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EDITORIAL COMMENT

Translational Insights in Coronary Microvascular Disease*

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Clinical studies over the past 2 decades have highlighted the importance of the coronary microvasculature and the significance of coronary microvascular disease (CMD). However, the field lags far behind coronary atherosclerosis in our understanding of pathophysiology, and, consequently, in directed therapies. Basic scientists are working hard to close the gap. In a timely study by Shah et al[1] in this issue of *JACC: Basic to Translational Science*, the investigators leverage their extensive and robust prior efforts to develop quantitative coronary microvascular imaging methods to probe the underlying biology of CMD.

The microvasculature is the highest resistance part of the coronary circulation and is responsible for regulating blood flow to meet cardiac metabolic demand. CMD refers to structural and functional abnormalities in coronary microvasculature, defined as coronary prearterioles, arterioles, and capillaries, which can impair proper function and lead to cardiac ischemia. CMD can lead to symptoms of angina or dyspnea and can worsen prognosis in patients with coronary artery disease or underlying cardiomyopathy.[2] Therefore, there is growing interest in developing novel therapies for CMD both to treat symptoms from CMD, and to modify downstream adverse outcomes including myocardial infarction, heart failure, and death. One of the biggest challenges in diagnosing and studying CMD has been the field's limited ability to properly quantify the phenotype. Direct visualization of the microvasculature is not technically feasible. Instead, diagnostic modalities have relied on the role of the coronary microvasculature in regulating blood flow. Several cardiac imaging modalities are now able to measure coronary flow at rest and under hyperemic stress conditions and calculate the myocardial perfusion reserve (MPR), which is the ratio of stress flow to rest flow and represents the ability of the microcirculation to vasodilate properly. These have facilitated numerous epidemiologic studies and form the foundation of our clinical understanding of CMD. The first significant step in studying CMD in preclinical models and in identifying novel therapies is to translate these clinical imaging tools to measure MPR in mice. The investigators have been leaders in this field.

By leveraging previously established tools that use arterial spin labeling cardiac magnetic resonance methods to quantify myocardial blood flow at rest and stress, Shah et al[1] show that C57BL/6J mice fed a high-fat high-sucrose diet develop CMD via an inducible nitric oxide synthase (iNOS)-dependent mechanism. They then administer selective iNOS inhibitor 1400X to improve MPR, establishing the role of iNOS in CMD and suggesting that iNOS inhibition may be a therapeutic option to consider for CMD. Prior work has established the role of iNOS in heart failure with preserved ejection fraction (HFpEF).[3] In linking iNOS to CMD, this work also serves to further support the hypothesis that CMD may be a precursor for HFpEF and represents an intermediate phenotype where intervention may prevent or delay the onset of HFpEF.

Whether selective iNOS inhibitors may prove to be a useful clinical target for CMD still remains to be seen.[4] There are concerns that off-target effects may

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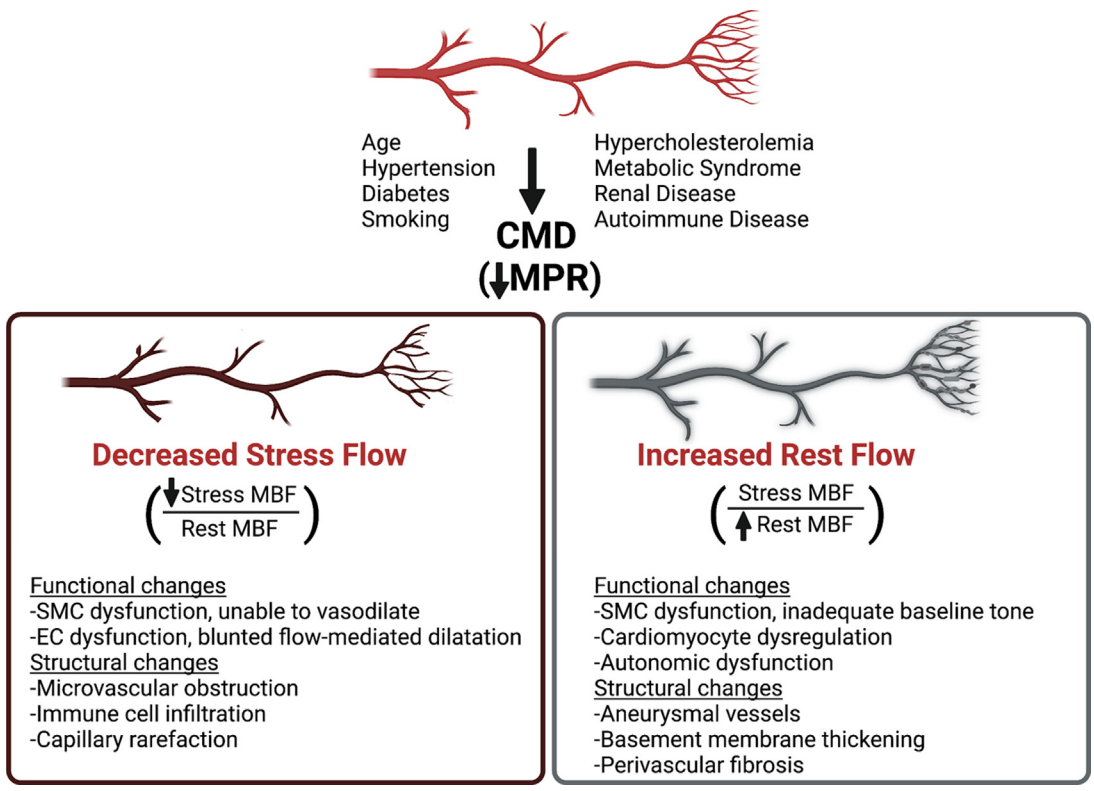
FIGURE 1 Schematic Overview of the Relationship Between CMD Phenotypes and Underlying Pathology



Pathologic changes seen in coronary microvascular disease (CMD) can lead to decreased myocardial perfusion reserve (MPR) by 2 potential mechanisms: decreasing stress flow **(left bottom)** or increasing rest flow **(right bottom).** Certain pathologies serve to increase distal resistance and limit the maximal flow that can be achieved in the coronary tree. Conversely, some pathologic changes drive increased blood flow at rest. EC = endothelial cells; MBF = myocardial blood flow; SMC = smooth muscle cells. Created with Biorender.com

have an impact on beneficial endothelial NOS and neuronal NOS. iNOS inhibitors also reduce blood pressure (as seen in this study[1] as well), which can also improve CMD. It is not known whether the beneficial effects of iNOS inhibition are therefore caused by a decrease in systemic blood pressure or direct improvement in coronary microvascular function. The investigators use ex vivo vascular reactivity studies to show that vessels from high-fat, high-sucrose diet-treated mice have an impaired arteriolar dilation response to adenosine, whereas iNOS$^{-/-}$ mice treated with the same diet do not. These studies directly address the effects of diet and iNOS on the vessel, and similar preclinical studies establishing the role of iNOS inhibitors in reversing arteriolar impairment would substantiate the potential of iNOS inhibitors to serve as a directed therapy for CMD.

Another more general consideration in translating these preclinical findings into human therapies is the phenotype heterogeneity of the disease. The hallmark of CMD is decreased MPR; however, decreased MPR can be caused by decreased stress blood flow or increased rest flow (Figure 1). In their paper, Shah et al[1] focus on iNOS as a mechanism that affects the vasculature, blunts stress myocardial blood flow, and reduces MPR. Others have shown that MPR may be driven by increased resting flow, especially in the setting of increased metabolic insults.[5] One potential interpretation is that the reduction in stress flow represents a primary vascular phenotype of CMD where functional and structural changes prevent appropriate increase in myocardial blood flow during hyperemia. As Shah et al[1] show, an example is a metabolic insult leading to increased vascular smooth muscle and macrophage iNOS that subsequently impairs arteriolar function directly and reduces MPR at the tissue level. Other scenarios that lead to this phenotype include capillary rarefaction or microvascular obstruction, causing increased distal resistance and limiting stress flow. The second scenario is

reduced MPR caused by high rest flow. Several potential functional and structural changes associated with CMD can cause this. For example, basement membrane thickening or perivascular fibrosis can impair proper oxygen transport from the vessel lumen to the cardiomyocytes. Blood flow is therefore increased to compensate and allow for an increased oxygen gradient and greater oxygen delivery to cardiomyocytes. Another scenario that has been described is inappropriate sympathetic tone that increases rest myocardial blood flow. Though these lists are far from comprehensive, they highlight how different well-described pathologies seen in CMD can lead to disparate flow-based phenotypes.

Though several of these features are well-established in CMD, future studies are needed to evaluate the interplay between cell types, understand the link between risk factor exposure and functional and structural changes, identify the most significant genes and pathways that drive or protect from disease, and ultimately pave the way for new therapies. There is much work to be done, and translational studies such as the one by Shah et al[1] are the crucial steps needed to bridge the current gap between clinical phenotypes and underlying pathobiology.

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