JACC: ADVANCES VOL. 3, NO. 2, 2024

EDITORIAL COMMENT

Uncovering Sex Differences in Type 2 Myocardial Infarction

Is Coronary Anatomy Enough?*

Nathaniel R. Smilowitz, MD, MS[a,b]

Type 2 myocardial infarction (MI) is a clinical syndrome characterized by myocardial injury that occurs in the setting of an imbalance in myocardial blood supply and demand, in the absence of plaque disruption or atherothrombosis. Since the universal definition of MI first introduced subtypes in 2007, it has become apparent that type 2 MI is underappreciated, more common than type 1 MI, and associated with substantial morbidity and mortality.[1,2] When compared to individuals with type 1 MI, those with type 2 MI tend to be older, are more likely to be female, and have a higher prevalence of cardiovascular comorbidities, such as heart failure and atrial fibrillation.[2] Yet unlike type 1 MI, for which pathophysiology is known and effective treatments are available, coronary mechanisms of type 2 MI have not been systematically elucidated. In a prior study of coronary computed tomography angiography (CCTA) in patients with type 2 MI vs type 1 MI, those with type 2 MI had smaller total, noncalcified, and low-attenuation plaque burdens than those with type 1 MI.[3] However, among patients with type 2 MI, sex-specific differences in clinical presentation and mechanism of MI have not been defined. Unfortunately, due to the deficiencies in our understanding of the pathogenesis of type 2 MI, few targeted therapies have been tested. Instead, supportive care addressing the provoking conditions of type 2 MI and management of traditional cardiovascular risk factors have remained the mainstay of treatment for type 2 MI.

In this issue of *JACC: Advances*, Lin et al[4] report a post-hoc analysis of sex differences in DEFINE TYPE 2 MI, a single-center prospective study of coronary anatomy among 25 males and 25 females with adjudicated type 2 MI.[5] All participants underwent CCTA during the index hospitalization for MI. Female participants with type 2 MI enrolled in the current study were significantly older than the corresponding males. Peak troponin levels were modest in both sexes (median hs-cTnT of 61 in females and 109 in males), and most participants had electrocardiogram changes or regional wall motion abnormalities by echocardiography, with or without symptoms, to fulfill the Universal Definition of MI criteria. Provoking conditions were heterogenous, and in this small cohort, cases of hypoxemic respiratory failure were numerically higher among males, while tachyarrhythmias, hypertensive urgency, and bleeding occurred in greater numbers among females. At the time of presentation, electrocardiographic ST-segment depressions were more often observed in females, while T-wave inversions were more common in males. Despite this, CCTA revealed no differences in coronary artery calcium scores by sex, and in both males and females with type 2 MI, nonobstructive coronary atherosclerosis was widely prevalent. No differences in calcified and noncalcified plaque volumes were observed in males and females. Women had lower levels of low-attenuation plaque volume, although the clinical relevance of this finding is uncertain. Perhaps most importantly, CCTA-defined

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* or the American College of Cardiology.

From the [a]Leon H. Charney Division of Cardiology, Department of Medicine, NYU Grossman School of Medicine, New York, New York, USA; and the [b]Cardiology Section, Department of Medicine, VA New York Harbor Healthcare System, New York, New York, USA.

The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100788

obstructive coronary artery disease (CAD), defined by diameter stenosis, or hemodynamically significant lesions, assessed by FFR_{CT} ≥0.80, were identified in only a quarter of males and females with type 2 MI, with no differences by sex.

The authors should be commended for conducting a prospective imaging study of males and females with type 2 MI. Although few sex-specific differences were identified, the findings provide incremental insights to our understanding of the clinical characteristics of type 2 MI. Surprisingly, obstructive coronary artery disease was present in less than one- third of cases in both males and females, raising substantial questions as to the mechanism of ischemic imbalances in patients in the cohort who did not have obstructive or functionally significant CAD. Unfortunately, coronary spasm testing was not performed, and spasm is well recognized as a mechanism for MI with nonobstructive coronary arteries.[6] Disorders of the microcirculation, comprised of arterioles and capillaries that cannot be visualized by CCTA, might also provoke or exacerbate imbalances in supply and demand during hemodynamic perturbations and cause type 2 MI. Without assessments for coronary spasm and microvascular dysfunction, mechanisms of type 2 MI cannot be adequately explained by plaque burden in many cases. There are other more minor limitations; coronary calcium was prevalent in this cohort, and calcium may impact the accuracy of coronary diameter assessments by CCTA and CT_{FFR}. Notably, the sample size was small and may have conferred insufficient statistical power to identify clinically meaningful sex differences in patient characteristics. Furthermore, the study enrolled a heterogenous cohort with multiple provoking causes of type 2 MI that were not matched by sex, potentially confounding sex-specific comparisons. Finally, a handful of patients with heart failure, in which the diagnosis of type MI can be challenging to adjudicate given the overlap of signs and symptoms of ischemia and volume overload, were included in the cohort.

Ultimately, this small single-center study highlights that remarkably few patients with type 2 MI have obstructive CAD, and this proportion did not differ by sex. Sex differences in plaque characteristics were modest and of uncertain clinical significance. Additional efforts are needed to understand mechanisms of type 2 MI and sex differences relevant to diagnosis and management. Larger studies incorporating coronary functional assessments in addition to coronary anatomy may be required to understand the pathophysiology of this complex and challenging MI subtype.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Smilowitz is supported, in part, by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number K23HL150315; and serves as a consultant for Abbott Vascular.

ADDRESS FOR CORRESPONDENCE: Dr Nathaniel R. Smilowitz, The Leon H. Charney Division of Cardiology, NYU Langone Health, NYU School of Medicine, 423 East 23rd Street, 12-West Cardiology, New York, New York 10010, USA. E-mail: nathaniel.smilowitz@nyulangone.org.

REFERENCES

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138(20):e618-e651. https://doi.org/10.1161/CIR.0000000000000617

2. McCarthy CP, Kolte D, Kennedy KF, Vaduganathan M, Wasfy JH, Januzzi JL Jr. Patient characteristics and clinical outcomes of type 1 versus type 2 myocardial infarction. *J Am Coll Cardiol*. 2021;77(7):848-857. https://doi.org/10.1016/j.jacc.2020.12.034

3. Meah MN, Bularga A, Tzolos E, et al. Distinguishing type 1 from type 2 myocardial infarction by using CT coronary angiography. *Radiol Cardiothorac Imaging*. 2022;4(5):e220081. https://doi.org/10.1148/ryct.220081

4. Lin C, McCarthy CP, Mohebi R, et al. Sex differences in coronary artery disease characteristics among patients with type 2 myocardial infarction. *JACC: Adv*. 2024;3(2):100795.

5. McCarthy CP, Murphy SP, Amponsah DK, et al. Coronary computed tomographic angiography with fractional flow reserve in patients with type 2 myocardial infarction. *J Am Coll Cardiol*. 2023;82(17):1676-1687. https://doi.org/10.1016/j.jacc.2023.08.020

6. Reynolds HR, Smilowitz NR. Myocardial infarction with nonobstructive coronary arteries. *Annu Rev Med*. 2022;74:171-188. https://doi.org/10.1146/annurev-med-042921-111727

KEY WORDS coronary computed tomography angiography, coronary angiography, coronary artery disease, coronary atherosclerosis, myocardial infarction, type 2 myocardial infarction