Microvascular Resistance Is Not Influenced by Epicardial Coronary Artery Stenosis Severity
Experimental Validation

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Background—The effect of epicardial artery stenosis on myocardial microvascular resistance remains controversial. Recruitable collateral flow, which may affect resistance, was not incorporated into previous measurements.

Methods and Results—In an open-chest pig model, distal coronary pressure was measured with a pressure wire, and the apparent minimal microvascular resistance was calculated during peak hyperemia as pressure divided by flow, measured either with a flow probe around the coronary artery (Rmicrapp) or with a novel thermodilution technique (apparent index of microcirculatory resistance [IMRapp]). These apparent resistances were compared with the actual Rmicr and IMR after the coronary wedge pressure and collateral flow were incorporated into the calculation. Measurements were made at baseline (no stenosis) and after creation of moderate and severe epicardial artery stenoses. In 6 pigs, 189 measurements of Rmicr and IMR were made under the various epicardial artery conditions. Without consideration of collateral flow, Rmicrapp (0.43 ± 0.12 to 0.46 ± 0.10 to 0.51 ± 0.11 mm Hg/mL per minute) and IMRapp (14 ± 4 to 17 ± 7 to 20 ± 10 U) increased progressively and significantly with increasing epicardial artery stenosis (P < 0.001 for both). With the incorporation of collateral flow, neither Rmicr nor IMR increased as a result of increasing epicardial artery stenosis.

Conclusions—After collateral flow is taken into account, the minimum achievable microvascular resistance is not affected by increasing epicardial artery stenosis. (Circulation. 2004;109:2269-2272.)

Key Words: microcirculation • coronary disease

The complex interrelationship between the coronary microcirculation and the epicardial coronary arteries remains poorly understood. In particular, the effect of increasing epicardial artery stenosis on microvascular resistance is controversial. Pioneering work by Gould and others1,2 revealed no change in dial artery stenosis on microvascular resistance is controversial. Poorly understood. In particular, the effect of increasing epicardial artery stenosis on myocardial flow (coronary flow plus collateral flow) when invasively evaluating microvascular resistance. Briefly, to estimate myocardial flow, it is necessary to measure the coronary wedge pressure, which is a reflection of collateral circulation (see Appendix).7

Recently, a pressure-temperature sensor-tipped guidewire has been developed, which allows simultaneous determination of coronary pressure and flow.8,9–11 Flow is estimated with the use of a coronary thermodilution technique to measure the mean transit time of an injectate. The inverse of the hemodynamic mean transit time has been shown to correlate with absolute coronary flow.8 Using this technique, we have proposed an invasive index for quantitatively assessing microvascular resistance independent of the epicardial artery, termed the index of microcirculatory resistance (IMR).12 In an animal model, IMR correlated well with an accepted experimental method for measuring microvascular resistance (Rmicr).12

In its simplest form, IMR is defined as the distal coronary pressure divided by the inverse of the mean transit time at peak hyperemia or, more simply, distal pressure multiplied by

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the mean transit time. However, as the mean transit time is a correlate of coronary flow and not myocardial flow, this simple definition of IMR (apparent IMR or IMR_app) will also overestimate microvascular resistance in the presence of an epicardial artery stenosis. For IMR to be universally applicable, even in the presence of a stenosis, collateral flow as measured by the coronary wedge pressure must be incorporated into the equation (see Appendix).

The goal of this study was to determine whether the apparent R_micro (R_micro_app) and IMR_app increase with increasing degrees of epicardial artery stenosis and to demonstrate that the actual R_micro and IMR, which incorporate collateral contribution, do not change.

Methods
Animal Preparation
The study was approved by Stanford’s Institutional Animal Care and Use Committee. Yorkshire swine were premedicated with intramuscular ketamine (20 mg/kg), xylazine (2 mg/kg), and buprenorphine (0.005 mg/kg). Anesthesia was maintained with 2% isoflurane, and supplemental oxygen was given via endotracheal intubation. An arterial sheath was surgically placed in the right carotid artery. Angiography was performed with a 6F catheter. A lateral thoracotomy was performed by a standard surgical technique, the pericardium was opened, and the proximal left anterior descending coronary artery (LAD) was circumscribed by a combination of sharp and blunt dissection. An ultrasonic flow probe (Transonic Systems, Inc) was placed around the proximal LAD; a vascular occluder (Harvard Apparatus) was placed distal to the flow probe, with care taken to ensure that there were no branch vessels between the two.

Coronary Pressure and Flow Measurements
A coronary pressure wire (Radi Medical Systems) was advanced to the distal LAD. After injection of intracoronary papaverine (5 mg), distal pressure and mean LAD transit time were measured with the pressure wire as previously described. Analysis of the coronary pressure wire data was done as described previously.

Statistical Analysis
Values are presented as mean ± SD. ANOVA was used to compare changes in mean values under the various epicardial artery settings. Post hoc analysis in which the Bonferroni multiple comparisons test was used was applied to assess statistical significance. A probability value <0.05 was considered significant. Statistical calculations were performed with Statview software (SAS Institute Incorporated).

Results
In a total of 6 pigs, 189 measurements of R_micro_app, IMR_app, R_micro, and IMR were made. Fifty-four measurements were in the setting of no epicardial artery stenosis, 80 with a moderate stenosis (average FFR_myo = 0.84 ± 0.05), and 55 with a more severe stenosis (average FFR_myo = 0.68 ± 0.07). The mean arterial pressure decreased from 69 ± 10 to 55 ± 8 mm Hg after administration of papaverine. The mean coronary wedge pressure was 15.0 ± 4.8 mm Hg. There was a significant inverse correlation between the hyperemic mean transit time and flow as measured with the flow probe (r = -0.41, P < 0.001). In contrast, after the effects of collateral flow were incorporated, neither R_micro (0.43 ± 0.12 to 0.46 ± 0.10 to 0.51 ± 0.11 mm Hg/mL per minute; P < 0.001; Figure 1) nor IMR_app changed significantly with increasing epicardial artery stenosis (14 ± 4 to 17 ± 7 to 20 ± 10 U; P > 0.05; Figure 1) nor IMR (14 ± 4 to 16 ± 7 to 16 ± 9 U; P = 0.30; Figure 2) changed significantly with increasing epicardial artery stenosis.

Discussion
In the present study two different measurements of microvascular resistance (R_micro and IMR) were obtained before and after we accounted for the contribution of collaterals to myocardial blood flow. Our findings suggest that microvascular resistance does not increase with increasing epicardial artery stenosis. Previous reports have documented increases in microvascular resistance in the presence of an epicardial artery stenosis; however, the present data indicate that this...
increase is only apparent and relates to neglecting the contribution of collateral hemodynamics. In addition, the present data further confirm the validity of IMR as a surrogate of absolute microvascular resistance.

Myocardial blood flow is the sum of antegrade coronary flow and collateral flow. With the increasing severity of an epicardial artery stenosis, collateral flow will increase. Because of this collateral flow, the distal perfusion pressure at peak hyperemia detected by the pressure wire will not decrease to zero but will approach the coronary wedge pressure as the epicardial artery stenosis approaches total occlusion. Yet, the measured antegrade coronary flow (whether determined with a Doppler velocity wire, with a flow probe, or by a thermodilution technique) will not incorporate collateral flow and does approach zero as the epicardial artery stenosis approaches total occlusion. Thus, the increase in collateral flow results in an increase in myocardial flow that is reflected by the distal pressure measurement (numerator in the equation for resistance) but not incorporated into current methods for measuring flow (denominator in the equation for resistance). These changes will result in a measured minimal microvascular resistance that is increased or overestimated. After removal of the epicardial artery stenosis and the collateral contribution, the measured distal pressure will return to its expected level, and the minimal microvascular resistance will appear to decrease.

Neglecting collateral flow, we found that microvascular resistance appeared to increase significantly (Figures 1 and 2). However, after incorporating collateral flow by measuring the coronary wedge pressure and by multiplying the apparent resistance by the ratio of FFRcorr to FFRmyo, we found no change in the minimum achievable microvascular resistance with increasing epicardial artery stenosis (see Appendix). These findings are clinically relevant as appreciation for the role of the microvasculature in determining outcomes has grown. To effectively diagnose and treat microvascular dysfunction, a better understanding of the relationship between the microvasculature and the epicardial coronary system will be critical.

**Limitations**

Although recruitable collateral flow in the porcine coronary system is similar to human coronaries, this study is limited by its use of an acute animal model with normal microvascular function. Furthermore, the epicardial artery stenoses were created acutely. It is possible that microvascular dysfunction or chronic stenoses might have a different impact on changes in microvascular resistance with epicardial stenoses. Moreover, we did not specifically assess changes in capillary resistance that might occur with creation of epicardial stenoses. Kaul and colleagues and Jayaweera et al. have demonstrated the importance of the capillary system in determining microvascular resistance; a more comprehensive hemodynamic assessment, including an evaluation of changes in capillary resistance, will be necessary to validate our findings.

The slope of IMR as stenosis severity increased was slightly positive, while the slope of Rmicro was slightly negative. Theoretically, the slopes should be zero; the slight deviation was statistically insignificant and presumably a result of measurement variation. The most severe stenoses in this study did not affect resting flow. The effect on the microvasculature of this subset of extreme stenoses requires further study.

**Conclusions**

If collateral flow is accounted for, the minimum achievable microvascular resistance is not significantly affected by increasing epicardial artery stenosis.

**Appendix**

See Aarnoudse et al. All measurements are made under conditions of maximal hyperemia. Qcor, Qmyo, and Qcollate indicate maximum myocardial, coronary, and collateral flow, respectively, in the absence of epicardial artery or microvascular disease. QN = Qcor + Qcollate, and because Qcollate = 0, Qcor = Qmyo. Qcor, Qmyo, and Qcollate indicate measured myocardial, coronary, and collateral flow, respectively. Pa, Pd, Pw, and Pv indicate aortic, distal coronary, central venous, and coronary wedge pressures, respectively.

The following equations were originally derived by Pijs et al.:

\[ Q_{\text{myo}} = Q_{\text{cor}} + Q_{\text{collate}} \]

\[ \text{FFR}_{\text{myo}} = Q_{\text{myo}} / Q_{\text{cor}} \]

\[ \text{FFR}_{\text{cor}} = Q_{\text{cor}} / Q_{\text{myo}} \]

\[ \text{FFR}_{\text{myo}}^{\text{corr}} = (P_{d} - P_{a}) / (P_{d} - P_{w}) \]

\[ Q_{\text{cor}} = 1/T_{\text{mn}} \text{ where } T_{\text{mn}} = \text{hyperemic mean coronary thermodilution transit time} \]

\[ (1) \quad \text{IMR}_{\text{app}} = (P_{d} - P_{a}) / (Q_{\text{cor}} / Q_{\text{myo}}) \times T_{\text{mn}} \]

\[ \text{R}_{\text{micro}}^{\text{app}} = (P_{d} - P_{a}) / Q_{\text{cor}} \]

\[ \text{IMR}_{\text{app}} = (P_{d} - P_{a}) / Q_{\text{cor}} \] (Restated, IMR = \[(P_{d} - P_{a}) / (Q_{\text{cor}} / Q_{\text{myo}})] / (Q_{\text{cor}} / Q_{\text{myo}})

\[ = \text{IMR}_{\text{app}} \times Q_{\text{cor}} / Q_{\text{myo}} \]

\[ = \text{IMR}_{\text{app}} \times (Q_{\text{cor}} / Q_{\text{myo}}) \times (Q_{\text{cor}} / Q_{\text{myo}}) \]

\[ = \text{IMR}_{\text{app}} \times (Q_{\text{cor}} / Q_{\text{myo}}) \]

Because QN = Qcor, IMR = IMRapp \times (FFR_{\text{cor}} / Q_{\text{myo}})

\[ = \text{IMR}_{\text{app}} \times (FFR_{\text{cor}} / Q_{\text{myo}}) \]

\[ = (P_{d} - P_{a}) / Q_{\text{cor}} \times \text{FFR}_{\text{cor}} \]

(2)

\[ \text{Assuming } P_{a} = 0, \text{ IMR} = P_{d} / T_{\text{mn}} \times \text{FFR}_{\text{cor}} \]

If Qmicro is substituted for IMR, Rmicro = IMRapp \times (FFR_{\text{cor}} / Q_{\text{myo}}). If there are no collaterals, as in the case of a normal epicardial artery, FFR_{\text{cor}} = FFR_{\text{myo}} and Equation 2 equals Equation 1. Equation 2 can be rewritten in terms of measured pressures, as follows:

\[ \text{IMR} = \left[ (P_{d} - P_{a}) / T_{\text{mn}} \right] \times \left[ (P_{d} - P_{a}) / (P_{d} - P_{w}) \right] \times \left[ (P_{d} - P_{a}) / (P_{d} - P_{w}) \right] \]

\[ = \left[ (P_{d} - P_{a}) / T_{\text{mn}} \right] \times \left[ (P_{d} - P_{a}) / (P_{d} - P_{w}) \right] \times \left[ (P_{d} - P_{a}) / (P_{d} - P_{w}) \right] \]

\[ = \left[ (P_{d} - P_{a}) / T_{\text{mn}} \right] \times \left[ (P_{d} - P_{a}) / (P_{d} - P_{w}) \right] \]

Assuming P_{a} = 0, IMR = P_{d} / T_{\text{mn}} \times \text{FFR}_{\text{cor}}

**References**


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