Microvascular Resistance Reserve for Assessment of Coronary Microvascular Function

JACC Technology Corner

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ABSTRACT

The need for a quantitative and operator-independent assessment of coronary microvascular function is increasingly recognized. We propose the theoretical framework of microvascular resistance reserve (MRR) as an index specific for the microvasculature, independent of autoregulation and myocardial mass, and based on operator-independent measurements of absolute values of coronary flow and pressure. In its general form, MRR equals coronary flow reserve (CFR) divided by fractional flow reserve (FFR) corrected for driving pressures. In 30 arteries, pressure, temperature, and flow velocity measurements were obtained simultaneously at baseline (BL), during infusion of saline at 10 mL/min (rest) and 20 mL/min (hyperemia). A strong correlation was found between continuous thermodilution-derived MRR and Doppler MRR ($r = 0.88; 95\%$ confidence interval: $0.72-0.93; P < 0.001$). MRR was independent from the epicardial resistance, the lower the FFR value, the greater the difference between MRR and CFR. Therefore, MRR is proposed as a specific, quantitative, and operator-independent metric to quantify coronary microvascular dysfunction.

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IMPORTANCE OF THE MICROCIRCULATORY COMPARTMENT

Ischemic heart disease and myocardial ischemia are often attributed solely to epicardial stenoses. Yet, coronary microvascular dysfunction (CMD) is increasingly recognized as another potential cause of angina (i). The reported prevalence of CMD is particularly variable probably reflecting the heterogeneity of its definitions and diagnostic approaches (2,3). Yet overall, CMD appears to be common in patients with chest pain, either in isolation, or in association with a broad spectrum of cardiovascular diseases and risk factors. In a large registry of patients who underwent a coronary angiogram for suspected CAD, approximately one-half of them were found to have no significant...
epicardial narrowing, even in case of typical angina (4). Among these patients, a sizable proportion is supposed to have CMD-related angina. In addition, the presence of CMD has been shown to be associated with a worse clinical outcome and increased resource utilization (5–7). Individualized treatment options are emerging (8). This has led to Class IIa guideline recommendation of a more nuanced diagnostic workup of CMD in patients with ANOCA (angina with no obstructive coronary arteries) (9). Currently, the index of microcirculatory resistance (IMR) (10) derived from bolus thermodilution is considered the standard of reference to diagnose CMD (8,9).

The reason why CMD remains rather ill-defined relates to at least 3 factors: 1) the microcirculation is difficult to visualize directly; 2) there is no animal model that emulates the human coronary microvascular disease (11); and 3) the extent of the dysfunction is currently difficult to quantify in absolute terms. Reliable methods to quantify CMD would make it possible to envisage the development and evaluation of better treatment options for CMD. A quantitative and operator-independent method would allow for a greater diagnostic certainty and therapeutic approach.

**CONTINUOUS THERMODILUTION TO ASSESS ABSOLUTE MICROVASCULAR RESISTANCE**

Recently, the principle of continuous thermodilution was applied to the coronary circulation to determine absolute coronary blood flow (12,13). The method is safe (14), reproducible (15), and can be semiautomated. Saline infusion through a dedicated catheter allows the absolute quantification of resting (16,17) and hyperemic flow (in mL/min) and resistance (in WU) (18). A strong agreement exists between continuous thermodilution-derived flow and [15O]H2O-PET-derived flow and resistance measurements (19).

Nevertheless, however accurate, hyperemic flow and resistance values are hampered by considerable interindividual variability, which makes these measurements less well suited for individual clinical decision making (20) without taking into account myocardial mass of the perfusion territory (21).

An ideal descriptor of microcirculatory function should be specific for the microcirculation, independent of the operator, the autoregulation, the epicardial resistance, and the myocardial mass and based on absolute values of flow and resistance.

Accordingly, in the next paragraphs, we describe the concept of microvascular resistance reserve (MRR) and its theoretical background, and provide an initial validation in humans. It is shown later that MRR can also be fully expressed in terms of coronary flow reserve (CFR), fractional flow reserve (FFR), and driving pressures and remains valid for any invasive or noninvasive measurement of pressure and flow or validated surrogate of flow.

**CONCEPT, MATERIALS, AND METHODS**

MRR is defined as the ratio of true resting to hyperemic microvascular resistance (Rm). By analogy to FFR, which expresses the fraction of maximal flow in the hypothetical case the epicardial artery were to be normal, MRR is the extent to which resting Rm would decrease in the hypothetical case the epicardial artery were to be normal. It should be realized that resting Rm measured for any myocardial territory is influenced by the presence of epicardial disease. Such epicardial disease, whether focal or diffuse, will lead to compensatory microvascular vasodilation by autoregulation (Supplemental Figure 1) (22). In such case, measured Rm is not true resting Rm but a compensated, decreased, value. True resting microvascular resistance means Rm as it would be with a completely normal coronary artery.

The theoretical framework of calculating true resting Rm, hyperemic Rm, MRR, and the relation among MRR, FFR, and CFR is described in detail in the supplemental material. First, it is shown that true resting microvascular resistance can expressed by the following:

\[
R_{m,\text{rest}} = P_{d,\text{rest}} / Q_{\text{rest}}
\]

Next, hyperemic microvascular resistance is given by the following:

\[
R_{m,\text{hyper}} = P_{d,\text{hyper}} / Q_{\text{max}}
\]

Consequently, MRR as defined above equals the ratio of Equations 1 and 2:

\[
\text{MRR} = (Q_{\text{max}} / Q_{\text{rest}}) \times (P_{d,\text{rest}} / P_{d,\text{hyper}})
\]

where \( P_{d,\text{rest}} \) and \( P_{d,\text{hyper}} \) are aortic pressure at rest and at maximum hyperemia, respectively, \( P_{d,\text{hyper}} \) is distal coronary pressure measured at hyperemia, and \( Q_{\text{rest}} \) and \( Q_{\text{max}} \) are the actually measured resting and hyperemic blood flow. Finally, it will be shown that MRR also can be expressed more generally in terms of CFR and FFR by the following:

\[
\text{MRR} = (\text{CFR} / \text{FFR}) \times (P_{d,\text{rest}} / P_{d,\text{hyper}})
\]

If \( P_{d,\text{rest}} = P_{d,\text{hyper}} \), which is generally the case with saline-induced hyperemia, Equation 4 can be further simplified: MRR = CFR / FFR.
If hyperemia is induced by adenosine or other drugs, $P_{a, \text{hyper}}$ and $P_{a, \text{hyper}}$ are usually different by 10%-30% (23) and the second term of Equation 4 needs to be taken into account to assess the mutual relation among MRR, FFR, and CFR.

Of note, Equations 1 to 4 are valid not only for flow calculation by continuous thermodilution, but also for flow or flow surrogates assessed by any other methodology such as Doppler, bolus-thermodilution-derived mean transit times, thermo convection, and noninvasive flow substitutes.

A number of characteristics, limitations, and practicalities of MRR measurements are discussed in the Supplemental Material.

### TABLE 1  Baseline Characteristics

<table>
<thead>
<tr>
<th>Age, y</th>
<th>65.4 ± 9.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84 ± 14.9</td>
</tr>
<tr>
<td>Height, cm</td>
<td>173.9 ± 7.54</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.7 ± 5.2</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>15 (55.6)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (40.7)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23 (85.2)</td>
</tr>
<tr>
<td>Familial history CAD</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>15 (48.1)</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td></td>
</tr>
<tr>
<td>CCS</td>
<td>26 (96.3)</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Angina class</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>2</td>
<td>4 (14.8)</td>
</tr>
<tr>
<td>3</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>GFR, mL/min</td>
<td>76.4 ± 17.3</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>58.5 ± 6.6</td>
</tr>
<tr>
<td>Medications</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>19 (70.4)</td>
</tr>
<tr>
<td>2nd antiplatelet</td>
<td>7 (25.9)</td>
</tr>
<tr>
<td>ACE inhibitors/ARBs</td>
<td>13 (48.1)</td>
</tr>
<tr>
<td>Ca blocker</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>Statin</td>
<td>21 (77.8)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>Oral antidiabetic drugs</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Insulin</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Access</td>
<td></td>
</tr>
<tr>
<td>Radial</td>
<td>18 (66.7)</td>
</tr>
<tr>
<td>Femoral</td>
<td>9 (33.3)</td>
</tr>
</tbody>
</table>

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; BMI = body mass index; CABG = coronary artery bypass; CAD = coronary artery disease; CCS = chronic coronary syndrome; GFR = glomerular filtration rate; LVEF = left ventricle ejection fraction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention.

### VALIDATION IN HUMANS

The methodological details are given in the Supplemental Material. In summary, 40 arteries were instrumented with a pressure/temperature-sensor wire (PressureWire X Guidewire, Abbott) connected to a dedicated software (Coroflow, Coroventis Research AB) and by a Doppler crystal-tipped flow velocity wire (FloWire, Volcano Corporation/Philips) connected to a dedicated console (FlowMap, Cardiometrics). All signals (ie, electrocardiogram, phasic and mean aortic pressure [$P_{a}$, in mm Hg], phasic and mean distal coronary pressure [$P_{d,i}$, in mm Hg], mean distal coronary temperature change [$T$, in °C], and Doppler-derived average peak coronary blood flow velocity [APV, in cm/s]) were obtained and recorded simultaneously and continuously, under baseline condition (ie, before the start of the infusion of saline), under resting conditions (ie, during infusion of saline at 10 mL/min), and during hyperemic conditions (ie, during infusion of saline at 20 mL/min). Saline was infused through a dedicated catheter (RayFlow, Hexacath) (24). Video 1 shows how to perform absolute flow and MRR measurement. Absolute coronary flow ($Q$, mL/min) was derived from continuous thermodilution as we originally described (12):

$$ Q = 1.08 \cdot \left( \frac{T_i}{T} \right) \cdot Q_i $$

where $Q_i$ is the infusion rate of saline by the infusion pump (in mL/min), $T_i$ is the temperature of the infused saline when it exits the infusion catheter, and $T$ is the temperature of the mixture of blood and saline in the distal part of the coronary artery during steady-state infusion.

### RESULTS

### PATIENTS AND VESSELS CHARACTERISTICS

Simultaneous Doppler flow velocity measurements and thermodilution measurements were attempted in 40 coronary arteries (37 patients). In 10 arteries, the quality of the Doppler tracings was considered insufficient for analysis. No patients were excluded due to insufficient quality of the thermodilution or pressure signals. Consequently, the final study population consisted of 30 coronary arteries (27 patients). The mean age was 65 ± 9 years. Twenty-four of them (89%) were men. In 20 (74.1%) patients the procedure was performed through radial access. The vessel evaluated was the left anterior descending artery (LAD) in 11 cases (37%), the left circumflex artery (LCX) in 4 cases (13%), and the right coronary artery (RCA) in 15 cases (50%). In 17 cases, the vessel evaluated had prior percutaneous coronary intervention (PCI): in 11 of these, the stent was implanted in a
previous procedure, whereas in 8 of them the measurements were performed immediately after PCI. The baseline characteristics and the reason for intracoronary physiologic measurements are detailed in Table 1. There were no complications related to the measurements.

PRESSURE RATIO AND AVERAGE PEAK VELOCITY. $P_a$ at baseline (ie, before the start of saline infusion), at rest (ie, during saline infusion of 10 mL/min), and at hyperemia (ie, during saline infusion of 20 mL/min) remained unchanged (88.6 ± 14.5 mm Hg vs 87.4 ± 12.4 mm Hg vs 86.5 ± 14 mm Hg, respectively; $P = 0.84$). Similarly, heart rate at baseline, at rest, and at hyperemia remained unchanged (67 ± 11 beats/min vs 68 ± 11 beats/min vs 67 ± 12 beats/min, respectively; $P = 0.89$) (Supplemental Figure 2). APV at baseline and at rest were similar (21.3 ± 8.2 cm/s vs 22.4 ± 8.2 cm/s, $P = 0.59$; mean differences −1.12 ± 2.49, ULA 3.77 and LLA −6.01) and individual APV values at baseline and at rest were highly correlated ($r = 0.95$; $P < 0.001$; 95% confidence interval [CI]: 0.90–0.98). APV increased significantly during hyperemia to 56.4 ± 24.12 cm/s, $P < 0.001$ vs both baseline and rest (Figure 2A). $P_d/P_a$ at baseline (before the start of saline infusion) and at rest (ie, during saline infusion at 10 mL/min) were similar (0.95 ± 0.05 vs 0.94 ± 0.06, $P = 0.55$; mean difference 0.009 ± 0.02, ULA 0.05 and LLA −0.03) and individual values correlated closely ($r = 0.95$; $P < 0.001$; 95% CI: 0.89–0.97). As expected, $P_d/P_a$ decreased significantly during hyperemia (0.82 ± 0.11, $P < 0.001$) vs both baseline and rest (Supplemental Figure 3). In summary, there were no differences in pressure or flow velocity between baseline and resting conditions (ie, infusion of 10 mL/min) with significant lower $P_d/P_a$ and higher flow velocity during hyperemia.

MRRThermo vs MRRDoppl. MRR as derived from thermodilution (Equation 3, MRRThermo) and its corresponding Doppler-derived index MRRDoppl (Equation 4) were similar (3.58 ± 1.25 vs 3.29 ± 1.18, $P = 0.36$) with a mean difference of 0.29 (ULA = −1.56 and LLA = −0.99 and $r = 0.88$; 95% CI: 0.72–0.93; $P < 0.001$). The Passing-Bablok analysis showed no systematic nor proportional differences between the 2 measurements (coefficient A 0.32, 95% CI: −0.44 to 1.18; coefficient B 0.79, 95% CI: 0.56–1.08) (Figure 2). When stratified by artery, the agreement between MRRThermo and MRRDoppl remained high (LAD: 3.85 ± 1.43, 1.43, and MRRThermo = 3.29 ± 1.43, $P = 0.60$ for MRRThermo and MRRDoppl, respectively).

MRR vs CFR. For arteries without or with neglectable epicardial disease (FFR close to 1), MRR and CFR were similar. But, with increasing epicardial resistance
MRR differed from CFR as a function of the FFR value (Figure 3A). Overall, MRR and CFR showed a fair correlation ($r = 0.68$; 95% CI: 0.75-0.94; $P < 0.001$). The relation between the difference in MRR vs epicardial resistance (as indicated by decreasing FFR) is shown in Figure 3B.

**DISCUSSION**

**SUMMARY OF FINDINGS.** We outline the theoretical framework and provide the first human measurements of a novel index, the MRR, to characterize the function of the coronary microvasculature. MRR is defined as $R_m$ at rest, as it would be in the theoretical case the epicardial artery were to be completely normal divided by $R_m$ during maximal hyperemia. The experimental data indicate that MRR based on quantitative absolute flow measurements as derived from continuous thermodilution correlates well with simultaneously obtained equivalent metric derived from coronary flow velocity. With increasing epicardial resistance, CFR progressively declined and separated from MRR, indicating that MRR is independent of epicardial resistance.

**WHAT IS NEW?** First, MRR is independent of the epicardial resistance to flow and thus truly specific of the microvasculature. In cases in which the epicardial resistance is negligible, MRR equals CFR; however, in many patients in whom microvascular function is assessed, epicardial arteries are not completely normal. In those cases, autoregulatory mechanisms will adjust $R_m$ to myocardial metabolic needs (25). Thus, actual resting $R_m$ no longer corresponds to truly normal $R_m$, as would be present in case of strictly normal epicardial artery. MRR equals CFR normalized for FFR; the latter representing epicardial conductance. In this paper, we calculated MRR primarily as given by Equation 3 because all parameters of that equation are measured quantitatively by the continuous thermodilution method. MRR also can be expressed more generally in terms of CFR and FFR according to Equation 4 and irrespective of how CFR and FFR are obtained. As such, MRR is a microcirculatory corollary of FFR (26,27).

Second, MRR does not depend on myocardial mass. A numerical example given in the Supplementary Material illustrates the fact that MRR is independent from mass.

Third, when measured by continuous coronary thermodilution, MRR is based on absolute values of flow (in mL/min) and of $R_m$ (in WU). The value of MRR can thus be complemented by these absolute values. Moreover, the infusion of saline can be fully automatized (Central Illustration), making the measurement fundamentally operator independent. This is in contrast with bolus thermodilution-based techniques, such as IMR, which are affected by the force of a manual injection of saline, the position of the

![Figure 2](https://example.com/f2.png)
catheter, and on the arbitrary decision to accept or discard $T_{mn}$ values outside the expected variability range. However, the calculation of MRR also can be obtained using pharmacological vasodilation and any other methods of flow measurement or surrogates of flow like Doppler velocity, thermoconvection-derived flow velocity, bolus thermodilution-derived $T_{mn}$ or noninvasively by computed tomography scanning, positron emission tomography, magnetic resonance imaging, or other methods, provided that an estimate of $P_{a,hyper}$ is available. In addition, $R_{m,rest}$ can be estimated fully noninvasively by such means.

**OTHER INDICES OF MICROVASCULAR FUNCTION.** A number of indices have been proposed to assess microvascular function. CFR, the ratio of hyperemic to resting flow (28), does not distinguish between epicardial and microvascular resistance. Proposing CFR as an index of microvascular function assumes that coronary driving pressure equals central aortic pressure, which is often not the case. The major difference between CFR and MRR is the contribution of epicardial resistance to 1 of the 2 CFR components.

The IMR (10), obtained by bolus thermodilution (29,30), is considered the invasive standard of reference for assessing microcirculatory function. IMR factors in distal coronary pressure ($P_d$), therefore accounting for the epicardial resistance, and hyperemic mean transit times. The major theoretical advantage of IMR is not to depend on “resting” measurements or on myocardial mass. However, mean transit time ($T_{mn}$, s) is only a surrogate for flow and is obtained by manual injection of saline at room temperature. It varies according to the position of the sensor in the artery (29) and it is not completely operator independent.

The ratio of baseline microvascular resistance and hyperemic microvascular resistance (31,32), based on Doppler flow velocity, and the resistance reserve ratio, based on bolus thermodilution (33), both assess the ratio of actual resting and hyperemic microvascular resistance. These approaches do not account for the influence of the epicardial component on resting $R_e$.

**PRACTICALITIES.** Although the application of continuous thermodilution to the coronary circulation was proposed more than 10 years ago, its application in humans became possible thanks to the development of a dedicated monorail infusion catheter, and of dedicated software that integrates these measurements instantaneously. The safety of infusion of saline at 20 mL/min through the side holes of the infusion catheter as well as the absence of hyperemic response at low infusion rates were also established recently (12,19).

The present data were obtained by performing separately resting measurements followed by...
hyperemic measurements. Yet, it is now possible to obtain resting and hyperemic measurements “in one shot” with a dedicated automatic injector. This greatly facilitates the measurements that then take no longer than 5 minutes (Video 1). An example is given in the Central Illustration.

In contrast to pharmacologic vasodilation, the infusion of saline at room temperature at a rate of 20 mL/min induces a particularly stable steady-state hyperemia within seconds without side effects and without changes in aortic pressure.

STUDY LIMITATIONS. A number of limitations must be discussed. First, unlike FFR and IMR, but akin CFR, MRR depends on resting physiology. Even though the measurement method itself does not modify baseline heart rate and systemic pressures, it is difficult, especially in the catheterization laboratory, to rule out a “higher than normal” myocardial resting flow.

Second, when measured by continuous thermodilution, the presence of the RayFlow infusion catheter in the proximal part of the coronary artery can lead to an increased epicardial resistance. However, MRR is independent of the epicardial resistance and, thus, the potential additional resistance provoked by the infusion catheter is accounted for in the MRR equation.

Third, like in most exploratory studies, patients were nonconsecutive, and their number is relatively limited, all vessels had at least mild atherosclerosis, no outcome data are provided, and no cutoff values can be proposed.

Fourth, thermodilution-derived MRR was validated against Doppler flow velocity measurements. In line with the literature (34,35), in almost one-fourth of cases no optimal flow velocity tracings could be obtained, whereas continuous thermodilution measurements could be obtained in 100% of cases.

Fifth, the set-up needed for thermodilution-derived MRR measurements needs some experience to become streamlined.
CONCLUSIONS

We describe the theoretical basis of MRR and its preliminary validation in humans as a novel index to quantify the function of the coronary microcirculation. MRR is specific for the microcirculation and independent of myocardial mass. When derived from absolute measurements of flow (in mL/min), pressure (in mm Hg), and resistance (in WU) obtained by continuous thermodilution, it is almost completely operator independent. In principle, it can be derived from any other method that assesses flow and distal coronary pressure. More research is needed to confirm some theoretical assumptions, to determine cutoff values, and to evaluate the clinical relevance of MRR in light of existing indices of microvascular function.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr De Bruyne has had a consulting relationship with Boston Scientific, Abbott Vascular, CathWorks, Siemens, and Coroventis Research; has received research grants from Abbott Vascular, Coroventis Research, Cathworks, and Boston Scientific; and holds minor equities in Philips-Volcano, Siemens, GE Healthcare, Edwards Life Sciences, HeartFlow, Opsens, and Cedia. Dr Pijs has received institutional grants from Abbott Vascular and Hexacath; has served as a consultant for Abbott Vascular, GE, and Opsens; and has minor equities in Philips, GE, ASML, and HeartFlow. Dr Collet has received research grants from Biosensor, GE Healthcare, Medis Medical Imaging, Pie Medical Imaging, Cathworks, Boston Scientific, Siemens, HeartFlow Inc, and Abbott Vascular; and has received consultancy fees from Heart Flow Inc, Opsens, Pie Medical Imaging, Abbott Vascular, and Philips-Volcano. Dr Barbato has received speaker’s fees from Abbott Vascular, Boston Scientific, and GE. Dr Fearon has received institutional research support from Abbott Vascular, Medtronic, and Edwards Lifesciences; has had a consulting relationship with CathWorks; and holds minor stock options with HeartFlow. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** absolute coronary flow, coronary flow reserve, fractional flow reserve, microvascular dysfunction, microvascular resistance

**APPENDIX** For supplemental theoretical framework, methods, figures, and a video, please see the online version of this paper.