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Coronary Inflammation and Cardiovascular Events in Patients Without Obstructive Coronary Artery Disease

Jia Ling Diau[1] · Richard A. Lange[1,2,3]

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Abstract

Purpose of Review This review evaluates the role of vascular inflammation in patients who develop myocardial infarction with non-obstructive coronary arteries (MINOCA). It also introduces pericoronary adipose tissue (PCAT) and epicardial adipose tissue (EAT) as possible biomarkers for risk prediction in patients with non-obstructive coronary artery disease (CAD).

Recent Findings PCAT and EAT contribute to the development and progression of coronary artery inflammation and plaque vulnerability. Coronary computed tomography angiography (CCTA) can detect localized areas of inflammation through changes in the attenuation values of PCAT and EAT. Attenuation values can be further integrated with traditional risk factors using artificial intelligence to generate risk scores that significantly enhance prognostic accuracy in patients with and without obstructive coronary artery disease.

Summary Assessing PCAT and EAT inflammation via CCTA and AI-driven risk algorithms enable precise risk prediction of MINOCA and major adverse coronary events (MACE) in patients with non-obstructive CAD.

Keywords MINOCA · Epicardial · Pericoronary adipose inflammation

Introduction

Acute myocardial infarction (AMI) is commonly caused by thrombus formation at the site of atherosclerotic obstruction of a coronary artery [1]. However, in approximately 6–8% of AMI cases, coronary computed tomography angiography (CCTA) reveals no significant stenosis (≥50% luminal diameter narrowing), leading to a diagnosis of myocardial infarction with non-obstructive coronary arteries (MINOCA) [1, 2].

MINOCA is a diagnosis of exclusion made only after ruling out obstructive coronary artery disease (CAD) and non-ischemic causes of myocardial injury (e.g., myocarditis and takotsubo syndrome) [3]. Possible causes are classified into atherosclerotic and non-atherosclerotic categories, with the former involving plaque disruption (e.g., plaque erosion and rupture) and the latter encompassing epicardial coronary vasospasm, coronary microvascular dysfunction, coronary embolism/thrombosis, supply-demand mismatch, and spontaneous coronary artery dissection (SCAD) [3, 4]. MINOCA is more commonly diagnosed in women and younger patients, with a higher prevalence observed in African American, Pacific Islander, and Hispanic American populations [5]. Sex-specific differences in MINOCA etiology are also evident, as women are more likely than men to have causes such as SCAD, plaque disruption, and coronary embolism, while coronary vasospasm is a more frequent cause in men [5].

Inflammation appears to play an important role in MINOCA and has emerged as a strong prognostic indicator, with several studies highlighting the role of inflammatory biomarkers in predicting outcomes. Plasma biomarkers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), reflect local levels of vascular inflammation associated with many of the non-atherosclerotic causes of MINOCA, such as coronary vasospasm and coronary microvascular dysfunction

✉ Richard A. Lange
Richard.Lange@ttuhsc.edu

Jia Ling Diau
Jidiau@ttuhsc.edu

1 Paul L. Foster School of Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

2 Department of Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA

3 TTUHSC-El Paso, 130 Rick Francis St. MC 11001, El Paso, TX 79905, USA

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[6]. MINOCA patients have lower serum levels of high-sensitivity cardiac troponin T (hs-cTnT) but higher serum levels of growth differentiation factor 15 (GDF-15) and high-sensitivity C-reactive protein (hs-CRP) than those with obstructive CAD. These observations suggest differences in the severity and inflammatory profiles among patients with MINOCA versus those with obstructive CAD [7].

Studies have also identified an association between pro-inflammatory cytokines released from pericoronary adipose tissue (PCAT) and the development of major adverse cardiac events (MACE) in MINOCA patients [6, 8]. Collectively, these findings underscore the value of inflammatory markers as predictive factors for the onset of cardiovascular events in patients without obstructive CAD.

Diagnostic Evaluation of MINOCA Patients

MINOCA is diagnosed through a variety of methods according to its underlying etiology. Initially, echocardiography is often used to evaluate cardiac wall motion abnormalities and conditions that cause myocardial injury, such as takotsubo syndrome and aortic dissection [9]. To further differentiate between ischemic and non-ischemic causes of myocardial injury, cardiac magnetic resonance (CMR) is commonly utilized within 10 days following an acute cardiac event. Through imaging sequences such as T2-weighted imaging and late gadolinium enhancement (LGE), CMR can detect edema and fibrosis of cardiac tissue, aiding in the confirmation or reclassification of initially suspected cases of MINOCA [10].

Following CMR, additional diagnostic procedures are often needed to pinpoint the root cause of MINOCA. Invasive coronary angiography is commonly used as a first-line diagnostic technique, where it is particularly effective for detecting SCAD and excluding obstructive CAD [2]. Additionally, in cases where a vasospastic cause of MINOCA is suspected, coronary angiography may be supplemented with the administration of acetylcholine or ergonovine to induce and evaluate vasospasm in the epicardial coronary arteries [11]. To assess atherosclerotic causes of MINOCA, advanced coronary imaging modalities such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) can be utilized. Using 40 MHz ultrasound waves, IVUS creates cross-sectional images of blood vessels that enable direct visualization of lesions, plaques, ulcerations, and fibrous tissue. Conversely, OCT employs infrared light to provide a detailed view of coronary wall structures such as fibrous caps, disrupted plaques, and SCAD [9]. Together, these imaging techniques provide a comprehensive assessment of the plaque-related causes of MINOCA.

Prognostic Indicators of MINOCA

Patients with MINOCA generally exhibit a better prognosis than those with obstructive CAD. Nevertheless, the mortality rate of MINOCA patients remains higher than that of the general population, highlighting the need to evaluate the prognostic value of current diagnostic techniques [2]. The United Kingdom QRISK3 and the American College of Cardiology Atherosclerotic Cardiovascular Disease (ASCVD) risk scores are widely used risk prediction algorithms that assess cardiovascular disease and MACE by accounting for common risk factors [12, 13]. However, both algorithms have limited ability for predicting MACE in patients with non-obstructive coronary arteries due to their reliance on traditional atherosclerotic risk factors like age, gender, cholesterol levels, blood pressure, smoking status, and diabetes mellitus. Additionally, they do not incorporate assessments of vascular inflammation that may play an important role in the etiology of MINOCA. Alternatively, most diagnostic tools for MINOCA– such as IVUS and OCT– primarily offer insight into the visualized lesions at the time of their assessment. CMR provides greater prognostic value than traditional risk scores in MINOCA patients by allowing for more targeted treatment due to its ability to differentiate ischemic and non-ischemic causes (i.e., ischemic causes are associated with higher rates of MACE later in life) [9, 10]. Together, these diagnostic tools provide useful prognostic information in patients who have already been diagnosed with MINOCA, but none can reliably assess the long-term risk of developing MINOCA or MACE in patients with chest pain who do not have obstructive CAD. This gap underscores the need to better understand and predict long-term cardiovascular risk in this patient population.

Assessing Risk in Non-Obstructive CAD: Role of Epicardial and Pericoronary Adipose Tissue

Pericoronary adipose tissue (PCAT) and epicardial adipose tissue (EAT) have emerged as possible indicators for predicting the onset of MINOCA and MACE in patients without obstructive CAD [8]. In addition to their role as an energy reserve system, PCAT and EAT contribute to the development and progression of coronary artery inflammation and plaque vulnerability. They also participate in the vascular response to sympathetic stimuli, myocardial ischemia, and arrhythmia.

Located surrounding the coronary arteries, PCAT releases adipokines, chemokines, and pro-inflammatory cytokines in response to metabolic dysfunction and cardiovascular stress, such as diabetes, and atherosclerotic CAD [8]. Conversely,

Table 1 Pro-inflammatory cytokines produced by epicardial and pericoronary adipose tissue

Epicardial Adipose Tissue (EAT)	Pericoronary Adipose Tissue (PCAT)
Interleukins: IL-1β, IL-6, IL-6 soluble receptor	Interleukins: IL-6
Tumor Necrosis Factor-α (TNF-α)	Monocyte Chemoattractant Protein-1 (MCP-1)
Adipokines	Growth factors
Angiotensin II	Angiotensin II
Plasminogen Activator Inhibitor-1 (PAI-1)	Plasminogen Activator Inhibitor-1 (PAI-1)
Free Fatty Acids (FFAs)	Interferon-gamma (IFN-γ)
Lysophosphatidic Acid (LPA)	
Interferon-gamma (IFN-γ)	

EAT envelopes the heart in the space between the myocardium and pericardium and is particularly abundant in the atrioventricular and interventricular sulci. It normally exerts a protective role on the heart through the release of anti-inflammatory and vasodilatory substances such as adrenomedullin [14, 15]. However, during periods of metabolic disturbance and cardiac stress, such as dyslipidemia and ischemia, EAT may shift to a pro-inflammatory state, releasing factors that contribute to coronary inflammation [8].

The pathogenesis of the pro-inflammatory properties of EAT and PCAT under stress-inducing conditions is primarily driven by the generation of reactive oxygen species (ROS), which promote the release of pro-inflammatory cytokines such as interleukins (IL) and interferon-gamma (IFN-γ). These cytokines, in turn, stimulate macrophages toward a pro-inflammatory phenotype (so-called, M1) that further exacerbates local inflammation. Simultaneously, the secretion of adiponectin– a molecule that typically counteracts inflammation and atherogenesis– is reduced. Together, these chemokines may diffuse into the coronary arteries and myocardium, potentially contributing to the development of atherosclerotic causes of MINOCA through plaque disruption. A list of pro-inflammatory cytokines produced by EAT and PCAT is summarized in Table 1 [8].

Inflammation from EAT and PCAT also appears to play an important role in non-atherosclerotic causes of MINOCA, such as coronary vasospasm and SCAD [8]. In vasospastic MINOCA, inflammatory factors produced by EAT and PCAT precipitate smooth muscle contraction by enhancing calcium influx through L-type calcium channels [16]. In SCAD, inflammation may contribute to vascular injury due to eosinophilic infiltration and the release of cytokines [17, 18] or occur in response to existing vascular damage [8]. Thus, pro-inflammatory factors serve as a well-established link to both vasospastic and SCAD-related causes of MINOCA.

Given their role in coronary inflammation and atherogenesis, detection and analysis of EAT and PCAT are increasingly viewed as a valuable source for predicting MACE and MINOCA, particularly in patients with chest pain and non-obstructed coronary arteries. Recently, coronary computed tomography angiography (CCTA) has emerged as a promising non-invasive imaging modality for detecting and evaluating these adipose tissue sites through its ability to identify areas of localized inflammation through attenuation. PCAT CCTA attenuation does not correlate with standard circulating inflammatory biomarkers, as shown in a post hoc analysis of the Scottish Computed Tomography of the HEART (SCOT-HEART) study [19]. This suggests that CT attenuation can identify coronary inflammatory status and active plaques that cannot be traced by systemic markers. Furthermore, CCTA offers detailed insights into the structural characteristics of coronary plaques, including their size, type, volume, and composition [9]. By incorporating measurements of EAT, PCAT, and plaque characteristics, CCTA has the potential to identify high-risk patients and guide clinical decision-making in the management of non-obstructive CAD [20].

Perivascular Fat Attenuation Index (pFAI) Measurement

The growing use of CCTA as a standardized first-line investigation for chest pain has facilitated the development of the perivascular fat attenuation index (pFAI), a novel biomarker that quantifies coronary vascular inflammation [21]. By analyzing 3D attenuation gradients from CCTA, the pFAI assesses inflammation by visualizing structural and compositional changes in the perivascular adipose tissue (PVAT)– the fat tissue surrounding a vessel at a radial distance that corresponds to the luminal diameter of the adjacent vessel [22].

During vascular inflammation, the lipid content of adipocytes is reduced through lipolysis, leading to a reduction in the size of adipocytes from larger, lipid-rich cells to smaller, more metabolically active ones. These smaller adipocytes subsequently secrete protective antioxidants, such as adiponectin, to counteract the oxidative stress caused by inflammation. Together, these changes in metabolism and adipocyte size result in an increase in the aqueous content and a decrease in the lipid content of the PVAT surrounding the inflamed artery. This manifests as changes in the CCTA attenuation [23]. CCTA attenuation values– measured at a radial distance from the vessel wall corresponding to the artery's diameter, excluding the proximal 10 mm of the vessel– normally range from −190 Hounsfield Units (HU) to -30 HU. When signals released from the inflamed coronary artery diffuse to the PVAT and inhibit local adipogenesis, the composition of the surrounding perivascular fat shifts

from predominantly lipid (with more negative HU values, closer to −190 HU) to an aqueous phase (with less negative HU values, closer to −30 HU). The weighted mean of these attenuation values is then calculated to derive the final pFAI, which offers a comprehensive summary of the cardiac inflammatory status that provides a more accurate reflection of coronary vascular inflammation than traditional systemic markers such as CRP [23]. The primary arteries evaluated for pFAI include the right coronary artery, the left circumflex, and the left anterior descending [22, 23]. However, inclusion of the side branches of the coronary vessels and other various anatomical variations in the measurement for pFAI improves the predictive accuracy of the generated result [22].

Prognostic Value of the Perivascular Fat Attenuation Index

The Cardiovascular RISk Prediction using Computed Tomography (CRISP-CT) study was the first to utilize pFAI to assess the risk of MACE in 3,912 patients undergoing CCTA. The study demonstrated that elevated pFAI values greater than −70.1 HU served as a reliable biomarker for coronary inflammation and cardiac mortality. Furthermore, pFAI was shown to be an independent prognostic cardiovascular risk factor, even after consideration of known contributory factors to MACE, such as the degree of coronary atherosclerosis, the presence of high-risk plaques (HRP), and traditional risk factors such as age, smoking, and hypertension. As attenuation values often fluctuate with changes in medical intervention or natural progression of the disease, pFAI may be valuable as a tool for monitoring patient response to treatment [24].

An elevated pFAI may indicate inflammation and increased cardiovascular risk, even in the absence of obstructive CAD. Studies show that patients with an elevated pFAI are at higher risk of MACE and MINOCA despite having non-obstructed coronary arteries and a low 10-year cardiovascular risk score [25]. pFAI is also instrumental in the exclusion of various causes of MINOCA [25]. Specifically, pFAI values in patients with myocarditis are lower than those in patients with MINOCA due to differences in their respective mechanisms of inflammation, highlighting the potential for pFAI to distinguish between different etiologies of myocardial injury [26]. Additionally, pFAI can differentiate between culprit and non-culprit plaques, as well as assess plaque instability, progression, and rupture, thereby making it particularly useful for patients with non-obstructive CAD at risk of developing atherosclerotic causes of MINOCA [23, 27, 28].

A pFAI score that indicates the severity of coronary inflammation is generated by incorporating attenuation values derived from CCTA and technical factors such as tube voltage, anatomical variations in fat, and patient demographics like age and sex [29]. Integrating this pFAI score with an artificial intelligence (AI)-enhanced cardiac risk prediction algorithm that incorporates: (a) coronary plaque metrics (e.g., coronary calcium, stenosis, and plaque characteristics); (b) functional factors (e.g., blood flow and coronary reserve); (c) traditional risk factors; (d) patient genetics; (e) lifestyle; and (f) environmental determinants can provide a personalized cardiovascular risk assessment over an 8-year period irrespective of coronary artery obstruction status [29].

Specialized branches of AI, particularly machine learning (ML) and its subfield of deep learning (DL), also offer highly accurate measurements of EAT, with results comparable to those obtained by experts, but in a fraction of the time (1.57 s for DL algorithms vs. 15 min for expert analysis) [30]. Recent advancements in radiomic profiling of PVAT further demonstrate the potential of AI to integrate coronary inflammation with imaging characteristics like fibrosis and vascularity, thereby improving the accuracy of cardiovascular risk predictions [31]. Ultimately, integrating AI with advanced imaging data offers a more precise and dynamic approach to assessing cardiovascular risk for MACE and MINOCA and guiding treatment decisions in high-risk patients with non-obstructed coronary arteries.

Artificial-Intelligence Risk Algorithm Utilizing Perivascular Fat Attenuation Index

The Oxford Risk Factors and Non-Invasive Imaging (ORFAN) Study evaluated the risk profile and event rates among patients undergoing CCTA as part of routine clinical care to test the hypothesis that coronary arterial inflammation drives cardiac mortality or MACE in patients with or without obstructive CAD. This longitudinal investigation conducted between 2010 and 2021 enrolled 40,091 patients aged 18 to 99 years from eight hospitals across the UK undergoing routine CCTA due to stable chest pain. In addition to evaluating the risks of MACE and cardiac mortality in individuals with both obstructive and non-obstructive CAD, the study aimed to validate the AI-Risk Algorithm– an AI-based tool originally tested in the U.S. population that integrates a patient's plaque burden, pFAI score, and individual risk factors– to predict cardiovascular risk over an 8-year period. Accordingly, the study tested the efficacy of the AI-risk classification system, which categorizes patients into risk groups of very high risk (≥10%), high risk (5% to <10%), and low or medium risk (<5%) of experiencing

cardiac mortality or MACE in order to guide clinical decision-making and management strategies [32].

In the 2.7 years median follow-up period, there were nearly twice as many cardiac deaths and major adverse cardiac events (in absolute numbers) among the group without obstructive CAD (a group that made up 81% of the cohort), compared with those with obstruction. This reinforces the importance of identifying patients without obstructive CAD who are at risk of MACE.

At a subsequent longer follow-up study (median 7.7 years), both the pFAI score and the AI-Risk algorithm were shown to be strong predictors of MACE and cardiac mortality independent from the presence or severity of CAD or traditional risk factors. The pFAI score was also predictive among patients with chronic inflammatory disease. The study further highlighted a strong association between the number of inflamed arteries identified by an elevated pFAI score and the risk of developing MACE or cardiac death.

Validation of the AI-risk classification system was also confirmed, as patients categorized into each risk group, regardless of whether they had obstructive or non-obstructive CAD, displayed MACE and cardiac death rates that aligned with the predicted outcomes. Additionally, combining the AI-risk score with the QRISK3 risk calculator significantly improved the predictive value in both obstructive and non-obstructive CAD populations [32].

The findings of this study have significant implications for clinical practice, as reclassification of patients based on the pFAI score and/or AI-risk algorithm– which incorporates FAI Score, the extent of coronary atheroma (if any), as well as the patient's traditional risk factors– can lead to more precise risk stratification, influencing treatment plans and management strategies.

Current treatments for MINOCA primarily target its underlying etiology [4], with common interventions including aspirin or dual antiplatelet therapy (DAPT), calcium channel blockers, statins, beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. Of these, statins, beta blockers, and DAPT have been associated with reduced mortality, though they do not significantly impact the risk of AMI development [33]. Given the strong link between inflammation and the onset of MINOCA and MACE in patients with non-obstructive CAD, targeting inflammation pharmacologically may represent a promising strategy. In support of this, studies have shown that rosuvastatin reduces MACE and mortality in patients with low LDL levels but elevated hs-CRP [34]. Similarly, anti-inflammatory agents such as colchicine and canakinumab (an interleukin-1 beta inhibitor) have demonstrated potential in lowering cardiovascular disease risk, although their effectiveness in MINOCA and non-obstructive CAD have yet to be confirmed in clinical trials [35, 36]. Nonetheless, the compelling relationship between inflammation and cardiovascular risk suggests that these therapies may offer therapeutic benefit for this patient population. Finally, a recent meta-analysis reported that women with MINOCA experienced a higher risk of in-hospital MACE compared with men [37], further suggesting a need for closer monitoring and optimal management through the possible inclusion of anti-inflammatory therapies in this cohort.

Conclusions

The development of MACE and MINOCA remains a significant concern in patients displaying stable chest pain with non-obstructive coronary arteries assessed by CCTA. Although traditional systemic inflammatory markers rise during episodes of cardiac injury and stress, recent research suggests that local (i.e., vascular) biochemical changes and CCTA attenuation in PCAT, EAT, and PVAT — reflecting the degree of inflammation in coronary arteries and surrounding cardiac tissue — serve as more reliable biomarkers for predicting MACE in patients with non-obstructive CAD. Advancement of diagnostic and prognostic tools, particularly with the integration of AI tools such as the pFAI, pFAI score, AI-Risk score, and AI-Risk classification systems significantly enhances predictive accuracy.

Incorporating these advanced tools into clinical practice may not only improve prognostic assessment but also guide more personalized treatment strategies. Given the strong association between inflammation and the onset of MACE in patients with non-obstructive CAD, future studies are needed to investigate the role of anti-inflammatory agents in the management of MINOCA and non-obstructive CAD.

While the findings of the ORFAN study provide important insights, there is still a need for larger, multicenter studies with diverse populations and extended follow-up periods to assess the long-term predictive value of the variables tested in this cohort. Additionally, further examination of the role of these prognostic tools and treatments can be generalized to broader patient populations, further enhancing the precision and impact of cardiovascular care.

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Findings from this study introduce pFAI and AI-Risk Algorithms as viable methods for the prediction of MACE and MINOCA in patients with non-obstructive CAD.

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Declarations

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