Primum non nocere…

James K. Min, MD[a]

[a] Weill Cornell Medicine, NewYork-Presbyterian, Dalio Institute of Cardiovascular Imaging, New York, NY

Received Aug 26, 2015; accepted Aug 27, 2015
doi:10.1007/s12350-015-0289-y

See related article, pp. 212–223

Over the course of the last 10 years, there has been much discussion about the use of ''functional'' versus ''anatomic'' imaging.[1,2] An array of modalities allow for assessment of either, with functional assessment of hemodynamically significant coronary artery disease (CAD) achievable through single-photon emission computed tomography (SPECT), cardiac magnetic resonance (CMR) imaging, or stress echocardiography (SE). Each of these modalities evaluates CAD in a slightly different fashion, with SPECT evaluating myocardial perfusion, CMR allowing for evaluation of both transmural and subendocardial perfusion, and SE enabling discrimination of stress-induced regional wall motion abnormalities.[3] These approaches focus on different points in the ischemic cascade but SPECT is performed most commonly. In contrast, anatomic imaging methods focus primarily on the use of computed tomography (CT), either by coronary artery calcium scoring (CACS) or coronary CT angiography (CCTA). Some have argued and evaluated the potential of hybrid imaging wherein a functional method is performed simultaneously with an anatomic method, in an effort to achieve the ''one stop shop'' evaluation of CAD.[4] Yet others have been dismissing this approach, given its generally higher radiation dose required.

In this issue of the *Journal*, Engbers et al take another approach to a selective hybrid imaging strategy wherein a prescribed workflow was prospectively performed for individuals with suspected CAD, while attempting to reduce the effective biological radiation doses.[5] They did so by initial performance of stress-only SPECT and CACS, followed by rest SPECT and CCTA, if feasible. Enrolling more than 5000 patients, stress-only SPECT was the only imaging study needed in more than half of the study population. Among the 48% of patients in whom stress-only SPECT was not sufficient, more than half could not undergo CCTA due to common CCTA limitations, chiefly due to severe CACS or fast and irregular heart rates. The authors noted a nearly 2/3 lower radiation dose in those requiring stress-only SPECT without further imaging.

These data presented by Engbers highlight several important issues, particularly related to safety. In recent years, stress-only SPECT has emerged as an effective method for exclusion of functionally significant CAD and, if normal, mitigates the need for rest SPECT evaluation. This method reduces the radiation dose to the patient by half. What is not as commonly practice (or espoused) is the simultaneous performance of CACS at the time of SPECT, which has been demonstrated to improve both diagnosis and prognosis of individuals undergoing stress imaging. Thus, the approach by Engbers—while not ubiquitously practiced—represents one in which safety comes first under a backdrop of parsimonious and judicious use of testing, with effective prognostic utility by both perfusion defects as well as CACS.

Interestingly, in the present study, among those individuals undergoing rest in addition to stress SPECT, perfusion was considered normal in half of the population, resulting in a normal stress test in more than 3/4 of the overall study cohort. Among the remaining, approximately 1 of 4 patients had equivocal defects, 1 of 3 patients had fixed defects, and 2 of 5 patients demonstrating ischemia. Despite this generally high prevalence of ischemia and fixed defects, the median CACS was only 39, suggesting an overall anatomically low coronary artery plaque burden. Yet the interquartile range of the CACS ranged from 0 to 282, with 20% exhibiting a CACS of >400.

Reprint requests: James K. Min, MD, Weill Cornell Medicine, NewYork-Presbyterian, Dalio Institute of Cardiovascular Imaging, 413 East 69th Street, Suite 108, New York, NY 10021; *jkm2001@med.cornell.edu*

J Nucl Cardiol 2017;24:224–5.
1071-3581/$34.00

Among individuals undergoing CCTA, approximately one-third demonstrated significant disease, with two-thirds requiring no further testing. Perhaps of equal import, CCTA could exclude 80% of patients from obstructive CAD when the stress test was considered normal, and 60% of patients for whom the stress test was considered abnormal. In this population, the normalcy rate of SPECT was 87% and the combination of SPECT and CCTA allowed for a normal final diagnosis in 83%. While these data appear generally high, they are consistent with present practice at other centers.

This diagnostic approach was associated with an enhanced and more precise ability to prognosticate imaging findings to future death and non-fatal myocardial infarction (MI), with increasing annual event rates for abnormal SPECT/normal CCTA (0.85%), normal SPECT/abnormal CCTA (1.64%), and abnormal SPECT/abnormal CCTA (2.15%).

The array of data presented by the authors represents important diagnostic and prognostic considerations at each step of the diagnostic pathway and it generate hypotheses of the optimal workflow of patients with suspected CAD. Further, numerous questions remain and limit, to some extent, the generalizability of these findings as an optimal pathway for diagnosis of CAD. First, the performance of CACS is not routinely performed in clinical practice settings, and the use of CACS by Engbers reflects their advanced understanding and expert protocols at their center.[6] Second, many have posited that SPECT may not be the ideal first-line test for patients with suspected CAD, given that a normal SPECT does not preclude the need for further assessment and that, in this study even among those considered as needing CCTA after SPECT, 60%-80% manifested no significant anatomic CAD. As such, whether SPECT first or CCTA first is a better strategy remains to be further understood.

Also, in recent past, numerous data have emerged as to the oversimplification of tests as ''abnormal'' vs ''normal,'' or ''obstructive'' vs ''non-obstructive.'' Indeed, there are many nuances for SPECT beyond whether a test is ''abnormal'' or not, including electrocardiographic findings, functional capacity, and other high-risk markers, such as pulmonary uptake of radiotracer and transient ischemic dilatation.[7] Similarly for CCTA, numerous other markers of risk and ischemia exist, including rest myocardial perfusion, plaque morphology and type, measures of arterial remodeling and most recently, fractional flow reserve derived non-invasively from a typically acquired CCTA.[1] As such, the ongoing CREDENCE trial (NCT02173275)—which is testing directly all of these parameters for SPECT versus CCTA—will add to the information gain by the present article.

Germane to the discussion of ''abnormal'' versus ''normal,'' the authors used a summed difference score of ≥ 2 as the cutoff of what is an ''abnormal'' SPECT. Indeed, prior data would suggest no mortality benefit—and potential harm—from referral to revascularization of more mild perfusion defects.[8] Thus, perhaps what is more relevant is the demonstration of at least moderate or severe ischemia in order to guide decisions of revascularization, a concept which is currently being tested in the ISCHEMIA trial (NCT01471522).

Nevertheless, despite these considerations—which are not limitations but rather only other factors to consider—the data by Engbers et al significantly add to the present scientific literature. In a logical approach, they demonstrated an enhanced ability to both diagnose and prognosticate CAD by a reduced radiation dose conferring method which could mitigate the need for nearly two-thirds of the radiation dose associated with more ''comprehensive'' testing. The authors should be lauded for the careful thought they have put into the development of such an approach. They have demonstrated that we, as a field, can ''first, do no harm,'' and gain the better for it.[9]

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