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EDITORIAL

# Angina and coronary microvascular dysfunction: unravelling the links

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In this issue of EuroIntervention, Nogami et al present insights into how chest pain phenotypes relate to coronary microvascular dysfunction (CMD) and outcomes in patients with angina and non-obstructive coronary arteries (ANOCA)[1]. Their retrospective study of over 1,200 patients who underwent coronary reactivity testing (CRT) is among the largest to examine the relationship between symptom type (rest, exertional, or both), CMD and cardiovascular events. Of these patients, 299 (23.7%) reported exertional chest pain only and 341 (27.0%) reported resting chest pain only; their median age was 52 [interquartile range 44, 62] years, and 418 (65.3%) were female.

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The work addresses an important clinical need. ANOCA is prevalent, affecting up to 50% of patients undergoing invasive coronary angiography for chest pain, and CMD is increasingly recognised as a central pathophysiological mechanism. However, symptom interpretation remains challenging in clinical practice. The authors demonstrated that participants with exertional chest pain had significantly lower coronary flow reserve (CFR; 2.8 vs 3.0; p<0.01) and blunted coronary blood flow (CBF) response to intracoronary infusion of acetylcholine (ACh) compared to those with resting symptoms. These findings suggest greater impairment in both endothelium-dependent and -independent microvascular pathways. CFR predicted major adverse cardiac events (MACE) in the exertional group only, indicating a possible link between symptom profile and coronary microvascular disease severity.

The study design is methodologically robust. The inclusion criteria specified a preserved left ventricular ejection fraction (to limit the confounding effects of symptoms secondary to left ventricular systolic dysfunction), and exclusion criteria included prior myocardial infarction, stroke, coronary revascularisation, or spasm; these eligibility criteria are consistent with other physiological studies assessing CFR[2]. Findings in the group of patients with exertional symptoms are in line with prior evidence linking CMD to worse outcomes[3].

Although large in scale, the study has methodological aspects which warrant consideration.

Symptom classification was retrospective and based on clinical records without the use of validated tools like the Seattle or Rose Angina Questionnaires. This likely introduced some inaccuracy. Future studies using standardised instruments could improve phenotyping.

The "both" group, comprised of patients with both resting and exertional symptoms (nearly half the sample, n=580), warrants further analysis. If exertional chest pain reflects greater CMD severity, affected individuals might be expected to have the worst microvascular dysfunction and an excess of MACE. Instead, they showed intermediate CFR and MACE rates like the resting-only group. This unexpected pattern underscores the complexity of CMD and highlights the need to investigate mixed symptom presentations. The findings echo other work[4] demonstrating that chest pain characteristics and CMD measures do not always align, reflecting the multifactorial nature of ANOCA.

The CFR difference between groups (exertional: 2.8 vs resting: 3.0) was small, and both CFR values were above the 2.0-2.5 "grey zone" used in diagnostic algorithms[5,6], suggesting only a modest difference in functional impairment. Still, the fact that this small difference predicted outcomes in the exertional group is clinically meaningful.

The CBF response to intracoronary infusion of ACh (%ΔCBF-ACh) demonstrated no prognostic association across any symptom group. Although some studies have suggested a link between %ΔCBF-ACh and MACE[7], this parameter has not been consistently validated as a prognostic marker. In this study, participants with significant coronary vasoconstriction were excluded, supporting the interpretation of %ΔCBF-ACh as a measure of microvascular endothelial function.

Coronary flow reserve and microvascular resistance reflect distinct vasoactive mechanisms, and abnormal CFR and elevated microvascular resistance reflect functional and structural microvascular remodelling, respectively[8]. Future studies incorporating microvascular resistance measurements, including the index of microvascular resistance (IMR; derived by coronary thermodilution as the product of the mean hyperaemic transit time and distal coronary pressure) and hyperaemic microvascular resistance (HMR; derived from the ratio of distal coronary pressure [Pd] to average peak velocity [APV]), could provide additional insights. IMR and HMR provide reasonably reproducible measures of microvascular resistance which are less affected by changes in heart rate, blood pressure, or other haemodynamic conditions. Unlike CFR, which can vary with resting flow and systemic factors, IMR (and HMR) more specifically reflects the condition of the microcirculation[9]. Using CFR and IMR (or HMR) together can help differentiate between functional and structural forms of CMD, potentially improving how patients are risk stratified. Microvascular resistance reserve (MRR) and, relatedly, resistance reserve ratio (RRR) reflect the vasodilator capacity of coronary resistance, taking account of resting and hyperaemic conditions. Since IMR and HMR are measures of resistance under hyperaemic conditions (only), these indices are distinct from MRR and RRR.

Baseline medication differences between the symptom groups represent potential confounders worth considering. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers, which are known to influence vascular tone and endothelial function, were more prevalent in the resting pain group. The study does not specify whether these medications were withheld before physiological testing.

The highly impressive 30-year data collection reflects a sustained commitment to CMD research and enables valuable long-term follow-up. This study provides clinically relevant insights by suggesting that exertional symptoms in ANOCA may help identify patients with higher-risk CMD phenotypes. For interventional cardiologists, these findings support comprehensive coronary function testing in patients presenting with exertional chest pain and non-obstructive coronary disease. The prognostic utility of CFR specifically in exertional presentations offers a practical tool for risk stratification and management decisions.

The complexity revealed by the "both" group underscores the heterogeneous nature of CMD, rather than detracting from the study's conclusions. The CorMicA trial[5] similarly showed that many patients exhibit both endothelium-dependent and -independent dysfunction and that stratified treatment based on physiological testing can improve symptoms and quality of life. These findings reinforce the value of integrating physiological assessment with careful symptom evaluation.

While the current study focused appropriately on MACE, CMD also has important implications for functional capacity and daily life. In ANOCA, CMD causes physical limitation including reduced exercise tolerance[10]. Future studies should incorporate standardised symptom questionnaires, full invasive testing including IMR and CFR, and prospective designs to capture both prognostic and quality-of-life outcomes. The "both" group deserves focused analysis as it may represent the most common and clinically relevant symptom presentation.

Nogami et al contribute important evidence linking symptom profile with CMD physiology and prognosis in ANOCA. Their findings support recognising exertional symptoms as clinically relevant and reinforce the role of physiological testing in guiding management. The study supports the growing recognition of CMD as a distinct and treatable contributor to angina and cardiovascular risk.

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## Conflict of interest statement

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