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Improved Precision of Initial Chest Pain Evaluation With Fractional Flow Reserve Computed Tomography

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Following publication of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) trial,[1] there has been a noticeable increase in the use of fractional flow reserve (FFR) in the cardiac catheterization laboratories across the country. The FAME study provided evidence in support of FFR-guided revascularization. This was a welcome change as opposed to trusting the gold standard visual estimation of invasive angiography. In the FAME trial, invasive FFR led to a reduction in the number of stents deployed, and this reduction in stent numbers was associated with a significant decrease in the primary end point of repeat revascularization, myocardial infarction, and death.

While use of invasive FFR is appealing, especially in patients presenting directly to invasive coronary angiography, a vast majority of patients with stable chest pain undergo noninvasive assessment for risk stratification before invasive coronary angiography.[2] Low diagnostic yield of invasive angiography in general practice calls for better noninvasive risk stratification.[2]

Noninvasive fractional flow reserve computed tomography (FFRCT) is a recent advancement that could further impact the landscape of diagnostic evaluation of chest pain. Using a computational fluid dynamics model, it is now possible to estimate the FFR of all major coronary vessels noninvasively, by analyzing a single set of coronary computed tomographic angiography (CTA) images, without administration of adenosine. This expands CTA use from pure anatomic evaluation of atherosclerotic plaque to functional assessment of stenosis, with less need for additional stress testing. Several studies[3] have shown how FFRCT analysis improves specificity of intermediate stenosis detected by CTA, even in patients with increased calcium burden.[4]

For FFRCT to have the greatest impact, we need to consider coronary CTA as the first test for evaluation of chest pain. Several studies have focused on the performance of CTA as the first test for chest pain evaluation.[5,6] The largest study on this subject was the PROMISE (The Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial.[7] It was designed to compare anatomic testing with CTA to functional testing in patients without prior history of coronary artery disease. The study included 10 003 outpatients with chest discomfort at moderate risk for coronary artery disease. Because of concerns for complications with invasive angiography,[8] the prespecified combined primary end point was not only death, myocardial infarction, and unstable angina, but also major complications with invasive procedures such as anaphylaxis, bleeding, stroke, and renal failure. Use of CTA as first test compared with stress testing was associated with a larger number of invasive angiograms (12.2% versus 8.1%) and more revascularization procedures (6.2% versus 3.2%, $P<0.001$). Despite a noticeable increase in percutaneous or surgical revascularization within the CTA arm, there were significantly fewer deaths or myocardial infarctions during the first 12 months among patients randomized to CTA (hazard ratio, 0.66; 95% confidence interval, 0.44–1.00; $P=0.049$). Over a median follow-up of 25 months, there was no difference in the incidence of the primary end point between patients randomized to CTA or functional testing (3.3% versus 3.0%, hazard ratio 1.04 with 95% confidence interval, 0.83–1.29, $P=0.75$). The main reason for not reaching a prespecified end point was increased frequency of unstable angina within the CTA arm, but there was no significant increase in complications with invasive angiography. The reason for increased unstable angina is most likely because of the fundamental difference between CTA and stress testing, where CTA is likelier to report intermediate obstructive coronary artery disease. Patients undergoing CTA might therefore be less likely to ignore worsening symptoms, whereas patients with a negative stress test might feel as if they were “cleared” and avoid reporting more symptoms. The PROMISE trial did not account for crossover and was not powered to assess the effect of invasive angiography. Other

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studies have also associated early CTA use with fewer heart attacks. Both meta-analysis of stable angina patients[5] and meta-analysis of emergency room patients[6] suggested a significantly lower incidence of myocardial infarction in those randomized to early CTA.

In 2009, before the above studies were published, investigators at Aarhus University Hospital in Denmark elected to use CTA as their first test for all patients with chest discomfort. Their decision was based on high sensitivity of CTA for detection of any coronary artery disease and concerns for lack of accuracy with stress testing (Bjarne Nørgaard, MD, PhD, personal communication, 2017). In this issue of *JAHA*, Nørgaard et al[9] describe their experience with the incorporation of FFRCT into their clinical pathway for evaluation of patients with stable chest pain. Their study shows 3 different phases of care with CTA as the first test. During the initial phase (May 2013–April 2014), nuclear myocardial perfusion imaging was used as the sole arbitrator for intermediate stenosis on CTA. The second phase (May 2014–December 2014) was an introductory phase to FFRCT with more frequent confirmation by standard invasive FFR. During the third phase (January 2015–December 2015) the goal was to use FFRCT for all intermediate lesions and myocardial perfusion imaging use was limited to inconclusive CTA. FFRCT analysis requires good image quality. FFRCT was performed off-site and results were available within 24 hours. During the study period, there was marked reduction in inconclusive CT studies, from 7% to 4.3%, despite an increase in age and calcium scoring. Overall this study showed that FFRCT was associated with 75% reduction in patients returning for a second noninvasive test and 50% fewer were found to have nonobstructive disease during invasive angiography. Propensity score analysis suggested 4.2% absolute risk reduction for performing invasive angiography with FFRCT, but there was a 14% increase in revascularization compared with the earlier myocardial perfusion imaging phase. Based on the national Danish registry, the overall annual mortality rate was only 0.5% throughout the study period. During 6 months of follow-up, only 8 patients died and of these only 2 had significant coronary artery disease.

This study nicely demonstrates how the precision of patient care is improved with FFRCT, leading to substantial reduction in need for additional imaging tests and fewer "negative" invasive angiograms. These results were expected based on multiple prior studies, but the clinical question remains, do all these patients truly need revascularization?

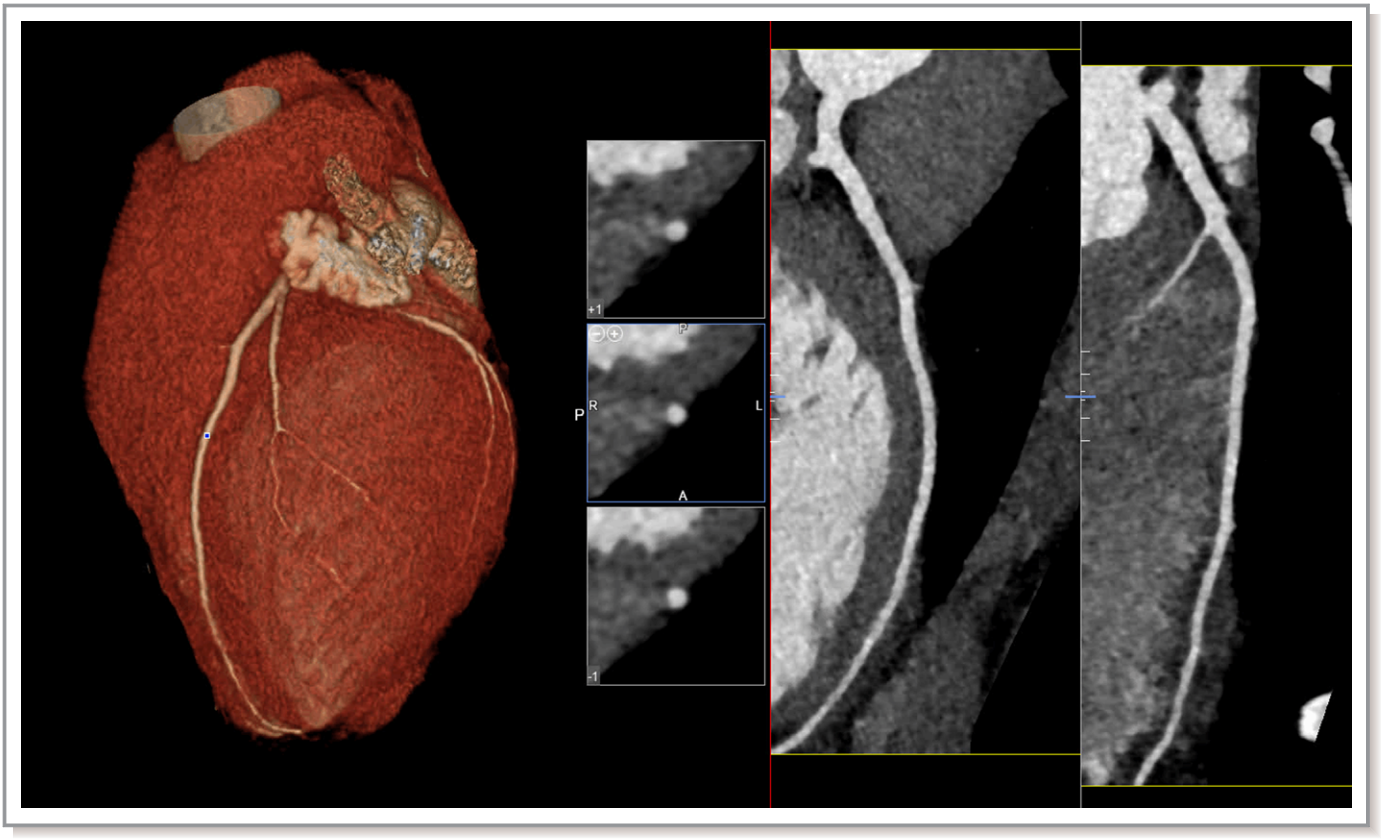

Figure. Radiation exposure on par with mammography. High-quality coronary CTA performed with 40 mL of contrast and effective radiation dose of 0.5 mSv, for individual with heart rate ranging from 45 to 77 beats per minute, weight 85 kg, and BMI 25 kg/m^2 (Courtesy of The University of Iowa Hospital and Clinics). BMI indicates body mass index; CTA, computed tomographic angiography.

Less than one fifth of the subjects had typical angina and there is limited survival benefit with revascularization of those with stable angina. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[10] and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D)[11] trials showed that medical therapy alone was sufficient in stable patients and revascularization could be reserved for patients with refractory angina. Subanalysis of the TACTICS TIMI 18 (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy–Thrombolysis in Myocardial Infarction 18) trial also showed that in those with acute coronary syndrome without elevation of troponin, hence unstable angina, there was no added benefit with revascularization.[12]

Of interest, the Scottish COmputed Tomography of the HEART (SCOT-HEART)[13] trial performed CTA after a patient had completed a treadmill test at a chest pain center. This was an open label randomized study where the other half of the patients only received treadmill testing. Adding the CTA to treadmill testing led to relatively fewer invasive angiograms and revascularization compared with the PROMISE trial in meta-analysis,[5] but there was still significant improvement in the rate of myocardial infarction and death within the CTA arm.[13] This might suggest the need for a prospective randomized study comparing how treadmill testing versus FFRCT can best aid the early CTA strategy.

State-of-the-art technology now allows for CTA with low contrast dose and radiation dose on par with mammography (Figure). Improved technology with higher spatial and temporal resolution allows for analysis of coronary plaque morphology. Positive remodeling of the plaque, low-attenuation areas within the plaque, and spotty calcifications all seem to predict increased risk for future events. Combining plaque morphology with stenosis severity can be a powerful predictor and when both of these features are abnormal, the event rate is high or about 5% per year.[14] Currently no study has assessed the impact of revascularization versus aggressive medical therapy alone in those with high-risk plaque. Aggressive medical therapy could be done with both dual antiplatelet therapy and PCSK9 inhibitors. Dual antiplatelet therapy is effective in unstable angina[15] and might help those with complex plaque. PCSK9 inhibitors might give additional improvement in these higher risk patients.

Mounting data for the benefit of early CTA led to change in the 2016 UK-NICE (United Kingdom - National Institute for Health and Care Excellence) guidelines. CTA is now considered the first-line test for chest discomfort in the United Kingdom, despite lack of facilities for adequate implementation.[16] In the United States, the practice of using CTA first for chest discomfort is limited by institutional availability, physician preference, and individual insurance policies. It seems that functional stress testing still trumps the use of CTA in the United States and is an indirect way to avoid the ever-prevailing oculostenotic reflex.[17] If we continue to use functional stress testing as first test, the greatest benefit of CTA might be limited to patients without indication for aspirin or statin therapy following a "negative" stress test. The 2013 guidelines have lowered the barrier to statin therapy, and this might further reduce the number of patients in whom early CTA changes medical therapy. The use of CTA as an initial test for chest discomfort is associated with fewer heart attacks per meta-analysis and this effect might be due to initiation of medical therapy.[5,6] FFRCT appears to offer improved precision of care with use of fewer resources. Hopefully, in the future, we can also consider CTA as a guide to medical therapy rather than accelerator to coronary stenting.

Disclosures

Dr Sigurdsson is a consultant for Medical Imaging Applications, LLC and owner of Advanced Coronary Calcium Screening, LLC.

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