MINOCA – Are we doing it wrong?

Introduction and definitions

The third universal definition of myocardial infarction was agreed upon by the European Society of Cardiology (ESC) in their expert consensus document in 2012. It put the rise and/or fall of cardiac biomarkers at the centre of the definition, stating that to apply the label of myocardial infarction the following criteria are required [1]:

The detection of a rise or fall of cardiac biomarker (preferably cardiac troponin) at least one value above the 99th percentile with at least one of the following:

- Symptoms of ischaemia
- New significant ST-T wave changes or new left bundle branch block
- Development of pathological Q waves on the ECG
- Imaging evidence of loss of viable myocardium or regional wall motion abnormalities
- Identification of an intracoronary thrombus by angiography or autopsy

Non-obstructive coronary artery disease (NCAD) is defined as the presence of atherosclerotic plaque that would not be expected to hinder coronary blood flow or cause angina. Our evidence base in patients with obstructive coronary artery disease is large, but there is no real evidence on how to investigate, manage or treat those with myocardial infarction with non-obstructive coronary arteries (MINOCA). To further add to confusion there is no consensus on what defines "non-obstructive" coronary arteries. Some reviews include 0% obstruction (i.e. angiographically normal coronaries) with a 1-50% stenosis, others take non- obstructive to mean anything less than 70% stenosis. A review of registry data from the US looking at patients undergoing elective coronary angiography found that 58.4% of patients had lesions between 1-50% [2].

MINOCA features in the new ESC Guidelines for ST elevation myocardial infarction. They agree that to diagnose MINOCA, three components are required.

1. Universal myocardial infarction criteria
2. Non-obstructive coronary arteries on angiography (defined as lesion < 50%)
3. No clinically overt specific cause for the acute presentation [3].

Meta-analyses suggest the prevalence of MINOCA is 6% and the patients more likely to be younger and female [4]. The presence of NCAD appears to be considerably higher in women. The CRUSADE quality initiative highlighted this difference, demonstrating that MINOCA had a prevalence of 12-37% in women and 9-16% in men following admission with non-ST elevation myocardial infarctions [5].

Differentials

Several pathophysiological mechanisms have been postulated describing why MINOCA occurs. However, we should be mindful that troponin rises can occur in a variety of conditions where there is NO coronary artery disease.

Pooled analyses of cardiac MRI studies suggest that the commonest finding in MINOCA patients was myocarditis (33%), followed by Tako-Tsubo (18%), hypertrophic cardiomyopathy (3%), dilated cardiomyopathy (2%) and "other" causes (7%) such as infiltrative conditions [4]. In this same study, no abnormality was seen in 26% and subendocardial infarction was seen in 24% [4]. It also showed that early MRI scans, within 6

weeks, increased the diagnostic yield with only 21% demonstrating no abnormality, when compared to late scans (56%).

Agewall et al succinctly summarises some of the potential causes of an elevated troponin [6]:

Table 1: Adapted from [6]

Coronary causes	**Non-Coronary causes (associated with cardiac)**	**Non-Coronary causes (associated with extra-cardiac)**
Plaque Rupture	Myocarditis	Stroke
Coronary artery spasm	Takutsubo	Pulmonary embolism
Spontaneous coronary dissection	Cardiomyopathies	Sepsis
Acute aortic dissection with coronary extension	Cardiac trauma	Adult respiratory distress syndrome
Coronary microvascular disorder	Strenuous exercise	End-stage renal failure
Spontaneous coronary thrombosis	Tachyarrhythmias	
Coronary emboli	Cardiotoxins (drugs)	
Sympathomimetic agents		

Given the above, it is therefore important to look for alternative causes for troponin release in the context of a 'troponinaemia'. We have all been involved in cases where an initially suspected ACS is eventually revealed to be an alternative diagnosis such as pulmonary embolus, and anecdotally, the increasing reliance on the troponin value may make this scenario more frequent. Even if an ACS is excluded, the correct diagnosis is still vitally important as a troponin release in this context may indicate a poorer prognosis [7].

Pathophysiology

There are a number of possible theories when considering the reason MINOCA has occurred. An ESC position paper divided them into 4 aetiological differentials [8]:

1. *Plaque Disruption:*

Despite being difficult to prove, it is accepted that plaque disruption is mediated by thrombosis, thromboembolism, superimposed vasospasm or a combination of these [8].

Coronary angiography by its very nature is a 2-dimensional lumenogram, it does not provide information regarding the vessel wall or plaques. Autopsy studies as far back as 1989 have shown that atheromatous plaque cause coronary arteries to dilate, therefore delaying obvious luminal stenosis [9]. Intravascular ultrasound (IVUS) imaging studies have previously demonstrated significant atherosclerosis in patients considered to have angiographically normal coronary arteries [10]. These patients have less calcific disease but proportionately more 'soft' plaque, rich in lipids with thin fibrous caps [11] and "positive remodelling" – the name given to the compensatory dilatation.

Small studies comparing IVUS to 64-slice CT coronary angiography (CTCA) have previously shown that with good quality images there is excellent agreement between the two in identifying non- calcific plaque and positive remodelling [12] [13]. Aldrovandi et al [14] published a study in 2012 where patients who had suffered an acute MI were prospectively enrolled over the course of 18 months. From a total of 2079 patients 50 were eventually

recruited with a standard coronary angiogram that demonstrated no significant stenosis but late gadolinium enhanced cardiac MRI that confirmed an acute infarct. In most of these patients they found disease located in culprit arteries detected by CTCA which most often had features of vulnerable plaque.

This study lends weight to the theory that plaque disruption may be the pathophysiological mechanism behind some MINOCA.

2. Coronary thromboembolism

Coronary embolisms (CE) are poorly characterised with few studies dedicated to clarifying its prevalence and prognosis. The largest retrospective analysis in patients with MINOCA suggests the prevalence of CE was 2.9%. Of these AF was found to be the commonest cause (73%) [15]. When the CE group was propensity score matched with a cohort of similar demographics within the MINOCA study, all-cause mortality and cardiac death was found to be significantly higher [15]. This was put down to inadequate treatment of the AF (nearly 50% were inadequately anticoagulated).

A separate review of the literature undertaken by Prasupathy et al reported a 14% prevalence of inherited thrombophilic disorders in patients with MINOCA [16]. Other causes reported in the literature include bacterial endocarditis, myxoma, rheumatic heart disease and (dilated) cardiomyopathies [15]. One should also consider the possibility of paradoxical emboli and the presence of a patent foramen ovale or atrial septal defect. Indeed, the ESC ST-elevation MI guidelines suggest bubble contrast echo as part of the workup in patients suspected of having MINOCA [3].

In the absence of worrying coronary features on CTCA, we should actively suspect an embolic event. A higher level of suspicion for conditions such as AF/thrombophilia could lead to an alteration in the management plan i.e. anticoagulation rather than antiplatelet therapy.

3. Coronary artery vasospasm

Constriction of smooth muscle in the arterial wall causes suddenly occlusive lesions that can also lead to myocardial infarction. In young adults, recreational drug use (predominantly cocaine) is an important cause to consider. Prasupathy et al reports that provocative spasm testing caused 27% of patients with MINOCA to have vasospasm [16]. It should be suspected in patients who have spontaneous episodes of angina at rest associated with significant ST changes that respond promptly to short acting nitrates [8]. The ESC recommends consideration of Ergonovine/Acetylcholine testing, especially given that nitrates and calcium channel blockers are effective treatments in vasospastic angina [3], but due to a lack of evidence around safety its use in MINOCA is less well delineated.

4. Coronary Dissection

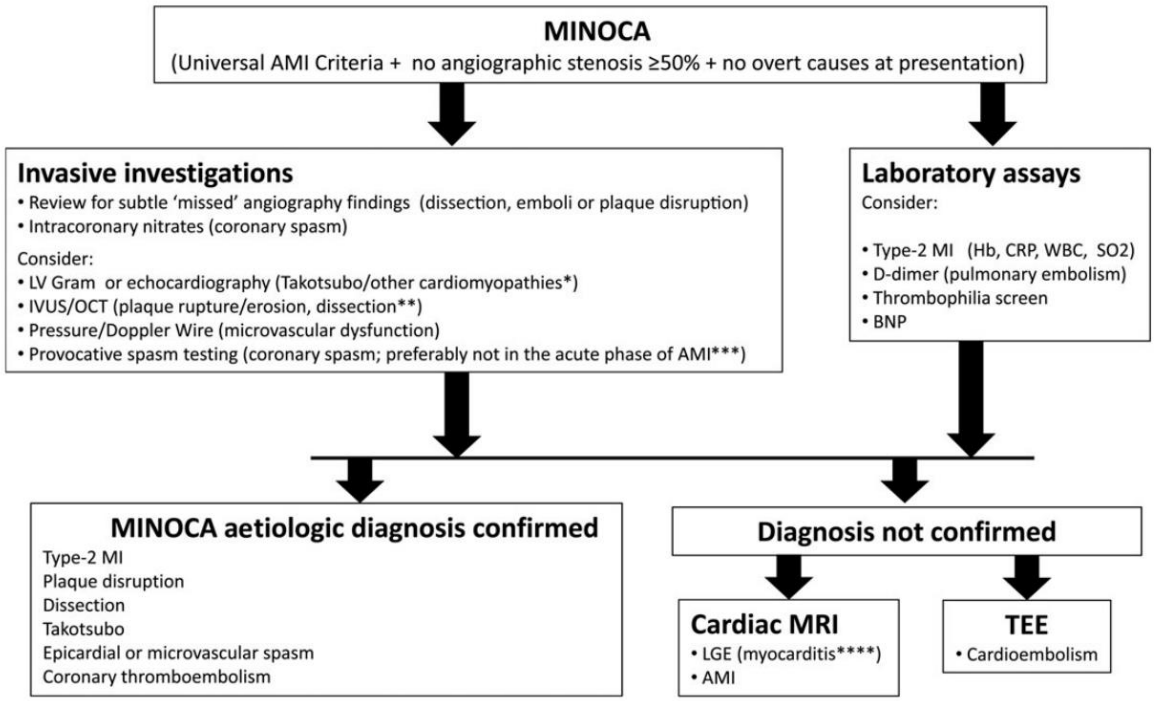
Spontaneous coronary artery dissection (SCAD) and intramural haematomas without intimal tearing are not always apparent on coronary angiography [8] [17]. A case series of 22 patients with SCAD demonstrated the vital role of intracoronary imaging (IVUS and OCT) in confirming the diagnosis [18]. When the diagnosis is unclear, as is the case in MINOCA, interventionalists should perhaps consider these strategies more regularly.

<u>Long-term outcome and Conclusion</u>

Patients with NCAD have consistently been demonstrated as having an increased risk of myocardial infarction. This risk increases progressively with the burden of atherosclerotic disease [19]. In the MINOCA population, registry data from SWEDEHEART which followed

up 9466 MINOCA patients over a mean 4.1 years found that 23.9% experienced a further major adverse cardiac event [20]. It indicated long term benefit in patients on statins and ACE-inhibitors, a positive trend with β-blocker treatment, and a neutral effect of dual antiplatelet therapy. The report makes for interesting reading, with such a large number of events in this population we should consider this a high-risk group that warrants close follow up. There remains a lot of uncertainty regarding optimal approach and adequate randomised trials are lacking, but as a group these patients are poorly managed. The figure below is taken from the ESC expert opinion paper suggests a framework investigation

Figure 1: Adapted from [8]



Certainly, consideration of intracoronary imaging, an early CMR to help confirm the diagnosis (whilst an inpatient), and then careful thought as to other further investigation is necessary and is likely to help identify a more precise cause in a significant proportion of patients in order to optimise treatment and clinical outcomes.

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