


# Research Progress in Imaging Evaluation of Myocardial Microcirculation

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**Abstract:** The critical role of myocardial microcirculation in maintaining cardiac function has become increasingly recognized with advancements in cardiovascular disease research. Non-invasive imaging techniques, including transthoracic Doppler echocardiography (TTDE), myocardial contrast echocardiography (MCE), computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and cardiac magnetic resonance imaging (CMRI), are widely used to assess myocardial microcirculation. This review summarizes the principles, clinical applications, and recent research progress of these imaging modalities in evaluating myocardial microcirculation, highlighting their diagnostic value, limitations, and future directions.

**Keywords:** Myocardial microcirculation, transthoracic Doppler echocardiography, myocardial contrast echocardiography, CT myocardial perfusion imaging, cardiac magnetic resonance imaging

## Introduction

Cardiovascular diseases (CVDs) remain a leading cause of global morbidity and mortality, with an increasing prevalence among younger populations. While coronary angiography (CAG) is the gold standard for assessing epicardial coronary artery stenosis, it is invasive and cannot visualize microvascular circulation.<sup>1,2</sup> Emerging evidence indicates that microvascular dysfunction contributes significantly to adverse cardiovascular outcomes, even after successful revascularization in acute myocardial infarction (MI).<sup>3,4</sup> Notably, despite signs and symptoms consistent with obstructive atherosclerotic epicardial coronary arteries, about two thirds of women and one third of men with chest pain, and approximately 10% of patients with acute myocardial infarction show no angiographic evidence for significant obstructive coronary lesions.<sup>5,6</sup> The 2017 Chinese expert consensus on coronary microvascular disease (CMVD) underscored the clinical significance of microcirculatory assessment, prompting increased research into non-invasive imaging techniques.<sup>7</sup>

Currently, no direct imaging modality can visualize coronary microvessels due to their small size.<sup>8,9</sup> Instead, microvascular function is assessed indirectly using various non-invasive imaging methods, including transthoracic Doppler echocardiography (TTDE), myocardial contrast echocardiography (MCE), computed tomography (CT), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and cardiac magnetic resonance imaging (CMRI). This review provides a comprehensive analysis of these techniques, their advancements, and their clinical utility in evaluating myocardial microcirculation.

## Physiology and Pathology of Myocardial Microcirculation

The coronary circulation comprises the coronary arteries, capillary network, and coronary veins. Anatomically, these three parts are difficult to distinguish. The coronary arteries are divided into epicardial vessels, pre-arterioles, and

intramyocardial arterioles. Epicardial vessels have diameters ranging from approximately 500  $\mu\text{m}$  to 5 mm and exhibit low internal blood flow resistance. Pre-arterioles, with diameters of about 100–500  $\mu\text{m}$ , are located outside the myocardium and are not directly influenced by myocardial metabolic products. Their function is to maintain stable arteriolar pressure when coronary perfusion pressure or blood flow changes. Intramyocardial arterioles, with diameters less than 100  $\mu\text{m}$ , experience the most significant drop in vascular pressure and are highly susceptible to myocardial metabolic products. Pre-arterioles and intramyocardial arterioles are not visible during coronary angiography but provide about 90% of the coronary flow reserve and 80% of coronary circulation resistance.<sup>10,11</sup> Myocardial microcirculation, composed of pre-arterioles, arterioles, capillaries, and venules, is the site of material exchange between myocardial cells and blood. It plays a crucial role in maintaining the normal physiological metabolism and function of myocardial cells.<sup>12,13</sup>

Myocardial microcirculation disorders can affect coronary microcirculation perfusion, leading to symptoms of myocardial ischemia, clinically manifested as X syndrome, no-reflow phenomenon, and slow blood flow after coronary recanalization.<sup>14,15</sup> Studies have shown that structural and functional impairments of the microcirculation are independent predictors of adverse outcomes in patients with coronary artery disease (CAD).<sup>16,17</sup> Research emphasizes the significance of myocardial microcirculation dysfunction in the development of periprocedural myocardial injury (PMI).<sup>18</sup> The mechanisms underlying myocardial microcirculation disorders remain unclear. Most scholars believe that changes in myocardial microcirculation are influenced by various factors, such as metabolism, hormones, autonomic nervous system variations, and endothelial regulation.<sup>19,20</sup>

## **Non-Invasive Imaging Methods for Myocardial Microcirculation**

### **Transthoracic Doppler Echocardiography (TTDE)**

TTDE can detect blood flow velocity in the epicardial coronary arteries. By measuring the ratio of blood flow velocity in the left anterior descending artery (LAD) during stress to that in a resting state, TTDE non-invasively determines the coronary flow velocity reserve (CFVR), thereby evaluating myocardial microcirculation.<sup>21</sup> Numerous studies have shown that the coronary blood flow velocities measured by TTDE correlate well with those obtained through intracoronary Doppler measurements, and TTDE can also assess the prognosis of patients with CAD.<sup>22</sup> Research has reported a correlation between CFVR measured by TTDE and coronary flow reserve (CFR) measured by continuous thermodilution before elective percutaneous coronary intervention.<sup>23</sup> TTDE has advantages such as being convenient, fast, and radiation-free. However, its reliability is best when evaluating the microvascular function of the left anterior descending artery, and it requires a high level of technical expertise from the operator, limiting its clinical application.

### **Myocardial Contrast Echocardiography (MCE)**

Myocardial contrast echocardiography (MCE) is a new technique that uses special microbubble contrast agents injected intravenously and ultrasound technology to visualize microbubbles within the myocardium, thus reflecting the status of myocardial microcirculation.<sup>24</sup> MCE stress echocardiography combines MCE with stress echocardiography, allowing for the quantitative assessment of myocardial perfusion by evaluating parameters such as microvascular blood volume, myocardial blood flow, and coronary flow reserve under stress conditions.<sup>25,26</sup> Studies have shown that myocardial perfusion reserve measured by MCE correlates well with coronary flow reserve measured by coronary angiography.<sup>27</sup> MCE is cost-effective, easy to obtain, and free of ionizing radiation, making it valuable for diagnosing and prognosticating CAD patients.<sup>28,29</sup>

### **Computed Tomography (CT)**

Advancements in CT hardware and software have made coronary computed tomography angiography (CCTA) a key tool for screening and diagnosing CAD.<sup>30</sup> Recently, computed tomography myocardial perfusion imaging (CT-MPI) has rapidly developed, enabling accurate assessment of coronary anatomy and myocardial perfusion, thereby evaluating myocardial microcirculation.<sup>31,32</sup> This one-stop anatomical and functional assessment has significant clinical value. CT-MPI can be performed using static or dynamic scanning methods. Static CT-MPI involves injecting a contrast agent

intravenously and capturing single-phase myocardial images to indirectly reflect myocardial perfusion by observing contrast distribution within the myocardium.<sup>33</sup> Dynamic CT-MPI involves continuous cardiac scanning while injecting a contrast agent, with subsequent image analysis in a specialized workstation to obtain myocardial perfusion parameters, including time to peak (TTP), mean transit time (MTT), blood flow (BF), and blood volume (BV), providing a quantitative assessment of myocardial microcirculation. Research by Yi et al involved scanning CAD patients with low-dose CT-MPI and extracting single-phase CCTA images from CT-MPI. They found that the diagnostic sensitivity, specificity, and accuracy of CT-MPI and CT-MPI combined with single-phase CCTA were 77.8%, 93.7%, and 84.1% versus 93.7%, 87.9%, and 90.2%, respectively.<sup>34</sup> This indicates that low-dose, one-stop CT-MPI has good myocardial ischemia detection performance with a lower radiation dose. Studies by Muscogiuri et al combined CT-MPI data with deep learning (DL) algorithms to predict hemodynamically significant coronary artery disease.<sup>35</sup> They found that the combined DL algorithm improved diagnostic accuracy for myocardial ischemia and shortened analysis time.

With ongoing development in CT software and hardware, artificial intelligence(AI) is now widely used in cardiovascular imaging for examination, image post-processing, diagnosis, treatment, and prognosis evaluation. The development of artificial intelligence (AI) and machine learning (ML) in recent decades has allowed healthcare professionals to make more effective and data-driven decisions.<sup>36</sup> Researchers have developed a multimodal deep learning model that integrates CT imaging with clinical data to accurately predict short-term mortality in patients with acute pulmonary embolism, demonstrating significantly superior performance compared to the current Pulmonary Embolism Severity Index scoring standard.<sup>37</sup> CT-MPI technology is expected to play an increasingly significant role in diagnosing cardiovascular diseases in the future.<sup>38</sup>

## Positron Emission Tomography (PET)

Positron emission tomography (PET) is currently the most accurate non-invasive imaging method for assessing coronary microcirculation. By injecting radiotracers, PET provides dynamic information on tracer uptake in the myocardium during both resting and stress conditions, allowing for the quantitative calculation of reliable myocardial blood flow and perfusion data, thus accurately evaluating myocardial microcirculation.<sup>39,40</sup> Commonly used tracers include <sup>82</sup>Rb, <sup>13</sup>N-ammonia, and <sup>15</sup>O-H<sub>2</sub>O. Miura et al reported that <sup>13</sup>N-ammonia PET has significant clinical value in prognostically assessing patients with non-obstructive coronary arteries.<sup>41,42</sup> Sakai et al found that reduced perfusion metabolic index and myocardial flow reserve are characteristic features of ischemia with no obstructive coronary arteries (INOCA) as shown by <sup>13</sup>N-ammonia PET, making it useful for monitoring the treatment process.<sup>43</sup> Specifically, the following content has been added to the manuscript: “In recent years, PET/CT, leveraging its superior spatial resolution and dynamic imaging features, has enabled the simultaneous acquisition of precise quantitative parameters such as myocardial blood flow (MBF) and myocardial flow reserve (MFR). This approach more accurately reflects myocardial microcirculatory function compared to conventional methods.<sup>44</sup> Some scholars have utilized the emerging imaging technology of <sup>68</sup>Ga-FAPI-04 PET/CT to non-invasively assess the degree of myocardial fibroblast activation. Their findings indicate that PET/CT imaging provides a more reliable molecular imaging basis for the early detection, risk stratification, prognosis evaluation, and clinical decision-making in Amyloid light-chain cardiac amyloidosis, demonstrating significant diagnostic potential and promising clinical application prospects.<sup>45</sup> Meanwhile, generative AI shows promise in synthesizing high-quality PET images from low-dose acquisitions, potentially reducing radiation exposure while maintaining diagnostic accuracy. These advances position PET as a powerful tool for both microcirculatory function assessment and molecular-level plaque characterization. However, PET has drawbacks such as long examination times, high costs, and exposure to radiation, which somewhat limit its widespread clinical application.

## Single Photon Emission Computed Tomography (SPECT)

Single photon emission computed tomography (SPECT) is one of the most commonly used methods for coronary artery imaging. By injecting tracers labeled with <sup>201</sup>Ti or <sup>99m</sup>Tc, SPECT records the radioactive activity in the myocardium during both resting and stress conditions, thereby obtaining myocardial perfusion information.<sup>46</sup> Studies have reported that SPECT is a highly sensitive and quantitative cell-tracking technique that can assess myocardial perfusion and function, holding significant clinical value.<sup>47</sup> Yoneyama et al suggested that combining CCTA with myocardial perfusion

SPECT fusion imaging helps identify culprit coronary arteries.<sup>48</sup> The diagnostic performance of AI in this context is comparable to that of nuclear medicine physicians. Research has indicated that myocardial perfusion imaging with cadmium-zinc-telluride SPECT shows a good correlation between coronary flow reserve (CFR) obtained from vascular regions and the fractional flow reserve (FFR) measured by CAG.<sup>39</sup>

## Cardiac Magnetic Resonance Imaging (CMRI)

Cardiac magnetic resonance imaging (CMRI) is highly valued for its ability to provide a comprehensive, non-invasive, and radiation-free evaluation of cardiac morphology, structure, function, and myocardial viability. It is considered the gold standard for cardiac function assessment and has significant clinical applications, particularly in the non-invasive evaluation of myocardial tissue characteristics.<sup>49,50</sup> CMRI utilizes gadolinium contrast agents for first-pass perfusion and delayed enhancement to obtain myocardial blood flow (MBF) and myocardial perfusion reserve index (MPRI), reflecting myocardial perfusion status.<sup>51</sup> Studies have shown that CMRI is crucial in evaluating myocardial microcirculation in patients with myocardial infarction with non-obstructive coronary arteries (MINOCA).<sup>52</sup> The microvascular obstruction (MVO) seen in CMRI, which appears as patchy low-signal regions within high-signal infarct areas on delayed enhancement images, is an independent predictor of adverse long-term outcomes.<sup>53</sup>

Recent advancements in MRI hardware and software have led to the development of new CMRI techniques, such as T1 mapping and T2 mapping, which allow for the non-invasive quantitative assessment of myocardial tissue characteristics.<sup>54</sup> Quantitative perfusion CMRI can non-invasively measure myocardial blood flow and myocardial perfusion reserve, providing a good reflection of myocardial microcirculation.<sup>55</sup> Studies have found a strong correlation between CMRI and <sup>13</sup>N-ammonia PET in measuring global MBF in stable CAD.<sup>56</sup> Hybrid positron emission tomography/magnetic resonance imaging (PET/MRI) is an emerging modality that combines metabolic and anatomical data, demonstrating promising diagnostic performance for various cardiac conditions.<sup>57</sup> Research exploring the characteristics of myocardial fibroblast activation protein inhibitor uptake using PET/MR in patients with coronary heart disease (CHD) and its relationship with abnormal myocardial wall motion has shown that simultaneous <sup>68</sup>Ga-FAPI PET/MR provides novel insights into the regional patterns of fibroblast activation in CHD, revealing an association between the fibroblast activation protein signal and abnormal wall motion.<sup>58</sup> However, CMRI requires patient cooperation, including breath-holding, has a long examination time, and is not suitable for patients with renal dysfunction, claustrophobia, or metallic implants, limiting its clinical application to some extent. In addition, quantifying MBF and MPRI using CMRI faces key limitations including limited spatiotemporal resolution, motion artifacts, and lack of standardized protocols. AI integration encounters challenges of scarce high-quality annotated data, model interpretability issues, and multicenter variability. Addressing these through advanced high-resolution sequences, motion-correction algorithms, semi-supervised learning, and federated learning could significantly improve assessment accuracy. Overcoming these barriers would enhance both research depth and clinical translation of microvascular dysfunction evaluation, potentially establishing CMRI-derived parameters as robust diagnostic and prognostic biomarkers.

## Conclusion

Non-invasive imaging plays a pivotal role in evaluating myocardial microcirculation, with each modality offering unique strengths and limitations. TTDE and MCE are accessible and cost-effective, whereas PET and CMRI provide high diagnostic accuracy. Emerging technologies, such as AI-enhanced CT-MPI and advanced CMRI mapping, hold promise for improving microcirculatory assessment. Future research should focus on optimizing these techniques to enhance clinical applicability and deepen our understanding of microvascular pathophysiology.

## Abbreviations

TTDE, transthoracic doppler echocardiography; MCE, myocardial contrast echocardiography; CT, computed tomography; PET, positron emission tomography; SPECT, single-photon emission computed tomography; CMRI, cardiac magnetic resonance imaging; CAG, coronary angiography; MI, myocardial infarction; CMVD, coronary microvascular disease; CAD, coronary artery disease; PMI, periprocedural myocardial injury; LAD, left anterior descending artery; CFVR, coronary flow velocity reserve; CFR, coronary flow reserve; CCTA, coronary computed tomography

angiography; CT-MPI, computed tomography myocardial perfusion imaging; TTP, time to peak; MTT, mean transit time; BF, blood flow; BV, blood volume; DL, deep learning; INOCA, no obstructive coronary arteries; MVO, microvascular obstruction; AI, artificial intelligence; ML, machine learning; MBF, myocardial blood flow; MFR, myocardial flow reserve; CHD, coronary heart disease.

## Consent for Publication

All authors agree the publication in this journal.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Chunlong Yan and Jinfeng Ma are co-first authors for this study. The authors declare no competing interests in this work.

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