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Editorial

Coronary Microvascular Dysfunction: Is It Distinct Clinical Entity or Common Physiologic Pathway?

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▸ See the article "Long-Term Patient Prognostication by Coronary Flow Reserve and Index of Microcirculatory Resistance: International Registry of Comprehensive Physiologic Assessment" in volume 50 on page 890.

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The coronary arterial system consists of large epicardial coronary arteries (>500 μm), prearterioles (100–500 μm), and intramural arterioles (<100 μm). Each component of the coronary arterial system plays a unique role in maintaining coronary blood flow. In the absence of obstructive stenosis, epicardial coronary arteries mainly serve as capacitance vessels with little resistance (up to 10%) to coronary blood flow. Coronary vascular resistance is mostly controlled by prearterioles (up to 25%) and arterioles (up to 55%) by altering myogenic constriction and vascular tone in response to mechanical, neural, and metabolic stimuli. Namely, coronary microcirculation is the main site for myocardial blood flow regulation beyond the epicardial coronary arteries.[1)2)]

Coronary microcirculation, despite its significant contribution to myocardial perfusion and ischemia, has not given as much attention as epicardial coronary artery disease because it does not allow direct visualization of human coronary microcirculation in vivo by using current technique. Therefore, the diagnosis, treatment, and prognosis of coronary artery disease has been based on the easily visualized epicardial coronary artery stenosis while coronary microvascular dysfunction has remained a black box and puzzled physicians being called "syndrome X", "microvascular angina", "chest pain without obstructive coronary artery disease", or "ischemia and no obstructive coronary artery disease".[3)]

For the last 2 decades, coronary microvascular dysfunction has been actively investigated and has been increasingly recognized as an important cardiac condition that can be responsible for myocardial ischemia, poor quality of life, and worse clinical outcomes in various cardiac conditions. The classification of coronary microvascular dysfunction was proposed on the basis of the clinical setting: primary microvascular dysfunction, microvascular dysfunction in the presence of myocardial disease, microvascular dysfunction in the presence of obstructive coronary artery disease, and iatrogenic microvascular dysfunction. In addition, heterogeneous underlying pathogenesis including functional (endothelial, smooth muscle cell, and autonomic dysfunction) and structural alteration (luminal obstruction, vascular wall infiltration, vascular remodeling, vascular rarefaction, and perivascular fibrosis) has been suggested. Nevertheless, effective therapy specifically targeting for microvascular dysfunction remains to be developed.[1)3)]

The development of a pressure-temperature sensor-tipped guidewire allows simultaneous measurement of coronary physiology such as fractional flow reserve (FFR), coronary flow reserve (CFR) and the index of microcirculatory resistance (IMR).[4] CFR is a dynamic test to evaluate the coronary vasodilatory capacity, defined as hyperemic coronary blood flow divided by resting flow. Because it interrogates both epicardial and microcirculation, CFR represents the ability of microcirculation to appropriately increase myocardial blood flow only in patients without obstructive epicardial coronary disease. Multiple studies have nicely demonstrated the role of CFR in coronary microcirculation investigation. IMR is a static physiologic index for hyperemic coronary microvascular resistance based on Ohm's law, defined as the distal coronary pressure (myocardial perfusion pressure) divided the inverse of the hyperemic mean transit time (coronary flow) at hyperemia. IMR was validated in various clinical setting in which microvascular dysfunction may be involved such as acute coronary syndrome, angina or objective ischemia without obstructive coronary artery disease, persistent chest pain after coronary intervention, post coronary intervention myocardial necrosis, post heart transplantation and myocardial diseases. As CFR and IMR evaluates coronary microcirculation, but different aspects of coronary microcirculation, simultaneous assessment combining CFR and IMR allows more comprehensive physiologic assessment for the identification of unique clinical, and physiologic phenotypes of patients.[5]

With this background in mind, it is interesting to read the paper from Lee et al.[6] in this issue of *Korean Circulation Journal*. In this study, these investigators evaluate the prognostic value of coronary microvascular dysfunction assessed by CFR and IMR (≥23) in lesions with FFR >0.80. They included 867 patients from multicenters in 3 countries (Korea, Japan, and China) underwent systematic coronary physiology evaluation including FFR, CFR, and IMR on at least one intermediate coronary artery stenosis: the majority of whom were men and presented with stable ischemic heart disease with typical cardiac risk factors. Patients who underwent coronary intervention, had hemodynamic instability and left ventricular dysfunction were excluded.

In this large cohort, they found that at 5-year follow-up, low CFR group (≤2.0) was significantly associated with patient oriented composite outcome in both low FFR (≤0.80) and high FFR (>0.80) group. In addition, when classifying lesions with FFR of >0.80 with CFR and IMR, low CFR (≤2.0) and high IMR (≥23) group were significantly associated with the higher rate of events. Interestingly, this group is responsible for the higher rate of cardiac death and myocardial infarction, but is not associated with the risk of target vessel revascularization. On multivariable analysis, low CFR and high IMR was an independent predictor of patient oriented composite outcome. The strengths of this study include larger sample size and longer complete clinical follow-up compared with the author's previous study.[7] In addition, as they measured FFR systematically, significant coronary artery stenosis could be excluded in the analysis of IMR and CFR.

Several findings from this study raise important clinical issues. First, it is surprising that 44.5% of patients have either low CFR or high IMR, namely microvascular dysfunction even in functionally insignificant coronary artery stenosis (FFR >0.80). Therefore, this study represents that microvascular dysfunction is not an unsolved mystery, but a reality we encounter everyday practice. Second, this study successfully prognosticated very high-risk population. Group with high IMR (≥23) and low CFR (≤2.0) which could be physiologically interpreted as high myocardial resistance and loss of microvascular reactivity was significantly associated with the higher risk of clinical outcomes. However, clinical phenotype

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of the high-risk group to define microvascular dysfunction as a clinical entity is unclear. Considering very high IMR value (41 unit) in this population, important clinical data such as hemodynamic parameters, diastolic dysfunction, and myocardial or infiltrative disease that need to characterize population more clearly may not be captured in this study. Third, this study showed that myocardial dysfunction appeared to be associated with thrombotic process rather than coronary luminal narrowing. Therefore, from a practical standpoint, the clinical utility of microvascular function tests seems to be discouraged in guidance of coronary revascularization. Instead, physicians pay more attention to optimal medical treatment and risk factor control. In addition, further study is expected to evaluate whether microvascular dysfunction is "marker" or "maker" of adverse outcomes.

This study has taken a very meaningful step to unravel the black box of coronary microcirculation and provides a possible explanation for mechanistic linkage of microvascular dysfunction and clinical events in patients without significant coronary artery disease (FFR >0.80). Lee et al.[6] should be congratulated on conducting a comprehensive and meticulous physiological study with complete outcome data.

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