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EDITORIAL

Microvascular Dysfunction in MINOCA: Still a Moving Target

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More than 8 decades after the first reports of myocardial infarction with nonobstructive coronary arteries (MINOCA),[1] uncertainty persists regarding its mechanisms and prognostic markers. Microvascular dysfunction has long been suspected as a major player, yet establishing a reproducible measure of microvascular injury in this heterogeneous condition remains elusive.

See Article by Abdu et al.

In this issue of the *Journal of the American Heart Association* (*JAHA*), Abdu and colleagues[2] attempt to connect angiography-derived index of microcirculatory resistance (caIMR) with infarct size, microvascular obstruction (MVO), and outcomes in patients with true ischemic MINOCA. Despite their efforts, the results underscore how difficult it remains to quantify coronary microvascular dysfunction (CMD) reliably in this setting.

THE PROMISE AND THE BOUNDARIES OF ANGIOGRAPHY-DERIVED IMR

The idea that the IMR can serve as an in vivo surrogate for microvascular integrity dates back to its original validation in acute coronary syndromes.[3] Building on that foundation, the caIMR extends this principle by using computational fluid dynamics to estimate microvascular resistance from standard coronary angiography, without a pressure wire or hyperemic agents.[4–6] The result is an accessible, noninvasive tool that bridges coronary physiology and imaging.The appeal of caIMR lies in its practicality: it can be obtained within minutes after angiography and has shown reasonable correlation with invasive IMR.[4–6] Yet, this correlation does not imply equivalence in prognostic value. The relationship reflects shared hemodynamic determinants rather than identical pathophysiological meaning, especially in syndromes such as MINOCA, where multiple mechanisms such as vasospasm, microthrombosis, inflammation, and supply–demand mismatch, may coexist.[7,8]

Thresholds established in chronic coronary syndromes or occlusive MI may not translate directly to MINOCA. The use of a caIMR >25 U as the cutoff for CMD, derived largely from nonacute cohorts, may underestimate the burden of microvascular injury in the acute setting, where edema and transient vasoconstriction elevate resistance. Prior studies, including those by the same group, have shown that higher cutoffs (≥40–43 U) better predict adverse outcomes in acute MI.[9] The absence of association between caIMR, MVO, and infarct size in this study may therefore reflect methodological limitations rather than a true dissociation between physiology and structure.

Ultimately, coronary physiology is context dependent. A single, universal IMR threshold for microvascular

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injury remains a mirage. In MINOCA, as in type 2 MI, pathophysiological heterogeneity challenges simplification, an observation that underscores the need to recalibrate our interpretive tools before drawing mechanistic conclusions.

WHAT caIMR ADDS AND WHAT IT DOES NOT

Against this background, the study by Abdu and colleagues[2] provides valuable insight into how caIMR performs in clinical practice. Despite theoretical appeal, caIMR failed to predict either infarct size or MVO among patients with true ischemic MINOCA. Moreover, in nearly one third of the cohort, neither CMD nor MVO was present, suggesting alternative mechanisms of injury.Although both MVO and caIMR capture aspects of microcirculatory disturbance, prior studies have reported discordance between the 2 measures in roughly one third of patients with ST-segment–elevation myocardial infarction (STEMI),[6,10] a discrepancy likely arising from both biological and technical factors.

First, microvascular injury in MINOCA likely differs fundamentally from that observed in STEMI.[8] In the latter, microembolization, inflammation, and reperfusion injury produce extensive structural damage, with CMR-MVO serving as an anatomical marker delineating the extent of MVO. In contrast, in MINOCA the predominant mechanism is often functional, epicardial coronary vasospasm, endothelial dysfunction, or impaired autoregulation, without overt myocardial necrosis. Accordingly, caIMR provides a functional assessment that reflects the physiological state and reactivity of the coronary microcirculation.

Second, both caIMR and MVO are dynamic parameters whose abnormalities may evolve or resolve after the acute phase of MI, making the timing of measurement critical. caIMR can be obtained immediately following coronary angiography, whereas CMR evaluation of MVO is typically performed several days later (2–7 days post event). IMR typically decreases within the first 24 hours, whereas CMR-defined MVO remains relatively stable during the first 4 to 48 hours and begins to diminish only by approximately day 10.[11,12] These temporal discrepancies can obscure relationships between physiological and imaging markers of injury.

Thus, although caIMR remains an attractive and practical index of microvascular resistance, its diagnostic granularity in MINOCA requires careful recalibration. No single metric can encompass the complexity of microvascular injury; an integrated, multimodal approach remains the cornerstone for understanding microvascular health and guiding patient care.

MINOCA IS NOT BENIGN, BUT NEITHER IS IT UNIFORM

MINOCA is not a single disease but a heterogeneous clinical syndrome encompassing both atherosclerotic and nonatherosclerotic mechanisms of myocardial injury. This heterogeneity fuels diagnostic uncertainty and complicates clinical management and follow-up. MINOCA accounts for ~5% to 30% of all MI, depending on the population and clinical presentation (STEMI versus non-STEMI).[7,13] Women are disproportionately represented among those presenting with non–ST-segment–elevation acute coronary syndromes, whereas sex differences are less apparent in STEMI.[7,13]The study reconfirms a key clinical point: MINOCA is not a benign entity.[2,14] One third of the patients experienced major adverse cardiovascular events during follow-up. Yet the gradient of risk mirrored the underlying burden of injury: the coexistence of CMD and large infarct size predicted the highest hazard (Figure).

Still, interpretation is limited by sample size, wide CIs, and the paradoxical distribution of classical risk factors, with smoking and hypertension unexpectedly concentrated in the "low-risk" group. Such patterns often reveal selection bias, unmeasured treatment effects, or the inherent unpredictability of small data sets. This, too, is part of the MINOCA story: its epidemiology is shaped as much by diagnostic selection and referral as by biology.

MICROVASCULAR OBSTRUCTION: A BIOMARKER SEARCHING FOR MEANING

The absence of prognostic value of MVO in this cohort contrasts with its established role in occlusive MI. However, MVO detection depends on imaging technique, timing, and resolution. A prevalence of 6% to 7% is considerably lower than reported with high-resolution CMR or advanced late gadolinium enhancement mapping, which may identify subendocardial necrosis invisible to standard sequences.[12] Therefore, negative findings should not be overinterpreted as absence of microvascular injury but rather as technical limitation.

METHODOLOGICAL CONSIDERATIONS AND CLINICAL PERSPECTIVE

In the present study, caIMR did not predict MVO or infarct size, and MVO on CMR was not associated with clinical outcomes. These negative findings, however, should be interpreted with caution. The study had a small sample size and a population with predominantly non-STEMI. The low prevalence of STEMI and MVO likely limited statistical power to detect associations

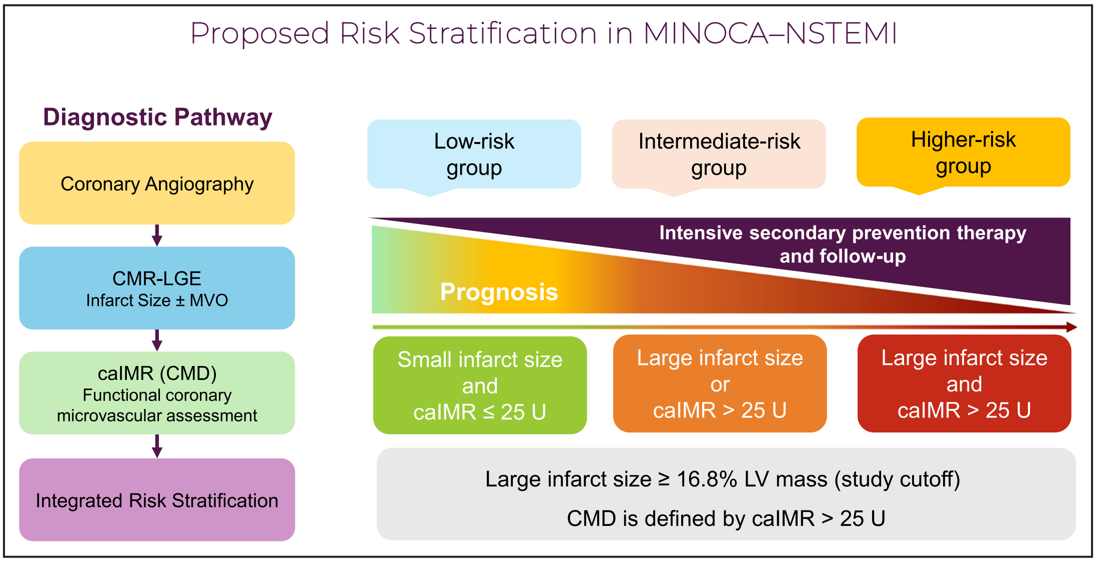

Figure. Proposed risk stratification in MINOCA–NSTEMI.
Diagnostic pathway integrating coronary angiography, CMR to quantify infarct size (with or without MVO), and caIMR to assess CMD. Risk stratification indicates that long-term prognosis is primarily driven by the combined burden of CMD and infarct size, with the highest-risk subgroup defined by CMD together with a large infarct (approximately ≥16.8% of LV mass in the study). This integrated structural (CMR-based) and functional (caIMR-based) assessment supports personalized secondary prevention strategies. caIMR indicates coronary angiography–derived index of microcirculatory resistance; CMD, coronary microvascular dysfunction; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricular; MINOCA, myocardial infarction with nonobstructive coronary arteries; MVO, microvascular obstruction; and NSTEMI, non-ST-segment–elevation myocardial infarction.

within these subgroups. Moreover, MVO primarily reflects mechanical obstruction of the microcirculation following a reperfusion event; it does not fully capture the intrinsic functional integrity of the microvasculature, which may be compromised independently of reflow phenomena. Taken together, the data suggest that in patients with MINOCA presenting with non-STEMI, it is the combined burden of CMD and infarct size, rather than angiographic appearance or MVO alone, that determines long-term prognosis.

FROM MECHANISMS TO MANAGEMENT

Importantly, the study also highlights lower use of statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta blockers, particularly among patients with both CMD and large infarct size. This paradox raises pressing questions about secondary prevention in MINOCA. Too often, the absence of obstructive disease translates into therapeutic nihilism. Yet these patients frequently harbor subclinical atherosclerosis and remain at high risk of recurrent ischemic events.Observational data indicate that ~50% of patients who experience reinfarction after MINOCA show progression to obstructive coronary artery disease, and nearly 25% continue to report angina at 12 months, rates comparable to those seen in patients with occlusive MI.[15,16] Such evidence argues strongly for comprehensive risk-factor modification and cardioprotective therapy. Beta blockers remain effective for controlling ischemia, and although the optimal treatment strategy is still uncertain, available data suggest that statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers should be considered first-line therapy for most patients.[17–20]

Clearly, the relationship between pharmacologic treatment and long-term outcomes in MINOCA warrants rigorous investigation. Randomized controlled trials are needed to test targeted strategies within defined pathophysiological subgroups: vasodilators for microvascular spasm, statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers for endothelial dysfunction, and anti-inflammatory or antithrombotic agents where plaque erosion or microembolization is implicated. Only through such mechanistically guided trials can secondary prevention in MINOCA evolve from extrapolation to evidence.

THE BROADER LESSON

Beyond the statistical details, this study reflects the enduring challenges in MINOCA research. Diagnostic pathways are inconsistent, CMR protocols vary, and physiologic thresholds borrowed from other populations are applied without adequate validation. The resulting literature is fragmented, with small cohorts and discordant findings that resist synthesis.A consistent message, however, does emerge: prognosis in MINOCA depends not on angiographic appearance but on the degree of microvascular and myocardial injury. Whether measured by late gadolinium enhancement, T1/T2 mapping, or invasive indices, structural and functional damage within the microcirculation remains the key determinant of outcomes.

CONCLUSION

Abdu and colleagues[2] should be commended for their systematic effort to link invasive and imaging markers in MINOCA, but their findings mainly remind us that the field is not yet mature for fixed physiologic definitions. Coronary microvascular dysfunction in MINOCA remains a moving target, elusive, multifaceted, and still searching for the right measure.The challenge for future research is not to multiply thresholds but to integrate physiology and imaging in a framework that respects the complex biology of ischemia without obstruction.

ARTICLE INFORMATION

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Disclosures

None.

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