and physiology to elucidate potential causes of ischemic chest pain (2). We appreciate the comments and interesting question Dr. Lozano and colleagues pose regarding microvascular dysfunction and ticagrelor. As they point out, ticagrelor, in addition to being a reversibly binding P2Y12 receptor blocker, is the only P2Y12 blocker or metabolite that inhibits the adenosine reuptake transporter, ENT-1 (type I equilibrative nucleoside transporter). Inhibition of the ENT-1 transporter by ticagrelor leads to enhanced extracellular adenosine concentration, which, in turn, can have a multitude of effects via the adenosine 1, 2A, 2B, and 3 receptors including additional inhibition of platelet aggregation/activation, cardioprotection, vasodilation, improvement in endothelial function, bradycardia, and a sensation of dyspnea. So, whether ticagrelor may favorably affect coronary microvascular function is certainly possible, although not well known. A prospective trial to investigate the effect of ticagrelor on patients with microvascular angina is under way (NCT02284048). Certainly, establishing robust reliable indexes of microcirculatory and endothelial function in the cardiac catheterization laboratory allows for detailed assessment of the effects of pharmacotherapy on many facets of human coronary atherosclerosis (3,4).

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We would like to thank Dr. Lozano and colleagues for their comments regarding our study (1). It is clear that our understanding of the coronary microcirculation remains incomplete. In our study, we undertook a detailed assessment of the microcirculation in the context of ST-segment elevation myocardial infarction using both thermodilution and Doppler wire techniques in the same vessels (1). This approach limited the restrictions of each individual methodology. Conversely Sara et al. (2) used Doppler wire to assess responses to intracoronary acetylcholine and adenosine, and Kobayashi et al. (3) used a thermodilution technique with peripheral adenosine infusion. Consequently, the definitions of microcirculatory function in each study differ depending on the applied methodology, and the understanding of how these measurements might interrelate needs clarification.

The potential that ticagrelor may have benefit in patients with stable coronary disease taking aspirin and the evidence of microcirculatory dysfunction is intriguing. In a 10-year follow-up study, Van de Hoef et al. (4) demonstrated adverse outcomes in those patients with impaired microcirculatory function, and some recent studies have suggested increased vasodilator response following ticagrelor (5). There remains a need to explore and understand the implications of these separate observations.

Nevertheless, we believe that the ability to risk stratify individual patients on the catheter laboratory table using coronary physiology indexes is relevant and may potentially lead to tailored therapy and improved outcomes in both stable and acute coronary presentations.

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Low Incidence of Diabetes Mellitus in Coronary Microvascular Dysfunction

An Intriguing Association

We immensely enjoyed reading the recently published article by Sara et al. (1) in JACC: Cardiovascular Interventions. Their endeavors to elucidate the spectrum of coronary microvascular abnormalities in patients with chest pain and nonobstructive coronary artery disease are commendable (1). In summary, they found that microvascular dysfunction occurred in two-thirds of these patients, and interestingly these were poorly associated with the conventional risk factors. This study echoes the results found by previous studies demonstrating the role of microvascular dysfunction in this patient population.

In their findings, we paid special attention to the low incidence of diabetes mellitus reported among all the study groups (7% to 12%). We would like to switch gears and bring the readers’ attention to a curious similarity between the population in this study and patients with Takotsubo cardiomyopathy (TC). A recent meta-analysis showed that the prevalence of diabetes mellitus in patients with TC was indeed low (2). This fact has been reproduced in subsequent smaller studies. It has been suggested that the blunted catecholamine secretions (autonomic neuropathy) may perhaps be protective against the development of TC (3,4). The success of sympathetic blockade for TC in animal model studies has further supported this hypothesis. It has long been accepted that diabetes mellitus is one of the strong risk factors for coronary microcirculatory disease (5), and the low incidence of diabetes in this study group was peculiar. It almost leads us to wonder whether there might be an overlap of some of these patients with TC, especially with atypical or chronic recurrent forms of TC. That potentially would explain the low incidence of diabetes, and the presence of microcirculatory dysfunction is consistent with the described pathophysiology of TC. Also, this thought-provoking correlation is compelling to suggest that female patients with microvascular dysfunction perhaps may have a unique nontraditional etiological background, for example, they seem less likely to be affected by diabetes mellitus (because both the current study population and previous TC studies demonstrated a female predominance) (1,2).

Although the authors were meticulous in their efforts, another aspect that caught our attention was the analysis of cardiac studies, specifically echocardiography and stress testing. The study duration was 20 years, and it is apparent that imaging parameters may vary considerably over time depending on the disease progression or risk-factor modification. It is not clear from their article at what point imaging was performed, and this might have some impact on the analysis of outcomes. The addition of that information could allow a more robust interpretation of these data. Future prospective studies are needed for a better understanding of the role of autonomic influences and clinical markers regarding their association with microvascular dysfunction.

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