JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2021 PUBLISHED BY ELSEVIER ON BEHALF OF THE
AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

VOL. 78, NO. 15, 2021

THE PRESENT AND FUTURE

JACC TECHNOLOGY CORNER

Microvascular Resistance Reserve for Assessment of Coronary Microvascular Function

JACC Technology Corner

Bernard De Bruyne, MD, PhD,[a,b,*] Nico H.J. Pijls, MD, PhD,[c,*] Emanuele Gallinoro, MD,[a,d] Alessandro Candreva, MD,[a] Stephane Fournier, MD,[b] Danielle C.J. Keulards, MD,[c] Jeroen Sonck, MD,[a,e] Marcel van't Veer, MS, PhD,[c,f] Emanuele Barbato, MD, PhD,[a,e] Jozef Bartunek, MD, PhD,[a] Marc Vanderheyden, MD,[a] Eric Wyffels, MD,[a] Annemiek De Vos, MD,[c] Mohamed El Farissi, MD,[c] Pim A.L. Tonino, MD, PhD,[c] Olivier Muller, MD, PhD,[b] Carlos Collet, MD, PhD,[a] William F. Fearon, MD[g]

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.
(J Am Coll Cardiol 2021;78:1541–1549) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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 (1). 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

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Cardiovascular Center Aalst, Aalst, Belgium; [b]Lausanne University Centre Hospital, Lausanne, Switzerland; [c]Department of Cardiology, Catharina Hospital, Eindhoven, the Netherlands; [d]Department of Translational Medical Sciences, University of Campania "Luigi Vanvitelli," Naples, Italy; [e]Department of Advanced Biomedical Sciences, University of Naples Federico II, Naples, Italy; [f]Department of Biomedical Engineering, Eindhoven University of Technology, Eindhoven, the Netherlands; and the [g]Division of Cardiovascular Medicine, Stanford University School of Medicine and Stanford Cardiovascular Institute, Stanford, California, USA. *Drs De Bruyne and Pijls contributed equally to this work.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received June 21, 2021; revised manuscript received August 16, 2021, accepted August 17, 2021.

ISSN 0735-1097/$36.00

https://doi.org/10.1016/j.jacc.2021.08.017

ABBREVIATIONS AND ACRONYMS

APV = average peak velocity as measured by a Doppler flow wire

CFR = coronary flow reserve

CMD = coronary microvascular disease

FFR = fractional flow reserve

IMR = Index of Microcirculatory Resistance

MRR = microvascular resistance reserve

Q = coronary blood flow

R_μ = microvascular resistance

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 [^{15}O]H_2O-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 (R_μ). 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 R_μ would decrease in the hypothetical case the epicardial artery were to be normal. It should be realized that resting R_μ 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 R_μ is not *true* resting R_μ but a compensated, decreased, value. True resting microvascular resistance means R_μ as it would be with a completely normal coronary artery.

The theoretical framework of calculating *true* resting R_μ, hyperemic R_μ, 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:

$$R_{\mu,rest} = P_{a,rest}/Q_{rest} \quad [1]$$

Next, hyperemic microvascular resistance is given by the following:

$$R_{\mu,hyper} = P_{d,hyper}/Q_{max} \quad [2]$$

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

$$MRR = (Q_{max} / Q_{rest}) \times (P_{a,rest} / P_{d,hyper}) \quad [3]$$

where $P_{a,rest}$ and $P_{a,hyper}$ are aortic pressure at rest and at maximum hyperemia, respectively, $P_{d,hyper}$ is distal coronary pressure measured at hyperemia, and Q_{rest} and Q_{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:

$$MRR = (CFR / FFR) \times (P_{a,rest} / P_{a,hyper}) \quad [4]$$

If $P_{a,rest} = P_{a,hyper}$, which is generally the case with saline-induced hyperemia, Equation 4 can be further simplified: MRR = CFR / FFR.

TABLE 1 Baseline Characteristics

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

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.

If hyperemia is induced by adenosine or other drugs, $P_{a,rest}$ and $P_{a,hyper}$ 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.

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, 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):

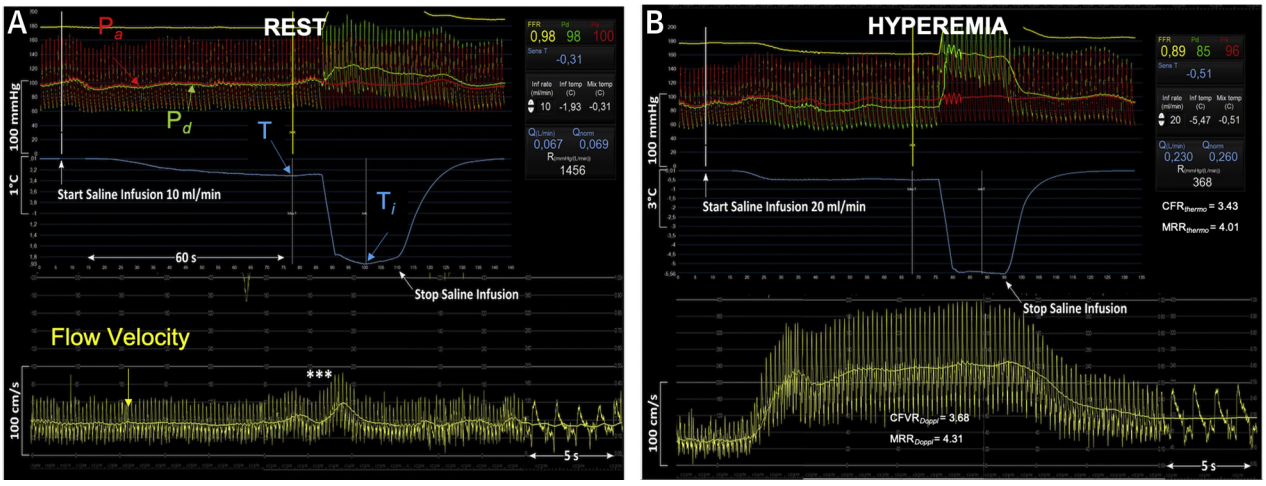
$$Q = 1.08 \cdot (T_i / T) \cdot Q_i \quad [5]$$

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

FIGURE 1 Simultaneous Recording of Coronary Pressure, Continuous Thermodilution, and Doppler Flow Velocity



From top to bottom: Aortic pressure (P_a) **(red)**, coronary pressure (P_d) **(green)**, coronary temperature **(blue)**, and phasic and mean Doppler flow velocity **(yellow)**. **(A)** (Rest): After the start of the infusion of saline at 10 mL/min, coronary temperature decreases by 0.31 °C below body temperature, whereas pressures and flow velocity do not change. When the pressure/temperature sensor is pulled back in the RayFlow catheter, the temperature drops to −1.93 °C, which represents the temperature of saline when entering the coronary artery (T_i). **(B)** (Hyperemia): After the start of the infusion of saline at 20 mL/min, coronary temperature decreases by 0.51 °C below body temperature, while P_d drops by 10 mm Hg and flow velocity increases. When the sensor is pulled back in the tip of the RayFlow infusion catheter, the temperature signal drops to −5.47 °C (T_i). Q = coronary blood flow (mL/min).

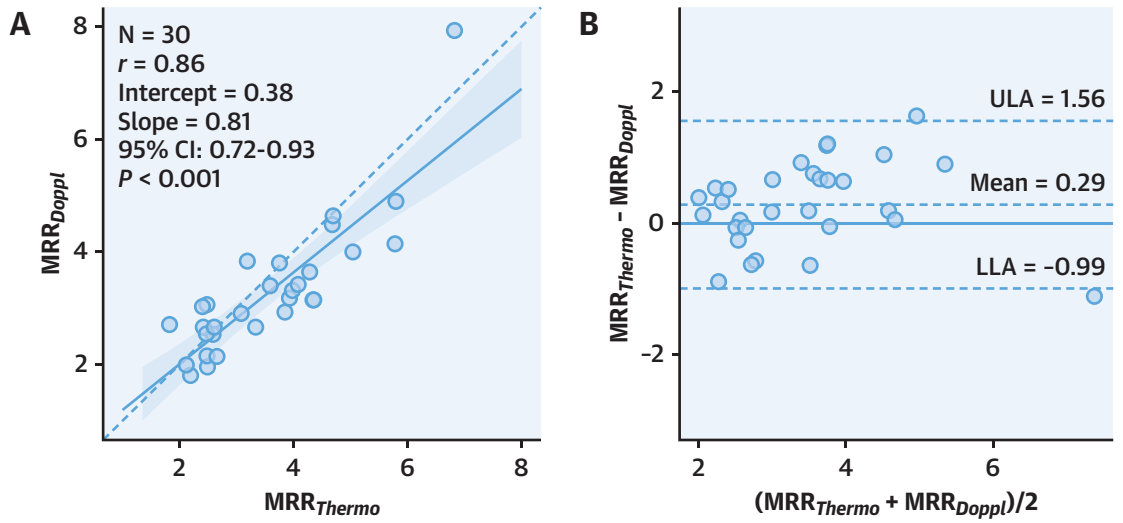
previous procedure, whereas in 8 of them the measurements were performed immediately after PCI. The baseline characteristics and the reason for intracoronary physiologic measurements are detailed in **Table 1**. There were no complications related to the measurements.

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.

MRR_{Thermo} VS MRR_{Doppl}. MRR as derived from thermodilution (Equation 3, MRR_{Thermo}) and its corresponding Doppler-derived index MRR_{Doppl} (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 MRR_{Thermo} and MRR_{Doppl} remained high (LAD: 3.85 ± 1.24 and 3.48 ± 0.961, $P = 0.65$; LCX: 3.06 ± 1.08 and 2.75 ± 0.61, $P = 0.89$; RCA 3.51 ± 1.32 and 3.29 ± 1.43, $P = 0.60$ for MRR_{Thermo} and MRR_{Doppl}, 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

FIGURE 2 Correlation Between MRR_{Thermo} and MRR_{Doppl} and Corresponding Bland-Altman Plot



(A) Plots of the individual values of MRR as derived from continuous thermodilution (MRR_{Thermo}) (Equation 3) vs the MRR as derived from Doppler flow velocity (MRR_{Doppl}) (Equation 4). **(B)** Corresponding Bland-Altman plot. LLA = lower limit of agreement; MRR = microvascular resistance reserve; ULA = upper limit of agreement.

(FFR <1) 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 − CFR vs epicardial resistance (as indicated by decreasing FFR) is shown in **Figure 3B**.

DISCUSSION

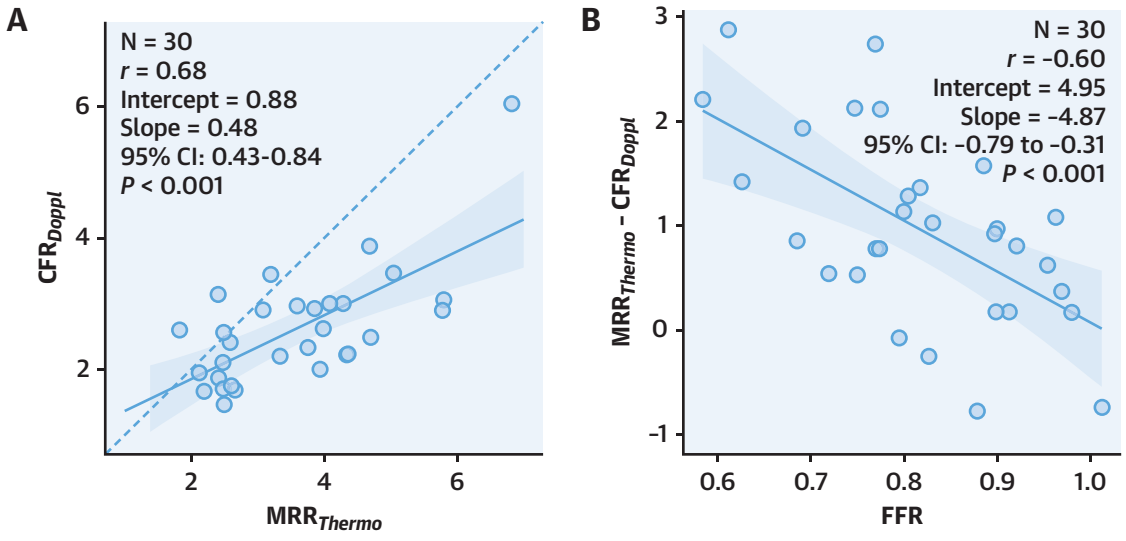
SUMMARY OF FINDINGS. We outline the theoretical framework and provide the first human measurements of a novel index, the MRR, to characterize the function of the coronary microvasculature. MRR is defined as R_μ at rest, as it would be in the hypothetical case the epicardial artery were to be completely normal divided by R_μ 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_μ to myocardial metabolic needs (25). Thus, actual resting R_μ no longer corresponds to truly normal R_μ, 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_μ (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 3 Correlation Among MRR_{Thermo}, CFR_{Doppl}, and FFR



(A) Plots of the individual values of MRR as derived from continuous thermodilution vs the CFR as derived from Doppler flow velocity. **(B)** Plots of the individual values of FFR vs the difference between the MRR_{Thermo} and CFR_{Doppl}. For arteries with no or neglectable epicardial disease (FFR close to 1), MRR and CFR are similar. CFR = coronary flow reserve; FFR = fractional flow reserve; other abbreviations as in Figure 2.

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 $P_{d,hyper}$ is available. In addition, $R_{\mu,rest}$ 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.

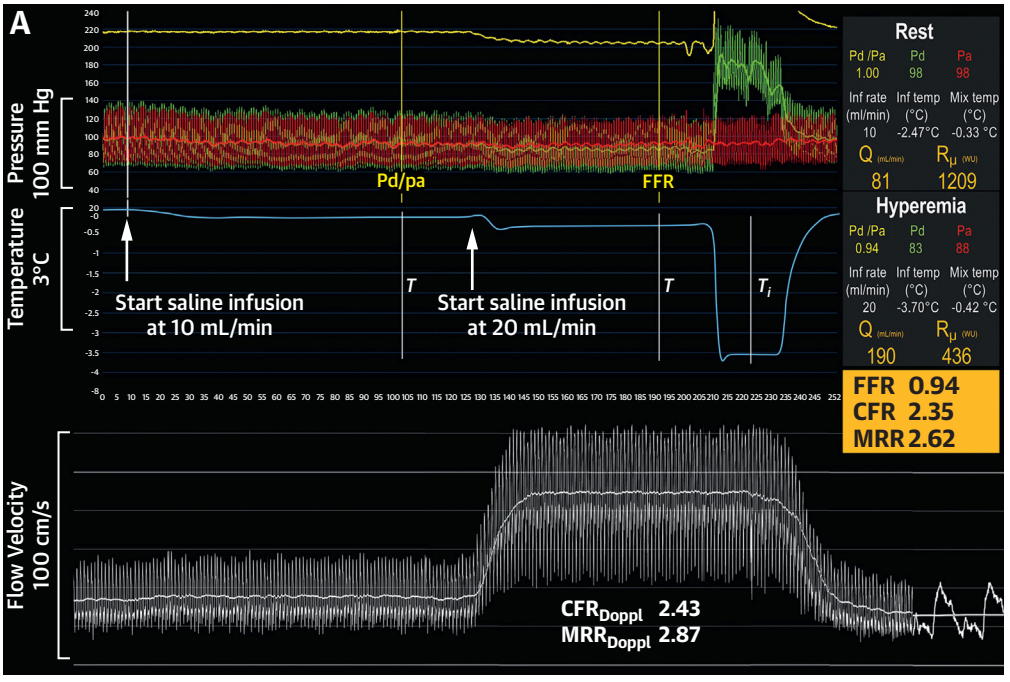
The IMR (10), obtained by bolus thermodilution (29,30), is considered the invasive standard of reference for assessing microcirculatory function. IMR factors in distal coronary pressure (P_d), therefore accounting for the epicardial resistance, and hyperemic mean transit times. The major theoretical 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_{μ}.

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

CENTRAL ILLUSTRATION **Simultaneous Registration of Pressures, Temperature, and Flow Velocity in the Right Coronary Artery**



De Bruyne, B. et al. J Am Coll Cardiol. 2021;78(15):1541–1549.

(A) Approximately 7 seconds after the start of the infusion of saline (10 mL/min), distal temperature (T) decreases and stabilizes at −0.33 °C, while Pa, Pd, and average peak velocity remain unchanged. After 2 minutes of steady-state infusion at 10 mL/min, the pump automatically switches to an infusion rate of 20 mL/min. This is paralleled by a decrease in temperature and by an increase in average peak velocity. All relevant values for P, Q, R, CFR, and MRR are automatically calculated and displayed at the right side of the screen. **(B)** Calculations of Q, R_μ, and of MRR (see text for details). **(C)** The distal end of the monorail infusion catheter. The radiopaque marker and the 4 side holes are well visible. CFR = coronary flow reserve; FFR = fractional flow reserve; MRR = microvascular resistance reserve; Pa = aortic pressure; Pd = distal coronary pressure; Q = coronary blood flow (mL/min); R_μ = microvascular resistance (WU); other abbreviations as in Figure 3.

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 Celiad. Dr Pijls 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.

ADDRESS FOR CORRESPONDENCE: Dr Bernard De Bruyne, Cardiovascular Center Aalst, OLV-Clinic, Moorselbaan, 164, B-9300 Aalst, Belgium. E-mail: bernard.de.bruyne@olvz-aalst.be. Twitter: @Bernard-Bruyne, @Egallinoro, @alecandreva, @ColletCarlos, @EmanueleBarba13, @jeroen_sonck.

REFERENCES

1. Kunadian V. An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries. *EuroIntervention*. 2020;16:23.

2. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018;72:2625–2641.

3. Murthy VL, Naya M, Taqueti VR, et al. Effects of sex on coronary microvascular dysfunction and cardiac outcomes. *Circulation*. 2014;129:2518–2527.

4. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.

5. Fearon WF, Low AF, Yong AS, et al. Prognostic value of the Index of Microcirculatory Resistance measured after primary percutaneous coronary intervention. *Circulation*. 2013;127:2436–2441.

6. Lee JM, Jung JH, Hwang D, et al. Coronary flow reserve and microcirculatory resistance in patients with intermediate coronary stenosis. *J Am Coll Cardiol*. 2016;67:1158–1169.

7. Gdowski MA, Murthy VL, Doering M, Monroy-Gonzalez AG, Slart R, Brown DL. Association of isolated coronary microvascular dysfunction with mortality and major adverse cardiac events: a systematic review and meta-analysis of aggregate data. *J Am Heart Assoc*. 2020;9. e014954-e014954.

8. Ford TJ, Stanley B, Sidik N, et al. 1-year outcomes of angina management guided by invasive coronary function testing (CorMicA). *J Am Coll Cardiol Intv*. 2020;13:33–45.

9. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J*. 2020;41:407–477.

10. Fearon WF, Balsam LB, Farouque HMO, et al. Novel index for invasively assessing the coronary microcirculation. *Circulation*. 2003;107:3129–3132.

11. Sorop O, van de Wouw J, Chandler S, et al. Experimental animal models of coronary microvascular dysfunction. *Cardiovasc Res*. 2020;116:756–770.

12. Aarnoudse W, van't Veer M, Pijls NHJ, et al. Direct volumetric blood flow measurement in coronary arteries by thermodilution. *J Am Coll Cardiol*. 2007;50:2294.

13. van't Veer M, Geven MCF, Rutten MCM, et al. Continuous infusion thermodilution for assessment of coronary flow: theoretical background and in vitro validation. *Med Eng Phys*. 2009;31:688–694.

14. Keulards DCJ, Van 't Veer M, Zelis JM, et al. Safety of absolute coronary flow and microvascular resistance measurements by thermodilution. *EuroIntervention*. 2021;17(3):229–232.

15. Xaplanteris P, Fournier S, Keulards Daniëlle CJ, et al. Catheter-based measurements of absolute coronary blood flow and microvascular resistance. *Circ Cardiovasc Interv*. 2018;11:e006194.

16. Gallinoro E, Candreva A, Colaiori I, et al. Thermodilution-derived volumetric resting coronary blood flow measurement in humans. *EuroIntervention*. Published online February 2, 2021. https://doi.org/10.4244/EIJ-D-20-01092

17. Gutiérrez-Barrios A, Izaga-Torralba E, Rivero Crespo F, et al. Continuous thermodilution method to assess coronary flow reserve. *Am J Cardiol*. 2020;141:31–37.

18. De Bruyne B, Adjedj J, Xaplanteris P, et al. Saline-induced coronary hyperemia. *Circ Cardiovasc Interv*. 2017;10:e004719.

19. Everaars H, de Waard GA, Schumacher SP, et al. Continuous thermodilution to assess absolute flow and microvascular resistance: validation in humans using [15O]H2O positron emission tomography. *Eur Heart J*. 2019;40:2350–2359.

20. Fournier S, Keulards DCJ, van 't Veer M, et al. Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans. *EuroIntervention*. 2020;17(4):e309–e316.

21. Keulards DCJ, Fournier S, van't Veer M, et al. Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement. *Heart*. 2020;106:1489–1494.

22. Gould KL, Lipscomb K, Calvert C. Compensatory changes of the distal coronary vascular bed during progressive coronary constriction. *Circulation*. 1975;51:1085–1094.

23. Kodeboina M, Nagumo S, Munhoz D, et al. Simplified assessment of the index of microvascular resistance. *J Interv Cardiol*. 2021;2021:9971874.

24. van 't Veer M, Adjedj J, Wijnbergen I, et al. Novel monorail infusion catheter for volumetric coronary blood flow measurement in humans: in vitro validation. *EuroIntervention*. 2016;12:701–707.

25. Di Gioia G, Melin JA, De Bruyne B. Coronary autoregulatory plateau in humans. *J Am Coll Cardiol*. 2020;76:1270–1271.

26. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and

collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation*. 1993;87:1354–1367.

27. De Bruyne B, Baudhuin T, Melin JA, et al. Coronary flow reserve calculated from pressure measurements in humans. Validation with positron emission tomography. *Circulation*. 1994;89:1013–1022.

28. Gould KL, Lipscomb K, Hamilton GW. Physiologic basis for assessing critical coronary stenosis. Instantaneous flow response and regional distribution during coronary hyperemia as measures of coronary flow reserve. *Am J Cardiol*. 1974;33:87–94.

29. De Bruyne B, Pijls Nico HJ, Smith L, Wievegg M, Heyndrickx Guy R. Coronary thermodilution to assess flow reserve. *Circulation*. 2001;104:2003–2006.

30. Pijls NH, De Bruyne B, Smith L, et al. Coronary thermodilution to assess flow reserve: validation in humans. *Circulation*. 2002;105:2482–2486.

31. Chamuleau SAJ, Siebes M, Meuwissen M, Koch KT, Spaan JAE, Piek JJ. Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. *Am J Physiol Heart Circ Physiol*. 2003;285:H2194–H2200.

32. Meuwissen M, Chamuleau SA, Siebes M, et al. Role of variability in microvascular resistance on fractional flow reserve and coronary blood flow velocity reserve in intermediate coronary lesions. *Circulation*. 2001;103:184–187.

33. Maznyczka AM, Oldroyd KG, Greenwood JP, et al. Comparative significance of invasive measures of microvascular injury in acute myocardial infarction. *Circ Cardiovasc Interv*. 2020;13:e008505.

34. Barbato E, Aarnoudse W, Aengevaeren WR, et al. Validation of coronary flow reserve measurements by thermodilution in clinical practice. *Eur Heart J*. 2004;25:219–223.

35. Everaars H, de Waard GA, Driessen RS, et al. Doppler flow velocity and thermodilution to assess coronary flow reserve: a head-to-head comparison with [15O]H2O PET. *J Am Coll Cardiol Intv*. 2018;11:2044–2054.

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.