Low diagnostic yield of coronary angiography or not catching up with heart disease pathophysiology?

Alda Huqi
Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Pisa, Italy

Correspondence: Dr Alda Huqi, Cardiovascular Medicine Division, Cardio Thoracic Department, University of Pisa, Via Paradisa, 2 56100 Pisa, Italy.
Tel: +39 32972 56426; e-mail: alda_h@hotmail.com

Fifty years after its introduction, coronary angiography remains the reference technique to assess coronary anatomy. Its impact on the diagnosis and management of ischemic heart disease (IHD) is corroborated by the fact that coronary angiography is still essential for aortocoronary bypass grafting and for percutaneous coronary interventions.

Given the invasiveness and the measurable risk associated with coronary angiography, noninvasive tests are widely used to select candidates for angiography and for therapy planning. The large majority of the noninvasive tests are focused on ischemia detection and left ventricular (LV) function assessment. Latest additions are more focused on coronary anatomy. In the early phase of application, all tests were extensively compared with coronary angiography as the gold standard and achieved reasonable sensitivity, specificity, and overall diagnostic accuracy. Heated debates and large trials have addressed the question of which test is the best, but final conclusions have not yet been reached and probably will never be. The main reasons for this are inconsistencies in the results of different tests in the same patient and the common assumption that coronary stenosis always implies myocardial ischemia. The frequent mismatch between noninvasive tests and coronary anatomy are justified by generic inaccuracies of the noninvasive tools or inaccurate measurement of stenosis severity.

Recently, a study with a catchy title— ''Low diagnostic yield of coronary angiography'' [1]— was published in the *New England Journal of Medicine*. Data were obtained from a large cardiac-catheterization registry to assess the effectiveness of current practices in enhancing the yield of diagnostic cardiac catheterization as measured by the prevalence of obstructive coronary artery disease (CAD). The study enrolled 397,954 patients without known CAD undergoing cardiac catheterization and noninvasive testing was performed in 83.9% of them. A positive test result was recorded in 68.6% of all the patients in the cohort. Surprisingly enough, only a minority of patients (37.6%) had obstructive CAD. Patients with higher Framingham Risk Score (FRS) were more likely to have obstructive CAD, but the results of the noninvasive testing had a limited additive value for presence of obstructive CAD. In light of such results, the authors concluded that ''better strategies for risk stratification, in order to increase the diagnostic yield of cardiac catheterization are needed.''

The claim that there is ''a need for better strategies to risk stratify patients'' represents just another coupler in the scaffold around the rising use of cardiac imaging modalities. Between 1993 and 2001, stress imaging (particularly stress gated single photon emission computed tomography [SPECT] imaging and stress echocardiography) presented an annual increase rate of 6%, which is far in excess with respect to the increase in cardiac catheterization, revascularization, or acute myocardial infarction [2]. More recently, morphologic imaging techniques such as magnetic resonance imaging (MRI) and computed tomography coronary angiography (CTCA) have become a more prominent component of the increase. However, this increasing use has also generated continuous disputation, mainly related to two worrisome issues.

Inconsistencies among different techniques and rate of ''false positive'' and ''false negative'' results with respect to the ''gold standard'' for coronary atherosclerosis: invasive coronary angiography (ICA)

A patient with angina and documented ischemia is classified as a patient with IHD only when coronary stenosis can be documented. A test result is rated as ''false positive'' even in the presence of symptoms and

signs of myocardial ischemia if no obstructive CAD can be detected at the control ICA. Conversely, a test result is rated as ''false negative'' if, in the absence of symptoms and signs of myocardial ischemia, obstructive CAD is detected at the control ICA. Despite continuous technical progress, differences in CAD detection continue to exist among the various techniques. The major gap is generally found between functional and morphological tests, often without any geographical association between the distribution of coronary plaque and perfusion defects [3]. Unfortunately, this issue does not seem to bother physicians, who are rather concentrated on improving their own technique, in order to ''unmask'' as much CAD as they can.

This behavior is unfortunately driving us into a blind alley. Although there are several technical challenges related to individual testing, these cannot explain the overall rate of ''false positive'' and ''false negative'' results. In the so-called ''real world'', CAD automatically implies ischemic heart disease. However, the presence of true stress-induced ischemia in the absence of obstructive CAD is a well-established phenomenon [4,5]. Conversely, 25% of patients with normal stress SPECT images have been reported to have obstructive CAD on CTCA [6]. In line with these findings, autopsy studies of young adults dying from traffic accidents, homicides, and suicides have found that 60% between the ages of 30 and 39 years of age have left anterior descending (LAD) plaques of American Heart Association (AHA) grade 2 or higher [7], nonetheless, none of them suffered ischemic heart disease.

The rate of ''false positives'' and ''false negatives'' should therefore not always be regarded as a technical challenge, but rather as a laid-back attitude to something we just do not get.

Economic issues together with the ability of a diagnostic test to predict future clinical outcomes and to affect prognosis

It should be admitted that, by its inherent properties as a diagnostic rather than therapeutic intervention, an imaging test merely supports clinical decision-making and does not by itself have an impact on outcomes. Moreover, additional concerns challenge the overall value of cardiologic diagnostic tests: a) dozens of studies in tens of thousands of patients have consistently shown that patients with known or suspected CAD who do not have demonstrable stress-induced ischemia have a good prognosis with very low event rates over the subsequent 3 to 7 years [8]; b) although abnormalities in perfusion imaging tests are associated with higher risk of death and myocardial infarction, this does not necessarily imply that treatment of patients with abnormal tests results in reduction of events [9,10]; and c) the preponderance of CAD responsible for myocardial infarction or sudden cardiac death is due to non-obstructive coronary artery plaques [11].

Given this intricate relationship between CAD and myocardial ischemia, the limited prognostic impact of noninvasive testing should no longer come as a surprise. Nevertheless, as mentioned previously, noninvasive testing currently constitutes one of the most blooming areas of cardiology. A carefully conducted study from Canada with contemporary controls [12] demonstrated that the rate of normal invasive coronary angiograms decreased after introduction of CTCA, but the overall rate of ICA increased.

Turning back to our study, is this the way authors hope to achieve a ''higher'' diagnostic yield of coronary angiography? For what purpose?

Ischemic heart disease, which includes acute coronary syndromes and chronic angina, is a leading cause of death all over the world. Because disease presentation is often fatal and a number of those who die suddenly have no previously recognized symptoms, the development of imaging strategies capable of predicting and thereafter preventing such a risk has been regarded as a remedy.

The first step in the evaluation of patients is a careful history and physical examination to provide an estimate of the likelihood of increased risk for coronary events. This is generally followed by a noninvasive assessment, which then determines the need for ICA. All these efforts point towards the same target: identification and local treatment of obstructive CAD.

Cardiologists have known for many years that coronary angiography yields similar results in patients with both stable and acute coronary syndromes. Now we have learned that coronary angiography yields similar results in patients with myocardial ischemia and in patients without. How can we still assume that coronary anatomy dictates clinical conditions?

In fact, studies aimed at determining the impact of removal of coronary stenosis have yielded disappointing results, both in terms of prognosis and symptom relief [9,13]. In line with these findings, there are no data to show that information from imaging techniques benefits patients. Morphologic imaging techniques consume large amounts of resources, yet their role, if any, appears to be in reclassifying patients at intermediate risk with traditional risk-factor models. On the other hand, it has been widely demonstrated that prevention is probably the most important part of managing heart disease [14]. It is also a definitively more economic strategy and can be based on simpler risk factor-models such as FRS, which seem to be good

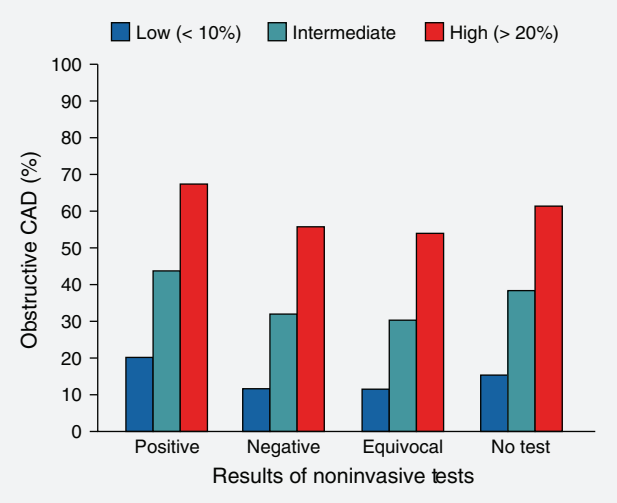

Figure 1. Patients with obstructive coronary artery disease (CAD), according to noninvasive test results. Results are presented according to the Framingham Risk Score (low, intermediate, or high). Reprinted with permission from [1]. ©2010 Massachusetts Medical Society. All rights reserved.

CAD predictors. Contrary to the authors' intentions, Patel et al.'s paper [1] provides strong evidence that coronary risk factors, as assessed by FRS, have a clear relation with coronary atherosclerosis but are not predictive of IHD (see *Fig. 1*).

In conclusion, CAD is a widely accepted predictor of adverse clinical outcomes and its extent and severity are considered important prognostic factors. However, its use as a surrogate marker does not always coincide with the presence of established IHD. In this regard, the ''low diagnostic yield'' of coronary angiography points to the flawed pathophysiological link between CAD and ischemic heart disease.

REFERENCES

1. Patel MR, et al. Low diagnostic yield of elective coronary angiography. *N Engl J Med*. 2010;362:886–895.
2. Lucas FL, et al. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993–2001. *Circulation*. 2006;113:374–379.
3. Lin F, et al. Multidetector computed tomography coronary artery plaque predictors of stress-induced myocardial ischemia by SPECT. *Atherosclerosis*. 2008;197:700–709.
4. Wieneke H, et al. Non-invasive characterization of cardiac microvascular disease by nuclear medicine using single-photon emission tomography. *Herz*. 1999;24:515–521.
5. Soman P, et al. Vascular endothelial dysfunction is associated with reversible myocardial perfusion defects in the absence of obstructive coronary artery disease. *J Nucl Cardiol*. 2006;13:756–760.
6. van Werkhoven JM, et al. Anatomic correlates of a normal perfusion scan using 64-slice computed tomographic coronary angiography. *Am J Cardiol*. 2008;101:40–45.
7. McGill HC Jr et al. Association of coronary heart disease risk factors with microscopic qualities of coronary atherosclerosis in youth. *Circulation*. 2000;102:374–379.
8. Gibbons RJ. Noninvasive diagnosis and prognosis assessment in chronic coronary artery disease: stress testing with and without imaging perspective. *Circ Cardiovasc Imaging*. 2008;1:257–269; discussion 269.
9. Boden WE, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356:1503–1516.
10. Henderson RA, et al. Seven-year outcome in the RITA-2 trial: coronary angioplasty versus medical therapy. *J Am Coll Cardiol*. 2003;42:1161–1170.
11. Narula J, Strauss HW. The popcorn plaques. *Nat Med*. 2007;13:532–534.
12. Chow BJ, et al. Diagnostic accuracy and impact of computed tomographic coronary angiography on utilization of invasive coronary angiography. *Circ Cardiovasc Imaging*. 2009;2:16–23.
13. Adamu U, et al. Results of interventional treatment of stress positive coronary artery disease. *Am J Cardiol*. 2010;105:1535–1539.
14. Mosca L, et al. Waist circumference predicts cardiometabolic and global Framingham risk among women screened during National Woman's Heart Day. *J Womens Health (Larchmt)*. 2006;15:24–34.