

Editorial

Endless Validation of Diagnostic Imaging Modalities to Assess Acute Coronary Syndrome: Has the Time Finally Come for Computed Tomography Angiography?



La interminable validación de las técnicas de imagen diagnósticas para evaluar el síndrome coronario agudo: ¿ha llegado finalmente la hora de la angiografía por tomografía computarizada?

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Acute chest pain as a presenting syndrome in the emergency department is by far one of the most prevalent worldwide. Validation of several diagnostic-imaging modalities for this syndrome has been the focus of several research groups over the last 3 decades. Unfortunately, from the simple and inexpensive exercise stress electrocardiography to the most advanced and complex tests such as positron emission tomography, cardiac computed tomography angiography (CTA), and magnetic resonance angiography, no imaging modality has been successfully validated to be the “reference standard” for this purpose. The difficulties start with the study methodology described in the manuscripts published to date. Designing a study to assess the diagnostic accuracy of a test in clinical practice can be cumbersome and problematic. First of all, the vast majority of studies have several recurrent limitations, most notably “differential verification bias” and “review bias.” This basically means that the index test results are verified by a different gold standard test. In this scenario, those patients with a positive noninvasive imaging test result will receive verification by one reference standard (ie, coronary angiography) whereas those with a negative test result will be discharged and followed up for the occurrence of major cardiovascular events. Conducting a study in which all patients undergo coronary angiography would require subjecting a large number of subjects to more than minimal risk simply for research purposes and would be considered unethical. Since only those patients with a positive noninvasive test result undergo cardiac catheterization, a “review bias” is introduced, leading to inflated measures of diagnostic accuracy because the analysis of the reference standard is influenced by knowledge of the results of the index test. Second, comparison of performance characteristics for different noninvasive tests has been attempted

mostly in different patient series. Head-to-head comparisons of 2 or more diagnostic tests on the same patient population are difficult to carry out due to cost and time considerations. Since relative contraindications vary for different tests (e.g., atrial fibrillation and renal insufficiency for CTA), the populations studied by different imaging modalities most likely carry different baseline characteristics, making these comparisons flawed. Additionally, the reference standard for all these studies has long been cardiac angiography, which only delineates luminal coronary anatomy but does not provide any meaningful information with respect to functional and hemodynamic characteristics of each lesion unless fractional flow reserve is performed. Consequently, estimates of the performance of a diagnostic test are based on the assumption that these tests are being compared to a reference standard, which is not always equivalent to a clinical outcome.¹

In the article published in *Revista Española de Cardiología*, Mas-Stachurska et al.² present a prospective study of the value of different diagnostic strategies using CTA and exercise stress echocardiography (SE). Their study overcomes one of the aforementioned limitations as they performed both diagnostic studies on each enrolled patient in order to be able to do head-to-head comparisons. An abnormal exercise SE was defined as the presence of segmental wall-motion abnormalities at baseline or when induced by exercise in at least 2 adjacent segments, whereas an abnormal CTA was defined as presence of luminal area stenosis > 50% in at least one coronary segment. In the Mas-Stachurska et al. study, CTA provided a higher sensitivity than exercise SE, whereas the latter provided higher specificity. By increasing the cut-off to diagnose a significant coronary lesion to > 70%, CTA increased its specificity to 88.4%, similar to SE, while maintaining a sensitivity of 100%. Although the present study has some of the pitfalls we previously mentioned, such as verification and review biases, it provides evidence that reinforces the utility of both CTA and SE and validates both technologies as equivalent alternatives for the assessment of chest pain in patients with intermediate risk of acute coronary syndrome.

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It is well established that CTA offers several advantages, given the fact that it allows detection of subclinical coronary atherosclerosis, therefore potentially identifying patients who may benefit from more intensive preventive strategies. It can also simultaneously rule out other life-threatening causes of chest pain (eg, aortic dissection, pulmonary embolism) and it is currently feasible to obtain in most centers, requiring less-intensive technical supervision. Several studies have demonstrated that CTA has very high sensitivity and negative predictive values, which corroborates its utility as a screening tool, particularly in the emergency department. However, specificity and positive predictive values differ greatly between studies. Our group recently performed a comprehensive meta-analysis comparing CTA (15 studies), exercise or dobutamine SE (9 studies), and single-photon emission computed tomography (13 studies), comprising a total of 7800 patients.³ All 3 modalities provided excellent negative predictive values. Nonetheless, CTA provided significantly higher sensitivity, specificity, and positive predictive values. Although these numbers seem to be sufficient to adopt CTA as the first and preferred approach to assess patients with chest pain, CTA has been heavily criticized, primarily because it is simply an anatomic test that lacks physiologic data. With this premise, CTA might in fact overdiagnose coronary artery disease, and even when these findings are corroborated by coronary angiography, the coronary stenosis might not be the actual cause of the patient's chest pain. In addition, patients undergoing CTA have higher rates of revascularization but have not been shown to have superior clinical outcomes.

To overcome some of the limitations of CTA, several investigators have proposed the use of a noninvasive estimation of fractional flow reserve to determine whether or not any particular obstructive coronary lesion may be causing myocardial ischemia.⁴ To date, 3 prospective studies (DISCOVER-FLOW, DeFACTO and NXT)⁵⁻⁷ have tried to determine the diagnostic performance of this technique when compared with fractional flow reserve measured during invasive coronary angiography, which has become the reference standard for lesion-specific coronary revascularization in the last decade. As of today, the results of these studies have been inconclusive and this methodology has not been validated for clinical purposes. Myocardial perfusion computed tomography imaging using vasodilator stress is another proposed method that might provide complementary information to the coronary angiographic analysis.⁸ More recently, a study that compared a combination of CTA and adenosine stress computed tomography perfusion to invasive fractional flow reserve coronary angiography demonstrated a marked improvement in diagnostic accuracy.⁹

Similarly, exposure to ionizing radiation –which not long ago was a significant disadvantage of the retrospective ECG-gated helical CTA technique– has been reduced up to 80% with the use of prospective ECG-gating.¹⁰ A recent study demonstrated that prospective, ECG-triggered, high-pitch spiral coronary CTA can be successfully performed with less than 1.0 mSv of radiation in nonobese patients (< 85 kg) with a low and stable heart rate.¹¹ These results are very encouraging and give CTA an advantage over myocardial perfusion imaging by single-photon emission computed tomography, one of the most frequently used tests for evaluation of patients with chest pain in emergency departments in the United States.

In all fairness, despite all the advancements in protocols and techniques to increase its diagnostic accuracy, CTA still might not be appropriate for a significant number of patients. Irregular rhythms and high heart rates can interfere with ECG-gating image acquisition. Significantly high coronary calcium scores, particularly in elderly patients, might be challenging because stenoses are

most often overestimated due to blooming artifact. Last but not least, the presence of diabetes and/or moderate to significant renal dysfunction puts patients at risk of contrast-induced nephropathy. These risks will potentially increase if patients ultimately undergo coronary angiography and revascularization, with the additional radiation and contrast media doses. Exercise or dobutamine SE is thus an alternative to CTA when CTA is contraindicated or unavailable. As shown by the authors², exercise SE has acceptable sensitivity and specificity similar to CTA. It evaluates functional impairment, as opposed to the anatomical burden of coronary artery disease, and indeed has some benefits over CTA. First, it is in most cases less expensive than CTA. Second, SE avoids exposure to radiation and iodinated contrast. Nonetheless, it also has drawbacks. There is the concern that stressing a patient with a possible acute coronary syndrome may increase myocardial necrosis or induce arrhythmias. Recent administration of beta-blockers reduces the diagnostic accuracy of this test, which is a disadvantage for many patients in the emergency department. False positives may result from hypertensive responses, underlying conduction abnormalities, or cardiomyopathies.¹²

In reality, missed diagnoses and failure to admit patients at risk of myocardial infarction carries a high social and medico-legal impact. Conversely, admitting the vast majority of these patients who do not require hospitalization represents a major burden to the health system.¹³ This is exactly why we will keep trying to find and validate the perfect diagnostic test for the assessment of these patients.

CONFLICTS OF INTEREST

None declared.

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