Editorial
Periprocedural myonecrosis: from a laboratory anomaly to a sentinel of risk

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Background

Percutaneous coronary intervention (PCI) is one of the commonly performed procedures in the United States with the annual number of procedures exceeding 1 million. The prevalence of coronary artery disease continues to increase globally and with the recent availability of anti-restenotic stents, the number of patients who undergo coronary PCI is expected to rise dramatically. PCI is usually performed for symptom relief although there are clear survival benefits in certain populations. Although fairly safe, the procedure is often accompanied by a small degree of myonecrosis as detected by a rise in creatinine kinase (CK)-MB isoenzyme or troponins[1].

The incidence of post-procedural CK-MB rise varies from 10-40% in various studies[1]. While there is general agreement that marked elevations in CK-MB carry an adverse prognosis, the significance of minor rise has been issue of some debate with some studies describing a worse outcome with any rise while others demonstrating a non linear effect with adverse outcome limited to patients with a CK-MB > 5× upper limit of normal (ULN)[1-19]. Further, while there is an increase in adverse events in the patients with post-PCI myonecrosis, it has been unclear as to the time course and determinants of this increased hazard.

Myonecrosis after PCI may be related to localized luminal obstruction as in acute vessel closure, coronary dissection or side branch compromise or may be related to distal embolisation[3]. Recently investigators at Northwestern University performed contrast enhanced magnetic resonance imaging on 14 patients who had undergone successful PCI[20]. Patients who had evidence of myonecrosis as determined by CK-MB rise showed evidence of localized myocardial injury visualized as discrete regions of hyper enhancement on magnetic resonance imaging. Two anatomic correlates of myonecrosis were identified; side branch occlusion and microvascular obstruction. The relative significance of these distinct causes of myonecrosis remains undefined.

Studies using intravascular ultrasound have demonstrated an association of post-procedural myonecrosis with greater plaque burden[15]. In a study of 2256 patients, Mehran et al.[15] reported an increased plaque size at both the lesion and the reference site in patients who subsequently developed an elevated CK-MB after PCI. It has been argued that CK-MB elevation may be a consequence of catheter-based intervention in more diseased arteries and hence the adverse prognosis associated with it may simply relate to its association with advanced coronary disease.

A recent study from our laboratory provides some further insight into the significance of myonecrosis after PCI. This study focused on the association of degree of myonecrosis and outcome, and the correlates of early mortality including the impact of post-discharge medication on the adverse impact of myonecrosis.

The study population consisted of 8409 patients undergoing successful PCI between January 1995 and June 2001. Patients with acute myocardial infarction and those with elevated CK-MB at baseline were excluded. Further exclusions included the patients defined as technical failures (lesion > 50% at end of procedure or TIMI flow ≤ 2), those needing emergency bypass

surgery, dying within 24 hours or those with Q wave infarction. Follow-up was 97.7% at 1 year. CK-MB was routinely ascertained 6-8 hours and the morning of the PCI and in the event of suspected ischemia. Myonecrosis, defined as any rise in CK-MB above ULN was seen in 17.2% (n = 1446) of the population. The 4 months immediately following PCI were associated with the greatest mortality hazard in patients with any myonecrosis. A non linear relation of post-PCI CK-MB rise and mortality was observed, with the 4-month risk of death being 1.2% in those with CK-MB ≤ ULN, 1.9% in those with CK-MB 1-5× ULN and 8.9% in those with CK-MB > 5× ULN. No deaths were reported in the CK-MB 1-5× ULN group within the first week. Although the mortality hazard in patients with CK-MB elevation remained significantly elevated beyond 4 months the association was somewhat attenuated with an excess risk of mortality (compared to those with normal CK-MB) at 4 years being 2% in those with CK-MB 1-5× ULN and 4.5% in those with CK-MB > 5× ULN.

In a multivariate model evaluating the entire population, the degree of CK-MB elevation, renal insufficiency, elevated post-procedural C-reactive protein, low ejection fraction, age, and NYHA congestive heart failure class were independent correlates of early death. Further, we compared patients with CK-MB elevation who died to a propensity-matched cohort of patients with CK-MB rise who were still alive at end of follow-up. In this cohort independent correlates of death were incomplete revascularization, congestive heart failure class, and hospital discharge without a statin. Discharge on a non steroidal anti-inflammatory medication was also associated with a protective, albeit weaker, association (p = 0.029).

Our work suggests that there is some hazard associated with any rise in CK-MB although the risk is significantly higher in those with a more substantial rise. Further, the significance of elevated C-reactive protein, statin therapy and possible non steroidal anti-inflammatory therapy in patients with myonecrosis as risk factors for death within 4 months of PCI suggests that inflammatory processes modulate at least part of the increased hazard. That there exists an early risk period of 3-4 months would suggest that the rise in CK-MB carries a prognosis worse than that due to an increased atherosclerotic burden, i.e. an independent effect of myonecrosis. It is plausible that myonecrosis triggers an inflammatory reaction that predisposes either to arrhythmogenesis, myocardial dysfunction or plaque instability. This hypothesis merits further investigation in prospective studies.

Our analysis helps select high-risk patients in whom CK-MB elevation carries a particularly adverse prognosis. Thus a patient with incomplete revascularization or with congestive heart failure would be at a greater risk after developing post-PCI myonecrosis and may merit closer follow-up. Further strategies at using anti-inflammatory agents prior to or after PCI need to be explored as means to possibly reduce the degree of myonecrosis and to attenuate the risk associated with it. Further the protective effect of statins demonstrated in our study adds to the evidence supporting the use of these agents in patients undergoing PCI[21]. Further research is warranted focusing on the relative significance of the two anatomical variants of myonecrosis, and the use of established and novel anti-inflammatory therapies for plaque stabilization as a means of preventing myonecrosis.

While it is customary for editorials to invoke a need for more research, it is also important to focus on the clinical ramifications of this study. Since CK-MB now has been established as a marker of risk, it should be routinely obtained in all patients undergoing PCI. While there is a growing displacement of CK-MB by troponin in patients with acute coronary syndromes, the significance of troponin elevation after PCI remains to be established before it can be introduced into the daily clinical practice. Strategies that have been demonstrated to reduce myonecrosis by either inhibiting platelets[22] or by mechanically preventing distal embolization[23] need to be utilized where appropriate. All patients who do not have an absolute contraindication should be on a statin after PCI. Finally the degree of CK-MB elevation may help risk stratify the need for prolonged hospitalization. A CK-MB rise of < 5× ULN does not by itself indicate a need for prolonged hospitalization, those with a greater rise may need closer observation based on presence of additional risk factors. Rather than being a laboratory anomaly, CK-MB has finally been established as a sentinel of increased risk in patients undergoing PCI.

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