Understanding Patient Characteristics and Coronary Microvasculature: Early Insights from the Coronary Microvascular Disease Registry

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Coronary angiography has limitations in accurately assessing the coronary microcirculation. A new comprehensive invasive hemodynamic assessment method utilizing coronary flow reserve (CFR) and the index of microvascular resistance (IMR) offers improved diagnostic capabilities. This study aimed to present early real-world experience with invasive hemodynamic assessment of the coronary microvasculature in symptomatic patients with nonobstructive coronary artery disease (CAD) from the Coronary Microvascular Disease Registry, which is a prospective, multi-center registry that standardized the evaluation of patients with angina and nonobstructive CAD who underwent invasive hemodynamic assessment of the coronary microvasculature using the Coroventis CoroFlow Cardiovascular System. All patients underwent comprehensive invasive hemodynamic assessment. Analysis was performed on the first 154 patients enrolled in the Coronary Microvascular Disease Registry; their mean age was 62.4 years and 65.6% were female. A notable proportion of patients (31.8%) presented with a Canadian Cardiovascular Society Angina Score of 3 or 4. Coronary microvascular dysfunction was diagnosed in 39 of 154 patients (25.3%), with mean fractional flow reserve of 0.89 ± 0.43, mean resting full cycle ratio of 0.93 ± 0.08, mean CFR of 1.8 ± 0.9, and mean IMR of 36.26 ± 19.23. No in-hospital adverse events were reported in the patients. This study demonstrates the potential of invasive hemodynamic assessment using CFR and IMR to accurately evaluate the coronary microvasculature in patients with nonobstructive CAD. These findings have important implications for improving the diagnosis and management of coronary microvascular dysfunction, leading to more targeted and effective therapies for patients with microvascular angina. **(Am J Cardiol 2023;205:97−103)**

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Angina pectoris affects 112 million people globally and is a prevalent symptom of myocardial ischemia.[1] The standard diagnostic approach involves coronary angiography to detect coronary artery stenosis.[2] However, nonobstructive coronary artery disease (CAD) is often dismissed, and coronary microvascular dysfunction (CMD) is commonly overlooked.[3] CMD, prevalent in patients with cardiovascular risk factors, escalates the risk of adverse cardiovascular events.[4] Unfortunately, CMD frequently remains undiagnosed, leading to persistent angina, readmissions, repeat angiography, and increased healthcare costs.[5] Even patients with epicardial CAD who undergo percutaneous coronary intervention may experience ongoing angina because of microvascular dysfunction.[6] The limitations of coronary angiography have prompted the exploration of noninvasive imaging techniques, but their sensitivity and specificity are inadequate.[7] Recent advancements in the field introduce invasive techniques such as measuring coronary flow reserve (CFR) and indexes of microvascular resistance (IMR) for accurate CMD diagnosis.[8] These novel diagnostic tools generate interest in diagnosing CMD, enabling tailored medical therapy and improved outcomes. The Coronary Microvascular Disease Registry (CMDR) is a prospective, multi-center registry enrolling patients with angina and nonobstructive CAD for invasive hemodynamic assessment of the coronary microvasculature. This study presents our initial real-world experience with invasive hemodynamic assessment in symptomatic patients with nonobstructive CAD.

Methods

The CMDR enrolls patients (both inpatient and outpatient) with myocardial infarction with nonobstructive coronary arteries (NOCA), ischemia with NOCA, and angina with NOCA who undergo invasive hemodynamic assessment of the coronary microvasculature. Data for the registry were sourced from established hospital or clinical care

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databases and any new or existing hospital data collection systems. No research-related interventional procedures were conducted solely for the purpose of this study. The procedures performed were based on clinical judgment and what was deemed optimal for each patient. The registry is aligned with the guidelines provided by the Institutional Review Board.

In this analysis, we present early results from initial patients enrolled in the CMDR at 2 MedStar Health centers (MedStar Washington Hospital Center, Washington, DC, and MedStar Southern Maryland Hospital Center, Clinton, Maryland). The registry enrolled its first patient in August 2021. Our primary objective is to elucidate the characteristics and trends observed in patients during the period spanning from the initial enrollment through May 2023.

Inpatients included those with an acute coronary syndrome presentation (myocardial infarction with NOCA or ischemia with NOCA), whereas outpatients included those referred specifically for CMD evaluation or those with nonobstructive CAD identified with left heart catheterization during evaluation for abnormal noninvasive cardiovascular testing ("ad hoc") and angina (angina with NOCA). The CMDR collected baseline characteristics, co-morbidities, medications, chest pain severity, noninvasive cardiovascular testing, coronary anatomy based on angiography, physiologic measurements, and postprocedural outcomes.

Microvasculature physiology was assessed using the Coroventis CoroFlow Cardiovascular System (Abbott Laboratories, Chicago, Illinois), measuring nonhyperemic resting indexes (resting full-cycle ratio) and hyperemic fractional flow reserve using a physiologic pressure wire (PressureWire X Guidewire, Abbott Laboratories) (Figure 1). The wire also measured CFR, IMR, and resistive reserve ratio (RRR) using thermodilution technology. All measurements were recorded and included in the CMDR, along with the anatomical disease on the coronary angiogram. Patients were divided into 2 cohorts: those diagnosed with CMD (CFR <2.0 and IMR ≥25) and all others. Borderline cases were discussed by a multidisciplinary heart team to determine the likelihood of CMD. The definition of CMD was based on multiple studies showing that only overt CMD (CFR <2.0 and IMR ≥25) possesses prognostic impact.[9,10]

The measurement protocol involved the insertion of an arterial sheath into either the radial or femoral artery. Intravenous administration of heparin followed. The targeted coronary artery was engaged with a guiding catheter, and intracoronary administration of 0.2 mg of nitroglycerin occurred. A guidewire equipped with a pressure and temperature sensor (PressureWire X, Abbott) was then passed through the guiding catheter, which allowed saline infusion and temperature measurement. The guidewire was equalized and positioned distally within the artery. To obtain measurements, 3 ml of saline was injected at rest, and subsequent saline injection measurements were taken after administering adenosine at a rate of 140 mcg/kg/min to obtain hyperemic measurements. The temperature of the saline/blood mixture was measured at the distal part of the coronary artery, ensuring a steady state, while simultaneously measuring resting pressure in the distal section of the vessel. The temperature of the infused saline was tracked using the sensor on the guidewire. Throughout the procedure, the measured temperatures and pressures were displayed on a screen through a thermodilution tracing.[11] After completing the measurements, the guidewire, infusion, and guiding catheter were removed from the artery. All coronary pressure tracings and temperatures were wirelessly transmitted and analyzed by a dedicated console equipped with software that automatically calculated the coronary microvasculature variables. By comparing the maximum blood flow during hyperemia to the blood flow at rest, CFR can be calculated. IMR is measured by recording

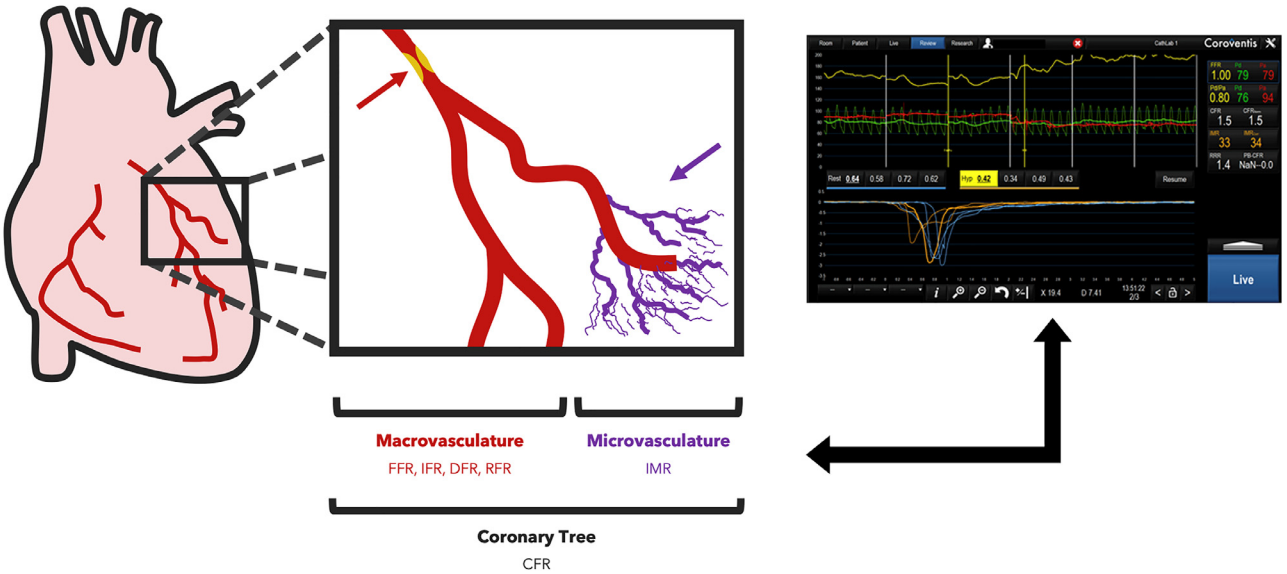

Figure 1. Illustration of the assessment of an epicardial artery using the Coroventis CoroFlow Cardiovascular System (Abbott Laboratories, Chicago, Illinois), which includes the measurement of CFR, FFR, and IMR.
FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; IMR = index of microvascular resistance; RFR = resting full-cycle ratio.

the average pressure gradient across the coronary microvasculature during the resting state. This provides an estimation of the resistance within the microvessels.

Mean invasive hemodynamic values and baseline characteristics were compared between the 2 cohorts using Student's *t* test for continuous variables and chi-square test for categorical variables. A p value below 0.05 was considered statistically significant. Data analysis was performed using SAS 9.2 (SAS Institute, Cary, North Carolina).

Results

In our registry, a comprehensive analysis was conducted on 154 patients who were available in the registry at the time of analysis. Of these patients, 33.9% (39 of 154) tested positive for CMD. Table 1 lists the baseline characteristics, which were found to be well-balanced between the CMD-positive and CMD-negative groups. The average age of the patients was 62.4 ± 10.7 years. Women constituted most of the patients (65.6%), with a slight inclination toward a higher proportion of women in the CMD-positive group (76.9% vs 61.7%, p = 0.085). Notably, when comparing the 2 groups, CMD-positive patients exhibited a lower body mass index (BMI) of 27.3 ± 5.9 kg/m^2 compared with CMD-negative patients (31.2 ± 6.9 kg/m^2, p = 0.002). Regarding racial distribution, 46.4% of the patients were African American, and 40.5% were White. Most patients (64.3%) reported never using tobacco. Hypertension was prevalent in 78.6% of patients, whereas hyperlipidemia was reported by 77.9%. Moreover, 31.8% of patients experienced limiting symptoms with a Canadian Cardiovascular Society Angina Score of 3 or 4, and 18.2% of patients were categorized as having unstable angina upon presentation.

In CMD-positive patients, the mean IMR was 36.3 ± 19.2, and the mean CFR was 1.8 ± 0.9 (Table 2). Most procedures (72.7%) were performed on an outpatient basis, resulting in a mean hospital stay of less than a day, as listed in Table 3. Of the patients diagnosed with CMD, 48.7% received outpatient care, whereas 51.3% required inpatient treatment. It is worth noting that even in the inpatient group, the length of stay was less than a day. Furthermore, there were no reported postprocedural complications in any of our patients. The medications administered before and after the procedure in both groups are listed in Table 4, revealing a trend toward increased usage of β-blockers in CMD-positive patients (33.3% vs 64.1%, p = 0.09).

Discussion

Our analysis revealed several important observations. First, approximately one-third of patients suspected of having CMD requiring invasive hemodynamic assessment were confirmed to be CMD-positive. This highlights the significance of recognizing CMD as a potential cause of symptoms in patients presenting with angina. Second, evaluating for invasive hemodynamic assessment is safe, as we demonstrate 0 complications in our registry.

Further, CMD was observed at a higher prevalence in female patients. This finding is not new, but gender-based differences warrant further investigation to better understand the underlying mechanisms and potential implications for clinical management.[12] Additionally, we found that CMD-positive patients had a lower BMI compared with

Table 1
Baseline characteristics

	CMD-Negative	CMD-Positive	Overall	p-Value
Age (years)	61.57±10.9	64.74±9.86	62.38±10.71	0.110
Body Mass Index (kg/m^2)	31.21±6.9	27.3±5.94	30.22±6.86	0.002
Female	61.7% (71/115)	76.9% (30/39)	65.6% (101/154)	0.085
Caucasian	39.5% (45/114)	43.6% (17/39)	40.5% (62/153)	0.651
African American	45.6% (52/114)	48.7% (19/39)	46.4% (71/153)	0.737
Hispanic	1.8% (2/114)	2.6% (1/39)	2% (3/153)	0.753
Tobacco use (current)	7.8% (9/115)	12.8% (5/39)	9.1% (14/154)	0.348
Tobacco use (past)	27.8% (32/115)	17.9% (7/39)	25.3% (39/154)	0.220
CCS Angina Score 3 or 4	32.8% (22/67)	28.6% (6/21)	31.8% (28/88)	0.714
Hypertension	77.4% (89/115)	82.1% (32/39)	78.6% (121/154)	0.540
Hyperlipidemia	78.3% (90/115)	76.9% (30/39)	77.9% (120/154)	0.862
Diabetes	28.7% (33/115)	25.6% (10/39)	27.9% (43/154)	0.713
Heart Failure	14.8% (17/115)	20.5% (8/39)	16.2% (25/154)	0.402
Chronic Kidney Disease (GFR<60 mL/min/1.73 m^2)	7% (8/115)	10.3% (4/39)	7.8% (12/154)	0.506
Peripheral Arterial Disease	1.7% (2/115)	2.6% (1/39)	1.9% (3/154)	0.747
Carotid Artery Disease	3.5% (4/115)	5.1% (2/39)	3.9% (6/154)	0.645
Permanent Pacemaker	3.5% (4/115)	5.3% (2/38)	3.9% (6/153)	0.623
Prior PCI	14.8% (17/115)	7.7% (3/39)	13% (20/154)	0.255
Prior CABG	1.7% (2/115)	0% (0/39)	1.3% (2/154)	0.407
Prior Stroke	9.6% (11/115)	15.4% (6/39)	11% (17/154)	0.316
Prior MI	20% (23/115)	15.4% (6/39)	18.8% (29/154)	0.524
Non-invasive ischemia evidence	31.3% (36/115)	25.6% (10/39)	29.9% (46/154)	0.504
Ejection Fraction %	56.31±8.72	55±12.65	55.95±9.9	0.587

CABG = coronary artery bypass graft, CCS = Canadian Cardiovascular Society, CMD = coronary microvascular dysfunction, GFR = glomerular filtration rate, MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2
Coronary anatomy and hemodynamics

	CMD-Negative	CMD-Positive	Overall	p-Value
Procedure Artery - LAD	97.8% (44/45)	94.1% (16/17)	96.8% (60/62)	0.467
IMR	13.34 ± 5.34 (115)	36.26 ± 19.23 (39)	19.14 ± 14.6	<0.001
FFR	0.9 ± 0.07 (110)	0.93 ± 0.08 (37)	0.91 ± 0.07	0.058
CFR	3.59 ± 1.93 (114)	1.8 ± 0.91 (39)	3.13 ± 1.9	<0.001
RFR	0.83 ± 0.3 (111)	0.89 ± 0.43 (36)	0.84 ± 0.34	0.452
RRR	4.03 ± 2.19 (112)	1.95 ± 1.03 (39)	3.49 ± 2.16	<0.001
No LM stenosis	100% (114/114)	100% (39/39)	-	100% (153/153)
No LAD stenosis	69.3% (79/114)	59% (23/39)	66.7% (102/153)	0.236
No LCX stenosis	93.8% (106/113)	82.1% (32/39)	0.029	90.8% (138/152)
No RCA stenosis	88.6% (101/114)	79.5% (31/39)	86.3% (132/153)	0.557
Slow Flow	2.6% (3/115)	0% (0/39)	1.9% (3/154)	0.308

CFR = coronary flow reserve; CMD = coronary microvascular dysfunction; FFR = fractional flow reserve; IMR = index of microcirculatory resistance; LAD = left anterior descending artery; LCX = left circumflex artery; LM = left main artery; RCA = right coronary artery; RFR = resting full-cycle ratio.
No stenosis = No lesion at all, even if nonsignificant.

Table 3
Hospital stay characteristics

	CMD-Negative	CMD-Positive	Overall	p-Value
Outpatient	80.9% (93/115)	48.7% (19/39)	72.7% (112/154)	<0.001
Inpatient	19.1% (22/115)	51.3% (20/39)	27.3% (42/154)	<0.001
Length of Stay (days)	0.71 ± 1.96 (115)	1.21 ± 1.56 (39)	0.84 ± 1.87	0.157
Unstable Angina	18.3% (21/115)	17.9% (7/39)	18.2% (28/154)	0.965

CMD = coronary microvascular dysfunction.

Table 4
Medications

	CMD-Negative	CMD-Positive	Overall	p-Value
Pre-procedure Medications				
Aspirin	55.7% (64/115)	43.6% (17/39)	52.6% (81/154)	0.192
Clopidogrel	6.1% (7/115)	5.1% (2/39)	5.8% (9/154)	0.825
Ticagrelor	2.6% (3/115)	2.6% (1/39)	2.6% (4/154)	0.988
Beta Blockers	43.5% (50/115)	33.3% (13/39)	40.9% (63/154)	0.265
Calcium Channel Blockers	38.3% (44/115)	41% (16/39)	39% (60/154)	0.760
Nitrates	21.7% (25/115)	15.4% (6/39)	20.1% (31/154)	0.392
Ranolazine	7% (8/115)	0% (0/39)	5.2% (8/154)	0.091
ACEI/ARB	48.7% (56/115)	48.7% (19/39)	48.7% (75/154)	0.998
High-Intensity Statin	35.7% (41/115)	25.6% (10/39)	33.1% (51/154)	0.251
Moderate-Intensity Statin	30.4% (35/115)	25.6% (10/39)	29.2% (45/154)	0.569
Diuretics	23.5% (27/115)	23.1% (9/39)	23.4% (36/154)	0.959
Novel Oral Anticoagulation	4.3% (5/115)	5.1% (2/39)	4.5% (7/154)	0.840
Vitamin K Antagonists	0.9% (1/115)	0% (0/39)	0.6% (1/154)	0.559
Post-procedure Medications				
Aspirin	59.1% (68/115)	66.7% (26/39)	0.404	61% (94/154)
Clopidogrel	7% (8/115)	12.8% (5/39)	0.255	8.4% (13/154)
Ticagrelor	2.6% (3/115)	0% (0/39)	0.308	1.9% (3/154)
Beta Blockers	55.7% (64/115)	64.1% (25/39)	0.356	57.8% (89/154)
Calcium Channel Blockers	40% (46/115)	48.7% (19/39)	0.341	42.2% (65/154)
Nitrates	24.3% (28/115)	25.6% (10/39)	0.871	24.7% (38/154)
Ranolazine	7% (8/115)	2.6% (1/39)	0.312	5.8% (9/154)
ACEI/ARB	47% (54/115)	48.7% (19/39)	0.849	47.4% (73/154)
High-Intensity Statin	40.9% (47/115)	43.6% (17/39)	0.766	41.6% (64/154)
Moderate-Intensity Statin	30.4% (35/115)	35.9% (14/39)	0.527	31.8% (49/154)
Diuretics	26.1% (30/115)	25.6% (10/39)	0.956	26% (40/154)
Novel Oral Anticoagulation	4.3% (5/115)	5.1% (2/39)	0.840	4.5% (7/154)
Vitamin K Antagonists	0.9% (1/115)	0% (0/39)	0.559	0.6% (1/154)

ACEI/ARB = angiotensin-converting enzyme inhibitors and angiotensin receptor blockers; CMD = coronary microvascular dysfunction.

CMD-negative patients, suggesting a potential association between CMD and lower BMI, contrary to what has been previously described.[13] It is worth noting that most baseline characteristics, and medication usage, were similar between CMD-positive and CMD-negative patients. This suggests that CMD may be a distinct entity regardless of these factors, reinforcing the need for targeted evaluation and management strategies specific to CMD.

Our study also reports the RRR, which is an emerging parameter in the diagnosis of CMD. It measures the resistance to blood flow in the microvasculature during stress compared with the resting state. A lower RRR value indicates reduced vasodilatory capacity and suggests the presence of CMD. RRR, along with other established parameters such as CFR and IMR, provides insights into microvascular function, helps differentiate CMD from other conditions, and contributes to understanding the underlying pathophysiology. Early evidence shows promise for enhancing diagnostic accuracy of CMD.[14]

In addition to the main findings, it is important to consider the broader implications and potential future directions based on our study. First, the confirmation of CMD in a significant proportion of patients suspected of having this condition emphasizes the need for increased awareness and recognition in healthcare providers. CMD has historically been underdiagnosed and underappreciated, as its symptoms can overlap with other cardiac conditions and traditional diagnostic tests may not detect the underlying microvascular dysfunction.[15] By highlighting the prevalence of CMD in this study, we hope to encourage clinicians to consider it as a possible etiology when evaluating patients with angina symptoms and nonobstructive coronary arteries. Furthermore, our study adds to the growing body of evidence supporting the safety and feasibility of invasive hemodynamic assessment for CMD because there were no adverse events in our registry. This approach allows for direct evaluation of coronary microvascular function, providing valuable insights into the pathophysiology of CMD, and should be the method of choice.

Coronary functional testing plays a crucial role in evaluating the complex nature of the microvasculature, encompassing not only CMD but also other components such as coronary vasospasm and structural and functional abnormalities.[16] Although CMD is an essential aspect of microvascular health, it is equally important to understand the broader spectrum of coronary functional abnormalities for comprehensive patient assessment. Therefore, in addition to measuring CFR and IMR, implementing a vasospastic challenge with acetylcholine should be considered to further evaluate and differentiate between vasospastic angina and CMD in cases of "unexplained" chest pain. This comprehensive approach ensures a more accurate and thorough assessment of the underlying condition, enabling clinicians to tailor treatment strategies accordingly. Although our study primarily focuses on CMD, we acknowledge the significance of investigating other functional abnormalities in future research. By expanding our investigation and registry in the future to include coronary vasospasm and assess structural and functional abnormalities, we aim to gain further insights into the complex interplay of factors affecting microvascular health. This expansion will allow us to provide more comprehensive care to our patients, with a better understanding of the underlying pathophysiology.

Collaborative efforts are essential to advance the field of CMD research. The establishment of nationwide or international CMD registries, such as the CMDR used in our study, promotes the pooling of data from diverse patient populations and healthcare settings. The CMDR aims to be a platform for patients who underwent testing for microvascular disease for devices approved for marketing by the United States Food and Drug Administration. Data submission and analysis are free for all sites interested in participating. A follow-up module will be added but will require patient consent. This registry enables a more comprehensive understanding of CMD, its clinical presentation, treatment patterns, and outcomes across different populations. Moreover, fostering collaboration in researchers, clinicians, and industry partners holds tremendous potential in advancing the development and validation of innovative diagnostic techniques and therapeutic approaches precisely designed for CMD. By tailoring medical therapy based on specific findings, the ability to stratify treatment can pave the way for more precise interventions and ultimately significantly enhance patient outcomes.

Invasive hemodynamic assessment of the coronary microvasculature has demonstrated safety and holds promise for guiding stratified medical therapy, thereby offering potential for more effective long-term treatment of angina in patients without obstructive CAD.[17] The significance of diagnosing CMD is further supported by the findings of the CORonary MICrovascular Angina (CORMICA) trial, which emphasized the role of CMD diagnosis in the management of these patients.[5] As we continue to diagnose and treat microvascular dysfunction, long-term follow-up data collected in the CMDR will provide valuable insights, enhancing the external validity of our findings and expanding the evidence base.

Although our study primarily focused on descriptive analysis, future investigations and results gained by our registry should strive to delve into the underlying mechanisms and potential risk factors associated with CMD. It is essential to identify specific patient characteristics, genetic factors, and co-morbidities that contribute to the development and progression of CMD. Such knowledge can greatly assist in risk stratification, early detection, and the implementation of tailored interventions. Furthermore, studying the natural history of CMD and its correlation with long-term outcomes, such as major adverse cardiovascular events, can provide valuable prognostic information and guide follow-up strategies.[18] To comprehensively evaluate the effectiveness of individualized treatment strategies, future studies should also assess their long-term impact on symptom management, quality of life, and overall clinical outcomes.

Despite the importance of our study, there are several limitations that should be acknowledged. First, the cohort size was relatively small, and the study was primarily descriptive. Additionally, patient selection for CMD assessment was left to the discretion of the operator, which introduces potential selection bias. Moreover, only patients who consented to participate in the registry were included, which could introduce further bias. We did not elaborate on

noninvasive tests performed before CMD assessment or clinical outcomes, as these are beyond the scope of this manuscript. Furthermore, we did not compare ad hoc to planned procedures or outpatients to inpatients, and this needs to be investigated in future studies. However, despite these limitations, our study represents the foundation and future potential of a nationwide, or even international, CMD registry.

In conclusion, our study contributes to the emerging body of evidence on CMD by highlighting its overall prevalence, gender differences, and possible association with BMI. Invasive hemodynamic assessment of the coronary microvasculature is safe and provides valuable insights for guiding individualized treatment strategies in patients with angina and nonobstructive CAD. Further research is needed to deepen our understanding of the underlying mechanisms, risk factors, and long-term outcomes associated with CMD. Continued efforts in collaborative research, registry development, and innovation in diagnostic and therapeutic methods will ultimately improve the care and outcomes of patients with CMD.

Declaration of Competing Interest

Hayder Hashim reports serving on the advisory boards of, and being a speaker for, Abbott Vascular, Boston Scientific, and Philips IGT.

Ron Waksman reports serving on the advisory boards of Abbott Vascular, Boston Scientific, Medtronic, Philips IGT, and Pi-Cardia Ltd.; being a consultant for Abbott Vascular, Biotronik, Boston Scientific, Cordis, Medtronic, Philips IGT, Pi-Cardia Ltd., Swiss Interventional Systems/SIS Medical AG, Transmural Systems Inc., and Venous MedTech; receiving institutional grant support from Amgen, Biotronik, Boston Scientific, Chiesi, Medtronic, and Philips IGT; and being an investor in Med, (Alliance) and Transmural Systems Inc.

The other authors have no competing interests to declare.

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