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(Epicardial and microvascular) angina or atypical chest pain: differential diagnoses with cardiovascular magnetic resonance

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Angina pectoris is a chest discomfort caused by myocardial ischaemia, and it is classified as 'typical' or 'atypical' if specific features are present. Unfortunately, there is a heterogeneous list of cardiac diseases characterized by this symptom as onset sign. Mostly, angina is due to significant epicardial coronary artery stenosis, which causes inadequate oxygen supply increase after raised myocardial oxygen demand. In the absence of significant epicardial stenoses, another potential cause of angina is microvascular dysfunction, related to inadequate response of resistance coronary vessels to vasodilator stimuli. The unique capability of cardiovascular magnetic resonance (CMR) in providing extremely detailed morphological and functional information, along with precise stress perfusion defects and wall motion abnormalities depiction, translates it into the test with one of the best diagnostic performance and prognostic stratification among non-invasive cardiac imaging modality. Moreover, CMR is also extremely accurate in detecting non-ischaemic cardiac causes of chest pain (such as myocardial and pericardial inflammation, or stress-related cardiomyopathy), and is very useful in helping physicians to correctly approach patients affected by chest pain.

Typical and atypical angina

Angina pectoris is defined as a chest discomfort caused by myocardial ischaemia.[1] It is traditionally classified as 'typical' when all three of the following characteristics are present: sub-sternal chest discomfort of characteristic quality and duration; provoked by exertion or emotional stress; relieved by rest and/or nitrates (strong vasodilators) within minutes.[2] When only two of them are present, this symptom is defined as 'atypical', due to the reduced probability of finding the presence of causes of myocardial ischaemia. When none or only one of these features are present, the term 'non-cardiac chest pain' is suggested.[2]

Pathophysiology of typical angina

From a pathophysiological point of view, angina pectoris results from myocardial ischaemia, caused by an imbalance between myocardial oxygen requirements and myocardial oxygen supply. The former may be elevated by increases in heart rate, left ventricle (LV) wall stress (mainly due to increase of blood pressure and blood volume), and contractility; the latter is determined by coronary blood flow and coronary arterial oxygen content.

One of the main determinants of myocardial oxygen supply is the patency of the epicardial coronary vessels. In the

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course of atherosclerotic disease, coronary plaques are able to progressively decrease the vessel lumen, until the increased epicardial artery resistance limits maximal myocardial perfusion, generating, in the context of an increase of myocardial oxygen requirement, myocardial ischaemia, and anginal symptoms.

Thanks to the widespread use of invasive coronary angiography, it has been described how nearly a half of patients with angina symptoms suggestive of obstructive coronary artery disease (CAD) present normal coronary arteries at invasive evaluation. In many of these patients, has been proved how symptoms are secondary to a coronary microcirculatory dysfunction, hence the term microvascular angina. Briefly, in this condition there is transient myocardial ischaemia secondary to a dysfunction of the resistance coronary vessels ($<500\,\mu m$). The dysfunction is documented, in the first instance, by a reduced vasodilator response of the small resistance coronary arteries, and could affect both the endothelium-independent and the endothelium-dependent vasodilation activity. Many hypotheses have been proposed to explain this functional impairment (mostly, increased adrenergic tone; increased insulin resistance; oestrogen deficiency) but the real mechanisms have not been fully understood yet.[3,4]

Causes of atypical angina

'Atypical angina' is defined as chest pain not fully satisfying criteria for 'typical' angina but somehow consistent with cardiac ischaemic cause. Atypical chest pain is the most common symptom complained by patients referring to emergency department or family practitioner, and approximately two-thirds of them have non-coronary aetiology.

If we exclude myocardial ischaemia and infarction, the most common causes of atypical chest pain are diseases related to gastrointestinal tract, chest wall syndromes, pericardial diseases, and vascular diseases; other less common diagnoses include pneumonia, pulmonary embolism, lung cancer, aortic aneurysm, myocarditis, stress-related cardiomyopathy (also called 'Takotsubo' syndrome), aortic stenosis, herpes zoster, and cardiac masses.[5]

After ruling-out acute myocardial infarction and other life-threatening conditions, usually related to cardiovascular compartment, the prognosis is generally very good. Physicians usually refer these patients to further ambulatory diagnostic evaluations, aware that in about 10% of these cases specific diagnosis will not be reached.[6]

Cardiovascular magnetic resonance in ischaemic heart disease

One of the main determinants of the prognosis of patients with known or suspected ischaemic heart disease is the presence of ischaemia.[7,8] For this reason, current international clinical guidelines strongly suggest to assess the presence of ischaemia with non-invasive stress tests before referring patients to invasive coronary angiography. When available, second-line stress tests, such as stress echocardiography, single photon emission computed tomography (SPECT), positron emission tomography, stress cardiovascular magnetic resonance (CMR) and, more recently, stress computed tomography perfusion are preferred.

The unique capability of CMR in providing extremely detailed morphological and functional information, along with precise stress perfusion defects and wall motion abnormalities (WMA) depiction, translates it into the test with one of the best diagnostic performance[9,10] and prognostic stratification[11,12] among cardiac non-invasive tests.

In epicardial stenoses, stress CMR, mainly with vasodilator stressor (i.e. adenosine, dipyridamole, and regadenoson) performs significantly better if head-to-head compared with other stress tests, like SPECT, and offers an accurate assessment of both single-vessel and multivessel coronary disease. Indeed, the additional clinical information provided by multiparametric CMR [balanced steady-state free precession (bSSFP) cine imaging for LV morphological and functional assessment; late gadolinium enhancement (LGE) imaging for scar detection; 3D magnetic resonance angiography for coronary arteries anatomy characterization] beyond perfusion evaluation, helps the physicians in addressing the correct diagnosis, key aspect for a better individual patient management.[9]

Non-invasive cardiac imaging methods have been assessed for their diagnostic performance largely against an ICA reference standard. There is consistent evidence that the assessment of CAD severity by ICA is limited, because the angiographic severity of a given epicardial stenosis does not necessarily accounts for its functional significance. For this reason, in the last few years several studies have been published advocating FFR as reference standard. Danad *et al*. recently performed a meta-analysis comparing the diagnostic performance of the main cardiac imaging tests with invasive FFR as reference standard. Cardiac MR had the highest performance for the diagnosis of haemodynamically significant CAD on both a per-vessel [area under the curve (AUC) 0.97] and a per-patient (AUC 0.94) basis,[10] thanks to excellent sensitivity and specificity.

Moreover, functional approach with stress CMR resulted to be superior in terms of cost-effectiveness when compared to anatomical approach with cardiac computed tomography angiography in the specific setting of revascularized patients complaining of new-onset chest pain.[13]

Utility of CMR was tested also in the setting of patients with angina and non-obstructive CAD. Microvascular dysfunction can induce myocardial hypoperfusion, visually depicted as regional or global perfusion defects. In the daily practice, this visual, qualitative assessment of hypoperfusion is the preferred analysis, mainly because it is of a fast use. Unfortunately, an important drawback of this approach is the poor information obtained in terms of exact severity or distribution of microvascular disease, resulting in a worse overall diagnostic accuracy compared to the setting of obstructive CAD.

New approaches for stress cardiovascular magnetic resonance

Thanks to advances in CMR image post-processing methods, semi-quantitative and quantitative approaches for

assessing perfusion defects have been developed, enabling detailed examination of myocardial perfusion reserve and myocardial blood flow.[14] These quantitative approaches, applicable to both epicardial and microvascular disease, are more time consuming, but are supported by a very high accuracy in detecting segmental and global impaired myocardial perfusion, increasing especially the diagnostic performance in the presence of microvascular dysfunction.

Novel and very intriguing approaches for perfusion abnormalities evaluation exploits direct quantification of the signal from the myocardium during first-pass perfusion, either at rest and after stressor administration. Each pixel in the image is coded in colour, reflecting the absolute value of myocardial blood flow. The main strengths of this novel approach are fully automated workflow, pixel-wise flow calculation, single-bolus contrast injection, and rapid processing.[15]

Another novel and promising approach describes ischaemia showing longitudinal relaxation time changes, influenced by free water content, before and after vasodilator stressor administration, displaying pre-contrast T1 values of imaged tissues on a pixel-by-pixel basis with colour-coded maps. According to depiction of different changes profiles, is it possible to differentiate between normal, ischaemic, infarcted, and remote myocardium, and, notably, this assessment is performed without gadolinium-based contrast agents (GBCAs) administration.[16]

Role of cardiovascular magnetic resonance in atypical angina

Myocarditis

After ruling out the presence of ischaemia, there are many cardiovascular diseases in which CMR plays a crucial role.

This non-invasive technique has the unique capability of detailed tissue characterization, either with non-contrast weighed images (different weighing according to T1, T2, proton-density, multiple inversion pulses, etc.), novel mapping techniques or T1-weighed images after GBCAs injection. For this reason, myocardial characterization with CMR in the clinical suspicion of myocarditis is nowadays considered mandatory.

The Lake Louise criteria (LLC) recommend combining different CMR techniques in patients with suspected myocarditis to determine myocardial oedema (T2-weighted imaging), hyperaemia (T1-weighted imaging), and fibrosis (LGE). The LLC use a semi-quantitative approach and allow detection of myocardial inflammation and necrosis. However, several technical limitations affect this approach. T1-weighted spin-echo sequences suffer from poor image quality, whereas T2-weighted spin-echo images have a low signal-to-noise ratio, and several artefacts in the interface blood pool-myocardium. Furthermore, LGE alone may fail to characterize acute myocarditis, as some patients only present with acute myocardial inflammation/oedema.[17] T1 and T2 mapping are novel CMR techniques for quantitative tissue characterization with tight normal ranges, which allow a more objective, and mostly, quantitative assessment of myocardial tissue properties. Importantly, parametric mapping techniques appear to overcome some of the aforementioned technical limitations of the LLC, and enable the assessment of diffuse myocardial injury, because they have been shown to be highly sensitive to increased free water content, rendering them ideal for detecting acute myocardial inflammation/oedema.[18]

Pericardial disease

The diagnosis of pericardial disease frequently remains clinically challenging, requiring integration of medical history and findings from physical examination, imaging, blood analyses, and, eventually, invasive haemodynamic measurements. The role of transthoracic echocardiography (TTE) in diagnosing pericardial diseases has been well recognized, allowing both structural assessment and evaluation of the physiologic consequences to the heart. However, TTE may sometimes fail to allow adequate evaluation of the pericardium, particularly in obese subjects, patients with severe chronic obstructive pulmonary disease or skeletal malformations. Moreover, TTE is limited in the assessment of focal effusions, pericardial thickness, and tissue characterization.

Improvements in MR imaging hardware and sequences design in the last 10 years have enhanced the diagnostic value of this modality for the study of pericardial disease, now become essential in providing a complete view of the physiology of the pericardium and the pathophysiology of pericardial diseases. A comprehensive MR imaging of the pericardium is composed by morphologic assessment of the heart, pericardium, and surrounding mediastinum; assessment of global and regional LV and RV function; assessment of ventricular coupling by using real-time imaging during free breathing; assessment of ventricular filling during breathholding or free breathing by using real-time imaging; tissue characterization, either without contrast injection or with late enhancement imaging; evaluation of pericardial mobility and fusion of pericardial layers. Thanks to this inclusive approach, it is possible to have a precise morphological assessment (close to CT imaging), the presence, amount, and distribution of fluid surrounding the heart is correctly depicted from the base to the apex, areas of inflamed pericardium can be assessed, along with concomitant myocardial inflammation, such as in the course of acute coronary syndromes or myo-pericarditis. The high spatial and temporal resolutions of bSSFP imaging can be applied in dynamic evaluation of the rigidity of the pericardial layers in patients with constrictive pericarditis. Fast cine sequences enable real-time evaluation of dynamic fast-changing physiologic events such as ventricular coupling, and real-time acquisition during free breathing is able to easily identify constrictive physiology.[19]

Takotsubo cardiomyopathy

Stress-related cardiomyopathy, also called ‘takotsubo’ cardiomyopathy (TC) due to typical shape of LV during systole resembling the octopus trap used by Japanese fishermen, is a reversible LV dysfunction with symptoms similar to those of acute coronary syndromes but typically without significant epicardial coronary lesions. The defining hallmark of this entity is the cardiac function recovery

occurring within days to weeks after index clinical presentation. The exact pathophysiology of TC is not clearly established, but possible mechanisms include myocardial stunning secondary to catecholamine toxicity, multivessel epicardial coronary spasm, or coronary microvascular dysfunction. The catecholamine hypothesis is supported by the presence of an emotionally or physically stressful trigger in a significant proportion of patients, very high levels of catecholamines reported in some patients, and similar acute myocardial dysfunction discovered in patients with pheochromocytoma and subarachnoid haemorrhage; moreover, contraction band necrosis, a feature of catecholamine toxicity, has been reported on endomyocardial biopsy specimens in these patients. Takotsubo cardiomyopathy has generally been considered as a relatively benign disease; however, it is characterized by substantial morbidity and mortality, and complications are more frequent than previously thought, occurring in up to 50% of patients.[20]

After exclusion of significant CAD during the index event, a significant role in the non-invasive diagnostic assessment in patients with these typical LV WMA is played by CMR, offering a unique combination of safety, detailed anatomical visualization, and tissue characterization.

In detail, in this peculiar clinical context, a standard CMR exam is composed by: bSSFP imaging for information on the hallmark of the disease, i.e. regional abnormal contractility not related to coronary territory (akinesia of mid-to-apical myocardium with the basal segments spared, and very often hyperkinetic); T2-weighted triple-inversion recovery sequences for oedema detection (native T1 mapping and T2 mapping can be performed as well for this purpose; the typical finding is the presence of marked myocardial oedema in the segments affected by WMA); early gadolinium enhancement images (acquired less than 2 min after GBCA injection), to look for a surrogate for capillary leakage and hyperaemia in the myocardium (the typical finding is increased myocardial signal in the context of WMA); LGE images, to investigate for altered tissue characterization (the usual finding is absence of significant myocardial LGE by visual analysis; quantitative software analysis with a variety of thresholds techniques can eventually detect small amounts of patchy LGE).[20]

If every step of the above mentioned CMR protocol is performed, it is possible to easily detect the typical features of TC or describe other pathological entities that otherwise would not be ruled out, particularly myocarditis and myocardial infarction with non-obstructive coronary arteries.

Conclusions

In the clinical setting of suspected ischaemic heart disease, CMR plays a crucial role in carefully detecting the presence of inducible ischaemia, usually localized if related to significant epicardial coronary artery stenosis or diffuse if related to microvascular dysfunction. This non-invasive diagnostic tool, compared to other non-invasive tests, gives the unique chance to assess the presence of tissue characterization abnormalities (such as in presence of myocarditis, previous myocardial infarction, other cardiomyopathies) and functional abnormalities (e.g. the abnormal ventricular coupling related to constrictive physiology as pericarditis sequelae) using the same technique, enabling the differential diagnosis between ischaemic and non-ischaemic cardiomyopathies, and among the latter, allowing identification of a specific type of myocardial disease thanks to specific hallmark findings.

Conflict of interest: none declared.

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