

Multimodal CT for Precision Diagnosis of Coronary Artery Disease: Integrating Anatomical and Functional Imaging

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Abstract: Precision diagnosis of coronary artery disease (CAD) requires the integration of multidimensional data, including coronary anatomy and physiological function, for a comprehensive evaluation. This article reviews recent advances in multimodal computed tomography (CT) technologies for diagnosing CAD, analyzing their complementary strengths and limitations. In anatomical imaging, coronary computed tomography angiography (CCTA) assesses the degree of coronary stenosis and plaque characteristics but has limited specificity in evaluating functional ischemia. Functional imaging methods, such as fractional flow reserve derived from CT (CT-FFR), which simulates coronary pressure changes using fluid dynamics, and computed tomography perfusion (CTP) for myocardial ischemia detection, significantly enhance the accuracy and reliability of functional evaluations in CAD. The synergistic use of multimodal CT technologies addresses the limitations inherent to single imaging modalities, reduces unnecessary invasive procedures, and optimizes revascularization decisions, facilitating hierarchical precision assessment from anatomical stenosis to functional ischemia.

Keywords: CAD; CCTA; CT-FFR; CTP

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1. Introduction

CAD is one of the leading causes of death and disability worldwide, and its early and accurate diagnosis plays a crucial role in improving clinical outcomes for patients ^[1]. The pathological hallmark of CAD is atherosclerotic plaque formation, leading to coronary artery stenosis or occlusion, subsequently resulting

in myocardial ischemia, hypoxia, or necrosis. Although invasive coronary angiography (ICA) is considered the gold standard for anatomical assessment of coronary stenosis, the invasive nature of the procedure and associated risks have highlighted the urgent need for noninvasive imaging alternatives ^[2].

In recent years, CCTA has emerged as the preferred noninvasive modality for diagnosing CAD due to its high spatial resolution. However, the degree of coronary artery stenosis does not always correlate with hemodynamic abnormalities, and traditional morphological assessment often fails to accurately identify functional ischemia ^[3]. This limitation has spurred rapid advancements in functional CT techniques. Specifically, CT-FFR calculates pressure gradients across coronary stenoses using hemodynamic modeling; and CTP detects myocardial perfusion defects during stress testing. These methods have expanded CAD diagnostics beyond anatomical stenosis assessment, enabling quantitative analysis of functional ischemia and enhancing detection of hemodynamically significant lesions. Multimodal CT integrates anatomical stenosis assessment and functional ischemia analysis to establish a multidimensional diagnostic framework (“anatomical-functional”), systematically enhancing diagnostic accuracy for CAD.

2. Functional imaging: The role of CT-FFR and CTP in coronary hemodynamic assessment

2.1. CT-FFR

2.1.1. Principles and measurement techniques of CT-FFR

Invasive fractional flow reserve (FFR) is currently considered the gold standard for assessing coronary functional stenosis, defined as the ratio of maximum perfused blood flow through a stenotic lesion relative to maximal perfusion in the vessel under normal conditions ^[4]. However, its clinical application is significantly restricted by invasiveness, procedural complexity, and high costs ^[5]. Recent breakthroughs in non-invasive FFR measurement techniques based on CCTA have emerged. These methods utilize three-dimensional reconstructions derived from CCTA data to establish patient-specific coronary hemodynamic models, enabling quantitative simulation of pressure gradients across stenotic segments. Consequently, this technology allows for assessment of coronary functional ischemia without the need for stress-inducing medications or additional radiation exposure ^[6,7]. This advancement represents a major innovation in noninvasive cardiovascular functional assessment.

In clinical practice, CT-FFR is typically measured 1 to 2 cm distal to the target lesion ^[8]. A CT-FFR ≤ 0.75 indicates a significantly increased risk of myocardial ischemia, warranting revascularization, whereas a CT-FFR > 0.80 suggests lower risk and favors medical therapy. Values between 0.76 and 0.80 represent a “gray zone,” necessitating comprehensive assessment of clinical symptoms and ancillary test results to guide decisions on revascularization ^[9]. This quantitative stratification strategy based on CT-FFR provides objective evidence for establishing revascularization indications and supports personalized, evidence-based treatment decisions.

2.1.2. Diagnostic value of CT-FFR for CAD

As a noninvasive imaging modality, CT-FFR can accurately evaluate hemodynamic changes resulting from CAD. Results from several large-scale clinical studies have confirmed its diagnostic value for identifying myocardial ischemia in CAD patients ^[5,10–12]. A prospective multicenter study employing a novel lumen-contour reconstruction algorithm demonstrated that CT-FFR achieved high sensitivity (95.3%), specificity

(89.8%), and overall accuracy (92.0%) at the vessel level, significantly outperforming CCTA alone (AUC 0.95 vs. 0.74, $P < 0.001$), with particular advantages observed in moderate stenoses and heavily calcified lesions^[13]. A retrospective multicenter study further validated the superiority of CT-FFR over CCTA in detecting lesion-specific ischemia, showing moderate correlation with invasive FFR measurements ($r = 0.52$, $P < 0.001$)^[11]. A comparative analysis by Driessen et al.^[14] revealed that at the vessel level, CT-FFR exhibited significantly higher sensitivity (90%) compared to CCTA (68%), single-photon emission computed tomography (SPECT, 42%), and positron emission tomography (PET, 81%). Its specificity (86%) was comparable to CCTA (83%) and PET (76%), though slightly lower than SPECT (97%). Overall diagnostic accuracy (AUC 0.94) of CT-FFR significantly surpassed that of CCTA (0.83), SPECT (0.70), and PET (0.87) (all $P < 0.001$). However, previous studies, primarily composed of male subjects, failed to assess the influence of gender on diagnostic performance systematically. Fairbairn et al.^[15] identified gender-related differences in CT-FFR values. Female patients demonstrated significantly higher CT-FFR values than male patients at equivalent stenosis levels (0.76 ± 0.10 vs. 0.73 ± 0.10 , $P < 0.0001$), resulting in a 12.2% lower positive detection rate using the ≤ 0.80 threshold in women. This discrepancy may be attributed to women's higher coronary artery volume-to-myocardial mass ratios compared to men ($26.17 \pm 7.58 \text{ mm}^3/\text{g}$ vs. $24.76 \pm 7.22 \text{ mm}^3/\text{g}$, $P < 0.0001$). Despite smaller coronary artery volumes, women have lower myocardial mass, resulting in improved matching between myocardial oxygen demand and blood supply capacity. These findings underscore the need for gender-specific CT-FFR thresholds to avoid clinical decision biases resulting from uniform diagnostic criteria.

Machine learning (ML)-based CT-FFR technology employs algorithms, such as multilayer neural networks, to analyze and train models using coronary anatomical datasets and hemodynamic databases, establishing intrinsic relationships between anatomical features and hemodynamic parameters^[16]. This approach enables CT-FFR values to be intelligently inferred directly from CCTA anatomical data, reducing the average analysis time to 8 minutes and achieving near-real-time CT-FFR assessment, thereby facilitating broader clinical application in CAD diagnosis^[17]. Multicenter studies have confirmed that ML-based CT-FFR significantly enhances overall diagnostic performance compared to CCTA alone, increasing the AUC by approximately 10% to 25%. This technology demonstrates particular advantages in evaluating mid-to-proximal LAD and LCX stenoses (AUC improved from 0.65–0.84 to 0.72–0.90); however, diagnostic improvements for mid-RCA stenoses remain limited due to factors such as motion artifact interference and lower lesion prevalence (AUC 0.73 vs. 0.74)^[18]. Clinical studies further validate ML-based CT-FFR, showing overall sensitivity and specificity of 85% and 94%, respectively, in diagnosing coronary artery-specific ischemia. For moderate stenoses (30–70%), ML-based CT-FFR maintains excellent sensitivity and specificity (84% and 92%), respectively^[19]. However, current research predominantly uses invasive FFR as the reference standard, lacking validation through multimodal imaging technologies. Consequently, CT-FFR may erroneously attribute myocardial ischemia caused by microvascular lesions to large vessel stenosis or fail to detect ischemia resulting from microcirculatory abnormalities. In comparison, cardiac magnetic resonance (MR), which directly quantifies myocardial perfusion reserve and MBF, achieves higher specificity (95% vs. 82%) and accuracy (95% vs. 81%)^[20]. Future research should therefore develop collaborative validation frameworks integrating CT-FFR with multimodal imaging modalities such as MR and PET, while incorporating parameters of microcirculatory function to minimize diagnostic errors.

2.1.3. Factors affecting the diagnostic accuracy of CT-FFR

The diagnostic performance of CT-FFR is closely associated with factors such as CAC load, CCTA image quality, and patient heart rate. Several studies have confirmed a significant negative correlation between coronary artery calcification burden and CT-FFR accuracy^[21,22]. Tesche et al.^[22] found that although CT-FFR outperformed CCTA in diagnosing myocardial ischemia across all CAC score levels, its accuracy decreased with increasing CAC score. In patients with mild-to-moderate calcification (CAC score 0–400), CT-FFR exhibited significantly higher diagnostic performance (AUC 0.86) than CCTA (AUC 0.63, $P < 0.001$). However, in cases of severe calcification (CAC score ≥ 400), this advantage diminished (CT-FFR AUC 0.71 vs. CCTA AUC 0.55, $P = 0.04$). A single-center study further demonstrated reduced concordance between CT-FFR and invasive FFR in patients with high calcification levels, characterized by decreased positive predictive value (PPV). This decline in predictive accuracy may lead to increased false-positive results, potentially prompting unnecessary revascularization procedures^[23]. Notably, different CT-FFR algorithm models exhibit varying sensitivities to calcification artifacts. Traditional algorithms heavily rely on accurate geometric lumen segmentation. However, halo and beam-hardening artifacts induced by severe calcification can compromise coronary centerline identification and lumen segmentation accuracy, resulting in systematic biases during hemodynamic assessment. In contrast, newer algorithms integrating TAG and additional hemodynamic parameters maintain consistent diagnostic accuracy across coronary arteries with different calcification levels, remodeling indices, and CAC stratifications by optimizing boundary conditions^[24]. Nevertheless, the performance of current CT-FFR models in patients with severe calcification requires further validation through large-scale studies. Consequently, there is an urgent need to develop CT-FFR models incorporating quantitative corrections based on calcification characteristics to mitigate assessment biases and enhance diagnostic reliability.

Image quality is another critical factor influencing the diagnostic accuracy of CT-FFR. A multicenter retrospective study demonstrated significantly higher diagnostic performance in the high-quality image group compared to the low-quality group (AUC: 0.93 vs. 0.80; specificity: 0.98 vs. 0.86; PPV: 0.95 vs. 0.82), confirming that reduced image quality diminishes the accuracy of vascular morphology reconstruction and lesion feature extraction^[25]. The same study also revealed that heart rate significantly affects diagnostic accuracy. Patients with low heart rates (≤ 70 bpm) exhibited superior specificity (0.98 vs. 0.89) and PPV (0.96 vs. 0.77) compared to those with higher heart rates (> 80 bpm). This difference primarily arises because stable heart rates reduce motion artifacts, thus optimizing the accuracy of vascular morphology reconstruction^[25]. Therefore, rigorous adherence to cardiovascular CT imaging protocols, optimization of scan parameters, and effective heart-rate control strategies are essential for improving CT-FFR diagnostic accuracy.

2.2. CTP

2.2.1. Principles and techniques of CTP

CCTA provides anatomical information regarding the coronary arteries, while CT-FFR allows noninvasive FFR assessment. However, neither modality can directly evaluate myocardial perfusion. To address this limitation, myocardial CTP technology has been introduced, enabling direct evaluation of myocardial perfusion status and microcirculatory function. The fundamental principle of CTP involves detecting reduced or delayed myocardial contrast uptake through subjective assessment and quantitative analysis^[26]. Specifically, following intravenous contrast injection via the antecubital vein, CTP identifies perfusion abnormalities by assessing

contrast distribution characteristics during its initial passage through the myocardium. A marked reduction in contrast concentration indicates potential myocardial perfusion defects ^[27,28].

CTP scanning protocols include resting and stress modes. At rest, MBF can remain normal even with coronary artery stenosis up to 85%, facilitated by collateral circulation or compensatory vasodilation. However, under stress conditions, microcirculation within stenotic vascular territories cannot adequately dilate, resulting in reduced regional MBF ^[29]. Due to differences in blood flow regulatory mechanisms, the primary limitation of resting CTP is its difficulty detecting cases with impaired coronary flow reserve but preserved resting perfusion. Conversely, stress CTP effectively exposes coronary flow reserve abnormalities through cardiac stress stimulation, significantly enhancing myocardial ischemia detection. In stress testing, adenosine is widely used due to its short half-life but is contraindicated in patients with airway hyperresponsiveness, such as chronic obstructive pulmonary disease (COPD), owing to its bronchoconstrictive effects. Lexiscan, a selective coronary vasodilator with rapid onset, prolonged action, and milder side effects, represents a preferable alternative for COPD patients ^[27].

2.2.2. Diagnostic value of CTP for CAD

The diagnostic efficacy of CTP has been validated in multiple studies. A comparative study by Nous et al. ^[30] demonstrated that combining dynamic CTP with CCTA significantly improved diagnostic specificity (89% vs. 72%) and overall accuracy (88% vs. 78%) compared to CCTA alone. This advantage was especially notable when distinguishing moderate stenoses (50–69%), elevating diagnostic accuracy from 44% to 71%. Although the combined method exhibited slightly lower sensitivity compared to CCTA alone (84% vs. 96%), it provided significant additional value through hemodynamic assessment. The median MBF in ischemic regions was 97 mL/100 mL/min, significantly lower than in non-ischemic regions (158 mL/100 mL/min), thereby offering important quantitative evidence for clinical decision-making. However, definitions of MBF thresholds vary across studies, and the lack of standardized parameters directly limits broader clinical adoption of CTP. Comparative studies indicate that dynamic CTP combined with CCTA achieves sensitivity and specificity comparable to MR and PET in detecting myocardial ischemia, surpassing SPECT. This combined modality is particularly suitable for patients contraindicated for MR or PET ^[31]. Notably, most current CTP studies utilize dual-source CT platforms and commonly exclude obese patients (BMI >30 kg/m²). Future prospective, multicenter studies involving conventional CT equipment and obese patient subgroups are needed to validate the clinical generalizability of this technology.

Evidence from multicenter studies shows clear advantages of integrating CTP with CCTA for optimizing ICA indications ^[32–35]. Notably, the PERFECTION study demonstrated that combining static CTP with CCTA significantly improved specificity (95% vs. 76%) and PPV (87% vs. 61%) compared to anatomical assessment alone, while maintaining high sensitivity (92%) ^[33]. This combined approach accurately identifies functionally ischemic lesions warranting revascularization, effectively excluding cases of anatomical stenosis without associated hemodynamic abnormalities, thus reducing false positives and unnecessary ICA procedures. However, the AMPLIFiED study found that dynamic CTP combined with CCTA improved specificity (from 36% to 75%) compared to CCTA alone but reduced sensitivity (from 93% to 72%). This sensitivity reduction may be related to the selected MBF threshold and the complexity of multivessel disease ^[32]. Therefore, considering its operational simplicity and high specificity, static CTP may be preferable for screening high-risk populations. Dynamic CTP, due to its longer imaging time and greater susceptibility to

artifacts, may lack sufficient resolution or demonstrate significant measurement inaccuracies when assessing multivessel disease or extensive perfusion defects.

2.2.3. Limitations and future directions of CTP

Although the clinical value of CTP in CAD diagnosis has been clearly demonstrated, radiation exposure remains a primary limitation hindering its broader clinical adoption. Static CTP has a significantly lower radiation dose than dynamic CTP (2.8 ± 1.2 mSv vs. 5.3 ± 0.7 mSv) ^[36]. Due to radiation safety concerns, clinical practice currently favors static CTP because of its lower radiation dose. Radiation exposure from CTP can be further minimized through techniques such as low-tube-voltage scanning and wide-coverage CT scanners ^[36,37].

In the future, PCCT is expected to enable precise quantitative analysis of myocardial contrast distribution, leveraging enhanced detector sensitivity and spatial resolution to substantially improve the accuracy of perfusion assessments ^[38]. Concurrently, deep learning (DL)-based image processing algorithms offer notable advantages for artifact suppression and image contrast enhancement, providing innovative solutions for optimizing CTP image quality.

3. Conclusion

Multimodal CT technology has reshaped the diagnostic paradigm for CAD by integrating anatomical imaging and functional assessment. As the cornerstone of anatomical imaging, CCTA has become the gold standard for noninvasive diagnosis of coronary artery stenosis due to its high spatial resolution. However, it inherently possesses limitations, including calcification artifacts and a lack of functional information. In functional imaging, CT-FFR employs computational fluid dynamics to simulate FFR, and CTP visualizes myocardial ischemia. Their combined use advances CAD diagnosis from anatomical stenosis evaluation to functional ischemia assessment, significantly reducing unnecessary invasive interventions. Multimodal CT integrates three-dimensional anatomical and functional information through single-visit examinations, elevating CAD assessment from purely anatomical description to comprehensive quantification. This integrated approach offers clinicians a more holistic perspective to support decision-making.

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Disclosure statement

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