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A new perspective on the role of adenosine in acute myocardial infarction therapy

Yetgin T, Uitterdijk A, Te Lintel Hekkert M, Merkus D, Krabbendam-Peters I, van Beusekom HM, et al. Limitation of infarct size and no-reflow by intracoronary adenosine depends critically on dose and duration. **JACC Cardiovasc Interv 2015;8:1990-9. http://doi.org/bbw3**

Despite advances in the treatment of ischemic heart disease, this is still the main cause of death and heart failure worldwide. Therefore, it is of paramount importance to develop new strategies to improve the prognosis of patients suffering from this disease. The main therapeutic strategy currently available is reperfusion; however, paradoxically, reperfusion injury limits the benefits of re-establishing blood flow in the ischemic coronary bed.

Different experimental methods have been described capable of limiting or even reducing the infarct area. Yet, only few have been successfully extrapolated to the clinical setting.

Adenosine is a substance that has attracted attention for several years. Specifically at the cardiovascular level, it inhibits neutrophil aggregation and adherence to the endothelium, attenuates ATP depletion during ischemia, stimulates glycolysis, inhibits platelet aggregation, and also participates in the ischemic preconditioning and postconditioning protection mechanism.

However, attempts to provide cardioprotection by adenosine administration during reperfusion have resulted in dissimilar outcomes, especially in the clinical setting. For example, recent studies using intracoronary bolus injections of adenosine in patients with acute myocardial infarction (AMI) could not demonstrate significant infarct size reduction. These inconsistent results can be related with several factors, including the bioavailability of adenosine during reperfusion and the brief window for its therapeutic application. In this sense, the optimal adenosine dose in AMI is undefined both in animal (dogs and rabbits) as in clinical studies. Due to the lack of an adjuvant treatment limiting reperfusion injury, and taking into account the aforementioned considerations, it is of interest to re-evaluate the effects of adenosine therapy in the context of AMI.

Bearing these concepts in mind, Yetgin et al. postulate that prolonged intracoronary adenosine administration at an optimal concentration is able to reduce infarct size and no-reflow area. This hypothesis was tested in a pig animal model subjected to 45 minutes anterior descending coronary artery occlusion followed by a 2-hour reperfusion period. A group of animals received an intracoronary bolus injection of adenosine at the onset of reperfusion, in an equivalent dose to that used in clinical trials. Then, in a second group of animals, the cardioprotective effect of an intracoronary high and prolonged dose of adenosine was assessed by drug administration during the 2-hour reperfusion period. In this study, a high-dose intracoronary adenosine infusion (50 mg/kg/min), delivered at the onset of reperfusion and maintained throughout its 2-hour duration, significantly decreased infarct size and no reflow area. Conversely, a single adenosine bolus (3 mg during 1 min) during the first minute of reperfusion was ineffective.

Prolonged adenosine infusion reduced neutrophil migration to the infarct area, especially in the no-reflow area. These actions, in turn, probably contributed to decreased neutrophil adherence to endothelial cells, preserving capillary permeability.

Adjuvant therapy with adenosine is a promising tool, particularly in patients undergoing primary angioplasty. However, there are still important issues for its utilization, and consequently, it is necessary to look for its optimal dose and administration time. Moreover, different from animals, patients present comorbidities that could confound or abolish the protective adenosine effects. It is therefore not surprising that clinical studies have not been conclusive.