CHAPTER 5

CORONARY MICROVASCULAR DYSFUNCTION: DIAGNOSTIC CHALLENGES AND EMERGING THERAPIES

Mehmet Semih BELPINAR[1]

INTRODUCTION

Coronary microvascular dysfunction (CMD) is defined by structural and functional abnormalities of the small coronary vessels (arterioles and capillaries) that impair the regulation of coronary blood flow, leading to myocardial ischemia in the absence of obstructive epicardial coronary artery disease.[1,2] CMD has gained recognition as an important cause of angina in patients with "normal" coronary arteries on angiography, and it contributes to a spectrum of cardiovascular conditions including ischemia with no obstructive coronary arteries (INOCA) and heart failure with preserved ejection fraction (HFpEF). [1,3] Once regarded as a relatively benign syndrome (formerly called "cardiac syndrome X"), it is now clear that CMD is associated with elevated risks of adverse outcomes such as myocardial infarction, stroke, heart failure, and cardiac death. [3–5] For example, women with angina and no obstructive coronary disease who have evidence of CMD experience higher rates of major adverse cardiac events (MACE) over time compared to those without CMD.[3,4] The prevalence of CMD is substantial – large angiographic series have shown that up to 50% of patients undergoing coronary angiography for anginal symptoms have no obstructive coronary artery disease (CAD)[6], and detailed testing reveals coronary microvascular or vasomotor dysfunction in a majority of these cases. [7,8] Despite these observations, CMD has often been under-recognized in clinical practice, as patients with angina and "normal" coronaries were historically mislabeled as having non-cardiac chest pain or anxiety. [2,9] Greater awareness and improved diagnostic techniques are now shedding light

1 M.D., Sivas Numune Hospital, Cardiology Clinic, mehmetsemihbelpinar@gmail.com, ORCID iD: 0000-0002-6768-3710

DOI: 10.37609/akya.3823.c796

REFERENCES

1. Rehan R, Yong A, Ng M, Weaver J, Puranik R. Coronary microvascular dysfunction: A review of recent progress and clinical implications. *Front Cardiovasc Med*. 2023;10:1111721. doi:10.3389/fcvm.2023.1111721
2. Bairey Merz CN, Pepine CJ, Shimokawa H, Berry C. Treatment of coronary microvascular dysfunction. *Cardiovasc Res*. 2020;116(4):856-870. doi:10.1093/cvr/cvaa006
3. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse Cardiovascular Outcomes in Women With Nonobstructive Coronary Artery Disease: A Report From the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med*. 2009;169(9):843. doi:10.1001/archinternmed.2009.50
4. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in Women With Myocardial Ischemia in the Absence of Obstructive Coronary Disease: Results From the National Institutes of Health–National Heart, Lung, and Blood Institute–Sponsored Women's Ischemia Syndrome Evaluation (WISE). *Circulation*. 2004;109(24):2993-2999. doi:10.1161/01.CIR.0000130642.79868.B2
5. Radico F, Zimarino M, Fulgenzi F, et al. Determinants of long-term clinical outcomes in patients with angina but without obstructive coronary artery disease: a systematic review and meta-analysis. *Eur Heart J*. 2018;39(23):2135-2146. doi:10.1093/eurheartj/ehy185
6. Patel MR, Peterson ED, Dai D, et al. Low Diagnostic Yield of Elective Coronary Angiography. *N Engl J Med*. 2010;362(10):886-895. doi:10.1056/NEJMoa0907272
7. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of Coronary Microvascular Dysfunction Among Patients With Chest Pain and Nonobstructive Coronary Artery Disease. *JACC Cardiovasc Interv*. 2015;8(11):1445-1453. doi:10.1016/j.jcin.2015.06.017
8. Ong P, Athanasiadis A, Borgulya G, Mahrholdt H, Kaski JC, Sechtem U. High Prevalence of a Pathological Response to Acetylcholine Testing in Patients With Stable Angina Pectoris and Unobstructed Coronary Arteries. *J Am Coll Cardiol*. 2012;59(7):655-662. doi:10.1016/j.jacc.2011.11.015
9. Filippo Crea, M.D. PGC. Coronary Microvascular Dysfunction. *N Engl J Med*. 356(8):830-840. doi:DOI: 10.1056/NEJMra061889
10. Chauhan A, Mullins PA, Taylor G, Petch MC, Schofield PM. Both endothelium-dependent and endothelium-independent function is impaired in patients with angina pectoris and normal coronary angiograms. *Eur Heart J*. 1997;18(1):60-68. doi:10.1093/oxfordjournals.eurheartj.a015119
11. Maseri A, Crea F, Kaski JC, Crake T. Mechanisms of angina pectoris in syndrome X. *J Am Coll Cardiol*. 1991;17(2):499-506. doi:10.1016/S0735-1097(10)80122-6
12. Rahman H, Demir OM, Khan F, et al. Physiological Stratification of Patients With Angina Due to Coronary Microvascular Dysfunction. *J Am Coll Cardiol*. 2020;75(20):2538-2549. doi:10.1016/j.jacc.2020.03.051
13. Moreau P. Structure and reactivity of small arteries in aging. *Cardiovasc Res*. 1998;37(1):247-253. doi:10.1016/S0008-6363(97)00225-3
14. Zeiher AM, Schächinger V, Minners J. Long-term Cigarette Smoking Impairs Endothelium-Dependent Coronary Arterial Vasodilator Function. *Circulation*. 1995;92(5):1094-1100. doi:10.1161/01.CIR.92.5.1094
15. Di Carli MF, Janisse J, Ager J, Grunberger G. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *J Am Coll Cardiol*. 2003;41(8):1387-1393. doi:10.1016/S0735-1097(03)00166-9
16. Murthy VL, Naya M, Taqueti VR, et al. Effects of Sex on Coronary Microvascular Dysfunction and Cardiac Outcomes. *Circulation*. 2014;129(24):2518-2527. doi:10.1161/CIRCULATIONAHA.113.008507
17. Kaski JC, Collins P, Nihoyannopoulos P, Maseri A, Poole-Wilson PA, Rosano GMC. Cardiac syndrome X: Clinical characteristics and left ventricular function. *J Am Coll Cardiol*. 1995;25(4):807-814. doi:10.1016/0735-1097(94)00507-M

18. Aldiwani H, Zaya M, Suppogu N, et al. Angina Hospitalization Rates in Women With Signs and Symptoms of Ischemia But no Obstructive Coronary Artery Disease: A Report from the WISE (Women's Ischemia Syndrome Evaluation) Study. *J Am Heart Assoc*. 2020;9(4):e013168. doi:10.1161/JAHA.119.013168
19. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol*. 2018;250:16-20. doi:10.1016/j.ijcard.2017.08.068
20. Bairey Merz CN, Handberg EM, Shufelt CL, et al. A randomized, placebo-controlled trial of late Na current inhibition (ranolazine) in coronary microvascular dysfunction (CMD): impact on angina and myocardial perfusion reserve. *Eur Heart J*. 2016;37(19):1504-1513. doi:10.1093/eurheartj/ehv647
21. Ford TJ, Stanley B, Good R, et al. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina. *J Am Coll Cardiol*. 2018;72(23):2841-2855. doi:10.1016/j.jacc.2018.09.006
22. Ford TJ, Stanley B, Sidik N, et al. 1-Year Outcomes of Angina Management Guided by Invasive Coronary Function Testing (CorMicA). *JACC Cardiovasc Interv*. 2020;13(1):33-45. doi:10.1016/j.jcin.2019.11.001
23. Taqueti VR, Solomon SD, Shah AM, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J*. 2018;39(10):840-849. doi:10.1093/eurheartj/ehx721
24. Galante D, La Vecchia G, Leone AM, Crea F. Coronary microvascular dysfunction in angina and no-obstructive coronary arteries: Pathophysiology, diagnosis, novel markers and therapy. *Pol Heart J*. Published online March 12, 2025:VM/OJS/J/105217. doi:10.33963/v.phj.105217
25. Del Buono MG, Montone RA, Camilli M, et al. Coronary Microvascular Dysfunction Across the Spectrum of Cardiovascular Diseases. *J Am Coll Cardiol*. 2021;78(13):1352-1371. doi:10.1016/j.jacc.2021.07.042
26. Schroder J, Michelsen MM, Mygind ND, et al. Coronary flow velocity reserve predicts adverse prognosis in women with angina and no obstructive coronary artery disease: results from the iPOWER study. *Eur Heart J*. 2021;42(3):228-239. doi:10.1093/eurheartj/ehaa944
27. Bairey Merz CN, Pepine CJ, Walsh MN, et al. Ischemia and No Obstructive Coronary Artery Disease (INOCA): Developing Evidence-Based Therapies and Research Agenda for the Next Decade. *Circulation*. 2017;135(11):1075-1092. doi:10.1161/CIRCULATIONAHA.116.024534
28. Reriani MK, Dunlay SM, Gupta B, et al. Effects of statins on coronary and peripheral endothelial function in humans: a systematic review and meta-analysis of randomized controlled trials. Eur J Cardiovasc Prev Rehabil. 2011;18(5):704-716. doi:10.1177/1741826711398430.
29. Pauly, D. F., Johnson, B. D., Anderson, R. D., et al. (2009). In women with symptoms of cardiac ischemia, nonobstructive coronary arteries, and microvascular dysfunction, angiotensin-converting enzyme inhibition is associated with improved microvascular function: a double-blind randomized study from the NHLBI Women's Ischemia Syndrome Evaluation (WISE). JAMA, 301(14), 1468–1476.
30. Chen JW, Hsu NW, Wu TC, Lin SJ, Chang MS. Long-term angiotensin-converting enzyme inhibition reduces plasma asymmetric dimethylarginine and improves endothelial nitric oxide bioavailability and coronary microvascular function in patients with syndrome X. *Am J Cardiol*. 2002;90(9):974-982. doi:10.1016/S0002-9149(02)02664-4
31. Masuda D, Nohara R, Tamaki N, et al. Evaluation of coronary blood flow reserve by 13N-NH3 positron emission computed tomography (PET) with dipyridamole in the treatment of hypertension with the ACE inhibitor (Cilazapril). Ann Nucl Med. 2000;14(5):353-360. doi:10.1007/BF02988695.
32. Togni M, Vigorito F, Windecker S, et al. Does the β-Blocker Nebivolol Increase Coronary Flow Reserve? *Cardiovasc Drugs Ther*. 2007;21(2):99-108. doi:10.1007/s10557-006-0494-7
33. Cannon RO, Watson RM, Rosing DR, Epstein SE. Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve. *Am J Cardiol*. 1985;56(4):242-246. doi:10.1016/0002-9149(85)90842-2
34. Kanatsuka H, Eastham CL, Marcus ML, Lamping KG. Effects of nitroglycerin on the co-

ronary microcirculation in normal and ischemic myocardium. J Cardiovasc Pharmacol. 1992;19(5):755-763.
35. Villano A, Di Franco A, Nerla R, et al. Effects of Ivabradine and Ranolazine in Patients With Microvascular Angina Pectoris. *Am J Cardiol*. 2013;112(1):8-13. doi:10.1016/j.amjcard.2013.02.045
36. Cox ID, Hann CM, Kaski JC. Low dose imipramine improves chest pain but not quality of life in patients with angina and normal coronary angiograms. *Eur Heart J*. 1998;19(2):250-254. doi:10.1053/euhj.1997.0615
37. Khuddus MA, Pepine CJ, Handberg EM, et al. An Intravascular Ultrasound Analysis in Women Experiencing Chest Pain in the Absence of Obstructive Coronary Artery Disease: A Substudy from the National Heart, Lung and Blood Institute–Sponsored Women's Ischemia Syndrome Evaluation (WISE). *J Intervent Cardiol*. 2010;23(6):511-519. doi:10.1111/j.1540-8183.2010.00598.x
38. Adingupu DD, Göpel SO, Grönros J, et al. SGLT2 inhibition with empagliflozin improves coronary microvascular function and cardiac contractility in prediabetic ob/ob−/− mice. *Cardiovasc Diabetol*. 2019;18(1):16. doi:10.1186/s12933-019-0820-6
39. Morrow AJ, Ford TJ, Mangion K, et al. Rationale and design of the Medical Research Council's Precision Medicine with Zibotentan in Microvascular Angina (PRIZE) trial. *Am Heart J*. 2020;229:70-80. doi:10.1016/j.ahj.2020.07.007
40. Mohri M, Shimokawa H, Hirakawa Y, Masumoto A, Takeshita A. Rho-kinase inhibition with intracoronary fasudil prevents myocardial ischemia in patients with coronary microvascular spasm. *J Am Coll Cardiol*. 2003;41(1):15-19. doi:10.1016/S0735-1097(02)02632-3
41. Kitsou V, Xanthos T, Roberts R, Karlis GM, Padadimitriou L. Enhanced external counterpulsation: mechanisms of action and clinical applications. Acta Cardiol. 2010;65(2):239-247. doi:10.2143/AC.65.2.2047060.
42. Sestito A, Lanza GA, Le Pera D, et al. Spinal cord stimulation normalizes abnormal cortical pain processing in patients with cardiac syndrome X. *PAIN*. 2008;139(1). https://journals.lww.com/pain/fulltext/2008/09300/spinal_cord_stimulation_normalizes_abnormal.10.aspx
43. Lanza GA, Sestito A, Sandric S, et al. Spinal cord stimulation in patients with refractory anginal pain and normal coronary arteries. Ital Heart J. 2001;2(1):25-30.
44. Aziz A, Hansen HS, Sechtem U, Prescott E, Ong P. Sex-Related Differences in Vasomotor Function in Patients With Angina and Unobstructed Coronary Arteries. *J Am Coll Cardiol*. 2017;70(19):2349-2358. doi:10.1016/j.jacc.2017.09.016
45. Reis SE, Holubkov R, Smith AJC, et al. Coronary microvascular dysfunction is highly prevalent in women with chest pain in the absence of coronary artery disease: Results from the NHLBI WISE study. *Am Heart J*. 2001;141(5):735-741. doi:10.1067/mhj.2001.114198
46. Aggarwal NR, Patel HN, Mehta LS, et al. Sex Differences in Ischemic Heart Disease: Advances, Obstacles, and Next Steps. *Circ Cardiovasc Qual Outcomes*. 2018;11(2):e004437. doi:10.1161/CIRCOUTCOMES.117.004437
47. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary Microvascular Reactivity to Adenosine Predicts Adverse Outcome in Women Evaluated for Suspected Ischemia. *J Am Coll Cardiol*. 2010;55(25):2825-2832. doi:10.1016/j.jacc.2010.01.054
48. Handberg EM, Merz CNB, Cooper-Dehoff RM, et al. Rationale and design of the Women's Ischemia Trial to Reduce Events in Nonobstructive CAD (WARRIOR) trial. *Am Heart J*. 2021;237:90-103. doi:10.1016/j.ahj.2021.03.011
49. De Luca M, Crisci G, Armentaro G, et al. Endothelial Dysfunction and Heart Failure with Preserved Ejection Fraction—An Updated Review of the Literature. *Life*. 2023;14(1):30. doi:10.3390/life14010030
50. Gdowski MA, Murthy VL, Doering M, Monroy-Gonzalez AG, Slart R, Brown DL. Association of Isolated Coronary Microvascular Dysfunction With Mortality and Major Adverse Cardiac Events: A Systematic Review and Meta-Analysis of Aggregate Data. *J Am Heart Assoc*. 2020;9(9):e014954. doi:10.1161/JAHA.119.014954