Computed Tomography-Based Fractional Flow Reserve (FFR-CT) – An Attractive Concept, But Still Lacking Proof of Clinical Utility –

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In this issue of the Journal, Miyoshi et al describe their results from a subset of Japanese patients in a clinical trial examining the diagnostic performance of computed tomography-based fractional flow reserve (FFR-CT). FFR-CT is a fascinating concept, applying computational fluid dynamics to computed tomographic angiography (CTA) images to in order to predict the hemodynamic significance of coronary lesions. Interestingly, a similar approach has recently been described that is based on 3D angiographic images obtained at rest and after induced hyperemia (Figure). In contrast to invasive FFR and 3D angiography-derived FFR, which use adenosine-induced hyperemia, FFR-CT is derived from anatomic images acquired at rest only, with subsequent mathematically simulated hyperemia. The analysis is based on complex mathematical assumptions and modeling derived from work of a group of investigators who have commercialized the system as HeartFlow Inc (Redwood City, CA, USA). It is important to consider that the analysis is currently performed exclusively on a computer system in a commercial core-laboratory owned by this company.

In initial studies, including the DISCOVER-FLOW and DeFACTO trial, the system was calibrated and compared against invasive FFR. The data demonstrated that the addition of FFR-CT to CTA alone led to improved identification of ischemia-inducing coronary lesions (FFR ≤0.8).

The study primary

Figure. Approach to calculating FFR-QCA during PCI: 3D QCA from 2 views, acquired with either mono- or biplane angiography (Left), and assessment of TIMI frame count under hyperemic conditions. Online computational fluid dynamics analysis allows calculation of FFR-QCA, displayed in a color map (Right). In this patient, FFR-QCA of 0.82 correlated well with standard FFR of 0.81. (Image courtesy Professor Hans Reiber.)
endpoint in the multicenter DeFACTO trial was whether FFR-CT plus CT could improve per-patient diagnostic accuracy such that the lower boundary of the 1-sided 95% confidence interval (CI) of this estimate exceeded 70%.

The study did not achieve this prespecified endpoint for per-patient diagnostic accuracy. Among 252 study participants, per-patient diagnostic accuracy, sensitivity, specificity, positive predictive value, and negative predictive value (NPV) of FFR-CT plus CT were 73% (95% CI, 67–78%), 90% (CI, 84–95%), 54% (CI, 46–83%), 67% (CI, 60–74%), and 84% (CI, 74–90%), respectively. Note that the specificity to identify lesions with FFR ≤0.8 (54%) is significantly lower than the specificity of CT to identify lesions with angiographically >50% lesions [91% (95% CI: 88, 94%)].

After further adjustment of the mathematical algorithms underlying the analysis system, the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) trial was designed. In this prospective, multicenter trial the diagnostic performance of FFR-CT versus coronary CTA to identify hemodynamically significant stenosis (FFR ≤0.8) was examined in 254 patients with suspected coronary artery disease. The data provided by Miyoshi et al describe results in a subset of Japanese patients. From 76 screened Japanese patients, 25% were excluded from analysis: 9 patients for ‘non-evaluable coronary CTA’, 2 for ‘analysis in small vessel diameter’ (<2 mm), and 8 patients for ‘other reasons’. In the remaining 57 patients, the per-patient diagnostic accuracy of FFR-CT (74%, 95% CI: 60–85%) was higher than for coronary CTA alone (47%, 95% CI: 34–61%, P<0.001). FFR-CT led to an improvement in specificity from 27% for CTA to 63% for FFR-CT (P<0.001). When patients with a coronary calcium Agatston score >1,000 were excluded, the per-patient accuracy of FFR-CT was 83%, with a specificity of 76%, comparable to the overall NXT trial findings (NXT per-patient accuracy 81%, CI 76–85%; specificity increased from 34% to 79%). Although not an endpoint in the NXT trial, the diagnostic accuracy of the Japanese subgroup would not have met the primary endpoint of the DeFACTO trial. It is also important to note that the NPV was not further improved (Miyoshi et al: NPV for FFR 100% (CI 86.8–100%) vs. CTA 100% (CI 71.5–100%); NPV in NXT FFR 93% (CI 87–96%) vs. CTA 92% (CI 83–97%).

The data show the feasibility of FFR-CT, but clinical utility remains unclear. Using modern acquisition protocols with relatively low radiation exposure, coronary CTA has evolved to a valuable test for symptomatic, low-intermediate risk population to rule out significant disease (defined as <50% lumenal diameter stenosis). Multiple studies and meta-analysis have documented a very high NPV (99% [95% CI, 97, 100%]), and prognostic value in these populations. A recent secondary analysis of the DeFACTO trial further demonstrate that atherosclerotic plaque characteristics, including aggregate plaque volume, positive remodeling, low attenuation plaque, and spotty calcification, by CTA improve identification of coronary lesions that cause ischemia. Based on current data, FFR-CT has no significant effect on NPV and therefore no incremental value for <50% lesions. If lesions with ≥50% diameter stenosis or intermediate lesions (specifically lesions with significant calcification/calcium-blooming) are identified with coronary CTA, additional testing to assess hemodynamic significance is considered in the clinical context. A high-risk lesion in the proximal vessel segments would most likely trigger a recommendation of cardiac catheterization with or without FFR, whereas for more distal lesions an imaging stress test or empirical medical management would be considered.

Choice of the most appropriate stress test is influenced by the mode of ischemia provocation: treadmill/bike exercise versus pharmacological provocation (dobutamine/adenosine). FFR-CT with simulated provocation/hyperemia could develop into an alternative approach to assessing intermediate and ≥50% lesions in subgroups of these patients. However, several questions remain. It remains unclear if in unselected patient populations the limitations of CTA and specifically calcification will effect the accuracy of FFR-CT. The results from the current trial of significantly improved accuracy in patients with lower coronary calcium scores despite a priori exclusion of approximately 25% of screened patients, suggest that this is the case. Most importantly, studies will need to be designed to show that the addition of FFR-CT has an effect on patient management and outcome, similar to studies of invasive FFR. In those studies of patients with stable coronary artery disease, invasive FFR-guided PCI improved clinical outcome in patients with hemodynamically significant lesions, whereas patients without ischemia had a favorable outcome with medical therapy alone. FFR-CT results will need to be compared with those of other stress modalities, including other novel CT-based approaches including CT perfusion imaging. In the meantime, technical limitations will need to be clarified. According to the HeartFlow Website (http://heartflow.com/overview/ [accessed December 5, 2014]) FFR-CT is currently not commercially available in the United States. However, it has recently obtained FDA clearance (http://www.fda.gov/NewsEvents/Newsroom/ PressAnnouncements/ucm424945.htm [accessed December 5, 2014]). The computationally demanding analysis cannot be performed at ‘point-of-care’. In clinical FFR-CT trials, coronary CTA images are transmitted to the company core laboratory for computational analysis. Such an approach would be of limited value for clinical application. Miyoshi et al discuss that ‘reduced order models’ for FFR-CT may allow onsite assessment in the future. However, it is unclear how such systems (from the same or other vendors) would perform in less-selected patient populations outside a trial and core laboratory setting. In summary, FFR-CT is an academically attractive approach, but its clinical value remains unclear. Until technical limitations are resolved and more data become available from larger trials with clinical endpoints, a change of the current practice of CT utilization as recommended by major professional organizations cannot be recommended.

References
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