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EDITORIAL COMMENT

Instantaneous Wave-Free Ratio Pressure Pullback With Virtual Percutaneous Coronary Intervention Planning

Seeing the Future of Coronary Interventions?*

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Andreas Gruentzig's invention of coronary balloon angioplasty (now called percutaneous coronary intervention [PCI]) revolutionized the field of cardiovascular medicine, bringing angina relief to millions of patients and reducing mortality for those with acute coronary syndromes. Even 40 years ago, though, Gruentzig appreciated the limitations of coronary angiography and insisted on measuring translesional pressure gradients (Pa − Pd = ΔP, where Pd is post-stenotic distal pressure and Pa is aortic pressure) through his balloon catheter to gauge angioplasty success. The introduction of a pressure sensor guidewire permitted the measurement of ΔP prior to PCI and enabled Pijls et al. (1) to develop and validate a hyperemic translesional physiological index, fractional flow reserve (FFR) ($Pd_{hyperemia}/Pa_{hyperemia}$ = FFR), which eliminates the uncertainty of visual angiographic lesion assessment. Supported by 2 decades of clinical outcome studies, FFR-guided PCI improves outcomes at a reduced cost compared with angiography-guided PCI and reduces adverse clinical events in patients with ischemic stable angina compared with optimal medical therapy alone.

In the past several years, a unique resting physiological index called the instantaneous wave-Free Ratio (iFR), which is the Pd/Pa ratio during a specific diastolic period, has been compared with FFR and found to be noninferior in 2 large clinical outcome studies (2,3). Because it obviates the need for hyperemia, iFR has become an attractive alternative to FFR but not without some skepticism. Nonetheless, the routine use of Pd/Pa at rest (e.g., iFR) or during hyperemia (i.e., FFR) has become an integral part of lesion assessment in most catheterization laboratories worldwide.

Although FFR and iFR are important adjuncts for simple lesions, controversies and complexities challenge the physiological approach to more advanced coronary disease involving serial and left main lesions. In particular, because of lesion interaction, maximal hyperemia for individual lesions in series cannot be achieved, such that the contribution of each lesion to the total resistance can be difficult to assess by FFR. Although a method to compute an individual FFR for each lesion in series has been described (4), it is mathematically complicated, requiring the input of coronary occlusion wedge pressure, making it impractical for clinical use. Instead, the current recommendation for serial lesion assessment is to measure FFR distally, perform a pressure pullback during maximal hyperemia, stent the lesion with the largest ΔP (not $FFR_{individual}$), and remeasure FFR.

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With this background in mind, in this issue of *JACC: Cardiovascular Interventions*, Kikuta et al. (5) report an alternative approach to serial lesions and present the value of iFR pullback measurements before angioplasty to: 1) assess how often the treatment strategy based on angiography alone was changed; and 2) predict the post-PCI hemodynamic

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result. In 168 lesions, operators submitted their revascularization plans on the basis of angiography alone and then again after iFR pullback with visual/mental coregistration with the angiogram. As the iFR pullback procedure identifies the relative ischemic contribution of each vessel segment toward the iFR value of the entire vessel, the operators changed their revascularization plan 31% of the time, with reductions in the average number and length of stents implanted.

At the same time, the pre-PCI iFR pullback was used to predict the post-PCI iFR measurement in 134 vessels (128 patients). Following PCI, the mean difference between predicted and actual post-PCI iFR was small at 0.011 ± 0.004, with a strong correlation ($r = 0.73$, $p < 0.001$). These results are consistent with Ohm's law, in that the total resistance of a vessel is the sum of the individual resistances in series. Assuming constant resting flow, the ratio of pressures over the whole vessel (total iFR) should be the sum of the pressure losses across each stenosis (ΔiFR). Thus, removing 1 or more stenoses by PCI increases the total iFR by the ΔiFR generated by the treated stenosis. Although this concept may seem intuitive, its simple assumptions may not always come true, as PCI affects coronary blood flow (CBF) in an unpredictable manner. No reflow or slow reflow complicates some PCI procedures because of distal embolization and microvascular vasoconstriction and may reduce resting CBF, whereas post-ischemic hyperemia or vasodilation may increase CBF. Variable changes in resting CBF velocity by intracoronary Doppler measurements often made coronary flow reserve ($CBF_{hyperemia}/CBF_{rest}$) unreliable, especially after PCI. As many as 20% of post-PCI patients show no improvement in coronary flow reserve despite minimal residual hemodynamic stenotic resistance (6). How iFR is affected by PCI remains to be fully explored, but if post-PCI iFR can be consistently predicted by pre-PCI pullback ΔiFR, the relative stability of resting CBF after PCI will have been confirmed.

A few outstanding issues should be considered. The iFR-angiographic coregistration in this study was achieved by operators mentally coregistering the iFR pullback pressure units with the position of the guidewire on fluoroscopy. Subsequently, automated coregistration software has become commercially available. Future trials will likely use such software to more precisely define the vessel segments that require stenting, reduce the errors inherent to visual coregistration, vessel motion, manual wire pullback rates, and enhance the accuracy and reliability of the pullback method.

A current point of contention is whether ΔP (or ΔiFR) at rest is as sensitive as hyperemic ΔP (not ΔFFR) in the assessment of serial lesions. Hyperemic flow will increase ΔP above that obtained during resting flow and should more precisely identify which lesion produces the greater resistance. In addition, a greater spread of ΔP values minimizes the adverse effects of signal drift on the accuracy of measurement (7). In contrast, if the risk for lesion interaction during hyperemia and the variability of adenosine hyperemia outweigh the benefit of a wider spread of ΔP, then resting measures will prove more reliable. The present study suggests that with an error of 1.4%, iFR predicts post-PCI values better than FFR, with reported rates of 4% to 11%.

Last, Van't Veer et al. (8) challenged the proprietary iFR algorithm presenting us with the diastolic pressure ratio. Their analysis indicates that almost any Pd/Pa ratio within the diastolic window, not just during the wave-free period, is numerically equivalent to the iFR, with differences ranging from 0.001 to 0.005. If the diastolic pressure ratio is identical to iFR in every respect, then the findings of the present study by Kikuta et al. (5) could be generalized to other pressure wire systems.

Kikuta et al. (5) are to be congratulated for a well-done, technically challenging study that sets the stage for new thinking about how we should be performing PCI not just in serial lesions but perhaps all coronary interventions. An accurate pressure pullback and prediction of post-PCI physiology could result in more precise and effective procedures that treat all hemodynamically significant lesions with the fewest stents possible. At the same time, such an assessment could distinguish between focal disease that is amenable to stenting and diffuse disease that might be best treated medically or with bypass surgery. Although it is currently unknown whether the changes in strategy on the basis of IFR pullback will produce better clinical outcomes, this would be the anticipated result. Stay tuned for outcome data.

Despite the academically healthy controversies around iFR, Pd/Pa, diastolic pressure ratio, and FFR, absent noninvasive evidence of ischemia, a physiological (read functional) measurement should be incorporated into every operator's angiographic assessment without fail, in accordance with professional societal guidelines. Kikuta et al. (5) reinforce the fact that the elucidation of the lesion significance by physiology and not by reliance on the operator's subjective observation reduces excess stenting and changes practice. IFR pullback coregistered to the angiographic images with PCI planning is one the biggest advances in the

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interventional physiology community in recent years. Looking into the future, we believe that the coregistration of a pressure pullback approach will be routinely incorporated into all physiology and imaging procedures.

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