Cardiac enzyme release following percutaneous coronary intervention

Introduction

The measurement of biochemical markers of myocardial cell damage is a key component of modern cardiology practice. The use of these tests in the diagnosis of myocardial infarction (MI) has been routine for three decades, with the measurement of serum levels of creatine kinase (CK) and its myocardial band isofraction (CK-MB) emerging as the traditional standard in this respect.

More recently, the use of cardiac troponins has been introduced. Troponins are more sensitive and more specific for myocardial cell damage than previous biochemical markers. Troponin estimation allows the detection of modest levels of myocardial cell injury. This has given troponin estimation a role in the risk stratification of patients presenting with unstable angina and has enabled MI events that may previously have gone unrecognised to be detected. A new consensus definition of MI has been framed by the American College of Cardiology and European Society of Cardiology. It recognises the negative impact of even minor levels of myocardial cell death and extends the diagnosis to include such cases.

There has been growing interest in the routine measurement of cardiac enzymes after the performance of percutaneous coronary intervention (PCI) procedures. These interventions involve deliberate rupture of atherosclerotic plaque, usually by barotrauma, creating a local pathology akin to an acute coronary syndrome event. Beyond this, there is potential for the closure of target or branch vessels, embolisation of atherosclerotic or thrombotic debris and the induction of ischaemia with balloon occlusion. The aim of this editorial is to describe the reported incidence of enzyme release following PCI, and its likely prognostic impact.

Incidence of cardiac enzyme release

The release of cardiac enzymes after PCI is surprisingly common, even in elective cases. Between 6% and 35%[2-5] of otherwise successful procedures and as many as 47% of vein graft PCI cases[6,7] may be followed by a detectable increase in CK-MB. The greater sensitivity of cardiac troponins is associated with an even higher rate of detectable enzyme release post-PCI. Published studies suggest between 17% and 48% of cases may be affected.[8-10]

Impact on outcome

A rise in cardiac enzymes has been shown to correlate with an increased incidence of adverse events, including medium-term mortality.[2,6-8] Saucedo *et al*. reported a prospective observational follow-up of 900 patients undergoing successful native vessel percutaneous transluminal coronary angioplasty (PTCA) and stenting.[2] Some 34.9% of all subjects had a rise in CK-MB: 26.4% had a CK-MB elevation of between one and five times the upper limit of the local reference range, and 8.5% had a rise greater than five times this value. Compared to those with no enzyme rise, the risk of recurrent chest pain, repeat catheterisation and pulmonary oedema whilst in hospital was increased in those with an intermediate CK-MB rise (10.2% *vs.* 5.9%; 4.9% *vs.* 2.1%; 3.2% *vs.* 0.8%, respectively). Observed differences were more marked in cases with a greater than five-fold CK-MB increase (31.6%, 13.9% and 8.8% respectively).

In a prospective follow-up study of 8,409 non-acute PCI cases, Ellis *et al*. found that mortality at four months was 8.9% for those with CK-MB elevation of more than five times normal, 1.9% in those with levels one to five times normal, and 1.2% in those with no rise.[11] Other studies have shown similar findings.[12]

Late outcome was also affected in the series of Saucedo *et al*. Mortality in those with an intermediate (1–5 xULN) CK-MB rise was no different to those without enzyme release. However, a post-procedural CK-MB of greater than five times the upper limit of normal was associated with a four-fold increase in mortality at a mean of 14 months (6.9% *vs.* 1.7%, p=0.01).[2]

In another large study of 4,484 patients undergoing successful PCI, outcome at a mean of 36 months was adversely affected by only a modest increase in CK. A CK rise to less than twice the upper limit of normal with a concurrent elevation of CK-MB isofraction greater than 4% carried a 30% increase in risk of death and a 30% increase in MI.[13]

Mechanism of enzyme release

An increase in circulating cardiac enzymes can only occur with myocardial cell membrane compromise. Usually this means cell death. A direct anatomical correlation of enzyme release with muscle infarction was demonstrated in a study using magnetic resonance imaging post-PCI.[14] Areas of hyperenhancement, which are known to represent discrete myonecrosis, were seen within the relevant arterial territory in subjects with an enzyme rise. These were absent in subjects without an enzyme rise.

The cause of cell injury and enzyme release due to PCI is multifactorial. Abrupt closure, dissection, spasm or loss of side branch may be associated with an enzyme rise. Distal embolisation of plaque or thrombus debris and the effect of local hypoperfusion from prolonged balloon inflation or systemic hypotension can be less evident at the time of the procedure, but may be equally relevant. In some cases an enzyme rise can be unheralded, although a larger rise (CK or CK-MB greater than five times normal) is more likely to be associated with discernible procedural complications.[5] Most subjects sustaining an enzyme rise will have pain or detectable electrocardiography (ECG) change during or after the procedure but ECG evidence of Q-wave infarction is rare (1%).[2]

Clearly, casemix may predispose to enzyme release, as may procedural factors. Age, diabetes, an unstable presentation, systemic atherosclerosis, diffuse coronary disease, chronic renal impairment, procedure length, total balloon inflation time and vein graft PCI have all been shown to correlate with enzyme rise post-procedure.[5,11] Studies have also shown the use of atherectomy (and other 'non-balloon' devices) to carry an independent risk of enzyme release.[5] Nevertheless, the majority of enzyme release events cannot be predicted prior to performance of the PCI procedure.

Implications

The general consensus from published reports is that enzyme release confers an increased risk of cardiovascular events, both in the short and long term. The bulk of published data relates to the use of CK and CK-MB. Few would argue with the prognostic impact of a large (greater than five times ULN) CK-MB rise, but there appears to be an incremental risk with increasing CK-MB release, with even small rises being clinically significant. A consensus report, published in 1998, recommended the use of CK-MB, with a level of three times normal being considered as an MI, and managed as such.[4]

Some authors have suggested that troponins may be 'too sensitive' for use in the context of post-PCI monitoring.[15] Such reports found no excess risk with small troponin rises. Other studies have refuted this concept and have found that the detection of low levels of circulating cardiac troponin denotes an increased risk. A threshold below which no adverse risk is suggested has yet to be clarified, hence the role of troponins in routine monitoring is less clear.[4,8,9]

The timing of sampling is also important. In most cases, the peak enzyme rise is observed at 6–8 hours but it may occur as late as 24 hours after a procedure.[5] The time course of enzyme release probably reflects the underlying mechanism of cell injury. A series of samples may be more reliable than a single sample in determining the peak enzyme rise, and should ideally include a pre-procedural assay and then further samples at eight and 16 hours after PCI.

Recommendations

Many operators are reluctant to accept that MI events occur in a substantial proportion of otherwise successful procedures. The dismissive terms 'enzyme leak' and 'microinfarction' are often used. Currently, the British Cardiovascular Interventional Society recommends that enzyme data be measured on all PCI cases. However, many centres do not routinely collect these data and, even when available, they do not influence the immediate clinical course.

In a minority of cases, enzyme release may be inevitable: it may be a marker of a high-risk procedure related to characteristics of the patient, clinical presentation or angiographic pattern of disease. Beyond these, however, the fact that enzyme elevation events are not universal implies that there must be scope for improved clinical outcome with greater attention to certain aspects of patient preparation or procedure performance.

There may be scope for expanded use of glycoprotein IIb/IIIa antagonists. These agents have a proven value in the limitation of per-procedural MI events.[16-19] Even with their routine application, there may be value in close attention to the induction of optimum platelet inhibition before initiation of PCI plaque disruption. This should include early pre-medication with oral agents[20] and prompt initiation of anti-glycoprotein IIb/IIIa therapy in the laboratory.

Data from cardiac and non-cardiac surgery have suggested that routine use of beta blockers and avoidance of preoperative anaemia may limit infarction complications.[21-23] Similar data have been published favouring the use of beta blockade in the setting of PCI.[24,25] It is possible that statin therapy or other anti-inflammatory therapy may emerge in the future.[26]

Procedural issues will also be important. It may be unwise to dismiss the importance of side branches, however small, and prolonged myocardial ischaemia and systemic hypotension should be avoided.

The key to progress is recognition that this is an issue that demands attention. The usual declaration of 'an excellent result' with a self-congratulatory review of the final angiogram is no longer acceptable.

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