Editorial

# The Phenomenon of Preconditioning Today

Dimitrios Th. Kremastinos

*2nd University Department of Cardiology, Attikon Hospital, Athens, Greece*

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*Address:*
Dimitrios Th. Kremastinos

*2nd Cardiology Department*
*Onassis Cardiovascular Surgical Centre,*
*356 Syngrou Avenue,*
*176 74 Athens, Greece*
*e-mail:*
*elbee@ath.forthnet.gr*

Acute thrombosis of a coronary artery at a certain point does not necessarily cause a specific myocardial infarction. The size of a myocardial infarction, apart from the anatomical location of the arterial obstruction, is mainly dependent on the degree of collateral circulation development and the presence of the phenomenon of ischaemic preconditioning.[1] In 1986, Murry et al first described the phenomenon of preconditioning as the increase of the tolerance of the heart to a prolonged ischaemic episode following one or more brief periods of ischaemia.[1]

The hard end-points of preconditioning are related to smaller infarct size, lower percentage of fatal arrhythmias, and lower patient mortality.[2] The soft end-points are related to the preservation of intracellular ATP, recovery of contractile myocardial function, reduction of ischaemic pain and ST-segment elevation on the ECG, and improvement of endothelium and platelet function.[2]

Reduction of infarct size through the mechanism of preconditioning has been observed in almost all studied species, regardless of the existence of collateral circulation. This cardioprotection is achieved by the stimulation of the membrane receptors by several ligands such as adenosine, bradykinin, opioids, NO, catecholamines, and by diazoxide, which opens the mitochondrial $K_{ATP}$ channels. The occupation of the proper receptors upregulates several second messengers which activate various intracellular pathways and finally phosphorylate an unknown end effector which confers the cardioprotection.[3]

Since the vast majority of experimental studies were performed on normal myocardium, the question arises whether preconditioning is equally effective in the pathological heart. In hypertrophied myocardium, ischaemic preconditioning limits infarct size in rats but in rabbits causes cellular electrical uncoupling. The duration of the process of ischaemia-induced electrical uncoupling in failing hearts is longer than in controls. Ischaemic preconditioning has detrimental effects in severely failing papillary muscles because it advances the moment of irreversible ischaemic damage.[4]

Theoretically, diabetes itself is a metabolic abnormality which confers protection because of the increased utilization of fatty acids, decreased glycolysis, and decreased $Na^+/H^+$ and $Na/Ca^{++}$ exchange.[5] The diabetic heart might be more tolerant to ischaemia in certain experimental animal models but comparable data do not exist in humans.[6] Diabetes in rabbits and rats induces a chronic and metabolic form of preconditioning. The diabetic myocardium may benefit more than normal, possibly as a result of the reduced production of glycolytic metabolites during sustained ischaemia and the concomitant attenuation of intracellular acidosis in humans.[7] Contrary to what the above metabolic changes would lead one to expect, diabetes mellitus seems to prevent ischaemic preconditioning in patients with a first acute

anterior myocardial infarction.[8] As a result, the infarct size is not different in diabetic patients with pre-infarction angina compared to those without pre-infarction angina,[9] which is considered the equivalent preconditioning stimulus in humans.[8] However, some investigators claim that diabetes itself is not responsible for the inactivation of preconditioning, but that this is due to the effect of some antidiabetic drugs. Glimepiride maintains myocardial preconditioning, while glibenclamide might prevent it. Glibenclamide blocks both mitochondrial and sarcolemmal $K_{ATP}$ channels and therefore prevents preconditioning, whilst glimebiride blocks only the sarcolemmal $K_{ATP}$ channels.[10,11]

However, we should take into account that antidiabetic drugs may not influence ischaemic preconditioning, since the concentrations of sulfonylureas required to block cardiac $K_{ATP}$ channels are between 100 and 1000 times higher than those required to induce pancreatic insulin release.[12]

Regarding hypercholesterolaemia, we found that preconditioning limits myocardial infarct size in hypercholesterolaemic rabbits,[13] while Li et al found that preconditioning protects the severely atherosclerotic mouse heart.[14] In contrast, another research group reported that ischaemic preconditioning is blunted by hypercholesterolaemia and that pravastatin restores the infarct size-limiting effect of preconditioning in rabbits.[15]

The thyroid gland seems to play a role in the mechanism of protection and pretreatment with thyroxine improves post-ischaemic recovery of function in isolated hearts.[16]

Pre-infarction angina protects against out-of-hospital ventricular fibrillation in patients with acute occlusion of the left coronary artery, independently of the presence of hypertension, hypercholesterolaemia and diabetes. This clinical evidence supports the view that preconditioning works in pathological conditions[17] and not only in normal myocardium.

Prodromal angina has also been found to protect patients with anterior myocardial infarction only if the episodes of ischaemia occurred within 24 hours before the infarction.[9] In the same study, a better patient outcome was observed during a five year follow-up period.[9] Our own recent data support this view, namely that pre-infarction angina is not protective if it occurs at any time prior to the infarction, but only within the last 24 hours. We found that whether pre-infarction angina occurs more or less than 48 hours before myocardial infarction does not alter infarct size and in-hospital patient outcome.[18]

More supportive evidence for the beneficial effect of preconditioning in humans comes from the TIMI trial. An ancillary study (TIMI 9B) investigating pre-infarction angina versus outcome in a 30-day period, combining the end-points of myocardial infarction, heart failure, cardiogenic shock and mortality, found a better outcome for the patients who had pre-infarction angina (4% vs. 17%, $p<0.03$).[19]

The exact relationship between time and the degree of protection provided by preconditioning have not yet been determined in humans. In rabbits, we found that the protection is gradually lost when the sustained ischaemia follows the preconditioning short ischaemic event by 65-70 minutes.[20] The protection of preconditioning started to be lost when more than 4 brief consecutive ischaemic events were applied, which means that this protection is limited.[21] The above parameters has also not been determined in humans.

There is evidence for time dependence of preconditioning since it was observed that the highest percentage of patients with no angina and no ST changes was in the group who underwent a percutaneous coronary intervention (PCI) during the first 6 hours of the unstable coronary event.[22]

Another point for discussion concerns the different triggers and different end-points used in the study of preconditioning. These differences in methodology yield different results. For instance, in one study using stress testing as trigger and end-point, the exercise-induced myocardial ischaemia triggered the early phase of preconditioning but not the late phase.[23] In contrast, when exercise was used as the trigger and the ST elevation on the ECG as the end-point, the exercise-induced ischaemia initiated the second window of protection in patients undergoing PCI.[24]

Drug related preconditioning, if it worked, would be very beneficial in clinical practice. Apart from adenosine, which has long been known as a preconditioning stimulant,[25] nicorandil is considered the drug which mimics preconditioning. It is a coronary vasodilator and a $K_{ATP}$ channel opener as well. The CESAR 2 trial found a reduction in total minutes of ischaemia and number of ventricular and supraventricular tachycardias in patients with unstable angina taking nicorandil.[26] The IONA trial also observed a reduction of coronary events in patients with stable angina taking nicorandil in a 2½ year mean follow-up period.[27] In rabbits, nicorandil administered orally for 5 consecutive days before an acute experimental myocardial infarction re-established the diminished protection of ischaemic preconditioning.[28] In the AMISTAD trial,

when adenosine was administered within 6 hours of pain onset and the infusion started as an adjunctive to thrombolytic therapy after establishing acute anterior myocardial infarction, it provoked a 33% overall reduction in the infarct size.[29]

To conclude, the phenomenon of ischaemic preconditioning is still open for further investigation. There are several unresolved issues in preconditioning, since the intracellular signalling pathways have not been fully elucidated.[30-32] The secrets of preconditioning and the drugs that mimic it in humans may be revealed through the discovery of exact pathogenetic mechanisms and the determination of the windows of protection in humans.

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