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EDITORIAL COMMENT

QFR and FFR_{CT}: Accurate Enough?*

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There are 2 important binary decision points in the evaluation and management of patients with known or suspected coronary artery disease (CAD): first, the decision to perform invasive coronary arteriography, and second, the decision to revascularize an identified coronary stenosis.

Currently, case selection at these 2 decision points makes use of physiology-based assessments of provokable ischemia. Patient selection for coronary arteriography is informed by stress testing using radiotracer perfusion imaging or echocardiography. Once coronary arteriography has been performed, selection of an intermediate stenosis for revascularization is informed by measuring fractional flow reserve (FFR).

Functional evaluations are of paramount importance to clarify the physiological significance of an intermediate stenosis. FFR has emerged as the best technique for this assessment (1). Although clinical management decisions are binary, FFR measurement yields a continuous variable. Consequently, a "cutpoint" that separates "functionally significant" from "not significant" is needed as a basis for management decisions. An FFR value <0.80 reliably identifies important stress-induced ischemia. Clinical outcomes studies have demonstrated that an FFR cutpoint of 0.80 identifies a boundary between benefit and no benefit (or even harm) from percutaneous coronary intervention (2). Thus, stenoses with FFR <0.80 are considered significant, and this cutpoint is accepted to select stenoses for intervention.

An accurate noninvasive estimate of FFR would have tremendous potential to inform case selection for invasive coronary arteriography and to select stenoses for revascularization. Overuse of coronary arteriography is undesirable, and percutaneous revascularization of insignificant stenoses has been shown to be detrimental (2).

More recently, with progressive engineering refinement of x-ray computed tomographic scanners, coronary computed tomographic angiography (CTA) has emerged as a highly sensitive test that is particularly effective at excluding the presence of epicardial CAD. Like invasive coronary arteriography, coronary CTA provides purely anatomic information and does not provide the functional evaluation of ischemia provided by stress testing and FFR.

Over the past several years, a collaboration between the engineering and medical communities has developed truly remarkable technologies that apply fluid dynamic principles to coronary CTA and invasive coronary arteriography to calculate estimates of the invasively measured FFR value. These parameters, termed FFR_{CT} and quantitative flow reserve (QFR), respectively, are estimates of a physiological measurement that are derived from purely structural data.

Although the role of FFR to evaluate the functional significance of an intermediate stenosis is clear, if FFR_{CT} and QFR are to serve as valid surrogates for FFR, they must provide requisite diagnostic accuracy.

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In this issue of *JACC: Cardiovascular Interventions*, Tanigaki et al. (3) address these issues by evaluating the performance of QFR, and FFR_{CT} versus FFR, in a cohort of patients with epicardial CAD. The investigators are to be congratulated for this well-done study that has 2 major strengths. First, the study cohort was selected to have intermediate-severity lesions visually estimated to be 30% to 70% stenosed. This is the stenosis population in which accurate physiological assessment is most important. Second, all stenoses were assessed using all 3

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modalities, providing a robust dataset for rigorous statistical analysis.

The findings of their important analysis are illuminating. The study cohort included 233 stenoses in 172 patients. Compared with traditional FFR thresholds (≤0.80), QFR (set to a threshold of ≤0.80 for hemodynamic significance) had a strong Pearson correlation coefficient of 0.82, with sensitivity of 0.90 and specificity of 0.82, resulting in a positive predictive value of 0.81 and a negative predictive value of 0.90 in this population. However, despite relatively good predictive indexes, QFR misclassified 14.6% of the stenoses with respect to the corresponding FFR determination of functional significance. Thus, if QFR were used as the basis of selection for percutaneous coronary intervention, 34 of the 233 stenoses either would receive inappropriate percutaneous coronary intervention or would not receive an appropriate intervention.

In the Tanigaki et al. (3) study, FFR_{CT} (also set to a threshold of ≤0.80 for hemodynamic significance), compared with FFR, had a lower Pearson correlation coefficient of 0.63, with sensitivity of 0.82 and specificity of 0.70, resulting in a positive predictive value of 0.70 and a negative predictive value of 0.82. These predictive indexes indicate that compared with FFR, FFR_{CT} would misclassify 24.6% of the stenoses in the study population.

It is noteworthy that the discriminatory performance of FFR_{CT} was weaker in the subgroups with intermediate stenoses (50% to 90%) as assessed by coronary CTA and weakest in the subgroup with FFR values between 0.70 and 0.85 (**Table 1**). These are the subgroups for which accurate discrimination is most important. Thus, the diagnostic accuracy for FFR_{CT} is the poorest in the subset of stenoses for which an accurate discriminatory measurement is most needed.

This study's findings are largely consistent with prior investigations of FFR_{CT}, including the DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained via Noninvasive Fractional Flow Reserve), NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps), DeFACTO, and PLATFORM studies (4–7). Differences among these studies' findings are likely due to differences in the stenosis severity distribution in the different study populations. The finding of poorest performance in the intermediate stenosis severity range is consistent with the Nørgaard et al. (5) previous findings.

FFR_{CT} has the potential to provide complete anatomic and functional evaluation of a patient's epicardial coronary system and possibly even guide intervention. However, to be trusted in this role, it must prove to be highly accurate. Physicians make binary clinical decisions on the basis of the value of the continuous variable returned by the test. How do we measure and judge accuracy?

TABLE 1 Summary of Correlative and Diagnostic Accuracy Statistics Comparing Fractional Flow Reserve Derived From Computed Tomography (Threshold ≤0.80) and Fractional Flow Reserve (Threshold ≤0.80)

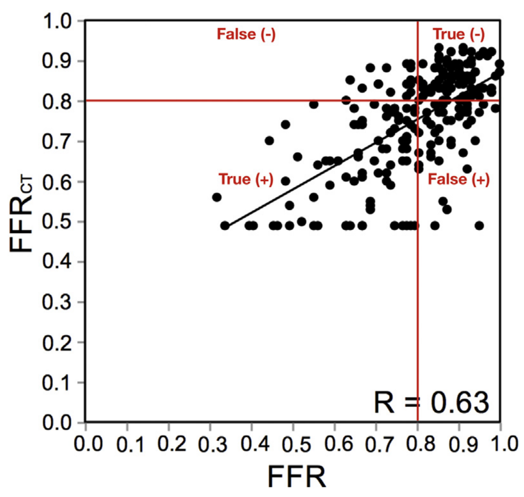
	Pearson Correlation Coefficient	Sensitivity	Specificity	Misclassification (%)
All patients	0.63	0.82	0.70	24.5
Intermediate stenosis on coronary CTA (50%–90%)	0.61	0.84	0.65	25.8
FFR (0.70–0.85)	0.26	0.75	0.58	30.4

CTA = computed tomographic angiography; FFR = fractional flow reserve.

Not all statistical methodologies are appropriate or informative for comparing these techniques, and the interpreter must apply statistical analysis with insight. For example, because the Pearson correlation incorporates all data points, it is leveraged substantially by reasonable agreement at the extreme values (FFR <0.70 and >0.90). Because accuracy is most important in the intermediate stenosis subset (FFR 0.70 to 0.85), a strong Pearson correlation coefficient can be misleading with respect to a test's discriminatory value. It is useful to study the scatterplots on which the Pearson correlation is based, as they display the frequency and magnitude of deviation of individual data points from the correlation regression line. Vertical and horizontal lines intersecting values of 0.80 divide the scatterplot into 4 quadrants (**Figure 1**). The "northeast" and "southwest" quadrants contain the correctly classified data points, while the "southeast" and "northwest" quadrants hold the misclassified points, in this case constituting 24.6% of the total. In receiver-operating characteristic curve analysis, the area under the curve can be similarly misleading, as only the discriminating cutpoint value is important. This point is quantified by the Youden J statistic, which is the distance between the curve and the line of chance at the identified cutpoint value and is a quantitative measure of the sensitivity-specificity relationship at that cutpoint. Bland-Altman analysis is quantitatively revealing, as it displays and quantifies the absolute magnitude of the differences between the 2 measured values.

Ultimately, the most important assessment of a test's performance is the frequency of classification agreement (1 – diagnostic accuracy) between the test and its reference comparator. How frequently does the test misclassify a nonsignificant stenosis as significant and vice versa? Thus, we are left to ask

FIGURE 1 Individual Comparison: FFR and FFR$_{CT}$



Scattergram comparing fractional flow reserve derived from computed tomography (FFR$_{CT}$) values with directly measured fractional flow reserve (FFR) from Tanigaki et al. (3). The **vertical and horizontal red lines** (added) divide the plot into the 4 quadrants (labeled with **red text**) that represent classification agreement and disagreement between FFR$_{CT}$ and FFR.

whether FFR$_{CT}$'s classification accuracy is "accurate enough" to serve as a valid screening test.

The Tanagaki et al. (3) findings demonstrate that compared with directly measured FFR, FFR$_{CT}$ has a substantial frequency of binary misclassification with respect to both sensitivity and specificity. Eighteen percent of stenoses that FFR$_{CT}$ deemed to not be hemodynamically significant were found to have FFR values of <0.80. On the basis of FFR$_{CT}$ alone, these patients may not have undergone diagnostic arteriography and intervention of a hemodynamically significant epicardial stenosis. Conversely, 30% of stenoses that were deemed by FFR$_{CT}$ to be hemodynamically significant had FFR values of >0.80. Using FFR$_{CT}$ alone would result in inappropriate invasive coronary arteriography for these patients and could potentially lead to inappropriate revascularization procedures. Furthermore, misclassification is most common in the important subgroup of intermediate severity stenoses.

These findings demonstrate that, currently, anatomically based estimates of the physiological effect of a coronary stenosis have accuracy limitations that undermine their ability to supersede direct physiology-based tests. FFR$_{CT}$ may not have the needed accuracy to serve as either a "rule-out" test to exclude the presence of hemodynamically significant epicardial CAD or as a "rule-in" test to justify intervention after a coronary stenosis is discovered. QFR is more accurate than FFR$_{CT}$. This is to be expected, as angiographic images provide greater detail and spatial resolution than coronary CTA. Nonetheless, QFR also misclassifies a large fraction of stenoses and may not serve as an adequate substitute for directly measured FFR.

Unless and until the accuracy of structure-based estimates of stenosis severity achieve better accuracy, direct physiology-based measurements of provokable ischemia should remain the basis for clinical decision making. Whether FFR$_{CT}$ can overcome the intrinsic limitations imposed by coronary CTA's lesser spatial resolution remains to be seen. It is noteworthy that ongoing development of angiography-based systems report improved, although still imperfect, accuracy compared with QFR (8,9). Thus, future refinements may enable angiography-based analytic systems to achieve sufficient accuracy to inform intraprocedural revascularization decision making.

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