Coronary computed tomographic angiography and exercise electrocardiography: a great match or unequal partners?

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This editorial refers to ‘Adjunctive value of CT coronary angiography in the diagnostic work-up of patients with typical angina pectoris’ by N.R. Mollet et al., on page 1872

Coronary computed tomographic angiography (CCTA) is emerging as a powerful non-invasive tool in the diagnosis of coronary artery disease (CAD). However, there is concern that CCTA is being used indiscriminately without sufficient examination of its added value vis-à-vis more established forms of non-invasive testing.1 With an ever-growing armament of non-invasive tests for the diagnosis and evaluation of CAD, cardiologists must consider the following questions in weighing up the implementation of a new diagnostic modality in the routine clinical setting. Is testing necessary for the diagnosis of CAD in a particular patient group? Will testing guide management decisions and identify patients who may benefit from coronary revascularization? Will the benefits of testing outweigh its potential risks?

The study by Mollet et al.2 provides important insights into the relationship between the findings of CCTA and conventional treadmill exercise electrocardiography (ECG), but also raises important issues regarding the role of both tests in the diagnosis of CAD. The authors examined, in 62 patients with typical angina pectoris, the diagnostic value of exercise ECG and 16-slice multidetector CCTA, alone and in combination, to predict ≥50% diameter stenoses detected on invasive, selective coronary angiography (SCA) in any coronary artery branch with a calibre of ≥2 mm. Exercise ECG data from 53 patients and CCTA data from 61 patients were included in the analyses. The sensitivity of exercise ECG was 78%, specificity was 67%, and positive and negative predictive values were 89 and 47%, respectively. The sensitivity of CCTA was 100%, specificity was 87%, and positive and negative predictive values were 96 and 100%, respectively. In an analysis based on Bayesian principles, an abnormal CCTA increased the post-test probability of significant CAD after a positive exercise ECG from 89 to 99% and after a negative exercise ECG from 58 to 91%. A normal CCTA reduced the post-test probability of significant CAD after a negative or a positive exercise ECG to 0%.

Clearly, 16-slice multidetector CCTA has very high sensitivity and negative predictive value, and is an accurate non-invasive test for excluding obstructive CAD even in a population with high pre-test likelihood. These findings are in agreement with those of other studies that examined the value of CCTA in lower-likelihood populations.3 Likewise, the specificity and positive predictive value of CCTA in the current study are similar to those reported in other patient populations.3

The diagnostic accuracy of exercise ECG in this high-likelihood cohort is in keeping with other studies reported in the literature4 and further emphasizes the rigorous methodology and competent execution of the current study. Other notable strengths of the study include the careful classification of patients into risk categories based on clinical predictors and the Bayesian analysis of the test results. The use of quantitative coronary angiography to measure the degree of coronary luminal narrowing reduces uncertainties related to the interobserver variability of visually estimating stenosis severity.

Based on the discordant diagnostic accuracy of exercise ECG and CCTA and their Bayesian analysis of post-test probabilities, the authors conclude that exercise ECG is of limited diagnostic value for the detection of significant CAD and that a diagnostic work-up that combines exercise ECG and CCTA markedly improved the post-test probability of the presence or absence of significant CAD. These conclusions invite a discussion of the questions raised in the first paragraph of this editorial.

Appropriate use and predictive value of non-invasive testing

Which patients should undergo CCTA for the diagnosis of CAD? To answer this question, it is important to examine...
the evidence base for the use of exercise ECG. The diagnostic power of exercise ECG is greatest when the pre-test probability of CAD is intermediate. In the current patient cohort, the pre-test likelihood of CAD, estimated on the basis of clinical characteristics, was 81%. A high pre-test likelihood in this range should be sufficient to establish a diagnosis of CAD. A positive test result will therefore only be confirmatory. On the other hand, a negative result may confuse rather than clarify the picture depending on the performance characteristics of the test. For example, in the current study, a negative exercise ECG transformed a high pre-test likelihood into an intermediate post-test likelihood. Consequently, the current 2002 guideline update for exercise testing issued jointly by the American College of Cardiology (ACC) and the American Heart Association (AHA) lists high pre-test probability of significant CAD among the conditions for which the usefulness and efficacy of exercise ECG to diagnose obstructive CAD are not well established by evidence or opinion (Class IIb indication).

Given the high diagnostic accuracy of CCTA reported in this study and others, further studies are warranted to determine how CCTA will fit into the established diagnostic algorithms in high-likelihood patients.

Can CCTA guide management decisions and identify patients who may benefit from coronary revascularization? The markers of poor prognosis on exercise ECG are well established, and patients with high-risk features should be referred for invasive SCA. Based on findings of randomized studies and large registries, patients with high-risk anatomy on SCA, such as left main and multivessel CAD in the presence of normal left ventricular function, may derive survival benefit from surgical revascularization. Current ACCF/AHA guidelines therefore consider exercise ECG useful in patients with a high pre-test likelihood to estimate prognosis and to guide therapy.

Studies examining the prognostic value of CCTA in various patient subgroups are only just now beginning to emerge. Because CCTA and SCA show very high concordance, it is tempting to assume that CCTA can allow therapeutic decision making similar or superior to SCA or exercise ECG. However, no studies to date support the notion that CCTA can replace SCA. Hence, choosing between testing strategies based on the findings of CCTA performed alone or in combination with stress testing is cost-effective or improves outcomes in any patient group. The appropriateness of any non-invasive diagnostic strategy is determined in large part by its prognostic benefit, and the need to assess the prognostic value of CCTA provides exciting prospects for designing future clinical trials.

Large-scale multicentre randomized trials such as the recently published Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial have not included the use of CCTA in their management algorithms. In the COURAGE trial, where most patients had stable angina, multivessel CAD (excluding left main coronary artery diameter stenoses >50%), and preserved left ventricular function, the rates of myocardial infarction and death were not significantly different in patients who underwent catheter-based percutaneous revascularization in addition to optimal medical therapy from those in patients who received optimal medical therapy alone. These findings will probably lead to changes in practice guidelines and the management of patients with stable angina. In such patients, the diagnostic focus may shift away from the identification of individual coronary artery stenoses, with a goal of catheter-based percutaneous revascularization, towards the exclusion of high-risk anatomy such as left main CAD. Given the high diagnostic accuracy of CCTA, particularly in large-calibre coronary segments, CCTA could potentially play a role in such new management strategies. On the other hand, however, based on the findings of the COURAGE trial, in the absence of left ventricular dysfunction, detection of CAD by CCTA other than left main CAD should not automatically prompt an invasive diagnostic strategy.

Anatomy vs. function: competing or complementary?

The current article by Mollet et al. also offers an opportunity to revisit the difficult yet important question of what constitutes ‘significant’ coronary artery stenoses. There are two fundamentally different approaches to assess CAD, functional and anatomical. From a functional perspective, a haemodynamically significant coronary stenosis renders coronary blood flow inadequate to meet the metabolic requirements of the dependent myocardium at rest or during stress, or both. This condition is referred to as reduced coronary flow reserve. However, which morphological features on anatomic imaging such as SCA or CCTA are associated with a trans-stenotic gradient is controversial. There is general consensus that coronary artery stenoses exceeding 70–75% of the reference diameter are likely to be haemodynamically significant and may warrant coronary revascularization. However, in the presence of ‘borderline coronary stenoses (50–60% diameter in locations other than the left main coronary artery)’, choosing coronary revascularization as a therapeutic strategy is supported by evidence only if there is ‘demonstrable ischemia on non-invasive testing’. The reason for this stipulation in the ACCF/AHA guidelines is that luminal diameter stenoses between 50 and 70% may not reduce coronary flow reserve as consistently as stenoses of >70%. Correlative clinical studies between invasive, selective angiography and exercise ECG have therefore been divided on the use of 50 or 70% luminal narrowing to define significant stenosis. While studies comparing CCTA with SCA have generally considered 50% diameter stenoses as ‘significant’, this criterion may not be ideally suited for comparing anatomical and functional testing for the detection of CAD. The discordance in diagnostic accuracy between functional testing and CCTA results in the current study and others is therefore not unexpected.

Is there a role for complementary non-invasive functional and anatomical assessment? Preliminary studies of integrated hybrid imaging combining CCTA and myocardial perfusion imaging for the assessment of CAD have demonstrated promising results, but the potential benefits must be weighed against the substantial radiation exposure. Prospective studies, such as the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD (SPARC) registry, that are designed to determine the prognostic value, cost-effectiveness, and associated risks of CCTA, hybrid imaging, single-photon emission tomography, and positron emission tomography, are ongoing and
will hopefully help define their role and value in the diagnostic work-up of patients suspected of having CAD.

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References