AMERICAN JOURNAL OF PHYSIOLOGY
HEART AND CIRCULATORY PHYSIOLOGY

Am J Physiol Heart Circ Physiol 330: H453–H467, 2026.
First published December 23, 2025; doi:10.1152/ajpheart.00555.2025

REVIEW

Translational Physiology

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

Alberto Polimeni,[1,2] Roberto Scarsini,[3] Marta Belmonte,[4,5] Vincenzo Sucato,[6,7] Pasquale Paolisso,[5] Alberto Foà,[8,9] Luca Bergamaschi,[9,10] Sara Amicone,[9,10] Antonio De Vita,[11] Angelo Villano,[11] Francesco Angeli,[9,10] Matteo Armillotta,[9,10] Saverio Tremamunno,[11] Doralisa Morrone,[12] Gaetano Antonio Lanza,[11] Alaide Chieffo,[13] Giovanni Esposito,[4] Ciro Indolfi,[14] Luigi Di Serafino,[4] Gianluca Campo,[15] Flavio Ribichini,[3] Emanuele Barbato,[4,16] Carmine Pizzi,[9,10]* and Emanuele Gallinoro[5]*; on behalf of the Coronary Physiopathology and Microcirculation Working Group of the Italian Society of Cardiology

[1]*Department of Pharmacy, Health and Nutritional Sciences, University of Calabria, Rende, Italy;* [2]*Division of Interventional Cardiology, Annunziata Hospital, Cosenza, Italy;* [3]*Division of Cardiology, Department of Medicine, University of Verona, Verona, Italy;* [4]*Division of Cardiology, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy;* [5]*Cardiology Unit, Sant'Andrea University Hospital, Rome, Italy;* [6]*Division of Cardiology, University Hospital Paolo Giaccone, Palermo, Italy;* [7]*Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (ProMISE) "G. D'Alessandro", University of Palermo, Palermo, Italy;* [8]*Cardiology Unit, Cardiac Thoracic and Vascular Department, IRCCS Azienda Ospedaliera-Universitaria di Bologna, Bologna, Italy;* [9]*Department of Medical and Surgical Sciences—DIMEC, Alma Mater Studiorum, University of Bologna, Bologna, Italy;* [10]*Cardiovascular Division, Morgagni-Pierantoni University Hospital, Forlì, Italy;* [11]*Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy;* [12]*Medical and Molecular Pathology and Critical Care Medicine-Cardiology Division, Department of Surgical, University Hospital of Pisa, Pisa, Italy;* [13]*Interventional Cardiology Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy;* [14]*Division of Cardiology, Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy;* [15]*Cardiology Unit, Azienda Ospedaliero Universitaria di Ferrara, Cona, Italy; and* [16]*Department of Clinical and Molecular Medicine, Sapienza University of Rome, Italy*

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

*C. Pizzi and E. Gallinoro contributed equally to this work.
Correspondence: C. Pizzi (carmine.pizzi@unibo.it).
Submitted 29 July 2025 / Revised 18 August 2025 / Accepted 16 December 2025

0363-6135/26 Copyright © 2026 The Authors. Licensed under Creative Commons Attribution CC-BY-NC-ND 4.0.
Published by the American Physiological Society.

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

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

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

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).

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

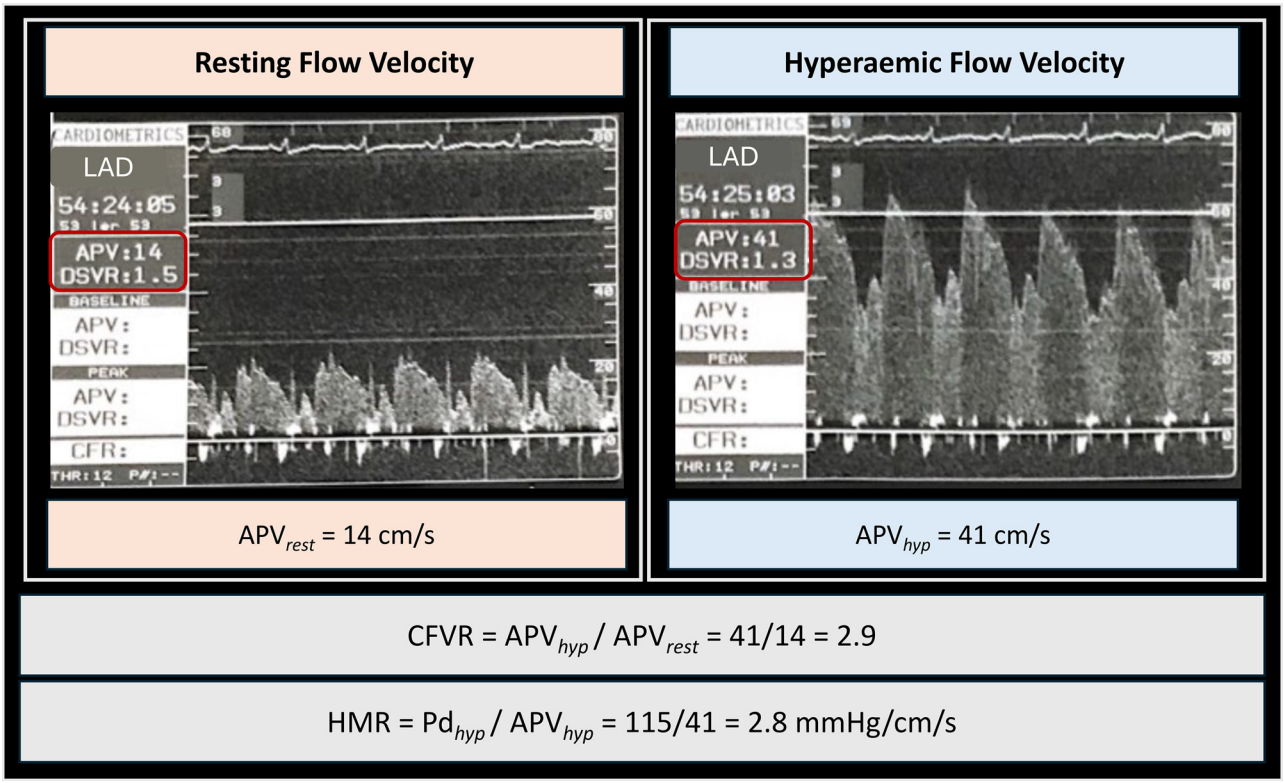

Figure 1. Intracoronary flow velocity measurement. Intracoronary flow velocity measurement: case example in the left anterior descending artery. A Doppler wire is placed in the coronary artery to be evaluated and connected to a dedicated console. Resting average peak velocity value in cm/s is displayed 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

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

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

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

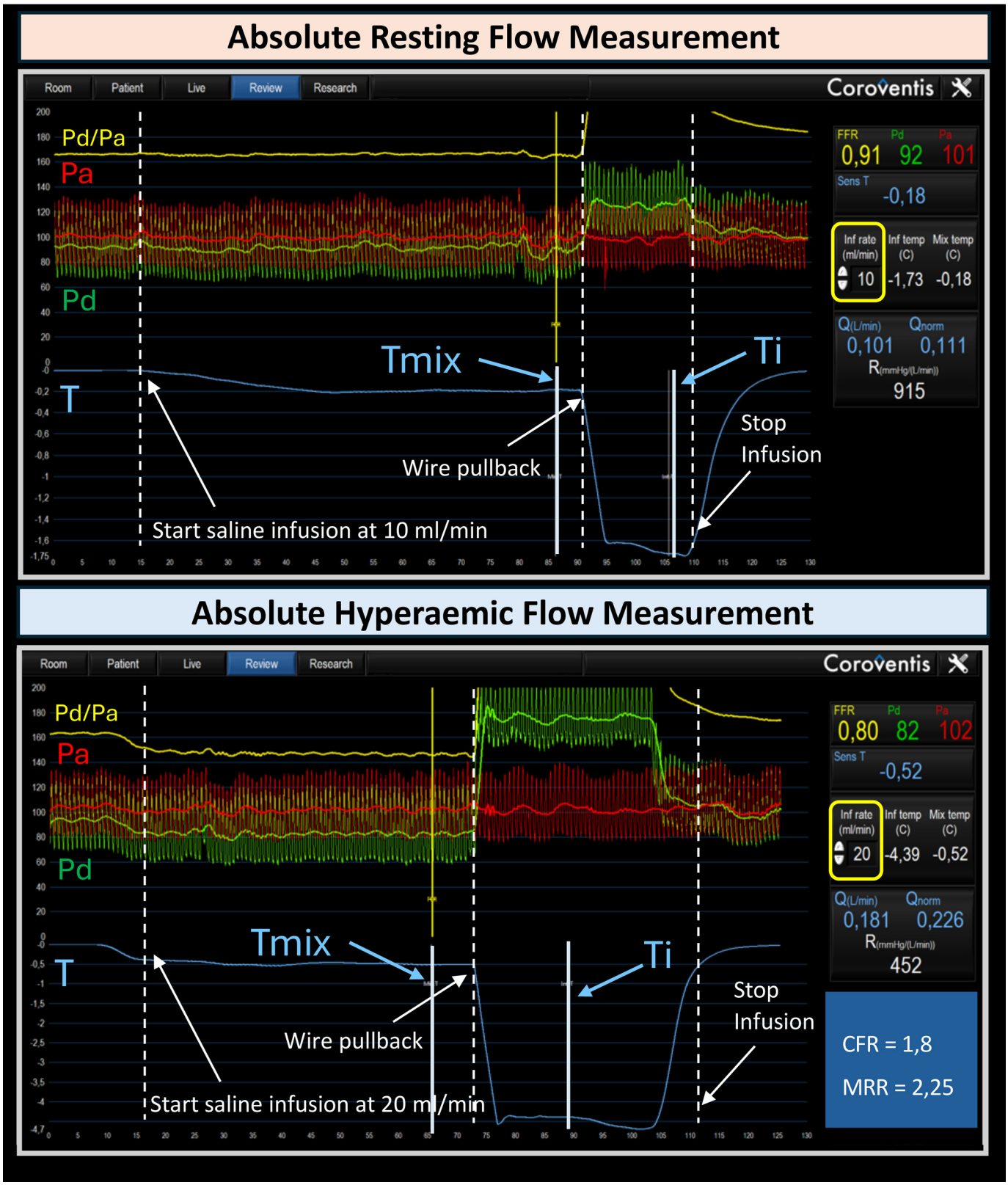

Figure 3. Absolute coronary flow measurement. Continuous thermodilution measurement of absolute coronary flow and resistance. Resting flow measurement (*top*) is performed in the left anterior descending artery (LAD) by using an infusion rate of 10 mL/min). By using an infusion rate of 20 mL/min (*bottom*), 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.

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

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,

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

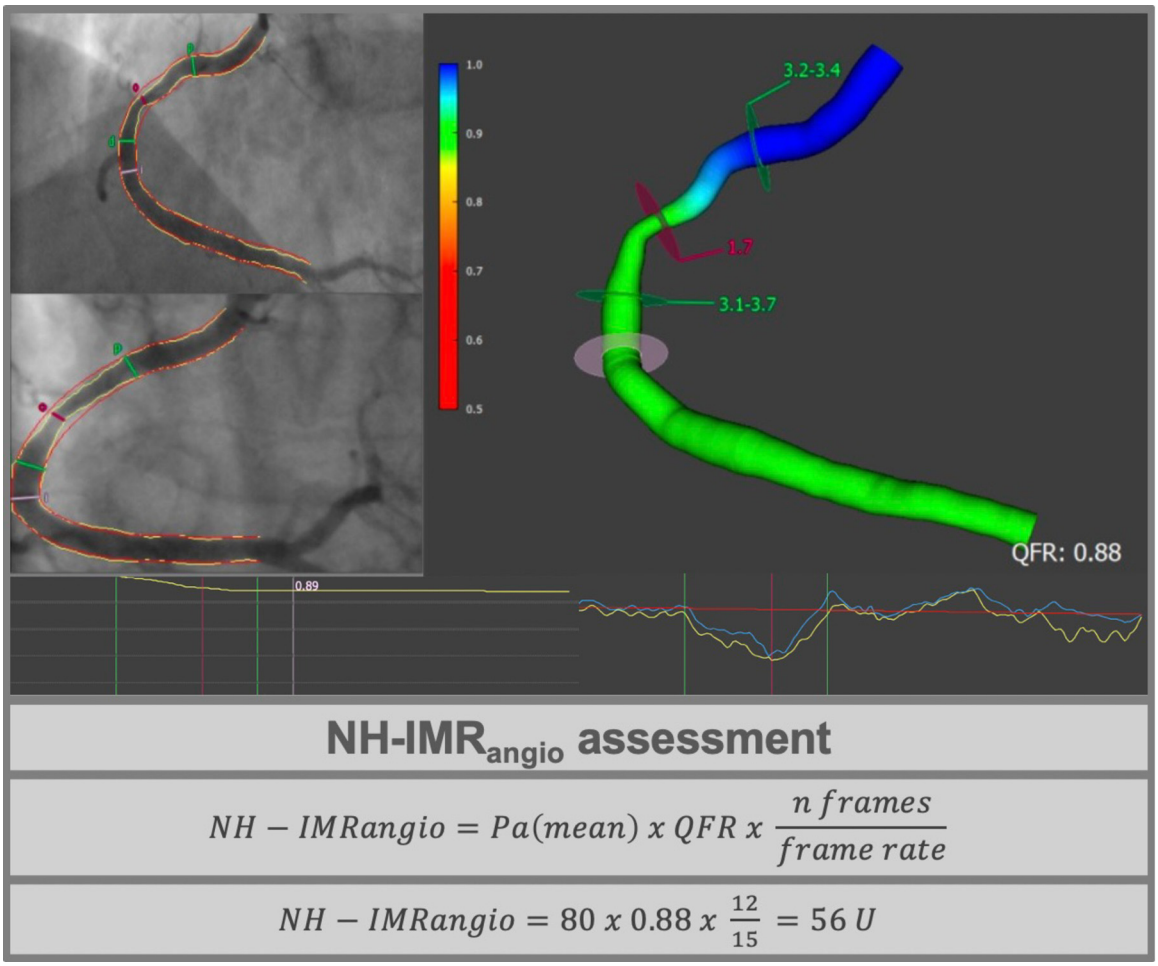

Figure 4. A clinical example of nonhyperemic angiography derived index of microcirculatory resistance (IMR) calculation. Nonhyperemic IMR$_{angio}$ was calculated based on mean aortic pressure and quantitative flow ratio (QFR) at completion of primary percutaneous coronary intervention (PCI) in a patient 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,

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

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.

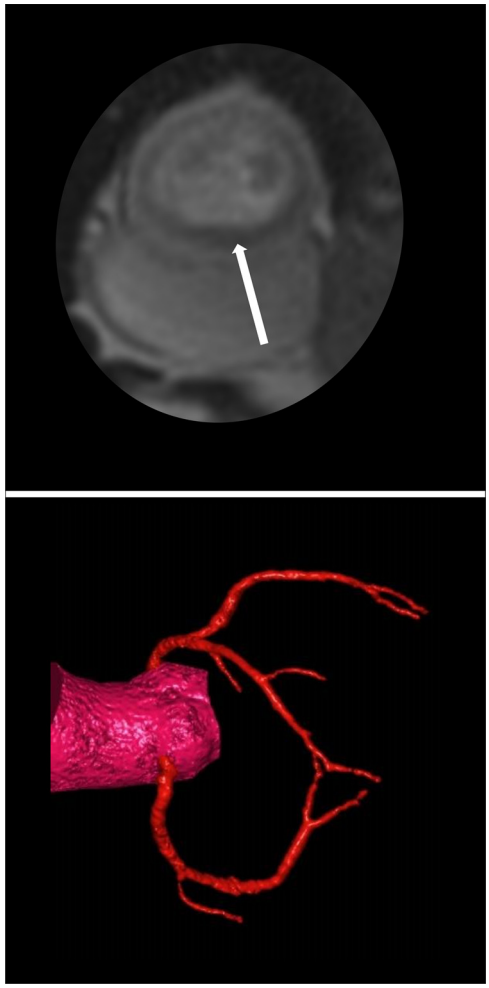

Figure 5. Noninvasive assessment of possible coronary microvascular dysfunction (CMD). *Top*: absence of obstructive coronary artery disease in a patient with angina symptoms. *Bottom*: a perfusion defect during stress cardiac magnetic resonance (CMR) (arrow).

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

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

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.

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

REFERENCES

1. **Kemp HG Jr.** Left ventricular function in patients with the anginal syndrome and normal coronary arteriograms. *Am J Cardiol* 32: 375–376, 1973. doi:10.1016/s0002-9149(73)80150-x.
2. **Cannon RO 3rd**, **Epstein SE.** "Microvascular angina" as a cause of chest pain with angiographically normal coronary arteries. *Am J Cardiol* 61: 1338–1343, 1988. doi:10.1016/0002-9149(88)91180-0.
3. **Crea F**, **Camici PG**, **Bairey Merz CN.** Coronary microvascular dysfunction: an update. *Eur Heart J* 35: 1101–1111, 2014. doi:10.1093/eurheartj/eht513.
4. **Kunadian V**, **Chieffo A**, **Camici PG**, **Berry C**, **Escaned J**, **Maas AHEM**, **Prescott E**, **Karam N**, **Appelman Y**, **Fraccaro C**, **Buchanan GL**, **Manzo-Silberman S**, **Al-Lamee R**, **Regar E**, **Lansky A**, **Abbott JD**, **Badimon L**, **Duncker DJ**, **Mehran R**, **Capodanno D**, **Baumbach A.** An EAPCI Expert Consensus Document on ischaemia with non-obstructive coronary arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *EuroIntervention* 16: 1049–1069, 2021. doi:10.4244/EIJY20M07_01.
5. **Belmonte M**, **Foà A**, **Paolisso P**, **Bergamaschi L**, **Gallinoro E**, **Polimeni A**, **Scarsini R**, **Muscoli S**, **Amicone S**, **De Vita A**, **Villano A**, **Angeli F**, **Armillotta M**, **Sucato V**, **Tremamunno S**, **Morrone D**, **Indolfi C**, **Filardi PP**, **Ribichini F**, **Lanza GA**, **Chieffo A**, **Barbato E**, **Pizzi C**; **Coronary Physiopathology and Microcirculation Working Group of the Italian Society of Cardiology (SIC).** Coronary microvascular dysfunction beyond the spectrum of chronic coronary syndromes. *Prog Cardiovasc Dis* 87: 73–82, 2024. doi:10.1016/j.pcad.2024.10.006.
6. **Padro T**, **Manfrini O**, **Bugiardini R**, **Canty J**, **Cenko E**, **De Luca G**, **Duncker DJ**, **Eringa EC**, **Koller A**, **Tousoulis D**, **Trifunovic D**, **Vavlukis M**, **de Wit C**, **Badimon L.** ESC Working Group on Coronary Pathophysiology and Microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease'. *Cardiovasc Res* 116: 741–755, 2020. doi:10.1093/cvr/cvaa003.
7. **Paolisso P**, **Gallinoro E**, **Belmonte M**, **Bertolone DT**, **Bermpeis K**, **De Colle C**, **Shumkova M**, **Leone A**, **Caglioni S**, **Esposito G**, **Fabbricatore D**, **Moya A**, **Delrue L**, **Penicka M**, **De Bruyne B**, **Barbato E**, **Bartunek J**, **Vanderheyden M.** Coronary microvascular dysfunction in patients with heart failure: characterization of patterns in HFrEF Versus HFpEF. *Circ Heart Fail* 17: e010805, 2024. doi:10.1161/CIRCHEARTFAILURE.123.010805.
8. **Paolisso P**, **Gallinoro E**, **Vanderheyden M**, **Esposito G**, **Bertolone DT**, **Belmonte M**, **Mileva N**, **Bermpeis K**, **De Colle C**, **Fabbricatore D**, **Candreva A**, **Munhoz D**, **Degrieck I**, **Casselman F**, **Penicka M**, **Collet C**, **Sonck J**, **Mangiacapra F**, **de Bruyne B**, **Barbato E.** Absolute coronary flow and microvascular resistance reserve in patients with severe aortic stenosis. *Heart* 109: 47–54, 2022. doi:10.1136/heartjnl-2022-321348.
9. **Scarsini R**, **Gallinoro E**, **Ancona MB**, **Portolan L**, **Paolisso P**, **Springhetti P**, **Della Mora F**, **Mainardi A**, **Belmonte M**, **Moroni F**, **Ferri LA**, **Bellini B**, **Russo F**, **Vella C**, **Bertolone DT**, **Pesarini G**, **Benfari G**, **Vanderheyden M**, **Montorfano M**, **De Bruyne B**, **Barbato E**, **Ribichini F.** Characterisation of coronary microvascular dysfunction in patients with severe aortic stenosis undergoing TAVI. *EuroIntervention* 20: e289–e300, 2024. doi:10.4244/EIJ-D-23-00735.
10. **Gallinoro E**, **Paolisso P**, **Bertolone DT**, **Esposito G**, **Belmonte M**, **Leone A**, **Viscusi MM**, **Shumkova M**, **De Colle C**, **Degrieck I**, **Casselman F**, **Penicka M**, **Collet C**, **Sonck J**, **Wyffels E**, **Bartunek J**, **De Bruyne B**, **Vanderheyden M**, **Barbato E.** Absolute coronary flow and microvascular resistance before and after transcatheter aortic valve implantation. *EuroIntervention* 20: e1248–e1528, 2024. doi:10.4244/EIJ-D-24-00075.
11. **Gallinoro E**, **Paolisso P**, **Candreva A**, **Bermpeis K**, **Fabbricatore D**, **Esposito G**, **Bertolone D**, **Fernandez Peregrina E**, **Munhoz D**, **Mileva N**, **Penicka M**, **Bartunek J**, **Vanderheyden M**, **Wyffels E**, **Sonck J**, **Collet C**, **De Bruyne B**, **Barbato E.** Microvascular dysfunction in patients with type II diabetes mellitus: invasive assessment of absolute coronary blood flow and microvascular resistance reserve. *Front Cardiovasc Med* 8: 765071, 2021. doi:10.3389/fcvm.2021.765071.
12. **Schelbert HR.** Anatomy and physiology of coronary blood flow. *J Nucl Cardiol* 17: 545–554, 2010. doi:10.1007/s12350-010-9255-x.
13. **Feher A**, **Sinusas AJ.** Quantitative assessment of coronary microvascular function: dynamic single-photon emission computed tomography, positron emission tomography, ultrasound, computed tomography, and magnetic resonance imaging. *Circ Cardiovasc Imaging* 10: e006427, 2017. doi:10.1161/CIRCIMAGING.117.006427.
14. **Pries AR**, **Badimon L**, **Bugiardini R**, **Camici PG**, **Dorobantu M**, **Duncker DJ**, **Escaned J**, **Koller A**, **Piek JJ**, **de Wit C.** Coronary vascular regulation, remodelling, and collateralization: mechanisms and clinical implications on behalf of the working group on coronary pathophysiology and microcirculation. *Eur Heart J* 36: 3134–3146, 2015. doi:10.1093/eurheartj/ehv100.
15. **Johnson NP**, **Gould KL**, **De Bruyne B.** Autoregulation of coronary blood supply in response to demand: JACC review topic of the week. *J Am Coll Cardiol* 77: 2335–2345, 2021. doi:10.1016/j.jacc.2021.03.293.
16. **Mohammed SF**, **Hussain S**, **Mirzoyev SA**, **Edwards WD**, **Maleszewski JJ**, **Redfield MM.** Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. *Circulation* 131: 550–559, 2015. doi:10.1161/CIRCULATIONAHA.114.009625.
17. **de Waha S**, **Patel MR**, **Granger CB**, **Ohman EM**, **Maehara A**, **Eitel I**, **Ben-Yehuda O**, **Jenkins P**, **Thiele H**, **Stone GW.** Relationship between microvascular obstruction and adverse events following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: an individual patient data pooled analysis from seven randomized trials. *Eur Heart J* 38: 3502–3510, 2017. doi:10.1093/eurheartj/ehx414.
18. **Bergamaschi L**, **De Vita A**, **Villano A**, **Tremamunno S**, **Armillotta M**, **Angeli F**, **Belmonte M**, **Paolisso P**, **Foà A**, **Gallinoro E**, **Polimeni A**, **Sucato V**, **Morrone D**, **Tuttolomondo D**, **Pavon AG**, **Guglielmo M**, **Gaibazzi N**, **Mushtaq S**, **Perrone Filardi P**, **Indolfi C**, **Picano E**, **Pontone G**, **Lanza GA**, **Pizzi C**; **Coronary Physiopathology and Microcirculation Working Group of the Italian Society of Cardiology (SIC).** Non-invasive imaging assessment in angina with non-obstructive coronary arteries (ANOCA). *Curr Probl Cardiol* 50: 103021, 2025. doi:10.1016/j.cpcardiol.2025.103021.
19. **Lanza GA**, **Morrone D**, **Pizzi C**, **Tritto I**, **Bergamaschi L**, **De Vita A**, **Villano A**, **Crea F.** Diagnostic approach for coronary microvascular dysfunction in patients with chest pain and no obstructive coronary artery disease. *Trends Cardiovasc Med* 32: 448–453, 2022. doi:10.1016/j.tcm.2021.08.005.
20. **Ong P**, **Camici PG**, **Beltrame JF**, **Crea F**, **Shimokawa H**, **Sechtem U**, **Kaski JC**, **Bairey Merz CN**; **Coronary Vasomotion Disorders International Study Group (COVADIS).** International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 250: 16–20, 2018. doi:10.1016/j.ijcard.2017.08.068.
21. **Gibson CM**, **Cannon CP**, **Daley WL**, **Dodge JT Jr**, **Alexander B Jr**, **Marble SJ**, **McCabe CH**, **Raymond L**, **Fortin T**, **Poole WK**, **Braunwald E.** TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation* 93: 879–888, 1996. doi:10.1161/01.cir.93.5.879.
22. **Gibson CM**, **Cannon CP**, **Murphy SA**, **Marble SJ**, **Barron HV**, **Braunwald E**; **TIMI Study Group.** Relationship of the TIMI myocardial perfusion grades, flow grades, frame count, and percutaneous coronary intervention to long-term outcomes after thrombolytic administration in acute myocardial infarction. *Circulation* 105: 1909–1913, 2002. doi:10.1161/01.cir.0000014683.52177.b5.
23. **Gibson CM**, **Cannon CP**, **Murphy SA**, **Ryan KA**, **Mesley R**, **Marble SJ**, **McCabe CH**, **Van De Werf F**, **Braunwald E.** Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 101: 125–130, 2000. doi:10.1161/01.cir.101.2.125.
24. **van 't Hof AW**, **Liem A**, **Suryapranata H**, **Hoorntje JC**, **de Boer MJ**, **Zijlstra F**; **on behalf of the Zwolle Myocardial Infarction Study Group.** Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Circulation* 97: 2302–2306, 1998. doi:10.1161/01.cir.97.23.2302.
25. **Atmaca Y**, **Duzen V**, **Ozdol C**, **Altin T**, **Tulunay C**, **Ertas F**, **Erol C.** Total blush score: a new index for the assessment of microvascular perfusion in idiopathic dilated cardiomyopathy. *Coron Artery Dis* 19: 181–185, 2008. doi:10.1097/MCA.0b013e3282f35901.
26. **Dutta U**, **Sinha A**, **Demir OM**, **Ellis H**, **Rahman H**, **Perera D.** Coronary slow flow is not diagnostic of microvascular dysfunction in

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

patients with angina and unobstructed coronary arteries. *J Am Heart Assoc* 12: e027664, 2023. doi:10.1161/JAHA.122.027664.

27. **Mayer M**, **Allan T**, **Harkin KL**, **Loftspring E**, **Saffari SE**, **Reynolds HR**, **Paul J**, **Kalathiya R**, **Shah AP**, **Nathan S**, **McCarthy MC**, **Smilowitz NR**, **Miner SES**, **Blair J.** Angiographic coronary slow flow is not a valid surrogate for invasively diagnosed coronary microvascular dysfunction. *JACC Cardiovasc Interv* 17: 920–929, 2024. doi:10.1016/j.jcin.2024.02.025.
28. **Gallinoro E**, **Paolisso P**, **Bermpeis K**, **Tino Bertolone D**, **Esposito G**, **De Bruyne B.** When "slow flow" is not "low flow". *JACC Cardiovasc Interv* 15: e119–e121, 2022. doi:10.1016/j.jcin.2022.02.015.
29. **Benchimol A**, **Stegall HF**, **Gartlan JL.** New method to measure phasic coronary blood velocity in man. *Am Heart J* 81: 93–101, 1971. doi:10.1016/0002-8703(71)90058-5.
30. **Cole JS**, **Hartley CJ.** The pulsed Doppler coronary artery catheter preliminary report of a new technique for measuring rapid changes in coronary artery flow velocity in man. *Circulation* 56: 18–25, 1977. doi:10.1161/01.cir.56.1.18.
31. **Hartley CJ**, **Cole JS.** An ultrasonic pulsed Doppler system for measuring blood flow in small vessels. *J Appl Physiol* 37: 626–629, 1974. doi:10.1152/jappl.1974.37.4.626.
32. **Doucette JW**, **Corl PD**, **Payne HM**, **Flynn AE**, **Goto M**, **Nassi M**, **Segal J.** Validation of a Doppler guide wire for intravascular measurement of coronary artery flow velocity. *Circulation* 85: 1899–1911, 1992. doi:10.1161/01.cir.85.5.1899.
33. **Kodeboina M**, **Nagumo S**, **Munhoz D**, **Sonck J**, **Mileva N**, **Gallinoro E**, **Candreva A**, **Mizukami T**, **Van Durme F**, **Heyse A**, **Wyffels E**, **Vanderheyden M**, **Barbato E**, **Bartunek J**, **De Bruyne B**, **Collet C.** Simplified assessment of the index of microvascular resistance. *J Interv Cardiol* 2021: 9971874, 2021. doi:10.1155/2021/9971874.
34. **Mizukami T**, **Sonck J**, **Gallinoro E**, **Kodeboina M**, **Canvedra A**, **Nagumo S**, **Bartunek J**, **Wyffels E**, **Vanderheyden M**, **Shinke T**, **Bruyne BD**, **Collet C.** Duration of hyperemia with intracoronary administration of papaverine. *J Am Heart Assoc* 10: e018562, 2021. doi:10.1161/JAHA.120.018562.
35. **Sara JD**, **Widmer RJ**, **Matsuzawa Y**, **Lennon RJ**, **Lerman LO**, **Lerman A.** Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv* 8: 1445–1453, 2015. doi:10.1016/j.jcin.2015.06.017.
36. **AlBadri A**, **Bairey Merz CN**, **Johnson BD**, **Wei J**, **Mehta PK**, **Cook-Wiens G**, **Reis SE**, **Kelsey SF**, **Bittner V**, **Sopko G**, **Shaw LJ**, **Pepine CJ**, **Ahmed B.** Impact of abnormal coronary reactivity on long-term clinical outcomes in women. *J Am Coll Cardiol* 73: 684–693, 2019. doi:10.1016/j.jacc.2018.11.040.
37. **Rahman H**, **Demir OM**, **Khan F**, **Ryan M**, **Ellis H**, **Mills MT**, **Chiribiri A**, **Webb A**, **Perera D.** Physiological stratification of patients with angina due to coronary microvascular dysfunction. *J Am Coll Cardiol* 75: 2538–2549, 2020. doi:10.1016/j.jacc.2020.03.051.
38. **Kelshiker MA**, **Seligman H**, **Howard JP**, **Rahman H**, **Foley M**, **Nowbar AN**, **Rajkumar CA**, **Shun-Shin MJ**, **Ahmad Y**, **Sen S**, **Al-Lamee R**, **Petraco R**; **Coronary Flow Outcomes Reviewing Committee.** Coronary flow reserve and cardiovascular outcomes: a systematic review and meta-analysis. *Eur Heart J* 43: 1582–1593, 2022 [Erratum in *Eur Heart J* 44: 27, 2023]. doi:10.1093/eurheartj/ehab775.
39. **Chamuleau SA**, **Siebes M**, **Meuwissen M**, **Koch KT**, **Spaan JA**, **Piek JJ.** Association between coronary lesion severity and distal microvascular resistance in patients with coronary artery disease. *Am J Physiol Heart Circ Physiol* 285: H2194–H2200, 2003. doi:10.1152/ajpheart.01021.2002.
40. **Feenstra RGT**, **Seitz A**, **Boerhout CKM**, **de Winter RJ**, **Ong P**, **Beijk MAM**, **Piek JJ**, **Sechtem U**, **van de Hoef TP.** Reference values for intracoronary Doppler flow velocity-derived hyperaemic microvascular resistance index. *Int J Cardiol* 371: 16–20, 2023. doi:10.1016/j.ijcard.2022.09.054.
41. **de Waard GA**, **Nijjer SS**, **van Lavieren MA**, **van der Hoeven NW**, **Petraco R**, **van de Hoef TP**, **Echavarría-Pinto M**, **Sen S**, **van de Ven PM**, **Knaapen P**, **Escaned J**, **Piek JJ**, **Davies JE**, **van Royen N.** Invasive minimal microvascular resistance is a new index to assess microcirculatory function independent of obstructive coronary artery disease. *J Am Heart Assoc* 5: e004482, 2016. doi:10.1161/JAHA.116.004482.
42. **Everaars H**, **de Waard GA**, **Driessen RS**, **Danad I**, **van de Ven PM**, **Raijmakers PG**, **Lammertsma AA**, **van Rossum AC**, **Knaapen P**, **van Royen N.** Doppler flow velocity and thermodilution to assess coronary flow reserve: a head-to-head comparison with [^{15}O]H_2O PET. *JACC Cardiovasc Interv* 11: 2044–2054, 2018. doi:10.1016/j.jcin.2018.07.011.
43. **Barbato E**, **Aarnoudse W**, **Aengevaeren WR**, **Werner G**, **Klauss V**, **Bojara W**, **Herzfeld I**, **Oldroyd KG**, **Pijls NHJ**, **De Bruyne B**; **Week 25 study group.** Validation of coronary flow reserve measurements by thermodilution in clinical practice. *Eur Heart J* 25: 219–223, 2004. doi:10.1016/j.ehj.2003.11.009.
44. **Candreva A**, **Gallinoro E**, **van 't Veer M**, **Sonck J**, **Collet C**, **Di Gioia G**, **Kodeboina M**, **Mizukami T**, **Nagumo S**, **Keulards D**, **Fournier S**, **Pijls NHJ**, **De Bruyne B.** Basics of coronary thermodilution. *JACC Cardiovasc Interv* 14: 595–605, 2021. doi:10.1016/j.jcin.2020.12.037.
45. **Samuels BA**, **Shah SM**, **Widmer RJ**, **Kobayashi Y**, **Miner SES**, **Taqueti VR**, **Jeremias A**, **Albadri A**, **Blair JA**, **Kearney KE**, **Wei J**, **Park K**, **Barseghian El-Farra A**, **Holoshitz N**, **Janaszek KB**, **Kesarwani M**, **Lerman A**, **Prasad M**, **Quesada O**, **Reynolds HR**, **Savage MP**, **Smilowitz NR**, **Sutton NR**, **Sweeny JM**, **Toleva O**, **Henry TD**, **Moses JW**, **Fearon WF**, **Tremmel JA**; **Microvascular Network (MVN).** Comprehensive management of ANOCA, part 1—definition, patient population, and diagnosis: JACC state-of-the-art review. *J Am Coll Cardiol* 82: 1245–1263, 2023. doi:10.1016/j.jacc.2023.06.043.
46. **Belmonte M**, **Gallinoro E**, **Pijls NHJ**, **Bertolone DT**, **Keulards DCJ**, **Viscusi MM**, **Storozhenko T**, **Mizukami T**, **Mahendiran T**, **Seki R**, **Fournier S**, **de Vos A**, **Adjedj J**, **Barbato E**, **Sonck J**, **Damman P**, **Keeble T**, **Fawaz S**, **Gutiérrez-Barrios A**, **Paradies V**, **Bouisset F**, **Kern MJ**, **Fearon WF**, **Collet C**, **De Bruyne B.** Measuring absolute coronary flow and microvascular resistance by thermodilution: JACC review topic of the week. *J Am Coll Cardiol* 83: 699–709, 2024. doi:10.1016/j.jacc.2023.12.014.
47. **Fearon WF**, **Balsam LB**, **Farouque HMO**, **Caffarelli AD**, **Robbins RC**, **Fitzgerald PJ**, **Yock PG**, **Yeung AC.** Novel index for invasively assessing the coronary microcirculation. *Circulation* 107: 3129–3132, 2003 [Erratum in *Circulation* 108: 3165, 2003]. doi:10.1161/01.CIR.0000080700.98607.D1.
48. **Fearon WF**, **Kobayashi Y.** Invasive assessment of the coronary microvasculature: the index of microcirculatory resistance. *Circ Cardiovasc Interv* 10: e005361, 2017. doi:10.1161/CIRCINTERVENTIONS.117.005361.
49. **Collet C**, **Yong A**, **Munhoz D**, **Akasaka T**, **Berry C**, **Blair JEA**, **Collison D**, **Engstrøm T**, **Escaned J**, **Fearon WF**, **Ford T**, **Gori T**, **Koo BK**, **Low AF**, **Miner S**, **Ng MKC**, **Mizukami T**, **Shimokawa H**, **Smilowitz NR**, **Sutton NR**, **Svanerud J**, **Tremmel JA**, **Warisawa T**, **West NEJ**, **Za A.** A systematic approach to the evaluation of the coronary microcirculation using bolus thermodilution: CATH CMD. *J Soc Cardiovasc Angiogr Interv* 3: 101934, 2024. doi:10.1016/j.jscai.2024.101934.
50. **Lee JM**, **Hwang D**, **Choi KH**, **Rhee TM**, **Park J**, **Kim HY**, **Jung HW**, **Hwang JW**, **Lee HJ**, **Jang HJ**, **Kim SH**, **Song YB**, **Cho YK**, **Nam CW**, **Hahn JY**, **Shin ES**, **Kawase Y**, **Matsuo A**, **Tanaka N**, **Doh JH**, **Koo BK**, **Matsuo H.** Prognostic implications of relative increase and final fractional flow reserve in patients with stent implantation. *JACC Cardiovasc Interv* 11: 2099–2109, 2018. doi:10.1016/j.jcin.2018.07.031.
51. **Ganz W**, **Tamura K**, **Marcus HS**, **Donoso R**, **Yoshida S**, **Swan HJ.** Measurement of coronary sinus blood flow by continuous thermodilution in man. *Circulation* 44: 181–195, 1971. doi:10.1161/01.cir.44.2.181.
52. **Aarnoudse W**, **Van't Veer M**, **Pijls NHJ**, **Ter Woorst J**, **Vercauteren S**, **Tonino P**, **Geven M**, **Rutten M**, **van Hagen E**, **de Bruyne B**, **van de Vosse F.** Direct volumetric blood flow measurement in coronary arteries by thermodilution. *J Am Coll Cardiol* 50: 2294–2304, 2007. doi:10.1016/j.jacc.2007.08.047.
53. **Gallinoro E**, **Candreva A**, **Fernandez-Peregrina E**, **Bailleul E**, **Meeus P**, **Sonck J**, **Bermpeis K**, **Bertolone DT**, **Esposito G**, **Paolisso P**, **Heggermont W**, **Adjedj J**, **Barbato E**, **Collet C**, **De Bruyne B.** Saline-induced coronary hyperemia with continuous intracoronary thermodilution is mediated by intravascular hemolysis. *Atherosclerosis* 352: 46–52, 2022. doi:10.1016/j.atherosclerosis.2022.05.011.
54. **Gallinoro E**, **Candreva A**, **Colaiori I**, **Kodeboina M**, **Fournier S**, **Nelis O**, **Di Gioia G**, **Sonck J**, **van 't Veer M**, **Pijls NHJ**, **Collet C**, **De Bruyne B.** Thermodilution-derived volumetric resting coronary blood flow measurement in humans. *EuroIntervention* 17: e672–e679, 2021. doi:10.4244/EIJ-D-20-01092.

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

55. **Seki R**, **Keulards DCJ**, **Gutiérrez-Barrios A**, **Fawaz S**, **Mahendiran T**, **Bertolone DT**, **Gallinoro E**, **Collet C**, **Keeble TR**, **Pijls NHJ**, **De Bruyne B.** Safety of continuous coronary thermodilution measurements. *JACC Cardiovasc Interv* 16: 2794–2796, 2023. doi:10.1016/j.jcin.2023.09.030.
56. **Gallinoro E**, **Bertolone DT**, **Fernandez-Peregrina E**, **Paolisso P**, **Bermpeis K**, **Esposito G**, **Gomez-Lopez A**, **Candreva A**, **Mileva N**, **Belmonte M**, **Mizukami T**, **Fournier S**, **Vanderheyden M**, **Wyffels E**, **Bartunek J**, **Sonck J**, **Barbato E**, **Collet C**, **De Bruyne B.** Reproducibility of bolus versus continuous thermodilution for assessment of coronary microvascular function in patients with ANOCA. *EuroIntervention* 19: e155–e166, 2023. doi:10.4244/EIJ-D-22-00772.
57. **Gallinoro E**, **Bertolone DT**, **Mizukami T**, **Paolisso P**, **Bermpeis K**, **Munhoz D**, **Sakai K**, **Seki R**, **Ohashi H**, **Esposito G**, **Caglioni S**, **Mileva N**, **Leone A**, **Candreva A**, **Belmonte M**, **Storozhenko T**, **Viscusi MM**, **Vanderheyden M**, **Wyffels E**, **Bartunek J**, **Sonck J**, **Barbato E**, **Collet C**, **De Bruyne B.** Continuous vs bolus thermodilution to assess microvascular resistance reserve. *JACC Cardiovasc Interv* 16: 2767–2777, 2023. doi:10.1016/j.jcin.2023.09.027.
58. **Candreva A**, **Gallinoro E**, **Fernandez Peregrina E**, **Sonck J**, **Keulards DCJ**, **Van't Veer M**, **Mizukami T**, **Pijls NHJ**, **Collet C**, **De Bruyne B.** Automation of intracoronary continuous thermodilution for absolute coronary flow and microvascular resistance measurements. *Catheter Cardiovasc Interv* 100: 199–206, 2022. doi:10.1002/ccd.30244.
59. **Mahendiran T**, **Fawaz S**, **Viscusi M**, **Keulards D**, **Crooijmans C**, **Jansen TPJ**, **Everaars H**, **Gallinoro E**, **Candreva A**, **Bouisset F**, **Mizukami T**, **Bertolone D**, **Belmonte M**, **Seki R**, **Svanerud J**, **Sonck J**, **Wilgenhof A**, **Keeble TR**, **Damman P**, **Knaapen P**, **Collet C**, **Pijls NHJ**, **De Bruyne B.** Simplification of continuous intracoronary thermodilution. *EuroIntervention* 20: e1217–e1226, 2024. doi:10.4244/EIJ-D-24-00215.
60. **Everaars H**, **de Waard GA**, **Schumacher SP**, **Zimmermann FM**, **Bom MJ**, **van de Ven PM**, **Raijmakers PG**, **Lammertsma AA**, **Götte MJ**, **van Rossum AC**, **Kurata A**, **Marques KMJ**, **Pijls NHJ**, **van Royen N**, **Knaapen P.** Continuous thermodilution to assess absolute flow and microvascular resistance: validation in humans using [15O]H2O positron emission tomography. *Eur Heart J* 40: 2350–2359, 2019. doi:10.1093/eurheartj/ehz245.
61. **Fournier S**, **Keulards DCJ**, **van 't Veer M**, **Colaiori I**, **Di Gioia G**, **Zimmermann FM**, **Mizukami T**, **Nagumo S**, **Kodeboina M**, **El Farissi M**, **Zelis JM**, **Sonck J**, **Collet C**, **Pijls NHJ**, **De Bruyne B.** Normal values of thermodilution-derived absolute coronary blood flow and microvascular resistance in humans. *EuroIntervention* 17: e309–e316, 2021. doi:10.4244/EIJ-D-20-00684.
62. **Keulards DCJ**, **Fournier S**, **van 't Veer M**, **Colaiori I**, **Zelis JM**, **El Farissi M**, **Zimmermann FM**, **Collet C**, **De Bruyne B**, **Pijls NHJ.** Computed tomographic myocardial mass compared with invasive myocardial perfusion measurement. *Heart* 106: 1489–1494, 2020. doi:10.1136/heartjnl-2020-316689.
63. **De Bruyne B**, **Pijls NHJ**, **Gallinoro E**, **Candreva A**, **Fournier S**, **Keulards DCJ**, **Sonck J**, **Van't Veer M**, **Barbato B**, **Bartunek J**, **Vanderheyden M**, **Wyffels E**, **De Vos A**, **El Farissi M**, **Tonino PAL**, **Muller O**, **Collet C**, **Fearon WF.** Microvascular resistance reserve for assessment of coronary microvascular function. *J Am Coll Cardiol* 78: 1541–1549, 2021. doi:10.1016/j.jacc.2021.08.017.
64. **Scarsini R**, **Shanmuganathan M**, **Kotronias RA**, **Terentes-Printzios D**, **Borlotti A**, **Langrish JP**, **Lucking AJ**, **Ribichini F**, **Ferreira VM**, **Channon KM**, **Garcia-Garcia HM**, **Banning AP**, **De Maria GL**; **OxAMI Study Investigators.** Angiography-derived index of microcirculatory resistance (IMR(angio)) as a novel pressure-wire-free tool to assess coronary microvascular dysfunction in acute coronary syndromes and stable coronary artery disease. *Int J Cardiovasc Imaging* 37: 1801–1813, 2021. doi:10.1007/s10554-021-02254-8.
65. **Mejia-Renteria H**, **Lee JM**, **Choi KH**, **Lee SH**, **Wang L**, **Kakuta T**, **Koo BK**, **Escaned J.** Coronary microcirculation assessment using functional angiography: development of a wire-free method applicable to conventional coronary angiograms. *Catheter Cardiovasc Interv* 98: 1027–1037, 2021. doi:10.1002/ccd.29863.
66. **Tebaldi M**, **Biscaglia S**, **Di Girolamo D**, **Erriquez A**, **Penzo C**, **Tumscitz C**, **Campo G.** Angio-based index of microcirculatory resistance for the assessment of the coronary resistance: a proof of concept study. *J Interv Cardiol* 2020: 8887369, 2020. doi:10.1155/2020/8887369.
67. **Choi KH**, **Dai N**, **Li Y**, **Kim J**, **Shin D**, **Lee SH**, **Joh HS**, **Kim HK**, **Jeon KH**, **Ha SJ**, **Kim SM**, **Jang MJ**, **Park TK**, **Yang JH**, **Song YB**, **Hahn JY**, **Doh JH**, **Shin ES**, **Choi SH**, **Gwon HC**, **Lee JM.** Functional coronary angiography-derived index of microcirculatory resistance in patients with ST-segment elevation myocardial infarction. *JACC Cardiovasc Interv* 14: 1670–1684, 2021 [Erratum in *JACC Cardiovasc Interv* 15: 2001, 2022]. doi:10.1016/j.jcin.2021.05.027.
68. **Scarsini R**, **Portolan L**, **Della Mora F**, **Marin F**, **Mainardi A**, **Ruzzarin A**, **Levine MB**, **Banning AP**, **Ribichini F**, **Garcia Garcia HM**, **De Maria GL.** Angiography-derived and sensor-wire methods to assess coronary microvascular dysfunction in patients with acute myocardial infarction. *JACC Cardiovasc Imaging* 16: 965–981, 2023. doi:10.1016/j.jcmg.2023.01.017.
69. **Mejía-Rentería H**, **Wang L**, **Chipayo-Gonzales D**, **van de Hoef TP**, **Travieso A**, **Espejo C**, **Núñez-Gil IJ**, **Macaya F**, **Gonzalo N**, **Escaned J.** Angiography-derived assessment of coronary microcirculatory resistance in patients with suspected myocardial ischaemia and non-obstructive coronary arteries. *EuroIntervention* 18: e1348–e1356, 2023. doi:10.4244/EIJ-D-22-00579.
70. **Li W**, **Takahashi T**, **Rios SA**, **Latib A**, **Lee JM**, **Fearon WF**, **Kobayashi Y.** Diagnostic performance and prognostic impact of coronary angiography-based Index of Microcirculatory Resistance assessment: a systematic review and meta-analysis. *Catheter Cardiovasc Interv* 99: 286–292, 2022. doi:10.1002/ccd.30076.
71. **Della Mora F**, **Portolan L**, **Terentes-Printzios D**, **Vicerè A**, **Andreaggi S**, **Biasin M**, **Pesarini G**, **Tavella D**, **Maffeis C**, **Tafciu E**, **Benfari G**, **Oikonomou D**, **Gkini KP**, **Galante D**, **Tsioufis K**, **Vlachopoulos C**, **Leone AM**, **Ribichini F**, **Scarsini R.** Comprehensive angiography-derived functional assessment of epicardial and microvascular coronary disease. correlation with non-invasive myocardial stress imaging. *Am J Cardiol* 217: 144–152, 2024. doi:10.1016/j.amjcard.2024.01.037.
72. **Picano E**, **Ciampi Q**, **Arbucci R**, **Cortigiani L**, **Zagatina A**, **Celutkiene J**, **Bartolacelli Y**, **Kane GC**, **Lowenstein J**, **Pellikka P.** Stress Echo 2030: the new ABCDE protocol defining the future of cardiac imaging. *Eur Heart J Suppl* 25: C63–C67, 2023. doi:10.1093/eurheartjsupp/suad008.
73. **Picano E**, **Pierard L**, **Peteiro J**, **Djordjevic-Dikic A**, **Sade LE**, **Cortigiani L**, **Van De Heyning CM**, **Celutkiene J**, **Gaibazzi N**, **Ciampi Q**, **Senior R**, **Neskovic AN**, **Henein M.** The clinical use of stress echocardiography in chronic coronary syndromes and beyond coronary artery disease: a clinical consensus statement from the European Association of Cardiovascular Imaging of the ESC. *Eur Heart J Cardiovasc Imaging* 25: e65–e90, 2024. doi:10.1093/ehjci/jead250.
74. **Ciampi Q**, **Zagatina A**, **Cortigiani L**, **Gaibazzi N**, **Borguezan Daros C**, **Zhuravskaya N**, **et al.** Functional, anatomical, and prognostic correlates of coronary flow velocity reserve during stress echocardiography. *J Am Coll Cardiol* 74: 2278–2291, 2019. doi:10.1016/j.jacc.2019.08.1046.
75. **Sicari R**, **Rigo F**, **Cortigiani L**, **Gherardi S**, **Galderisi M**, **Picano E.** Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries. *Am J Cardiol* 103: 626–631, 2009. doi:10.1016/j.amjcard.2008.10.033.
76. **Rodriguez-Zanella H**, **Arbucci R**, **Fritche-Salazar JF**, **Ortiz-Leon XA**, **Tuttolomondo D**, **Lowenstein DH**, **Wierzbowska-Drabik K**, **Ciampi Q**, **Kasprzak JD**, **Gaibazzi N**, **Lowenstein J**, **Posada-Martinez EL**, **Arias-Godinez JA**, **de la Fuente-Mancera JC**, **Picano E**; **on behalf of the Stress Echo Study Group Of The Italian Society Of Echocardiography And Cardiovascular Imaging Siecvi.** Vasodilator strain stress echocardiography in suspected coronary microvascular angina. *J Clin Med* 11: 711, 2022. doi:10.3390/jcm11030711.
77. **Picano E.** Economic, ethical, and environmental sustainability of cardiac imaging. *Eur Heart J* 44: 4748–4751, 2023. doi:10.1093/eurheartj/ehac716.
78. **Bedetti G**, **Pasanisi EM**, **Pizzi C**, **Turchetti G**, **Lore C.** Economic analysis including long-term risks and costs of alternative diagnostic strategies to evaluate patients with chest pain. *Cardiovasc Ultrasound* 6: 21, 2008. doi:10.1186/1476-7120-6-21.
79. **Bergamaschi L**, **Pavon AG**, **Angeli F**, **Tuttolomondo D**, **Belmonte M**, **Armillotta M**, **Sansonetti A**, **Foa A**, **Paolisso P**, **Baggiano A**,

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

Mushtaq S, **De Zan G**, **Carriero S**, **Cramer MJ**, **Teske AJ**, **Broekhuizen L**, **van der Bilt I**, **Muscogiuri G**, **Sironi S**, **Leo LA**, **Gaibazzi N**, **Lovato L**, **Pontone G**, **Pizzi C**, **Guglielmo M.** The role of non-invasive multimodality imaging in chronic coronary syndrome: anatomical and functional pathways. *Diagnostics (Basel)* 13: 2083, 2023. doi:10.3390/diagnostics13122083.

80. **Ong P**, **Seitz A.** Advances in risk stratification of patients with coronary microvascular dysfunction: usefulness of stress perfusion CMR. *JACC Cardiovasc Imaging* 14: 612–614, 2021. doi:10.1016/j.jcmg.2020.09.036.
81. **Kotecha T**, **Martinez-Naharro A**, **Boldrini M**, **Knight D**, **Hawkins P**, **Kalra S**, **Patel D**, **Coghlan G**, **Moon J**, **Plein S**, **Lockie T**, **Rakhit R**, **Patel N**, **Xue H**, **Kellman P**, **Fontana M.** Automated pixel-wise quantitative myocardial perfusion mapping by CMR to detect obstructive coronary artery disease and coronary microvascular dysfunction: validation against invasive coronary physiology. *JACC Cardiovasc Imaging* 12: 1958–1969, 2019. doi:10.1016/j.jcmg.2018.12.022.
82. **Zhou W**, **Lee JCY**, **Leung ST**, **Lai A**, **Lee TF**, **Chiang JB**, **Cheng YW**, **Chan HL**, **Yiu KH**, **Goh VK**, **Pennell DJ**, **Ng MY.** Long-term prognosis of patients with coronary microvascular disease using stress perfusion cardiac magnetic resonance. *JACC Cardiovasc Imaging* 14: 602–611, 2021. doi:10.1016/j.jcmg.2020.09.034.
83. **Cheng AS**, **Pegg TJ**, **Karamitsos TD**, **Searle N**, **Jerosch-Herold M**, **Choudhury RP**, **Banning AP**, **Neubauer S**, **Robson MD**, **Selvanayagam JB.** Cardiovascular magnetic resonance perfusion imaging at 3-tesla for the detection of coronary artery disease: a comparison with 1.5-tesla. *J Am Coll Cardiol* 49: 2440–2449, 2007. doi:10.1016/j.jacc.2007.03.028.
84. **Morrone D**, **Gentile F**, **Aimo A**, **Cameli M**, **Barison A**, **Picoi ME**, **Guglielmo M**, **Villano A**, **DeVita A**, **Mandoli GE**, **Pastore MC**, **Barilla F**, **Mancone M**, **Pedrinelli R**, **Indolfi C**, **Filardi PP**, **Muscoli S**, **Tritto I**, **Bergamaschi L**, **Pizzi C**, **Camici PG**, **Marzilli M**, **Crea F**, **Caterina R**, **Pontone G**, **Neglia D**, **Lanza GA**; **Coronary Physiopathology and Microcirculation Working Group and Cluster Imaging of the Italian Society of Cardiology (SIC).** Perspectives in noninvasive imaging for chronic coronary syndromes. *Int J Cardiol* 365: 19–29, 2022. doi:10.1016/j.ijcard.2022.07.038.
85. **Heydari B**, **Ge Y**, **Antiochos P**, **Islam S**, **Steel K**, **Bingham S**, **Abdullah S**, **Mikolich JR**, **Arai AE**, **Bandettini WP**, **Patel AR**, **Shanbhag SM**, **Farzaneh-Far A**, **Heitner JF**, **Shenoy C**, **Leung SW**, **Gonzalez JA**, **Raman SV**, **Ferrari VA**, **Shah DJ**, **Schulz-Menger J**, **Stuber M**, **Simonetti OP**, **Kwong RY.** Sex-specific stress perfusion cardiac magnetic resonance imaging in suspected ischemic heart disease: insights from SPINS retrospective registry. *JACC Cardiovasc Imaging* 16: 749–764, 2023. doi:10.1016/j.jcmg.2022.11.025.
86. **Groenhoff L**, **De Zan G**, **Costantini P**, **Siani A**, **Ostillio E**, **Carriero S**, **Muscogiuri G**, **Bergamaschi L**, **Patti G**, **Pizzi C**, **Sironi S**, **Pavon AG**, **Carriero A**, **Guglielmo M.** The non-invasive diagnosis of chronic coronary syndrome: a focus on stress computed tomography perfusion and stress cardiac magnetic resonance. *J Clin Med* 12: 3793, 2023. doi:10.3390/jcm12113793.
87. **Tonet E**, **Pompei G**, **Faragasso E**, **Cossu A**, **Pavasini R**, **Passarini G**, **Tebaldi M**, **Campo G.** Coronary microvascular dysfunction: PET, CMR and CT assessment. *J Clin Med* 10: 1848, 2021. doi:10.3390/jcm10091848.
88. **Punzo B**, **Cavaliere C**, **Maffei E**, **Bossone E**, **Saba L**, **Cademartiri F.** Narrative review of cardiac computed tomography perfusion: insights into static rest perfusion. *Cardiovasc Diagn Ther* 10: 1946–1953, 2020. doi:10.21037/cdt-20-552.
89. **Mushtaq S**, **Baggiano A**, **Cannata F**, **Del Torto A**, **Fazzari F**, **Fusini L**, **Junod D**, **Maragna R**, **Tassetti L**, **Volpe A**, **Carrabba N**, **Conte E**, **Guglielmo M**, **La Mura L**, **Pergola V**, **Pedrinelli R**, **Perrone Filardi P**, **Guaricci AI**, **Pontone G.** How to perform and evaluate a myocardial perfusion imaging by computed tomography. *Eur Heart J Imaging Methods Pract* 3: qyaf001, 2025. doi:10.1093/ehjimp/qyaf001.
90. **Taylor CA**, **Fonte TA**, **Min JK.** Computational fluid dynamics applied to cardiac computed tomography for noninvasive quantification of fractional flow reserve: scientific basis. *J Am Coll Cardiol* 61: 2233–2241, 2013. doi:10.1016/j.jacc.2012.11.083.
91. **Ihdayhid AR**, **Fairbairn TA**, **Gulsin GS**, **Tzimas G**, **Danehy E**, **Updegrove A**, **Jensen JM**, **Taylor CA**, **Bax JJ**, **Sellers SL**, **Leipsic JA**, **Norgaard BL.** Cardiac computed tomography-derived coronary artery volume to myocardial mass. *J Cardiovasc Comput Tomogr* 16: 198–206, 2022. doi:10.1016/j.jcct.2021.10.007.
92. **Oikonomou EK**, **Marwan M**, **Desai MY**, **Mancio J**, **Alashi A**, **Hutt Centeno E**, **Thomas S**, **Herdman L**, **Kotanidis CP**, **Thomas KE**, **Griffin BP**, **Flamm SD**, **Antonopoulos AS**, **Shirodaria C**, **Sabharwal N**, **Deanfield J**, **Neubauer S**, **Hopewell JC**, **Channon KM**, **Achenbach S**, **Antoniades C.** Non-invasive detection of coronary inflammation using computed tomography and prediction of residual cardiovascular risk (the CRISP CT study): a post-hoc analysis of prospective outcome data. *Lancet* 392: 929–939, 2018. doi:10.1016/S0140-6736(18)31114-0.
93. **Pasqualetto MC**, **Tuttolomondo D**, **Cutruzzola A**, **Niccoli G**, **Dey D**, **Greco A**, **Martini C**, **Irace C**, **Rigo F**, **Gaibazzi N.** Human coronary inflammation by computed tomography: relationship with coronary microvascular dysfunction. *Int J Cardiol* 336: 8–13, 2021. doi:10.1016/j.ijcard.2021.05.040.
94. **Del Buono MG**, **Montone RA**, **Camilli M**, **Carbone S**, **Narula J**, **Lavie CJ**, **Niccoli G**, **Crea F.** Coronary microvascular dysfunction across the spectrum of cardiovascular diseases: JACC state-of-the-art review. *J Am Coll Cardiol* 78: 1352–1371, 2021. doi:10.1016/j.jacc.2021.07.042.
95. **Lanza GA**, **Camici PG**, **Galiuto L**, **Niccoli G**, **Pizzi C**, **Di Monaco A**, **Sestito A**, **Novo S**, **Piscione F**, **Tritto I**, **Ambrosio G**, **Bugiardini R**, **Crea F**, **Marzilli M**; **Gruppo di Studio di Fisiopatologia Coronarica e Microcircolazione, Società Italiana di Cardiologia.** Methods to investigate coronary microvascular function in clinical practice. *J Cardiovasc Med (Hagerstown)* 14: 1–18, 2013. doi:10.2459/JCM.0b013e328351680f.
96. **Schindler TH**, **Fearon WF**, **Pelletier-Galarneau M**, **Ambrosio G**, **Sechtem U**, **Ruddy TD**, **Patel KK**, **Bhatt DL**, **Bateman TM**, **Gewirtz H**, **Shirani J**, **Knuuti J**, **Gropler RJ**, **Chareonthaitawee P**, **Slart R**, **Windecker S**, **Kaufmann PA**, **Abraham MR**, **Taqueti VR**, **Ford TJ**, **Camici PG**, **Schelbert HR**, **Dilsizian V.** Myocardial perfusion PET for the detection and reporting of coronary microvascular dysfunction: a JACC: Cardiovascular Imaging Expert Panel Statement. *JACC Cardiovasc Imaging* 16: 536–548, 2023. doi:10.1016/j.jcmg.2022.12.015.
97. **Di Carli MF**, **Dorbala S**, **Curillova Z**, **Kwong RJ**, **Goldhaber SZ**, **Rybicki FJ**, **Hachamovitch R.** Relationship between CT coronary angiography and stress perfusion imaging in patients with suspected ischemic heart disease assessed by integrated PET-CT imaging. *J Nucl Cardiol* 14: 799–809, 2007. doi:10.1016/j.nuclcard.2007.07.012.
98. **Schindler TH**, **Dilsizian V.** Coronary microvascular dysfunction: clinical considerations and noninvasive diagnosis. *JACC Cardiovasc Imaging* 13: 140–155, 2020. doi:10.1016/j.jcmg.2018.11.036.
99. **Kogame N**, **Ono M**, **Kawashima H**, **Tomaniak M**, **Hara H**, **Leipsic J**, **Andreini D**, **Collet C**, **Patel MR**, **Tu S**, **Xu B**, **Bourantas CV**, **Lerman A**, **Piek JJ**, **Davies JE**, **Escaned J**, **Wijns W**, **Onuma Y**, **Serruys PW.** The impact of coronary physiology on contemporary clinical decision making. *JACC Cardiovasc Interv* 13: 1617–1638, 2020. doi:10.1016/j.jcin.2020.04.040.
100. **Collet C**, **Johnson NP**, **Mizukami T**, **Fearon WF**, **Berry C**, **Sonck J**, **et al.** Impact of post-PCI FFR stratified by coronary artery. *JACC Cardiovasc Interv* 16: 2396–2408, 2023. doi:10.1016/j.jcin.2023.08.018.
101. **Ford TJ**, **Stanley B**, **Sidik N**, **Good R**, **Rocchiccioli P**, **McEntegart M**, **Watkins S**, **Eteiba H**, **Shaukat A**, **Lindsay M**, **Robertson K**, **Hood S**, **McGeoch R**, **McDade R**, **Yii E**, **McCartney P**, **Corcoran D**, **Collison D**, **Rush C**, **Sattar N**, **McConnachie A**, **Touyz RM**, **Oldroyd KG**, **Berry C.** 1-Year outcomes of angina management guided by invasive coronary function testing (CorMicA). *JACC Cardiovasc Interv* 13: 33–45, 2020. doi:10.1016/j.jcin.2019.11.001.
102. **Vrints C**, **Andreotti F**, **Koskinas KC**, **Rossello X**, **Adamo M**, **Ainslie J**, **Banning AP**, **Budaj A**, **Buechel RR**, **Chiariello GA**, **Chieffo A**, **Christodorescu RM**, **Deaton C**, **Doenst T**, **Jones HW**, **Kunadian V**, **Mehilli J**, **Milojevic M**, **Piek JJ**, **Pugliese F**, **Rubboli A**, **Semb AG**, **Senior R**, **Ten Berg JM**, **Van Belle E**, **Van Craenenbroeck EM**, **Vidal-Perez R**, **Winther S**; **ESC Scientific Document Group.** 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 45: 3415–3537, 2024 [Erratum in *Eur Heart J* 46: 1565, 2025]. doi:10.1093/eurheartj/ehae177.
103. **Bertolone DT**, **Gallinoro E**, **Esposito G**, **Paolisso P**, **Bermpeis K**, **De Colle C**, **Fabbricatore D**, **Mileva N**, **Valeriano C**, **Munhoz D**, **Belmonte M**, **Vanderheyden M**, **Bartunek J**, **Sonck J**, **Wyffels E**, **Collet C**, **Mancusi C**, **Morisco C**, **De Luca N**, **De Bruyne B**, **Barbato E.** Contemporary management of stable coronary artery disease.

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.

High Blood Press Cardiovasc Prev 29: 207–219, 2022. doi:10.1007/s40292-021-00497-z.

104. **Fearon WF**, **Low AF**, **Yong AS**, **McGeoch R**, **Berry C**, **Shah MG**, **Ho MY**, **Kim HS**, **Loh JP**, **Oldroyd KG.** Prognostic value of the Index of Microcirculatory Resistance measured after primary percutaneous coronary intervention. *Circulation* 127: 2436–2441, 2013. doi:10.1161/CIRCULATIONAHA.112.000298.
105. **Fahrni G**, **Wolfrum M**, **De Maria GL**, **Cuculi F**, **Dawkins S**, **Alkhalil M**, **Patel N**, **Forfar JC**, **Prendergast BD**, **Choudhury RP**, **Channon KM**, **Banning AP**, **Kharbanda RK.** Index of microcirculatory resistance at the time of primary percutaneous coronary intervention predicts early cardiac complications: insights from the OxAMI (Oxford Study in Acute Myocardial Infarction) Cohort. *J Am Heart Assoc* 6: e005409, 2017. doi:10.1161/JAHA.116.005409.
106. **De Maria GL**, **Alkhalil M**, **Wolfrum M**, **Fahrni G**, **Borlotti A**, **Gaughran L**, **Dawkins S**, **Langrish JP**, **Lucking AJ**, **Choudhury RP**, **Porto I**, **Crea F**, **Dall'Armellina E**, **Channon KM**, **Kharbanda RK**, **Banning AP.** Index of microcirculatory resistance as a tool to characterize microvascular obstruction and to predict infarct size regression in patients with STEMI undergoing primary PCI. *JACC Cardiovasc Imaging* 12: 837–848, 2019. doi:10.1016/j.jcmg.2018.02.018.
107. **Lodi Rizzini M**, **Candreva A**, **Chiastra C**, **Gallinoro E**, **Calò K**, **D'Ascenzo F**, **De Bruyne B**, **Mizukami T**, **Collet C**, **Gallo D**, **Morbiducci U.** Modelling coronary flows: impact of differently measured inflow boundary conditions on vessel-specific computational hemodynamic profiles. *Comput Methods Programs Biomed* 221: 106882, 2022. doi:10.1016/j.cmpb.2022.106882.
108. **Demir OM**, **Boerhout CKM**, **de Waard GA**, **van de Hoef TP**, **Patel N**, **Beijk MAM**, **Williams R**, **Rahman H**, **Everaars H**, **Kharbanda RK**, **Knaapen P**, **van Royen N**, **Piek JJ**, **Perera D**; **Oxford Acute Myocardial Infarction (OxAMI) Study.** Comparison of Doppler flow velocity and thermodilution derived indexes of coronary physiology. *JACC Cardiovasc Interv* 15: 1060–1070, 2022. doi:10.1016/j.jcin.2022.03.015.
109. **Mahendiran T**, **Bertolone D**, **Viscusi M**, **Gallinoro E**, **Keulards D**, **Collet C**, **Sonck J**, **Wilgenhof A**, **Pijls NH**, **De Bruyne B.** The influence of epicardial resistance on microvascular resistance reserve. *J Am Coll Cardiol* 84: 512–521, 2024. doi:10.1016/j.jacc.2024.05.004.
110. **de Vos A**, **Jansen TPJ**, **van 't Veer M**, **Dimitriu-Leen A**, **Konst RE**, **Elias-Smale S**, **Paradies V**, **Rodwell L**, **van den Oord S**, **Smits P**, **van Royen N**, **Pijls N**, **Damman P.** Microvascular resistance reserve to assess microvascular dysfunction in ANOCA patients. *JACC Cardiovasc Interv* 16: 470–481, 2023. doi:10.1016/j.jcin.2022.12.012.
111. **Boerhout CKM**, **Lee JM**, **de Waard GA**, **Mejia-Renteria H**, **Lee SH**, **Jung JH**, **et al.** Microvascular resistance reserve: diagnostic and prognostic performance in the ILIAS registry. *Eur Heart J* 44: 2862–2869, 2023. doi:10.1093/eurheartj/ehad378.

Downloaded from journals.physiology.org/journal/ajpheart (087.026.064.245) on January 31, 2026.