Brief Rapid Communication

Novel Index for Invasively Assessing the Coronary Microcirculation

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Background—A relatively simple, invasive method for quantitatively assessing the status of the coronary microcirculation independent of the epicardial artery is lacking.

Methods and Results—By using a coronary pressure wire and modified software, it is possible to calculate the mean transit time of room-temperature saline injected down a coronary artery. The inverse of the hyperemic mean transit time has been shown to correlate with absolute flow. We hypothesize that distal coronary pressure divided by the inverse of the hyperemic mean transit time provides an index of microcirculatory resistance (IMR) that will correlate with true microcirculatory resistance (TMR), defined as the distal left anterior descending (LAD) pressure divided by hyperemic flow, measured with an external ultrasonic flow probe. A total of 61 measurements were made in 9 Yorkshire swine at baseline and after disruption of the coronary microcirculation, both with and without an epicardial LAD stenosis. The mean IMR (16.9 ± 6.5 U to 25.9 ± 14.4 U, P = 0.002) and TMR (0.51 ± 0.14 to 0.79 ± 0.32 mm Hg · mL⁻¹ · min⁻¹, P = 0.0001), as well as the % change in IMR (147 ± 66%) and TMR (159 ± 105%, P = NS versus IMR % change), increased significantly and to a similar degree after disruption of the microcirculation. These changes were independent of the status of the epicardial artery. There was a significant correlation between mean IMR and TMR values, as well as between the % change in IMR and % change in TMR.

Conclusion—Measuring IMR may provide a simple, quantitative, invasive assessment of the coronary microcirculation. (Circulation. 2003;107:3129-3132.)

Key Words: microcirculation • coronary disease • pressure

The importance of the coronary microcirculation in determining patient outcomes has been demonstrated in a number of clinical settings.¹–⁴ Current methods for evaluating the status of the microcirculation are limited because they are qualitative, are cumbersome, rely on sophisticated analyses, or do not independently interrogate the microcirculation.¹,⁵–⁸ Furthermore, many techniques are noninvasive and not readily applicable in the cardiac catheterization laboratory, where many patients first present for evaluation of their coronary circulation.⁹

Recent technological advances have made it feasible to measure coronary artery pressure invasively and to estimate coronary artery flow with a single coronary pressure wire.¹⁰,¹¹ Modified software allows the pressure sensor of the wire to act also as a distal thermistor, while the shaft of the wire serves as a proximal thermistor. In this manner, the mean transit time of saline injected down a coronary artery can be derived from a coronary thermodilution curve. De Bruyne, Pijls and colleagues¹⁰,¹¹ applied this technique in an experimental model and found a strong correlation between the inverse of the mean transit time and absolute flow. These investigators showed that the thermodilution-derived coronary flow reserve (CFR), defined as the resting mean transit time divided by the hyperemic mean transit time, correlated well with standard CFR, both in their experimental model and in humans.¹⁰,¹¹

Use of CFR to assess the microcirculation independently, however, is limited in that CFR interrogates the flow status of both the epicardial artery and the microcirculation.⁶ Calculation of the microvascular resistance by dividing the distal coronary pressure by absolute coronary flow would provide an independent assessment of microcirculatory function.

We postulate that a novel index of microcirculatory resistance (IMR), defined as distal coronary pressure divided by the inverse of the hyperemic mean transit time (a correlate to absolute flow), measured simultaneously with the coronary pressure wire, will evaluate microvascular resistance, independent of epicardial stenoses. Because both distal pressure and flow will drop in the presence of an epicardial stenosis, microcirculatory resistance and IMR should be unaffected. IMR is derived from the assumption that at peak hyperemia the variability of resting vascular tone and hemodynamics

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will be eliminated, and the minimum microvascular resistance will be achieved. The goal of the present study is to demonstrate that IMR correlates with a standard experimental method for measuring microcirculatory resistance.

**Methods**

**Protocol**

Stanford’s Institutional Animal Care and Use Committee approved the study protocol. In an open-chest porcine model, the true microcirculatory resistance (TMR), defined as distal coronary pressure divided by absolute coronary flow (mm Hg · mL⁻¹ · min⁻¹) at hyperemia, was compared with IMR, defined as distal coronary pressure divided by the inverse of the hyperemic mean transit time, or more simply, distal coronary pressure multiplied by the hyperemic mean transit time (mm Hg · seconds, or units [U]).

Measurements were made in the left anterior descending artery (LAD) at baseline and after induction of an epicardial stenosis. The microcirculation was then disrupted with embolized microspheres and measurements were repeated with a normal epicardial artery and after creation of an epicardial stenosis.

**Animal Preparation**

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 of the LAD was performed with a 6F catheter. A lateral thoracotomy was performed by using standard surgical technique, the pericardium was opened, and the proximal LAD was dissected free. 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, making sure that there were no branch vessels between the two. A bolus of 300 U/kg of heparin was administered intravenously.

**Coronary Pressure and Flow Measurements**

A coronary pressure wire (Radi Medical Systems) was calibrated and advanced to the distal LAD. After achieving maximal hyperemia with intracoronary papaverine (20 mg), the distal coronary pressure was recorded from the pressure wire and the coronary flow (mL/min) was recorded from the external flow probe, which measures volume flow directly and independent of vessel diameter. The hyperemic mean transit time was recorded after rapid injection of 3 mL of room-temperature saline through the coronary catheter, as previously described. The hyperemic mean transit time was measured 3 times and averaged. IMR and TMR were calculated as described above. CFR was calculated from the ratio of hyperemic to resting coronary flow recorded from the flow probe.

Epicardial stenoses were created by using the vascular occluder so that the distal coronary pressure was 90% of the proximal coronary pressure at rest. The microcirculation was disrupted by selectively injecting 100 μm × 103 fluorescent microspheres (Interactive Medical Technologies) down the LAD.

**Statistics and Analyses**

Continuous values are presented as a mean±SD. Mean values were compared with Student’s t test. ANOVA was used to analyze differences between mean values under the different epicardial and microcirculatory conditions. Post-hoc analysis with the Bonferroni multiple-comparisons test was applied to assess statistical significance. Linear regression analysis was used to compare the relationship between IMR and TMR. A probability value <0.05 was considered statistically significant.

**Results**

Sixty-one pairs of measurements of TMR, our reference standard for microvascular resistance, and IMR were performed in 9 pigs. The variance within the 3 hyperemic transit time measurements was 14±9%. In the setting of a normal microcirculation, the mean TMR was 0.51±0.14 mm Hg · mL⁻¹ · min⁻¹, including measurements with (n=16) and without (n=19) an epicardial stenosis. The mean TMR with a disrupted microcirculation was significantly higher, 0.79±0.32 mm Hg · mL⁻¹ · min⁻¹ (P<0.0001), and again included measurements with (n=11) and without (n=15) an epicardial stenosis. The corresponding mean IMR was 16.9±6.5 U, which increased significantly to 25.9±14.4 U (P<0.002) (Table).

<table>
<thead>
<tr>
<th></th>
<th>Normal Microcirculation</th>
<th>Abnormal Microcirculation</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMR, U</td>
<td>Total group</td>
<td>16.9±6.5</td>
<td>25.9±14.4</td>
</tr>
<tr>
<td></td>
<td>Stenosis absent</td>
<td>14.7±4.8</td>
<td>23.9±3.8</td>
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<tr>
<td></td>
<td>Stenosis present</td>
<td>19.2±7.3</td>
<td>28.6±14.5</td>
</tr>
<tr>
<td>TMR, mm Hg · mL⁻¹ · min⁻¹</td>
<td>Total group</td>
<td>0.51±0.14</td>
<td>0.79±0.32</td>
</tr>
<tr>
<td></td>
<td>Stenosis absent</td>
<td>0.48±0.14</td>
<td>0.71±0.25</td>
</tr>
<tr>
<td></td>
<td>Stenosis present</td>
<td>0.58±0.16</td>
<td>0.90±0.39</td>
</tr>
</tbody>
</table>

The % change in TMR from baseline to after disruption of the microcirculation was 159±105%, whereas the corresponding value for IMR was 147±66% (P=NS, compared with TMR % change). There was a significant correlation between the % change in TMR and IMR (% change) (r=0.60, P<0.001).

Without an epicardial stenosis, the % change in TMR from baseline to after disruption of the microcirculation was 150±67%, compared with 166±89% for IMR (P=NS), with a significant correlation between the % changes (r=0.75, P<0.001). With an epicardial stenosis present, the percent change in TMR was 173±115% compared with 141±68%.
for IMR (P=NS), with a significant correlation between the % changes (r=0.87, P<0.001) (Figure 2).

CFR at baseline was 2.8±0.7 and decreased significantly to 2.1±0.9 after creation of an epicardial stenosis (P<0.003). CFR after microcirculatory disruption was 1.4±0.5, which decreased after creation of an epicardial stenosis to 1.3±0.4 (P=NS).

**Discussion**

In this investigation, we found that a novel index of microcirculatory resistance, IMR, distinguishes between normal and abnormal microcirculatory function and is not significantly affected by the presence of an epicardial stenosis. Furthermore, the changes in IMR between the various epicardial and microcirculatory conditions mirrored those of TMR, our reference standard for microvascular resistance. These findings suggest that measurement of IMR could be applied in the cardiac catheterization laboratory as a means for interrogating and quantifying microcirculatory resistance.

The advantages of measuring IMR over other current methods for assessing the microcirculation include the relative ease of its performance in the cardiac catheterization laboratory. IMR is measured with a single coronary pressure wire and does not require other personnel or sophisticated equipment and analyses. It is quantitative and appears to be independent of epicardial artery disease. Because the method employs a standard coronary pressure wire, fractional flow reserve can be determined simultaneously and further help to distinguish epicardial disease from microcirculatory dysfunction. Lastly, IMR can be measured in both the acute and chronic states, although serial measurements will be limited by its invasive nature.

The limitations of the present study include the method of disrupting the microcirculation. Embolized microspheres result in acute structural microvascular changes that may mimic only certain types of clinical microcirculatory dysfunction, such as that after coronary intervention or during acute myocardial infarction. Recent data, however, suggest that coronary microembolization may be a more prevalent condition than initially appreciated. The degree of microvascular disruption in the present study was variable, possibly because some animals may have had a greater dispersion of the microspheres, resulting in less significant microvascular changes. Variability in the degree of microvascular obstruction, however, would make it more difficult to demonstrate a difference in IMR between the normal and abnormal microcirculatory conditions. Moreover, because IMR and TMR measurements were made simultaneously, their comparison should remain valid.

Another limitation of the present study relates to the fact that coronary flow was measured in the proximal LAD to derive TMR, although the temperature sensor used to measure the mean transit time of saline in order to derive IMR was placed in the distal LAD. This difference could contribute to variability in the correlation between IMR and TMR. Because the location of the sensor in the LAD is an important determinant of the mean transit time, standardizing the distance the sensor is placed down the LAD also could improve the correlation between IMR and TMR.

Finally, although TMR and IMR appeared to be independent of the status of the epicardial artery, both increased nonsignificantly after creation of an epicardial stenosis. The stenoses in the present study were severe, potentially resulting in collateral recruitment. Collateral circulation could lessen the drop in distal coronary pressure due to a stenosis, without changing coronary flow, and thereby lead to an increase in the measured microvascular resistance. This theory will need to be tested further by measuring IMR and TMR in a variety of stenosis severities.

**Conclusion**

Measuring IMR may represent a new method for simply, quantitatively, and invasively assessing the status of the coronary microcirculation. The value of IMR will need to be tested in humans.

**References**

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In the article, “Platelet/Endothelial Biomarkers in Depressed Patients Treated With the Selective Serotonin Reuptake Inhibitor Sertraline After Acute Coronary Events: The Sertraline AntiDepressant Heart Attack Randomized Trial (SADHART) Platelet Substudy” by Serebruany et al, which appeared in the August 26, 2003, issue of the journal (Circulation. 2003;108:939–944), some information was inadvertently omitted from the conflict-of-interest disclosure footnote. The following disclosures are added:

Dr Califf has received research support from and served as a consultant for Pfizer (all proceeds donated to Duke University). Dr O’Connor has received research support from and has consulted for Pfizer, GlaxoSmithKline, Eli Lilly, and Forest Pharmaceuticals, and holds patents for selective serotonin reuptake inhibitor research.

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In the article, “Physiology and Pathophysiology of Vascular Signaling Controlled by Cyclic Guanosine 3’,5’-Cyclic Monophosphate–Dependent Protein Kinase” by Münzel et al, which appeared in the November 4, 2003, issue of the journal (Circulation. 2003;108:2172–2183), the word “cyclic” was mistakenly duplicated in the title. The title should have read as follows:

Physiology and Pathophysiology of Vascular Signaling Controlled by Guanosine 3’,5’-Cyclic Monophosphate–Dependent Protein Kinase

DOI: 10.1161/01.CIR.0000112319.29689.0C

In the article, “Novel Index for Invasively Assessing the Coronary Microcirculation” by Fearon et al, which appeared in the July 1, 2003, issue of the journal (Circulation. 2003;107:3129–3132), an author (Anthony D. Caffarelli) was inadvertently omitted from the byline. The byline should have read as follows:

William F. Fearon, MD; Leora B. Balsam, MD; H.M. Omar Farouque, MB, BS, PhD; Anthony D. Caffarelli, MD; Robert C. Robbins, MD; Peter J. Fitzgerald, MD, PhD; Paul G. Yock, MD; Alan C. Yeung, MD

DOI: 10.1161/01.CIR.0000112321.37196.64

In the article, “Comparison of Coronary Thermodilution and Doppler Velocity for Assessing Coronary Flow Reserve” by Fearon et al, which appeared in the November 4, 2003, issue of the journal (Circulation. 2003;108:2198-2200), an author (Anthony D. Caffarelli) was inadvertently omitted from the byline. The byline should have read as follows:

William F. Fearon, MD; H.M. Omar Farouque, MB, BS, PhD; Leora B. Balsam, MD; Anthony D. Caffarelli, MD; David T. Cooke, MD; Robert C. Robbins, MD; Peter J. Fitzgerald, MD, PhD; Alan C. Yeung, MD; Paul G. Yock, MD

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