American Heart Journal Plus: Cardiology Research and Practice 40 (2024) 100381

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Physiology and functional significance of the coronary microcirculation: An overview of its implications in health and disease

Samir Alam [a,*], Carl J. Pepine [b]

[a] American University of Beirut Medical Center, Beirut, Lebanon
[b] Department of Medicine, University of Florida, Gainesville, FL, United States of America

ARTICLE INFO

Keywords:
Microcirculation
Coronary blood flow
Ischemia and no obstructive disease
Cardiooncology
Coronary spasm

ABSTRACT

Ischemic, Coronary Heart Disease (CHD) is a leading cause of morbidity and death worldwide.

Ischemic, Coronary Heart Disease (CHD) is a leading cause of morbidity and death worldwide. Despite major advances in clinical, pharmacology and technology utilization in treatment, there still exists a concerning trend manifested by rising Global Cardiovascular deaths linked to a growing Global Burden of Cardiometabolic Risks. Additionally, there is significant regional Variation in CVD Burden and large Burden of CVD in Low-Middle Income Countries [1].

Myocardial ischemia is the major pathophysiologic link to CHD morbidity and key adverse events. Decades of progress have focused on identification and treatment of atherosclerotic coronary plaque-related narrowing, and interventions aimed at alleviating the plaque hemodynamic obstruction. However, besides coronary plaque-related stenosis, there may be numerous additional contributors to myocardial ischemia, with or without upstream stenosis. Principal among these elements, is the dynamic performance of the coronary microcirculation [2–7].

The coronary microcirculation comprises >90 % of the myocardial blood vessels and is an extensive network of vessels near <200 μ in diameter, endowed with a monolayer of endothelial cells. The latter serve not only as anatomic barriers but participate in principal biologic processes and regulate critical homeostatic functions that control vascular reactivity and thrombogenesis. Exposure of endothelium to metabolic factors may provoke inflammation by triggering specific pathways and evoking a host of inflammatory cytokines, adhesion molecules and inflammatory cells. Of special relevance, the oxidation of low-density lipoprotein cholesterol and other oxidative stressors play a major role in disrupting endothelial function by reducing bioavailability of nitric oxide and activating pro-inflammatory signaling pathways. Additionally, release of endothelium-derived vasoconstrictors antagonizes endothelium-derived vasodilation to limit the size of the microvascular bed and may lead to vasoconstriction and/or thrombosis [8,9].

It should be also appreciated that endothelial cells of different vascular beds are heterogeneous regarding structure and/or function and are thereby able to perform special tasks while responding in a similar and universal pattern to risk factors and vessel injury. For example, in the kidney, increased albumin excretion rates (AER) are known to independently predict worsening CVD and outcomes, including increased mortality, in a wide range of clinical settings. A large body of evidence has established this direct relation of systematically worse clinical outcomes with increasing levels of AER to be derivative of endothelial injury (dysfunction) that may be observed in diabetic, hypertensive, and non-diabetic individuals. Among nontraditional risk factors and markers of subclinical atherosclerosis, albuminuria is associated with incident coronary artery calcification in persons ≥65 years of age [10,11].

Whereas albuminuria may be a late reflection of renal endothelial injury that is detectable in relatively advanced vascular disease, increased albumin filtration is invariably accompanied by injury to subjacent glomerular epithelial cells (podocytes). Recent studies have strongly correlated shedding of podocytes with albuminuria. Hence, podocytes may provide an early biomarker of systemic endothelial dysfunction, preceding emergence of moderate albuminuria and would potentially facilitate earlier diagnosis of affected individuals [10].

* Corresponding author.
E-mail address: salam@aub.edu.lb (S. Alam).

https://doi.org/10.1016/j.ahjo.2024.100381
Received 5 February 2024; Received in revised form 28 February 2024; Accepted 3 March 2024
Available online 8 March 2024

In the heart, and peculiar to the coronary circulation, the microvessels play a critical role in the fine control of the volume and distribution of coronary blood and nutrient flow, which during diastole must compensate for flow interruption caused by systolic obliteration of the embedded micro-vessels thereby matching flow to oxygen requirements and sustaining aerobic myocardial metabolism despite wide fluctuations. Thanks to autoregulation, under physiologic conditions and intact micro-vascular function, a 3–4-fold coronary flow reserve (CFR) can be realized. Dysregulation of coronary micro-vessel function secondary to myocardial structural, embolization, or impairment of endothelial function may cause limitation in CFR. Recent evidence has validated CFR <2 as a key determinant of cardiac morbidity and mortality in a wide range of clinical conditions, including acute myocardial infarction, heart failure phenotypes, INOCA and hypertrophic cardiomyopathies.

These coronary physiologic characteristics are pertinent to the understanding and interpretations of diverse situations in cardiac physiologic and pathologic conditions [12].

1. Physiologic testing in stable CAD and ACS

Fractional Flow Reserve (FFR) physiologic testing has emerged as a readily obtained and reliable tool for physiologic assessment of intermediate-obstructive coronary lesions based on trans lesional-pressure drop [13–17]. This physiologic measure, however, requires near maximal microcirculatory vasodilation achieving minimal coronary resistance. Recent clinical trials have demonstrated inconsistency in the clinical validity of the test as compared to the landmark Deferral versus Performance of Percutaneous Transluminal Coronary Angioplasty in Patients Without Documented Ischaemia (DEFER) and Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) trials which confirmed safety of deferring lesion intervention based on an FFR >0.8. This discrepancy can be accounted for, in part, by the heterogenous patient population studied, particularly inclusion of patients with recent ACS, where microvascular function can be affected for an indeterminate duration [18–22].

The FAME 3 trial tested the noninferiority of FFR-guided PCI to coronary artery bypass grafting (CABG) for patients with three-vessel obstructive disease. That trial demonstrated that FFR-guided PCI using current-generation DES did not meet criteria for noninferiority compared with CABG among patients with angiographic three-vessel disease. At 3 years, no difference was noted between the two arms of the trial, but MI and repeat revascularization were both higher with PCI. A feature of that trial is the inclusion of patients with recent ACS with potential microvascular dysfunction, which may have influenced the results of physiology testing [19]. A similar finding was reported in the FUTURE trial where FFR-based clinical decisions post recent ACS/AMI were associated with worse outcome leading to trial termination [23]. Acute Coronary Syndrome/Myocardial Infarction comprise a spectrum of changes in local and remote vascular beds, including up-regulation of endothelial inflammatory adhesion molecules and platelet-endothelial adhesion from endothelial-associated VWF multimers. These remote vascular alterations persist longer in the presence of hyperlipidemia. The effects of the ACS-related inflammation on microvascular function and attenuated dilatation capacity are relevant to the results and interpretation of physiologic testing as well as explaining the disparity and discordance of iFR/FFR under variable anatomic and physiologic settings. The injury induced by micro emboli to the microcirculation could result in both, ischemia and triggering of inflammation [23,24].

2. Ischemia and Non Obstructive Coronary Disease (INOCA)

Over half a century ago, Licoff, Segal and Kasparian described 15 women with angina, ischemic exercise ECGs despite the absence of coronary obstruction suggesting coronary microvascular abnormality. This was confirmed using atrial pacing tachycardia or IV isoproterenol infusion that produced LV diastolic pressure and myocardial metabolic abnormalities of ischemia in patients with chest pain without angiographically confirmed obstructive CAD. Cannon and Epstein then confirmed reduced coronary vasodilator reserve and used the term “microvascular angina” [24–29].

In the original Women's Ischemic Syndrome Evaluation (WISE) cohort, women with symptoms and/or signs of ischemia despite absence of obstructive CAD with CFR <2.3, had impaired SAQ angina frequency scores and increase adverse outcomes. This finding has been confirmed multiple times as the clinical syndrome of “Open Artery Ischemia (Angina with Non-Obstructive Coronary Arteries/Ischemia with Non-Obstructive Coronary Arteries/Myocardial Infarction with Non-Obstructive Coronary Arteries) ANOCA/INOCA/MINOCA”. This complex clinical phenotype is underpinned by coronary microvascular dysfunction with a spectrum of pathophysiologic-clinical endotypes ranging from impaired dilatation to endothelial dependent large coronary artery spasm, microvascular spasm, impaired microvascular dilation, clinical disability and or, cardiac events including sudden death [4,30–34].

Utilization of PET coronary flow and catheter based coronary functional testing have advanced our understanding of the pathophysiology and characterization of ANOCA/INOCA/MINOCA and their various endotypes. In a study by Sinha et al. of 102 patients with ANOCA (65 % women, mean age 60 ± 8 years), 32 patients developed ischemia during exercise stress testing. Using endothelium-independent and endothelium-dependent microvascular dysfunction as the reference standard, the false positive rate of exercise stress test (ETT) dropped to 0 %, suggesting that among patients with ANOCA, ischemia on ETT was highly specific of an underlying ischemic substrate. Furthermore, accumulating evidence supports the notion that coronary spasm and vasomotor dysfunction may be the underlying cause in more than half of the myocardial infarctions (MIs) in patients with MINOCA, in addition to being a common cause of chest pain ANOCA [32,34].

3. Heart Failure and preserved Ejection Fraction (HFpEF)

Heart failure with preserved ejection fraction (HFpEF) is a prevalent adult heart failure phenotype accounting for ~40 % of the clinical HF burden. A proposed hypothesis in the pathogenesis of HFpEF is the combined effects of daily life ischemia, aging, obesity, diabetes, chronic lung disease and hypertension with underlying inflammation leading to functional micro-vascular dysfunction, hypoperfusion and consequential myocardial structural changes which perpetuate the ischemic insult.

One putative mechanism includes effects of proinflammatory mediators leading to reduction in nitric oxide (NO) bioavailability, (cGMP), and eventual protein kinase G activity in cardiomyocytes and endothelial dysfunction reducing CFR, interstitial fibrosis, and myocyte hypertrophy. Several studies have reported associations between elevated inflammatory biomarkers, limitation of CFR and incident HFpEF, as well as the severity and outcome [35–38].

4. Intersection with cardio-oncology

Cancer and CVD are highly prevalent and commonly coexist, to the extent that cancer is now considered a CVD risk factor. They share several risk factors and pathophysiologic mechanisms including aging, inactivity, CHIP, atrial fibrillation, atherosclerosis, and alterations in platelet function with increased risk of bleeding and thrombosis [33,39]. Of special relevance is the vascular adverse effects of many classes of anti-cancer treatments such as immune modulators and targeted therapy protocols. Although attention has traditionally focused on cardiomyocyte toxicity, vascular dysfunction could play a key role in the development of CV complications. Mounting evidence suggests that oncologic therapies damage endothelial cells, reduce NO bioavailability, and promote endothelial dysfunction. These effects have important systemic implications and can result in thrombosis, tissue ischemia, accelerated atherosclerosis, and hypertension. Several studies report an

increased incidence of atherosclerotic CVD after immune check point inhibitor (ICI) administration, with incident MI, ischemic stroke, and CAD-related events. Cardiotoxicity may be an important side effect of vascular endothelial growth factor (VEGF) inhibitor therapy used in the treatment of various malignancies, leading to CV morbidity and mortality including hypertension, cardiac ischemia as potential consequences of endothelial toxicity, thrombosis, and microvascular constriction or damage. This toxicity is mediated by adverse effects on endothelial and microvascular function through VEGF inhibition and oxidative stressors, which increase expression of proinflammatory genes with acceleration of arterial and venous thrombotic events, including cardiac and cerebral ischemia [40–44].

The above themes and more, are comprehensively addressed in this Special Issue dedicated to the advancement of knowledge pertinent to coronary microcirculation. This Special Issue offers interesting original and review manuscripts with intensive insight, analysis and perspectives for clinical utilization, evidence gaps, and future investigation.

On behalf of our Co-Guest Editors, we extend our gratitude to all the contributing authors for their expert and valuable input, the reviewers for providing timely assessment, and the AHJPlus editorial and management team for their guidance, support, and assistance.

CRediT authorship contribution statement

Samir Alam: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Carl J. Pepine:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] A.M. George, V. Fuster, C.J. Murray, et al., Global burden of cardiovascular diseases and risks, 1990–2022, J. Am. Coll. Cardiol. 82 (25) (2023) 2350–2473.
[2] William Likoff, Bernard L. Segal, Hratch Kasparian, Paradox of normal selective coronary arteriograms in patients considered to have unmistakable coronary heart disease, New Engl. J. Med. 276 (19) (1967) 1063–1066.
[3] Michael V. Herman, William C. Elliott, Richard Gorlin, An electrocardiographic, anatomic, and metabolic study of zonal myocardial ischemia in coronary heart disease, Circulation 35 (5) (1967) 834–846.
[4] Carl J. Pepine, D. Anderson, B. Sharaf, et al., Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia: results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study, J. Am. Coll. Cardiol. 55 (25) (2010) 2825–2832.
[5] R.S. Schwartz, A. Burke, A. Farb, et al., Microemboli and microvascular obstruction in acute coronary thrombosis and sudden coronary death: relation to epicardial plaque histopathology, J. Am. Coll. Cardiol. 54 (2009) 2167–2173.
[6] C. Michael Gibson, Albert Schömig, Coronary and myocardial angiography: angiographic assessment of both epicardial and myocardial perfusion, Circulation 109 (25) (2004) 3096–3105.
[7] V. Bodi, et al., Impact of persistent microvascular obstruction late after STEMI on adverse LV remodeling: a CMR study, JACC Cardiovasc. Imaging (7) (2023) 919–930.
[8] S.E. Alam, S.S. Nasser, K.E. Fernainy, et al., Cytokine imbalance in acute coronary syndrome, Curr. Opin. Pharmacol. 4 (2) (2004) 166–170.
[9] F. Moccetti, E. Brown, A. Xie, et al., Myocardial infarction produces sustained proinflammatory endothelial activation in remote arteries, J. Am. Coll. Cardiol. 72 (9) (2018) 1015–1026.
[10] A.A. Eid, R.H. Habib, O. Chehab, et al., Podocyturia: an earlier biomarker of cardiovascular outcomes, Sci. Rep. 12 (1) (2022) 21563.
[11] A.C. Razavi, O. Dzaye, E.D. Michos, et al., Nontraditional risk markers for incident coronary artery calcium among persons ≥ 65 years of age, JACC Adv. 3 (2) (2024) 100755.
[12] Nils P. Johnson, K. Lance Gould, Bernard De Bruyne, Autoregulation of coronary blood supply in response to demand: JACC review topic of the week, J. Am. Coll. Cardiol. 77 (18) (2021) 2335–2345.
[13] L.X. van Nunen, F.M. Zimmermann, P.A. Tonino, et al., Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial, Lancet 386 (10006) (2015) 1853–1860.
[14] William F. Fearon, F. Zimmermann, B. De Bruyne, et al., Fractional flow reserve–guided PCI as compared with coronary bypass surgery, N. Engl. J. Med. 386 (2) (2022) 128–137.
[15] William Fearon, Age-related iFR/FFR discordance: does it matter?: coronary physiology and age, EuroIntervention 17 (9) (2021) 704.
[16] Y. Kobayashi, N.P. Johnson, F.M. Zimmermann, et al., Agreement of the resting distal to aortic coronary pressure with the instantaneous wave-free ratio, J. Am. Coll. Cardiol. 70 (17) (2017) 2105–2113.
[17] S.H. Lee, K.H. Choi, J.M. Lee, et al., Physiologic characteristics and clinical outcomes of patients with discordance between FFR and iFR, J. Am. Coll. Cardiol. Intv. 12 (20) (2019) 2018–2031.
[18] A. Jiménez-Partinen, M.A. Molina-Cabello, K. Thurnhofer-Hemsi, et al., Fractional flow reserve versus angiography for guiding percutaneous coronary intervention, New Engl. J. Med. 360 (3) (2009) 213–224.
[19] Guy R. Heyndrickx, Gábor G. Tóth, The FAME trials: impact on clinical decision making, Intervent. Cardiol. Rev. 11 (2) (2016) 116.
[20] F.M. Zimmermann, A. Ferrara, N.P. Johnson, et al., Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial, Eur. Heart J. 36 (45) (2015) 3182–3188.
[21] N.H.J. Pijls, van Schaardenburgh P., G. Manoharan, et al., Percutaneous coronary intervention of functionally nonsignificant stenosis: 5-year follow-up of the DEFER study, J. Am. Coll. Cardiol. 49 (21) (2007) 2105–2111.
[22] Erik B. Schelbert, Javed Butler, Javier Diez, Why clinicians should care about the cardiac interstitium, JACC Cardiovasc. Imaging 12.11 (Part 2) (2019) 2305–2318.
[23] G. Rioufol, F. Dérimay, F. Roubille, T. Perret, et al., Fractional flow reserve to guide treatment of patients with multivessel coronary artery disease, J. Am. Coll. Cardiol. 78 (19) (2021) 1875–1885.
[24] J. Layland, K.G. Oldroyd, N. Curzen, et al., Fractional flow reserve vs. angiography in guiding management to optimize outcomes in non-ST-segment elevation myocardial infarction: the British Heart Foundation FAMOUS–NSTEMI randomized trial, Eur. Heart J. 36 (2) (2015) 100–111.
[25] R.O. Cannon III, R.M. Watson, D.R. Rosing, et al., Efficacy of calcium channel blocker therapy for angina pectoris resulting from small-vessel coronary artery disease and abnormal vasodilator reserve, Am. J. Cardiol. 56 (4) (1985) 242–246.
[26] J.C. Kaski, G.M. Rosano, P. Collins, et al., Cardiac syndrome X: clinical characteristics and left ventricular function. Long-term follow-up study, J. Am. Coll. Cardiol. 25 (1995) 807–814, https://doi.org/10.1016/0735-1097(94)00507-M.
[27] C.N. Bairey Merz, C.J. Pepine, M.N. Walsh, et al., Ischemia and no obstructive coronary artery disease (INOCA) developing evidence-based therapies and research agenda for the next decade, Circulation 135 (11) (2017) 1075–1092.
[28] P. Ong, P.G. Camici, J.F. Beltrame, et al., International standardization of diagnostic criteria for microvascular angina, International Journal of Cardiology 250 (2018) 16–20, https://doi.org/10.1016/j.ijcard.2017.08.068.
[29] H.G. Kemp, The anginal syndrome with normal coronary arteriography, Trans. Assoc. Am. Physicians 80 (1967) 59–70.
[30] J.C. Kaski, C. Vitale, Microvascular angina and systemic hypertension, E-Journal Cardiol Pract 14 (2016).
[31] T.S. Kenkre, P. Malhotra, B.D. Johnson, et al., Ten-year mortality in the WISE study (Women's Ischemia Syndrome Evaluation), Circ. Cardiovasc. Qual. Outcomes 10 (12) (2017) e003863.
[32] Z.S. Yaker, A.M. Lincoff, L. Cho, et al., Coronary spasm and vasomotor dysfunction as a cause of MINOCA, EuroIntervention 20 (2024) e123–e134, https://doi.org/10.4244/EIJ-D-23-00448.
[33] P. Libby, R. Sidlow, A. Lin, et al., Clonal hematopoiesis: crossroads of aging, cardiovascular disease, and cancer: JACC review topic of the week, J. Am. Coll. Cardiol. 74 (4) (2019) 567–577.
[34] A. Sinha, U. Dutta, O.M. Demir, et al., Rethinking false positive exercise electrocardiographic stress tests by assessing coronary microvascular function, J. Am. Coll. Cardiol. 83 (2) (2024) 291–299.
[35] R.A. De Boer, M. Nayor, C.R. DeFilippi, et al., Association of cardiovascular biomarkers with incident heart failure with preserved and reduced ejection fraction, JAMA Cardiol. 3 (3) (2018) 215–224.
[36] Carl J. Pepine, John W. Petersen, C. Noel Bairey Merz., A microvascular-myocardial diastolic dysfunctional state and risk for mental stress ischemia: a revised concept of ischemia during daily life, JACC Cardiovasc. Imaging 7 (4) (2014) 362–365.
[37] B.A. Borlaug, K. Sharma, S.J. Shah, et al., Heart failure with preserved ejection fraction: JACC scientific statement, J. Am. Coll. Cardiol. 81 (2023) 1810–1834.
[38] J.M. Bilak, U. Alam, C.A. Miller, et al., Microvascular dysfunction in heart failure with preserved ejection fraction: pathophysiology, assessment, prevalence and prognosis, Card. Fail. Rev. 8 (2022).
[39] D. Mihalcea, H. Memis, S. Mihaila, D. Vinereanu, Cardiovascular toxicity induced by vascular endothelial growth factor inhibitors, Life 13 (2) (2023) 366.
[40] Brian B. Hasinoff, Daywin Patel, Wu. Xing, Molecular mechanisms of the cardiotoxicity of the proteasomal-targeted drugs bortezomib and carfilzomib, Cardiovasc. Toxicol. 17 (2017) 237–250.
[41] Rhian M. Touyz, Joerg Herrmann, Cardiotoxicity with vascular endothelial growth factor inhibitor therapy, NPJ Precis. Oncol. 2 (1) (2018) 13.

[42] Alan C. Cameron, Rhian M. Touyz, Ninian N. Lang, Vascular complications of cancer chemotherapy, Can. J. Cardiol. 32 (7) (2016) 852–862.
[43] A. Soultati, G. Mountzios, C. Avgerinou, G. Papaxoinis, et al., Endothelial vascular toxicity from chemotherapeutic agents: preclinical evidence and clinical implications, Cancer Treat. Rev. 38 (5) (2012) 473–483.
[44] S. Tan, D. Day, S.J. Nicholls, E. Segelov, Immune checkpoint inhibitor therapy in oncology: current uses and future directions: JACC: cardiooncology state-of-the-art review, Cardio Oncol. 4 (5) (2022) 579–597.