Peri-procedural myocardial injury during percutaneous coronary intervention: an important target for cardioprotection

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Percutaneous coronary intervention (PCI) has become the predominant procedure for coronary revascularization in patients with both stable and unstable coronary artery disease (CAD). Over the past two decades, technical advances in PCI have resulted in a better and safer therapeutic procedure with minimal procedural complications. However, about 30% of patients undergoing elective PCI sustain myocardial injury arising from the procedure itself, the extent of which is significant enough to carry prognostic importance. The peri-procedural injury which accompanies PCI might therefore reduce some of the beneficial effects of coronary revascularization. The availability of more sensitive serum biomarkers of myocardial injury such as creatine phosphokinase MB isoenzyme (CK-MB), Troponin T, and Troponin I has enabled the quantification of previously undetectable myocardial injury. Peri-procedural myocardial injury (PMI) can also be visualized by cardiac magnetic resonance imaging, a technique which allows the detection and quantification of myocardial necrosis following PCI. The identification of CAD patients at greatest risk of sustaining PMI during PCI would allow targeted treatment with novel therapies capable of limiting the extent of PMI or reducing the number of patients experiencing PMI.

Keywords
- Percutaneous coronary intervention
- Ischaemia
- Reperfusion
- Myocardial infarction

Introduction

Although medical therapy can be used for prognostic and symptomatic benefit, coronary revascularization by either coronary artery bypass graft surgery or percutaneous coronary intervention (PCI) remains an important approach for the treatment of occlusive coronary artery disease (CAD). In Europe, the number of PCIs increased from 184 000 to 885 000 during the period 1992 to 2004 and in 2006, 1 001 000 PCIs were reported. It is projected to increase to 1.5 million procedures by 2010. In the USA, 1.3 million PCI procedures were performed in 2006. Changing patient demographics mainly linked to increased life expectancy have resulted in the increased prevalence and complexity of CAD affecting an older age group.

Since the first description of coronary angioplasty in man by Andreas Grüntzig in 1977, the procedure has been extensively modified. The technical advances coupled with the use of coronary stents and adjuvant drug therapy have resulted in high procedural success rates and low re-stenosis rates. Older patients are now being treated, and more complex multiple coronary lesions deemed appropriate for PCI. Percutaneous coronary intervention improves symptoms in patients with stable CHD, but does not improve clinical outcomes. About one-third of all elective PCI procedures are associated with significant myocardial injury (termed peri-procedural myocardial injury, PMI), which has been associated with increased subsequent mortality. This underscores the importance of risk stratifying prior to the procedure to identify the patient group most likely to develop PMI. If PMI incidence can be reduced clinical outcomes would be expected to improve. In this article, we review the underlying aetiological factors resulting in PMI, the methods available for its detection and quantification, its prognostic significance and the treatment strategies currently available and emerging, designed to reduce this injury.

Incidence and prognostic significance of peri-procedural myocardial injury

Cardiac biomarkers have been extensively used in the past two decades to establish the incidence and the prognostic implication of PMI. For the most part, these studies have focused on patients...
with stable CAD undergoing planned PCI, although patients with unstable CAD undergoing urgent PCI have also been included in some studies. The choice of the cardiac enzyme assay, the proportional increase in the enzyme level, the criteria of enzyme cut-off value used to define PMI, and the timing and frequency of blood analysis can all affect the incidence of the PMI in studies evaluating cardiac biomarkers.

**Creatine phosphokinase MB isoenzyme**

Although controversies regarding the prognostic significance of individual cardiac biomarkers persist, creatine phosphokinase MB isoenzyme (CK-MB) elevation is widely accepted as a biomarker with prognostic significance when raised post-PCI. Elevation of CK-MB above the normal levels occurs in about 30% of patients undergoing elective PCI. More than 60 studies in the past two decades have assessed the prognostic significance of elevations in total CK and/or CK-MB fraction following PCI. Table 1 lists some of the meta-analyses that have analysed the majority of the prospective randomized studies and few PCI registry studies. All three meta-analyses evaluating the prognostic value of CK-MB release during PCI have inferred the proportionate increase in the early and late mortality with increased CK-MB release peri-procedurally.

**Troponins**

Troponins (Troponin I and Troponin T) are more sensitive and more specific markers of cardiac injury than CK-MB. Troponin increases following PCI had originally thought to carry less prognostic importance than CK-MB elevations, although recent studies and meta-analyses have shown that troponin elevations post-PCI are prognostically significant. Nienhuis et al. in their meta-analysis of 15,581 patients from 20 studies over a 19-year period reported the incidence of troponin release post-PCI in elective PCI to be 33.0% and increased mortality was significantly associated with troponin elevation after PCI (4.4 vs. 3.3%, P = 0.001; OR 1.35).

The controversy over whether the increased mortality in patients with PMI is due to causative effect of PMI or is due to the underlying predisposing factors which caused PMI in the first place still continues. The causative role is particularly convincing in type 1 PMI with large enzyme release. Smaller enzyme release, particularly associated in type 2 PMI, is not thought to have a causal effect on mortality, but instead thought to be a marker of other high risk systemic factors like arterial inflammation and aspirin resistance.

**New definition of peri-procedural myocardial infarction during percutaneous coronary intervention**

The Joint ESC/ACCF/AHA/WHF Task Force Universal definition of Myocardial Infarction 2007 recently defined PMI during PCI, as an elevation of serum biomarkers (preferably cardiac troponins) above the 99th percentile upper reference limit (URL) after PCI, assuming a normal baseline troponin value. According to these published guidelines, an elevation in serum cardiac enzyme to more than three times the 99th percentile URL has been defined as a Type 4a PCI-related myocardial infarction. Applying the new definition of peri-procedural myocardial infarction (MI) to the existing studies, Testa et al. in their recent meta-analysis of 15 studies incorporating 7578 patients observed that 15% of patients met the new criteria for peri-procedural myocardial infarction and these patients are at high risk of further adverse events both during the hospital stay and at 18 months.

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**Table 1** Peri-procedural myocardial injury incidence and prognostic significance of cardiac biomarker

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>No. of patients</th>
<th>Studies analysed</th>
<th>Cardiac biomarker</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simoons et al.</td>
<td>5025</td>
<td>CAPTURE,6 EPIC,7 EPILOG</td>
<td>CK and CK-MB ratio</td>
<td>There was a consistent gradual increase in 6-month mortality related to the post-procedural CK-MB level and CK level as well as CK and CK-MB ratios. 1.1, 2.1, 1.8, 3.6, and 6.7% for CK-MB ratios (relative to ULN) &lt;1, 1–3, 3–5, 5–10, and &gt;10, respectively.</td>
</tr>
<tr>
<td>Akkerhuis et al.</td>
<td>8838</td>
<td>PURSUIT,9 IMPACT II,10 CAPTURE,4 EPIC,7 EPILOG</td>
<td>CK-MB level</td>
<td>Proportional relationship between post-procedural CK-MB levels (&lt;48 h after PCI) and 6-month mortality. In patients with CK-MB ratios 0–1, 1–3, 3–5, 5–10, and &gt;10, the risk of death was 1.3, 2.0, 2.3, 4.3, and 7.4%, respectively.</td>
</tr>
<tr>
<td>Ioannidis et al.</td>
<td>23230</td>
<td>Meta-analysis of 11 RCTs</td>
<td>CK-MB level</td>
<td>There was a dose–response relationship with relative risks for death with increasing CK-MB. CK-MB ratios 1–3, 3–5, &gt;5 had relative risks of mortality of 1.5, 1.8, 3.1, respectively. Overall PMI incidence of 31%</td>
</tr>
<tr>
<td>Nienhuis et al.</td>
<td>15581</td>
<td>Meta-analysis of 20 RCTs. Troponin I and Troponin T levels</td>
<td>Overall, PMI incidence of 32.9%. Increased mortality was significantly associated with troponin elevation after PCI (4.4 vs. 3.3%, P = 0.001; OR 1.35)</td>
<td></td>
</tr>
<tr>
<td>Testa et al.</td>
<td>7578</td>
<td>Meta-analysis of 15 RCTs</td>
<td>Troponin T and Troponin I levels</td>
<td>Troponin elevation occurred in 28.7% of the procedures. The incidence of PCI-related MI according to the new definition was 14.5%. Patients with PCI-related MI had an increased risk of death at 18 months.</td>
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</table>
ECG changes
Although a 12-lead surface ECG is continuously recorded during the cardiac catheterization procedure, the sensitivity of the ECG for detecting ischaemia during PCI has been disappointing. Unipolar intra-coronary ECG recording appears to be more sensitive and reliable in detection of ischaemia during PCI. Balian et al. in their recent study have shown that sensitivity and specificity of intracoronary ECG in predicting PMI was 74 and 95%, respectively. Importantly, surface ECG recordings showed changes only in 13% of enzymatic proven PMI patients compared with 93% in the intra-coronary ECG group. Despite the low cost, ease of use, and predictive accuracy, intra-coronary ECG has not been generally adopted yet during PCI, its role being relegated to historical interest only.

Cardiac magnetic resonance imaging
Non-invasive imaging of the heart by cardiac magnetic resonance (CMR) imaging can be used to detect the location of the PMI and quantify its extent. The presence and extent of increased signal intensity on late gadolinium enhancement CMR can be used to image myocardial injury directly following PCI, with minimal inter-observer and intra-observer variability. Selvanayagam et al. showed a very strong correlation with CMR defined new myocardial infarction post-PCI and elevated troponins post-PCI, thereby validating troponin release post-PCI as a marker of myocardial necrosis (Figure 1). Delayed enhancement CMR can be particularly useful to identify myocardial infarction in patients who are outside the window of cardiac troponins. The ability to detect microvascular obstruction (MVO) and ability to differentiate new and old infarcts makes this diagnostic modality far more superior in infarct assessment.

Mechanisms of myocardial injury during percutaneous coronary intervention
The most common mechanisms of myocardial injury during PCI are distal embolization and side branch occlusion (SBO). Other significant causes include dissection, thrombus, no reflow/slow flow, or coronary perforation. Herrmann in his review in 2005 classified PMI into two types: Type 1 (proximal type), which is in proximity to the target lesion of PCI and may be due to SBO, and Type 2 (distal type), which is in the perfusion territory of the treated coronary artery and mainly due to structural and functional MVO. Fifty to 75% of all the PMI is Type 2 (distal type) (Figure 2).

Type 1 or proximal type of peri-procedural myocardial injury
Proximal type of PMI is most often seen adjacent to treated arterial segment. This type of myocardial injury is mainly attributed to SBO which can happen during balloon inflation or with stent insertion. Side branches are within the vicinity of the angioplasty site in over 50% of cases and although many are unaffected, a considerable proportion are compromised by the procedure. Occlusion of a side branch has been reported in 12.5–19% of cases in which a stent was placed across a major side branch (>1 mm). Most

Figure 1  Mechanisms of peri-procedural myocardial injury.
occlusions occur after post-stent dilation performed with high-pressure inflations.30 Side branches originating from within the lesion of the native coronary artery are at higher risk of occlusion during PCI and if ostial disease is present in the branch vessel, there is a 5–10-fold increase in the possibility of side branch compromise.30,32–34 Other influencing factors include the branch relationship to parent vessel lesion, branch vessel size, and balloon to artery ratio.10,32–34 The proposed mechanisms of SBO include snow plough effect (plaque shift), thrombus formation, dissection of the dilated artery involving the take-off of the side branch, side branch spasm, and plaque embolization.32,33,35

**Type 2 or distal type of peri-procedural myocardial injury**

This type of myocardial injury is seen in the distal perfusion territory of the treated epicardial artery and accounts for 50–75% of PMI.28 The atherosclerotic plaque disruption and local vessel trauma are the predominant cause in the distal injury and possess occlusion potential of both epicardial vessels and myocardial microvascular levels.28 The potential mechanisms through which this disrupted plaque and local trauma leads to distal perfusion territory insult include

(i) distal embolism of atheromatous debris and thrombotic debris;
(ii) platelet activation and thrombosis leading to microvascular plugging of platelets and neutrophils;
(iii) neuro-hormonal activation and modulation of vascular and myocardial functions;
(iv) oxidative stress and inflammation

**Distal embolism of atheromatous debris and thrombotic elements**

Distal embolization, as a result of plaque denudation during percutaneous trans-luminal angioplasty (PTCA), was first described in the 1980s.36 Recent advances in intravascular imaging, which include intravascular ultrasound (IVUS), virtual histology (VH) IVUS, integrated backscatter IVUS, optical coherent tomography (OCT), and near-infrared (NIR) spectroscopy, have contributed to the understanding of atherosclerotic plaque morphology and its components.37,38 Compared with balloon angioplasty in which the lumen expansion is predominantly due to plaque redistribution and plaque dissection, lumen enlargement after stenting involves a combination of plaque redistribution, plaque extrusion, vessel expansion, plaque compression, and plaque embolization.39,40 Atherosclerotic plaque of the lesion, which have larger necrotic core (NC), are at higher risk of plaque rupture and microembolization during PCI and subsequent cardiac enzyme release.37,41 The necrotic core component contains fragile tissues such as lipid deposition with foam cells, intramural bleeding, and/or cholesterol crystals, and these tissues are often separated from the vessel lumen by only a thin fibrous cap, and hence they are thought to be easily liberated as small emboli during coronary stenting.31–43

Using filter devices distal to the lesion, studies have identified that the embolization of plaque fragments frequently occurs during PCI.44,45 The atherosclerotic plaque burden in the lesion before intervention is correlated with increased PMI as evidenced by subsequent cardiac enzyme elevation.46 The development of IVUS VH has enabled in vivo identification of the histopathological characteristics of plaques and the usage of Doppler wire, and evaluating high-intensity signals (HITS) enables direct detection of small embolic particles which could not be detected with conventional angiography.41 Using these techniques, Kawamoto et al.41 have shown the impact of distal emboli and plaque characteristics on coronary microcirculation as assessed by coronary flow velocity reserve (CFVR) during PCI, in a study involving 44 patients with stable angina. Patients in the highest tertile of HITS had a significantly larger necrotic core area compared with patients in lower tertiles. In addition, there was a small but significant negative correlation between HITS and CFVR after PCI. Virtual histology intravascular ultrasound however cannot detect thrombus, which might, in fact, appear as either fibrotic or fibrofatty plaque
depending on the age of thrombus. Optical coherence tomography with its high spatial resolution detects platelet-rich thrombus and therefore has a better tissue characterization profile. Optical coherence tomography with its high sensitivity in detection of the thin fibrous cap atheroma and macrophage detection appears to be able to detect vulnerable plaque in vivo. Tanaka et al., in their study involving NSTEACS patients undergoing urgent PCI, have shown that OCT detected TCFA and lipid arc size in the culprit plaque both correlated to post-PCI no-reflow phenomenon. Due to limited tissue penetration, OCT is, however, limited in its ability to assess plaque burden. Near-infrared spectroscopy is the other intravascular imaging modality, currently being studied intensively. The lipid burden index derived by NIR spectroscopy correlates well with histologically determined fibro-atheromatous volume in vivo coronary segments in autopsied hearts.

**Platelet activation and thrombosis leading to microvascular plugging of platelets and neutrophils**

During PCI plaque rupture, the arterial endothelial barrier is denuded, and atherosclerotic material, connective tissue elements, and sub-endothelial matrix proteins (collagen, von Willebrand factor) are exposed to blood. Platelets adhere to collagen and von Willebrand factor via specific cell receptors [glycoprotein (GP) VI, GP Ia/IIa, GP Ib-IX] and become activated. Activated platelets de-granulate and secrete agonists, chemotaxins, clotting factors, and vasoconstrictors that promote platelet aggregation, thrombin generation, and vasospasm. Increased platelet aggregation during PTCA was shown in 1993 by Gasperetti et al., in the blood drawn of coronary sinus during angioplasty. In a recent study by Mahemuti et al., a transient significant increase in tissue factor (TF) (14%; P = 0.004), prothrombin fragments 1 and 2 (40%; P = 0.001), and F-VIIa (31%; P = 0.007) following angioplasty were reported, although the levels returned to normal after stents were deployed. Cusset et al. in 2007 showed the higher incidence of PML in low responders to dual antiplatelet therapy in a non-ST elevation acute coronary syndrome (NSTEACS) patient cohort. This was established using high post-treatment platelet reactivity (HPRR) (maximal intensity of ADP 10 μM induced platelet aggregation >70%) which identifies low responders to dual antiplatelet therapy (aspirin and clopidogrel). Peri-procedural myocardial injury occurred significantly more frequently in patients with HPRR than in the normal responders as evidenced by post-procedure Troponin I release (43 vs. 24%, P = 0.014). Previously Chen et al. had shown that aspirin resistance is associated with a high incidence of myonecrosis after non-urgent PCI despite clopidogrel pre-treatment using rapid platelet function assay-acetyl salicylic acid (RPPA-ASA). The incidence of any CK-MB elevation was 51.7% in aspirin-resistant patients and 24.6% in aspirin-sensitive patients (P < 0.006). Elevation of cTnI was observed in 65.5% of aspirin-resistant patients and 38.5% of aspirin-sensitive patients (P < 0.012).

The release of potent bio-factors like TF leading to microvascular thrombosis and no-reflow during in vivo plaque disruption by PTCA was demonstrated by Bonderman et al.

Mizuno et al. showed increased levels of coagulation factors in coronary circulation after PTCA despite adequate administration of intravenous heparin. Tissue factor levels in coronary sinus blood were elevated 4 h after PTCA, followed by increased levels of thrombin–antithrombin III complex, a specific and sensitive marker for thrombin generation, 24 h after PTCA. It was further confirmed that a significant amount of TF is released in situ immediately after PCI in saphenous venous grafts (SVGs) measured by aspiration through export catheter by Salloum et al.

**Neuro-hormonal activation and modulation of vascular and myocardial function**

Coronary vasospasm distal to the PTCA site was shown in arteriographic analysis by Fischell et al. Microcirculatory vasospasm is thought to be an important phenomenon, occurring during coronary interventions. Potent vasoconstrictors like serotonin (5-HT) and endothelin, which are released by activated platelets, were shown to be significantly increased in the distal coronary bed during SVG PCI.

Microcirculatory vasospasm is thought to play a significant role in the ‘No reflow phenomenon’ frequently seen during primary PCI. The neural mechanism of vasoconstriction is supported by studies which have shown that alpha-adrenoreceptor blockade by drugs like urapidil and yohimbine attenuates coronary vasoconstriction and increases coronary flow reserve (CFR) during coronary angioplasty and rotational atherectomy.

**Oxidative stress and inflammation**

Angioplasty-associated increase in isoprostane-PG(F2)Alfa and ischaemia modified albumin, which are associated with free radical damage through reactive oxygen species generation, suggests oxidative stress to be an important mechanism of PML. However, most of the studies on oxidative stress were carried out on primary PCI patients, many of whom have completely occluded arteries suggesting that oxidative stress in these conditions owes more to reperfusion injury.

Rises in inflammatory markers interleukin-6 and C-reactive protein levels post-angioplasty and PCI have been shown in clinical studies. Bonz et al. showed that the inflammatory markers were higher in patients who had significant troponin release post-PTCA when compared with patients who had no troponin release post-procedure suggesting inflammation as one of the mechanisms of PML. Gach et al. showed early increased release of neutrophil markers (myeloperoxidase, lactoferrin) in patients undergoing stents which did not increase with diagnostic angiography.

**Factors influencing peri-procedural myocardial injury**

The key factors which influence the incidence and magnitude of PML could be broadly classified into patient factors, angiographic or lesion related factors, and procedural factors. Assessment of these factors prior to the intervention allows risk stratification for PML.
Patient factors

Patient factors implicated for higher incidence of PMI include older age, multi-vessel CAD, diffuse CAD, systemic atherosclerosis, pre-existing renal impairment, presence of anaemia, pre-procedural C-reactive protein elevation, and pre-procedural white blood cell count $>9.5 \times 10^6$ per L. Also, patients with evolving MIs with elevated cardiac enzymes before the procedure are at increased risk of PMI. This was shown in a sub-analysis from the IMPACT-II trial. In the setting of unstable angina and acute coronary syndromes (ACS), troponin T elevation is associated with more complex coronary stenoses and an increased likelihood of multi-vessel CAD. The plaque seen in coronary arteries of ACS have large lipid cores and a thin capsule, the so-called ‘vulnerable plaque’ compared with coronary arteries in patients with stable angina, which appear to have a thick capsule. The unstable plaque in the setting of an ACS is more likely to denude during revascularization procedures. In the non-ST elevation acute coronary syndrome (NSTEACS), this increased PMI with early intervention was shown in a recent trial of 1200 troponin positive patients; ICTUS (Invasive Versus Conservative Treatment in Unstable Coronary Syndromes Investigators). The incidence of PMI was significantly higher in the early-invasive-strategy group than the selective invasive group (11.3 vs. 5.4%, $P = 0.001$).

In the case of primary PCI, myocardial injury also occurs due to reperfusion injury with a mechanism distinct from that associated with peri-procedural injury. As both reperfusion injury and PMI are associated with cardiac enzyme rise, it is difficult to separate the relative contributions towards myocardial injury by these two processes. Interpretation is further complicated by the cardiac enzyme released due to the infarction itself.

Angiographic or lesion-related factors

Complexity of the arteriosclerotic lesions and coronary anatomy influence the amount of PMI, presumably due to prolonged and aggressive catheter manipulation. The plaque burden, number of lesions, presence of bifurcation lesions, tortuosity, and calcification are all likely to influence myocardial injury during PCI. A recent study investigating the ability of four angiographic classification schemes to predict PMI in patients undergoing PCI for stable angina found the syntax scoring system to be reliable in predicting PMI.

In addition, coronary embolization of atherothrombotic debris, resulting in elevated cardiac enzymes and an ST-elevation or non-ST elevation MI during catheter intervention, is a more common problem after PCI in SVGs than in native coronary arteries. A possible explanation is that atherosclerotic plaques in vein grafts are softer, more friable, and are more commonly associated with thrombus and platelet activation compared with plaques in native coronary arteries, all these features making SVG lesions prone to fragmentation and distal embolization during PCI.

Procedural factors

The incidence of PMI with elevation of cardiac enzymes is significantly higher in directional coronary atherectomy compared with PTCA (16 vs. 6%; $P < 0.0001$). Also, suboptimal stenting has been shown to be associated with increase in the peri-procedural incidence of non-ST elevation MI (NSTEMI) (8.7 vs. 4.2%, $P = 0.003$). Longer stent length is also implicated for increased myocardial enzyme release in a recent study by Hoole et al.

Therapeutic strategies to protect from peri-procedural myocardial injury

The therapeutic strategies being pursued to combat PMI can largely be divided into three subgroups (Figure 3).

(i) Strategies to prevent SBO.
(ii) Strategies to prevent distal embolization and microvascular coagulation.
(iii) Strategies of protecting the myocardium itself against PMI (cardioprotection).

Strategies to prevent side branch occlusion

Bifurcation lesions are always difficult to treat. Although strategies of stenting both main vessel and side branch using drug eluting stents using different techniques like ‘crush’ and ‘culotte’ are evaluated, no long-term benefits have been found in RCTs. In fact, in BBC-ONE trial, there was a higher MI incidence including PMI in ‘complex stent strategy’. A ‘simple strategy’ of main vessel PCI with an option of side branch stenting or balloon, only if warranted, appears to be the current preferred practice.

Strategies to prevent distal embolization and microvascular coagulation

Antiplatelet and antithrombotic drugs

Platelet activation plays a cardinal role in the pathophysiology of PMI. Antiplatelets and antithrombotics are used as first line preventative drugs to counteract the pro-coagulant milieu created during coronary interventions and hence to minimize myocardial damage.

Aspirin

Aspirin has been known to be protective against peri-procedural Q-wave MI, for more than 20 years. There have been no randomized trials to determine optimum loading dose of aspirin prior to PCI, but the guidelines suggest dosages of 75–325 mg in patients already on long-term low-dose aspirin, and 300–325 mg aspirin before PCI if not previously treated with aspirin. The need for additional antiplatelet treatment in PCI is due to aspirin being a comparatively weak inhibitor of platelet function and high prevalence of aspirin resistance of up to 24% in the community.

Thienopyridines

Thienopyridine drugs include the antiplatelet agents clopidogrel, ticlopidine, and prasugrel. The metabolites of these drugs irreversibly bind to ADP (P2Y12) receptors on the platelet, thus attenuating ADP-mediated GP IIb/IIIa receptor activation and platelet aggregation. Clopidogrel has been adopted as the drug of...
choice over ticlopidine in view of enhanced safety and tolerance. The results from the ARMYDA 2 trial suggested that a 600 mg loading dose of clopidogrel safely and more effectively reduced the occurrence of peri-procedural infarctions than did a 300 mg loading dose.\textsuperscript{103} Multivariable analysis showed that pre-treatment with the 600 mg clopidogrel loading regimen was associated with an approximately 50% risk reduction of peri-procedural myocardial infarction (odds ratio 0.48, $P = 0.044$). Prasugrel, a new thienopyridine, has been found to have much less variability in response compared with clopidogrel and appears not to have non-responders; however its role in PMI reduction is not yet established.\textsuperscript{104}

**GPIIb/IIIa inhibitors**

Platelets adhere to collagen and von Willebrand factor via specific surface membrane glycoprotein cell receptors and become activated. The platelet GP IIb/IIIa receptor is of particular interest because of its central role in platelet aggregation. Three intravenous GP IIb/IIIa inhibitors are currently available for clinical use: abciximab, tirofiban, and eptifibatide. There are numerous trials which have evaluated the potential merits of GPIIb/IIIa inhibitors during PCI compared with placebo. A recent meta-analysis evaluating 21 randomized controlled trials which included 23,941 patients comparing GPIIb/IIIa inhibitors and placebo inferred a reduced 7-day post-procedure MI incidence in the GPIIb/IIIa inhibitor treated group (4.31 vs. 6.97%, OR 0.59 CI 0.46–0.75).\textsuperscript{105} The relative clinical efficacy of abciximab, tirofiban, and eptifibatide at currently recommended doses has been uncertain for patients undergoing PCI. One meta-analysis in 2001 compared relative efficacy of individual GPIIb/IIIa inhibitors analysing eight RCTs with 14,644 patients. Abciximab resulted in a significant reduction of post-procedure MI from 8.5 to 4.3% (OR 0.49; 95% CI 0.40–0.59); compared with tirofiban and eptifibatide both of which showed non-significant reduction in MI from 6.9 to 5.9% (OR 0.85; 95% CI 0.69–1.04).\textsuperscript{106} GPIIb/IIIa inhibitors, however, increase bleeding and in the era of preloading with clopidogrel/prasugrel and increased use of bivalirudin, their role is diminishing.

**Antithrombotics**

Unfractionated heparin, which was the predominant antithrombotic treatment when PTCA was the only intervention, continues to be used in most PCI procedures. The other antithrombotics that have been evaluated in recent years include low molecular weight heparin and the direct thrombin inhibitors bivalirudin and fondaparinux. However, there have been no randomized trials showing reduction in peri-procedural MI in elective PCI by any of the above antithrombotics.

**Distal protection devices**

Two types of embolic protection devices are in current usage, filters and aspiration (thrombectomy) catheters. Distal protection using filters appears to be of benefit in SVG interventions but is not routinely used in PCI of native coronary arteries. In the SAFER trial,\textsuperscript{107} use of the embolic protection device in SVG interventions, with or without the concomitant administration of a glycoprotein IIb/IIIa inhibitor, significantly reduced the incidence of myocardial infarction (8.6 vs. 14.7%) and the no-reflow phenomenon (3 vs. 9%) with a 42% relative risk reduction in MACE at 30 days.

**Proximal protection devices**

These devices are an alternative when distal protection is not feasible in SVG interventions. In PROXIMAL trial evaluating SVG interventions, these devices were non-inferior to distal protection.
devices in reduction of primary composite endpoint of death, myocardial infarction, or target vessel revascularization at 30 days with similar PMI incidence in both distal and proximal protection strategies.108

**Direct stenting**

Direct stenting of the coronary lesion without pre-dilatation was found to reduce post-procedural Troponin I levels over 24 h in a randomized controlled trial involving 311 patients by Nageh et al.109 In a recent study by Cuisset et al.,110 direct stenting in stable-angina patients was associated with reduced microvascular dysfunction induced by PCI when compared with conventional stenting. It appears that further studies are required to establish the usefulness of direct stenting in reduction of PMI. One meta-analysis comparing outcomes of direct stenting with conventional stenting found no benefit in MACE with non-significant trend towards reduction in early MI and death post-PCI.111 Prospective trials will be needed, as the use of direct stenting may select less complex lesions in which less PMI might be expected.

**Strategies for protecting the myocardium against peri-procedural myocardial injury (cardioprotection)**

Much of the existing medical therapy administered during PCI is to maintain the patency of the coronary artery and comprises primarily of antiplatelet and antithrombotic therapy. In cases of coronary no-reflow, intracoronary adenosine, calcium channel blockers, or nitrates may be administered with the intention to improve myocardial reperfusion and maintain microvascular perfusion. However, an attractive alternative strategy may involve rendering the myocardium resistant to the detrimental effects of PMI by pharmacological or novel interventions.

**Statins**

In addition to its lipid-lowering effect, some of the beneficial effects elicited by this class of drugs may be attributed to a variety of non-lipid lowering pleiotropic effects, including improved endothelial function, reduced oxidative stress, less platelet adhesion, and increased atherosclerotic plaque stability.112 Nitric oxide has been implicated as a crucial signalling molecule in cardioprotection and is involved in the other pleiotropic effects of statin therapy.112

Pre-procedural atorvastatin treatment was shown to reduce PMI in the elective PCI settings compared with controls in both the ARMYDA trial and the recent NAPLES II trial.113,114 In ACS patients undergoing urgent PCI, both atorvastatin and rosuvastatin have been shown to reduce PMI compared with control group.115,116 The ARMYDA-RECAPTURE trial117 studied atorvastatin reload in patients on chronic statin therapy undergoing PCI. They randomized 383 patients with both stable angina (53%) and non-ST-segment elevation ACS (47%) who were on previous statin therapy to have 80 mg loading of atorvastatin 12 h before PCI and a further dose of 40 mg atorvastatin pre-PCI vs. a non-loading control group. This study inferred a lower incidence of post-procedural CK-MB and Troponin I elevation greater than ULN in the atorvastatin arm (13 vs. 24%, \( P = 0.017 \), and 37 vs. 49%, \( P = 0.021 \), respectively). Of note, the stable angina patients who had PCI did not benefit from atorvastatin reload.

A meta-analysis by Merla et al.118 evaluating nine trials with 4751 patients, which assessed the impact of statin pre-treatment on peri-procedural myonecrosis, found 9% incidence in the statin-treated group when compared with 17.5% in the control group (OR 0.45, 95% CI 0.33–0.62, \( P < 0.01 \)).

**Beta-blockers**

Intra-coronary propranolol at a dose of 15 \( \mu \)g/kg administered across the stenosis before the balloon dilation was shown to reduce peri-procedural incidence of CK-MB and Troponin T elevation compared with control patients by Wang et al.119

When intracoronary propranolol administered with the GPIIIaIIb inhibitor eptifibatide, the post-procedural CK-MB was significantly reduced compared with placebo,120 highlighting an additive benefit of a beta-blocker with a GPIIIaIIb inhibitor. Post-PCI CK-MB elevation greater than ULN occurred significantly more frequently in the placebo (21.5%) than in the propranolol (12.5%) group (RR 0.42; 95% CI 0.09–0.63; \( P = 0.016 \)).120 It has been suggested that reduction in myocardial oxygen consumption may have accounted for the observed beneficial effect of propranolol. Another mechanism of benefit that has been suggested is an increase in the endocardial/epicardial ratio of tissue perfusion in the ischaemic area.121

**Adenosine**

Adenosine is a naturally occurring nucleoside with a half-life in blood of less than 10 s. Adenosine, administered via the intravenous or intracoronary route, produces a hyperaemic effect that is commonly used in the measurement of CFR and fractional flow reserve during PCI.122 Intra-coronary adenosine infusion, which pharmacologically mimics preconditioning, has been shown to significantly decrease peri-procedural cardiac enzyme rise in a small randomized study by Desmet et al.123 involving 28 patients. This study, however, involved infusion of adenosine over 10 min followed by 90 s of balloon inflation. A more recent randomized placebo-controlled trial involving 62 patients undergoing non-urgent PCI showed reduction in peri-procedural biomarker elevation in patients randomized to receive a bolus of intracoronary adenosine 50 \( \mu \)g before ‘wiring’ when compared with the placebo group (adjusted \( OR = 0.19 \), 95% CI 0.05–0.75, \( P = 0.017 \)).124 Larger studies are required to establish adenosine’s benefit and feasibility for routine adoption.

**Trimetazidine**

Trimetazidine is a piperazine derivative anti-anginal drug with a vasodilatory effect on coronary arteries and has been extensively studied due to its additional cardioprotective preconditioning properties. The mechanism of cardioprotection by trimetazidine appears to be modulation of mitochondrial homeostasis downstream of the preconditioning pathway.125 One placebo-controlled, randomized, controlled trial involving 266 patients studied a loading dose of 60 mg trimetazidine 30 min before re-canalization. This study showed significant reduction in post-procedural Troponin I levels in the trimetazidine group at all time points and also a significant reduction in the total Troponin I area under the curve.126 This drug is still not available in Europe.
Emerging therapeutic alternatives in prevention of peri-procedural myocardial injury

**Novel pharmacological agents**

New potent antiplatelet agents and antithrombotics with better safety profile are understandably promising in better tackling PMI, however studies are yet to be reported. These new drugs include antiplatelet agents prasugrel, ticagrelor, canagrelor, and direct thrombin inhibitor bivalirudin. Cyclosporine-A with its direct attenuation of mitochondrial permeability transition pore opening and preservation of mitochondrial function in myocellular cells is a novel cardioprotective agent with promising profile.\(^{127}\) Cyclosporine’s role in reducing reperfusion injury in primary PCI setting was shown by Ovize and co-authors.\(^{128}\)

**Non-pharmacological interventions**

**Ischaemic and remote ischaemic preconditioning**

Ischaemic preconditioning (IPC) refers to a powerful endogenous cardioprotective phenomenon whereby brief episodes of non-lethal ischaemia to the myocardium confer protection against a longer lethal ischaemic insult.\(^{129}\) The mechanisms underlying these endogenous cardioprotective phenomena are complex in nature and the reader is directed to a more comprehensive review of the phenomenon.\(^{130}\) Laskey\(^{131}\) studied the effect of IPC during PTCA by two 90 s coronary balloon inflations separated by 5 min, among 150 patients randomized to either IPC or control. A significant reduction in CK elevation (7.1% in IPC group vs. 25% in control group, \(P < 0.005\)) was reported.\(^{131}\) Intriguingly, it transpires that similar levels of cardioprotection can be achieved by applying the brief episodes of non-lethal ischaemia and reperfusion to an organ or tissue remote from the heart, thereby obviating the need to ‘condition’ the heart directly.\(^{130}\)

This phenomenon has been termed remote ischaemic preconditioning (RIPC). In the setting of elective PCI, Hoole et al.\(^{132}\) in a randomized controlled trial evaluating RIPC, involving 242 patients, showed significant reduction in Troponin I in the patients randomised to RIPC. The RIPC protocol consisted of a blood pressure cuff applied to the upper arm inflated to 200 mmHg pressure for 5 min, following by 5 min of deflation, a cycle repeated three times. The median Troponin I at 24 h after PCI was significantly lower in the RIPC compared with the control group \((0.06 \text{ vs. } 0.16 \text{ ng/mL; } P = 0.040)\). This cardioprotective intervention is non-invasive, simple, and virtually cost-free and has no apparent side effects. In other settings of ischaemia reperfusion injury, such as coronary artery bypass surgery and abdominal aortic aneurysm repair, RIPC has been shown an ability to reduce myocardial injury.\(^{133,134}\)

**Conclusion**

Although known about for some time, PMI complicating routine and emergency PCI has not received as much emphasis as other aspects of PCI, yet prognosis is adversely affected. Routine pre-procedure administration of statins and potent antiplatelet agents along with interventional strategies of thrombus aspiration, filter devices, and improved procedural techniques have reduced the incidence of PMI, however PMI still occurs in a significant proportion of interventions. The patients who are at risk of developing PMI may be identified pre-procedure but many at risk will only be identified during the PCI procedure due to anatomical and procedural difficulties encountered. Most institutions have no mandate to measure post-procedure enzymes; however, as both short-term and long-term outcomes are influenced by PMI, a strong case can be made for peri- and post-procedural enzyme markers to be a part of any quality outcome audit.

There are now a number of techniques available to clinicians to reduce the incidence and extent of PMI. Some involve commonly used drugs but some relatively simple techniques, such as pre-procedural limb cuff inflation (RIPC), may also be employed to advantage. In order to further improve PCI outcome, greater attention is needed on this aspect of care. It may require some organizational changes to apply these therapies to larger numbers of patients, but the expected long-term improvement in outcomes should be a sufficient driver to further reduce MACE rates. Novel pharmacological drugs aimed at better platelet inhibition and cardioprotection along with the ongoing developments in embolic protection offer hope in further reduction in the incidence of PMI.

Those patients with stable angina unfortunate enough to suffer PMI which may constitute up to 30% of the total, deserve an intensive application of secondary prevention as patients suffering classical myocardial infarction.

**Conflict of interest:** none declared.

**References**

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