Microvascular Dysfunction
– Clinically Relevant But Still Difficult to Detect –
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With the availability of noninvasive imaging technology that includes nuclear perfusion imaging, magnetic resonance and myocardial contrast echocardiography, microvascular dysfunction has been documented in a far greater proportion of patients than ever conceived, not only in those with ischemic heart disease but also in other clinical cases. The linkage between microvascular dysfunction and unfavorable long-term clinical prognosis has been established in many studies. Furthermore, therapeutics shown to improve microvascular dysfunction may result in better clinical outcomes. These observations clearly necessitate a well-validated and reliable quantitative index of microvascular dysfunction.

Coronary physiology assessed by pressure and flow wire is the only way of separately evaluating epicardial stenosis and microvascular resistance in the clinical setting. Figure shows a schematic representation of a physiologically-derived index obtained in a catheterization laboratory. By using coronary physiology, epicardial and microvascular circulations, as well as collateral circulation, can be assessed. In brief, myocardial fractional flow reserve (FFRmyo) is well validated as an accurate and specific index of epicardial stenosis severity, and instantaneous wave-free ratio has been recently advocated as a specific index of epicardial stenotic resistance. On the other hand, coronary flow reserve (CFR) measured by the Doppler or thermodilution method assesses both epicardial and microvascular disease but does not differentiate between them. Therefore, simultaneous measurement of CFR and FFRmyo should give clinician a better insight to the respective contribution of the epicardial vessels and microvasculature.

The newly developed “index of microcirculatory resistance (IMR)” is unique because of its specificity to microcirculatory abnormalities that are independent of epicardial stenosis severity. Although the microvascular resistance index (h-MR) has been advocated as a specific index for microvascular abnormality, it requires both pressure and flow wires, because flow is estimated by coronary flow velocity, which is measured by a Doppler wire. Importantly, using Doppler velocity as a surrogate for myocardial flow is correct only in the absence of an epicardial stenosis, when collateral flow can be assumed to be zero and coronary flow equals myocardial flow. In the presence of an epicardial stenosis, myocardial blood flow consists of both coronary and collateral blood flow, suggesting an underestimation of myocardial flow and overestimation of myocardial resistance that is not correctable by this method. The IMR is calculated as the distal coronary pressure at maximal hyperemia divided by the inverse of the hyperemic mean transit time and is also influenced by collateral circulation. This collateral effect can be eliminated by coronary wedge pressure. Compared with CFR and h-MR, the IMR has shown to be a more reproducible assessment of the microcirculation, independent of hemodynamic perturbations. Simultaneous measurement of FFRmyo and IMR by pressure wire may provide a comprehensive and specific assessment of coronary physiology at the epicardial and microvascular levels, respectively. Several clinically important observations of the use of

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the IMR are reported in the setting of medical and reperfusion therapy, including acute myocardial infarction and periprocedural leakage of creatine kinase after percutaneous coronary intervention, against various patients’ backgrounds.\textsuperscript{13,14}

In this issue of the Journal, Mukai et al report several interesting findings about the IMR.\textsuperscript{15} A relatively wide, skewed distribution of the IMR was shown in their study, and they reconfirmed the lack of correlation of IMR with functional stenosis severity assessed by FFRmyo. Furthermore, only 2 factors influenced the value of IMR: location of the right coronary artery and a history of hypertension. These findings include some very important implications for using the IMR in the clinical setting. First, the exact normal value of the IMR in a respective artery is unknown, because the gold standard of normal microcirculation has not been established. Microvascular abnormalities may be caused not only by cellular damage such as a reperfusion injury, distal embolization, or inflammation, but also simply because of aging or coronary risk factors such as diabetes, dyslipidemia and hypertension. IMR values may be very difficult to obtain in normal subjects (young subjects with no cellular injury, no coronary risk factors, etc), and this limitation leads to the difficulty of quantitative as well as qualitative evaluation of microcirculation abnormalities by this index. If IMR values depend on the location of the measured artery, comparison of different vessels in different patients may warrant caution, although comparison of the vessels supplying the same territory is quite meaningful. This is perhaps the reason why many of the previous papers based on clinical data contained measurements of only the left anterior descending artery,\textsuperscript{8,12} and otherwise focused on serial changes with intervention in the respective arteries.\textsuperscript{13,14}

For the reasons mentioned, despite the relevance and necessity of evaluating microvascular dysfunction, it is still difficult to detect. However, although all the details about microcirculation abnormalities have not yet been brought to light, the IMR may facilitate the understanding of such conditions.

References
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