Anatomy and physiology in coronary artery disease imaging

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INTRODUCTION

For decades, cardiac imaging underwent constant evolution and was the driving force of the development of new technologies and new technical approaches for the assessment and quantification of ischemia. A massive burden of literature has been produced using inducible ischemia as the imaging/clinical endpoint for revascularization and clinical choices. The knowledge at some point became habit and determined somehow a ''tunnel-vision'' approach toward the search for a stenosis to revascularize, often, no matter what.

In almost all fields of imaging, and also during medical school, we developed our clinical knowledge starting from the assessment of anatomy and its alterations, followed by function and its alterations; in clinical practice, the preliminary and advanced assessment of anatomical alterations has been performed mostly with noninvasive techniques (i.e., Ultrasound, Computed Tomography, Magnetic Resonance). In the field of coronary artery disease (CAD), coronary anatomical assessment has been out of reach from noninvasive imaging modalities for decades; in 1999, computed tomography coronary angiography (CCT) showed for the first time that it was possible to see the coronary arteries and CAD without using a catheter. Electron Beam CT and Magnetic Resonance tried it before, but with quite limited results. After then, the development of CT technology has been very fast and all the main issues have been resolved (i.e., radiation, calcifications, heart rate, speed).

Nevertheless, despite the constant development in this field of cardiovascular imaging (while functional imaging still kept developing), still the capability of selecting only patients worthy of revascularization for conventional coronary angiography (CAG) has been dramatically inadequate (Table 1).[1]

We should consider that the reasons for this inadequacy are probably not solely related to clinical or test performance factors. For instance, in many healthcare systems the model for reimbursement has been more rewarding with higher uncertainty prior to CAG. Anyway, today CCT is one of the most studied and well-validated cardiac imaging techniques we can conceive and is ready to play a significant and growing role in cardiovascular medicine.[2-9]

THE NEW LANDSCAPE AFTER UPDATED NICE GUIDELINES 2017

Until now, CCT has been progressively classified as an alternative tool for the diagnosis of inclusion/exclusion of obstructive CAD, and it has been mentioned in several guidelines, however, never with a primary role and, even more, never with a primary role in stable patients.

With the 2017 update of the guidelines of the National Institute for Health and Care Excellence (NICE) from the UK NHS, we have seen a quantum leap into the new paradigm of CAD assessment and diagnosis, namely the use of CCT as the first/main diagnostic imaging tool (with some exclusion criteria) in patients with suspected CAD. This is a major step

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Table 1. Performance of diagnostic tests for obstructive coronary artery disease

Diagnostic test	Sensitivity (%)	Specificity (%)
Exercise ECG	61	70
Stress echocardiography	85	77
SPECT	88	61
CMR WM	83	86
CMR perfusion	89	76
CCT	99	89
CT perfusion (static)	85	81
CT perfusion (dynamic)	77	89
Combined CCT+CTP	84	93

The table shows the performance of diagnostic tests for obstructive coronary artery disease. Pooled data from several different meta-analyses
CAD, coronary artery disease; *CCT*, CT coronary angiography; *CMR*, cardiac magnetic resonance; *WM*, Wall Motion; *CTP*, CT perfusion; *SPECT*, single-photon emission computed tomography

forward in accepting what has been discussed for more than a decade now.[10-12] This modification of the approach that has been anticipated by the implementation of CCT in the stratification of Chest Pain of recent onset in the context of ER (still from NICE in 2010) has the potential to radically change the way we make diagnosis, the way we treat our patients, and also the way we organize our services (Hospitals, Diagnostic Centers,…) in the clinical field.

In fact, the clinical cardiologist would be forced to start thinking about atherosclerosis before thinking about ischemia. It may seem trivial to a certain extent but it is actually Copernican.

Just as an example, the recent PICTURE trial demonstrates that CCT is sharply superior to Myocardial Perfusion Imaging (MPI) in the reliable detection >50% and >70% stenosis in stable chest pain patients.[13] In this study, the diagnostic accuracy of MPI is quite far from the one of CCT (Sensitivity 59% vs. 93%; Specificity 82% vs. 89%; PPV 71% vs. 84%; NPV 71% vs. 83%; for >70% stenosis). We may argue that until we use a morphological reference standard like CAG, functional imaging will always have a limited possibility to be really validated. However, this is how we have always performed this kind of studies.

The SPARC study and the SCOT-HEART study showed that this diagnostic advantage translates into a significantly better prognosis.[14,15] One of the possible explanations is that CCT can always show and diagnose subclinical atherosclerosis (regardless the degree of stenosis), thereby inducing more aggressive medical therapy and more motivation for adherence to therapeutic schemes.

MORPHOLOGICAL CT-BASED TECHNIQUE TO ESTIMATE CORONARY FLOW ALTERATIONS

In this issue of the Journal, Benz et al. performed a validation of Corrected Coronary Opacification (CCO) as derived from CCT using quantitative 13N-ammonia Positron Emission Tomography.[16]

Coronary Opacification (CO) difference (i.e., difference of luminal attenuation across a coronary stenosis in Hounsfield Units) was the first ''flow parameter'' derived from CCT and it was further improved into ''Corrected Coronary Opacification'' (CCO) difference; these parameters are related to abnormal resting coronary blood flow. Transluminal Attenuation Gradient (TAG) is considered as a more recent and accurate version of CO and CCO; it reflects the kinetics of iodinated contrast media within the coronary arteries and across stenosis and it seems to be a reproducible method. TAG corresponds to the linear regression coefficient between luminal attenuation and axial distance from the coronary ostium. TAG is able to improve sensitivity and specificity of CCT over stenosis degree assessment alone.[17] As for CO and CCO, it is a parameter that can be calculated even without sophisticated software and the assessment is implemented into the most advanced processing software available on the market.

This is the first study to compare CCO with stress Myocardial Blood Flow (MBF) and to report on its ability to predict abnormal Relative Flow Reserve (RFR)[16]; the study shows that the presence of an abnormal CCO decrease is associated with significantly lower RFR even though with moderate diagnostic accuracy; however, the absence of CCO decrease excludes an abnormal RFR with high negative predictive value. Hence, one may elaborate that adding this parameter to conventional anatomical CCT assessment may impact significantly (i.e., reduce) the prevalence of false positives (i.e., specificity and positive predictive value). In this perspective, the usefulness of the parameter may be more for a per-patient overall evaluation, rather than a per-segment/per-segment analysis in multivessel disease.

In fact, the potential of this method could be interesting when the approach of the operator to CCT is the more traditional one: aiming for high sensitivity and high negative predictive value. This has been the strength of CCT from the very beginning, while specificity and positive predictive value were reduced due to the variable impact of stenosis degree on inducible myocardial ischemia. The Authors of the current paper

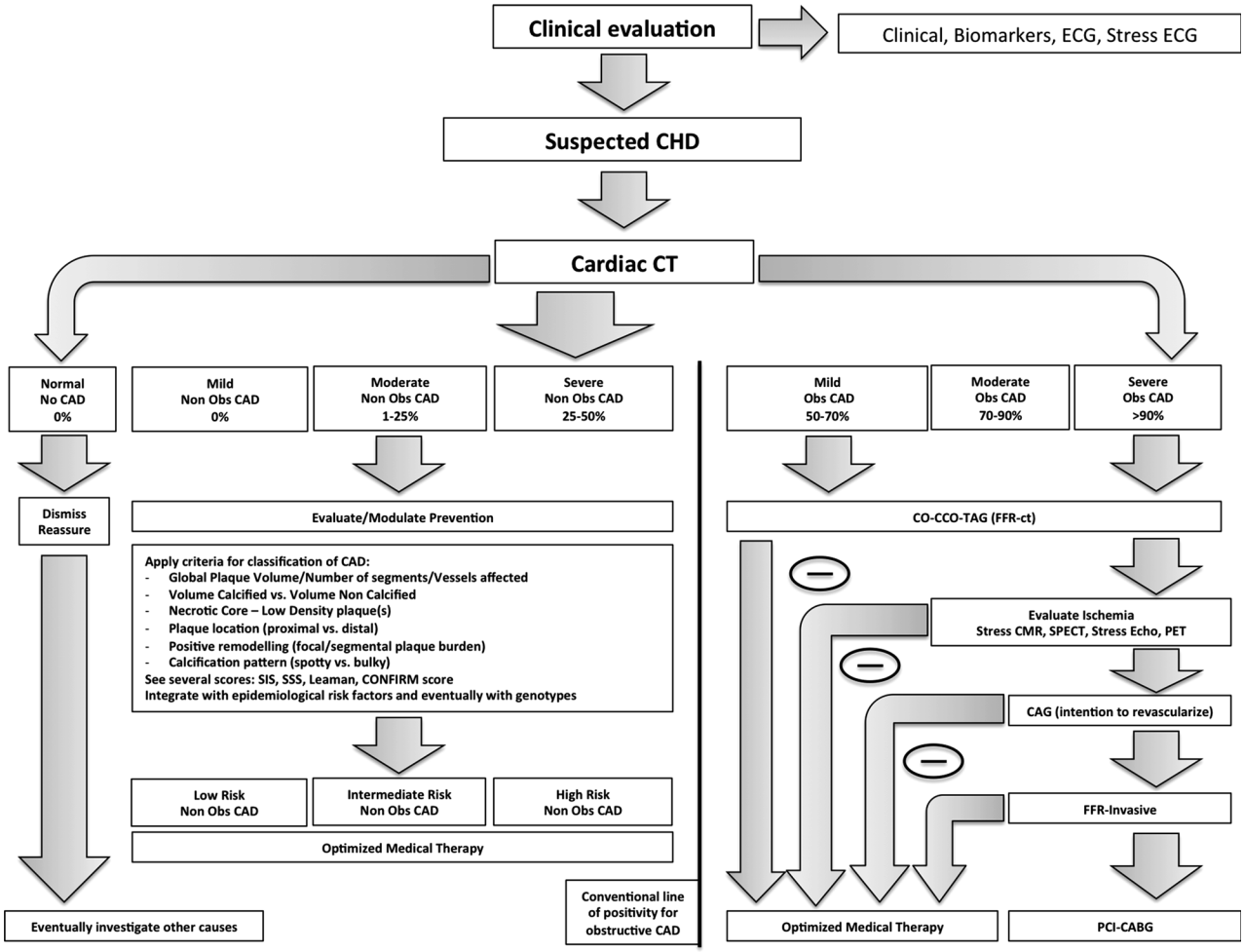

Figure. 1. Paradigm shift for the assessment of coronary artery disease. An algorithm showing the paradigm shift for the assessment of coronary artery disease in clinical practice. Individualized prevention and medical treatments should be more based on direct stratification of individual plaque burden (quantitative and qualitative features), while functional methods applied to CCT should help improving (i.e., reducing) the referral for advanced stress imaging and ultimately for CAG. Abbreviations: *ECG*, electrocardiogram, *CHD*, coronary heart disease, *CT,* computed tomography, *non Obs,* nonobstructive, *Obs,* obstructive, *CAD,* coronary artery disease, *CO*, coronary opacification, *CCO*, corrected coronary opacification, *TAG*, transluminal attenuation gradient, *CMR*, cardiac magnetic resonance, *SPECT*, single-photon emission computed tomography, *Echo*, echocardiography, *PET*, positron emission tomography, *CAG*, conventional coronary artery angiography, *PCI,* percutaneous coronary intervention, *CABG*, coronary artery bypass graft, *FFR*, fractional flow reserve.

did not provide this kind of analysis, and in fact it would be quite interesting to see; from the clinical standpoint, all patients who would get a CCO evaluation would anyway get also a conventional CCT stenosis assessment.[16]

CT-derived Fractional Flow Reserve (FFRct) is a computational fluid dynamics simulation of adenosine-mediated hyperemia applied to CCT imaging. As for TAG, one of the main parameters is attenuation through the coronary artery associated with morphology of the vessel lumen and other parameters. This proprietary method has been demonstrated to be somehow effective in providing the information about flow-limiting stenosis,[18-20] even though there are few studies and there is little information about the actual correspondence between FFRct-driven revascularization and outcomes, or medium/long-term longitudinal outcome studies.

For many of us, it may still seem somehow strange that we may be able to collect functional information

that is comparably accurate to intracoronary assessment using a static evaluation, without a stressor, with a spatial resolution that is not comparable to the one of CAG, and for which consolidated in vivo stress imaging tools have often difficulties. Nevertheless, we could see them as additional tools able to improve mostly the specificity and positive predictive value of CCT alone.

HOW TO LOOK AT CORONARY ARTERY DISEASE

As previously observed, CCT is changing the way we look at stable and acute heart disease (Figure 1). We are starting to look at CAD as we look at several other diseases (e.g., carotid artery disease, peripheral vascular disease,…); in other words, we have noninvasive access to coronary anatomy, coronary atherosclerotic disease, and ultimately coronary artery stenosis. With the implementation of new algorithms for image analysis, we may soon be able to quantify flow alterations (i.e., FFR) without using a stressor or an intracoronary catheter.

However, until we do not pair a cultural paradigm shift with this technological paradigm shift, we will keep searching for stenosis and validate new information only against stenosis, maintain our current ''tunnel-vision'' approach.

In a meta-analysis from Smulders et al., newer evidence suggests that the negative predictive value of all main cardiac diagnostic techniques is clearly influenced by pretest probabilities and clinical presentation, but it also shows that CCT has by far the highest negative predictive value for future events.[21] And this is without taking into account that the criterion for a ''negative'' test on CCT was ''<50% luminal narrowing,'' thereby not separating the so-called ''normal coronary arteries'' from nonobstructive CAD.

CONCLUSIONS

Functional derivative methods are interesting when applied to CCT and they can bring some incremental value. How the incremental is used depends on what is the approach to CCT. When you search for a balance between sensitivity and specificity, anatomical functional methods may deliver the additional negative predictive value which is actually what clinicians expect from the method. Instead, when you focus on sensitivity and negative predictive value (which is the standard expectation of anyone sending a patient to CCT), functional methods may be used as a surrogate of stress imaging to increase specificity and positive predictive value, ultimately improving the gatekeeping capabilities of the algorithm.

Disclosure

All authors declare that they have no conflict of interest.

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