Reserve of Coronary Flow Deserves Predictor of Cardiovascular Events
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Coronary blood flow (CBF) remains constant even with changes in myocardial perfusion pressure, as long as myocardial oxygen consumption is kept constant, known as autoregulation, which is attributable to the corresponding alternation in the vascular tone of coronary resistance vessels. Because of the principle feature of the coronary circulation that myocardial oxygen extraction is near maximal at rest, increases in myocardial oxygen consumption are primarily met by a proportional increases in CBF. Coronary flow reserve (CFR) represents the capacity to dilate of the coronary circulation following an increase in myocardial oxygen demand and is defined as the ratio between the values of CBF under the maximal coronary vasodilation and in the resting condition. In the absence of significant epicardial coronary artery narrowing, CFR depends on the vascular resistance of coronary microcirculation.

The coronary arterial bed can be classified into 3 segments depending on functional and anatomical characteristics: conductive arteries (diameter >500 μm), pre-arterioles (diameter 500–100 μm), and arterioles (diameter <100 μm). Conductive arteries are represented by epicardial arteries and resistance is insignificant as long as the reduction in diameter is less than 50%. In fact, the major fraction of coronary vessel resistance is assigned to the pre-arterioles and arterioles; 75% of the total coronary vascular resistance is located distal to the small arteries of 200 μm in diameter. Vascular tone of pre-arterioles is regulated by local physical factors such as shear stress (flow-induced responses) and luminal pressure changes (myogenic responses). Flow-mediated vasodilation depends on endothelium and is mediated by endothelium-derived nitric oxide (NO) and/or endothelium-dependent hyperpolarizing factor. Arterioles respond to not only local physical forces but also changes in local metabolic needs. Therefore, arterioles are predominant sites of metabolic and ischemic vasodilation in which adenosine works as a metabolic mediator and directly controls perfusion of the coronary capillary bed. NO also promotes metabolic coronary dilation by preserving the tone and vasodilator reserve of arterioles by dilating predominantly the pre-arterioles. Other factors such as autacoids (histamine and bradykinin), prostacyclin, and norepinephrine-induced β-adrenergic receptor (AR)-mediated vasodilation also contribute to the vasodilation of resistance vessels, all of which may be ultimately controlled by opening of coronary smooth muscle K+-ATP channels. On the other hand, there are counteracting factors against these vasodilatory mechanisms. Alpha-AR mediated vasoconstriction opposes metabolic vasodilation, the effect of which is especially prominent during hyperperfusion. Angiotensin II can cause vasoconstriction of coronary resistance vessels in the normal or ischemic heart. Both endothelin-1 and platelet products, such as thromboxane A2 and 5-hydroxytryptamine, are also responsible for coronary vasoconstriction. Eventually, all these factors are integrated into a net resistance vessel tone and thus regulate CBF. Therefore, the measurement of CBF or CFR indicates not only a physiological parameter for the assessment of coronary reserve, but also the neurohumoral and mechanical states of the heart.

Measurement of CFR has been accepted as a useful diagnostic approach for risk stratification of patients with cardiovascular diseases, and a cut-off value of CFR ≤2.0 has been widely used in many studies to predict cardiovascular events. Historically, CFR ≤2.0 was first determined by Doppler guide wire as a strong predictor of abnormal myocardial perfusion and single-photon emission computed tomography has also provided the value of CFR ≤2.0 as a clinically meaningful reduction in maximum flow correlating with stress-induced ischemia. Transthoracic Doppler echocardiography (TTDE)-derived CFR ≤2.0 also enables detection obstructive coronary artery narrowing and adverse cardiovascular events.

In this issue of the Journal, however, Nakashima K et al re-evaluate the widely-accepted single cut-off value of TTDE-derived CFR ≤2.0 from the standpoint of predicting favorable long-term cardiovascular outcomes. They measured the TTDE-derived CFR in 272 patients with coronary artery disease without obstructive narrowing (≥50%) in the left anterior descending artery and evaluated its predictive value for future cardiovascular events. During the follow-up period of 4.0±1.9 years, cardiovascular events occurred in 32 (11.8%) patients, including acute coronary syndrome (ACS) in 17 patients and heart failure (HF) in 15 patients. Surprisingly, 47% of patients with cardiovascular events had CFR >2.0, indicating that CFR greater than 2.0 was not a suitable predictor for favorable long-term outcome. Indeed, CFR <2.4 was the best cut-off value for cardiovascular events prediction (area under the curve (AUC) 0.82, sensitivity 75% and specificity 76%). Interestingly, CFR excellently predicted the development of HF (AUC 0.95, sen-
sitivity 93% and specificity 88%) compared with ACS events (AUC 0.67, sensitivity 82% and specificity 53%).

What then is the implication of a reduced CFR? Although how a reduced CFR modulates the pathophysiological processes is not still exactly known, a potential mechanism is that the reduced CFR increases the risk of having easily inducible, subendocardial ischemia. On the top of this, chronic myocardial hypoperfusion or repetitive myocardial ischemia attributable to abnormal microvascular circulation could play a detrimental role in cardiovascular events. Clinically, 2 major pathophysiological conditions that affect CFR are left ventricular hypertrophy (LVH) and endothelium dysfunction, both of which are common features in HF. In this article, TTDE-derived CFR was a more specific predictor of the development of HF than of ACS. According to the definition, a reduction in CFR is caused by decreased maximal CBF as well as inappropriate elevations in resting CBF. Thus, many factors that affect CFR are involved in the development of HF, as follows: (1) endothelial dysfunction blunts both the vasodilative response of pre-arterioles to shear stress and the vasodilative response of arterioles to metabolic demands; (2) vasoconstrictive factors, as described here, reduce maximal CBF; (3) elevated diastolic ventricular pressure impedes coronary perfusion by passive compression of microvascular vessels; (4) tachycardia shortens the diastolic time available for subendocardial perfusion and reduces maximal flow; (5) LVH increases resting CBF because myocardial mass increases without concomitant proliferation of microcirculatory vessels; and (6) anemia can also increase it. Thus, CFR can be regarded as a comprehensive functional parameter of coronary circulation, which integrates endothelial function, histopathologic cardiac changes, hemodynamics, and general condition.

In summary, coronary microvascular dysfunction may represent a common pathway leading to progression in different heart diseases, but the degree of contribution of the factors affecting CFR will vary according to the underlying disease and comorbidities. However, many concerns remain to be solved. Are the best cut-off values of CFR different among the underlying diseases? Is improvement of CFR by treatment associated with a favorable outcome? Can CFR become a guidepost or a new therapeutic target? TTDE can provide both imaging and an assessment of CFR in a relatively inexpensive, non-invasive, and repeatable manner. It allows us to obtain important functional information of microvascular circulation over time during follow-up of patients, and may offer the best answers to these questions.

References