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ARTICLE

Bridging the gap: integrating stress echocardiography, iFR, CFR, and FFR in the evaluation of coronary artery disease

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Abstract

Accurate evaluation of coronary artery disease (CAD) requires the integration of noninvasive and invasive diagnostic modalities. Stress echocardiography provides a noninvasive assessment of ischemia, while invasive physiological indices such as fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), and coronary flow reserve (CFR) offer lesion-specific and microvascular evaluations. Despite their complementary roles, the combined use of these tools in clinical practice remains inconsistent. This review explores the evolving landscape of CAD assessment, highlighting the strengths and limitations of each modality. Evidence from landmark trials and recent guidelines underscores the advantages of physiology-guided decision-making, optimizing revascularization strategies while identifying patients who may benefit from medical therapy. Emerging noninvasive computational tools, including FFR-CT and quantitative flow ratio (QFR), are reshaping CAD evaluation by reducing the need for invasive testing. An integrated approach that leverages both functional imaging and invasive physiology is essential for improving diagnostic accuracy and tailoring treatment to individual patient needs. A comprehensive literature review was conducted, focusing on clinical studies published between 2018 and 2024 regarding stress echocardiography and invasive coronary physiology. Landmark trials and recent guideline documents from the European Society of Cardiology (ESC) and the American College of Cardiology (ACC)/American Heart Association (AHA) were analyzed to evaluate best practices for integrating these diagnostic tools. Tables and figures were updated to reflect the latest findings on revascularization outcomes and the comparative performance of physiological indices. Findings confirm that stress echocardiography demonstrates a high concordance (~87%) with FFR in identifying ischemia-producing lesions, while iFR exhibits slightly lower agreement (~72%). Key FFR trials (DEFER, FAME, FAME-2) reinforce the safety of deferring intervention for non-ischemic lesions and the improved outcomes of FFR-guided revascularization over angiography alone. iFR-based strategies, (iFR-SWEDEHEART) yield similar clinical outcomes to FFR-guided approaches while reducing stent implantation rates. CFR offers additional insights, particularly in cases of microvascular dysfunction, which is present in up to 50% of patients with angina and non-obstructive CAD (INOCA). Recent advances in computational modeling, including FFRCT and angiography-derived quantitative flow ratio (QFR), show promise for streamlining physiology-based assessments. The integration of stress echocardiography with invasive indices enhances diagnostic accuracy and refines treatment strategies. FFR and iFR aid in revascularization decisions, while CFR and the index of microcirculatory resistance (IMR) help unmask microvascular dysfunction. Clinical guidelines now advocate for a physiology-driven approach to both obstructive and non-obstructive CAD, yet real-world implementation remains suboptimal. Future research should focus on the broader adoption of noninvasive computational techniques and further validation of emerging technologies in diverse patient populations. A structured diagnostic approach combining stress echocardiography with invasive physiology optimizes CAD evaluation. Stress echocardiography serves as an effective gatekeeper, guiding patients toward appropriate invasive assessment. FFR/iFR refines lesion-specific management, while CFR/IMR helps tailor treatment for microvascular disease. The evolving landscape of noninvasive physiology promises further enhancements in clinical decision-making, reducing unnecessary interventions while ensuring that ischemic lesions receive appropriate treatment. The latest ESC and ACC/AHA guidelines underscore the value of this integrated strategy, heralding a shift toward comprehensive, physiology-based CAD management.

Key words: coronary artery disease; fractional flow reserve; instantaneous wave-free ratio; stress echocardiography; coronary microvascular dysfunction.

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Introduction

Assessment of coronary artery disease traditionally spans anatomic imaging and functional testing.[1] Coronary angiography delineates lesion severity, but it may over- or underestimate the hemodynamic significance of intermediate stenoses. Noninvasive stress tests (such as stress echocardiography) evaluate myocardial ischemia, yet they cannot pinpoint the precise lesion or differentiate epicardial versus microvascular causes in all cases. This "gap" between anatomical and functional evaluation can lead to suboptimal decision-making in CAD management. Integrating stress echocardiography findings with invasive physiological indices – fractional flow reserve (FFR), instantaneous wave-free ratio (iFR), and coronary flow reserve (CFR) – offers a more complete picture of coronary pathophysiology.[2,3] FFR and iFR quantify lesion-specific ischemia, while CFR gauges overall perfusion reserve (reflecting both epicardial and microcirculatory health).[4,5] By combining these modalities, clinicians can identify which lesions require stenting, which patients have microvascular angina, and who may be managed with medical therapy alone. In this expanded review, we discuss the evidence and practical approaches for integrating stress echocardiography with invasive pressure-flow measurements. We incorporate pivotal historical studies and the latest research to provide a state-of-the-art perspective on how these tools, used together, can optimize the evaluation and treatment of patients with stable CAD and those with angina and no obstructive CAD.

Stress echocardiography for ischemia detection

Stress echocardiography (stress echo) is a cornerstone noninvasive test for inducible ischemia.[1-3] By imaging regional wall motion during stress (exercise or pharmacologic), it detects myocardial segments with impaired contractile response due to upstream flow-limiting stenoses. Decades of data support its prognostic value and diagnostic accuracy. In comparative studies, dobutamine stress echocardiography (DSE) shows strong agreement with invasive FFR measurements (~87% concordance).[1] This indicates that a positive stress echo generally corresponds to an FFR ≤0.80 in the subtending artery. Discordances can occur, however, especially in cases of balanced ischemia or microvascular dysfunction. Interestingly, the same study found only ~72% agreement between DSE and iFR,[1] suggesting that the hyperemic condition of DSE aligns more closely with FFR (which is measured during maximal hyperemia) than with resting indices like iFR.

Stress echo's advantages include its wide availability, lack of ionizing radiation, and ability to evaluate valvular and ventricular function concurrently.[6] It can localize ischemia to specific coronary territories.

Limitations include operator dependence and reduced sensitivity in those with suboptimal acoustic windows. Moreover, stress echo provides a binary ischemia assessment, whereas invasive physiology can quantify ischemic severity.[2] Despite these limitations, in the initial workup of stable CAD, a stress echo can effectively triage patients: those with significant ischemia can be referred for invasive angiography, and those with negative tests can safely continue medical management if symptoms are mild and overall risk is low.[6] When stress echo results and angiographic findings conflict, or in borderline lesions, invasive physiological measurements become crucial.

A complementary role of stress echocardiography is in uncovering microvascular ischemia. While wall motion abnormalities on DSE typically imply epicardial stenoses, a small portion of patients without epicardial disease may exhibit ischemic responses due to microvascular dysfunction or spasm.[7,8] Advanced echo techniques (e.g., myocardial contrast echocardiography, Doppler flow in the left anterior descending artery) can directly assess microvascular perfusion and flow reserve. A CFR <2.0 measured in this setting suggests a microvascular abnormality if angiographically significant stenoses are excluded. Stress echo not only detects epicardial disease but, when combined with other modalities, helps identify patients who might have microvascular angina (INOCA). Overall, stress echocardiography provides the initial functional bridge, indicating whether ischemia is present, which can then be investigated in detail with invasive tools like FFR, iFR, or CFR for precise pathophysiological delineation.

Invasive physiological assessment: FFR and iFR

Fractional flow reserve (FFR) revolutionized the catheterization lab by providing a lesion-specific measure of ischemia. FFR is defined as the ratio of distal coronary pressure (Pd) to aortic pressure (Pa) during maximal hyperemia.[2] An FFR of 0.80 means that the distal pressure is 80% of aortic pressure, indicating a 20% drop across the lesion under hyperemic flow. Foundational trials demonstrated FFR's clinical utility. The DEFER study (2001) showed that deferring percutaneous coronary intervention (PCI) in lesions with FFR >0.75 was safe, with no increase in adverse events long term.[2,3] The FAME trial[4] randomized multivessel CAD patients to FFR-guided *vs* angiography-guided PCI. In FFR-guided management, fewer stents

were used, and 1-year outcomes were superior (13.2% *vs* 18.3% for death/myocardial infarction/repeat revascularization). The follow-up FAME 2 trial affirmed that lesions with FFR ≤0.80 benefit from revascularization, reducing urgent revascularization significantly.

Instantaneous wave-free ratio (iFR) was introduced as a vasodilator-free alternative to FFR.[7,8] Measured during a specific resting diastolic interval, iFR avoids hyperemic agents, offering procedural simplicity. DEFINE-FLAIR and iFR-SWEDEHEART (combined ~4,500 patients) confirmed that an iFR ≤0.89 is non-inferior to an FFR ≤0.80 for guiding revascularization decisions, with similar 1-year and 5-year outcomes.[7-10] iFR tends to reduce the number of stents placed by classifying some borderline lesions as physiologically insignificant.[8,10]

While safe and effective in stable CAD, iFR may show discrepancies in acute or complex scenarios, emphasizing the need for clinical judgment.

FFR/iFR in special scenarios

Most FFR/iFR data derives from stable CAD. In acute coronary syndromes (ACS), microvascular dysfunction in the culprit territory can transiently alter measurements.[9] Nonetheless, the iFR-SWEDEHEART study included approximately 27% ACS patients and found consistent outcomes.[8,10] In left main disease, FFR is validated, but borderline cases often require intravascular imaging for confirmation. Resting indices like iFR may be advantageous if adenosine is contraindicated (e.g., in patients with asthma or high-degree AV block), allowing physiologic assessment when FFR is not feasible. Overall, FFR/iFR have transformed stable CAD management by enabling physiology-guided revascularization, preventing both undertreatment and overtreatment of moderate lesions.

Coronary flow reserve and microvascular dysfunction

While FFR/iFR interrogate the pressure gradient across epicardial lesions, CFR assesses the flow capacity of the coronary circulation.[11,12] CFR is the ratio of maximal hyperemic flow to resting flow, typically considered abnormal if less than 2.0. Discordances between FFR and CFR frequently occur: a lesion may have an FFR >0.80 but a CFR <2.0, pointing to microvascular dysfunction. Alternatively, an abnormal FFR (≤0.80) with a normal CFR (>2.0) suggests a focal epicardial lesion with compensatory microvascular dilation.

Combining FFR with CFR (or IMR) refines diagnosis. Patients with microvascular dysfunction have angina despite non-obstructive coronaries (INOCA). The CorMicA trial showed that tailoring therapy to microvascular or vasospastic findings significantly improved angina severity and quality of life.[13] The index of microcirculatory resistance (IMR) is another invasive metric that specifically quantifies microvascular resistance (with values ≥25 indicating dysfunction).[12] Such parameters clarify whether epicardial stenting will help or whether medical therapy targeting the microcirculation (e.g., vasodilators) is needed. Up to 50% of angina patients without obstructive CAD have evidence of microvascular ischemia, underscoring the clinical impact of these assessments.[13,14]

Integrating modalities in clinical practice

A typical pathway might involve a stress echo to detect ischemia, followed by invasive angiography for patients with positive or equivocal findings.[15,16] Intermediate lesions (50-70% stenosis) on angiography undergo FFR/iFR to confirm physiological significance. When results are discordant or the angiogram is normal despite clinical suspicion of ischemia, CFR/IMR can unveil microvascular problems.

Patients initially undergo a noninvasive stress test (e.g., stress echocardiography). If results indicate significant ischemia, invasive angiography with FFR/iFR clarifies lesion-level significance. If no obstructive disease is found, or if FFR/iFR are normal but symptoms persist, measuring CFR/IMR and performing vasospasm testing (using acetylcholine) can diagnose microvascular dysfunction or vasospastic angina.

Non-invasive physiology: CT-FFR, QFR, and emerging technologies

Coronary physiology is now extendable beyond the cath lab *via* computational modeling.[16,17] FFR-CT applies fluid dynamics (or deep learning) to coronary CT angiography, simulating hyperemic flow. Studies such as DISCOVER-FLOW and NXT have validated FFR-CT against invasive FFR, demonstrating strong correlation (r ~0.8-0.9) and approximately 80-90% diagnostic accuracy.[16,18] This helps avoid unnecessary invasive angiography. Another tool, QFR (Quantitative Flow Ratio), uses standard angiographic images to compute an FFR-equivalent measure without a pressure wire.[17,19] QFR has shown high concordance (~90-95%) with invasive FFR in multiple FAVOR trials. These "wire-free" indices can streamline physiology assessment and potentially reduce costs. Additionally, artificial intelligence (AI) further refines these methods, enabling machine-learning algorithms to predict FFR or microvascular indices from routine imaging or clinical data.[20] As computational approaches mature, the synergy between noninvasive imaging and invasive verification will likely accelerate the adoption of physiology-based care (Table 1).

Clinical guidelines and emerging frontiers

Contemporary guidelines strongly endorse physiology-based decision-making. The 2019 ESC Chronic Coronary Syndrome guidelines and the 2021 ACC/AHA Chest Pain Guidelines des-

Table 1. Comparative summary of physiological indices.

Index	Mechanism and measurement	Hyperemia?	Threshold (ischemia)	Interpretation
FFR	Invasive pressure wire; ratio of distal to aortic pressure at maximal hyperemia.[2]	Yes	≤0.80	Epicardial lesion severity. Validated by multiple trials.[2-6]
iFR	Invasive pressure wire; resting diastolic Pd/Pa ratio.[7,8]	No	≤0.89	Epicardial lesion severity without hyperemia; trials confirm non-inferiority to FFR.[9,10]
CFR	Ratio of hyperemic to resting flow (invasive or noninvasive).[11]	Yes	<2.0 = abnormal	Global flow capacity (epicardial + microvascular). Low CFR with normal FFR suggests microvascular dysfunction.
IMR	Invasive measure of microvascular resistance (Pd × hyperemic transit time).[12]	Yes	≥25 = microvascular dysfunction	Specifically indexes the microcirculation; unaffected by epicardial gradient.
FFR/CT	Noninvasive fluid dynamic modeling of CT angiography.[16]	Virtual (computed)	≤0.80	Predicts lesion significance from coronary CT scans, often guiding the need for invasive angiography.
QFR	3D reconstruction from biplane angiography + flow estimation (no wire).[17]	Virtual (computed)	≤0.80	"Wire-free" FFR in the cath lab. High correlation with invasive FFR.[17,19]

ignate FFR/iFR as Class I for intermediate stenoses.[19,21] The 2024 ESC update specifically includes iFR with Level A evidence, reflecting data from DEFINE-FLAIR and iFR-SWEDE-HEART.[9,10,22] These guidelines also promote invasive microvascular evaluation (using CFR, IMR, and vasospasm testing) in patients with angina and no obstructive CAD.[15,22]

Looking forward, key research areas include microvascular disease in heart failure with preserved ejection fraction (HFpEF), post-PCI ischemia evaluation, and AI-based "virtual stenting." In parallel, noninvasive physiology tools (such as FFRCT and QFR) are increasingly integrated into clinical pathways, reducing the need for invasive tests when clearly normal or severely diseased arteries are identified.[16,17] The synergy between imaging and computational modeling promises to further embed physiology into everyday practice, potentially allowing many decisions to be made with minimal invasiveness.

Conclusions

In the evaluation of coronary artery disease, integrating noninvasive stress imaging (e.g., stress echocardiography) with invasive physiologic measurements (FFR, iFR, CFR, IMR) yields greater diagnostic clarity and directs therapy more precisely. Stress echo localizes ischemic territories, while FFR/iFR confirm lesion-specific significance and guide revascularization. CFR/IMR expose microvascular dysfunction, enabling medical therapy for patients with angina but no obstructive CAD. This multimodal approach reduces both missed lesions and unnecessary interventions, embodying evidence-based, patient-specific care. As noninvasive computational methods like FFR-CT and QFR mature, the boundaries between anatomic and functional testing continue to blur, fostering a comprehensive yet streamlined assessment of CAD. Current guidelines from ESC and ACC/AHA affirm the importance of physiology-driven strategies in both obstructive and non-obstructive CAD, ushering in a new era of personalized cardiology grounded in robust pathophysiological understanding.

Contributions

All authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no competing interests, and all authors confirm accuracy.

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