We recently showed that coronary microvascular dysfunction (CMD) in patients with nonobstructive coronary artery disease (CAD) correlates poorly with so-called traditional cardiovascular risk factors (1). Other studies have similarly shown that traditional risk factors are poor predictors of CMD. In their letter, Dr. Chhabra and colleagues highlight the potential overlap between patients with CMD and those with Takotsubo cardiomyopathy, which is underscored by our observation that coronary endothelial dysfunction is prevalent in patients with Takotsubo, and that it is predictive of recurrent events (2). As atypical risk profiles are implicated in both CMD and Takotsubo cardiomyopathy, there may be an opportunity to learn more about one pathological entity from the other and vice versa. We recently showed that hypothyroidism is independently associated with microvascular endothelial dysfunction in women with nonobstructive CAD (3), and so it could potentially be a common novel risk factor for Takotsubo. Similarly, if sympathetic blockade has been shown to be protective against Takotsubo, this may be mediated through its effects on coronary microvascular function.

The finding of a low prevalence of diabetes mellitus (DM) among patients with CMD was a particularly noteworthy finding in our study. The association between microvascular disease and DM is well established in the nervous system, eyes, and kidneys; however, this relationship has been demonstrated less consistently in the myocardium. Although some reports have shown that chronic hyperglycemia is associated with impaired endothelial-dependent and -independent microvascular function, others have shown that hyperinsulinemia or insulin resistance is not associated with CMD once confounders are accounted for (4). Further studies have suggested that improving insulin sensitivity improves endothelial function and decreases myocardial ischemia in patients with nonobstructive CAD, yet we recently demonstrated that good glycemic control among diabetic patients is not associated with better coronary microvascular function (5). The use of variable, albeit established, indexes to define DM and good/poor glycemic control could account for some of the discrepant findings across studies. Nevertheless, one would expect a more compelling correlation between DM and CMD not only because of the long-established relationships between microvascular disease and DM in other organs, but also because endothelial dysfunction is a systemic disorder affecting multiple vascular beds and can be regarded as an integrated index of overall cardiovascular risk burden. Given that optimal glycemic control does not always mitigate cardiovascular events, it may be that alternative indexes of diabetic control that better reflect cardiovascular risk need to be developed. CMD occurs early in the development of atherosclerotic CAD and is independently linked to cardiovascular events, and so these alternative indexes of diabetic control could be developed in parallel to testing strategies for CMD. In this way, CMD could provide an alternative functional perspective to the management of DM by paving the way for novel therapeutic targets that are more useful for the prevention of cardiovascular events in diabetic patients.

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