

## Opioids in acute coronary syndromes: friend or foe?

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A recent article in 'Cardiovascular Drugs and Therapy' by Xu *et al.* has addressed the intriguing question of the mechanism by which the opioid receptor agonist morphine reduces infarct size in the setting of myocardial ischaemia/reperfusion [1].

Alleviation of chest pain in patients with ST-elevation myocardial infarction (STEMI) is vitally important. Traditionally, opioids are commonly used for this purpose (class IIa in recommendations of the European Society of Cardiology). However, the effects of this group of drugs on patients with acute myocardial infarction are not fully understood.

A number of experimental studies, starting from 1981, have demonstrated the expression of opioid receptors in the heart (reviewed in [2, 3]), including human atrial muscle [4]. Furthermore, opioid agonists clearly limit infarct size both in *in vivo* and *ex vivo* models of ischaemia/reperfusion, as well as in isolated cardiomyocytes subjected to hypoxia/reoxygenation [2].

As opioid agonists are currently an essential component of standard care of patients with acute coronary syndromes (ACS), it is ethically difficult to evaluate the true effect of opioids on infarct size in these patients. In addition, the patients who receive opioids in this setting are often clinically incomparable to those who do not. For example, in a recent multicentre trial in 734 STEMI patients undergoing primary percutaneous coronary intervention (PCI), morphine administration resulted in significantly smaller infarcts and reduced microvascular obstruction in the subgroup of patients with early reperfusion within 120 min and reduced flow in the infarcted vessel (Thrombolysis in Myocardial Infarction (TIMI) flow  $\leq 2$  before PCI) [5]. However, it should not be overlooked that patients receiving morphine were younger and had a lower incidence of hypertension and diabetes as compared to patients without morphine use. A favourable effect of morphine on infarct size and

microvascular obstruction was also reported in another clinical trial in 380 patients with ACS (either STEMI or non-STEMI) [6]. Interestingly, cardioprotective effects of morphine were not observed in patients receiving metoclopramide. The authors claim that there were no significant differences in clinical characteristics between the placebo group and the respective treatment arms in this study, except for a higher number of patients with immediate multivessel PCI in the morphine with metoclopramide group [6].

As opposed to these positive results, a recent meta-analysis of 5 randomised controlled trials and 12 observational studies enrolling 69,993 participants showed that morphine use was associated with an increased risk of in-hospital mortality and major adverse cardiac events, albeit with a high risk of bias [7]. In agreement with this meta-analysis, retrospective cohort analysis of the AVOID study discovered association between higher dose of morphine in STEMI patients and more severe myocardial damage [8]. However, the authors admit, that high doses of opioids were more likely administered to patients with TIMI flow 0-1 pre-PCI and to those undergoing thrombus aspiration, suggesting a greater thrombus burden in these patients. In its turn, this higher thrombus burden could be associated with gastroparesis secondary to high-dose opioids, leading delayed absorption and action of P2Y<sub>12</sub> inhibitors prior to PCI. This “morphine paradox” has previously been reported in a number of clinical trials [7]. Alternatively, TIMI flow 0-1 may have prompted administration of higher doses of opioids due to more severe chest pain. However, this detrimental effect of higher doses of morphine could also be explained by the loss of selectivity to  $\delta$ -opioid receptors. As demonstrated in an earlier pre-clinical study, the infarct-limiting effect of  $\delta$ -opioid agonist in isolated hearts was lost at increasing doses [9]. In addition,  $\kappa$ -opioid agonist increased infarct size to an “anti-preconditioned” state via  $\kappa_1$  receptors. These uncertainties on the results of clinical trials indicate the need to conduct further experimental studies to deeper understand the effects of opioid agonists on the heart.

Importantly, opioid receptors are known to be an integral part of the innate cardioprotective phenomena. First, opioid-induced cardioprotection and classical ischaemic preconditioning (IPC) are known to share common pathways. More than 20 years ago it was shown that i.v. morphine administration mimics the cardioprotective effect of IPC, and conversely, naloxone abolishes IPC [2, 4]. These and earlier studies demonstrated that preconditioning effect of opioids is mediated via K<sub>ATP</sub> channels through the activation of protein kinase C (PKC) [2-4].

The cardioprotective phenomenon of remote ischaemic conditioning (RIC) was also demonstrated to be mediated via opioid receptors [2]. Namely, the beneficial effect of transfer of coronary effluent from pre-conditioned hearts to other isolated hearts was blocked by opioid receptor antagonist. Further to this, morphine enhanced the infarct-limiting effect of RIC in STEMI patients undergoing PCI (reviewed in [2]). It has been speculated that the cardioprotective effect of morphine is mediated via opioid receptors centrally, as intrathecal administration of morphine reduced infarct size in the heart subjected to ischaemia/reperfusion [3]. Importantly, this effect was comparable to that of i.v. administration of morphine and was dose independent. Furthermore, the infarct-limiting effect of intrathecal morphine was abolished by either  $\kappa$ -,  $\delta$ - or  $\mu$ -receptor antagonists administered intrathecally, but not by their intravenous administration. In addition, this cardioprotective effect was blocked with hexamethonium, which indicates the possible involvement of autonomic nervous system activation. In this regard, it is not clear how this mechanism can be balanced with the fact that opioid agonists reduce infarct size in *ex vivo* models. Conceivably, these can be different cardioprotective pathways. Of note, intracoronary administration of morphine failed to limit myocardial infarct size in recent clinical trials [10]. However, the common limitation of these trials is randomization is performed after diagnostic angiography and morphine is administered

intracoronary at reperfusion. Therefore, some patients from both trial arms will have already received intravenous morphine in the emergency room according to the existing protocol for pain control.

Regarding the molecular mechanism of opioid-induced cardioprotection, a number of experimental studies suggest the existence of crosstalk between opioid receptor family and other G-protein-coupled receptors as well as with epidermal growth factor receptor (EGFR) [3]. As such, Downey's research group described the molecular cascade in response to  $\delta$ -receptor activation in an isolated heart. It was demonstrated that  $\delta$ -receptor activation increased production of reactive oxygen species and that this effect was Akt- and ERK1/2-dependent, while Akt- and ERK1/2- phosphorylation was mediated via EGFR (reviewed in [3]). This effect of  $\delta$ -opioid agonists was further investigated by Xu et al. in their recently published study [1]. They showed that EGFR activity was markedly increased by morphine via  $\delta$ -receptors. Importantly, this study clearly demonstrated the crucial role of this cascade in opioid-induced cardioprotection in *ex vivo* ischaemia/reperfusion model, as EGFR inhibitor abolished the infarct-limiting effect of morphine. It is interesting that morphine was not observed to inhibit apoptosis, which contrasts with a previous study showing fewer apoptotic cells following activation of  $\delta$ -opioid receptors by i.v. morphine administration both in an *in vivo* and *ex vivo* models of ischaemia/reperfusion injury as well as in isolated cardiomyocytes [2].

The effects of morphine should be taken into consideration in clinical trials aimed at evaluating the benefits of new cardioprotective strategies. In addition, an essential component should be an understanding of the role and influence of the cocktail of drugs routinely given to patients presenting with an acute myocardial infarction (MI). This was clearly demonstrated in an animal study in which 3 drugs (a morphine analogue, a P2Y<sub>12</sub> inhibitor and heparin), routinely given to patients who present with an acute MI, demonstrated a significant reduction in infarct size in rats, with no further protection given when remote conditioning was added. The conclusion was that these agents directly precondition the heart [11].

Currently, opioid agonists are the standard and the only available option for analgesia in many patients with ACS. In spite of the long history of their use in this scenario, further studies are needed to fully understand their mechanism and their place in acute myocardial infarction.

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### **Competing Interests**

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### **Ethics approval**

No ethical approval was required