CMR should be a mandatory test in the contemporary evaluation of "MINOCA"

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Introduction

Myocardial infarction with non-obstructive coronary arteries (MINOCA) is defined as acute MI with no angiographic obstructive coronary artery disease (CAD) (≥ 50% diameter stenosis in a major epicardial vessel), according to the latest Fourth Universal Definition of Myocardial Infarction (2018) (1). In particular, these guidelines stipulate that MINOCA, like the diagnosis of MI, implies an ischemic mechanism (i.e. non-ischemic causes, such as myocarditis, have been excluded), and requires that obstructive CAD has not been inadvertently overlooked (1). The estimated prevalence of MINOCA is around 6 – 8% among patients presenting with acute MI, and is more common in women than men (1). After excluding non-ischemic etiologies, the possible mechanisms for MINOCA include rupture of atherosclerotic plaques, coronary thrombosis/emboli, microvascular disease, coronary spasm and spontaneous coronary dissection. Using only routine investigations such as ECG, troponins and invasive coronary angiography, clinicians are often left wondering about the true etiology of this clinical syndrome in any given patient, frequently defaulting to non-ST-elevation myocardial infarction (NSTEMI) as the discharge diagnosis, along with lifelong secondary prevention treatments. MINOCA is only a working diagnosis until a specific cause has been secured (2), so that clinicians looking after these patients may institute appropriate treatment and assess prognosis based on etiology.

The clinical utility of CMR and other diagnostic tests in MINOCA

The definition of MINOCA has been evolving. Previously, "MINOCA" had encompassed all patients who present with cardiac symptoms (typically, chest pain) associated with positive blood biomarkers of myocardial injury (e.g. troponins) but non-obstructive coronaries on angiography, without necessarily having ruled out non-ischemic etiologies, such as myocarditis. In this context, many studies have demonstrated the utility of cardiovascular

magnetic resonance (CMR) in providing a diagnosis or reclassifying a presumed diagnosis of MI (3). With its multiparametric capabilities in assessing cardiac structure, function and tissue characterization, CMR is a considered an important diagnostic tool by the ESC working group on myocardial infarction with non-obstructive coronary arteries (2). Based on a meta-analysis of studies using CMR as a diagnostic tool in MINOCA, myocarditis is the leading diagnosis (3), and when performed early, CMR can secure a diagnosis in up to 87% of the cases (4). Myocarditis may be confirmed histologically on endomyocardial biopsy (EMB), and molecular techniques on EMB may identify a viral etiology. However, EMB is invasive and suffers from sampling error, but may be useful in selected cases to guide treatment options (e.g. giant cell myocarditis). CMR or other imaging-guided EMB can increase diagnostic yield. Fluorine-18 fluorodeoxyglucose-positron emission tomography (FDG-PET) has been shown to be in good agreement with CMR in detecting acute myocarditis (5), and hybrid positron emission tomography-magnetic resonance (PET-MR) is an emerging imaging technology that can offer information on metabolism and disease activity in myocarditis. Novel CMR T1- and T2-mapping are highly sensitive, quantitative techniques that have recently been incorporated into updated Lake Louise criteria on using CMR to detect myocardial inflammation (6), and are promising in locating the area of injury responsible for the acute presentation in MINOCA, especially in cases with normal LV ejection fraction, no regional wall motion abnormalities or late gadolinium enhancement (LGE).

Other etiologies in MINOCA, as diagnosed by CMR, commonly include Takotsubo cardiomyopathy, acute MI, hypertrophic or dilated cardiomyopathy, and non-cardiac causes (like pulmonary embolism). While CMR can provide excellent characterization of the downstream myocardium in MINOCA, additional diagnostic testing of the upstream coronary

arteries, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) may further elucidate the mechanism of MINOCA, including atherosclerotic plaque rupture, erosion, and spontaneous coronary dissection, while provocative testing may support coronary vasospasm as a potential etiology. These ancillary tests for assessing the coronary arteries are invasive, but coronary CT angiography (CCTA), including the novel Fat Attenuation Index (FAI), which have been shown to identify vulnerable coronary plaques and predict future MIs by detecting vascular inflammation (7) may have a role in assessing MINOCA patients as a non-invasive tool to interrogate the coronary arteries.

Prognosis of MINOCA patients

In this issue of the *Journal*, Dastidar et al. retrospectively identified 388 consecutive MINOCA patients who underwent CMR assessment, and were prospectively followed up for all-cause mortality. CMR assessment included cardiac structure and function (cine imaging), edema (T2-weighted) imaging and LGE. CMR was performed at a median of 37 days from presentation, and identified the cause for the troponin rise in 74% of the patients (25% myocarditis, 25% MI and 25% cardiomyopathy), whilst the remaining 26% had a normal CMR. Over a median follow-up of 3.5 years, 5.7% patients died. Patients with cardiomyopathy had the worst prognosis (mortality 15%, log rank 19.9 $p<0.001$), followed by MI (4% mortality), and myocarditis and normal CMR (2% mortality in both). In a multivariable cox regression model (including clinical and CMR parameters), CMR diagnosis of cardiomyopathy and ST-segment elevation on presentation ECG remained the only two significant predictors of mortality. Using ST-elevation on presentation ECG and CMR diagnosis of cardiomyopathy as risk factors, the presence of 0, 1 and 2 factors were associated with a mortality risk rate of 2%, 11% and 21%, respectively ($p<0.0001$). The investigators concluded that, in MINOCA, a CMR diagnosis of cardiomyopathy had the highest mortality, followed by a CMR diagnosis of MI. The strongest predictor of mortality

was a combination of ST-elevation on presentation ECG and CMR diagnosis of cardiomyopathy.

The strengths of this study and discussion

This study by Dastidar et al. makes a worthwhile contribution to the diagnostic, and especially, the prognostic value of CMR in MINOCA patients. This is another study demonstrating that MINOCA is not benign (8), including patients with Takotsubo cardiomyopathy (9). Pasupathy et al (2015) (3) reported a 12-month all-cause mortality of 4.7% (95% CI 2.6-6.9) in MINOCA patients, while Kang et al reported similar clinical outcomes and prognosis in MINOCA patients compared with one- or two-vessel CAD patients presenting with an acute MI (12-month MACE of 7.8% vs 12.2%; p=ns). Dastidar et al not only showed that MINOCA patients confirmed to have sustained an MI on CMR has increased morality rates (4% over a median of 3.5 years), but also that the non-ischemic causes, like cardiomyopathy and myocarditis, also carry increased risk (15% and 2% respectively), even if the CMR was "normal" (2% risk). The diagnostic yield of CMR in this study (74%), performed at a median of 37 days from presentation, was lower compared to studies that had performed early CMR (e.g. 87%) (4); this may be improved by performing CMR as early as feasible and within the first week of acute presentation (10), with fuller coverage of the left ventricle (more than 3 slices) using edema-imaging. The use of newer CMR T1 and T2-mapping techniques covering the LV may also improve detection of myocardial injury on a pixel level, and, if "normal", may potentially signify a lower-risk profile with a better prognosis; further research in this area is required.

CMR can further refine the diagnostic labelling of MINOCA patients, which directly impacts on treatment strategies and prognosis based on etiology (or at least more specific

categorization). Consider the recent study by Lindahl et al. (2017) (8) using the SWEDEHEART registry examining 9466 consecutive MINOCA patients and the effects of common treatments for acute coronary syndrome on MACE (all-cause mortality, hospitalization for MI, ischemic stroke, and heart failure). Treatments assessed included statins, angiotensin-converting enzyme inhibitors / angiotensin receptor blockers (ACEI/ARB), β-blockers, and dual antiplatelet therapy. During follow-up (mean 4.1 years), 23.9% patients experienced a MACE. There was a reduced hazard ratio (95% confidence intervals) for MACE in MINOCA patients on statins (0.77; 0.68-0.87), ACEI/ARB (0.82; 0.73-0.93), and β-blockers (0.86; 0.74-1.01). There was a neutral effect of dual antiplatelet therapy for 1 year (0.90; 0.74-1.08), with a non-significant 33% higher risk a bleeding event requiring hospitalization (1.33; 0.73–2.42). This study by Lindahl et al. did not report the use of additional diagnostic tests (such as CMR, IVUS, OCT, etc) to further identify the cause of MINOCA in these patients.

Summary and future directions

This highlights the potential benefit of using additional testing to further evaluate MINOCA patients for better-tailored treatment based on etiology. CMR is increasingly available, and can confirm MI for accurate patient categorization according to the contemporary definition of MINOCA (2). Additional tests of the upstream coronary arterial system may provide further insights into the etiology for MINOCA patients confirmed to have sustained an MI, but are invasive. CMR is non-invasive, and can differentiate MI from myocarditis and various cardiomyopathies, further enabling correct diagnosis, personalized treatment pathways and assessment of prognosis. The optimal management pathways for MINOCA patients remain to be determined using evidence-based medicine, including large clinical trials and cost-benefit analysis.

The time is ripe for an outcomes-based clinical trial evaluating the value of CMR-guided treatment and management of MINOCA patients. A suitable, multiparametric CMR protocol may include functional imaging and advanced tissue characterization techniques (such as mapping and LGE) that is performed early (within 1 week of the acute presentation) with full LV coverage to provide a comprehensive assessment. For those with a clear, non-ischemic etiology, standard ACS-treatment may not be beneficial or may even be harmful. For patients presenting with acute myocarditis, especially those with an impaired LVEF, regional wall motion abnormalities or extensive LGE, whether standard treatment for heart failure, such as ACEI and beta-blockers, are beneficial in decreasing the risk of developing DCM and/or significant arrhythmias would benefit from more evidence. The advantages of using CMR to guide management in MINOCA include securing a true diagnosis of MI, to distinguish from non-ischemic etiologies, and establish the extent and functional impact of the acute myocardial injury, allowing more individualized treatment of each patient. However, CMR alone cannot confirm the exact mechanism of an MI or the etiology of non-ischemic myocardial inflammation. CCTA and the novel FAI may have a role in the non-invasive assessment of the coronary arterial system in MINOCA. Ultimately, the most non-invasive and comprehensive assessment of the upstream coronary arteries and downstream myocardium that lead to the most personalized management strategy would be desirable for MINOCA patients. As a step forward, CMR has demonstrated added clinical utility in both the diagnosis and prognostication in MINOCA, and should be in clinical guidelines as one of the frontline diagnostic tests to enable further stratification of these patients.

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