INVITED EDITORIAL ARTICLE

**PROVOCATIVE TESTS FOR CORONARY ARTERY SPASM IN MINOCA: NECESSARY AND SAFE?**

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Acute myocardial infarction (AMI) usually results from thrombotic events developing at the site of atherosclerotic plaque erosion or rupture. Despite the high prevalence of obstructive coronary artery disease (CAD) in AMI (around 90% in STEMI and 60% in NSTEMI), a sizeable proportion of AMI patients have no obstructive CAD (MINOCA) amounting to up to 13% of all patients with a clinical diagnosis of AMI (1-3). As recently reviewed by Pasupathy et al (4) MINOCA patients represent a conundrum given the very many possible aetiologies and pathogenic mechanisms associated with this syndrome. Indeed, MINOCA can be triggered by coronary artery dissection, coronary embolism, takotsubo syndrome, myocarditis, arrhythmias, mild plaque disruption, a hypercoagulable status, and coronary artery spasm, to name but a few. Uncertainties currently exist regarding the characterisation, diagnostic strategies and clinical outcomes in these patients.

Age, clinical presentation and CAD risk factors are similar in MINOCA and CAD-related AMI (CAD-AMI) patients. It is not known, however, whether clinical outcomes differ markedly in MINOCA patients and patients with MI triggered by obstructive CAD and coronary plaque disruption. In a recent systematic review, Pasupathy et al (4) reported that all-cause in-hospital mortality was 0.9% (95% CI, 0.5%– 1.3%) and 12-month mortality 4.7% (95% CI, 2.6%–6.9%), respectively. Comparison of mortality data in 6 studies that included MINOCA as well as CAD-AMI patients showed that the latter had higher both all cause in-hospital mortality (3.2% versus 1.1%) and 12-month all cause mortality (6.7% versus 3.5%). Pasupathy et al (4) and other authors (2,5,6) have demonstrated –in different ethnic populations- that patients with MINOCA have a guarded prognosis.

Ascertaining in MINOCA patients the cause and pathophysiological mechanisms, as well prognostic markers, is crucial to establish appropriate management strategies. As proposed by Agewall et al (1), the diagnosis of MINOCA should be considered “work in progress” with every patient having to undergo thorough diagnostic investigations to identify the causal mechanisms. These authors (1) proposed a diagnostic algorithm that involves the systematic use of clinical and biochemical variables, cardiac imaging techniques and coronary arteriography with provocative tests for coronary artery spasm. Coronary artery spasm, whether epicardial and/or microvascular, is one of the mechanisms that needs to be investigated thoroughly in every suitable case given that specific treatment of coronary spasm with calcium channel blockers may improve symptoms and clinical outcomes in MINOCA patients.

In this issue of the Journal, Montone et al (7) assessed the safety and prognostic value of intracoronary provocative testing in patients presenting with MINOCA and in whom other “specific” causes of MINOCA were excluded. This was a single centre, prospective study involving 80 (mean age 63.0±10.7 years; 50% men) of 238 patients admitted to hospital with a diagnosis of MINOCA. Patients with myocarditis and takotsubo syndrome were not included in the study. Inclusion of these patients, however, would have allowed a more comprehensive assessment of the role of epicardial and/or microvascular spasm in MINOCA, as studies have highlighted the importance of coronary spasm in myocarditis (8) and takotsubo syndrome (9). All patients in the Montone study (7) underwent diagnostic coronary arteriography within 48 hours of admission to hospital, immediately followed by provocative tests for coronary artery spasm using intracoronary acetylcholine (ACh) (54% of cases) or ergonovine (46% of cases). Both epicardial and microvascular coronary artery spasm were diagnosed based on currently accepted definitions. Patients with documented coronary spasm received treatment with calcium channel blockers. After hospital discharge, patients were followed up at regular intervals up to 60 months with outpatient clinic visits and/or telephone interviews. All cause mortality, cardiac death, recurrence of AMI and recurrence of angina were specifically annotated.

Provocative tests were positive in 46 % of patients and there were no significant differences regarding clinical characteristics when patients with and without coronary artery spasm were compared. The prevalence of MINOCA in the Montone study (7) is in agreement with that in larger studies (1,3,4) and so is the high prevalence of coronary artery spasm (10-13). The Montone paper conveys –like previous studies in the field- an important message namely that coronary spasm is frequent in different forms of ischaemic heart disease and provocative tests are useful for the identification of these patients.

Of interest, in the Montone paper patients with positive tests for spasm had significantly worse clinical outcomes –including all cause mortality, cardiac death, readmission with AMI and frequency of angina episodes- compared with patients with a negative response to ACh or ergonovine testing during a follow up ranging from 12 to 60 months. Impaired clinical outcomes in the Montone paper are at odds with data from previous studies in patients with ACS (10,12,14). Reasons for the discrepancies among these studies are discussed by Montone et al (7) and it is likely that different inclusion criteria and a larger proportion of patients with AMI in their study could explain the worse clinical outcomes reported by the authors. Of importance, patients who received reduced doses of calcium channel blockers during follow up had increased mortality rates compared to those who continued taking high doses. Albeit an intuitively expected outcome, conclusions regarding this issue need to be taken with caution given that data relate to only 12 patients. This issue needs to be assessed in *ad hoc* properly powered studies. Compared with patients with microvascular spasm those with epicardial coronary artery spasm had a higher prevalence of all cause mortality and worse angina status at 1-year follow up but the Montone study is probably underpowered to provide definitive comparative prognostic data between epicardial and microvascular spasm. As proposed recently by Arrebola-Moreno et al (16) and Crea et al. (16) microvascular spasm, being able to cause perfusion and contractile abnormalities and cardiac troponin elevations (17) may have the potential to lead to adverse clinical outcomes during long term follow up.

Another important issue addressed by Montone et al (7) is the safety of provocative tests for spasm using either ergonovine or ACh, even when performed within 48 hours after the index event in patients with MINOCA. These findings confirm data from previous studies in patients with different presentations of ischaemic heart disease, including ACS, that tests to trigger coronary artery spasm can be carried out safely in the catheter laboratory when performed by trained personnel and following a strict protocol (10-14). No complications were reported by Montone et al (7) and this is probably due to the expertise of the team and the relatively small number of patients assessed in their study. A recent systematic review evaluated the safety of pharmacologic testing with ACh or ergonovine in over 9,400 patients presenting with stable angina or ACS (13). The overall occurrence of major (0.8%) and minor (4.7%) complications was low and no deaths were reported. The most common major complication were sustained ventricular tachycardia or ventricular fibrillation, which occurred in 0.69% of cases, cardiogenic shock (0.03%), AMI (0.01%), cardiac tamponade (0.01%), prolonged spasm (0.01%) and coronary dissection (0.01%) Compared to ergonovine, ACh showed a significantly higher rate of major (1.09% vs 0.15%; p<0.001) and minor adverse events (5.87% vs 2.36%; p<0.001). The most common minor event (2.17% of cases) was marked bradycardia and/or second- or third-degree AV block when ACh was injected into the right coronary artery. Although not reported by Montone et al (7), it is an almost universal finding that the injection of ACh in the right coronary artery induces transient AV block, which in most cases resolves spontaneously within 3-5 seconds –causing little if any symptoms- if the injection is either discontinued or slowed down. This phenomenon could actually be considered to represent a “normal” response to the injection of ACh rather than a complication. Perhaps the fact that a cut off of 3-second duration was used in the Montone study to define a bradyarrhythmia, resulted in the absence of this minor “complication”.

The relatively small number of patients representing a very selected patient population and the fact that this was a single centre study are important limitations, which make it imperative that Montone’s findings are confirmed and endorsed by rigorously conducted larger multicentre studies. Despite these limitations, Montone et al’s manuscript (7) makes a major contribution to the current debate regarding the role of abnormal coronary vasomotion as a trigger of both stable and unstable angina syndromes and a prognostic marker. Their paper has three crucial messages i.e. 1. In MINOCA patients, provocative tests for spasm identify a large proportion of patients who would otherwise be discharged from hospital without a firm pathogenic diagnosis

2. Provocative tests for spasm have prognostic significance and

3. Provocation of spasm can be performed safely in the catheter laboratory even when performed in the acute or sub-acute phases (i.e. within 48 hours) of MINOCA.

Hopefully, findings in the Montone study (7), in conjunction with data in previous studies in the field (10-15) will encourage both clinical teams to incorporate tests of coronary spasm to their routine clinical practice and clinical research groups worldwide to join forces to design definitive trials that can help establishing the true role of provocative testing for coronary artery spasm.

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