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CORONARY CT ANGIOGRAPHY, ECG STRESS TEST AND NUCLEAR IMAGING AS SOURCES OF FALSE POSITIVE RESULTS IN THE DETECTION OF CORONARY ARTERY DISEASE

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Abstract

In the decision-making algorithm of patients with suspected stable Coronary Artery Disease (CAD), clinical assessment for the presence of CAD should be performed after the determination of its Pre-Test Probability (PTP). In order to optimize the accuracy of noninvasive testing, an individualized strategy should be based on patient's PTP and suitability to different diagnostic modalities.

The exercise ECG testing (ExET) is the most inexpensive and widely used first-level tool, but it has a low specificity; in order to minimize the high rate of false positive results, the measurement of the ST-HR hysteresis – the ratio of the area included between the recovery and exercise ST-segment depression values and the Heart Rate (HR) variation in the recovery phase – increases the accuracy of ExET in patients with left ventricular hypertrophy and in subjects with "equivocal" findings.

Local availability and expertise must be taken into account for the selection of "second-level" imaging techniques, in order to minimize false positive results. Stress imaging techniques should be advocated in patients with intermediate-high PTP and/or left ventricular dysfunction. Coronary CT angiography should be used for patients with intermediate-low PTP, given the high negative predictive value of this diagnostic modality. Therefore, patients with suspected stable CAD should be referred for ICA only in cases of a high PTP or after the documentation of ischemia by noninvasive testing.

The most important goal of a diagnostic test is to discriminate patients with from patients without disease. The accuracy of a diagnostic test is evaluated by comparing the results of a test with a 'gold standard', i.e. with a test considered by most as the actual means to achieve an unequivocal diagnosis. In cardiology, Invasive Coronary Angiography (ICA) has been usually deemed the means to diagnose Coronary Artery Disease (CAD); however, apart from not being devoid of risks, ICA alone depicts the anatomical severity of a coronary lesion, but cannot accurately identify its hemodynamic relevance, that is frequently confirmed with Fractional Flow Reserve (FFR), as invasively assessed through the measurement of coronary pressure distal to the lesion after minimization of microvascular resistance – usually with adenosine i.v. infusion or intracoronary bolus. Therefore, there is a clinical need for accurate, non-invasive tests that would allow to make a diagnosis in a simpler, non-invasive, less risky and in a repeatable way.

As recently stated by the European Society of Cardiology (ESC) guidelines on the management of patients with suspected CAD [1], the interpretation of non-invasive cardiac tests requires a Bayesian approach to diagnosis (tab. I). Sensitivity and specificity are the basic measurements of accuracy: sensitivity describes the ability of a test to exclude the "false negative" results, and allows the correct diagnosis of a disease when a disease is actually present; specificity conversely identifies the ability to correctly rule out the "falsely positive" presence of disease when disease is truly absent. In order to identify the best compromise between sensitivity and specificity for any given test, the Receiver-Operator Characteristics (ROC) curve has been developed, as a plot of the sensitivity of a test vs its "false positive" rate (1-specificity) for all possible cut points. The ROC curve area may have values ranging between 0.0 and 1.0. The straight line defining an area of 0.5 is called the "chance diagonal". A test with an area under the ROC curve of 1.0 is perfectly accurate, because sensitivity is 100% when the false positive rate is 0%.

However, although guidelines repeatedly recommend the functional confirmation of the severity of CAD, and therefore the documentation of "myocardial ischemia" before and beyond the identification of a coronary lesion, there is an extremely wide geographical variability in the use of stress testing, with most patients with stable CAD still undergoing myocardial revascularization after ICA without a prior documentation of ischemia [2].

The first step in the management of patients with suspected CAD requires an evaluation of the Pre-Test Probability (PTP), where a CAD consortium clinical score - incorporating age, sex, angina typicality, diabetes mellitus, smoking status, hypertension, and dyslipidemia - has recently documented a better discrimination than the formerly adopted Diamond-Forrester score [3]. The ESC guidelines [1] discourage non-invasive testing in subjects with either a very-low (PTP <15%) or a very-high likelihood of CAD (PTP >85%), with

Table I - Definition of true/false positives and negatives in a diagnostic test.

Sensitivity	TP/TP + FN
Specificity	TN/TN + FP
Positive predictive value	TP/TP + FP
Negative predictive value	TN/TN + FN
Overall accuracy	TP + TN/TP + TN + FP + FN

FN: False Negative; FP: False Positive; TN: True Negative; TP: True Positive.

the recommendation to directly proceed to ICA only in the latter subgroup of patients, especially in cases with typical angina if no satisfactory control of symptoms is possible with initial medical therapy.

Non-invasive testing for CAD

Patients with suspected CAD and intermediate PTP of 15–85% should undergo non-invasive testing (fig. 1).

The very high negative predictive value of a coronary CT-angiography (CCTA) makes the test potentially useful mostly in patients at low-intermediate PTP (15-65%).

Among subjects with intermediate PTP (15-65%) the evaluation of Left Ventricular (LV) function is of utmost relevance, and can be easily assessed with trans-thoracic echocardiography. Patients with preserved LV Ejection Fraction (LVEF ≥50%) should undergo symptom/sign-limited exercise ECG testing (ExET), performed without the influence of anti-ischemic drugs, if feasible, and with imaging stress testing performed only if local expertise and availability permit. Patients with high-intermediate PTP (65-85%) or reduced LVEF (<50%) should be referred to stress imaging as a first-line strategy, limiting ExET only where resources for stress imaging are not available.

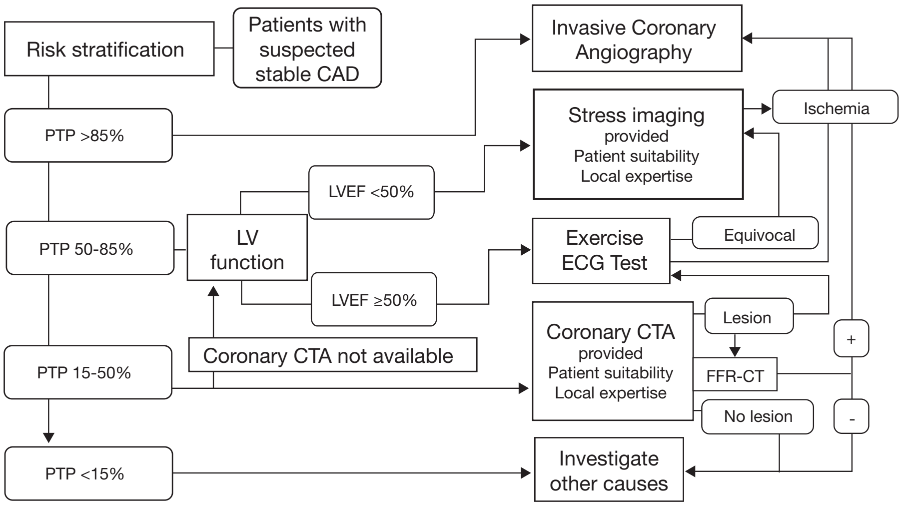

Fig. 1. Initial diagnostic management of patients with suspected stable coronary artery disease (modified from ESC guidelines [1]).
Note that a functional assessment of ischemia, with either exercise ECG, stress imaging or Computed Tomography-derived Fractional Flow Reserve (FFR-CT) should be mandatory before proceeding to invasive coronary angiography in patients with intermediate Pre-Test Probability (PTP) of Coronary Artery Disease (CAD).
CTA = Computed Tomography Angiography; ECG = ElectroCardioGram; LVEF = Left Ventricular Ejection Fraction.

The exercise ECG stress test

ExET is the least expensive and the most widely used method to begin an evaluation for suspected CAD. Using horizontal exercise ST-depression ≥0.1 mV or 1 mm at 60-80 ms after the J-point to define a positive test, the reported sensitivities and specificities for the detection of significant CAD range between 23-100% (mean 68%) and 17-100% (mean 77%), respectively [1].

The ExET has no diagnostic value in the presence of left bundle branch block, paced rhythm and the Wolff-Parkinson-White syndrome, in which cases ECG changes are non-interpretable. Additionally, the test specificity is low in the special patient subsets of subjects with Left Ventricular Hypertrophy (LVH), electrolyte imbalance, intra-ventricular conduction abnormalities, atrial fibrillation, and the use of digitalis glycosides. Aiming at improving the diagnostic value of ExET in such subsets with dubious findings, the measurement of the ST/HR hysteresis – the ratio of the area included between the recovery and exercise ST-segment depression values and the Heart Rate (HR) variation in the recovery phase – has been proposed (fig. 2). LVH is a condition characterized by prolonged repolarization and impaired compensatory mechanisms for counteracting perturbations of repolarization – the so called "reduced repolarization reserve" [4]. Such electrophysiological features, coupled with altered loading conditions, may be responsible for ECG repolarization abnormalities,

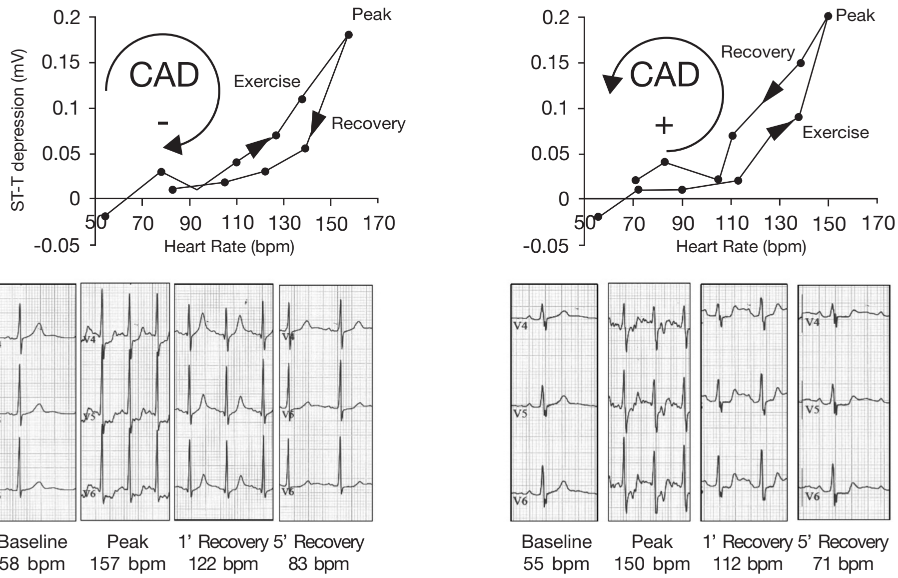

Fig. 2. Patterns of ST/HR hysteresis. The ST/HR hysteresis is the ratio of the area included between the recovery and exercise ST-segment depression values and the Heart Rate (HR) variation in the recovery phase. The area included between the two piecewise linear functions (exercise - peak - recovery) can be negative ("clockwise" recovery loop, left panel) or positive ("counterclockwise" recovery loop, right panel). A negative area is usually present in normal subjects, without Coronary Artery Disease (CAD) while a positive area suggests myocardial ischemia, generally due to CAD; bpm= beats per minute.

sometimes present at baseline, but mostly occurring during exercise. The conventional association of ST segment depression and CAD has been found to be inconsistent in hypertensive patients with LVH, in whom false positive results are frequent and the specificity of ST-T segment interpretation is compromised [5]. In this setting, the use of the ST/HR hysteresis appears to be extremely useful: it appears to discriminate ST-T depression due to CAD-related sub-endocardial ischemia, which persists during recovery, from changes largely due to myocardial strain, that rapidly recover after termination of the exercise. We recently documented that, when adding the ST/HR hysteresis to the traditional ST-segment depression criterion, the ExET shows a higher specificity (75 vs. 36%) and a significantly increased diagnostic accuracy, as documented with a higher area under the ROC curve (0.75 vs. 0.57; $P<0.001$), compared with the standard criteria [6]. We have also similarly documented that the ST/HR hysteresis improves the diagnostic performance of ExET in a cohort of patients with "equivocal" ECG findings – horizontal ST-T segment depression 0.05 ÷ 0.10 mV or up sloping ST-T segment depression 0.10 ÷ 0.15 mV –, and in this common clinical setting out performs also the cardiopulmonary exercise test for the detection of exercise-induced ischemia, as documented with nuclear imaging [7].

In patients with suspected CAD, the ExET should be performed after adequate discontinuation of anti-ischemic drugs. When 85% of maximum HR is not achieved in the absence of symptoms or signs of ischemia, when exercise is limited by non-cardiac problems, or when ECG changes are equivocal, an alternative non-invasive imaging test with pharmacologic stress should be performed.

The ExET can be also useful to evaluate the efficacy of medical treatment or after revascularization, or to assist the prescription of exercise after control of symptoms.

Nuclear Imaging

ExET, the most widely used first-level diagnostic tool in the diagnosis of CAD, is known as the worst in terms of sensitivity and specificity among the other diagnostic strategies, although we must acknowledge that, in the absence of significant CAD, myocardial ischemia may in fact derive from a functional disorder of epicardial vessels and/or coronary microcirculation [8]. Myocardial perfusion imaging, with Single Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET) can assess perfusion and tissue metabolic activity, providing functional information on lesion severity. PET is superior to SPECT imaging for the detection of stable CAD in terms of image quality, interpretative certainty and diagnostic accuracy [9]. However, SPECT scanners and imaging radiotracers are more widely available and less expensive than PET scanners and positron-emitting radiotracers. Technetium-99m (99 mTc) is the most commonly used tracer employed with SPECT, in association with a symptom-limited exercise test on either a bicycle ergometer or a treadmill. Thallium-201 (^{201} Tl) is associated with a higher radiation and is less commonly used. Regardless of the radiopharmaceutical or camera used, SPECT perfusion scintigraphy is performed to produce images of regional tracer uptake, which reflect relative regional myocardial blood flow. With this technique, local areas of myocardial hypoperfusion are characterized by areas of relatively reduced tracer uptake during stress, in comparison with the uptake at rest. Pharmacological stress testing with adenosine or dobutamine is indicated in patients who are unable to exercise adequately or may be used as an alternative to exercise stress.

To date, the radiation dose and the scan-time have been significantly reduced with the development of recent ultrafast cardiac-SPECT cameras with cadmium-zinc-telluride-based detectors [10]. The main technical limitations responsible for false positive results or pitfalls are still represented by the limited spatial resolution (e.g., in areas of thin sub-endocardial ischemia), left bundle branch block, balanced-ischemia, LVH, breast attenuation along the LV anterior wall, as in large breasts assuming a different position on the rest and stress images and resulting in a reversible defect, motion artifacts, large body size, the prominent activity in sub-diaphragmatic organs (the bowel and the hepatobiliary system) adjacent to the heart, along the LV inferior wall, and dextrocardia [11].

Coronary CT Angiography

Coronary CT Angiography (CCTA) is currently the only non-invasive diagnostic tool able to define coronary anatomy and to distinguish normal coronary artery segments, non-obstructive or obstructive atherosclerotic lesions. The remarkable technical evolution in Computed Tomography (CT) in the past 15 years with the development and widespread use of the newest multi-detector CT scanners, characterized both by high temporal (66-175 ms) and spatial (240-600 μm) resolutions, as well as with a larger scan coverage, the availability of prospective or retrospective ECG-gating, and – above all – the dramatic reduction and better control of the radiation dose (now even <1 mSv) [12] have made the non-invasive CT imaging of the coronary arteries more and more practical, reliable, and affordable.

The diagnostic accuracy of this technique has been extensively documented in a patient-based meta-analysis of several studies, whereby 64-row CCTA has shown a pooled sensitivity of 97%, specificity of 90%, a positive predictive value of 93%, and a negative predictive value of 96% for detecting CAD [13]. Given a high negative predictive value, CCTA seems to be extremely suited for ruling-out coronary stenoses in such patients if good image quality and a reasonably low radiation exposure can be expected and if adequate technology and expertise are available [14]. CCTA should also be considered in patients with a stress test result that contradicts clinical judgment, because of its high negative predictive value [15-17], again in order to rule-out the presence of CAD.

With the exception of patients with renal failure – who may have medial calcification – coronary calcium is exclusively a consequence of coronary atherosclerosis. The amount of calcium correlates roughly with the total amount of atherosclerosis present in the coronary arteries, but the correlation with the degree of luminal narrowing is poor. Since the specificity of CCTA decreases with increasing amounts of coronary calcium, and since the prevalence of coronary artery stenosis was found to be high in symptomatic individuals with an Agatston score >400, it is reasonable not to proceed with CCTA in such cases. Therefore, only patients with adequate breath-holding capabilities, without severe obesity, with a favorable calcium score (Agatston score <400) and distribution, in sinus rhythm and with a heart rate of ≤75 beats per minute (otherwise the use of short-acting beta-blockers is strongly recommended) should be considered for CCTA [1].

CCTA remains less reliable in patients with small size (<3 mm) coronary stents, due to artifacts caused by metal and the limited spatial resolution of CT [18]. The assessment of coronary artery by-pass grafts is highly accurate [19], while the evaluation of native coronary vessels in post-by-pass patients may result difficult and prone to false positive findings.

CCTA seems to be the optimal diagnostic tool to detect CAD also among patients with stable chest pain and intermediate likelihood of CAD [20]. Indeed, the recent Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease (EVINCI) study [21] showed that both myocardial perfusion and wall motion imaging had a lower accuracy as compared with CCTA in the detection of CAD. However, the clinical relevance of such findings is still unclear. Indeed, in patients with suspected CAD, CCTA recently failed to add any clinically relevant information over non-invasive functional diagnostic tests: in the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) [22], a strategy of initial anatomical assessment with CTA compared with functional testing did not improve 2-year clinical outcomes in 10.003 patients. Compared with subjects undergoing a functional assessment, subjects in the CTA group underwent catheterization more frequently (12.2% vs. 8.1%, P<0.001) and had a higher overall radiation exposure (12.0 mSvvs: 10.1 mSv; P<0.001). However, the interpretation of this trial result is quite limited by the low event-rate – likely due to the high rate of the optimal medical therapy – the relatively short follow-up period, as well as the lack of a controlled group of patients who received medical therapy but did not undergo testing.

The main determinant for false positive results or overestimation in CCTA is typically represented by the high amount of calcium deposition in the context of a coronary plaque, irrespective of the CT technology. This occurs because of the well know blooming artifacts, hampering the adequate assessment of the residual vessel lumen [23]. Furthermore, the recognized Achille's heel of CCTA has been represented by the frequent identification of intermediate stenoses (50-70%), requiring a downstream testing to assess or rule-out the presence of associated ischemia.

The FFR assessed by CT (FFR-CT) is a novel CT imaging technique helpful to determine the physiological significance of a lesion detected by CCTA, allowing the integration of the anatomical and functional information from the same non-invasive imaging test without further radiation dose or contrast material administration. The recent advances in computational fluid dynamics and individual image-based modeling permit the assessments of coronary blood flow and pressure from a standard acquired CCTA data-set, allowing a more lesion-specific assessment of ischemia similarly to the invasive FFR, considered nowadays the gold standard for the functional evaluation of CAD. Simplifying, the FFR-CT is based on three simple assumptions: the total coronary blood flow is proportional to the oxygen demand of the myocardial mass; the resistance at rest of coronary micro-circulation is inversely proportional to the size of the feeding vessels; and, finally, the coronary microcirculation has a predictable response to a vasodilator. The use of FFR-CT allows a significant reduction of the CCTA false positive results with increased specificity and positive predictive value [24]; the increased accuracy translated into a significant reduction (61%) of planned ICA in patients with suspected CAD, when undergoing CCTA with FFR-CT, as recently documented in the Prospective LongitudinAl Trial of FFR-CT: Outcome and Resource iMpacts (PLATFORM) [25]. FFR-CT may therefore act as gatekeeper to the cath-lab in non-emergent symptomatic patients with intermediate-range CAD: in the event of FFR CT <0.75, the risk of a CAD false positive result seems very low (<10%), while subjects with FFR-CT >0.80 may be deferred from ICA with a favorable short-term prognosis; a non-negligible number of FP results may be still expected in cases with FFR-CT 0.76-0.80 [26].

Conclusions

Non-invasive testing can establish the likelihood of the presence of obstructive CAD with an acceptable degree of certainty, provided that careful patient selection, based on his risk assessment and suitability to different diagnostic modalities, is performed. The local availability and expertise must also be taken into account for the selection of "second-level" imaging techniques in order to minimize false-positive results. Patients with suspected stable CAD should be referred to ICA only in cases of a high PTP or after the documentation of ischemia by non-invasive testing.

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