TO THE EDITOR

Differences Between Fractional Flow Reserve and Instantaneous Wave-Free Ratio Clarified by Consideration of a Mathematical Model of Diffuse Coronary Stenosis

With interest, we read the article by Kikuta et al. (1) in which they assessed the accuracy of instantaneous wave-free ratio (iFR) pullback measurements for predicting the post-percutaneous coronary intervention iFR in tandem and diffuse coronary disease. They concluded that iFR pullback predicted the post-percutaneous coronary intervention iFR with a high degree of accuracy. As they described, the behaviors of fractional flow reserve (FFR) and iFR in the treatment of diffuse coronary lesions are completely different. However, why and how this difference happens was not fully described. Consider a mathematical model of coronary sequential lesions: It is important to note that FFR is measured at maximal hyperemia where the resistance of the microvasculature is minimal and stable, whereas iFR is measured at rest where the coronary flow is kept constant. Post-intervention FFR (FFR_{post}) can be expressed in equation 1 (E1) (2), which is derived from the equation for predicting the FFR in a tandem lesion (3). On the other hand, post-intervention iFR (iFR_{post}) is the sum of baseline iFR and ΔiFR as shown in equation 2 (E2) (1,4). Pressure-derived collateral flow index (CFI) is calculated as CFI = $(P_w - P_v)/(P_a - P_v)$. All the other abbreviations are consistent with the previous studies, and P_v is considered zero.

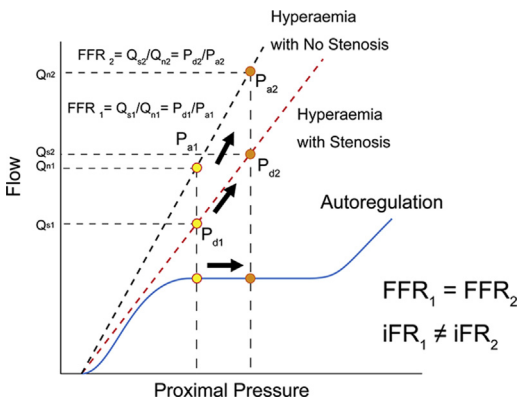
$$FFR_{post} = \frac{P_d - P_w}{P_a - \Delta P - P_w} + \frac{P_w(P_a - \Delta P - P_d)}{P_a(P_a - \Delta P - P_w)} = \frac{FFR_{pre}(1 - CFI) - CFI\Delta FFR}{1 - \Delta FFR - CFI} \quad \text{(Equation 1)}$$

$$iFR_{post} = iFR_{pre} + \Delta iFR \quad \text{(Equation 2)}$$

iFR_{post} can be calculated using a very simple equation, whereas FFR_{post} requires complex calculations because of "autoregulation." FFR is measured during maximal hyperemia, when autoregulation of the coronary blood flow is not maintained and a linear relation exists between perfusion pressure and blood flow because microvascular resistances are minimal and constant. By contrast, iFR is measured at rest, when the coronary blood flow is kept constant.

Although utilization of iFR_{post} has an advantage for predicting the post-intervention physiological value of coronary sequential or diffuse lesions, it has several potential limitations. Most importantly, iFR is theoretically dependent on the systemic pressure because coronary flow reserve is influenced by blood pressure changes (5). **Figure 1** describes the reasons why iFR is influenced by blood flow changes, but FFR is not. Although iFR pullback is a convenient and useful, several issues still need to be considered.

FIGURE 1 Pressure-Flow Relationship in the Coronary Circulation



In the figure, FFR is constant. When blood pressure changes from P_{a1} to P_{a2}, P_{d1} also changes to P_{d2}. Thus, FFR_1 is equal to FFR_2. Therefore, FFR is not affected by blood pressure changes. iFR is measured at rest when autoregulation of the coronary flow is maintained, thus iFR changes when blood pressure changes. This characteristic of iFR is similar to that of coronary flow reserve. FFR = fractional flow reserve; iFR = instantaneous wave-free ratio.

Yusuke Yoshikawa, MD
***Naritatsu Saito, MD**
*Department of Cardiovascular Medicine
Kyoto University
54 Shogoin-Kawahara-cho
Sakyo-ku, Kyoto, 606-8507
Japan
E-mail: naritatu@kuhp.kyoto-u.ac.jp

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TO THE EDITOR

Clinical Sequelae of Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement at Medium-Term Follow-Up

We read with interest the article by Ruile et al. (1) regarding leaflet thrombosis (LT) following transcatheter aortic valve replacement. The authors demonstrate that the prevalence of LT is consistent with pooled analyses (2), finding similar mortality and cerebrovascular event (CVE) rates between patients with and without LT. The study adds to the published reports and provides important prognostic information on patients with LT. However, we were concerned about methodological issues that have the potential to influence the conclusions drawn.

Previous studies and pooled analyses demonstrate increased risk of CVE in patients with LT (2,3). In this current study (1), rates of CVE were 2.3% at a median of 406 days, much lower than reported in previous randomized trials (4). Such low event rates undoubtedly reduce our ability to detect meaningful statistical differences between groups. Follow-up was also performed via questionnaires/telephone interviews, which potentially leads to under-reporting of brief, but important, events, such as transient ischemic attacks. This is concerning because LT appears most strongly associated with the occurrence of transient ischemic attacks (2,3).

The authors also defined LT as hypoattenuated leaflet thickening compared with the arguably more important imaging endpoint of restricted leaflet motion that was the focus of previous trials (3,5). Restricted leaflet motion has a stronger association with CVE than hypoattenuated leaflet thickening (2), and we believe the occurrence of both findings should be reported to ensure consistency between studies (5). Finally, the identification of early LT altered patient treatment (anticoagulation), which is very likely to have affected the risk of CVE observed. Thus, whereas we are encouraged by further studies assessing the clinical significance of LT, adequately powered trials will be required to define the true relationship between LT and CVE.

Hashrul N. Rashid, MBBS
Arthur Nasis, MBBS, PhD
Robert P. Gooley, MBBS, PhD
James D. Cameron, MBBS, MD
***Adam J. Brown, MBBChir, PhD**

*Monash Medical Centre
246 Clayton Rd
Clayton, Melbourne
Victoria 3168
Australia
E-mail: adam.brown@monash.edu

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REPLY: Clinical Sequelae of Leaflet Thrombosis Following Transcatheter Aortic Valve Replacement at Medium-Term Follow-Up

We thank Dr. Rashid and colleagues for their interest in our paper. Similar to other studies, recently reviewed by Rashid et al. (1) in a meta-analysis, the patients in our study were not systematically readmitted for follow-up, and we obtained documentation of the neurological work-up. Although this approach may have resulted in underreporting of transient ischemic attacks, the rate of stroke in patients with leaflet thrombosis