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REVIEW

Translational Physiology

Bridging the gap: a comprehensive toolkit for assessment of coronary microcirculation in clinical practice

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Abstract

Coronary artery disease (CAD) has traditionally been diagnosed and managed based on anatomical assessments of the epicardial coronary arteries. However, a growing body of evidence highlights the limitations of coronary angiography in evaluating the ischemic burden of atherosclerotic plaques. The coronary microcirculation is increasingly recognized for its pivotal role in myocardial ischemia. Coronary microvascular dysfunction (CMD) contributes significantly to both acute and chronic coronary syndromes, even in the absence of obstructive epicardial disease. Despite its clinical significance, CMD remains underdiagnosed due to the lack of routine assessment in contemporary cardiac catheterization practices. Emerging invasive and noninvasive techniques now enable comprehensive evaluation of coronary microvascular dysfunction (CMD) by assessing microvascular resistance, coronary flow reserve, and tissue-level perfusion. Advances in thermodilution-based indices, intracoronary Doppler, and functional coronary angiography continue to provide quantitative insights into microvascular physiology, whereas noninvasive modalities—including cardiac magnetic resonance (MRI), positron-emitted tomography (PET), transthoracic Doppler echocardiography, and computed tomography-based perfusion imaging—offer powerful tools for diagnosing CMD without the need for catheter-based assessment. Integrating these complementary approaches into clinical practice enhances risk stratification and supports personalized management strategies, particularly in patients with ischemia and nonobstructive coronary arteries (INOCA). This review explores in-depth the diagnostic tools and the quantitative metrics used or the invasive assessment of CMD, emphasizing their clinical utility and impact on patient management.

angina; coronary flow reserve; microvascular dysfunction; multimodality imaging; physiology

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INTRODUCTION

The link between myocardial ischemia and obstructive coronary artery disease is well established; however, over the past decades, several studies have reported the occurrence of angina and/or ischemia even in the absence of epicardial disease. Historically, the concept of "*Syndrome X*" was coined by Kemp (1) to define patients presenting with angina and objective evidence of ischemia who demonstrated angiographically normal or near-normal coronary arteries. This concept was later refined by Cannon and Epstein (2), who introduced the concept of "*microvascular angina* (*MVA*)" to denote myocardial ischemia due to microvascular disorder and has lately evolved into the modern concept of coronary microvascular dysfunction (CMD) (3). Nowadays, it is widely recognized that a comprehensive understanding of myocardial ischemia requires a detailed evaluation of the coronary microcirculation and that CMD emerges as a critical field where therapeutic innovations are still lacking, presenting significant challenges in diagnosis (4). This condition is integral to the spectrum of coronary syndrome presentations, encompassing both acute and chronic coronary syndromes, irrespective of the presence of concomitant epicardial coronary artery disease (5, 6).

Implementing routine, systematic assessments of microvascular dysfunction at the time of cardiac catheterization could revolutionize risk stratification, facilitating the development of personalized therapeutic approaches. This could significantly improve symptom management and prognostic outcomes for a wide range of cardiac diseases, marking a substantial advancement in the field of cardiovascular medicine (5, 7–11).

In this review, we provide a comprehensive analysis of invasive and noninvasive methodologies for the assessment of CMD in the catheterization laboratory (Graphical Abstract), with a focus on their technical principles, clinical applications, and implications for daily clinical practice.

BASIC CONCEPTS OF THE CORONARY MICROCIRCULATION AND CORONARY MICROVASCULAR DYSFUNCTION

The coronary microvasculature comprises vessels with a diameter less than 500 μm, encompassing intermediate-size arterioles (500–200 μm), small intramyocardial arterioles (<200 μm), capillaries, and venules (12). These vessels not only act as capacitance structures, containing up to 90% of the blood volume within the myocardium, but also play a pivotal role in the regulation of myocardial blood flow. This regulatory function is key, especially in the case of epicardial stenoses, where coronary autoregulation is essential to preserve blood flow (13). Even in the absence of stenosis, the microvascular system adjusts blood flow in accordance with changing physiological needs, such as during physical activity (14, 15).

The term coronary microvascular dysfunction encompasses a spectrum of pathophysiological conditions, including infiltration of the vascular wall, extraluminal compression, disturbances in sympathetic nerve function, and abnormal vascular remodeling. Despite this, the precise mechanisms underlying these pathologies are not fully elucidated (16). These mechanisms are not mutually exclusive and often coexist, resulting in a spectrum of functional and structural abnormalities.

Endothelial dysfunction is a hallmark of CMD and is characterized by reduced nitric oxide (NO) bioavailability, increased oxidative stress, and upregulation of vasoconstrictor pathways such as endothelin-1 signaling. This imbalance favors impaired endothelium-dependent vasodilation and inappropriate vasoconstriction, leading to a blunted coronary flow reserve (CFR) despite angiographically normal epicardial vessels (3).

Structural remodeling of the coronary microcirculation encompasses pathological changes such as arteriolar wall thickening, perivascular fibrosis, and microvascular rarefaction, which reduce luminal cross-sectional area and increase minimal resistance to flow. Such alterations are particularly prevalent in systemic hypertension, diabetes mellitus, and heart failure with preserved ejection fraction (HFpEF), where impaired compliance and fibrosis limit the vasodilatory reserve (16).

Extravascular compressive forces may physically compress intramyocardial arterioles, whereas impaired metabolic signaling disrupts the tight coupling of myocardial oxygen consumption and coronary flow and may lead to CMD in clinical conditions such as left ventricular hypertrophy with increased left ventricular wall stress or interstitial edema in acute ischemic syndromes (13).

Inflammatory and thrombotic mechanisms further exacerbate microvascular dysfunction. In the context of acute coronary syndromes, distal microembolization and leukocyte recruitment contribute to microvascular obstruction, worsening infarct size and prognosis despite successful epicardial reperfusion (17).

Finally, neurohormonal dysregulation is increasingly recognized as a modulator of microvascular tone. Enhanced sympathetic activity, reduced parasympathetic input, and altered adrenergic receptor signaling can provoke dynamic vasoconstriction at the microvascular level, compounding structural and endothelial abnormalities.

Various methodologies (both invasive and noninvasive) are currently available for the clinical assessment of the coronary microcirculation (18, 19). More recently, angio-based indices that do not require the use of a coronary guidewire have emerged as highly promising.

INVASIVE ASSESSMENT OF CORONARY MICROCIRCULATION

Angio-Based Assessment

Before the advent of contemporary invasive tools for diagnosing CMD, coronary angiography-based indices were adopted to diagnose microvascular angina, named TIMI Frame Count (TFC) and Myocardial Blush Grade (MBG) (20).

TFC quantifies coronary flow by counting the number of cine frames required for a contrast agent, injected during coronary angiography, to reach and opacify a predefined distal "landmark," likely reflecting the characteristics of coronary microcirculation (21). In case of CMD, coronary flow slows

due to downstream obstruction in the microcirculation, leading to an increased number of frames required for the contrast medium to reach the distal landmark (22, 23).

MBG, on the other hand, is a qualitative angiographic index, used to assess myocardial tissue perfusion; the term "blush" (redness) refers to the extent and intensity of contrast opacification within the myocardial microcirculation and the rate at which the contrast agent is washed out (23, 24). Gibson described the existence of four degrees of MBG (0–3), from no blush to normal perfusion. Atmaca et al. (25) proposed an index called Total Myocardial Blush Score (TMBS), calculated as the sum of the MBG of each coronary territory that defines the overall microvascular functionality. However, over the years, the introduction of novel invasive diagnostic tools of coronary microvascular function has raised questions about the relevance of these indices, revealing their low diagnostic accuracy (26–28).

Doppler-Based Assessment

The advent of pulsed Doppler-based technologies allowed for invasive assessment of coronary blood flow by converting Doppler shifts from changing flow velocities into coronary flow velocity estimates (29). Early intracoronary Doppler catheters introduced in 1971 by Benchimol et al (29) and validated by Hartley and Cole (30, 31) were limited by their 3 Fr size, restricting the use to proximal coronary segments. Miniaturization of the piezoelectric ultrasound transducer led to the development of a 0.018 in. flexible Doppler guidewire (FloWire, Cardiometrics, Inc, Mountain View, Ca) with a 12-MHz piezoelectric transducer incorporated in the tip, enabling the interrogation of any part of the vessel without affecting the flow velocity profiles (32). Flow velocity data are processed in real time via fast Fourier transformation and displayed on a console as average peak velocity (APV) in cm/s, which represents the average of instantaneous peak velocity spectra over a 2-s segment (Fig. 1) (32). Doppler-derived coronary blood flow (CBF) can be measured combining APV with quantitative coronary angiography (QCA) (32) according to the formula:

$$\mathrm{CBF} = 0.5 \times \mathrm{APV} \times (\mathrm{D}^2 \times \pi)/4,$$

where D is the vessel diameter calculated by quantitative coronary angiography (QCA).

Assuming that epicardial vessel diameter remains unchanged during hyperemia, coronary flow reserve (CFR) can be expressed as coronary flow velocity reserve (CFVR) and calculated as the ratio between hyperemic and resting APV ($\mathrm{APV_{hyper}}$ and $\mathrm{APV_{rest}}$, respectively)

$$\mathrm{CFVR} = \mathrm{APV_{hyper}}/\mathrm{APV_{rest}}.$$

The usual approach to induce a stable steady-state hyperemia is the administration of intravenous adenosine (140 μg/kg/min) or intracoronary papaverine (8–10 mg for the right coronary artery and 12–15 mg for the left coronary artery) (33, 34). A CFVR < 2.5 is considered abnormal (35–37) and related to worse clinical outcome (38).

Combining pressure and velocity measurement, it is possible to measure the hyperemic microvascular resistance (HMR) calculated as follows (39):

$$\mathrm{HMR} = \mathrm{Pd}/\mathrm{APV_{hyper}},$$

in mmHg/cm/s. The Combowire (Philips Volcano) integrates Doppler and pressure sensors for simultaneous measurements when the wire is connected to a dedicated station (ComboMap, Volcano Corporation, San Diego). However, the optimal HMR threshold remains debated. A small observational study proposed a cut-off of 2.5 (40).

In the presence of epicardial stenosis, HMR could be overestimated by the presence of collateral flow. To address this, the minimal microvascular resistance (mMR) has been introduced as a novel index of microvascular function independent of epicardial atherosclerosis (30) calculated as the ratio of hyperemic distal coronary pressure and hyperemic APV, both measured during the wave-free (wf) period window (41). However, its prognostic value is still unclear and its clinical applicability in clinical practice remains very low:

$$\mathrm{mMR} = \mathrm{wf} - \mathrm{Pd_{hyper}}/\mathrm{wf} - \mathrm{APV_{hyper}}.$$

Pros and cons in clinical application.

Doppler-derived coronary flow reserve (CFVR) has demonstrated a good correlation with [15O]H_2O PET (42). However, its widespread adoption remains limited mainly due to the technical challenges to achieve good and reliable Doppler traces; it has been reported, indeed, that up to 30%–40% of Doppler traces are suboptimal (42, 43).

Thermodilution-Based Assessment

Coronary thermodilution is the most widely used technique to assess coronary microvascular function. Based on the indicator-dilution principle, it measures the coronary blood flow fluid flow by tracking the dilution of an injected indicator (saline) within the coronary circulation (44). The indicator can be injected as bolus or can be infused continuously. The method requires the use of the pressure-temperature sensor-tipped guidewire (Pressure Wire X, Abbott) and the CoroFlow Cardiovascular System (Coroventis, Abbott). Standardized protocols to ensure consistent and reliable results have been established (45, 46).

Bolus thermodilution.

The pressure-temperature guidewire is advanced in the distal part of the vessel to be interrogated. A bolus injection (3 mL) of saline is performed through the guiding catheter, and, by measuring the proximal and distal temperatures with the Pressure Wire, the Coro Flow system detects the bolus traveling down the artery and derives the mean transit time (T_{mn}), which represents, the time taken by the bolus of saline to travel down the coronary artery (Fig. 2). Assuming the vascular volume (V) to be constant, T_{mn} serves as an index of coronary blood flow (Q) exhibiting an inverse relationship with coronary flow velocity:

$$\mathrm{Q} = \frac{\mathrm{V}}{T_{\mathrm{mn}}} \approx \frac{1}{T_{\mathrm{mn}}}.$$

Three bolus injections of 3 mL of room temperature saline are performed at rest and during hyperemia and then averaged to obtain the mean transit time at ($T_{\mathrm{mn,rest}}$ and $T_{\mathrm{mn,hyp}}$, respectively).

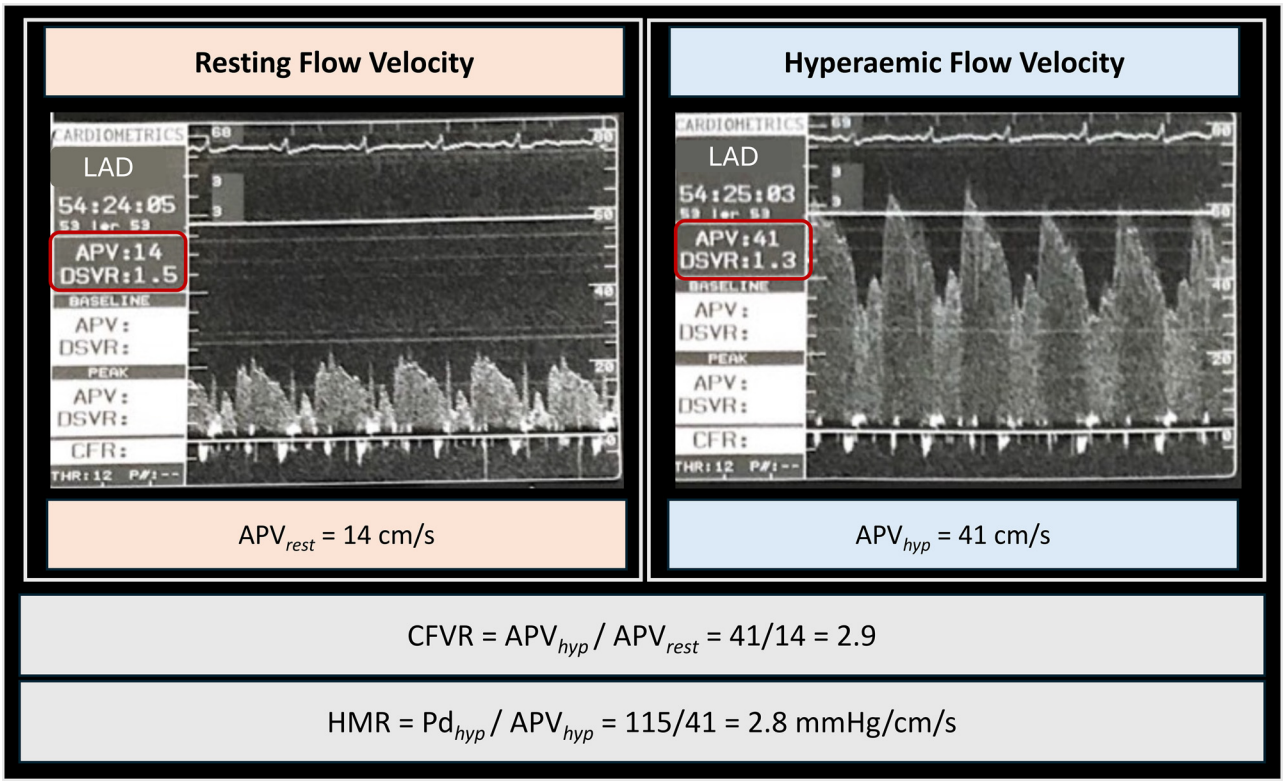

Figure 1. Intracoronary flow velocity measurement. Intracoronary flow velocity measurement: case example in the left anterior descending artery. A Doppler wire is placed in the coronary artery to be evaluated and connected to a dedicated console. Resting average peak velocity value in cm/s is displayed in real time (14 cm/s). After inducing hyperemia (intracoronary papaverine was used in this specific case), flow velocity increases up to an average peak velocity (APV) value of 41 cm/s. Coronary flow velocity reserve (CFVR) can be calculated as the ratio between hyperemic and resting APV (2.9). If simultaneous intracoronary pressure measurement is performed, hyperemic microvascular resistance (HMR) can be derived as the ratio between P_d and APV both measured during hyperemia, in mmHg/cm/s. APV_{rest}, average peak velocity at rest; APV_{hyp}, average peak velocity during hyperemia. Courtesy of Dr. Bernard De Bruyne.

Therefore, bolus thermodilution-derived coronary flow reserve (CFR_{bolus}) can be calculated as the ratio between $T_{mn,rest}$ and $T_{mn,hyp}$:

$$CFR_{bolus} = \frac{Q_{hyp}}{Q_{rest}} = \frac{T_{mn,rest}}{T_{mn,hyp}}.$$

Based on measurements of bolus thermodilution-derived T_{mn}, Fearon et al. (47, 48) introduced the index of microvascular resistance (IMR), a dimensionless index to specifically assess the hyperemic microcirculatory resistance calculated as follows:

$$IMR = P_d \times T_{mn,hyp},$$

where P_d is the distal coronary pressure. A cutoff of 25 units is used to define CMD (49). Finally, the resistive reserve ratio (RRR) represents the vasodilatory capacity of the microcirculatory bed and is calculated as the ratio of IMR compared with the ratio of "resting" IMR (resting thermodilution transit time and distal pressure):

$$RRR = \frac{T_{mn,rest} \times P_{d,rest}}{T_{mn,hyper} \times P_{d,hyper}}.$$

In a large cohort of patients with both obstructive and nonobstructive CAD, a cut-off of 3.5 for the RRR yielded a clinical prognostic value up to 5 yr of follow-up (50).

Pros and cons in clinical application. Bolus thermodilution is a rapid and user-friendly technique for the assessment of microvascular function. However, the method is highly operator-dependent as it requires manual saline injection, which may hamper accuracy and reproducibility.

Continuous intracoronary thermodilution. Originally proposed 40 yr ago by Ganz et al. (51) to measure the flow in the coronary sinus, continuous thermodilution was adapted in 2007 for coronary flow measurement (Fig. 3) (52). Coronary blood flow can be measured by knowing the temperature of the blood, of the infused indicator (saline at room temperature, T_i) and of the mixture downstream from the infusion site and the infusion rate of the indicator (Q_i). That stated, the temperature of the mixture in the distal coronary artery is inversely proportional to the coronary blood flow. A dedicated 2.52 Fr monorail infusion microcatheter, the RayFlow, with four lateral distal side holes, is used to infuse saline at room temperature (typically between 20 and 23°C), in the proximal part of the interrogated coronary artery (33, 41). This catheter is connected to an infusion pump and placed over a pressure/temperature sensored wire (PressureWire, Abbott Vascular, Santa Clara, CA) placed in the distal part of the coronary artery that records temperature changes through a dedicated software (Coroventis CoroFlow Cardiovascular System, Uppsala, Sweden) (46). The infusion of saline at room temperature is started at the desired infusion rate (Q_i), thus inducing a decline in

Figure 2. Bolus thermodilution. Microvascular assessment using thermodilution. Mean transit times (T_{mn}) are calculated as the mean of three measures at rest (blue) and after the induction of hyperemia (orange). Index of microcirculatory resistance (IMR) is defined as the product between distal hyperemic pressure and hyperemic T_{mn}.

temperature of the blood/saline mixture (T). When a steady state of T has been reached, P_d, P_a, and T are measured, and the wire sensor is pulled back into the tip of the RayFlow catheter to measure the temperature of saline when it enters the coronary artery (T_i). Absolute coronary blood flow in mL/min is calculated according to the formula:

$$Q = 1.08 \times \frac{T_i}{T} \times Q_i.$$

The method allows for the calculation of both resting (Q_{rest}) and hyperemic (Q_{hyper}) flow by changing the infusion rate (Q_i) of saline (8–10 mL/min for resting flow measurement and 15–20 mL/min for hyperemic flow (53, 54). After measuring Q and distal coronary pressure (P_d), absolute microvascular resistance (R_μ in WU) can be calculated according to Ohm's law as:

$$R_\mu = \frac{P_d}{Q}.$$

The method is safe (55), operator independent and reproducible (56, 57), and, with an appropriate setting of the infusion, it can be semiautomated (58, 59).

Coronary flow reserve derived by continuous thermodilution (CFR_{cont}) can be calculated by dividing the hyperemic for resting absolute coronary flow:

$$CFR_{cont} = \frac{Q_{hyper}}{Q_{rest}}.$$

Pros and cons in clinical application. Continuous thermodilution is a precise, reliable, and operator-independent method to quantify absolute flow and microvascular resistance. However, the cost related to the infusion microcatheter may restrict its routine use in clinical practice.

Novel Metrics of Coronary Microcirculation: The Microvascular Resistance Reserve

An ideal microcirculatory metric should be specific to the microcirculation, independent of operator technique and coronary autoregulation, and based on absolute flow and resistance. CFR does not distinguish between epicardial and microvascular function and making it useful for assessing microvascular status only when the epicardial arteries are strictly normal. Although continuous thermodilution has enabled the quantification of absolute coronary flow and microvascular resistance (60), these values often show substantial interindividual variability and do not account for myocardial mass, limiting their reliability for personalized clinical decision-making (10, 61, 62). Therefore, De Bruyne et al (63) have provided the theoretical framework of microvascular resistance reserve, an index that represents the true vasodilatory capacity of coronary microcirculation. To simplify, MRR equals CFR divided by FFR and corrected by the driving pressures and can be calculated with the following formula:

$$MRR = \frac{CFR}{FFR} \times \frac{P_{a,rest}}{P_{a,hyper}}.$$

If $P_{a,rest} = P_{a,hyper}$, which is generally the case with saline-induced hyperemia, the previous equation can be further simplified as: MRR = CFR/FFR. If hyperemia is induced by adenosine or other drugs, $P_{a,rest}$, and $P_{a,hyper}$ are usually different by 10%–30% and the second term of the equation needs to be taken into account to assess the mutual relation between MRR, FFR, and CFR. Of note, the MRR formula is applicable to other methodologies, including intracoronary Doppler, bolus thermodilution, thermoconvection, and noninvasive

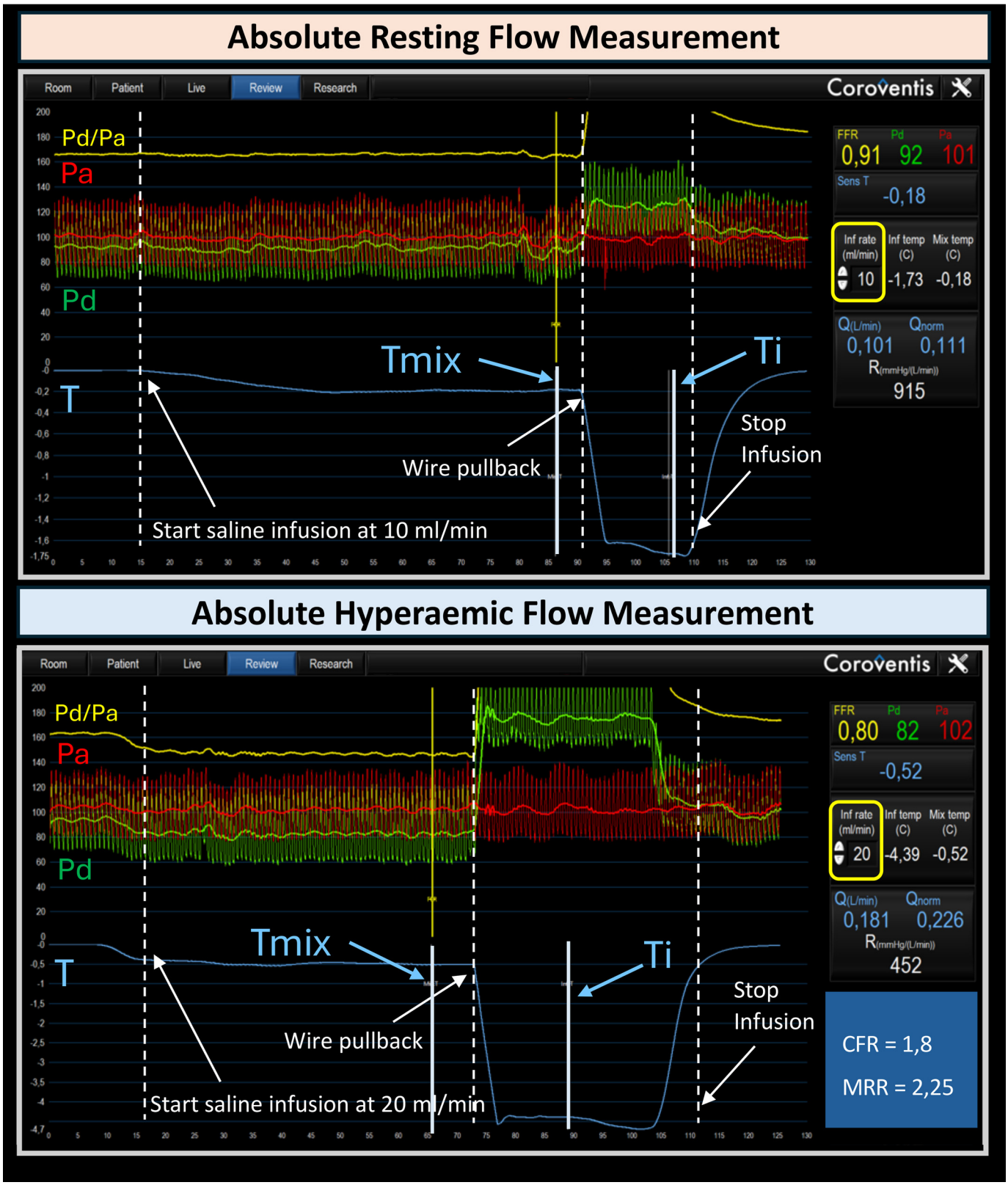

Figure 3. Absolute coronary flow measurement. Continuous thermodilution measurement of absolute coronary flow and resistance. Resting flow measurement (*top*) is performed in the left anterior descending artery (LAD) by using an infusion rate of 10 mL/min). By using an infusion rate of 20 mL/min (*bottom*), maximal hyperemia is induced: flow increases and fractional flow reserve (FFR) decreases. Coronary flow reserve and microvascular resistance reserve can be calculated by combining resting and hyperemic measurement. P_d, distal coronary pressure; P_a, aortic pressure; Q, absolute coronary flow; T_{mix}, mixed temperature measured in the distal coronary artery; T_i, infusion temperature measured at the tip of the Rayflow Catheter; *R*, microvascular resistance; CFR, coronary flow reserve; MRR, microvascular resistance reserve. Courtesy of Dr. Bernard De Bruyne.

flow substitutes, although all these methods cannot be considered equivalent.

Angiography-Derived Indexes of Microvascular Resistance

The adoption of functional assessment of coronary microcirculation in clinical practice remains limited by the need for specialized equipment, coronary instrumentation, and pharmacologic hyperemia. Angiography-derived physiology may overcome some of these limitations, being wire-free, obviating the need for hyperemic drugs, and having the potential for off-line analysis. Among the CMD angio-derived indices, IMRangio (Fig. 4) was originally proposed and validated starting from the IMR formula as follows:

$$IMR_{angio} = P_{a,hyp} \times QFR \times T_{mn,hyp},$$

where $P_{a,hyp}$ is the aortic pressure measured during steady-state hyperemia, QFR is the quantitative flow ratio performed as a surrogate of FFR, and the transit time (T_{mn}) is proportional to the time required by the contrast media to travel from the guiding catheter to a distal reference point in the coronary vessel during steady-state hyperemia. The transit time can also be expressed as the ratio between the number of frames (Nframes) and the acquisition rate (fps). So, the IMRangio formula becomes:

$$IMR_{angio} = P_{a,hyp} \times QFR \times \frac{Nframes}{fps}.$$

Subsequently, several angiography-derived indices—NH-IMRangio, cAngio-IMR, A-IMR, Ca-IMR, and AMR—of microcirculatory resistances have also been validated using standard angiographic views acquired at rest (without adenosine administration) based on different formulas and using different angiography-derived FFR surrogates from different vendors (64–67). Their correlation with invasive measurements has been explored in different clinical settings, showing different degrees of accuracy (68, 69). A pooled meta-analysis demonstrated a good diagnostic accuracy of the angiography-derived IMR tools with a pooled AUC of 0.86 (70). Furthermore, combining systematically QFR and IMRangio measurements significantly increased the diagnostic accuracy in detecting myocardial ischemia (71).

Pros and cons in clinical application.

Angiography-derived software enables a wire-free and drug-free assessment of microcirculation, facilitating its use even in centers without expertise in coronary physiology. However, robust validation studies are still lacking, limiting their widespread adoption.

NONINVASIVE ASSESSMENT OF CORONARY MICROCIRCULATION

Noninvasive imaging plays a pivotal role in the evaluation of CMD, providing anatomical and functional insights without the need for invasive instrumentation. These approaches allow the assessment of global and regional myocardial perfusion, quantification of CFR or myocardial perfusion reserve (MPR), and estimation of myocardial blood flow (MBF). By integrating structural and functional information, noninvasive modalities enable the identification of both functional and structural microvascular abnormalities, guiding patient management in the setting of chronic coronary syndromes and ischemia with nonobstructive coronary arteries (INOCA/ANOCA) (18, 19, 45).

Stress Echocardiography

Stress echocardiography with Doppler assessment of the left anterior descending artery represents a cost-effective and radiation-free technique for CMD evaluation (72). Measurement of coronary flow velocity reserve (CFVR) during pharmacologic vasodilation (typically with adenosine, dipyridamole, or regadenoson) provides quantitative information on microvascular vasodilatory capacity (73). A CFVR < 2.0 identifies impaired microvascular function and correlates with worse clinical outcomes (74, 75). In addition to CFVR, two-dimensional speckle-tracking echocardiography can assess layer-specific myocardial deformation, with reduced strain during vasodilator stress indicating microvascular ischemia (76). Artificial intelligence-based tools are being introduced to improve reproducibility, automate flow tracing, and reduce operator dependence, addressing one of the main limitations of the technique (77).

Pros and cons in clinical application.

Practical first-line approach in centers with adequate expertise, combining accessibility, low cost, and prognostic value (73, 78, 79). However, the technique is operator-dependent, acoustic windows may limit image quality, and measurements can be technically challenging.

Stress Cardiac Magnetic Resonance

Stress cardiac magnetic resonance (CMR) provides comprehensive anatomical, functional, and tissue-level information without ionizing radiation. Through first-pass perfusion imaging during pharmacologic stress, CMR allows both visual and quantitative assessment of myocardial perfusion and the derivation of MPR as a surrogate of CFR (80). Quantitative perfusion mapping now enables automatic pixel-wise generation of MBF maps at rest and stress, improving diagnostic accuracy for CMD and minimizing observer variability (81). An MPR < 1.47 has been associated with adverse cardiovascular outcomes and is considered a prognostic marker in patients with ANOCA (82). Owing to its high spatial resolution, CMR can detect diffuse subendocardial ischemia typical of CMD, while also providing late gadolinium enhancement (LGE) and T1/T2 mapping for myocardial characterization.

Pros and cons in clinical application.

High-resolution, excellent diagnostic accuracy and no radiation exposure. However, its use is limited by costs, examination duration, and availability, and contraindications in patients with implanted devices or severe renal impairment (83–85).

Computed Tomography Angiography and Perfusion

Coronary computed tomography angiography (CCTA) combined with stress computed tomography perfusion (CTP) allows simultaneous anatomical and functional assessment of coronary circulation. Dynamic CTP quantifies MBF and evaluates endocardial-to-epicardial perfusion gradients,

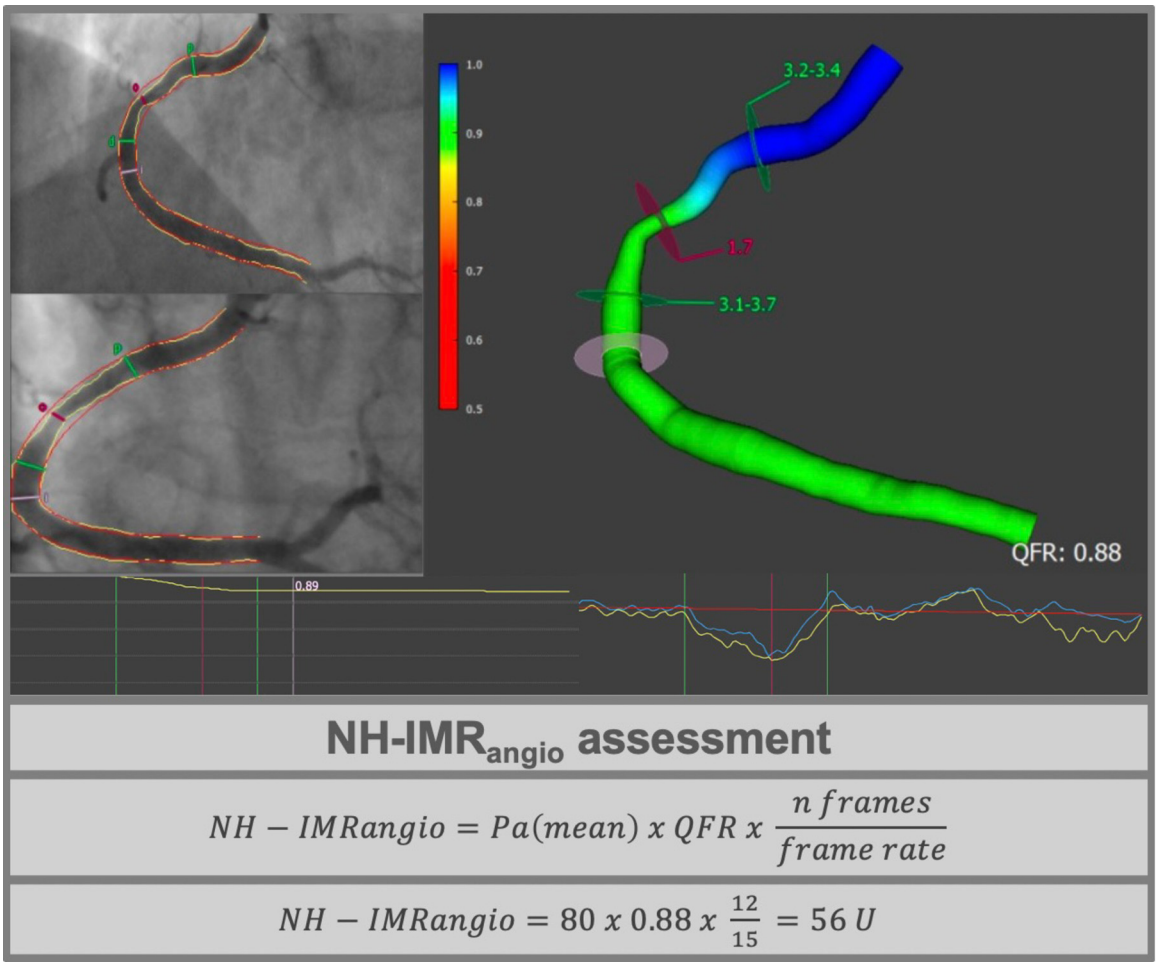

Figure 4. A clinical example of nonhyperemic angiography derived index of microcirculatory resistance (IMR) calculation. Nonhyperemic IMR_{angio} was calculated based on mean aortic pressure and quantitative flow ratio (QFR) at completion of primary percutaneous coronary intervention (PCI) in a patient with STEMI. NH-IMR_{angio} was abnormal (56 U). High values of NH-IMR_{angio} in patients with STEMI who underwent with primary PCI were associated with microvascular obstruction and higher risk of adverse events at short and long-term follow up after STEMI.

helping to identify diffuse subendocardial hypoperfusion consistent with CMD (86–89). Novel computational models, such as fractional flow reserve derived from CT (FFR-CT), can estimate flow and resistance in the coronary tree and microcirculation, providing a bridge between anatomical and physiological information (90, 91). In addition, peri-coronary adipose tissue attenuation (PCAT) analysis has emerged as a CT-based biomarker of local vascular inflammation and correlates with impaired CFVR (92, 93). These developments highlight the growing role of cardiac CT as a hybrid platform capable of evaluating both macro- and microvascular components.

Pros and cons in clinical application.

High-resolution anatomy and promising functional tools. However, limitations include radiation exposure, need for iodinated contrast, and dependence on high-quality image acquisition (18, 79).

Positron Emission Tomography

Cardiac positron emission tomography (PET) is regarded as the reference standard for noninvasive quantification of MBF and myocardial flow reserve (MFR) (94). Using radiotracers such as ^{15}O-water, ^{13}N-ammonia, or ^{82}Rb, PET enables absolute measurement of rest and stress MBF, detecting CMD even in the absence of regional perfusion defects (95, 96). The global reduction in hyperemic MBF and MFR identifies diffuse microvascular dysfunction, whereas hybrid PET/CT or PET/MR imaging provides a comprehensive assessment integrating anatomy, perfusion, and tissue characteristics (97).

Pros and cons in clinical application.

PET offers the most accurate noninvasive quantification of MBF and MFR, providing robust detection of CMD. However, its use is limited by limited accessibility, high costs, and the need for radiopharmaceuticals (18, 79).

Integrated Multimodality Imaging

Given the complementary nature of these techniques, a multimodal imaging strategy can optimize CMD evaluation. Stress echocardiography and CMR are ideal for initial screening and follow-up due to their availability and absence of radiation, whereas PET remains the quantitative benchmark for MBF and MFR assessment. CT-based methods,

by integrating anatomical and functional data, are emerging as comprehensive "one-stop" imaging solutions (Fig. 5). The combination of these modalities supports a patient-tailored approach, enhancing diagnostic precision and potentially improving clinical outcomes (18, 79, 94, 98).

PRACTICAL CONSIDERATIONS AND CLINICAL IMPLICATIONS

The invasive functional assessment of coronary microcirculation is crucial for comprehending the mechanisms underlying ischemic cardiopathy optimizing tailored patient care and enhancing the treatment and management of affected patients (99).

Invasive Assessment in the Setting of CCS

In the setting of chronic coronary syndrome (CCS), ~40% of those referred for coronary angiography have no obstructive lesions and about one-third of those who undergo percutaneous coronary intervention (PCI) continue to experience angina after undergoing percutaneous coronary intervention (PCI), underscoring the need to address the root causes of persistent symptoms (100). The Coronary Microvascular Angina (CorMicA) trial demonstrated that combining traditional coronary angiography with comprehensive physiological assessments (FFR, CFR, IMR, and vasoreactivity tests) allows endotype stratification and tailored therapy, resulting in better symptom control and quality of life (101). Yet, the invasive examination of microvascular function in patients with ischemia and nonobstructive coronary artery disease is currently a class Ib recommendation by the European Society of Cardiology (102, 103). Considering the cut-offs of CFR (or CFVR) and IMR (or HMR), four possible scenarios could be encountered: *1*) low flow reserve and high microvascular resistance, which represents the "structural pattern" of CMD; *2*) low flow reserve and normal microvascular resistance, which is usually characterized by increased basal CBF and normal hyperemic flow, configuring the "functional" pattern of CMD; *3*) normal flow reserve and normal microvascular resistance, which excludes the disruption of endothelium-independent dilation of the coronary microvasculature; and *4*) normal flow reserve and high microvascular resistance, which may be suggestive of initial structural CMD. Despite the available evidence, the impact of routine invasive assessment of coronary microvascular function on long-term clinical outcomes remains debated, highlighting the need for more extensive randomized clinical trials.

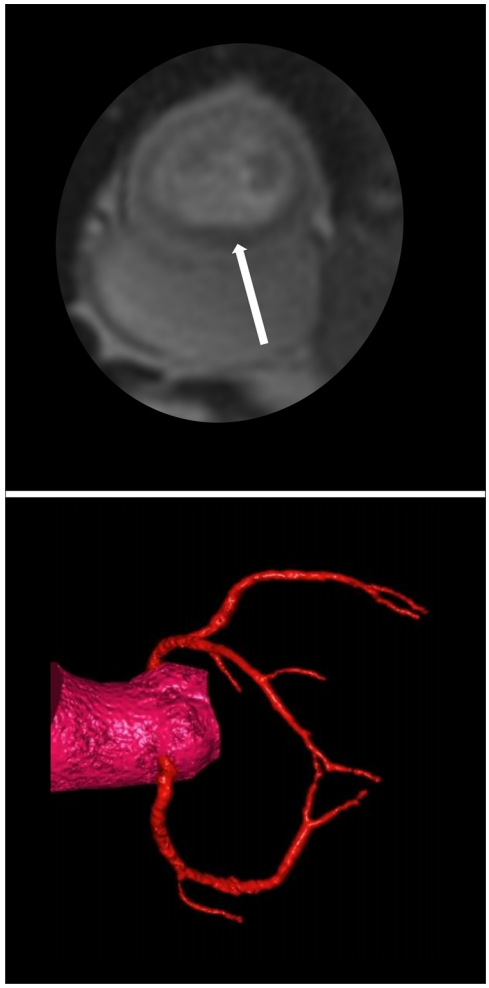

Figure 5. Noninvasive assessment of possible coronary microvascular dysfunction (CMD). *Top*: absence of obstructive coronary artery disease in a patient with angina symptoms. *Bottom*: a perfusion defect during stress cardiac magnetic resonance (CMR) (arrow).

Invasive Assessment in the Setting of ACS

Microvascular obstruction may complicate up to half of successful primary PCI procedures despite a timely reperfusion therapy, and is associated with adverse outcomes such as increased mortality, heart failure hospitalizations within one year follow-up, and early major cardiac complications (17, 104, 105). Hence, the measurement of microvascular function after primary PCI may provide predictive information regarding the size of the infarct, left ventricular ejection fraction, and the potential for myocardial salvage (106).

Complementary Noninvasive Approaches

Noninvasive tests (stress echocardiography, PET, perfusion CCTA, and CMR) allow diagnosing ANOCA/INOCA by measuring the CFR. However, despite their excelled negative predictive value, CAD needs to be ruled out before diagnosis of CMD can be made. Only hybrid techniques (i.e., perfusion CCTA and PET-CT) allow a simultaneous visualization of epicardial arteries in a single test. Nevertheless, noninvasive modalities may lack of spatial resolution or direct measurement of microvascular resistance, vasoreactivity tests cannot be performed and perfusion images may be influenced by hemodynamic variables. Thus, guidelines emphasize the role on noninvasive imaging for initial screening and follow-up but in case of persistent symptoms, unclear mechanisms or highly suspicious of coronary microvascular dysfunction, invasive function test should be prompted.

Comparative Insights of Invasive Approaches

There is currently a wide range of invasive tools and metrics that could be used to practically assess coronary

Table 1. *Overview of invasive and noninvasive methods for coronary microvascular assessment*

Method	Metrics	Normal/Abnormal Cut-off	Advantages	Limitations
Bolus thermodilution	$IMR = P_d \times T_{mn}$ $CFR = T_{mn,rest}/T_{mn,hyp}$ $RRR = T_{mn,rest} \cdot P_{d,rest}/T_{mn,hyp} \cdot P_{d,hyp}$	$IMR < 25$ $IMR > 25$ (CCS); $IMR > 40$ (ACS) $CFR > 2.0–2.5$ $RRR > 3.5$	Fast User Friendly	Variability Operator dependent
Continuous thermodilution	$Q = 1.08 \cdot T_i/T$ $R\mu = Q/P_d$ $CFR = Q_{hyp}/Q_{rest}$ $MRR = CFR/FFR \cdot P_{a,rest}/P_{a,hyp}$	$R_{\mu\text{-}hyp} < 500$ WU $CFR > 2$ $MRR > 2.5–3$	Accurate Reproducible	Additional cost related to the microcatheter
Doppler flow velocity	$CFVR = APV_{hyp}/APV_{rest}$ $HMR = P_{dhyp}/APV_{hyp}$	$CFVR > 2.5$ $HMR < 2.5$	Real time analysis (temporal resolution)	Technically challenging Low quality of traces
Coronary angiography	TFC = number of cine frames needed for contrast to reach a distal landmark MBG = contrast appearance and clearance in the myocardium.	TFC < 21 frames (LAD corrected) (normal flow) MBG = Grade 2–3 = adequate perfusion (Grade 0–1 = abnormal)	No additional tools	Low accuracy Semiquantitative
Angio-based software	$IMR_{angio} = P_{a,hyp} \times QFR \times$ Nframes/fps	$IMR_{angio} < 25$ (proposed cut-off, under validation) $CFR_{angio} > 2.0$	No pressure wire or hyperemia fast, Retrospective	Depends on angiographic quality Less validated requires postprocessing software

This table compares commonly used techniques and metrics to evaluate coronary microvascular function. APV, average peak velocity; CFR, coronary flow reserve; CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; fps, frames per second; HMR, hyperemic microvascular resistance; IMR, index of microcirculatory resistance; MBG, myocardial blush grade; MRR, microvascular resistance reserve; Nframes, number of cine frames; P_a, aortic pressure; P_d, distal coronary pressure; Q, absolute coronary flow; R_μ, absolute microvascular resistance; RRR, resistive reserve ratio; T_{mn}, mean transit time; TFC, TIMI frame count.

microvascular function (Table 1). In contemporary practice, these techniques are not always equivalent, and these methodologies should be regarded as complementary components of a diagnostic toolkit (Graphical Abstract).

Among invasive techniques, intracoronary Doppler offers direct flow assessment but is technically demanding; thermodilution methods are more pragmatic for routine use whereas continuous thermodilution offers accurate and reproducible flow quantification but is resource-intensive. Angiography-derived indices obviate wires and pharmacological hyperemia but the precision of these methodologies may be impacted by various hemodynamic assumptions (such as boundary conditions), thereby necessitating further rigorous clinical validation, particularly in the context of chronic coronary syndromes (107).

CFR remains the cornerstone metric in the diagnostic assessment of CMD with a traditional cut-off of 2 (4). However, recent data show only a modest correlation between CFR_{bolus} and CFVR, the latter showing a significantly higher correlation with PET-derived CFR than CFR_{bolus}; overall, bolus thermodilution tends to overestimate CFR compared with both Doppler and continuous thermodilution-derived CFR (42) and an optimal CFR_{bolus} threshold of 2.5 has been suggested with a sensitivity of 75% and a specificity of 81% compared with CFVR (108).

Unlike CFR—that is influenced by the presence of epicardial disease, by resting flow, and driving blood pressure (109) MRR is truly specific for the microcirculation and independent by epicardial disease. Although the optimal threshold is still debated, a value below 2.3 is suggestive of CMD, whereas a value above 2.7 virtually excludes it (110). A recent study has shown a diagnostic advantage of MRR over other indices of vasodilatory capacity in patients with hemodynamically significant epicardial CAD (111). Yet, bolus thermodilution also overestimates MRR compared with continuous thermodilution, with a mean difference of 1.2, and a weak correlation was found between the two techniques (56).

CONCLUSIONS

CMD is highly prevalent and poses significant clinical challenges in everyday medical practice. Both functional and structural anomalies in the microcirculation can cause ischemia even in the absence of epicardial stenosis or can aggravate existing CAD across its spectrum, including CCS and ACS, such as STEMI. Evidence suggests that the information derived from this thorough evaluation is essential for making informed clinical decisions, ultimately aiming to improve patient symptoms and long-term outcomes. Future research should focus on clinical trials that utilize these diagnostic approaches to explore new therapies and determine the best treatment options for each endotype, as well as their effects on long-term cardiovascular outcomes.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.S., M.B., V.S., P.P., A.F., L.B., S.A., A.V., and E.G. prepared figures; R.S., V.S., P.P., L.B., S.A., A.D.V., A.V., and E.G. drafted manuscript; A.P., R.S., A.F., L.B., S.A., A.D.V., A.V., F.A., M.A., S.T., D.M., G.A.L., A.C., L.D.S., E.B., C.P., and E.G. edited and revised manuscript; A.P., R.S., A.D.V., A.V., F.A., M.A., S.T., D.M., G.A.L., A.C., G.E., C.I., L.D.S., G.C., F.R., E.B., C.P., and E.G. approved final version of manuscript.

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