Fractional Flow Reserve: From Homeland to Colony

Guo-Xin Fan[1], Jia-Chen Luo[2], Zhi Zhou[1], Yue-Ye Wang[2], Ji-Kun Wang[3]

[1]Department of Orthopedics, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China
[2]Department of Cardiology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai 200072, China
[3]Department of Applied Psychology, Key Laboratory of Brain Functional Genomics, Ministry of Education, Shanghai Key Laboratory of Brain Functional Genomics, School of Psychology and Cognitive Science, East China Normal University, Shanghai 200062, China

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Introduction

In current catheter research, there are 3 main directions with respect to fractional flow reserve (FFR), including instantaneous wave-free ratio, noninvasive measurement of FFR, and FFR transferred from coronary circulation to other ischemia-inducing circulation. Recently, an interesting study was published, in which FFR was performed to diagnose and guide stenting in chronic mesenteric ischemia (CMI).[1] We herein highlighted, the implications and limitations of FFR from coronary artery to renal artery and mesenteric artery for future investigations, respectively.

Coronary Fractional Flow Reserve

In patients with coronary artery disease (CAD), inducible ischemia is closely correlated with the symptoms and outcomes.[2] Therefore, it is pivotal to discriminate those lesions, which are causing ischemia, which will benefit the stenting or bypass surgery.[3] FFR is an accurate and lesion-specific index to indicate whether a particular stenosis should be responsible for ischemia.[4] FFR is defined as the ratio of maximum blood flow in a stenotic artery to maximum blood flow, if the same artery was normal.[5] FFR can be easily presented as the ratio of Pd/Pa[6] (Pd: Distal coronary pressure, which is measured by a pressure monitoring guidewire; Pa: Aortic pressure, which is measured by the guiding catheter).

Plentiful unique characteristics enable FFR for functional assessment of coronary stenosis and decision-making particularly suitable: (1) FFR has a theoretical normal value of 1 for every patient and culprit vessel; (2) FFR is not influenced by systemic hemodynamics; (3) comparing with other functional test, FFR reaches per-segment accuracy with a more precise spatial resolution of a few millimeters. In the 2-year follow-up analysis of the Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study, FFR-guided stenting decreased the rates of death, myocardial ischemia, and repeat revascularization all by approximately 30–35% after 1 year. Besides, FFR-guided percutaneous coronary intervention (PCI) in multivessels resulted in a shorter hospitalization duration, less contrast agent utilization and was also cheaper in absolute terms.[7] More recently, a 5-year follow-up analysis of FAME study reported that the clinical outcome in the FFR-guided group was achieved with a lower number of stented arteries and less resource use, whereas the risks of major adverse cardiac events for both groups developed similarly.[8] The results of FAME II study presented that FFR-guided PCI plus the best available medical therapy was superior to the best available medical therapy alone in the requirement of urgent revascularization.[9] Furthermore, the FAME II group also found that in 1220 patients with stable CAD, FFR-guided PCI did improve the clinical outcomes, as compared with medical therapy alone.[10]

Nevertheless, FFR has not been widely performed (<10%) in routine clinical practice. The administer of adenosine to induce maximal vasodilatation restricts its widespread use.[11] Furthermore, as an invasive examination, which was based

Address for correspondence: Prof. Ji-Kun Wang, Key Laboratory of Brain Functional Genomics, Ministry of Education, Shanghai Key Laboratory of Brain Functional Genomics, School of Psychology and Cognitive Science, East China Normal University, Shanghai 200062, China
E-Mail: jkwang@psy.ecnu.edu.cn

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on the procedures of coronary angiography, complications also have to be prevented.

Although there are several limitations in FFR, it is still considered as the "gold standard" to estimate the functionally significant of a coronary artery stenosis, due to its numerous merits of hemodynamic evaluation and guided stenting. However, whether it is also vital in discriminating functional significance of renal artery and inferior mesenteric artery (IMA) stenosis remains to be elucidated.

Renal Fractional Flow Reserve

To date, atherosclerotic renal artery stenosis (RAS) is one of the most common causes of secondary hypertension and impaired renal function. Although interventional approaches (percutaneous stenting or bypass grafting) were introduced to control the progress of RAS, clinical benefits from revascularization still controversial.[12] Balk *et al*.[13] demonstrated a weak evidence that no large differences in mortality rates or cardiovascular events between medical and revascularization therapies. Bax *et al*.[14] suggested that interventions were associated with serious complications. In addition, current randomized controlled trials comparing percutaneous angioplasty and optimal medical therapy did not prove the distinct advantages of revascularization.[15-17] Therefore, it was of key importance to select the proper patients, and identify the predictors for improving postprocedural prognosis.

The first published study has validated renal FFR (rFFR) as a dynamic assessment of renal functional stenosis under hyperemic conditions.[18] It indicated that rFFR was a promising tool to evaluate moderate RAS with an excellent correlation among rFFR, and the hyperemic mean translesional pressure gradient (TSPG) ($r = -0.94$; $P < 0.0001$) and the resting mean TSPG ($r = -0.76$; $P = 0.0016$). Similarly, Mitchell *et al*.[19] suggested that in the refractory hypertension and moderate to severe unilateral RAS population, after stenting procedures, patients in abnormal rFFR group experienced more benefits from the blood pressure control than the normal rFFR group ($P = 0.04$).

As a pressure-derived index, the merits of rFFR are as follows: (1) it is lesion-specific to provide a measure of the reduction in renal blood flow caused by the stenosis; (2) it takes into account of the collateral flow, which can render an anatomical blockage without functional significance; (3) a morphological severe stenosis may not induce a significant TSPG, if the artery has slow flow due to renal parenchymal impairment, which, in contrast, adds to the feasibility of assessing the severity of RAS diagnosed by rFFR; (4) besides, Colyer *et al*.[20] reported that a 4-F catheter significantly overestimated the severity of RAS, because 0.014-inch pressure guide wire compared with a 4-F catheter would occupy 6% versus 24% of the renal artery, respectively; (5) FFR will not be affected by systemic blood pressure and the state of renal blood flow and the renal microvasculature (hyperemic vs. nonhyperemic).[21]

However, rFFR has its own limitations. Subramanian *et al*.[18] found that the measurement of rFFR needed to assume a very low (zero) central venous pressure, so it could not be used in patients with decompensated heart failure. Furthermore, not all studies found that rFFR had a well correlation with patients' hypertension improvement. Kadziela *et al*.[21] presented a disappointing result, in which, baseline Pd/Pa ratio and rFFR did not predict hypertension response after renal artery stenting. The reason why rFFR is not as viable as coronary FFR may be explained as follows: (1) coronary artery and renal artery has two different circulation patterns. The coronary artery perfuses myocardium in diastole phase, while renal artery perfuses the kidney in systole phase. Cardiac circulation seeks to maintain a flow at the cost of reduced pressure, whereas renal circulation seeks to maintain pressure at the cost of flow. Moreover, renal auto-regulation occurs primarily in the preglomerular afferent arterioles, and it is modulated by various degrees of afferent and efferent arteriolar constriction. (2) Hyperemic stimuli in the heart do not work in the same way in the kidney, because the afferent and efferent renal arterioles may not respond the same to pharmacologic agents in coronary artery (e.g., adenosine, a potent coronary vasodilator constricting renal arterioles). In addition, a precisely defined cutoff point for the rFFR to discriminate normal and functionally significant stenosis of RAS was absent. Kapoor *et al*.[22] demonstrated that rFFR of 0.90 could be considered as a hemodynamically significant stenosis, as the rennin production (an index of renal ischemia) increased distinctly. Mitchell *et al*.[19] suggested that the postoperative blood pressure improved significantly in patients with an abnormal rFFR (<0.80) compared with patients with a normal rFFR (≥0.80). However, Kadziela *et al*.[21] revealed comparable outcomes with respect to the blood pressure improvement between the normal and abnormal rFFR (0.80) groups. Therefore, in the future, more studies were essential to ascertain the adequate cutoff point of rFFR.

Fractional Flow Reserve in Chronic Mesenteric Ischemia

In clinical practice, abdominal pain is a very common complaint, which is often caused by digestive tract infections, ulcers, tumors, etc. However with the high presence rates of atherosclerosis, the mesenteric artery occlusion caused more and more cases of chronic abdominal pain. Interestingly, the symptoms of small bowel ischemia are likely to manifest rather than ischemia colitis, while the "culprit vessel" is often found as IMA. When the IMA became narrow or even obstructed by atherosclerosis plaque, the flow from the superior mesenteric artery (SMA) via the arc of Riolan (marginal artery) to the IMA compromises flow reserve to the small intestine, which result in the symptom of small bowel ischemia.[23]

Nowadays, computed tomography angiography, magnetic resonance angiography or conventional angiography is the main tools to assess the morphological features of stenosis in

mesenteric arteries. However, it is well known that no matter in coronary vascular bed or renal vascular bed, angiography can only evaluate the anatomical severity of a stenosis, as for estimating hemodynamically significant stenosis, and it seems to be meaningless. Thus, the clinicians need to develop a threshold pressure gradient across the narrowing to assess the physiologic significant of a vascular stenosis. However, an end-hole catheter needs to advance across the stenosis of mesenteric artery, which may result in overestimation as the intravascular cavity was small.[20] Differently, the technique of FFR assessment with a 0.014 inch pressure wire helps to minimize the potential for catheter-induced obstruction and vessel trauma, including dissection and atheroembolization. Sadiq *et al*.[1] applied the FFR measurement in a CMI case, and demonstrated that the baseline resting pressure gradient of stenosis in SMA was 14 mmHg (FFR = 0.87), hyperemic pressure gradient was 37 mmHg (FFR = 0.65). After stenting, the FFR results became 0.95 and 0.85, which suggested a significant improvement postintervention. This anecdotal case, clearly demonstrated the feasibility of adjunctive invasive diagnostic testing such as pressure gradient or FFR, which is very helpful in identifying novel applications of available technology in the assessment of patients with CMI. Moreover, they also reported a case in which a 47-year-old symptomatic woman, who underwent angiography, complemented by the assessment of FFR and intravascular ultrasound, and results convincingly demonstrated the dynamic nature of the obstructive characteristic of median arcuate ligament syndrome.[24]

Nevertheless, we must be aware that this case did not provide compelling evidence for the wholesale clinical application of FFR in CMI. First, the threshold of a clinically significant gradient or FFR in the mesenteric bed has not been validated. Thus, doctors do not have a definite cut-off point to discriminate, whether a stenosis influence the hemodynamics or not. Second, unlike the brief and transient changes in renal vasomotor tone, the flow is dynamic with routine postprandial hyperemia in the mesenteric arterial bed.[1] Thus, it is crucial to induce hyperemic condition in measuring a FFR in the mesenteric arteries, particularly in SMA, as hyperemic flow mimics the routine postprandial flow. Last but not least, the circulatory control of splanchnic perfusion is still poorly understood, so is the response to pharmacologic induced hyperemia in mesenteric arteries.[23] Only when suitable vasodilator drugs and validated threshold are established with compelling evidences, FFR may play an alternative role in diagnosing suspected CMI and guiding revascularization. Will FFR emerge as a significant role in CMI diagnosis and intervention just like coronary FFR, or is it finally found with multiple limitations in clinical application? Only time will tell.

In conclusion, unlike the successful application of FFR in CADs, the value of it in renal or mesenteric vascular beds was still controversial. As a functional index, in the future, if FFR could be confirmed as a useful technology to discriminate stenoses which are responsible for inducible ischemia in renal or mesenteric artery, more and more patients would benefit from a more favorable prognosis and less medical costs. Wishing the day come soon!

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Conflicts of interest

There are no conflicts of interest.

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