Slow but steady progress towards understanding peri-procedural myocardial infarction

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This editorial refers to ‘Frequency, causes, predictors, and clinical significance of peri-procedural myocardial infarction following percutaneous coronary intervention’, by D.-W. Park et al., on page 1662

Despite over two decades of research, the clinical significance and optimal management of peri-procedural myocardial infarction (PMI) remains a matter of considerable controversy. The topic is important because percutaneous coronary intervention (PCI) is the dominant method for revascularization, with over a million patients around the world receiving the therapy each year. The large body of data correlating PMI with adverse clinical outcomes provides compelling evidence that it may be a clinically meaningful complication of PCI. However, our knowledge of this entity is limited by the fact that virtually all data published to date are retrospective, demonstrate an association with outcomes but not a causal relationship, pre-date the use of contemporary cardiac troponin (cTn) assays with the recommended 99th percentile cut-off value for the upper reference limit (URL), and do not provide an explanation for the fact that even a trivial elevation in a biomarker is associated with an unfavourable outcome. From a clinician’s perspective, the unanswered questions are—whether one should routinely screen for PMI, which patients need to be observed in hospital for a longer duration after PMI, what are the therapeutic implications, what should we tell patients who sustained a PMI despite an otherwise successful procedure, and is PMI prognostically equivalent to spontaneous myocardial infarction (MI)? The recently published third universal definition of MI attempts to provide some guidance by defining PMI in patients with normal (<99th percentile URL) baseline cTn concentrations as an elevation of >5 × URL within 48 h of the procedure together with either (i) evidence of prolonged (>20 min) ischaemia as demonstrated by chest pain; (ii) ischaemic ST changes or new pathological Q waves; (iii) angiographic evidence of a flow-limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolization; or (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.3 The key changes from the second universal definition are that cTn is now the only biomarker recommended, the threshold has been increased from 3 × URL to 5 × URL, and clinical criteria have been added for defining PMI.4 Nevertheless, even this revised definition is far from perfect, with the authors of the document acknowledging that it remains arbitrary.

Creatine kinase-MB vs. troponin

Park et al. have presented a comprehensive analysis of the incidence, mechanisms, risk factors, and relationship to outcomes of PMI following PCI, defined as post-procedural creatine kinase-MB (CK-MB) mass >3 × URL in patients with a normal baseline values or a ≥50% increase in those with elevated but stable or falling pre-procedural levels.5 The incidence of PMI was 7.1% among the 23,604 patients derived from eight clinical trial databases and three registries. The incidence is similar to previous studies,6 although there are two aspects regarding the choice of the biomarker that are noteworthy.

First, CK-MB mass, rather than activity, was used because it was the test that was reimbursed in the investigators’ country at the time of the studies. However, this assay is not widely used in contemporary practice, which limits the applicability of the findings. Secondly, a major limitation of the study is that cTn levels were not measured. By virtue of the greater sensitivity and specificity of cTn, its assessment can greatly improve risk stratification, especially with regards to the pre-procedural risk. Patients with elevated pre-procedural cTn, even at very low levels, are characterized by greater atherosclerotic burden and disease aetiology. In a large single-centre study from the Mayo Clinic, in which the 99th percentile URL was used as the cut-off value for a contemporary cTnT assay, among those with normal pre-procedural values the extent of PCI-related myonecrosis was exceedingly small (inter-quartile range of <0.01–0.04 ng/mL).2 CK-MB >5 × URL occurred in only 3.5%, and Q-wave infarction occurred rarely (<0.1%). CK-MB elevation of >5 × URL was generally observed in patients with significantly elevated pre-procedural cTnT.5 Similar results have been reported by Cavallini et al. using cTnI.7 Thus, it is very likely that a large proportion of patients in the
study by Park et al., and similar previous studies, who had been classified as biomarker-negative prior to PCI using CK or CK-MB, actually had non-ST-segment elevation MI as their presenting diagnosis by contemporary definitions. For these reasons, some experts have stated that ‘CK-MB no longer has a role in defining post-PCI injury’ and increasingly many hospitals are no longer routinely measuring CK-MB. Conversely, the major challenge with using cTn, due to its sensitivity, is the high frequency (30–40%) of myonecrosis detected following PCI, an issue that is likely to become even more acute with the introduction of high sensitivity assays. Thus, there is an urgent need to determine how best to define PMI using cTn, and identify if there are clinically meaningful cut-off values following PCI which almost certainly need to be at a higher threshold than the 5× URL currently recommended by the universal definition.

**Defining peri-procedural myocardial infarction in patients with elevated pre-procedure biomarkers**

Patients with acute coronary syndrome represent an increasing proportion of those undergoing PCI, and hence defining PMI in this subset is important. Park et al. included patients presenting...
Mechanisms for peri-procedural myocardial infarction

Park et al. have probably conducted the largest systematic review of angiograms to establish the mechanism of PMI and confirm the findings reported in previous smaller studies. Side-branch occlusion was the most common cause (57.3%). Other reasons included slow- or no-reflow, flow-limiting dissection, and distal embolization. Notably, no mechanism could be identified in 21% of cases in whom microembolization and microvascular injury were the likely mediators of myocardial damage (Figure 1). Understanding these mechanisms is important because that may allow us to devise strategies for preventing and treating clinically significant PMI.

Clinical significance of peri-procedural myocardial infarction

Park et al.’s conclusion that CK-MB $>3\times$ URL is associated with statistically significant and, by implication, clinically meaningful increased risk of mortality is consistent with previous studies using this biomarker because the analyses share the limitation of inadequate assessment and adjustment for the pre-procedural risk, as discussed above. The confounding factor in these studies is that patients with PMI, compared with those without, have a greater burden of atherosclerosis and more complex coronary lesion anatomy. Recent studies using contemporary cTn assays with appropriate cut-off values have better addressed this limitation, and report low, if any, independent predictive value of PMI for adverse outcomes.2,7,9 Similarly, an analysis from the ACUITY trial database in patients presenting with non-ST-segment elevation acute coronary syndrome found that spontaneous MI was a powerful independent predictor of mortality, but, in comparison, PMI was not.10 This fact is highlighted in a recent investigation from the EARLY-ACS and SYNERGY trial databases consisting of 9087 patients who underwent PCI. The CK-MB threshold for PMI that achieved a similar prognostic significance to a spontaneous MI was 2.77 (95% confidence interval 13.9–58.4) × URL.11 These studies clearly illustrate that spontaneous MI, and PMI defined using biomarkers alone at the currently recommended cut-off values, do not have similar prognostic implications.

In conclusion, recent studies suggest that in general, PMI defined by biomarker levels alone is a marker of atherosclerosis burden and procedural complexity, but in most cases does not have independent prognostic significance. Although, large PMIs may impact prognosis, these rarely occur in patients with normal baseline cTn or in the absence of procedural complications. Future research needs to establish the optimal cTn threshold for defining a clinically significant PMI, and determine the appropriateness and utility of the third universal definition of PMI (type 4a).

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References