Myocardial Preconditioning in Humans

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Ischemic preconditioning refers to the ability of short periods of ischemia to render the myocardium more resistant to a subsequent ischemic insult. This term was first introduced by Murry et al. [1] who found that, in a canine model, four consecutive periods of coronary occlusion (5 minutes followed by reperfusion) were able to reduce by 75% the infarct size caused by a subsequent 40 minute period of occlusion. Cohen and coworkers [2] showed that preconditioning in rabbits can lead to enhanced recovery of contractile function of the myocardial region at risk. The chain of events that confers resistance to ischemia is only partially understood. Downey and Cohen [3] developed the hypothesis that stimulation of a variety of G protein-coupled receptors results in the activation of protein kinase C. This, in turn, leads to the translocation of PKC from the cytoplasm to the sarcolemma, where it phosphorylates a substrate protein (possibly the ATP-sensitive K^+[K_{ATP}] channel), which confers resistance to ischemia.

It is now well established that the protective effects of preconditioning are transient and last for less than 2 hours [4,5]. However, a so-called second window of protection or delayed ischemic preconditioning has been demonstrated in different species, occurring 24 hours after the preconditioning stimulus and lasting for about 48 hours [6]. This time course is consistent with the concept that the second window of protection is mediated by the activation of genes encoding for cytoprotective proteins, such as heat shock proteins or antioxidant enzymes [6]. Endogenous activation of adenosine receptors, α_1-adrenergic receptors, bradykinin B_2 receptors, and opioid receptors has been shown to be involved in the infarct size reduction achieved by ischemic preconditioning.

Reimer and researchers [7] found that myocardial preconditioning reduces cumulative loss of ATP, and Kida and coworkers [8] showed that preconditioning preserves creatine phosphokinase and intercellular pH. Przyklenk et al. [9] noted in a canine model that brief episodes of ischemia and reperfusion in the territory of the circumflex coronary artery, followed by occlusion of the left anterior descending artery, was accompanied by smaller infarct size in the LAD territory (which was not preconditioned). Therefore, the authors assume that preconditioning is mediated by factors activated, produced or transported through the heart during brief ischemia and reperfusion. Liu et al. [10] were the first to suggest that preconditioning is mediated by the release of adenosine from ischemic myocytes (breakdown of ATP) and the consequent activation of adenosine A1 receptors. It is thought that release of adenosine by ischemic cells results in activation of PKC, which in turn causes opening of the mitochondrial potassium-sensitive ATP channels and leads to resistance to ischemia [11].

Xuan and coworkers [12] observed that ischemic preconditioning in rabbits increased induced nitric oxide synthase activity 24 hours after the ischemic insult, indicating that iNOS is a mediator of late preconditioning. These data suggest that oxyradical generation and PKC activation during the initial ischemic insult serve as the signal to activate iNOS expression. Ueda et al. [13] demonstrated that hypercholesterolemia blunted ischemic preconditioning in rabbits, while cholesterol lowering was associated with restoration of preconditioning. Morris and Yellon [14] found that angiotensin-converting enzyme inhibitors potentiate preconditioning through bradykinin B_2 receptor activation in human atrial trabeulae. This observation, according to the authors, may explain the reduction of ischemic events among patients treated with ACE inhibitors.

Coronary angioplasty

For obvious reasons, experimental studies on the reduction of infarct size by preconditioning cannot be performed in humans. However, in recent years, myocardial preconditioning was studied extensively during repeat coronary balloon-induced ischemia [15–17]. Deutsch and coworkers [15] performed repeated 90 seconds LAD occlusion in 12 patients with a 5 minute interval between the two inflations. They observed reduction in the degree of ST shift from 4.4 to 2.1 mm ($P<0.001$) with reduction in anginal score between the first and second inflation. There was also a reduction in pulmonary artery pressure. This adaptation to ischemia during repeated coronary angioplasty suggests that myocardial preconditioning plays a role in the reduction and extent of ischemia. Since there was no increase in great cardiac vein flow in this study, the authors also concluded

PKC = protein kinase C
LAD = left anterior descending coronary artery
iNOS = induced nitric oxide synthase
ACE = angiotensin-converting enzymes

that the attenuation of ischemia was not due to increased collateral flow. Some studies did not observe any adaptation to repeat ischemia, probably because the balloon inflation was too short [16,18]. It seems that not only the duration but also the severity of ischemia, which depends also on the presence or absence of collateral circulation, determines the development of myocardial preconditioning [19]. The effect of adenosine on myocardial preconditioning during balloon angioplasty was assessed by Leesar et al. [17] in a study of 30 patients with single vessel disease without collateral circulation. They noted a marked reduction in ST shift in the control group, as recorded by intracoronary electrocardiogram between the first, second and third intracoronary inflations. Pretreatment with adenosine reduced the initial ST shift by 72%, lowered the chest pain score, and abolished preconditioning. Thus, since pretreatment with adenosine mimicked preconditioning, the authors assumed that endogenous adenosine mediates ischemic preconditioning in humans.

In order to assess whether activation of potassium-sensitive ATP channels are responsible for myocardial preconditioning in humans, Tomai and co-workers [20] randomized 20 patients undergoing one vessel coronary angioplasty to receive either 10 mg of glibenclamide, a selective K_{ATP} channel blocker, or placebo. The authors found that in the glibenclamide-treated patients the mean ST segment shift on intracoronary ECG during the second balloon inflation was identical to the first, while in the control group there was a marked reduction in ST shift, indicating loss of myocardial preconditioning in the glibenclamide-treated group.

The role of collateral circulation during repeat coronary inflation is not clear. Sakata and coworkers [21] studied 12 patients with no collaterals and 6 with collaterals who had repeated balloon coronary angioplasty. In the patients with no collaterals, ST shift was reduced from 4 mm to 2.7 mm, and angina score was reduced from 4.3 to 3.1. In patients with collaterals, the initial ST shift was significantly smaller (0.4 mm) with no change on the second inflation. Thus in patients with collaterals the ischemia was less severe and no preconditioning was observed. Billinger et al. [22], studying 30 patients who had three balloon inflations during coronary angioplasty, recorded intracoronary ECG and coronary flow distal to the coronary occlusion by intracoronary pressure wire, and observed that during coronary angioplasty the ST score was significantly reduced on the third inflation compared to the first. This was associated with a 50% increase in distal coronary flow. They concluded, therefore, that myocardial adaptation to repetitive ischemia is related to recruitment of collaterals. Patients with more pronounced collaterals had more significant reduction in ST score. Using the same technique in 10 patients who had two balloon inflations to the LAD, Edwards et al. [23] found that the reduction in magnitude of ST shift and chest pain score was not associated with a change in collateral flow index. Also investigating the protective effect of myocardial preconditioning during coronary angioplasty was Laskey [24]. He noted that in 150 patients with unstable ischemic syndromes the creatine kinase level increased in 7.1% of patients who, prior to the coronary angioplasty, had two periods of 90 seconds of balloon occlusion and 5 minutes of reperfusion; whereas a release of creatine kinase occurred in 25% of patients who had regular angioplasty. These findings clearly show that preconditioning reduced myocardial damage during coronary angioplasty in this group of patients.

Exercise and daily activity

In order to assess whether myocardial preconditioning exists during daily life we performed two studies [25,26]. In the first we studied 26 patients with positive stress tests who underwent three treadmill stress tests at 30 minute intervals. We observed a considerable reduction in total ischemic time between the first and second test, from 633 to 399 seconds, as well as in recovery time, from 159 to 126 seconds. There was no further improvement on the third test. Time to 1 mm ST depression significantly increased (from 487 to 593 seconds), as did the double product on the second test compared to the first, implying a higher ischemic threshold [25]. In a second study [26] we examined 20 patients with proven coronary artery disease, positive exercise tests and evidence of ischemia during daily life as recorded by Holter monitoring. Patients were instructed to walk three times within 45 minutes (15 minutes each walk) the same route that had previously caused myocardial ischemia. In spite of the identical maximal heart rate achieved during the three walks, myocardial ischemia was markedly attenuated on the second and third walks compared to the first. Ischemic time was reduced from 472 seconds on the first walk to 223 and 207 seconds on the second and third walks respectively, and maximal ST depression was reduced from 2 mm on the first walk to 1.6 mm and 1.4 mm on the second and third walks respectively. Bogaty and researchers [27] also noted attenuation of myocardial ischemia during repeat exercise tests. In a more recent study, Tomai et al. [28] found that gilbenclamide abolished the improvement in ischemia on repeated exercise tests [warm-up], indicating that ischemic preconditioning plays a key role in the "warm-up" phenomenon, and is mediated by activation of ATP-sensitive potassium channels.

Pre-infarction angina

Several studies have shown that patients with myocardial infarction preceded by angina have smaller infarcts and a better in-hospital outcome than patients without pre-infarction angina [29–32]. Anzai et al. [29] studied 291 patients with first Q wave myocardial infarction and found that those with pre-infarction angina prior to their infarct had lower levels of creatine kinase, less ventricular tachycardia, less congestive heart failure, and lower mortality. At one year the protective effect was still present; fewer patients with pre-infarction angina had clinical congestive heart

failure, they had a better left ventricular ejection fraction and lower mortality.

Kloner et al. [30] observed that patients with angina within 48 hours of myocardial infarction had a lower in-hospital death rate and a smaller infarct size than patients without angina, despite their similar extent of coronary collaterals as assessed by angiography performed 90 minutes after the infarct. The authors assumed that the initial ischemia during the period of pre-infarction angina might render the myocardium more resistant to infarction (preconditioning). Ishihara et al. [31] found that prodromal angina in the 24 hours prior to infarction, but not angina at a later time, was associated with reduction of infarct size and improved 5 year prognosis.

Additional evidence on the protective role of pre-infarction angina was provided by Andreotti et al. [32], who showed that thrombolytic therapy resulted in a more rapid reperfusion and smaller infarcts, thus suggesting a faster and more efficient thrombolysis in patients with preceding angina. Angina in the 24 hours before infarction, but not angina occurring at a later time, was associated with a better outcome. These findings are supported by animal experiments in which coronary injury resulted in cyclic coronary flow with formation of platelet-rich thrombi [33]. Coronary occlusion for 10 minutes and reperfusion (preconditioning) preceding the coronary injury markedly reduced platelet-mediated thrombosis and improved coronary flow.

Bypass surgery

Intermittent ischemia induced by aortic cross-clamping prior to coronary bypass surgery has been used as a clinical model of ischemic preconditioning. Yellon and researchers [34] performed two periods of ischemic aortic cross-clamping followed by 2 minutes of reperfusion prior to bypass surgery, with distal coronary anastomosis performed during aortic cross-clamping. Myocardial biopsies taken after 10 minutes of aortic cross-clamping exhibited a higher content of ATP in the group of patients exposed to aortic cross-clamping prior to the bypass surgery than the control group. Illes and Swoyer [35] studied 70 patients undergoing open heart surgery who were randomized to preconditioning plus intermittent cold blood cardioplagia or intermittent cold blood cardioplagia alone. Myocardial preconditioning was produced by 1 minute of aortic cross-clamping and 5 minutes of reperfusion. They observed that following surgery, cardiac output was significantly higher within the first 12 hours in those who had myocardial preconditioning, and that inotropes were required by 13 patients in the control group but by none in the preconditioned group. Thus preconditioning significantly improved postoperative hemodynamics. Jenkins et al. [36] showed a reduction in troponin T release in patients exposed to two 3 minute periods of myocardial ischemia prior to revascularization surgery. It has also been shown that pretreatment with adenosine during coronary bypass surgery improves postoperative left ventricular function [37]. It seems, therefore, that myocardial preconditioning has a potential role in preservation of myocardial function in patients undergoing coronary bypass surgery or valve replacement.

The search for myocardial preconditioning-mimicking drugs is in its infancy. Recently, Patel et al. [38] studied 188 patients with unstable angina pectoris on maximal anti-ischemic therapy. All patients underwent 48 hours of Holter monitoring. Patients were randomized to nicorandile, which is an ATP-sensitive potassium channel opener, 20 mg bid, or to placebo. In the drug-treated group, nicorandile significantly reduced the number of ischemic episodes and, interestingly, also reduced the percent of patients who exhibited cardiac arrhythmia. The authors concluded that the anti-ischemic and anti-arrhythmic effect of the drug may be related to pharmacological preconditioning.

Summary

The exact role of myocardial preconditioning in patients with coronary artery disease is not clear. Preconditioning rapidly develops during coronary angioplasty. Myocardial preconditioning probably plays a role in reducing the myocardial infarct size in patients with preceding angina by direct effect, rendering the myocytes more resistant to ischemic injury, by acceleration of thrombolysis, and probably by the increasing recruitment of collaterals. It is also possible that the higher mortality among diabetic patients on sulfonylureas, and their worse outcome during acute myocardial infarction, are related to blockade of preconditioning [39,40].

Myocardial preconditioning does exist during daily life, explaining the well-known phenomenon of "walk-though angina" and the more common "walk-through ischemia." It is hoped that drugs that mimic or enhance preconditioning will be developed, which will provide powerful myocardial protection.

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Capsule

Too many doing too little

Familial hemophagocytic lymphohistiocytosis (FHL) is a genetic disorder that dysregulates the immune system and leads to excesses of lymphocytes, macrophages, and inflammatory cytokines. Two genetic loci have been identified and linked to the disease. Stepp et al. identified the defective gene in the l0q2l-22 linked patients as the gene coding for perform, a protein released from cytotoxic lymphocytes to kill the target cell. This finding provides insight into the biological role of perform as a mechanism for turning off immune responses, perhaps through the elimination of antigen-presenting cells or the cytotoxic T cells themselves.

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