# Reducing reperfusion injury during percutaneous coronary intervention

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Acute myocardial infarction (AMI) is the leading cause of death in the developed world, and reperfusion therapy with primary percutaneous coronary intervention (PCI) is the standard of care after AMI. Despite dramatic improvements in door-to-balloon times, gaps and opportunities remain in terms of improving outcomes.[1] To achieve further reductions in mortality, there is a need to focus on other mechanisms such as reperfusion injury, which remains a major unsolved clinical entity post PCI.[2]

Reperfusion injury occurs in both experimental models as well as patients with AMI, based on the observation that therapeutic interventions applied solely at the onset of myocardial reperfusion reduced infarct size.[2] Gottlieb et al[3] demonstrated that reperfusion-induced myocyte death is due to a process called apoptosis (programmed cell death) and is a response specific to reperfusion but not ischaemia. A subsequent human study confirmed that myocyte apoptosis is a clinical process that occurs during reperfusion following AMI.[4] Thus, the restoration of blood flow to the ischaemic myocardium facilitated by PCI does not necessarily translate to infarct size reduction. In fact, this process induces myocardial reperfusion injury and can paradoxically reduce the benefit of reperfusion therapy.

In a recent article in the *Singapore Medical Journal*, Wang et al[5] attempted to determine the beneficial effects of prior PCI administration of recombinant human brain natriuretic peptide (rhBNP) in ST-elevation myocardial infarction (STEMI) patients. The study assessed the effects of rhBNP on the incidence of reperfusion arrhythmia, thrombolysis in myocardial infarction (TIMI) frame count, and the myocardial blush grade of culprit vessels in rhBNP treatment and placebo groups undergoing PCI. It demonstrated that frequent ventricular premature beats and ventricular tachycardia, but not accelerated idioventricular rhythm, were decreased in the rhBNP-treated group. The authors also reported that despite the improved TIMI frame count in culprit vessels, there was no significant difference in myocardial blush grade in the rhBNP-treated group. Unfortunately, the study did not examine the biochemical or anatomic changes related to reperfusion injury.

Traditionally, reperfusion arrhythmias consist of accelerated idioventricular rhythms and ventricular arrhythmias, including premature ventricular complexes, ventricular tachycardia and fibrillation. These arrhythmias originate from the ischaemia-reperfused zone. In the thrombolytic era, reperfusion arrhythmia was considered as an early successful reperfusion marker. Subsequent evidence indicated that the pathophysiological basis for reperfusion arrhythmias and reperfusion injury shares the same intracellular mechanism. Both conditions should not be seen as separate entities but as one and the same process resulting in two different manifestations. Therefore, reperfusion arrhythmias should serve as a potential bioelectrical marker for fatal reperfusion injury.[6] Accordingly, a reduction in reperfusion arrhythmia in the rhBNP-treated group, as reported by Wang et al,[5] indicates that rhBNP reduces reperfusion injury. Although epicardial coronary artery blood flow seemed to improve based on TIMI frame count, the myocardial blush grade – an angiographic marker of tissue-level reperfusion – was not significantly different in the two different groups. Evidently, rhBNP therapy adjuvant to PCI did not further improve myocardial tissue reperfusion at the microvascular level. This might be an expected result in the era of fully developed PCI technology. Nevertheless, the results of Wang et al's study are encouraging, since rhBNP treatment prior to PCI appears to reduce reperfusion injury in STEMI patients, at least from a bioelectrical perspective.

How can rhBNP possibly reduce reperfusion injury in reperfused STEMI patients? rhBNP is structurally and biochemically identical to the endogenous brain natriuretic peptide (BNP). The interaction between BNP and its cognate receptor activates guanylyl cyclase, resulting in increased cyclic guanosine monophosphate (cGMP) production. cGMP is a second messenger of intracellular signalling. A recent clinical trial highlighted that cGMP-mediated cardioprotection can be of clinical relevance in a STEMI setting.[7] In a randomised, double-blind, placebo-controlled, multicentre study, investigators demonstrated that in a STEMI patient prior to PCI, an intravenous infusion of high-dose N-acetylcysteine combined with low-dose nitroglycerin had an absolute 5.5% infarct size reduction on early cardiac magnetic resonance imaging assessment. It was proposed that N-acetylcysteine may have exerted its beneficial effects via potentiating nitroglycerin's cardioprotective effect.[7] Similar to BNP, nitroglycerine is well known to activate guanylyl cyclase, increasing intracellular cGMP.

The mechanisms underlying cGMP-mediated cardioprotection are not fully understood. Among several proposed mechanisms, the crosstalk between cGMP and cyclic adenosine monophosphate (cAMP) is worth noting, both being important second messengers in cell signalling. Phosphodiesterase 3 ($PDE_3$), an enzyme that deactivates cAMP, is referred to as the cGMP-inhibited PDE since it exhibits a high affinity for both cAMP and cGMP.[8] cAMP and cGMP are mutually competitive substrates for $PDE_3$. Under certain

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physiological conditions, cGMP inhibits the cAMP-hydrolysing activity of PDE$_3$ competitively.[8] In fact, some biological effects of cGMP may be mediated by PDE$_3$ inhibition, which activates cAMP-dependent protein kinase A (i.e. protein kinase A) signalling.[8,9] It is unknown whether rhBNP-mediated cardioprotection is involved in the cAMP-dependent signalling pathway. Nonetheless, non-β1-adrenergic, cAMP-dependent protein kinase A cell signalling has emerged as an important cardioprotective mechanism against ischaemia-reperfusion injury. Protein kinase A-mediated infarct size reduction has been independently demonstrated in various ischaemia-reperfusion animal models.[10-12] This cAMP-dependent protein kinase A activation activates multiple prosurvival signalling pathways, leading to Akt activation and therefore reduced myocyte apoptosis.[12]

It must be emphasised that facilitated myocardial perfusion does not necessarily translate to clinical benefit in STEMI patients. For ultimate proof of the benefit of adjuvant therapy to PCI in STEMI patients, we await biochemical and/or anatomic evidence of infarct size reduction. This remains a challenge for clinical cardiology.

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