

Remote conditioning: Molecular mechanisms and clinical relevance

Benedikt Preckel

Academic Medical Center, Amsterdam, The Netherlands

Interruption of the blood flow of an organ submits this organ to ischaemia, which eventually leads to necrosis of the affected tissue. Paradoxically, the restoration of blood flow, i.e. reperfusion, also contributes to tissue damage. This process is most extensively researched in myocardium. Key processes in the development of ischaemia-reperfusion injury are resupply of oxygen, an increase in intracellular calcium and correction of the pH. Resupply of oxygen leads to the formation of reactive oxygen species. Intracellular calcium is increased during ischaemia and further during reperfusion, causing hypercontracture of the cardiomyocytes. The increased calcium, oxidative stress and corrected pH cumulate in the opening of the mitochondrial permeability transition pore (mPTP). The mPTP is a nonselective channel in the inner membrane of the mitochondrion, and its opening leads to further depletion of the ATP stores and ultimately cell death. Additionally, the supply of blood brings neutrophils, attracted to the infarcted area by chemo-attractants, augmenting cellular damage. So, while reperfusion is essential to reduce cell death, its full potential is reduced by the presence of reperfusion injury. (for review see [1])

Intriguingly, when a period of ischaemia is preceded by a number of shorter periods of ischaemia and reperfusion, the amount of damage is significantly reduced [2]. This phenomenon, called ischaemic preconditioning, activates an intracellular pathway of kinases, such as protein kinase C- ϵ (PKC- ϵ) and the mitogen activated protein kinase (MAPK) p38 and ERK 1/2. This cascade inhibits opening of the mPTP during reperfusion, thereby stabilizing the mitochondrial membrane. In the presence of blockers of the aforementioned signalling proteins, direct inhibition of the mPTP by cyclosporine A restores protec-

tion. However, in hyperglycaemic or diabetic subjects, ischaemic preconditioning fails to provide cardioprotection. (for review [3]). Ischaemic preconditioning requires both access to the coronary circulation and a predictable ischaemic event, reducing its value in the clinical setting. However, it seems that the protective effect of ischaemic preconditioning is not limited to the vascular bed at which it was applied. This was first demonstrated by Przyklenk in an experiment in dogs, when preconditioning the ramus circumflexus provided protection against myocardial infarction in the left anterior descending bed [4]. Later, inter organ transferability was demonstrated as well. For example, preconditioning the kidney or even skeletal muscle protects the heart from subsequent infarction [5]. How this protection is transferred is not fully understood, although both humoral and neurological factors are involved. Whether remote ischaemic preconditioning provides a clinically relevant protective effect has to be examined. A number of small trials have shown promising results, however, a recent larger trial found no benefit [6,7].

References

1. Yellon DM, Hausenloy DJ. *N Engl J Med* 2007; 357: 1121-35
2. Murry CE, Jennings RB, Reimer KA. *Circulation* 1986; 74: 1124-36
3. Hausenloy DJ, Yellon DM. *Atherosclerosis* 2009; 204: 334-41
4. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P. *Circulation* 1993; 87: 893-99
5. Kharbanda RK et al. *Heart* 2006; 92: 1506-11
6. Hausenloy DJ et al. *Lancet* 2007; 370: 575-79
7. Rahman JA et al. Presented at American Heart Association 2009