The Evolving Story of Fractional Flow Reserve CT

An important and effective noninvasive test for evaluating ischemia without the need for additional testing or radiation exposure.

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Over the last decade, coronary CTA (CCTA) has gone from being a test that is simply used to exclude obstructive coronary artery disease (CAD) in a low-risk population to one that is now being considered as the appropriate first-line test in patients, regardless of their pretest likelihood of CAD.[1-3] In fact, a recent meta-analysis of large prospective randomized trials suggests that performing CTA as a first-line test may help inform clinical decision-making in a fashion that enables a reduction in myocardial infarction (MI) as compared to noninvasive stress testing.[1,3,4]

Despite the ongoing improvement in image quality, diagnostic accuracy, reduction in radiation dose, and increasing clinical utility, patients are more likely to undergo invasive coronary angiography (ICA) after CCTA than patients evaluated with upfront stress testing. In the PROMISE trial, in which more than 10,000 patients were randomized between CCTA and traditional stress testing, 12.2% of patients in the CTA arm underwent ICA versus 8.5% in the stress testing arm. Despite this higher rate of ICA in the CTA arm, the rate of nonobstructive disease was significantly lower at 28% versus 52% in the stress testing arm ($P < .001$) (Figure 1).[2]

Although patients undergoing ICA after CTA have consistently been shown to have a greater likelihood of obstructive disease than those undergoing ICA after stress testing, the rate is nonetheless concerning in the context of extending CTA as a first-line test to a higher-risk population, as recommended in the recently updated NICE guidelines. This is particularly worrisome if the goal is to increase the likelihood of functionally significant coronary lesions as defined by invasive fractional flow reserve (FFR) and not only anatomic stenosis.

Noninvasive computationally derived FFRCT is obtained from a resting coronary CT without adminis-

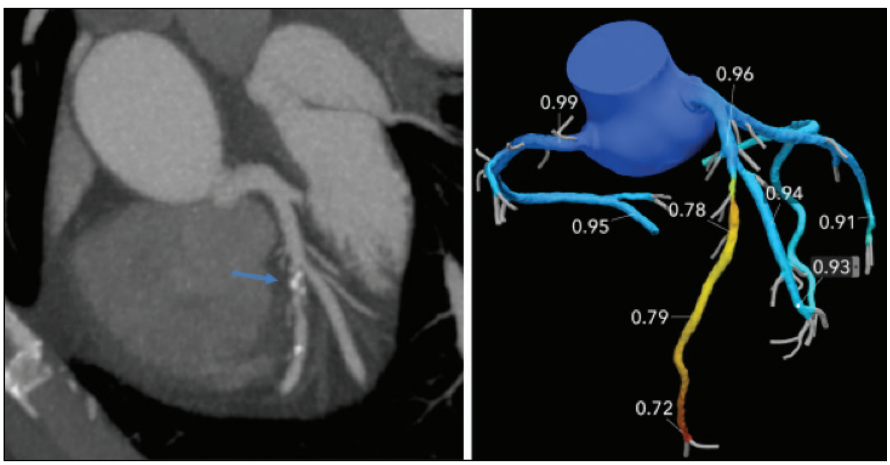

Figure 1. A 68-year-old man with atypical chest pain who underwent CCTA to exclude CAD was found to have a moderate (50%–69%) stenosis in the mid-left anterior descending artery. The lesion was uploaded for FFRCT analysis, which documented borderline lesion-specific ischemia with FFRCT value of 0.78.

tration of additional medication (ie, adenosine), additional radiation exposure, or changes to the CCTA scan parameters.[5-8] There is growing evidence that the diagnostic performance of FFRCT is better when best practice CTA acquisition protocols are used, including the administration of sublingual nitroglycerin spray. This methodology has previously been extensively described, but in short, FFRCT helps to enable accurate anatomic modeling of the coronary arteries and myocardium, integration of physical laws that govern flow, microcirculatory resistance and coronary branching, and simulated hyperemia. Finally, the Navier-Stokes equations used to solve for velocity, resistance, and pressure for all Newtonian fluids can be applied to provide a three-dimensional pressure map across the coronary tree. Importantly, these advanced off-site computational analyses have the potential to improve anatomic modeling through the development of large data sets and the maturation of deep and machine learning.

FFRCT is feasible for stable patients presenting with acute or chronic chest pain in the absence of surgical revascularization. After PCI, patients can undergo FFRCT, but the stented vessel cannot be evaluated. CTA best practice acquisition guidelines should be followed with appropriate β blockade and the administration of sublingual nitroglycerin to mediate coronary vasodilation.

CLINICAL UTILITY OF FFRCT

FFRCT has been shown to enable a marked reduction in the false-positive rate of CTA alone versus FFR-adjudicated ischemia, with 68% of false-positive CT interpretations in the NXT trial reclassified as true negative. The safety and utility of a CT/FFRCT strategy was also tested in the PLATFORM study, in which two nonoverlapping cohorts of patients referred for ICA were assigned to either a conventional ICA strategy or CTA/FFRCT; patients in the latter group only underwent ICA based on the results of the CTA/FFRCT. The CTA/FFRCT arm showed significant enrichment of the catheterization lab, with the burden of nonobstructive disease reduced from 73% to 12% with stable obstructive disease and no events in the 61% of patients in whom ICA was deferred through 12 months.[9]

The utility of FFRCT in clinical practice is increasingly becoming well established, and it is used to help guide clinical decision-making across a spectrum of coronary disease, resulting in higher rates of obstructive disease in the invasive catheterization laboratory in a cost-effective fashion.[9,10] Although much of the early focus was on reducing unnecessary referral for ICA, more recently, there has been growing interest in using FFRCT to enhance catheterization lab efficiencies by increasing the percutaneous coronary intervention (PCI)/cath ratio and providing information to aid the physician in their review of revascularization strategies before invasive angiography.[11]

The PCI/cath ratio has been shown to increase across a variety of health care systems, with the greatest benefit being found in patients considered to have a higher pretest likelihood of obstructive CAD. The SYNTAX III REVOLUTION trial (NCT02813473), which is currently enrolling patients, aims to explore the potential of a CTA/FFRCT strategy to guide revascularization decision-making. In this prospective randomized trial, heart teams are randomized to evaluate patients with complex CAD using either a CCTA/FFRCT strategy or a conventional ICA strategy to guide revascularization decision-making.

Importantly, FFRCT is not only being used in a binary fashion but also as a means to provide a richer understanding of the severity of ischemia and degree of pressure loss across the epicardial coronary system. Although randomized trial data are needed, some experts with extensive real-world experience using FFRCT have advocated for ischemia-guided revascularization based on FFRCT alone if FFRCT is < 0.75 distal to a focal lesion. Patients with a lesion with FFRCT of 0.75 to 0.80 are considered to be in a "gray zone" and are closely followed.[12] Importantly, a noninvasive computational model FFRCT provides certain clinical challenges, including how to interpret and integrate a pressure map that allows for the adjudication of ischemia across the entire coronary tree.

Current recommendations are that ischemia is evaluated in a fashion similar to that of FFR or instantaneous wave-free ratio distal to a focal lesion and not based on the nadir FFR value. The ADVANCE registry has completed enrollment, with 5,000 patients undergoing clinically indicated FFRCT, and will soon report on both site- and core laboratory–determined reclassification of anatomic lesions identified by CCTA with FFRCT as well as the downstream clinical outcomes.[13,14]

RECENT LEARNINGS

The clinical integration of FFRCT and ongoing work in atherosclerosis imaging with CT is introducing new opportunities to learn more about mechanisms of ischemia and clinical risk. Growing data are linking previously described adverse plaque features shown to be associated with an increased risk of MI with lesion-specific ischemia. Ahmadi et al recently built on these findings by noting that adverse bulky plaques with significant low-attenuating components, a feature seen

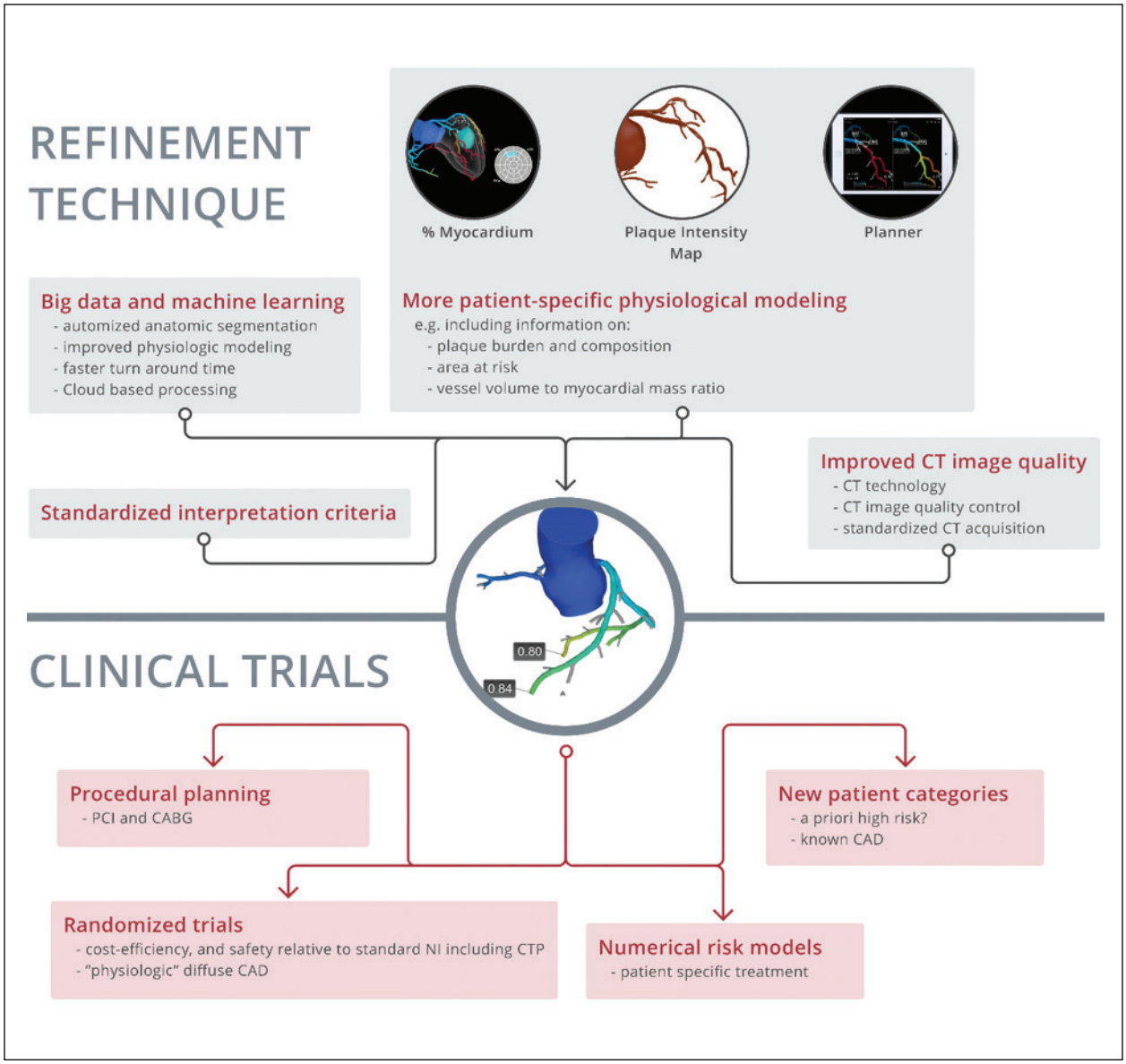

Figure 2. The potential course for ongoing technologic development and scientific evaluation of FFRCT. CABG, coronary artery bypass grafting; CTP, CT perfusion.

in thin-cap fibroatheromas evaluated by optical coherence tomography, were associated with an increased likelihood of FFRCT positivity; the opposite also held true in that FFRCT-negative lesions were exceptionally unlikely to have a significant low-attenuating plaque component.[15,16]

Beyond plaque, through advanced analytics, there is the potential to explore alternate mechanisms for the induction of ischemia. It has been proposed that some patients may have inadequate coronary volume to meet their myocardial demand. Although an interesting theory, this was difficult to prove or refute with angiography, owing to the limitations of myocardial segmentation. Using CT and advanced computational analytics used to generate FFRCT, a three-dimensional model of the coronary arteries can be produced and normalized to the myocardial mass.

In a recent subanalysis of the NXT trial, Taylor et al noted that patients with ischemia but no obstructive CAD were more likely to have low coronary volume to mass.[17,18] Whether this reflects poor nitrate vasodilation of potentially genetic predisposition is uncertain, but

what is clear is that volume to mass may represent a new opportunity to understand mechanisms of angina in the absence of obstructive CAD.

FUTURE OPPORTUNITIES AND OUTSTANDING CLINICAL QUESTIONS

In 2014, the possibility of noninvasively simulating correction of arterial narrowing was introduced with a prospective analysis of 44 patients and eight lesions. In this analysis, baseline FFR and FFRCT values were obtained prior to PCI in a fashion similar to that used in other FFRCT accuracy studies. However, FFRCT was also calculated after modifying the computational model to restore the area of the target lesion based on proximal and distal reference areas and was compared with invasively measured FFR after PCI. These data were highly provocative, with an accuracy of 96% (sensitivity, 100%; specificity, 96%; positive predictive value, 50%; and negative predictive value, 100%) (Figure 2).[19]

Although these data are very compelling, there has been a lull in additional scientific validation, and further advancements in computational processing are needed to enable its more routine evaluative use. With the necessary computational capacity now available, larger prospective trials are set to begin to not only evaluate the diagnostic accuracy of FFRCT following remodeling, but also to evaluate its impact on catheterization laboratory resource utilization and likelihood of complete ischemic revascularization.

Additionally, although there are growing clinical utility data, there is a paucity of randomized trial data evaluating the cost-effectiveness of a CTA/FFRCT strategy in patients with chest pain and suspected (but not yet diagnosed) CAD, as well as in evaluating FFRCT to help guide revascularization as compared with invasive FFR. To that end, the first randomized clinical trial measuring outcomes has begun in the United Kingdom (FORECAST), which will enroll 1,400 patients with stable chest pain and suspected CAD. Patients will be randomized to a CCTA/FFRCT arm versus traditional CCTA, with a primary endpoint of resource utilization and cost-effectiveness. Although continued learning and assessment are needed, FFRCT has rapidly become an important and effective test for the adjudication of ischemia without the need for additional testing or radiation exposure. ■

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