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EDITORIAL COMMENT

A Multi-Biomarker Approach to Understanding Coronary Microvascular Dysfunction

Making Sense of a Complex Disease*

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Ischemia with no obstructive coronary arteries (INOCA) affects up to 3 to 4 million people in the United States and is associated with significant morbidity and healthcare utilization.[1,2] Nearly half of all patients referred for coronary angiography to evaluate angina have <50% stenosis of all major epicardial coronary arteries, with a higher proportion among women.[3,4] Patients with INOCA are at increased risk for major adverse cardiac events and all-cause mortality when compared to asymptomatic patients without cardiovascular disease.[2,5] It is now recognized that INOCA may be caused by multiple potential mechanisms, or endotypes, which can occur alone or in combination, including coronary microvascular dysfunction (CMD) and coronary vasospasm.[2] CMD occurs in 40 to 50% of INOCA patients, and can result from structural mechanisms, including structural abnormalities (remodeling or extravascular compression of the coronary microcirculation) or functional etiologies characterized by vasomotor dysregulation of the coronary arterioles (high resting microcirculatory flow or microvascular spasm).[2,6] CMD can be measured by invasive or noninvasive testing. The gold standard is invasive assessment, using either intracoronary Doppler or thermodilution measures of coronary flow. Invasive assessment has advantages over other modalities given the ability to simultaneously evaluate for epicardial disease, coronary flow reserves (CFRs), resistance indices, and test for coronary spasm.[2] However, invasive testing may not always be possible due to high costs and limited availability. Positron emission tomography-computed tomography is also a well validated modality to noninvasively determine global CFRs.[2] CMD is defined by reduced CFR <2.0 to 2.5 or abnormal microcirculatory resistance measures (eg, index of microcirculatory resistance ≥25).[2] Despite the significant number of patients with INOCA, there are few clinical prediction tools to identify those who would benefit from invasive testing.

Mechanisms of CMD remain poorly understood, limiting our ability to identify targets for disease-modifying therapy. Prior studies have shown some association with pro-inflammatory markers in women, suggesting that inflammation may be important in the pathophysiology of CMD.[7-9] One small study of 174 women with low coronary flow velocity reserve (CFVR) measured by Doppler echocardiography reported a significant association between the tumor necrosis factor-alpha-interleukin-6-C-reactive protein pro-inflammatory pathway and microcirculatory function.[8] Another study of 97 women found 4 biomarkers were significantly associated with CMD diagnosed by cardiac PET (GDF-15, tissue plasminogen activator, Galectin-4, von Willebrand factor), suggesting a role of inflammation and disorders of coagulation.[10]

In this issue of *JACC: Advances*, Prescott et al[11] sought to evaluate mechanistic pathways associated with CMD in INOCA, and to identify biomarker

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signatures that, when combined with clinical factors, may identify patients with CMD. To this end, they analyzed 184 cardiovascular protein biomarkers in 1471 women enrolled in the iPOWER (Improve diagnosis and treatment of women with angina pectoris and microvessel disease) study, a prospective cohort study of women with angina with nonobstructive coronary artery disease. Participants in the iPOWER study underwent noninvasive measurements of microvascular function using Doppler echocardiography with measurement of CFVR of the left anterior descending artery.[11] The authors used high-throughput multiplex immunoassays to measure a panel of proteins, and data-driven analyses to identify pathways associated with low CVFR. They considered a diagnosis of CMD when CVFR was below 2.25. Principal component analyses and weighted correlation network analyses were used to untangle the complex relationships between biomarkers associated with CMD. Machine learning methods were used to develop prediction models for CMD.

This study identified 61 biomarkers significantly correlated with CFVR in univariate analyses. Principal component analysis of these 61 biomarkers identified 7 principal components significantly associated with CFVR, and weighted correlation network analyses identified 2 clusters (of 32 and 47 biomarkers, respectively) negatively correlated with CFVR. Multiple machine learning algorithms incorporating clinical factors and biomarkers were used to develop models to predict for CMD. At best, machine learning models were only modestly predictive of CMD with an area under receiver operating curve of 0.66. After pathways and prediction analyses, 7 biomarkers of importance were identified: renin, growth differentiation factor-15, Brain natriuretic peptide/Pro-BNP, adrenomedullin, chitinase 3 like 1, TRAIL receptor 2, and IL-6. The emergence of these biomarkers suggests multiple mechanistic pathways for the development of CMD, including increases in cardiac loading, potentially related to hypertensive disease, progressing to cardiac remodeling, development of diastolic dysfunction, and heart failure with preserved ejection fraction. The strong association of IL-6 with low CFVR also supports inflammation as an important contributor to CMD pathogenesis, which may be a distinct mechanistic pathway.

The authors should be congratulated for their important contributions to our understanding of INOCA pathogenesis. This is the largest study to date leveraging multiple protein biomarkers in a cohort of patients with INOCA, with and without CMD. The authors use rigorous data-driven approaches to identify mechanistic pathways and develop prediction models. Still, some limitations are worth noting. Doppler echocardiography was used to estimate CVFR in this study. Unfortunately, Doppler has been validated against invasive measures in only small cohorts of patients.[12,13] When compared to CFR measured by PET, a well validated noninvasive tool to diagnose global measures of CMD, CFVR by Doppler echocardiography demonstrated only modest agreement.[14] Measurement of Doppler echocardiography by CFVR requires substantial technical expertise, and this may be particularly difficult in overweight and obese patients, potentially conferring selection bias. Since Doppler CFVR is not performed in routine clinical practice, it limits the external validity and applicability of these data to contemporary care. Furthermore, this cohort was not evaluated for coronary spasm, which is relevant because overlap syndromes are common in INOCA.[15] Endothelial-dependent microvascular spasm, which is a component of microvascular angina, was also not evaluated in this study. Furthermore, heterogeneity in potential mechanisms of CMD was similarly not addressed, and the authors are unable to provide data stratified by structural vs functional CMD subtypes.

Thus, CFVR by Doppler may not provide the complete picture of CMD pathogenesis that would be ideal for assessment of biomarker associations with CMD subtypes. Finally, this study only included women and did not compare biomarker signatures against patients with obstructive coronary artery disease or healthy controls.

Still, the findings of the current study provide incremental advances in our understanding of the complex pathophysiologic mechanisms involved in the development of CMD.[11] The current analysis confirms hypothesized paradigms involving hypertension, cardiac remodeling, heart failure with preserved ejection fraction, and inflammation. Efforts are needed to validate these biomarkers in cohorts with CMD diagnosed by invasive coronary testing, and to determine the relationships between biomarkers and symptom burden. Ultimately, this study lays a foundation for future INOCA research, from the development of preclinical animal models for CMD to the development of targeted therapy to improve health outcomes in INOCA patients with CMD.

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REFERENCES

1. Schumann CL, Mathew RC, Dean J-HL, et al. Functional and economic impact of INOCA and influence of coronary microvascular dysfunction. *Cardiovasc Imaging*. 2021;14(7):1369–1379.

2. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J*. 2020;41(37):3504–3520.

3. Patel MR, Peterson ED, Dai D, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362(10):886–895.

4. Humphries KH, Pu A, Gao M, Carere RG, Pilote L. Angina with "normal" coronary arteries: sex differences in outcomes. *Am Heart J*. 2008;155(2):375–381.

5. Herscovici R, Sedlak T, Wei J, Pepine CJ, Handberg E, Bairey Merz CN. Ischemia and no obstructive coronary artery disease (INOCA): what is the risk? *J Am Heart Assoc*. 2018;7(17):e008868.

6. Ong P, Camici PG, Beltrame JF, et al. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol*. 2018;250:16–20.

7. Recio-Mayoral A, Rimoldi OE, Camici PG, Kaski JC, et al. Inflammation and microvascular dysfunction in cardiac syndrome X patients without conventional risk factors for coronary artery disease. *J Am Coll Cardiol Img*. 2013;6(6):660–667.

8. Schroder J, Mygind ND, Frestad D, et al. Pro-inflammatory biomarkers in women with non-obstructive angina pectoris and coronary microvascular dysfunction. *Int J Cardiol Heart Vasc*. 2019;24:100370.

9. Ishimori ML, Martin R, Berman DS, et al. Myocardial ischemia in the absence of obstructive coronary artery disease in systemic lupus erythematosus. *J Am Coll Cardiol Img*. 2011;4(1):27–33.

10. Schroder J, Zethner-Moller R, Bové KB, et al. Protein biomarkers and coronary microvascular dilatation assessed by rubidium-82 PET in women with angina pectoris and no obstructive coronary artery disease. *Atherosclerosis*. 2018;275:319–327.

11. Prescott E, Bang Bove K, Frestad Bechsgaard D, et al. Biomarkers and coronary microvascular dysfunction in women with angina and no obstructive coronary artery disease. *JACC Adv*. 2023;2(2):100264.

12. Hildick-Smith DJ, Maryan R, Shapiro LM. Assessment of coronary flow reserve by adenosine transthoracic echocardiography: validation with intracoronary Doppler. *J Am Soc Echocardiogr*. 2002;15(9):984–990.

13. Caiati C, Montaldo C, Zedda N, et al. Validation of a new noninvasive method (contrast-enhanced transthoracic second harmonic echo Doppler) for the evaluation of coronary flow reserve: comparison with intracoronary Doppler flow wire. *J Am Coll Cardiol*. 1999;34(4):1193–1200.

14. Michelsen MM, Mygind ND, Pena A, et al. Transthoracic Doppler echocardiography compared with positron emission tomography for assessment of coronary microvascular dysfunction: the iPOWER study. *Int J Cardiol*. 2017;228:435–443.

15. Ford TJ, Yii E, Sidik N, et al. Ischemia and no obstructive coronary artery disease: prevalence and correlates of coronary vasomotion disorders. *Circ Cardiovasc Interv*. 2019;12(12):e008126.

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