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EDITORIAL COMMENT

The Dye Don't Lie But May Not Tell the Truth

Combining Coronary Computed Tomography Angiography With Myocardial Perfusion Imaging*

Kelley R. Branch, MD, MSc,[a] Christian Hamilton-Craig, MBBS, PhD, BMedSci(Hons)[b]

Coronary computed tomography angiography (CTA) is well known to have high sensitivity and negative predictive value to rule out anatomic coronary artery disease, but can have a relatively low specificity to detect obstructive coronary disease and ischemia (1). Accurate predictions of physiologic myocardial blood flow determined on the basis of anatomic coronary artery stenosis, be it from coronary CTA or from invasive coronary angiography, have been in a quandary for decades. Numerous previous studies have shown only an average correlation between angiographic stenosis and measures of ischemia such as myocardial perfusion imaging (MPI) assessments with positron emission tomography (PET), cardiac magnetic resonance (CMR), or invasive fractional flow reserve (FFR) (2-4). Despite this finding, angiographic stenosis evaluation remains the most common decision point for whether a patient receives further study or treatment. Thus, contrast dye does not lie with regard to the presence of coronary stenosis, but it is then challenged to identify myocardial ischemia.

In many cases, especially in patients with intermediate (50% to 70%) coronary stenosis, functional myocardial blood flow evaluation is performed to identify myocardial ischemia and determine whether treatment such as revascularization would be salutary (5). Most commonly, MPI using nuclear radiotracers or contrast enhancement with CMR is performed. In this issue of *iJACC,* Rizvi et al. (6) provide an excellent systematic review of the combined use of CTA and various MPI techniques. Not surprisingly, coronary CTA performed well, with high per-patient sensitivity at levels nearly identical to those of combined coronary CTA and MPI. At the per-vessel level, coronary CTA outperformed MPI; the finding that an anatomic study effectively "ruled out" obstructive coronary artery stenosis may not be surprising. Thus, in a patient with a negative coronary CTA test result, no further testing is generally needed. This is a primary reason that National Institute for Health and Care Excellence guidelines (7) placed coronary CTA as the first-line test in low- to intermediate-risk patients. However, when coronary CTA was used for the detection of coronary artery disease, the specificity (66%) was modest and rendered coronary CTA findings of "obstructive" coronary stenosis clinically uncertain. The addition of MPI with either stress nuclear scanning or CMR significantly improved the per-patient specificity to 93%, with an absolute 17% or 10% improvement over solitary coronary CTA or MPI, respectively. These data are important and in many ways replicate contemporary cardiovascular care. By reducing the false-positive rate to improve specificity, anti-ischemic therapies and revascularization are applied with a higher degree of certainty to improve patients' outcomes. The present meta-analysis by Rizvi et al. (6) lends further validation to this approach.

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However, Rizvi et al. (6) correctly point out that the incremental benefit of adding functional MPI to anatomic coronary CTA information is not as robust as expected. There can be various reasons for these findings, some of which are noted by Rizvi et al. (6). First, the gold standard for measurement of

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From the [a]Division of Cardiology, University of Washington, Seattle, Washington; and the [b]Division of Cardiology, University of Queensland, Brisbane, Australia. Dr. Branch has received research grants from the National Institutes of Health, Astellas, and Bayer; and is on the Advisory Board of Janssen. Dr. Hamilton-Craig has received research grants from Siemens.

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myocardial ischemia in humans is arguably invasive FFR. In the current study, invasive quantitative coronary angiography was used the imaging standard, and this anatomic-only evaluation likely led to misclassification of ischemia (8). Using this "bronze" standard for ischemia is a critical limitation of the study, as pointed out by Rizvi et al. (6). Second, Rizvi et al. (6) also correctly point out that the patient sample size was small, a feature that blunts statistical power, causes wide confidence intervals, and may result in type II errors. Third, analyzed studies dated back over 15 years, and older MPI and coronary CTA studies did not benefit from the significant technical improvements over the past decade and a half. Higher nonevaluable coronary CTA coronary segments or equivocal MPI segments resulting from artifacts with older technology most certainly attenuated accuracy measures. Fourth, MPI strategies in the meta-analysis by Rizvi et al. (6) predominantly consisted of vasodilator stress, which has various limitations to exercise MPI testing, and stress echocardiography could not be included in the present meta-analysis. Finally, heterogeneity among the analyzed studies can alter results both positively and negatively. Importantly, the degree of heterogeneity in the study by Rizvi et al. (6) suggests that the meta-analytic results should be interpreted with some caution.

There are additional limitations with the combined coronary CTA and MPI approach. Clinical use of separate MPI and coronary CTA adds inconvenience for patients, with separate-day testing, expense, risk from stress testing, and considerable radiation (in the case of nuclear imaging). Given the robust data on invasive FFR to determine cardiac intervention, an argument could be made for proceeding to invasive angiography with determination of lesion-specific ischemia by using FFR in patients with intermediate- to high-grade coronary CTA stenosis (9). However, this issue is irrelevant in cardiac catheterization laboratories that do not routinely use FFR throughout the range of stenoses that may or may not be ischemic. Fervent belief in the dye may propagate a lie in some patients.

Competition is also growing from new functional strategies that do not require patients to leave the CT suite. CT-specific technologies of CT-based MPI and FFR using CT images (FFR_{CT}) have shown improvements in diagnostic accuracy measures similar to those of the presented hybrid techniques. CT myocardial perfusion (CTP) is an emerging modality that replicates MPI techniques and may provide information similar to that of current hybrid measures. Recent meta-analytic data, using invasive FFR as the standard, measured stress CTP patient- and vessel-level specificity at 87% and 86%, respectively, and a diagnostic odds ratio similar to those of CMR and PET but higher than single-photon emission CT and echocardiography (10). Although these data are compelling, they are typically measured in isolation and are not combined with coronary CTA data. Combined functional and anatomic data are expected to improve diagnostic measures further, although larger studies, as well as meta-analysis similar to that of Rizvi et al. (6), are needed.

Another competitor of MPI is FFR_{CT}, which uses existing CT images to model myocardial blood flow primarily on the basis of coronary CTA anatomy to estimate the presence of ischemia. In a recent meta-analysis using invasive FFR as the gold standard, FFR_{CT} showed per-patient and per-vessel improvement in specificity to 71% and 83% over coronary CTA-only specificities of 39% and 58%, respectively (8). The FFR_{CT} overall specificity was similar to that of single-photon emission CT and even invasive angiography, but these specificities were all lower than that of CMR (94% and 85%, respectively). Diagnostic accuracy, as measured by diagnostic odds ratio, was highest for FFR_{CT} and CMR, but as Rizvi et al. (6) correctly point out, clinical use of FFR_{CT} is constrained by access and cost limitations.

What does it all mean? Most cardiologists routinely use combination or hybrid testing in clinical practice, but there have been hitherto minimal large-scale data to demonstrate the efficacy of this strategy. Data from Rizvi et al. (6) support this intuitive approach and guideline-based strategies. Future approaches may involve single-test hybrid approaches or more sophisticated combination cardiac testing to optimize evaluation of both anatomy and function.

ADDRESS FOR CORRESPONDENCE: Dr. Kelley R. Branch, Division of Cardiology, University of Washington, Box 356422/Cardiology, 1959 NE Pacific Street, Seattle, Washington 98195. E-mail: kbranch@u.washington.edu.

REFERENCES

1. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol 2008;52:1724–32.

2. Bartúnek J, Sys SU, Heyndrickx GR, Pijls NHJ, De Bruyne B. Quantitative coronary angiography in predicting functional significance of stenoses in an unselected patient cohort. J Am Coll Cardiol 1995; 26:328–34.

3. Chamuleau SAJ, Meuwissen M, Koch KT, et al. Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate stenosis. Am J Cardiol 2002;89:377–80.

4. Heller LI, Cates C, Popma J, et al. Intracoronary Doppler assessment of moderate coronary artery disease: comparison with [201]-Tl imaging and coronary angiography. Circulation 1997;96:484–90.

5. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol 2014;64:1929–49.

6. Rizvi A, Han D, Danad I, et al. Diagnostic performance of hybrid cardiac imaging methods for assessment of obstructive coronary artery disease compared with stand-alone coronary computed tomography angiography: a meta-analysis. J Am Coll Cardiol Img 2018;11:589–99.

7. National Institute for Health and Care Excellence (NICE). Chest Pain of Recent Onset: Assessment and Diagnosis of Recent Onset Chest Pain or Discomfort of Suspected Cardiac Origin. Clinical guideline CG95. London, UK: NICE; 2016.

8. Danad I, Szymonifka J, Twisk JW, et al. Diagnostic performance of cardiac imaging methods to diagnose ischaemia-causing coronary artery disease when directly compared with fractional flow reserve as a reference standard: a meta-analysis. Eur Heart J 2017;38:991–8.

9. De Bruyne B, Pijls NH, Kalesan B, et al. Fractional flow reserve-guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991–1001.

10. Takx RA, Blomberg BA, El Aidi H, et al. Diagnostic accuracy of stress myocardial perfusion imaging compared to invasive coronary angiography with fractional flow reserve meta-analysis. Circ Cardiovasc Imaging 2015;8:e002666.

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