

Coronary microvascular dysfunction: Filling the research gaps with careful patient selection

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Although obstructive coronary artery disease (CAD) has long been considered the cause of myocardial ischemia, there is increasing recognition of a subclass of patients who present with evidence of ischemia and are found to have no significant epicardial CAD. These patients with ischemia and no obstructive coronary disease (INOCA) have been shown to have worse outcomes than patients without ischemia.¹ Jespersen et al. examined more than 11,000 subjects who presented with chest pain and had normal coronaries or diffuse nonobstructive CAD on angiography. After controlling for other cardiac risk factors, patients with symptoms of ischemia and normal coronary arteries had a 52% increased risk of major adverse cardiac events, defined as cardiovascular death, stroke, heart failure, or myocardial infarction, compared with a reference population without ischemic heart disease or symptoms thereof.²

The mechanisms by which INOCA occurs and leads to worse outcomes have not been fully elucidated, but possible mechanisms include epicardial endothelial dysfunction and coronary microvascular dysfunction (CMD). CMD includes both microvascular endothelial and nonendothelial dysfunction that results in decreased

myocardial perfusion.¹ CMD can be assessed through evaluation of the myocardial flow reserve (MFR), which is also referred to as coronary flow reserve or myocardial perfusion reserve. MFR is defined as the ratio of coronary flow under maximal vasodilation to resting flow. In the absence of epicardial stenosis, the microvasculature primarily determines flow resistance. As a result, MFR is determined by the microvasculature in patients without obstructive epicardial CAD.³ Multiple studies have shown PET to be an accurate and reproducible technique for measuring myocardial blood flow (MBF) and MFR and has been used in multiple studies to examine the diagnostic and prognostic impact of this measurement.^{4–12} A MFR < 2.0 has frequently been used as a threshold to diagnose CMD, but an exact cutoff remains unclear, as various studies have used MFR values ranging from 1.5 to 2.6 to diagnose CMD.¹³

Irrespective of the cutoff used, impaired MFR has been shown to predict worse outcomes. Brainin et al. performed a meta-analysis that included 10 studies that used PET to diagnose CMD. They found that CMD patients without obstructive CAD had an overall relative risk (RR) of major adverse cardiac events of 2.44 (95% CI 1.80 to 3.30).¹⁴ In a subgroup analysis of the six studies in patients with CMD whose presentation was stable angina, they found an overall RR of MACE of 2.52 (95% CI 1.85 to 3.43).^{7–12} Figure 1 highlights two limitations of the studies included in this meta-analysis when used to assess patients with CMD and no obstructive epicardial CAD: (1) follow-up was only short term; (2) obstructive CAD was not specifically excluded through noninvasive or invasive angiography. In the largest study in this meta-analysis, Murthy et al. performed a seminal and robust analysis of > 1200 subjects with no evidence of obstructive CAD on rest/stress PET imaging. They found patients with CMD to have a significant increase in MACE (HR 0.8 per 10% improvement in MFR), which was defined as cardiac

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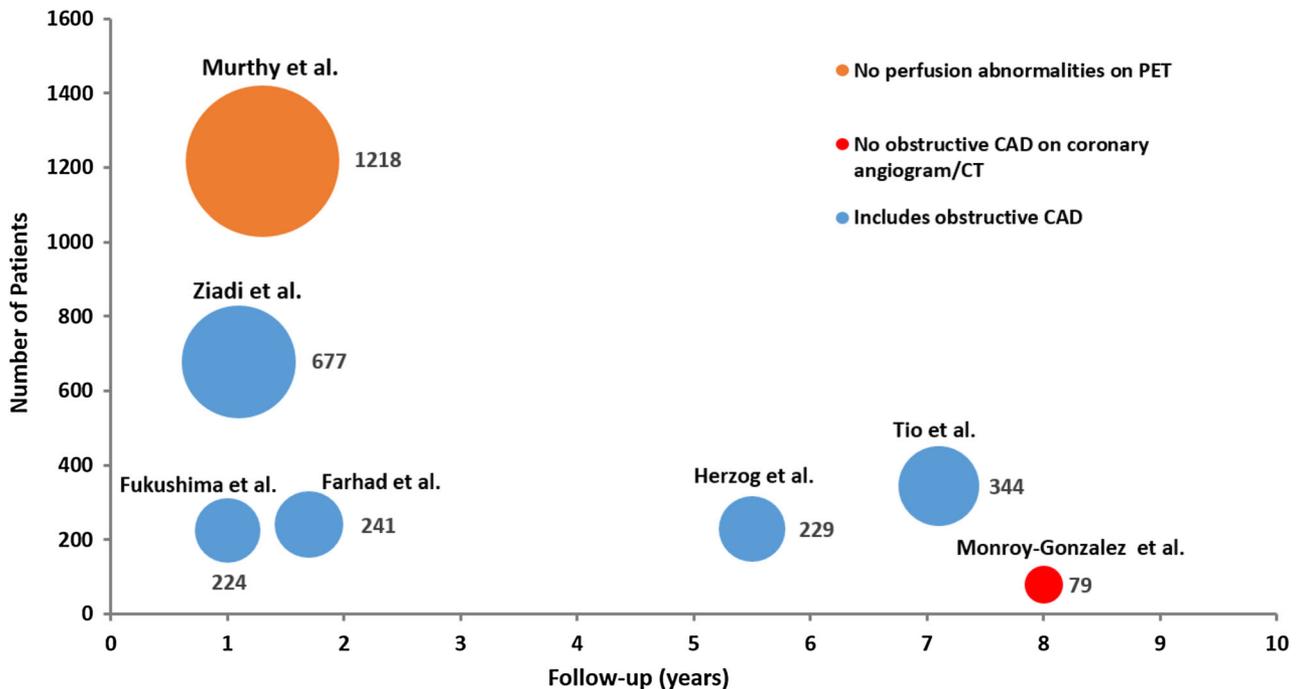


Figure 1. Comparison of number of patients, follow-up duration, and the presence of obstructive CAD in coronary microvascular dysfunction prognostic studies.

death, nonfatal MI, late revascularization, or CHF hospitalization.¹⁰ This study had a short-term follow-up horizon (mean of 1.1 years). In addition, while patients with perfusion abnormalities on rest/stress PET were excluded, the absence of obstructive CAD was not confirmed on invasive or CT coronary angiography. Thus, some patients with epicardial obstructive CAD may have been included. The other studies in the meta-analysis expressly included patients with obstructive epicardial CAD, resulting in a heterogenous study population.

As highlighted in Figure 1, there is a current gap in the literature assessing the prognostic impact of patients with chest pain and the confirmed absence of obstructive epicardial CAD on angiography over long-term follow-up. In this issue of the Journal, Monroy-Gonzalez et al. start filling in this research gap. They conducted a retrospective analysis of patients with the confirmed absence of obstructive epicardial CAD (no stenosis $\geq 30\%$ on invasive or CT coronary angiography). The study population was composed of 79 patients who underwent PET myocardial perfusion imaging (MPI) with quantitation of MBF and MFR. They found 43% prevalence of reduced MFR < 2.0 . Mortality and MACE (cardiac death, heart failure hospitalization, nonfatal MI, or late revascularization ≥ 90 days) were assessed over a long-term follow-up median of 8 years (IQR 3 to 14 years). Unadjusted Kaplan-Meier analysis showed a

significantly increased mortality risk and rate of MACE in subjects with CMD with a MFR < 2.0 . Univariable Cox regression analysis showed MFR to be a significant predictor of both mortality and MACE. Stress MBF only predicted MACE but not all-cause mortality. As illustrated in Figure 1, this study stands out from prior CMD studies by both reporting long-term data and by explicitly excluding patients with obstructive epicardial CAD identified on angiography.

Limitations of this study include a low sample size (79 patients) and high rate of incomplete follow-up (35/79, 44.3%) for MACE. Mortality data were available for all patients with the inherent limitations of government mortality databases. In addition, the absolute number of events in this study was low, with only 6 deaths and 6 MACE events; however, the relative event rate was adequate to produce a statistically significant result through univariable analysis. Multivariable analysis was unable to be performed due to the low number of events.

While Monroy-Gonzalez et al. add an important contribution to the CMD literature by looking at long-term outcomes in the absence of obstructive epicardial CAD that is confirmed, the next steps in CMD research should include larger prognostic studies evaluating long-term outcomes data in this population. In addition, there is a significant need for prospective trials to evaluate CMD treatments. Given the significant symptom morbidity and multiple studies that have demonstrated

increased mortality and MACE rates in patients with CMD, the need for effective therapies is apparent. Unfortunately, there is little data to support specific therapies in CMD. A systematic review by our group (Marinescu et al.) illustrates the lack of data to support treatment strategies in patients with the confirmed CMD.¹⁵ In our review of the literature, we noted that treatment studies for patients with chest pain and no obstructive epicardial CAD often included a heterogeneous patient population. Without specifically testing for CMD, these study populations included patients with other causes of chest pain such as noncardiac chest pain, pericardial pain, and coronary vasospasm. We identified only 8 studies that met our inclusion criteria of evaluating patients with angina, no obstructive epicardial CAD, and a MFR cutoff of < 2.5 as assessed by robust noninvasive (PET or CMR) or invasive techniques. Studies involving ACE inhibitors, estrogen, and use of TENS units showed benefit in patients with improvement in angina or MFR. The other treatments studied, involving statins, calcium-channel blockers, alpha-blockers, and L-arginine, showed no improvement. However, all of these studies were limited by very small sample sizes (median sample size of 11). A recent study randomized 63 normotensive patients with reported CMD (coronary flow velocity reserve (CFVR) < 2.2 as assessed by adenosine stress echo) to ramipril vs placebo. They found no difference between the two groups in regards to symptoms or CFVR, suggesting that past studies showing benefit of ACE inhibitors may have been due to antihypertensive effects, with no benefit realized in normotensive patients.¹⁶ Further randomized prospective trials to evaluate CMD treatment strategies are clearly needed.

Another step in the process of improving our understanding of CMD is the need for routine testing of MFR in patients with INOCA. The differential diagnosis of patients with chest pain and no obstructive epicardial CAD includes both CMD and noncardiac causes, and it is imperative that testing for CMD be done to rule out this entity. Unfortunately, patients without obstructive epicardial CAD are often told their pain is noncardiac; no further work-up is done, resulting in missed opportunities to diagnose and explore treatments for CMD for both symptom management and risk reduction. Alternatively, some clinicians assume patients with chest pain and no obstructive epicardial CAD have CMD without making a formal diagnosis. They start these patients on antianginal treatments that are unnecessary in many instances given that many of these patients will have noncardiac chest pain. In order to determine effective therapies for CMD, it is critical that a formal diagnosis be made, either noninvasively with PET/CMR, or using invasive techniques during coronary angiography. A

clinical trial is currently underway that will examine the use of coronary function testing during invasive coronary angiography for patients with angina and no obstructive epicardial CAD. The study cohort will be randomized to assessment of coronary function and subsequent treatment or standard care without this testing. In the coronary function diagnosis/treatment group, MFR will be measured invasively during coronary angiography. If a diagnosis of CMD is made, these patients will be started on an antianginal regimen. This study will provide the first randomized assessment of whether routine testing for CMD translates into clinical benefits.¹⁷

In summary, the study by Monroy-Gonzalez et al. is significant for demonstrating the long-term prognostic implications for patients with CMD and the confirmed absence of obstructive epicardial CAD. These results further indicate the need to fill the research gap with larger prognostic studies looking at long-term outcomes, assessing whether routine testing for CMD affects outcomes, and evaluating CMD treatments.

Disclosure

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