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Unrecognized myocardial infarction: time to rectify failures of detection and failures of prevention

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Unrecognized myocardial infarction: prevalent and deleterious

While the medical community champions the importance of the patient history since time immemorial, the visceral nervous system can fail to detect serious underlying cardiac pathology. Regions of myocardium can sustain necrosis without any patient awareness. Symptoms can be so nonspecific that an individual may not attribute their origins to the heart. Structured interviews document symptom variation in those feeling poorly enough to present with elevated troponins as well as other evidence of myocardial infarction (MI), e.g., prolonged ischemic signs/symptoms and/or electrocardiographic ST changes. Only 70% of such patients who present and who are ultimately diagnosed with MI actually experience chest discomfort. (1) Even in those where sudden coronary death represents their first (and last) symptom of coronary disease, pathologic examination reveals a considerable burden of both previously healed coronary plaque ruptures and healed MI that remains clinically unrecognized. (2)

Beyond these data depicting symptom variation for MI, clinical experience inevitably demonstrates that an MI can occur even without any symptoms. Any cardiovascular magnetic resonance (CMR) practitioner will encounter such scenarios. One of the authors vividly recalls one such patient, a middle-aged woman who presented only with orthopnea and dyspnea attributed to pleural effusions. She was articulate, educated, entirely, and lucid. She adamantly denied any ischemic symptoms in the days or even weeks preceding her hospital admission. Only markedly elevated troponin I levels revealed the root cause of her presentation: acute MI. CMR with late gadolinium enhancement (LGE) confirmed a large acute MI in the left circumflex territory with microvascular obstruction and no residual viability.

CMR with LGE represents the gold standard imaging test to diagnose MI, (3) possessing a sensitivity down to 0.7 g of infarcted myocardium or 0.4% of left ventricular mass. (4) ECG requires a certain mass of MI for detection, (5) and ECG sensitivity varies with infarct location. (6) CMR with LGE is more sensitive than SPECT (7) or PET. (8)

Studies in several clinical cohorts document a significant prevalence of unrecognized MI (UMI) that associates with atherosclerosis and also poor prognosis. (9-11) A large community-based cohort
study, the ICELAND MI substudy of the Age, Gene/Environment Susceptibility–Reykjavik Study, employing CMR with LGE confirmed the high prevalence, associations with atherosclerosis, and adverse prognosis associated with UMI in older patients with a mean age of 75 years. Yet, these results did not extend to MESA participants characterized by lower risk profiles for coronary disease. Nor did they extend to much younger community-based cohorts with a mean age of 53 years suggesting a strong relationship with age. Indeed, UMI prevalence appears to accelerate with age such that the prevalence of UMI in older individuals exceeds the prevalence of recognized MI (RMI) with an approximate 2:1 ratio and a similar mortality rate. Importantly, the ICELAND MI study revealed that coronary risk factors measured in mid life associate with UMI 31 years later, suggesting a long latent period and an opportunity to modify risk and halt disease progression.

In this issue of the Journal, Amier and colleagues contribute to the UMI literature by reporting the prevalence and prognosis of UMI specifically in those ostensibly presenting with their first MI. Their LGE data from two CMR centers in the Netherlands between 2003-2013 demonstrate that UMI occurred in 8.2% (32 of 392) patients of those presenting with AMI, specifically without any history of prior MI. Furthermore, while relatively small (~5 g of myocardium), these UMI’s nonetheless associated with adverse events. UMI significantly associated with all-cause death in multivariable analysis (HR 3.87, 95% CI 1.21–12.38, p=0.023) adjusting for age, sex, study site, medication, AMI type, multivessel disease, reperfusion strategy, ejection fraction, infarct size and microvascular obstruction. Multivariable analysis yielded similar results modeling death, hospitalization for acute MI, coronary artery bypass grafting and/or ischemic stroke (HR 3.10, 95% CI 1.22–7.86, p=0.017). UMI by ECG did not stratify risk.

The authors’ fine work underscores the concept that UMI represents a worrisome event in the progression of coronary artery disease, representing a more advanced phenotype with more coronary plaque instability. Remarkably, another group recently corroborated the findings from Amier and colleagues; Omori and colleagues report that, “Among patients with a first clinical episode of AMI, unrecognized [non-infarct-related] myocardial scar provides incremental prognostic value for predicting MACE beyond that of common clinical, angiographic and functional variables.”
A failure of detection and a failure of prevention

The aggregate UMI data provide compelling evidence that despite the era of guidelines and risk calculators, routine cardiac care misses prognostically important coronary disease. UMI represents the “footprint” of prior unstable coronary artery disease,(2) where the patient survived, but remains vulnerable to adverse events with progressively diverging survival curves. Astonishingly, in the elderly, epidemiologic data indicate that recognized MI represents only the “tip of the iceberg,” with 1-2 additional UMI patients for every patient with a recognized MI in this age demographic.

Call to Action

Given these truly disturbing data, we propose the following recommendations to the cardiology community:

1. Inclusion of CMR with LGE as an endpoint in future therapeutic intervention trials attempting to lower the incidence of MI—both primary and secondary prevention trials. ECG is inadequate. We have concerns that if one does not measure the incidence of UMI in vulnerable patients, one will underestimate the true therapeutic efficacy of the intervention.

2. Primary UMI prevention trials in those at risk, especially the elderly and/or those with diabetes.(12)

3. Secondary prevention trials of risk factor modification in those with UMI.

Although unconfirmed, it seems intuitive that therapeutic lifestyle changes, and potentially even statins or PCSK9 inhibition, could prevent UMI. These efficacious interventions are known to improve outcomes. At a minimum, the cardiology community should strive to accurately phenotype those with known or suspected coronary artery disease, especially the elderly, where UMI are more prevalent than
recognized MI. These strategies may advance our pathophysiologic understanding of coronary artery
disease and UMI, and may improve patient outcomes.

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