Combined functional and anatomical imaging for the detection and guiding the therapy of coronary artery disease

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This editorial refers to ‘Combined non-invasive functional and anatomical diagnostic work-up in clinical practice: the magnetic resonance and computed tomography in suspected coronary artery disease (MARCC) study’, by J.G.J. Groothuis et al., on page 1990

Cardiac imaging is used to confirm the diagnosis of coronary artery disease (CAD), to document ischaemia in patients with stable symptoms, to risk stratify patients, and to help choose treatment options and evaluate their efficacy.1 In the classic diagnostic path, the pre-test probability of CAD is estimated based on symptoms, sex, risk factors, biomarkers, and, when available, the result of exercise electrocardiography (ECG). Non-invasive imaging tests are recommended for patients with an intermediate probability (15–85%) of obstructive CAD, while symptomatic patients with a high probability (>85%) can undergo direct invasive examination (Figure 1A). On many occasions the choice of the non-invasive imaging method is based on local expertise and availability of the test. In this path, the final diagnosis and the decision about the revascularization method and the vessels treated are often determined using invasive coronary angiography (ICA). The role of non-invasive tests is mainly to select whether the patients need invasive testing.

Coronary computed tomography angiography (CTA) has become an established non-invasive method for anatomical detection of CAD. Current techniques allow robust assessment of coronary atherosclerosis with acceptable radiation dose.2 Multicentre studies have demonstrated high diagnostic accuracy of CTA for the identification of >50% coronary artery stenoses, and most studies have shown a particularly high negative predictive value (NPV), making CTA an excellent tool for exclusion of CAD especially in symptomatic patients with a lower range of intermediate pre-test probability of CAD.1

The angiographic severity of a coronary lesion (detected either invasively or non-invasively) is a poor predictor of its haemodynamic significance. As expected, only a proportion of stenoses in CTA are associated with myocardial ischaemia. In stable CAD, the target of revascularization therapy is myocardial ischaemia, not the epicardial coronary artery disease itself. Revascularization procedures performed in patients with documented ischaemia reduce total mortality1 through reduction in ischaemic burden.14 Thus, functional assessment, non-invasive or invasive, is essential for intermediate stenoses.5

Interrogation of both coronary anatomy and function is important in order to offer the most appropriate treatment strategy in patients with stable CAD. Non-invasive imaging can provide information on both of these, even in the same imaging session using hybrid imaging. Recently, several studies have combined evaluation of anatomy with CTA and perfusion imaging using either single photon emission tomography (SPECT) or positron emission tomography (PET). These studies have consistently shown improved diagnostic accuracy of combined or hybrid imaging as compared with the single techniques.6–9 Furthermore, vessel-specific functional information allowing targeted revascularization strategies can be obtained. Recently, it was also shown that combining anatomy and function added independent prognostic information.10

Groothuis et al.11 have now investigated the combined use of CTA and cardiac magnetic resonance imaging (CMR) for the diagnostic evaluation of patients with suspected coronary artery disease (CAD). The authors enrolled 192 patients with low or intermediate pre-test probability of CAD. The patients with obstructive CAD on CTA and/or myocardial ischaemia on CMR were referred for ICA. In addition to anatomical assessment in ICA, functional evaluation of intermediate lesions (30–70% diameter stenosis) with the use of fractional flow reserve (FFR) was planned as the reference method. The combination of CTA and CMR significantly improved specificity and overall accuracy (91%) for the detection of significant CAD as compared with stand-alone CTA or CMR.

The results are in good agreement with previous data published on combined anatomical and functional imaging for the detection of CAD. The combination of CMR with CTA has also been studied previously,12 but the study of Groothuis et al. included a larger population. In addition to perfusion, CMR can provide useful information

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The classic diagnostic path of symptomatic patients with suspected coronary artery disease (CAD) starts by estimation of the pre-test probability of disease. The symptomatic patients with high pre-test probability are referred directly to invasive coronary angiography (ICA), while those with intermediate probability are recommended to have further non-invasive diagnostic testing by imaging. The most commonly used imaging tests (perfusion imaging or stress echo) detect myocardial ischaemia. Recently, anatomical imaging of CAD by CT angiography (CTA) has also been recommended in the patients with a lower range of pre-test probability due to high negative predictive value, but only moderate positive predictive value. If the non-invasive tests are positive, ICA is often used to diagnose the CAD, assess its severity, and make decisions on revascularization. Invasive functional testing [fractional flow reserve (FFR)] is recommended to guide revascularization if functional information is not available from earlier non-invasive testing. Typically patients with a low probability of CAD, mild ischaemia, or non-obstructive CAD may also enter primary prevention or optimal medical therapy without ICA.

The new proposed diagnostic path including hybrid imaging starts with a similar selection process based on the pre-test probability of CAD. The first imaging test in patients with intermediate probability would be CTA. The patient without CAD on CTA can be recommended for primary prevention, whereas the patients with suspicion of obstructive CAD continue with a non-invasive test to detect ischaemia in a region supplied by the corresponding vessel. Those with CAD but no ischaemia can be recommended aggressive secondary prevention. Those patients with anatomical evidence of both epicardial CAD and ischaemia have the highest likelihood of benefiting from revascularization and can be referred to ICA for the final decision on treatment to be made.
about ventricular and valvular function as well as myocardial and aortic diseases. An obvious strength of CMR is that it does not cause any additional exposure to ionizing radiation. When considering any test to detect CAD, it is important to take into account the risks associated with the test itself. The risks of exercise, pharmacological stressors, contrast agents, invasive procedures, and cumulative ionizing radiation must be weighed against the risk of disease or delayed diagnosis.

Some limitations in the study need to be taken into account. The initial dropout rate was ~10% since 22 patients had some limitations that prevented them undergoing the required tests. In addition, less than half of the patients finally had ICA performed, because only those with a positive result in either non-invasive test were referred to ICA. Ideally, referral bias could have been avoided by performing ICA in all of these symptomatic patients, similar to an earlier study with hybrid PET/CT. The fact that the remaining patients did not have any events during 1.5 years of follow-up does not exclude the presence of CAD. However, given the high NPV of CTA, this is probably not a major limitation.

Another limitation is that FFR was not used systematically since only 28 (76%) out of 37 intermediate lesions were studied by FFR. In only 10 of these was FFR abnormal. The rest of the intermediate lesions with >50% luminal narrowing were classified as obstructive based on anatomy, as were all the lesions with >70% stenosis in ICA, although it has been shown that of the stenoses ranging from 70% to 90% only 72–82% have an abnormal FFR. The incidence of obstructive CAD in the studied population was very low. Significant CAD was detected only in 26 (13.5%) out of the 192 enrolled patients. Most of them (19) had single-vessel disease and only two had three-vessel disease. Thus, most patients either did not have CAD or had low risk disease. In this kind of population, the relatively low accuracy of CTA (57%) as compared with CMR (83%) was surprising given the high NPV of CTA. Based on the low incidence of CAD, one would expect the opposite. Probably related to the low number of diseased vessels, vessel-based analysis was not performed in the study of Groothuis et al. However, the possibility of disease localization at the level of the vessel is an important benefit of combined/hybrid imaging.

Perfusion CMR is currently also limited by the fact that it can only acquire perfusion information in three distinct short axis slices. This contrasts with SPECT and PET which generally provide 3D information of the entire left ventricle and also provide very comprehensive 3D hybrid images. In the future, this problem should be solved by more rapid perfusion sequences in CMR, which might provide 3D information.

Despite these above-described limitations, the study of Groothuis et al. nicely confirms the benefits of combining imaging of both anatomy and function, and adds data about potential novel combination of CMR with CTA. The drawback is that no hybrid CT/CMR device is commercially available currently, and thus another imaging session needs to be scheduled, which is not the case with real hybrid SPECT/CT or PET/CT systems.

This study as well as some earlier studies lends support to the new potential diagnostic path in which combined or hybrid imaging is utilized for the detection of CAD. There are several potential benefits of such an approach, described in Figure 1B. On one hand, only those patients with obstructive disease causing ischaemia are referred to ICA, potentially limiting the use of invasive tests only to those who have the highest probability of benefiting from revascularization. On the other hand, CTA can efficiently identify subclinical, non-obstructive coronary atherosclerosis in patients with normal myocardial perfusion. Many studies have shown that identification of non-obstructive CAD by CTA has a negative impact on prognosis and these patients can be provided with effective secondary prevention. In addition, a significant fraction of the patients without any coronary atherosclerosis can be guided to less aggressive primary prevention.

In addition to diagnosing and selecting patients for ICA, the benefits of hybrid imaging can potentially be extended to evaluation of the functional impact of each individual coronary lesion and thus help to decide whether revascularization options during cardiac catheterization. Although more non-invasive tests are potentially performed, the approach can be expected to be cost-effective if obstructive CAD can be efficiently excluded after CTA and/or functional imaging and invasive tests better targeted.

It is obvious that larger prospective multicentre trials are needed to confirm the validity of this new diagnostic path involving combined imaging of anatomy and function in the diagnostic evaluation of CAD and to assess whether therapies based on the results of combined hybrid imaging may have an impact on the patients' prognosis. Results of ongoing prospective multicentre trials such as SPARC, EVINCI, and PROMISE are therefore eagerly awaited and will hopefully shed more light on the future of cardiac hybrid imaging.

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**References**


A 64-year-old man with chronic liver disease presented with dyspnoea, and a chest contrast computed tomography (CT) was performed to evaluate the suspect of pulmonary embolism (Panel A).

A mass occupying the right atrium, of the same density of the myocardium at early-phase scan, was diagnosed as thrombus by CT findings. Echocardiography (Panel B) was performed with a continuous infusion of contrast and flash-replenishment assessment to dynamically evaluate whether the mass was filled by microbubbles (an intravascular tracer), vascularization raising the possibility of malignancy.

The mass filled with contrast at a similar rate compared with the myocardium (Panel B, lower panel, Supplementary material online, Video S1) confirming vascularization.

[18]FDG positron emission tomography showed hyperaccumulation of the radioactive marker in the right atrium and liver (Panels C and D), confirming the malignancy. The general conditions quickly worsened and the patient died. The autopsy confirmed liver lesions and the 4 cm right atrium lesion (Panel E). The histopathology of both the liver (Panel F, upper) and atrial (Panel F, lower) lesions showed features of poorly differentiated adenocarcinoma; haematoxylin–eosin staining (left) and immunohistochemistry positivity for Citytocheratin 7 (mid) and cytoplasmic pCEA (right) were consistent for cholangiocarcinoma, rather than hepatocellular carcinoma.

Supplementary material is available at European Heart Journal online.