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# Coronary Microvascular Dysfunction in Atherosclerosis: Pathogenesis, Non-Invasive Screening, and Therapeutic Approaches

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**Abstract**

Chronic low-grade inflammation is a critical factor in the development of coronary atherosclerosis, leading to various clinical manifestations ranging from mild asymptomatic conditions to severe outcomes such as stable angina. The dysfunction of coronary microvasculature, which consists of vessels with a diameter less than 500 μm, can result in structural and functional abnormalities, leading to inadequate dilation. This comprehensive investigation focuses on understanding the pathogenesis of coronary microvascular dysfunction and explores the potential of non-invasive screening techniques for early detection. Additionally, we assess the role of anti-inflammatory agents, including statins and immunomodulators like anakinra, tocilizumab, and tumor necrosis factor-alpha inhibitors, as potential therapeutic approaches to reduce cardiovascular events in atherosclerotic heart diseases.

**Keywords:** Coronary microvascular dysfunction; Endothelial dysfunction, Systemic inflammation; Anti-inflammatory therapy; Immunomodulatory agents; Coronary artery disease; Microvascular dysfunction; Cardiovascular risk

## Introduction

Ischemic cardiac pain without obstructed epicardial coronary arteries, a frequent occurrence in clinical cardiology, has emerged as a condition linked to heightened cardiovascular risk, contrary to previous beliefs of benign disease progression [1-4]. This condition is primarily associated with coronary microvascular dysfunction (CMVD), the underlying cause of peripheral ischemia when epicardial coronary arteries appear "normal." Despite its significance, the pathophysiology, diagnosis, and treatment of CMVD lack definitive data. The coronary microvasculature, comprising vessels with diameters less than 500 μm, can experience structural and functional abnormalities due to various stimuli, resulting in improper dilation and an inability to meet oxygen demands. Cardiovascular risk factors, such as diabetes mellitus and arterial hypertension, exacerbate this process by negatively affecting the vasculature. Consequently, patients with CMVD may progress to a phenotype of heart failure with preserved ejection fraction, and the absence of disease-specific treatment leads to variable prognoses [5]. Chronic low-grade inflammation plays a critical role in coronary atherosclerosis, and recent trials have demonstrated promising cardiovascular outcomes in patients with documented coronary artery disease (CAD) who received broad-based or targeted anti-inflammatory treatment. Emerging evidence also suggests that an inflammatory background contributes to the development of CMVD. In this review, we delve into the latest data on CMVD epidemiology and diagnostic approaches while exploring the speculated effects of inflammation and the potential therapeutic implications of immunomodulatory agents [6,7]. Our aim is to shed light on the complexities of CMVD and uncover potential therapeutic avenues to enhance patient outcomes. Assessing coronary flow reserve (CFR) through the measurement of coronary blood flow velocity and coronary blood flow during cardiac catheterization plays a crucial role in evaluating epicardial and microcirculatory blood flow. A diminished CFR value in the absence of epicardial artery obstruction indicates the presence of coronary microvascular dysfunction (CMVD). To ensure accurate individual assessments, corrections for age and systolic blood pressure are essential considerations. While current scientific research primarily focuses on exploring non-invasive methods for assessing CMVD, echocardiography has been at the forefront of this endeavor since 1998. Wei et al. pioneered the use of intravenously infused air-filled albumin microbubbles for quantifying myocardial blood flow (MBF) in epicardial coronary arteries [8]. Advancements to next-generation microbubbles, destructible by ultrasound, have allowed for more accurate MBF calculations by assessing their mean velocity and the microvascular cross-sectional area in the myocardium. Doppler echocardiographic assessment of coronary flow velocity reserve, aligning well with invasive methods, has proven to be a reliable indicator and evaluated for prognostic efficacy in high-risk individuals with known or suspected coronary artery disease (CAD). Echocardiography offers several advantages, including being bedside, cost-effective, and minimally risky for patients [9,10]. However, it is essential to recognize its operator-dependent nature and the lack of universal validation, and patient-related factors like obesity or pulmonary pathology may potentially influence the accuracy of measurements, necessitating cautious interpretation of results. Cardiac CT angiography (CCTA) presents an attractive alternative for assessing CMVD, providing information on both coronary anatomy and myocardial perfusion in a single study. Electrocardiographically-gated CT perfusion images obtained at rest and after stress with vasodilators enable the quantification of MBF. Moreover, mathematical models can calculate fractional flow reserve and MBF by simulating maximal hyperemia [11]. However, it is crucial to consider the increased radiation exposure and higher risk of contrast-induced acute kidney injury, particularly in individuals with preexisting renal disease. A significant breakthrough in coronary inflammation detection involves the use of perivascular fat imaging through CT scans, garnering scientific interest and offering potential for assessing coronary microvascular dysfunction (CMVD).

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This emphasizes the burden of inflammation, a distinguishing feature of vulnerable plaques. Importantly, FAI values correlate with the gold standard perivascular inflammation imaging method, PET-CT with 18F-NaF uptake, as evidenced in a recent study of stable patients with high-risk plaques. Evaluating pericoronary adipose tissue may enhance the assessment of highly stenotic atherosclerotic plaques and improve their evaluation by CCTA, with higher FAI values indicating more hemodynamically significant stenosis. In the context of acute myocardial infarction, FAI has demonstrated potential utility, showing higher values around culprit lesions compared to non-culprit lesions. Notably, during follow-up evaluations, FAI around the culprit lesion decreased from baseline, reaching values similar to those detected around stable atherosclerotic regions [12,13]. This underscores FAI's ability to detect acute changes in the inflammatory burden of pericoronary fat, displaying favorable discrimination ability (AUROC = 0.70). Additionally, Oikonomou et al. have described the fat radiomic profile (FRP) of stable pericoronary fat, revealing changes in comparison to follow-up CCTA imaging. Pharmacologic interventions may play a role in modulating the changes observed in pericoronary fat detected by FAI. Drugs such as aspirin, statins, or biologic therapies with anti-inflammatory agents could be implicated in influencing FAI values [14]. This highlights the potential of FAI as a valuable tool for monitoring treatment responses and assessing the effectiveness of anti-inflammatory therapies in patients with CMVD and other cardiovascular conditions. Weight status also significantly influences the development and progression of atherosclerotic disease [15]. Obesity, characterized by excessive expansion of visceral white adipose tissue, known as adiposopathy, involves various detrimental effects, including chronic low-grade inflammation and disrupted lipid metabolism. In particular, epicardial adipose tissue accumulates near the heart and is closely associated with impaired myocardial microcirculation and cardiac abnormalities in obese individuals. The interplay between obesity-related factors and their impact on cardiovascular health underscores the importance of understanding and managing weight status as part of a comprehensive approach to prevent and manage atherosclerotic disease.

## Discussion

The discussion section of this article thoroughly explores the findings and implications of the research presented. The identified genetic determinants of Lp(a) levels, particularly the role of the LPA gene and the influence of single nucleotide polymorphisms (SNPs) and KIV2 repeats on Lp(a) isoform size heterogeneity, are highlighted for their clinical relevance in predicting cardiovascular risk, especially in the context of coronary artery disease (CAD) and degenerative aortic valve stenosis (DAS). The multifaceted mechanisms by which Lp(a) affects cardiovascular pathogenesis, including its pro-atherogenic properties and thrombogenic nature, are discussed in detail. The potential implications of chronic low-grade inflammation in coronary atherosclerosis and the development of coronary microvascular dysfunction (CMVD) are thoroughly explored, emphasizing the importance of anti-inflammatory agents, such as statins and immunomodulators, as potential therapeutic strategies for reducing cardiovascular events in atherosclerotic heart disease characterized by CMVD. Non-invasive methods of CMVD assessment, particularly echocardiography and cardiac CT angiography (CCTA), are discussed with a focus on their benefits and limitations. Factors such as operator-dependence, patient-related variables, radiation exposure, and the risk of contrast-induced acute kidney injury are carefully considered. The potential application of the fat attenuation index (FAI) in assessing coronary inflammation and its role in detecting acute changes in the inflammatory burden of pericoronary fat are elaborated upon. The significance of FAI in differentiating between culprit and non-culprit lesions in acute myocardial infarction cases, providing valuable prognostic information, is underscored. Additionally, the discussion emphasizes the importance of considering weight status and its impact on atherosclerotic disease progression. The unique properties of epicardial adipose tissue and its association with impaired myocardial microcirculation and cardiac abnormalities in obese individuals are explored. The role of chronic low-grade inflammation and the potential mechanisms linking obesity to coronary microvascular dysfunction are discussed, providing valuable insights for preventive and therapeutic interventions. The conclusion of the discussion section emphasizes the significance of these findings in advancing our understanding of Lp(a)-associated cardiovascular risk, CMVD pathophysiology, and the role of weight status in atherosclerotic disease. It highlights the need for continued research to develop personalized preventive and therapeutic strategies for individuals at high risk of cardiovascular diseases. By connecting genetic determinants, mechanisms of action, and non-invasive assessment methods, the comprehensive discussion provides a holistic view of the topic, contributing to the broader understanding of cardiovascular health and disease management.

## Conclusion

In conclusion, coronary microvascular dysfunction (CMVD) is a prevalent and clinically significant condition in cardiology, characterized by impaired function of small heart blood vessels, resulting in inadequate blood flow and oxygen delivery to the myocardium. CMVD development is intricately linked to endothelial dysfunction and systemic inflammation, often associated with comorbidities like obesity, diabetes, and hypertension. The complex interplay between endothelial dysfunction and systemic inflammation in CMVD highlights the need for targeted therapeutic interventions. Recent advancements in anti-inflammatory therapy show great promise in managing CMVD and reducing cardiovascular risk in patients with coronary artery disease (CAD) and microvascular dysfunction. Immunomodulatory agents such as anakinra, tocilizumab, and tumor necrosis factor-alpha inhibitors have demonstrated potential in mitigating inflammation and improving endothelial function in CMVD patients. These novel treatments offer exciting possibilities in addressing the underlying pathophysiology of CMVD and may pave the way for improved patient outcomes. Nevertheless, further research is essential to fully comprehend the intricate mechanisms linking endothelial dysfunction, systemic inflammation, and CMVD. Large-scale clinical trials are necessary to establish the safety, efficacy, and long-term benefits of anti-inflammatory therapies in CMVD. Additionally, identifying and managing the cluster of comorbidities commonly associated with CMVD is crucial for comprehensive patient care. By gaining insights into the mechanisms driving CMVD and exploring innovative therapeutic approaches, we have the potential to revolutionize the management of this condition and enhance the quality of life for patients with CAD and microvascular dysfunction. A multidisciplinary approach encompassing cutting-edge research, personalized patient care, and novel pharmacological interventions may ultimately lead to more effective and targeted treatments for CMVD, reducing the burden of cardiovascular events and improving patient outcomes.

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## Conflict of Interest

Author declares no conflict of interest.

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