1.94, P = 0.02).

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/female 27/13</td>
</tr>
<tr>
<td>Age (y)</td>
<td>61.2 ± 1.8</td>
</tr>
<tr>
<td>Symptom duration (days)</td>
<td>38 (Q1, Q3/6, 367)</td>
</tr>
<tr>
<td>Culprit vessel</td>
<td>LAD 17 (42.5), LCx 14 (35), RCA 9 (22.5)</td>
</tr>
<tr>
<td>Nonculprit vessel</td>
<td>LAD 17 (42.5), LCx 16 (40), RCA 7 (17.5)</td>
</tr>
<tr>
<td>HMG co-enzyme A inhibitor</td>
<td>33 (82.5)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>17 (43.6)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>28 (71.8)</td>
</tr>
<tr>
<td>Smoker</td>
<td>21 (51.2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14 (34.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>28 (68.3)</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>63 ± 2.1</td>
</tr>
</tbody>
</table>

Continuous variables expressed as mean ± SEM. Discrete variables expressed as number and percentage in brackets. Non-normally distributed variables expressed as median plus QI, Q3.

Drug treatment mentioned refers to percentage of patients on specific medication at the time of the procedure.

LAD indicates left anterior descending artery; LCx, left circumflex artery; RCA, right coronary artery; HMG, HMG : 3-hydroxy-3-methylglutaryl-coenzyme A; ACE, angiotensin converting enzyme; LV, left ventricle.

### Table 2. Angiographic Data

<table>
<thead>
<tr>
<th>Procedural Data</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA lesion class</td>
<td>A (25), B (75), C (0)</td>
</tr>
<tr>
<td>DES/BMS</td>
<td>35/5 (87.5/12.5)</td>
</tr>
<tr>
<td>QCA pre PCI (%)</td>
<td>72.13 ± 2.7</td>
</tr>
<tr>
<td>QCA post PCI (%)</td>
<td>64.1 ± 1.3</td>
</tr>
<tr>
<td>Stent size (diameter mm)</td>
<td>3.01 ± 0.07</td>
</tr>
<tr>
<td>Maximum pressure (atm)</td>
<td>18.2 ± 0.58</td>
</tr>
<tr>
<td>No. of inflations</td>
<td>4.5 ± 0.35</td>
</tr>
</tbody>
</table>

Continuous variables expressed as mean ± SEM. Discrete variables expressed as No. and percentage in brackets.

AHA indicates American Heart Association; DES, drug eluting stent; BMS, bare metal stent; QCA, quantitative coronary angiography; atm, atmospheres.

American Heart Association lesion class A (low risk, >85% success rate), B (moderate risk, 60% to 85% success rate).
Coronary blood flow indices improved following PCI (pre PCI Culprit TmnBase 0.64 ± 0.07 versus post PCI TmnBase 0.57 ± 0.06, P < 0.0001; pre PCI TmnHyp culprit 0.57 ± 0.06 versus post PCI TmnHyp 0.25 ± 0.03, P < 0.0001), but there was no difference between indices of coronary blood flow between post PCI values in the culprit vessel and the nonculprit territory (nonculprit TmnBase 0.64 ± 0.07 versus post PCI TmnBase 0.57 ± 0.06, P = 0.32; nonculprit TmnHyp 0.24 ± 0.02 versus post PCI TmnHyp 0.25 ± 0.03, P = 0.7).

**Discussion**

Our results suggest that, when the effect of microvascular collaterals is accounted for, epicardial stenosis does not affect microvascular resistance.

The effect of collateral circulation pre PCI is accounted for by using the corrected IMR equation that incorporates coronary wedge pressure. In accordance with prior studies, improvements in antegrade flow following PCI meant that the contribution of microvascular collaterals was assumed to be negligible, and thus correction for collaterals was not performed. However, for completeness of data we have provided the corrected IMR as well as the simplified IMR post PCI.

Secondly, as stenosis severity increased, both resting and hyperemic blood flow was reduced. However, there was an increasing contribution of collaterals, evident from an increase in coronary wedge pressure, suggesting a possible compensatory mechanism to maintain myocardial blood flow and maintain patency of the microvessels.

The concept of increasing stenosis severity leading to increased microvascular resistance is controversial. Some have shown that as the severity of epicardial stenosis increases, microvascular resistance increases. Using combined Doppler and pressure derived measures, Chamuleau et al demonstrated that minimal microvascular resistance increased distal to a significant epicardial stenosis when compared with a normal vessel without stenosis in the same

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**Table 3. Coronary Physiology Pre- and Post-PCI**

<table>
<thead>
<tr>
<th></th>
<th>Nonculprit</th>
<th>Culprit Pre PCI</th>
<th>Culprit Post PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR</td>
<td>0.93 ± 0.05</td>
<td>0.65 ± 0.03*</td>
<td>0.92 ± 0.01†</td>
</tr>
<tr>
<td>CFR</td>
<td>2.81 ± 0.18</td>
<td>1.97 ± 0.18*</td>
<td>2.41 ± 0.17†</td>
</tr>
<tr>
<td>sIMR</td>
<td>18.37 ± 1.89</td>
<td>26.68 ± 2.06*</td>
<td>18.51 ± 1.94†</td>
</tr>
<tr>
<td>cIMR</td>
<td>‡</td>
<td>16.96 ± 1.78</td>
<td>17.06 ± 1.88</td>
</tr>
<tr>
<td>TmnBase</td>
<td>0.64 ± 0.07</td>
<td>0.92 ± 0.09*</td>
<td>0.57 ± 0.06†</td>
</tr>
<tr>
<td>TmnHyp</td>
<td>0.24 ± 0.02</td>
<td>0.57 ± 0.36*</td>
<td>0.25 ± 0.03†</td>
</tr>
</tbody>
</table>

Values displayed as mean ± SEM.  
FFR indicates fractional flow reserve; CFR, coronary flow reserve; sIMR, simplified index of microcirculatory resistance; cIMR, corrected index of microcirculatory resistance; TmnBase, mean baseline transit time; TmnHyp, hyperemic mean transit time.

*Significant (P < 0.05) difference between pre PCI and nonculprit values. †Significant (P < 0.05) difference between pre and post PCI values. ‡Value not calculated (see text for explanation).
Patient. Verhoef and colleagues drew similar conclusions, showing that microvascular resistance increased secondary to a coronary stenosis in 23 patients with stable angina. Furthermore, following PCI, resistance fell below the level of an angiographically normal reference vessel also studied. However, despite the measurement of collateral flow, this was not incorporated into the calculation of microvascular resistance, and therefore this may have been overestimated in patients with significant epicardial stenoses. Thus, by using a TPSG for IMR analysis and incorporating the effect of collaterals into the calculation of microvascular resistance, we have expanded significantly on these findings.

Prior animal models using IMR as a technique to investigate the impact of a stenosis on minimal achievable resistance demonstrated that there was no increase in microvascular resistance secondary to an epicardial stenosis. However, previous IMR studies in humans have measured microcirculatory resistance using balloon inflation within a stent to mimic a stenosis post PCI rather than actual de novo stenoses. Furthermore, the impact of peri-procedural infarction on IMR has not been documented well, and the incidence of cardiac biomarker elevation was not reported in previous IMR studies. Significant myonecrosis is likely to confound evaluation of microvascular resistance by increasing distal pressure and limiting capillary recruitment. Although not statistically significant, Cuisset et al demonstrated a higher IMR following PCI, which was associated with higher troponin levels. In our population, significant myonecrosis was incorporated into our exclusion criteria to minimize its confounding effect. Thus, we were able to use the post PCI IMR value reliably as a point of reference. Our findings may, therefore, be more representative of coronary physiology than artificially induced stenoses post PCI. We also have extended this concept to incorporate assessment of a nonculprit, angiographically normal vessel as a further point of reference.

In our population, there was no significant difference between microvascular resistance pre PCI compared with post PCI values. There also was no difference between the nonculprit and the post PCI microvascular resistance values when we accounted for the effect of collaterals. This suggests that microvascular resistance is not related to epicardial stenosis severity because there is no difference between the culprit and the nonculprit, or the culprit and post PCI values.

Prior animal studies have demonstrated that resting coronary blood flow only begins to reduce once a coronary stenosis reaches 85%. In contrast, hyperemic blood flow reduced when an epicardial stenosis was greater than 50%. In a group of 35 humans with single vessel coronary artery disease using positron emission tomography, Uren and colleagues suggested that epicardial stenosis had no influence on resting coronary blood flow, but hyperemic blood flow began to reduce once a stenosis reached 40%. The conflicting results can be explained by the inherent differences between animals and humans, but also by the fact that the stenoses included in the human study were less severe. A further point is that collateral flow was not accounted for in the animal study, so that true myocardial flow may have been underestimated. Our results are in accordance with previous human studies suggesting that basal flow is not significantly influenced by epicardial stenosis severity as assessed angiographically, but hyperemic blood flow progressively reduces as the stenosis severity increases. However, we did find a significant negative correlation between FFR and basal coronary blood flow suggesting that, contrary to our angiographic estimation of severity, FFR estimation was a better predictor for the hemodynamic consequence of a stenosis compared with angiographic assessment. Stenosis is only 1 determinant of the hemodynamic significance of a lesion, and the poor correlation between angiographic severity and FFR has been confirmed with recent clinical trials.

When using the nonculprit vessel as a control, we assume homogeneity of microvascular resistance within the myocardium, an assumption that has underpinned other studies. Our results suggest that microvascular resistance is homogeneously distributed between different vascular territories within the same patient. However, as we are measuring thermodilution derived blood flow rather than absolute myocardial blood flow in the calculation of microvascular resistance, we cannot be certain of this relationship. Furthermore, not all epicardial vessels were assessed in each patient.

Limitations
The complexity of our study was such that only a small number of patients were studied. However, it is one of the largest cohorts of patients studied in this field, with sufficient power to explore the underlying hypotheses. A small proportion of our patients had a postprocedural troponin elevation, and this may have had an effect on the distal pressure and thus, IMR. Troponin elevation following PCI is common, and studies showing an incidence of up to 30% in elective PCI. However, we excluded any patient with a troponin rise greater than 12 times the upper limit of normal, as elevations above this level have been shown to correlate with areas of infarction on cardiac magnetic resonance imaging. In fact, no patient had a troponin level greater than 5 times the upper limit of normal. Lower troponin levels are not associated with myocardial injury on magnetic resonance imaging, and thus their effect on IMR is likely to be minimal.

As the decision to perform PCI was at the discretion of the operators, some patients with an FFR >0.8 underwent intervention. This may have tended to underestimate the impact that an epicardial stenosis has on microvascular resistance in...
the overall cohort. However, by including such patients, a broader range of actual stenoses was assessed so that more informed conclusions about the effects of epicardial stenosis on microvascular resistance could be made.

Adjustment for multiple comparisons was not undertaken, however, and where statistically significant, the differences in measurements were substantial, making a Type I error unlikely.

**Conclusion**

In conclusion, when collateral flow is accounted for we have shown that epicardial stenosis does not increase microvascular resistance.

**Disclosures**

None.

**References**


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