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, 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. Low diagnostic yield of invasive angiography in general practice calls for better noninvasive risk stratification.

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 have shown how FFRCT analysis improves specificity of intermediate stenosis detected by CTA, even in patients with increased calcium burden.

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. The largest study on this subject was the PROMISE (The Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial. 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, 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 in 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
studies have also associated early CTA use with fewer heart attacks. Both meta-analysis of stable angina patients and meta-analysis of emergency room patients 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 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/m² (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) and Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) 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.

Of interest, the Scottish COnRupted Tomography of the Heart (SCOT-HEART) 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 since the patients only received treadmill testing. Adding the CTA to treadmill testing was an open label randomized study where the other half of the patients had completed a treadmill test at a chest pain center. This randomized study comparing how treadmill testing versus 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. FFRTCT 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.

References

1. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikono F, van’t Veer M, Klauss V, Manoharan G, Engstrom T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF, FAME Study Investigators. Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med. 2009;360:213–224.

2. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, Brindis RG, Douglas PS. Low diagnostic yield of elective coronary angiography. N Engl J Med. 2010;362:886–895.

3. Min JK, Taylor CA, Achenbach S, Koo BK, Leipsic J, Norgaard BL, Pijls NJ, De Bruyne B. Noninvasive fractional flow reserve derived from coronary CT angiography: clinical data and scientific principles. JACC Cardiovasc Imaging. 2015;8:1209–1222.

4. Norgaard BL, Gaur S, Leipsic J, Ito H, Miyoshi T, Park SJ, Ziwiega M, Tzemos N, Jensen JM, Hansson N, Ko B, Bezerra H, Christiansen E, Kaltoft A, Lassen JF, Baltzer HE, Achenbach S. Influence of coronary calcification on the diagnostic performance of CT angiography derived FFR in coronary artery disease: a substudy of the NXT trial. JACC Cardiovasc Imaging. 2015;8:1045–1055.

5. Bittencourt MS, Hulten EA, Murthy VL, Cheezum M, Rochitte CE, Di Carli MF, Blankstein R. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. Circ Cardiovasc Imaging. 2016;9:e004419.

6. Hulten E, Pickett C, Bittencourt MS, Villenes TC, Petritello S, Di Carli MF, Blankstein R. Outcomes after coronary computed tomography angiography in the emergency department: a systematic review and meta-analysis of randomized, controlled trials. J Am Coll Cardiol. 2013;61:880–892.

7. Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, Cole J, Dolor RJ, Fordyce CB, Huang M, Khan MA, Kosiinski AS, Krucoff MW, Malhotra V, Picard MH, Udelson JE, Velazquez EJ, Yow E, Cooper LS, Lee KL, PROMISE Investigators. Outcomes of anatomical versus functional testing for coronary artery disease. N Engl J Med. 2015;372:1291–1300.

8. Becker MC, Galla JM, Nissen SE. Left main trunk coronary artery dissection as a consequence of inaccurate coronary computed tomographic angiography. Arch Intern Med. 2011;171:698–701.

9. Norgaard B, Gormsen L, Botker HA, Parner E, Nielsen L, Mathiasen O, Grove E, Ørvehus K, Gaur S, Leipsic J, Pedersen K, Terkelsen CJ, Christiansen E, Kaltoft A, Maen M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz Khan S. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. Circ Cardiovasc Imaging. 2016;9:e004419.

10. Boden WE, O’Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, Knudtson M, Dada M, Casperson P, Harris CL, Chaitman BR, Shaw L, Gosselin G, Nawaz Khan S. Clinical outcomes after evaluation of stable chest pain by coronary computed tomographic angiography versus usual care: a meta-analysis. Circ Cardiovasc Imaging. 2016;9:e004419.

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S, Title LM, Gau G, Blaustein AS, Booth DC, Bates ER, Spertus JA, Berman DS, Mancini GB, Weintraub WS; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.

11. BARI 2D Study Group, Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, Orchard TJ, Chatman BR, Genuth SM, Goldberg SH, Hlatky MA, Jones TL, Molitch ME, Nesto RW, Sako EY, Sobel BE. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360:2503–2515.

12. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, Neumann FJ, Robertson DH, DeLucca PT, DiBattiste PM, Gibson CM, Braunwald E; TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)-Thrombolysis in Myocardial Infarction 18 Investigators. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879–1887.

13. Williams MC, Hunter A, Shah AS, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J, McLean S, Roditi G, van Beek EJ, Timmis AD, Newby DE; SCOT-HEART Investigators. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67:1759–1768.

14. Yamamoto H, Kitagawa T, Ohashi N, Utsunomiya H, Kunita E, Oka T, Urabe Y, Tsushima H, Awai K, Kihara Y. Noncalcified atherosclerotic lesions with vulnerable characteristics detected by coronary CT angiography and future coronary events. *J Cardiovasc Comput Tomogr*. 2013;7:192–199.

15. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494–502.

16. Moss AJ, Williams MC, Newby DE, Nicol ED. The updated NICE guidelines: cardiac CT as the first-line test for coronary artery disease. *Curr Cardiovasc Imaging Rep*. 2017;10:15.

17. Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation*. 1995;92:2333–2342.

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