Interconnection of coronary macro- and microcirculation to each other: each component has relations that express all the others

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A sizeable number of patients undergo invasive or non-invasive computed tomography coronary angiography (CTA) because of typical or atypical chest pain, as the tenet is that atherosclerotic disease of the epicardial coronary arteries is the leading cause of symptoms. The finding of normal coronary arteries or non-obstructive Coronary Artery Disease (CAD) (stenosis <50%) is not uncommon. The real significance of anginal symptoms accompanied by electrocardiographic changes during stress without evidence of obstructive lesions has puzzled clinicians for many years, as their efforts to improve the symptoms of these patients were unsatisfactory. In the late 80s, Cannon and Ebstein proposed that dysfunction of the physiologic vasodilatory mechanism of intramural small arteries and arterioles could be the cause of the disease they named microvascular angina. The fully quantitative assessment of myocardial perfusion using positron emission tomography (PET) has allowed to test the function of the coronary microvascular bed by measuring coronary flow reserve (CFR)\(^2\)-\(^4\), thus, gaining insight into the integrated coronary circulatory function. Coronary microvascular dysfunction (CMD) would explain a variety of clinical scenarios characterized by reduced CFR and evidence of ischaemia in the absence of haemodynamically significant epicardial stenoses. The coexistence of CAD either focal or diffuse and CMD provides an adjunctive adverse prognostic value.\(^5\),\(^6\)

Stenström et al.\(^7\) report the relative frequency and angiographic characteristics of CMD in symptomatic patients with intermediate pre-test probability of CAD assessed by means of hybrid PET/CTA. These combined techniques allow the characterization of stenosis severity, plaque composition and CFR. Patients underwent also invasive angiography to assess stenosis severity and fractional flow reserve (FFR). The mean radiation dose for CT angiography and transmission for attenuation correction varied between 2 and 8 mSv and for PET it was 1 mSv. A major strength of modern PET imaging, especially for the evaluation of younger and female patients, is that superior image quality and diagnostic yield are feasible with limited patient exposure to ionizing radiation; resulting in an effective radiation dose in the environment of annual background exposure levels (<3 mSv). In this medium-sized cohort of 189 patients, 23% had normal coronary arteries and 40% had non-obstructive atherosclerosis. The majority of patients had a normal hyperaemic myocardial blood flow (MBF). Diffuse reduction of CFR classified as CMD was observed only in 9% of the study cohort with normal coronary arteries or non-obstructive lesions. Interestingly, hyperaemic MBF was not correlated with the extent of coronary calcium in the absence of obstructive CAD.

Female gender was the only factor independently associated with global stress MBF, CFR, and coronary resistance. Risk factors were equally distributed between the two groups and well controlled by current therapy. The lower prevalence of CMD with normal or non-obstructed coronary arteries reported in this low-intermediate pre-test probability of CAD cohort with respect to other studies might be explained by a series of factors: ethnic distribution, studies from USA have a more consistent population of African Americans, the exclusion of patients with previous history of diabetes or acute coronary syndromes and myocardial infarction. A better adherence to therapy could also be hypothesized as all the patients at the time of scanning were treated for major cardiovascular risk factors.

This article is flawed by the poor capability of both invasive angiography and CTA to quantify diffuse disease thus the relative atherosclerotic burden was only based on severity of focal stenosis. Moreover, measurement of FFR does not discriminate upstream focal and diffuse disease and can be miscalculated in the presence of a normal distal pressure which can be due to increased microvascular resistance. van de Hoef et al.\(^9\) elegantly demonstrated that a normal FFR with an abnormal coronary velocity flow reserve was associated with significantly increased major adverse cardiac events rate throughout 10 years of follow-up, regardless of the FFR cut-off which was applied.

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Accurate detection of the onset and rate of progression of CMD is a major challenge, if the suspicion arises with symptoms suggestive of myocardial ischaemia the proposed diagnostic algorithm should be based on the following criteria: (i) objective documentation of myocardial ischemia; (ii) absence of obstructive CAD; (iii) confirmation of a reduced CFR; and (iv) in patients with normal CFR, invasive test for macro-/micro-vascular spasm with acetylcholine. The hybrid scanning PET/CTA would, in a single session, explore criteria 1, 2, and 3 leaving to invasive angiography the assessment of macro-/micro-vascular spasm. Nowadays, data supporting use of PET in the evaluation of symptomatic patients for suspected ischaemic heart disease are increasingly accrued. A non-invasive procedure could be more acceptable for patients and enhance the diagnostic strategy of detection, mainly for female patients with intermediate pre-test probability of CAD. Recent evidence, however, suggests that CMD is equally prevalent among individuals with risk factors, and is associated with adverse outcomes regardless of gender. The downside of purely anatomical studies is the downstream increase of catheterizations and revascularizations. A normal CFR is associated with excellent prognosis, hence, concomitant assessment of MBF and CFR can avoid unnecessary invasive procedures.

The prognostic value of quantification of MBF and CFR is highlighted in a recent study by Taqueti et al. females showed a lower prevalence of obstructive CAD and pre-test probability of CAD but experienced more cardiovascular adverse events than males, in particular those with very low CFR (<1.6). This excess risk was mediated in part by the low CFR value. This latter can integrate the functional consequences of obstructive, non-obstructive CAD, and CMD and express the complexity of the functional interactions between epicardial conductive arteries and regulatory intramural small arteries and arterioles.

The data reported by Stenstro¨m et al. and the recent data supporting the role of combined functional anatomical assessment were collected in centres with high level, extensive experience with CTA, PET, and myocardial perfusion measurements. It remains to be ascertained if the same diagnostic procedures can be extended to current clinical practice all over Europe.

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References