Invasive Assessment of the Coronary Microcirculation
Superior Reproducibility and Less Hemodynamic Dependence of Index of Microcirculatory Resistance Compared With Coronary Flow Reserve

Martin K.C. Ng, MBBS, PhD; Alan C. Yeung, MD; William F. Fearon, MD

Background—A simple, reproducible invasive method for assessing the coronary microcirculation is lacking. A novel index of microcirculatory resistance (IMR) has been shown in animals to correlate with true microvascular resistance and, unlike coronary flow reserve (CFR), to be independent of the epicardial artery. We sought to compare the reproducibility and hemodynamic dependence of IMR with CFR in humans.

Methods and Results—Using a pressure-temperature sensor-tipped coronary wire, thermodilution-derived CFR and IMR were measured, along with fractional flow reserve (FFR), in 15 coronary arteries (15 patients) under the following hemodynamic conditions: (1) twice at baseline; (2) during right ventricular pacing at 110 bpm; (3) during intravenous infusion of nitroprusside; and (4) during intravenous dobutamine infusion. Mean CFR did not change during baseline measurements or during nitroprusside infusion but decreased during pacing (from 3.1±1.1 at baseline to 2.3±1.2 during pacing, P<0.05) and during dobutamine infusion (from 3.0±1.0 to 1.7±0.6 with dobutamine, P<0.0001). By comparison, mean values for IMR and FFR remained similar throughout all hemodynamic conditions. The mean coefficient of variation between 2 baseline measurements was significantly lower for IMR (6.9±6.5%) and FFR (1.6±1.6%) than for CFR (18.6±9.6%; P<0.01). Mean correlation between baseline measurements and each hemodynamic intervention was superior for IMR (r=0.90±0.05) and FFR (r=0.86±0.12) compared with CFR (r=0.70±0.05; P<0.05).

Conclusions—Compared with CFR, IMR provides a more reproducible assessment of the microcirculation, which is independent of hemodynamic perturbations. Simultaneous measurement of FFR and IMR may provide a comprehensive and specific assessment of coronary physiology at both epicardial and microvascular levels, respectively. (Circulation. 2006;113:2054-2061.)

Key Words: microcirculation ■ pressure ■ coronary disease

The state of the coronary microcirculation is an important determinant of patient outcomes in a number of clinical settings, including acute coronary syndromes, percutaneous coronary interventions, and cardiac transplantation–related allograft vasculopathy.1–4 However, to date, a simple and reproducible invasive method for assessing the coronary microcirculation has been lacking. Current techniques for evaluating the coronary microcirculation are limited because they are cumbersome, are qualitative, rely on complex analyses, or do not independently interrogate the coronary microcirculation.5–7

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Guidewire-based measurement of coronary flow reserve (CFR), either by Doppler flow or thermodilution techniques, has become an increasingly important invasive method for assessing the physiological significance of coronary disease.7,8 However, use of CFR to interrogate the microcirculation independently is limited because CFR interrogates the flow status of both the epicardial artery and the microcirculation but does not allow discrimination between these 2 components.7 Furthermore, CFR is limited by its dependence on heart rate and blood pressure, thereby calling into question its reproducibility.8

With recent technological advances, it is now possible to measure pressure and to estimate coronary artery flow simultaneously with a single pressure-temperature sensor-tipped coronary wire.10,11 By the thermodilution technique, the mean transit time (Tmn) of room-temperature saline injected down a coronary artery can be determined and has been shown to correlate inversely with absolute flow.10 From this technique, a thermodilution-based CFR can be derived that has been shown to correlate well with Doppler velocity wire-derived CFR and with absolute flow as measured by a flow probe but that has the same conceptual disadvantages as Doppler-derived CFR.8,11 Using this thermodilution method, we re-
ently proposed and validated a novel index of microvascular
to assess the status of the microcirculation independent of the epicardial artery.12 In an
animal model, IMR, defined as the distal coronary pressure divided by the inverse of the hyperemic mean transit time, correlated well with an accepted experimental method for measuring microvascular resistance.12

Unlike CFR, IMR is derived at peak hyperemia, thereby eliminating the variability of resting vascular tone and hemodynamics. We therefore hypothesized that IMR would not only be a more specific but also a more reproducible measure of coronary microcirculatory status that may be less subject to hemodynamic variation. This is especially relevant in the catheterization laboratory, particularly during interventional procedures, during which changes in heart rate, blood pressure, and cardiac contractility are likely to occur. The goal of the present study was to evaluate the feasibility, reproducibility, and hemodynamic dependence of IMR compared with CFR in humans.

Methods

The study population comprised 15 patients over the age of 21 years who were electively referred for coronary angiography. Because severe epicardial stenoses may affect measurement of microvascular resistance,13 only coronary arteries without high-grade epicardial stenoses (angiographic stenosis ≥50% and fractional flow reserve [FFR] >0.75) were included in the study. Patients were excluded if they had significant renal insufficiency (serum creatinine >1.5 mg/dL), recent acute myocardial infarction (within 1 week), or congestive heart failure. The study protocol was approved by Stanford University’s Administrative Panel on Human Subjects. Every patient provided informed written consent.

All patients were brought to the cardiac catheterization laboratory in a fasting state without discontinuation of their cardiac medications. After conventional diagnostic coronary angiography was performed, 3000 to 5000 U of intravenous heparin was administered, and a 6F coronary guiding catheter was used to engage the coronary artery of interest. Intracoronary nitroglycerin (200 μg) was given. A 0.014-in coronary pressure wire (Radi Medical Systems, Wilming-
ton, Mass) was calibrated, equalized to the guiding catheter pressure with the sensor positioned at the ostium of the coronary artery, and then advanced to the distal coronary artery (at least two thirds of the way down the vessel). CFR, IMR and FFR were then measured under a variety of hemodynamic conditions as described below.

Coronary Physiology Measurements

CFR, IMR, and FFR were measured by methods described previ-
ously.12,14 Briefly, with commercially available software (Radi Medical Systems) the shaft of the pressure wire can act as a proximal thermistor by detecting changes in temperature-dependent electrical resistance. The sensor near the tip of the wire simultaneously measures pressure and temperature and can thereby act as a distal thermistor. The transit time of room-temperature saline injected down a coronary artery can be determined with a thermodilution technique.10,11 Three injections of 3 mL of room-temperature saline were made down the coronary artery, and the resting mean transit time (Tmn) was measured. Intravenous infusion of adenosine (140 μg · kg⁻¹ · min⁻¹) was then administered to induce steady state maximal hyperemia, and 3 more injections of 3 mL of room-
temperature saline were made, and the hyperemic Tmn was measured. Simultaneous measurements of mean aortic pressure (Pao) by guiding catheter) and mean distal coronary pressure (Pd) by pressure wire) were also made in the resting and maximal hyperemic states. CFR was calculated as resting Tmn divided by hyperemic Tmn. IMR was calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of the hyperemic Tmn. FFR was calculated by the ratio of Pd/Pao at maximal hyperemia.

To investigate the effects of hemodynamic changes on coronary physiology measurements, CFR, IMR, and FFR were measured under 4 different hemodynamic conditions: (1) Baseline: To study the intrinsic variability of the coronary physiology indices, measurements were made twice under baseline conditions, once before any hemodynamic intervention compared with a second measurement after all hemodynamic interventions described below had been completed. (2) Tachycardia: The measurements were repeated during right ventricular pacing at 110 bpm (with a 5F bipolar pacemaker lead introduced via the right femoral vein). (3) Hypotension: The measurements were repeated during intravenous infusion of nitroprusside (0.5 to 2 μg · kg⁻¹ · min⁻¹) titrated to achieve a reduction of systolic blood pressure of ~20 mm Hg. (4) Increased cardiac contractility: Measurements were repeated during a 5-minute intravenous dobutamine infusion starting at 10 μg · kg⁻¹ · min⁻¹, which then was increased to 20 μg · kg⁻¹ · min⁻¹ provided there was no significant increase in heart rate at the lower dose (Figure 1). After each intervention, heart rate, mean aortic pressure, mean coronary transit time, and distal coronary pressure were allowed to return to their baseline values before the next intervention. In 4 patients, the resting blood pressure was too low to allow nitroprusside infusion. In 4 patients, a repeat baseline measurement after all interventions was not performed: 2 (who also underwent percutaneous intervention during the same procedure) because of excessive procedure time and 2 because of a combination of dyspnea arising from intrave-
rous adenosine infusion and prolonged procedure time. Three patients were excluded from the dobutamine arm because of concurrent β-blocker usage. Hence, the baseline variability pro-
tocol was completed in 11 patients; the effect of tachycardia was studied in 15 patients; the effect of nitroprusside was studied in 11 patients; and the effect of dobutamine was studied in 12 patients.

Statistical Analysis

Continuous values are presented as mean±SD. Mean values were compared with Student paired and unpaired t tests. Differences in study variables between baseline and different hemodynamic condi-
tions were compared by 2-way ANOVA for repeated measures with assessment of intergroup differences by Bonferroni multiple compar-
tion test. Linear regression analysis was used to compare the relationship between IMR, CFR, and FFR values under different hemodynamic conditions. Probability values of <0.05 were consid-
ered statistically significant.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Fifteen coronary arteries were studied in 15 patients. Clinical and procedural characteristics of study subjects are presented in Table 1. Two thirds of patients were male; 33% had diabetes mellitus, 80% had hypertension, and 87% had at least 2 risk factors for coronary artery disease. The angiographic degree of stenosis within the studied arteries ranged from 0% to 50%.

Reproducibility of Thermodilution Measurements

IMR and thermodilution-derived CFR could be easily mea-
sured in all cases. The coefficient of variation of 3 consecu-
tive thermodilution-derived coronary transit time measure-
ments at baseline was 7.2±3.0% at rest and 4.4±3.0% at maximal hyperemia (P=0.02). The distance of the pressure-
temperature sensor of the coronary wire from the guide
catheter tip has been noted as a potential source of error for
obtaining coronary thermodilution curves, with short distances being associated with time intervals that are too short to allow for adequate curve fitting. In the present study, the wire sensor was located in the distal third of the coronary artery in all cases; the mean transducer distance from the guide tip was 9.6 ± 2.0 cm, and there was no significant correlation between transducer distance and mean resting or hyperemic coronary transit times (P>0.1).

**Figure 1. Hemodynamic dependence of CFR, IMR, and FFR.** Representative hemodynamic recordings are shown for a single patient under the following hemodynamic conditions: (A) baseline; (B) right ventricular pacing at 110 bpm; (C) nitroprusside infusion; and (D) dobutamine infusion. Each graph is divided into 2 windows; the upper window displays the pressure segments recorded during each thermodilution injection. The segments are separated from each other by white vertical lines. The upper window displays aortic (P_a) phasic and mean pressure in red and distal coronary (P_d) phasic and mean pressure in green. The lower graph displays the thermodilution injections (baseline injections in blue and hyperemic injections in orange). Between the 2 graphs are the mean T_mn values. To the right of each panel, the values of mean hyperemic P_a and P_d, FFR, CFR, and IMR are shown. Hyp indicates hyperemic.

**TABLE 1. Patient and Procedural Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>10/5</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>80 (12)</td>
</tr>
<tr>
<td>Hypercholesterolemia, % (n)</td>
<td>80 (12)</td>
</tr>
<tr>
<td>Diabetes mellitus, % (n)</td>
<td>33 (5)</td>
</tr>
<tr>
<td>Family history of coronary disease, % (n)</td>
<td>33 (5)</td>
</tr>
<tr>
<td>Ever smoked, % (n)</td>
<td>40 (6)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>31 ± 9</td>
</tr>
<tr>
<td>Vessels studied</td>
<td></td>
</tr>
<tr>
<td>LAD/LCx/RCA, n</td>
<td>10/1/4</td>
</tr>
<tr>
<td>% Stenosis</td>
<td>17 ± 20</td>
</tr>
<tr>
<td>Transducer distance, cm</td>
<td>9.6 ± 2.0</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending artery; LCx, circumflex artery; and RCA, right coronary artery. Transducer distance refers to the distance of the coronary wire pressure transducer from the guide catheter tip.

Baseline Hemodynamics and Intrinsic Variability of CFR and IMR

To evaluate the intrinsic variability of CFR and IMR under baseline conditions, we compared 2 baseline measurements, 1 taken before hemodynamic interventions (baseline 1 [B1]) and a second after a series of hemodynamic interventions (baseline 2 [B2]) that included right ventricular pacing at 110 bpm, nitroprusside infusion, and dobutamine infusion. The hemodynamic variables and calculated indices for both baseline conditions are shown in Table 2. In the resting state, heart rate, mean coronary transit times, and systemic and distal coronary pressures were similar between the 2 baseline measurements. During B1, intravenous adenosine infusion increased heart rate (from 69±10 to 76±13 bpm) and reduced both mean systemic pressure (mean reduction 19±13 mm Hg) and mean distal coronary pressure (mean reduction 22±12 mm Hg; P<0.05 for hyperemia versus rest). Similar responses to adenosine infusion were observed during the second baseline measurements (Table 2). Mean values for CFR (2.8±0.8 and 2.7±1.1 for B1 and B2, respectively) and IMR (22.6±6.0 and 21.9±7.2 for B1 and B2, respectively) were similar between the 2 baseline measurements. IMR values between the first and second baseline measurements were very highly correlated (r=0.96, y = −4.0+1.1x, P<0.0001). The correlation between first and second baseline CFR values was significant but weaker (r=0.77, y = −0.20+1.1x, P=0.0055). The coefficient of variation
between first and second baseline measurements was significantly better for IMR (6.9±6.5%) than for CFR (18.6±9.6%; \( P<0.01 \); Figure 2).

**Hemodynamic Dependence of CFR and IMR**

To evaluate the hemodynamic dependence of CFR and IMR, we also measured these indices during a variety of hemodynamic interventions including right ventricular pacing at 110 bpm, nitroprusside infusion, and dobutamine infusion. A representative series of measurements for 1 patient is shown in Figure 1.

To study the effects of heart rate changes on CFR and IMR, we measured these indices before and during right ventricular pacing at 110 bpm. The hemodynamic variables and calculated indices for baseline and pacing conditions are shown in Table 3. Right ventricular pacing increased the mean heart rate by 39±10 bpm at rest and by 32±14 bpm at peak hyperemia (\( P<0.0001 \) versus baseline). Resting systemic and coronary pressures were similar between baseline and pacing conditions. Pacing was associated with a reduction in resting \( T_m \), from 0.97±0.33 to 0.83±0.30 seconds, but this was not statistically significant. At peak hyperemia, mean values for \( T_m \) and distal coronary pressure for baseline and pacing conditions were similar (Table 3). CFR decreased significantly from 3.1±1.1 at baseline to 2.3±1.2 during pacing (\( P<0.05 \)). In contrast, IMR during pacing (22.9±6.9 U) was similar to that at baseline (21.8±6.5 U; \( P=NS \); Figure 3). IMR values during pacing were highly correlated to those at baseline (\( r=0.91, y=2.0+0.96x, P<0.0001 \)). In comparison, CFR values during pacing had a weaker correlation with baseline CFR values (\( r=0.65, y=0.21+0.72x, P=0.009 \)).

![Figure 2](http://image-url.com)

**Figure 2.** Coefficient of variation between pairs of values of IMR and CFR measured twice under baseline conditions. IMR demonstrates lower intrinsic variability than CFR at baseline (*\( P<0.01 \) vs baseline).
had no effect on $T_{mi}$ during maximal hyperemia induced by adenosine infusion ($0.34\pm0.11$ at baseline versus $0.35\pm0.13$ with dobutamine, $P=NS$). As a consequence of increased resting coronary flow induced by dobutamine, CFR values measured during dobutamine infusion were significantly lower than those at baseline ($3.0\pm1.0$ at baseline versus $1.7\pm0.6$ with dobutamine, $P<0.0001$). In contrast, IMR values were unchanged by dobutamine infusion ($22.2\pm6.0$ at baseline versus $23.6\pm8.2$ with dobutamine, $P=NS$). IMR values during dobutamine infusion correlated well with those at baseline ($r=0.84$, $y=-1.7+1.2x$, $P<0.0001$). In comparison, CFR values during dobutamine infusion exhibited a significant but less robust correlation with those at baseline ($r=0.67$, $y=0.40+0.47x$, $P=0.007$). The mean correlation between baseline measurements and each hemodynamic intervention (including repeat baseline measurements) was superior for IMR compared with CFR ($r=0.90\pm0.05$ for IMR versus $r=0.70\pm0.05$ for CFR, $P<0.05$; Figure 3).

**Discussion**

In many patients presenting to the cardiac catheterization laboratory, the status of the coronary microcirculation, not just the epicardial arteries, is of clinical and prognostic relevance. However, to date, there is no simple, specific, and reproducible invasive measure of the status of the coronary microcirculation. In the present study, we compared a novel IMR with thermodilution-derived CFR in terms of reproducibility and dependence on hemodynamic changes. We also concurrently measured FFR, an index specific for the degree of epicardial coronary artery stenosis, under different hemodynamic conditions.

The salient findings of the present study are as follows: (1) IMR demonstrates less intrinsic variability and better reproducibility at baseline than CFR, and (2) whereas CFR is very sensitive to hemodynamic changes, IMR is largely independent of variations in hemodynamic state. Furthermore, FFR (when simultaneously measured with IMR and CFR) is highly reproducible and also largely independent of hemodynamic state. These findings suggest that IMR could be reliably applied in the catheterization laboratory for interrogation of microcirculatory resistance. Furthermore, simultaneous measurement of FFR and IMR with a single pressure-temperature sensor-tipped coronary wire may provide a simple means for comprehensive and specific assessment of coronary physiology at both epicardial and microvascular levels, respectively.

In a recent study using a porcine animal model, we found that IMR distinguished between normal and abnormal microcirculatory function and correlated well with true microcirculatory resistance as measured by an external flow probe and pressure wire. Furthermore, IMR, in its simplest form, was not significantly affected by the presence of a moderate to severe epicardial stenosis and is therefore a specific measure of the state of the microcirculation, unlike CFR. In more severe stenoses, in which collateral flow may be contributing to myocardial perfusion, a more complex form of IMR, which...
incorporates the coronary wedge pressure, is necessary to accurately determine microvascular resistance.13,15

Because IMR is derived at peak hyperemia, we postulated that it would be independent of resting vascular tone and hemodynamics. The present study demonstrates that IMR is easily measured in humans with a commercially available pressure-temperature sensor-tipped coronary wire and that its values are highly reproducible. Furthermore, variations in hemodynamic status, including changes in heart rate, blood pressure, and contractility, do not significantly affect IMR measurements. During all hemodynamic interventions in the present study (rapid right ventricular pacing, nitroprusside infusion, and dobutamine infusion), IMR exhibited greater hemodynamic stability than CFR.

Use of CFR to evaluate the microcirculation is limited by the fact that CFR interrogates the entire coronary system, including the epicardial artery and the microcirculation.7 For this reason, a patient with epicardial disease but with normal microcirculatory function can have an abnormal CFR, which potentially limits the applicability of CFR when assessing microvascular disease. Furthermore, because CFR represents a ratio between peak hyperemic and resting coronary flow, factors that affect resting hemodynamics, such as heart rate and contractility, may affect the reproducibility of CFR.9 Previous studies have shown that Doppler flow velocity–derived CFR is significantly reduced by tachycardia9,16,17 and by increased contractility9 but is not significantly affected by changes in blood pressure due to compensatory changes in coronary blood flow.9,16,17 Consistent with these previous studies, the present study documents the hemodynamic dependence of thermodilution-derived CFR. In the present study, hypotension induced by nitroprusside infusion had no effect on thermodilution-derived CFR. In contrast, right ventricular pacing–induced tachycardia and dobutamine infusion were both associated with significant reductions in thermodilution-derived CFR values, largely due to an increase in resting coronary blood flow (and hence a reduction in resting Tm). Hence, like Doppler flow velocity–derived CFR, interpretation of serial measurements of thermodilution-derived CFR are limited by a high degree of hemodynamic variability, largely as a result of changes in basal coronary blood flow.

FFR is measured during maximal hyperemia and therefore is not prone to variability due to fluctuations in baseline hemodynamic state. In the present study, we show that when peak hyperemia is induced by intravenous adenosine, the intrinsic variability of FFR is very low (<2%) and may be superior to that for FFR measured with intracoronary adenosine,9 a route of administration that may not induce as strong a hyperemic response and that is associated with a very short half-life and hence is potentially subject to greater variability. FFR measurements, like IMR, demonstrated no significant

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**TABLE 4. Effects of Nitroprusside Infusion on Hemodynamic Variables and Calculated Indices**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Nitroprusside</th>
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<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Hyperemia</td>
<td>Rest</td>
<td>Hyperemia</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>98±13</td>
<td>83±19*</td>
<td>79±7†</td>
<td>71±10†</td>
</tr>
<tr>
<td>Distal coronary</td>
<td>93±12</td>
<td>73±14*</td>
<td>74±6†</td>
<td>61±7†</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>73±10</td>
<td>82±9*</td>
<td>78±16</td>
<td>84±17*</td>
</tr>
<tr>
<td>Coronary transit time, s</td>
<td>0.96±0.36</td>
<td>0.33±0.08*</td>
<td>0.96±0.50</td>
<td>0.40±0.13*</td>
</tr>
<tr>
<td>CFR</td>
<td>2.9±0.9</td>
<td></td>
<td>2.5±1.2</td>
<td></td>
</tr>
<tr>
<td>IMR, U</td>
<td>23.85±6.1</td>
<td>24.00±7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.88±0.04</td>
<td></td>
<td>0.87±0.05</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 for hyperemia vs rest; †P<0.05 for nitroprusside infusion vs baseline.

**TABLE 5. Effects of Dobutamine Infusion on Hemodynamic Variables and Calculated Indices**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th></th>
<th>Dobutamine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Hyperemia</td>
<td>Rest</td>
<td>Hyperemia</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>95±19</td>
<td>78±23*</td>
<td>99±18</td>
<td>79±14*</td>
</tr>
<tr>
<td>Distal coronary</td>
<td>90±20</td>
<td>69±20*</td>
<td>92±18</td>
<td>68±12*</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>71±11</td>
<td>79±14*</td>
<td>85±17†</td>
<td>97±16†</td>
</tr>
<tr>
<td>Coronary transit time, s</td>
<td>0.99±0.36</td>
<td>0.34±0.11</td>
<td>0.55±0.17†</td>
<td>0.35±0.13</td>
</tr>
<tr>
<td>CFR</td>
<td>3.0±1.0</td>
<td></td>
<td>1.7±0.6†</td>
<td></td>
</tr>
<tr>
<td>IMR, U</td>
<td>22.2±6.0</td>
<td>23.6±8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFR</td>
<td>0.88±0.06</td>
<td></td>
<td>0.87±0.06</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05 for hyperemia vs rest; †P<0.05 for dobutamine infusion vs baseline.
variation during any of the hemodynamic conditions in the present study.

Study Limitations

IMR, FFR, and CFR are limited by their reliance on the achievement of maximal hyperemia. Failure to achieve peak hyperemia, by not achieving maximal reduction in microvascular resistance, may result in overestimation of IMR. Conversely, CFR will be underestimated in the absence of maximal hyperemia. In the case of FFR, if maximal hyperemia does not occur, the pressure gradient across a stenosis will be underestimated and the FFR overestimated. For these reasons, intravenous adenosine, considered the reference standard for induction of peak hyperemia, was used for the present study. Use of less effective hyperemic agents/protocols may affect the reproducibility of these indices.

In the present study, dobutamine infusion was associated with an increase in heart rate, which in itself, can produce increased contractility. However, although the influences of contractility and heart rate were not divorced from each other, the heart rate increase observed with dobutamine infusion was much less than that observed with right ventricular pacing, which suggests that an increase in contractility had indeed been tested.

The effect of the severity of epicardial stenosis on measurement of microvascular resistance is controversial. Some have suggested that the minimum achievable microvascular resistance increases with the increasing severity of an epicardial artery stenosis. In contrast, we and others have reported that microvascular resistance is not affected by increasing epicardial artery stenosis if collateral flow is taken into account. In the present study, all coronary physiological measurements were made in arteries that were either normal or had only minor angiographic stenoses. In cases with severe epicardial stenosis, the simplified measurement of IMR, as used in the present study, may overestimate resistance because it does not account for collateral flow, and a more complex measurement of IMR that incorporates the coronary wedge pressure is necessary.

Microvascular resistance has also been determined invasively by measuring distal pressure and estimating flow with a Doppler wire. Because of the additional complexity of using a Doppler wire, we did not test the reproducibility or hemodynamic dependence of this technique.

Lastly, the distance of the pressure wire down a vessel will impact the measured hyperemic transit time and the IMR. The variability of IMR depending on the distance of the wire down the vessel was not tested in the present study, although in this study, there was no correlation between transducer distance and transit times.

Conclusions

Despite the importance of the status of the microcirculation in determining clinical outcomes in a wide variety of cardiovascular conditions, a simple and reproducible method for invasively assessing the state of the coronary microcirculation has been lacking. Measurement of CFR for assessing the coronary microcirculation has been limited by its lack of specificity and its high degree of hemodynamic variability. IMR is a new index for specific and quantitative assessment of coronary microcirculatory resistance that can be measured easily in the cardiac catheterization laboratory. IMR, by virtue of being more reproducible and less hemodynamically dependent than CFR, appears to be superior to CFR for assessing the coronary microcirculation. Finally, simultaneous measurement of FFR and IMR, by specifically quantifying the status of the epicardial artery and microcirculation, respectively, may provide a simple, comprehensive means of evaluating the physiological state of a coronary artery in the catheterization laboratory.

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Disclosures

None.

References


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**CLINICAL PERSPECTIVE**

The state of the coronary microcirculation is an important determinant of outcomes in a number of clinical settings such as acute coronary syndromes and percutaneous coronary interventions. However, to date, a simple and reproducible invasive method for assessing the coronary microcirculation in the cardiac catheterization laboratory has been lacking. Guidewire-based assessment of coronary flow reserve (CFR) has been used to assess the microcirculation, but it is limited by a lack of specificity for the microcirculation and by suboptimal reproducibility. It is now possible to simultaneously measure pressure and estimate coronary artery flow by thermodilution with a single pressure-temperature sensor-tipped coronary wire. Using this method, we recently validated a novel and specific index of microcirculatory resistance (IMR) in an animal model. In the present study, we have compared the reproducibility and hemodynamic dependence of IMR, CFR, and fractional flow reserve (FFR, an epicardial artery–specific index) in humans under different hemodynamic conditions, including baseline, right ventricular pacing at 110 bpm, nitroprusside infusion, and dobutamine infusion. Compared with baseline, CFR values decreased significantly during nitroprusside infusion and during dobutamine infusion. By comparison, IMR and FFR values remained similar throughout all hemodynamic conditions. The mean coefficient of variation between 2 baseline measurements was significantly better for IMR (6.9±6.5%) and FFR (1.6±1.6%) than for CFR (18.6±9.6%; P<0.01). These findings suggest that IMR provides a reproducible interrogation of microcirculatory resistance, which is independent of hemodynamic perturbations. Simultaneous measurement of FFR and IMR may provide a simple means for comprehensive and specific assessment of coronary physiology at both epicardial and microvascular levels, respectively.
Invasive Assessment of the Coronary Microcirculation: Superior Reproducibility and Less Hemodynamic Dependence of Index of Microcirculatory Resistance Compared With Coronary Flow Reserve
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