Prognostic Relevance of Discordant Results Between Fractional Flow Reserve and Resting Indices

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Fractional flow reserve (FFR) is an established physiologic index of coronary stenosis.^{1–5} The DEFER trial (Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis) showed that outcome after deferral of revascularization of an intermediate coronary stenosis based on FFR was excellent.⁶ FFR is measured by intracoronary pressure guidewire during maximal hyperemia. Recently, instantaneous wave-free ratio (iFR), resting distal to aortic coronary pressure (resting Pd/Pa), resting full-cycle ratio (RFR), and diastolic pressure ratio (dPR) have emerged as resting physiologic indices that do not require the pharmacological induction of maximal hyperemia (**Figure**). To date, several studies have demonstrated good correlations and agreements between FFR and these resting indices. Moreover, especially in iFR, the DEFINE-FLAIR trial (Functional lesion assessment of intermediate stenosis to guide revascularisation) and the iFR-SWEDEHEART trial (Instantaneous wave-free ratio versus fractional flow reserve in patients with stable angina pectoris or acute

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coronary syndrome) revealed that iFR was non-inferior to FFR for guiding deferral of revascularization with respect to clinical outcomes.^{7,8} The current ESC/EACTS Guidelines on myocardial revascularization define both FFR and iFR equally as Class IA to assess the hemodynamic relevance of intermediate-grade stenosis.⁹ Because the resting indices can be measured easily and less invasively compared with FFR, their use is rapidly increasing. However, it is not rare to have discordant results between FFR and the resting indices, which can create confusion about the treatment strategy. It is a serious clinical problem if a necessary revascularization is deferred or an unnecessary revascularization is performed in a patient with discordant results.

In this issue of the Journal, Lee et al¹⁰ report 2-year clinical outcomes of coronary lesions deferred from revascularization because of discordant results between FFR and resting indices such as iFR, resting Pd/Pa, RFR, and

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dPR. The authors show that the incidence of coronary events (comprising cardiac death, target vessel-related myocardial infarction and target vessel-related ischemia-driven revascularization) was similarly low in the groups with normal FFR and abnormal resting index, abnormal FFR and normal resting index, and normal FFR and normal resting index, which suggests that deferral of revascularization is a possible option for lesions with discordant results between FFR and the resting indices.

The prognostic relevance of discordant results between FFR and the resting indices in patients with deferral of revascularization is controversial. A post-hoc analysis of DEFINE-FLAIR trial showed that patients with left anterior descending artery lesions in whom iFR-guided deferral was performed had significantly lower event rates than those with FFR-guided deferral.¹¹ Also, an analysis in the merged populations of the DEFINE-FLAIR trial and the iFR-SWEDEHEART trial demonstrated that when using iFR rather than FFR, the lesion was deferred more frequently from revascularization without increasing the risk of coronary events.¹² Those 2 studies consistently suggested the possible superiority of iFR-guidance in deferral of revascularization compared with FFR-guidance. In contrast, a substudy of the DEFINE-FLAIR trial showed that there was no difference in the risk of coronary events after deferral of revascularization between FFR and iFR in a diabetes population.¹³ In line with that previous substudy, the study by Lee et al suggest comparable safety between FFR and iFR in guiding the deferral of revascularization.¹⁰

Some possible mechanisms of the difference in prognostic value between FFR and iFR have been proposed. Compared with FFR, iFR shows better agreement with coronary flow reserve (CFR).¹⁴ Therefore, abnormal CFR, a powerful predictor of coronary events, may be less frequently seen in lesions deferred from revascularization with normal iFR compared with normal FFR. This may explain the superiority of iFR-guidance for deferral of revascularization. On the other hand, FFR, but not iFR, is potentially associated with the presence of vulnerable plaques, because the vasodilatory ability at maximum hyperemia is impaired in such lesions¹⁵ and suggests that FFR may be more sensitive for detecting high-risk lesions.

The prognostic value of resting indices other than iFR has not been fully investigated. Importantly, the study by Lee et al showed that discordant results not only between FFR and iFR but also between FFR and other resting indices such as resting Pd/Pa, RFR, and dPR were not associated with increased risk of coronary events after deferral of revascularization.¹⁰ If the differences in measurement algorithm among the physiologic indices have no effect on patient prognosis, resting Pd/Pa, RFR, and dPR can be used interchangeably with iFR. The results of the study by Lee et al¹⁰ will help to extend the clinical recommendations of FFR and iFR to other resting indices and accelerate the replacement of FFR with simpler and less invasive resting indices in daily clinical practice.

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