Is Coronary Physiology Assessment Valid in Special Circumstances?

Aortic Stenosis, Atrial Fibrillation, Left Ventricular Hypertrophy, and Other

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KEYWORDS

• Fractional flow reserve • Nonhyperemic pressure ratios • Atrial fibrillation • Aortic stenosis
• Left ventricular hypertrophy • Serial lesions

KEY POINTS

- Although fractional flow reserve (FFR) and nonhyperemic pressure ratios (NHPRs) such as instantaneous wave-free ratio (iFR) are widely used to evaluate the hemodynamic significance of coronary lesions, both have important limitations in a variety of clinical scenarios that operators should be cognizant of.
- Aortic stenosis leads to increased left ventricular systolic and diastolic filling pressures, which seems to affect NHPR to a greater degree than FFR.
- Atrial fibrillation can have significant variability in beat-to-beat cardiac output, which leads to a significant reduction in reproducibility of iFR, although FFR evaluation remains largely reproducible and reliable.
- FFR has limitations for evaluating the hemodynamic significance of individual lesions in series, whereas NHPRs may be a more clinically relevant alternative for procedural planning.

INTRODUCTION

Fractional flow reserve (FFR) is defined as the ratio of the measured pressure distal of coronary stenosis (Pd) in relation to the pressure proximal to the stenosis (Pa). Although a direct comparison of flow in the presence and absence of a lesion would be ideal, pressure measurements are correlated with blood flow when coronary resistance is minimal and provide a useful surrogate. Although hyperemic agents are excellent tools to achieve minimal resistance, there are clinical scenarios in which they can be unreliable.

As the more recent introduction of nonhyperemic pressure ratios (NHPRs) such as relative flow reserve (RFR) and instantaneous wave-free ratio (iFR), there has been debate over the benefits or shortcomings of these techniques compared to FFR. FFR has greater than 20 years of data in well-conduced randomized trials showing clinical benefit for greater than 10 years,[1] something that NHPR overall lack. Nonetheless, NHPR indices have the benefit of simpler protocols, quicker evaluations, and the ability to exclude hyperemic medications that have potential side effects on patients. NHPRs are now integrated within most

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current pressure wire systems and are widely available in cath laboratories. When deciding to use one index over another, not only procedural and patient-level risk versus benefits have to be weighed, but also reliability and accuracy. We discuss clinical scenarios outside of isolated stable coronary artery disease (CAD) where FFR and NHPR have been evaluated, to help clinicians understand the limitations and benefits of different coronary physiology assessment tools.

Aortic Stenosis

CAD is a common comorbidity in many patients with severe calcific stenosis. The prevalence of CAD is high not only in those with high- and intermediate-risk patients undergoing transcatheter aortic valve replacement (TAVR) at approximately 66%,[2,3] but also in those considered low-risk at nearly 30%.[4] Thus, oftentimes the assessment of significant CAD can play a role not only in the decision between surgical aortic valve replacement (SAVR) with coronary versus TAVR with PCI, but also the decisions regarding whether to proceed with PCI before TAVR. However, PCI before TAVR has not been associated with lower in-hospital or 1 year mortality.[5] These findings suggest that there is some ambiguity regarding identifying lesions that are hemodynamically significant before aortic valve intervention.

Evaluation of coronary physiology remains a commonly used tool when assessing the need for revascularization before either SAVR or TAVR. The hemodynamics associated with aortic stenosis (AS) is increased left ventricular systolic and diastolic filling pressures with impaired diastolic dysfunction. Similar to those with heart failure (HF), patients with severe AS will have increased left ventricular end-diastolic pressures (LVEDPs) and elevated venous pressures, with effects on coronary pressure and flow. Increased systolic myocardial compressive forces associated with severe AS may also affect physiological indices.

When evaluating FFR pre-TAVR versus post-TAVR in those with CAD, an initial observational study suggested that there were changes in FFR values although minimal and most notably in those with hemodynamically significant stenoses to start, which subsequently worsened after TAVR (0.71 ± 0.11 vs. 0.66 ± 0.14).[6] The postulated reason was that reduction of aortic outflow gradient post-TAVR leads to increased coronary flow, which may decrease post-TAVR FFR values. Overall, there was no difference in average FFR values pre-TAVR and post-TAVR and importantly only a small proportion (6%) crossed the 0.80 threshold. The effects of TAVR on iFR seem to be more dramatic than on FFR. Scarsini and colleagues[7] showed that individual-level differences in pre-iFR versus post-iFR varied significantly, and that the increased variation in iFR values correlated well with the degree of post-TAVR gradient drop. Further, 15% of coronary lesions crossed the 0.89 threshold.

One of the first studies evaluating coronary physiology showed that patients with severe AS and post-TAVR had improvement in coronary flow reserve (CFR) at 12 month follow-up (**Fig. 1**).[8] In addition, immediate reductions in afterload post-TAVR may improve microvascular function.[9] Comparing patients without CAD, Wiegerinck and colleagues found that CFR was lower (1.9 ± 0.5 vs. 2.7 ± 0.7, $P < 0.001$) and hyperemic microvascular resistance was higher (2.10 ± 0.69 vs. 1.80 ± 0.60 mm Hg·cm·s^{-1}, $P = 0.096$) in the presence of AS. Among the 27 patients with AS, immediate post-TAVR hyperemic microvascular resistance decreased resulting in an increased CFR (1.9 ± 0.4 to 2.2 ± 0.6, $P = 0.009$) compared with pre-TAVR. This improved CFR, in turn, may explain why post-TAVR FFR values generally decrease in patients with CAD. The direction of change in NHPR in patients with TAVR is not completely clear, although a likely increase in basal flow would affect the values.

Most recently, a substudy of the randomized Nordic Aortic Valve Intervention trial revisited the effects of TAVR in intermediate coronary lesions pre-TAVR and post-TAVR at 6 months.[10] After ensuring no significant change in percent stenosis from baseline to 6 months in 50 lesions, they found that FFR did not significantly change from baseline to follow-up, while RFR (evaluated in 36 lesions) did significantly improve baseline to follow-up (0.88 vs. 0.92, $P = 0.003$). There were 8% (4) lesions that became positive after TAVR, whereas there were 31% (11) lesions that were initially RFR positive that became RFR negative after TAVR.

These findings suggest that FFR and NHPRs should be used with caution by making definitive decisions for revascularization before aortic valve interventions with AS. Fortunately, the risk of a particular lesion crossing the ischemic threshold is small, especially when using FFR. Also reassuring is that FFR guidance, as compared with angiographic guidance, was associated with fewer MACE events despite whatever changes occur around TAVR.[11] This was in the setting of a high deferral rate in most of the lesions (78.2%) in view of a preserved FFR greater than 0.80. Overall, these findings suggest that even if there is a small change in FFR after TAVR, it may only rarely be clinically relevant.

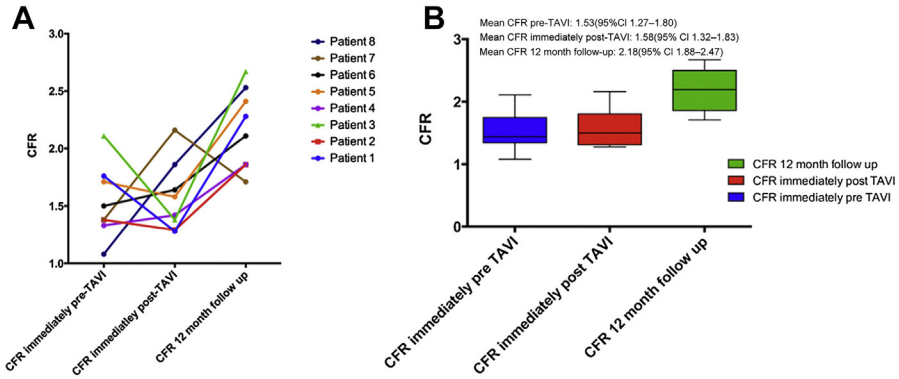

Fig. 1. (*A*) Individual patient serial CFR data with all patients having an improvement in CFR from baseline to 12 month assessment after transaortic valve implantation. (*B*) Serial mean CFR recordings (with 95% CI and ranges). The improvement in CFR from baseline to follow-up was statistically significant using a repeated-measures analysis of variance ($p = 0.0055$). (*From* Camuglia AC, Syed J, Garg P, et al. Invasively assessed coronary flow dynamics improve following relief of aortic stenosis with transcatheter aortic valve implantation. *J Am Coll Cardiol*. 2014;63(17):1808-1809. https://doi.org/10.1016/j.jacc.2013.11.040.)

Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common arrhythmias seen concomitantly in those with CAD. Despite the use of FFR and NHPRs in these patients, there is a paucity of evidence regarding their reliability in AF given the variability in beat-to-beat cardiac output. Not surprisingly, this is of particular importance when patients with AF have rapid ventricular rates (RVRs), as myocardial oxygen demand increases inducing a pseudo-hyperemic state that could adversely affect baseline Pd/Pa documentation and iFR measurements.[12] However, even in non-RVR states, patients with AF have microvascular dysfunction that could affect the assessment of these baseline indices.[13] As shown in the verification of iFR and FFR for the Assessment of Coronary Artery Stenosis Severity in Everyday Practice study, NHPRs such as iFR are particularly susceptible to resting (nonhyperemic) heart rate and blood pressure variations with 2.5 to 4.4 times larger variance than FFR differences.[14]

Recently, Bentea and colleagues[15] conducted a small retrospective study comparing patients with AF undergoing FFR and iFR to those in sinus rhythm (SR) without a history of AF. The coefficient of variation was calculated for iFR based on dividing the area under the Pd curve by the area under the corresponding Pa curve for the number of beats considered in the analysis. FFR values were analyzed based on calculating seven beats centered around the minimum Pd/Pa during hyperemia. The coefficient of variation of beat-to-beat measurements for FFR was not significantly different between those in AF versus SR; however, there was significant beat-to-beat variability in iFR measurements in the AF versus SR groups (2.65 95% confidence interval [CI]: 1.33–4.04 vs. 0.69 95% CI: 0.24–1.98, <0.01) (Fig. 2). The coefficient of variation of iFR correlated positively with the variability of heart rate. Furthermore, when evaluating the reproducibility of FFR and iFR at test–retest in AF and SR, FFR was reproducible in both groups, whereas iFR was only reproducible in the SR group. Two replicated iFR measures did not correlate in the AF group ($p = 0.1352$, $p > 0.05$; Spearman correlation) and led to the reclassification of 53.8% of patients using an iFR cut-off of 0.89. When analyzed per each vessel, the quantitate assessment of coronary stenosis correlated with the corresponding FFR values in both AF and SR rhythm groups (see Fig. 2). The degree of stenosis also correlated with the corresponding iFR measurement in the AF and SR groups, but there was a significant difference in the slopes of these two regression lines with the SR group showing a more pronounced decrease of iFR values with increasing stenosis severity as compared with the AF group.

Ultimately, it seems that FFR evaluation remains reproducible and reliable in patients with AF, whereas the reproducibility of iFR in patients with AF is far less. These findings are likely related to the fact that coronary blood flow occurs primarily in diastole and drops significantly during systole.[16] Although the duration of systole remains nearly constant regardless of heart rate, the duration of diastole is highly dependent on heart rate, thus affecting NHPRs disproportionately compared with FFR.

Left main coronary artery disease and serial coronary lesions

Left main coronary artery (LMCA) disease is often seen in those undergoing coronary angiography.

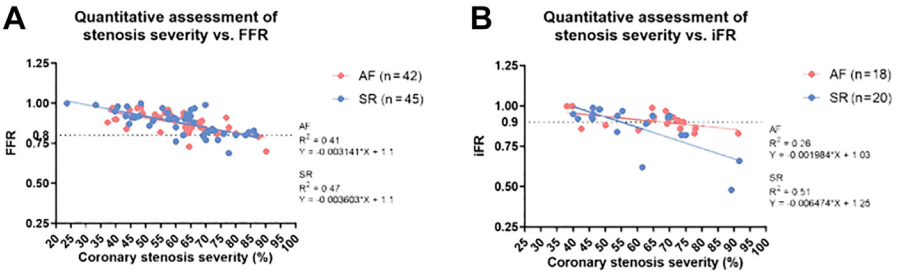

Fig. 2. Linear regression analysis of the quantitative assessment of coronary stenosis severity versus FFR (*A*) and versus iFR (*B*). For iFR, the slopes of the regressions are significantly different between AF and SR groups ($p < 0.05$), but not for FFR ($p = 0.58$). (*From* Pintea Bentea G, Berdaoui B, Samyn S, Morissens M, Rodriguez JC. Reliability of Fractional Flow Reserve and Instantaneous Wave-Free Ratio in Assessing Intermediate Coronary Stenosis in Patients With Atrial Fibrillation. *Am J Cardiol*. 2022;162:105-110. https://doi.org/10.1016/j.amjcard.2021.09.028.)

Studies have demonstrated the usefulness and benefit of FFR to guide the revascularization of the intermediate left main (LM) disease.[17] Hamilos and colleagues showed that among those with intermediate LMCA disease, deferring CABG based on an FFR greater than 0.80 led to similar 5 year mortality as compared with those who underwent bypass grafting based on an FFR less than 0.80. Event-free survival rates at 5 years were 74.2% and 82.8% in the nonsurgical and surgical groups, respectively ($P = 0.50$). However, LMCA stenosis in isolation is rare, with the downstream disease being the norm.[18]

Given that downstream disease in a vessel such as the left anterior descending coronary artery (LAD) will affect the assessment of LM disease severity by FFR when the pressure-sensor wire is in the LAD,[19,20] it is recommended to place the pressure-sensor in an artery that is free of stenosis. However, given blood flow across the LM is dependent on the outflow of branch vessels (in this case both the LAD and left circumflex artery [LCx]), disease in either vessel could alter the FFR value even if the pressure sensor is in the nondiseased vessel. To further elucidate the possibility of this phenomenon, Yong and colleagues[21] created a sheep model for various scenarios of downstream epicardial disease with variable degrees of stenosis created in the LM. LM stenosis was evaluated by having a pressure wire in a nonstenosed vessel and then doing pre-FFR (true FFR) and post-FFR (apparent FFR) evaluations after producing stenosis in the other branch vessel. The results of the study showed that LMCA FFR measurement may be overestimated in the presence of downstream epicardial disease despite measuring FFR in a nondiseased epicardial vessel (true FFR) and apparent FFR correlated with composite FFR of the LM plus stenosed artery ($r = -0.31$; $P < 0.001$). This difference in the true and apparent FFR was most pronounced with increasing branch vessel epicardial stenosis. Fearon and colleagues[22] further confirmed these findings in humans after creating a model in which an intermediate LMCA stenosis was artificially created by balloon inflation in patients undergoing PCI in the LAD, LCx, or both to evaluate true versus apparent FFR in 91 pairs of measurements in 25 patients. True FFR of the LMCA was found to be significantly lower than apparent FFR (0.81 ± 0.08 vs. 0.83 ± 0.08, $p < 0.001$). A case example of the effect of variable downstream disease creation in a branch vessel on LM FFR is shown in **Fig. 3**. Similarly, in the animal model, the difference correlated with the severity of the downstream disease ($r = 0.35$, $p < 0.001$). Importantly, this FFR difference was found to be small, and in all cases in which apparent FFR was greater than 0.85, FFR, the true FFR was greater than 0.80. Because of these differences in LM FFR values in the setting of downstream disease, NHPR has been suggested as an alternative. Although little data correlating FFR and NHPR indices exist for the LM, the ongoing iLITRO study will aim to evaluate the concordance of FFR and iFR in LMCA lesions, while also evaluating a composite major adverse cardiac events outcome at 30 days, 1 year, and 5 years.[23]

Beyond evaluating LM stenosis in those with additional epicardial CAD, FFR generally has limitations for evaluating individual lesions in series. To calculate an accurate FFR, maximal hyperemia must be achieved, which is not possible when the first stenosis limits maximal flow across a downstream lesion. A commonly used technique to circumvent this is to do a pressure pull back during continuous hyperemia if the summed FFR is less than 0.80, allowing for the evaluation of which lesion has the largest effect on the Pd/Pa value.

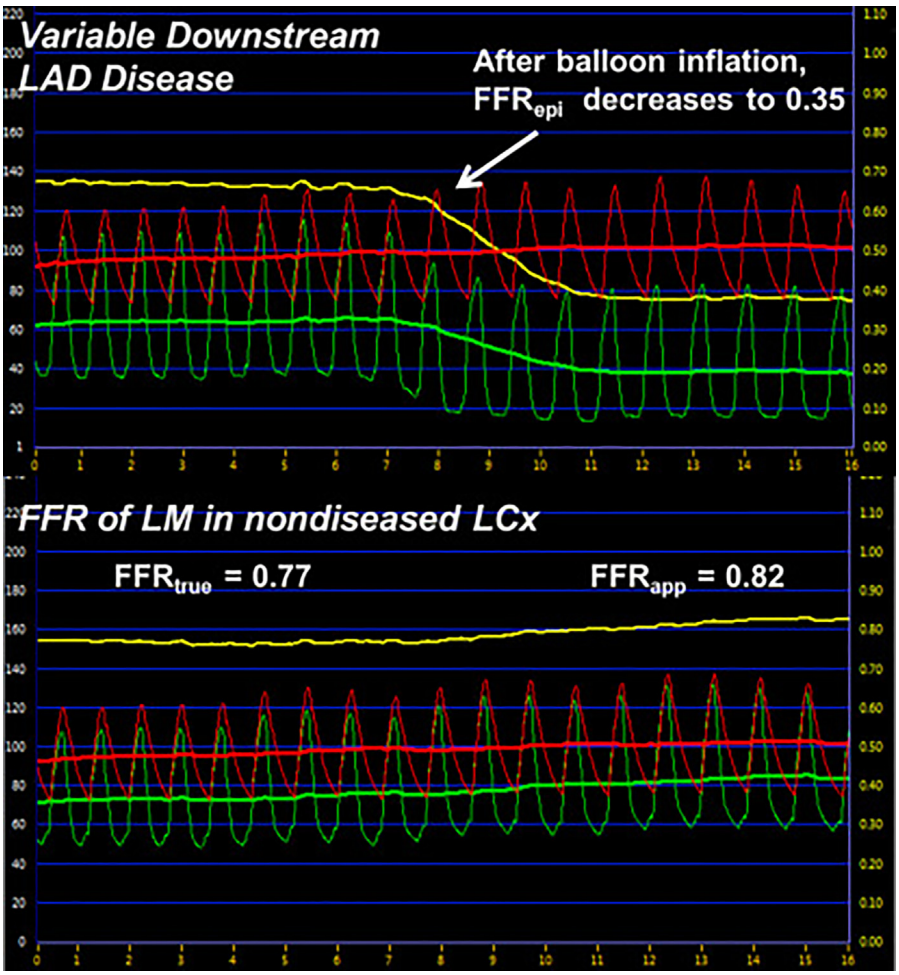

Fig. 3. Case example of LM FFR by use of simultaneous coronary pressure recordings during the creation of variable downstream stenosis using balloon inflation. (*Top panel*) The coronary pressure is recorded from the LAD pressure wire before and after balloon inflation within a newly placed LAD stent (the *green line* is distal coronary pressure, the *red line* is aortic pressure, and the *yellow line* is FFR value). (*Bottom panel*) The coronary pressure is recorded simultaneously from the LCx pressure wire (FFR_{true} and FFR_{app}) before and after inflation of the balloon in the LAD, ultimately leading to complete occlusion (the *green line* is distal coronary pressure, the *red line* is aortic pressure, and the *yellow line* is the FFR value). (*From* Fearon WF, Yong AS, Lenders G, et al. The impact of downstream coronary stenosis on fractional flow reserve assessment of intermediate left main coronary artery disease: human validation. *JACC Cardiovasc Interv.* 2015;8(3):398-403. https://doi.org/10.1016/j.jcin.2014.09.027.)

Although not completely accurate, pullbacks are less complicated procedurally and mathematically than evaluating individual FFR for serial lesions with balloon occlusion.[19] IFR is noninferior in large clinical outcome trials,[24,25] and more recently has been of interest in evaluating the hemodynamic significance of individual lesions in series. Kikuta and colleagues[26] showed that iFR pullback was not only accurate in predicting physiological outcomes of PCI, but changed revascularization procedural planning in about one-third of the patients when compared with those making angiographic guidance-based decisions. Such a method has particular utility to differentiate the hemodynamic significance of a long lesion with the diffuse disease compared with a focal lesion that is amenable to PCI. The importance of defining the lesion of hemodynamic significance was brought to light in the DEFINE PCI study. In this multicenter, prospective, observational study, blinded iFR pullback was done in 562 vessels (500 patients) with angiographically successful PCI.[27] Residual ischemia (defined as iFR<0.90) was present in 24% of patients with a mean iFR in that

population of 0.84 ± 0.06 (range 0.60–0.89). Importantly, among those patients with impaired post-PCI iFRs, 81.6% had untreated focal stenoses that were angiographically inapparent, suggesting they could be amenable to further optimization. Although these findings are interesting, it is unclear whether PCI optimization based on iFR translates to improved clinical outcomes. The currently enrolling, DEFINE GPS study will address whether iFR pullback guided PCI of lesions post-PCI will improve clinical outcomes.[28]

Left ventricular hypertrophy

The relationship between left ventricular hypertrophy (LVH) with FFR is complex. In general, there is an inverse relationship between the degree of territory, or in this case, myocardial mass, that a vessel with stenosis supplies and the FFR value. Essentially, similar stenosis would have a lower FFR value in the presence of a larger jeopardized myocardial mass. For example, an angiographically stenotic lesion in the proximal LAD will have a significantly lower FFR value compared with a similar one in the distal LAD, LCx, or right coronary artery (0.80 ± 0.09 vs. 0.84 ± 0.08 vs. 0.88 ± 0.09 vs. 0.91 ± 0.04, respectively; $P < 0.0001$).[29]

However, clinical studies investigating the impact of LVH on FFR have found no significant difference in values between those with and without LVH.[30] Further, in a substudy of the DANAMI-3 PRIMULTI, those with cardiac magnetic resonance defined LVH did not seem to interact with the correlation of diameter stenosis to FFR.[31] Furthermore, the presence of LVH did not seem to impact the clinical benefits of FFR-guided complete revascularization as compared with angiographic revascularization in this substudy. These clinical findings may be related to the fact that LVH is related to microvascular dysfunction and decreased coronary flow. With systole comes shortening and thickening accompanied by elevated cardiac muscle strain. This in addition to high intraventricular pressures is responsible for systolic flow impairment that can be seen in LVH.[16] Extravascular compression (in both systole and diastole) of the microvascular circulation in theory could elevate FFR.

The hemodynamic effects of elevated LVEDP and increased central venous pressure in the setting of diastolic dysfunction associated with LVH are also thought to complicate the reliability of FFR. Leonardi and colleagues[32] compared FFR preuse and postuse of nitroprusside (meant to reduce afterload) to evaluate the effects of increased LVEDP on FFR values in 528 cardiac cycles. The study showed that in multivariate analysis LVEDP was positively associated with FFR, increasing by 0.008 for every 1 mm Hg increase in LVEDP ($p < 0.001$), with a stronger correlation of 0.01 for every 1 mm Hg increase in LVEDP for those lesions with an FFR less than 0.80 ($p < 0.001$). These findings suggest in the setting of increased LVEDP (LVH, AS, and decompensated HF), evaluating moderate severity lesions with FFR could underestimate the hemodynamic significance. Central venous pressure had been included in the experimental validation of myocardial FFR [(Pd-right atrial pressure)/(Pa-right atrial pressure)],[33] the predecessor of the clinically used FFR. Central venous pressure was excluded in the commonly used (and clinical trial proved) FFR calculation as it was thought to be negligible. Toth and colleagues[34] largely proved this negligibility when comparing myocardial FFR to clinically used FFR in 1,676 stenoses. The median difference, although statistically significant, was an FFR difference of 0.01 when comparing myocardial FFR to FFR across a wide range of right atrial pressures. Nonetheless, there were larger differences between myocardial FFR to FFR as the right atrial pressure approached 12 mm Hg (median difference 0.02, IQR 0.01 to 0.03). These findings suggest that those with markedly elevated central venous pressures may have ischemic reclassification. However, in this study, a central venous pressure greater than 10 mm Hg had limited clinical impact as only 9% of those classified with an FFR greater than 0.80 were reclassified with a myocardial FFR of less than 0.80.

The degree of the myocardium, microvascular dysfunction, and hemodynamic effects associated with LVH plays a complex role in obtaining the simple hyperemic Pd/Pa calculation for FFR. It is possible that in patients with LVH, the FFR-decreasing effects that a myocardial territory a stenosed vessel may be balanced out by the FFR-increasing effects that occur with increased LVED and microvascular resistance. Ultimately, FFR seems to be reliable and useful when evaluating intermediate coronary lesions in those with LVH.

Older age

Increasing age leads to increased microvascular dysfunction and increased flow velocity, which in turn leads to reduced coronary filling. In nonhyperemic states, these findings would affect the evaluation of Pd/Pa. However, even with hyperemia, studies have suggested that in those with increased age with intermediate stenosis similar to their younger counterparts, FFR values were higher.[35] Lin and colleagues showed that in 178

left anterior descending evaluations with FFR that elderly patients (aged >70 years) had a smaller difference in the resting Pd/Pa and FFR (ΔFFR) compared with a younger age group (0.13 ± 0.05 vs. 0.15 ± 0.05, P = 0.014) and age was independently associated with FFR and ΔFFR in multivariate analysis. It is hypothesized that elderly patients have a reduced hyperemic response to adenosine. This, in turn, could lead to underestimation of lesion severity, although myocardial resistance should still be minimal in the presence of microvascular disease. Whether the difference in FFR values in older adults translates to clinical differences is unclear. A substudy of the FAME trial showed that although FFR is less likely to be abnormal in older adults for any given stenosis, FFR-guided PCI was equally beneficial compared with angiography-guided PCI for those aged more than 65 years as compared with those aged less than 65 years. These findings have spurred the FIRE trial which has been enrolling those aged more than 75 years to evaluate the difference in clinical outcomes between FFR guidance complete revascularization versus culprit only revascularization in those presenting with ST or non-ST elevation MI as has been done in prior trials in a younger population.[36,37]

SUMMARY

With the dramatic increase of FFR use in the cath laboratory coupled with the more recent emergence of NHPRs, accurate interpretation of these hemodynamic indices has become paramount. As additional evidence supporting the use of NHPRs emerges, more clinicians are using these indices in addition to FFR or in-lieu of FFR when relative or absolute contra-indications exist to induce hyperemia. However, both FFR and NHPRs have limitations that operators need to be cognizant of. Particular clinical and procedural scenarios may call for use of one over the other. For example, FFR seems to have more accuracy and reproducibility in those with AF undergoing evaluation of an intermediate lesion, whereas the future may show iFR to be superior to FFR when evaluating which lesion in series has a higher ischemic burden. Importantly, the outcome data for use of FFR or NHPRs in patients with special clinical scenarios are limited, let alone using one over the other in these scenarios. Ultimately, the goal moving forward in patients undergoing physiologically guided revascularization is accuracy, reliability, and translation to improvement in clinical outcomes. Understanding pitfalls, limitations, and strengths for FFR and NHPRs will help guide us to that goal.

CLINICS CARE POINTS

- Post-transcatheter aortic valve replacement (TAVR) for aortic stenosis, there seems to be an average decrease in fractional flow reserve (FFR) values for coronary lesions; however, this change is rarely clinically relevant and the decision to defer revascularization based on pre-TAVR seems to be safe.
- When comparing pre-TAVR versus post-TAVR, nonhyperemic pressure ratio (NHPR) for coronary lesions has significant variability, suggesting that FFR may be a more reliable alternative.
- FFR evaluation remains reproducible and reliable in patients with atrial fibrillation (AF), whereas the reproducibility of NHPR like instantaneous wave-free ratio (iFR) in patients with AF is far less.
- FFR evaluation seems to be a reliable marker of hemodynamic significance in patients with left ventricular hypertrophy and a coronary lesion, despite the concern of coronary territories providing large myocardial territories.
- Evaluation of left main coronary artery disease during FFR and NHPR is best evaluated with the pressure wire down a branch vessel with minimal-to-no disease.
- Serial coronary lesions affect the accurate evaluation of FFR for each individual lesion.
- iFR pullback may provide a more reliable modality to evaluate the hemodynamic significance of individual coronary lesions in series as compared with FFR, especially when comparing focal versus diffusely diseased lesions in series. However, whether intervening on these lesions based on iFR change leads to improved clinical outcomes is unknown.

DISCLOSURE

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