COMMENTARY

# Linking Coronary Microvascular and Cardiac Diastolic Dysfunction in Diabetes: Are Women More Vulnerable?

Shawn B. Bender

Diabetes 2019;68:474–475 | https://doi.org/10.2337/dbi18-0053

Accumulating evidence has demonstrated a clear association of coronary microvascular dysfunction with poor cardiac outcomes (1–4). For example, in patients with normal myocardial perfusion imaging, coronary microvascular dysfunction is a powerful predictor of major adverse cardiac events and improves risk discrimination in clinical risk models (1). Furthermore, these studies suggest that coronary microvascular dysfunction may underlie the increased cardiac risk associated with some comorbid conditions. Particularly, in patients with diabetes, the presence of coronary microvascular dysfunction effectively accounted for all of the increased cardiac mortality compared with patients with diabetes with no coronary microvascular dysfunction (5). Whether sex differences exist with regard to coronary dysfunction and outcomes in patients with diabetes has not been addressed; however, it is critically needed given the impact of diabetes to abrogate the cardiovascular protection afforded by female sex hormones (6).

Coronary microvascular dysfunction is defined clinically as a coronary flow reserve (CFR) (ratio of resting to maximal hyperemic coronary blood flow) $<2$ in the absence of obstructive coronary artery disease (CAD) (4). Previous work has revealed important sex-specific relationships between coronary dysfunction and ultimate outcomes in broad patient populations referred for angiography (1,3). Namely, prospective examination revealed that symptomatic intermediate-to-high–risk women, but not men, with impaired CFR experience increased cardiovascular events (3). This has been attributed largely to the underlying cause of impaired CFR in women being primarily coronary microvascular dysfunction as opposed to primarily obstructive CAD in men (3). It is notable, however, that women in this study had higher rates of obesity and diabetes than men, suggesting important sex-specific links between these conditions, coronary microvascular dysfunction, and outcomes.

In this issue of *Diabetes*, Haas et al. (7) interrogate potential sex differences in coronary microvascular dysfunction in patients with diabetes and whether these measures correlate with cardiac diastolic function, via post hoc analysis of previously published data (8). Specifically, quantitative positron emission tomography–derived CFR, echocardiography-derived E/e′ (an index of cardiac diastolic function), and the aldosterone response to angiotensin II infusion were assessed in 46 men and 27 women with type 2 diabetes. Patients included in this study were in good cardiometabolic control and had no obstructive CAD. Results demonstrate lower CFR in women with diabetes compared with men with diabetes owing to increased resting coronary blood flow (CBF) in women. Increased resting CBF in women was related, in part, to systolic blood pressure and age. Moreover, women with diabetes had worse diastolic function (i.e., higher E/e′) than men with diabetes, and, for women with diabetes, E/e′ correlated significantly with resting CBF independent of blood pressure. Lastly, men and women with diabetes had similar basal plasma aldosterone concentrations; however, women with diabetes exhibited a greater increase in circulating aldosterone in response to angiotensin II infusion compared with male counterparts. Together, these data suggest significant sex specificity in the coronary microvascular phenotype in diabetes and, perhaps more importantly, suggest a mechanistic link between coronary microvascular and cardiac diastolic dysfunction with critical clinical implications for women with diabetes.

Several fundamental considerations arise from this study. First, it should be noted that, as groups, the men and women included in this study do not meet the CFR criteria for coronary microvascular dysfunction (CFR $<2$) (4). That women with diabetes have lower CFR than the men with diabetes largely within the normal range and that this correlates with cardiac function, however, may necessitate revision of CFR criteria for dysfunction in this patient population. Moreover, that reduced CFR in women with diabetes occurs due to increased resting CBF with no sex difference in maximal hyperemic CBF may indicate

Biomedical Sciences, University of Missouri, Columbia, MO
Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO
Research Service, Harry S. Truman Memorial Veterans' Hospital, Columbia, MO
Corresponding author: Shawn B. Bender, benders@missouri.edu



See accompanying article, p. 631.

resting CBF as a more appropriate index of coronary microvascular dysfunction in this setting. An important caveat in this regard involves the tight coupling of CBF to myocardial metabolism (9) and that the present data set does not provide insight into whether myocardial work was similar between men and women with diabetes. This concern is partly offset by a similar report in a larger patient population (3) and, more importantly, by the strong association of resting CBF with diastolic function in women with diabetes. The latter is suggestive of dynamic changes in mechanisms of CBF regulation, coronary anatomy, or both in women with diabetes worthy of further examination.

Second, the paradigm of a coronary microvascular origin of cardiac diastolic dysfunction and heart failure with preserved ejection fraction (HFpEF) in comorbid conditions has recently been proposed (10). Indeed, association of impaired CFR and cardiac diastolic dysfunction has been reported in patients with diabetes (11). The present analysis may expand these findings by suggesting that this process is accelerated in women versus men with diabetes and, if confirmed prospectively, that resting CBF could be predictive of diastolic dysfunction in women with diabetes. Regardless, further delineation of mechanisms underlying this coronary-cardiac link in women with diabetes is critical in light of recent evidence that patients with both coronary microvascular and diastolic dysfunction have a fivefold increased risk of ultimate HFpEF hospitalization versus patients with either condition alone (12). To this end, aldosterone/mineralocorticoid receptor (MR) signaling would appear to be a promising therapeutic target (13). Indeed, women with diabetes had a greater aldosterone response to angiotensin II infusion than men with diabetes. Sex-specific aspects of aldosterone/MR signaling in normal and comorbid conditions have been reported, including that deletion of endothelial cell MR prevents obesity-associated diastolic dysfunction in female mice (13–16). Importantly, the data utilized in this post hoc analysis originated from previously published work demonstrating that MR antagonism improves CFR in men and women with diabetes, although sex differences were not examined (8). Furthermore, despite its shortcomings, post hoc analysis of the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) trial revealed reduced cardiovascular events following MR antagonism in the Americas cohort that included a greater percentage of patients with diabetes (17).

In summary, this timely analysis by Haas et al. (7) advances our understanding of the nuances underlying coronary microvascular and cardiac dysfunction in diabetes, particularly as it relates to sex differences. Follow-up to this hypothesis-generating study would ideally include prospective clinical and preclinical studies to further characterize sex-specific mechanisms of coronary dysfunction in diabetes, its relationship to cardiac function, and potential involvement of MR signaling.

**Funding.** The research of the author is supported by funding from the National Institutes of Health National Heart, Lung, and Blood Institute (R01 HL136386). This work was also supported with resources and the use of facilities at the Harry S. Truman Memorial Veterans' Hospital in Columbia, MO.

**Duality of Interest.** No potential conflicts of interest relevant to this article were reported.

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