UNTREATABLE CORONARY ARTERY DISEASE

Prognostic Importance of Myonecrosis after Percutaneous Coronary Interventions

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ABSTRACT: Occurrence of myonecrosis can be documented after percutaneous coronary interventions (PCI). Data have correlated this phenomenon with late mortality, and with diffuse atherosclerotic disease. While controversy still exists, the potential for improved mortality after PCI should be fully explored in a systematic way.

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Although improvements in operator technique and equipment have reduced the incidence of death or emergency coronary artery bypass surgery during and after a percutaneous coronary intervention (PCI), procedural myonecrosis remains the most common complication of PCI. Creatine kinase myocardial band isoenzyme (CK-MB) elevation after PCI has been reported in up to one third of PCIs and even as high as 47% following successful saphenous vein graft (SVG) angioplasty. While the prognostic importance of a relatively small increase of CK-MB above normal levels in unstable angina or with myocardial infarction (MI) are well recognized, there is significant controversy regarding the prognostic importance of myonecrosis after technically successful PCI.

Prognostic significance of myonecrosis. Early data from small studies on low-risk patients with limited long-term follow-up suggested that elevation of cardiac enzymes after PCI might be rather inconsequential. In contrast, large datasets have progressively established the unfavorable association between myonecrosis after PCI and late mortality (Table 1). Abdelmeguid et al. examined 4,484 patients who underwent successful angioplasty or directional atherectomy and showed that those with elevated CK-MB had a significantly higher incidence of cardiac death and subsequent MI.

Kong et al. followed 253 patients with both total CK and CK-MB elevation and 120 control patients without CK elevation after PCI, and also found increased cardiac mortality and subsequent MI in patients with high (> 3.0 times normal) and intermediate (1.5–3.0 times normal) CK elevation compared to those with mild (1.0–1.5 times normal) or no CK elevation.

Tardiff et al. examined these relations in patients enrolled in the Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis-II (IMPACT-II) trial. It was shown that patients who had an elevated CK-MB level after PCI were at increased risk for death, subsequent MI, and urgent revascularization at 30 days, and for death, subsequent MI, and surgical revascularization at 6 months. The degree of risk was proportional to the magnitude of CK-MB elevation.

The risk for development of CK-MB elevation after saphenous vein graft intervention is also high, as reported by Hong et al. In 1,056 PCI patients with successful vein graft intervention, one-year mortality was 4.8%, 6.5%, and 11.7% in patients with no elevation, minor elevation and major CK-MB elevation, respectively ($p < 0.05$). The same one-year mortality relationship persisted even when patients who had any intra-procedure angiographic complications or any in-hospital complications were excluded.

Device use and CK-MB elevation. The risk of CK-MB elevation increases significantly with the use of new devices such as directional and rotational atherectomy. Harrington et al. reported on findings in 1,012 patients
enrolled in the randomized Coronary Angioplasty Versus Excisional Atherectomy (CAVEAT) trial comparing directional coronary atherectomy with PTCA. Atherectomy was associated with a greater incidence of enzyme-positive events, and CK-MB elevation (> 3 times normal) was associated with higher rates of 1-year mortality (5.4% vs. 1.5%, respectively; \( p < 0.05 \)).

The IMPACT-II trial also demonstrated that the use of directional (n = 369) or rotational atherectomy (n = 292) was associated with more frequent and greater CK-MB elevation. CK-MB elevation was associated with increased 30-day and 6-month event rates, regardless of device.

Kugelmass et al.\(^8\) evaluated 565 patients treated with directional atherectomy (n = 274) and stenting (n = 291). There was a significant reduction in survival in patients with CK-MB level > 50 IU/l (2.3% of the patients). In contrast, there was no significant difference in 2-year survival between patients with CK-MB elevation < 50 IU/l (9.2% of the patients) and those with no CK elevation.

Saucedo et al.\(^9\) recently evaluated data from 900 patients (1,213 lesions) undergoing successful stenting in native vessels. Based on the CK-MB levels after coronary stenting, patients were classified into three groups: normal, group 1 (n = 585); elevation of 1 to 5 times normal, group 2 (n = 238); and elevation of > 5 times normal, group 3 (n = 77). Long-term clinical events were similar between groups 1 and 2. However, patients in group 3 had an increased incidence of late mortality compared with patients in groups 2 and 1 (6.9%, 1.2% and 1.7%, respectively, \( p = 0.01 \)).

Cutlip et al.\(^10\) analyzed the pooled data from 3,387 patients treated with various interventional devices enrolled in the Balloon versus Optimal Atherectomy Trial (BOAT), Stent Anti-Thrombotic Regimen Study (STARS) Registry, and the Study to determine Rotablator and Transluminal Angioplasty Strategy (STRATAS) trials. Devices included balloon angioplasty (14%), directional atherectomy (14%), stent (57%), and rotational atherectomy (15%). Patients were classified into 3 groups: Type 1, CK-MB ratio > 1 and < 3; Type 2, CK-MB ratio > 3 and < 8 or CK-MB ratio > 1 and < 3 with ST abnormalities; and Type 3, Q-wave MI or CK-MB ratio > 8. Unlike other studies, there was no association between any cardiac enzyme elevation and late mortality.

Kini et al.\(^11\) evaluated the relationship between CK-MB elevation and mid-term survival after PCI using current devices (PTCA, 10.4%; rotational atherectomy, 25.1%; stent, 28.5%; rotational atherectomy and stent, 31.9%; others, 4.1%). CK-MB elevation was detected in 18.7% of 1,675 patients (1–3 times normal in 12.8%; 3–5 times normal in 3.5%; and > 5 times normal in 2.4% of patients). CK-MB elevation was more common after non-balloon devices (19.5% vs. 11.5%; \( p < 0.01 \)). During a mean follow-up of 13 ± 3 months, the incidence of death in the CK-MB elevation group was 1.6% vs. 1.3% in the normal CK-MB group (\( p = 0.43 \)), although patients with > 5 times normal CK-MB elevation had a higher incidence of cardiac death (7.5%) compared to those in other groups (\( p = 0.016 \)).

**Mechanisms responsible for CK-MB elevation.**

The data from non-human primate models suggest that CK-MB elevation may occur without evidence of myocardial necrosis by standard histopathologic techniques following transient coronary artery occlusion.\(^{14}\)
However, once intracellular enzymes start leaking from myocardial cells, cellular injury is usually considered to have reached a stage of irreversibility. Histological data confirmed that CK-MB elevation, even without an abnormal elevation of total CK activity, could be associated with several small areas of myocardial necrosis. Myocardial necrosis in this setting could result from embolization of plaque microparticles, debris of intravascular friable material, clots, or cholesterol crystals. Also, minor in-lab complications (e.g., transient vessel closure, side-branch compromise, major dissection, and significant hypotension) are conditions that may potentially cause small zones of necrosis because of myocardial and coronary blood flow disturbance. However, CK-MB elevation is sometimes observed even among patients with successful PCI and no minor in-lab complications. The IMPACT-II trial demonstrated, in 441 of 557 patients (79.2%) with post-procedural CK-MB elevation, that there were no residual stenoses > 50%, and no thrombus, side-branch occlusion, distal embolization, or abrupt closure. Similar findings were reported by Hong et al. following successful vein graft PCI in patients without any major or even minor in-lab complications.

**Potential mechanisms of adverse cardiac events in patients with CK-MB elevation.** Although some of the previous studies demonstrated a prognostic significance for mild-to-moderate CK-MB elevation after PCI, the mechanism by which CK-MB elevation affects long-term prognosis has not been established. It is not clear whether myocardial necrosis or severity of the patient’s underlying illness is responsible for the associated risk. It is likely that increased cardiac enzymes reflect small zones of necrosis, providing a nidus for lethal ventricular arrhythmias. Another potential mechanism is the compromise of coronary collaterals by coronary embolization, which could lead to a higher incidence of ventricular arrhythmias and a larger infarct when the subsequent ischemic event develops.

Alternatively, CK-MB elevation might represent a marker of a high-risk population with other risk factors that can adversely affect long-term prognosis. CK-MB elevation may occur predominantly in patients with more severe disease, particularly in those with more diffuse atherosclerosis; from this perspective, adverse long-term prognosis may not be due to myocardial necrosis reflected by CK-MB elevation itself, but due to underlying severity of the patients. However, some studies have failed to show that the adverse events associated with CK-MB elevation are explained by more severe underlying disease. It may be that, despite adjusting for all known risk factors for cardiac mortality, patients with CK elevation have more extensive disease that cannot be accounted for with routine angiographic methods.

Mehran et al. recently examined 2,256 patients who underwent intervention of 2,780 native coronary artery lesions and had complete pre-intervention intravascular ultrasound (IVUS) imaging. It was demonstrated that IVUS plaque burden at both the lesion and reference segments was an independent predictor of CK-MB elevation after PCI, together with de novo lesions, atheroablative technique, and final minimum lumen diameter. This supports an association between CK-MB elevation and diffuse atherosclerotic disease.

**Clinical implications and future directions.** Because CK and CK-MB elevation are still common complications of PCI, it is an important issue in clinical practice. The real question is how to treat patients with CK-MB elevation. It is clear that high CK-MB elevation is associated with later adverse events. However, there is still controversy regarding the prognostic importance of mild-to-moderate CK-MB elevation. In this situation, we think that until this issue is clarified, mild-to-moderate CK-MB elevation after PCI should be treated as MI. Routine post-procedural CK-MB evaluation as well as electrocardiogram should be recommended after PCI and patients with CK-MB elevation should be carefully followed during the first few years after the procedure. Previous studies showed lower incidences of CK elevation after PCI in patients treated with platelet glycoprotein IIb/IIIa inhibitors and β-blocker prior to PCI. Therapeutic strategies to reduce the incidence of CK-MB elevation are clearly warranted in high-risk patients. In addition, the value of continued careful follow-up of patients after PCI is also warranted.

The potential for improved survival after PCI is too important to be dealt only with theoretical arguments. It should attract a serious investigational effort in the near future, and should constitute a prime target of interventional cardiology research. Periprocedural myonecrosis is already important because it has indicated the direction for future, meaningful investigation, even if it may be just an “innocent bystander.”

**REFERENCES**


