How Do We Improve the Utility of Fractional Flow Reserve? — For Precise Diagnosis of Myocardial Ischemia —

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Studies have suggested that the benefit of percutaneous coronary intervention (PCI) is less clear in lesions without evidence of myocardial ischemia, compared with medical therapy alone, although the benefit of PCI is significant in coronary lesions related to a large risk area (>10%).¹ In such situations, physiological examinations to prove myocardial ischemia has been recently recommended to perform coronary revascularization.² Fractional flow reserve (FFR) is very useful for detecting myocardial ischemia and FFR-guided PCI is an option to assess the physiological significance of coronary stenosis.^{3–5}

Unfortunately, uncertain results of FFR may lead to an inappropriate judgement, so confirmation of the certainty of the FFR value is essential. To obtain a reliable FFR measurement, optimal hyperemia must be induced to avoid the effect of microvascular resistance.⁶ In the clinical setting, either continuous intravenous administration of adenosine

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triphosphate (ATP) (150–180 $\mu\text{g/kg/min}$) via the forearm or femoral vein, or intracoronary injection of ATP (40–80 μg) are the current standard methods of achieving maximal coronary hyperemia.⁷ Because ATP has several advantages, such as short duration of action, it is widely used, but it can also induce atrioventricular (AV) conduction delay, ventricular arrhythmia and dyspnea caused by bronchial hyper-reactivity.⁸ Moreover, we may sometimes miss a caffeine attenuated adenosine-induced hyperemic response caused by blocking of adenosine receptor activity.⁹

Other disadvantages of FFR include a significantly longer procedural time and increased vasodilator side-effects of using agents for hyperemia, compared with resting indexes such as the instant wave-free ratio. In this issue of the

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Journal, Ishibuchi et al¹⁰ report that intracoronary administration of 2 mg nicorandil produced a more pronounced hyperemia during FFR measurement, compared with continuous intravenous ATP. In Japan and Korea, injectable nicorandil has been widely used as treatment for ischemic heart disease,¹¹ so it is well known that the technique is simple, with relatively short injection time, and safe, without major complications. Previous reports have already suggested that intracoronary bolus injection of nicorandil can achieve steady-state hyperemia during assessment of FFR.^{12,13} Another study has reported that the plateau time of intracoronary 2-mg doses of nicorandil is approximately 26 s,¹² which is sufficient to measure FFR in pressure pullback tracings. However, more importantly, the present study suggests that intravenous ATP infusion at 150 $\mu\text{g/kg/min}$ for 2 min, which is used in clinical practice, achieves maximum hyperemia in only 54% of cases. As maximal coronary hyperemia is needed for reliable FFR measurement, these findings have clinical significance.

As well as adequate hyperemia, various aspects that may be missing in daily practice should be reconsidered to obtain precise values of FFR (**Figure**). First, FFR is usually calculated as the mean coronary blood pressure distal to the stenosis divided by the mean aortic pressure without accounting for mean right central venous pressure. Therefore, precise evaluation may not be obtained in patients with high venous pressure, such as those on hemodialysis. Second, pressure drift might be induced by body temperature as well as disconnecting and reconnecting the wire from the connector. Third, valvular heart disease such as aortic valve stenosis affects coronary circulation.¹⁴ Fourth, increased microvascular resistance, which is seen in old myocardial infarction, may increase FFR because of impairment of hyperemic coronary flow, which limits maximal and constant vasodilation.¹⁵ In such cases, significant ischemia may be underestimated. Therefore, we should take these factors into consideration to avoid “white noise”.

In conclusion, physiological assessments such as FFR are very important for diagnosing myocardial ischemia and determining coronary revascularization with PCI or CABG. However, there are some pitfalls in FFR measurement, as mentioned above. We have to pay attention to obtaining a precise diagnosis of myocardial ischemia and do everything to improve the utility of FFR.

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