INTRODUCTION

Patients who suffer acute myocardial infarction (AMI) frequently experience prodromal symptoms preceding the attack itself. The term "pre-infarction angina" has come to encompass a spectrum of symptoms suggestive of pre-existing deterioration in the balance between oxygen supply and demand in a coronary circulation compromised by obstructive arterial disease [(1)].

Previous studies demonstrated that patients with pre-infarction angina have a smaller infarct size and better in hospital outcome after acute myocardial infarction, than those without angina. This protective effect has been attributed to ischemic preconditioning, to earlier reperfusion or better collateral circulation development [(2)].

After acute myocardial infarction, the presence of ischemic preconditioning as a result of pre-infarction angina has a protective role, limiting necrosis extent and guaranteeing greater myocardial functional recovery [(3)].

Preconditioning is the process by which brief, repetitive episodes of ischemia reduce the size of a subsequent myocardial infarction [(4)].

Although not fully clarified, the mechanisms underlying ischemic preconditioning have been unveiled to a considerable extent [(5-7)]. Classical preconditioning appears to involve a

complex series of reactions initiated by agonists such as adenosine, formed during ischemia, that activate second messenger pathways involving protein or tyrosine kinases with subsequent opening of mitochondrial adenosine triphosphate sensitive potassium channels (mK^{+}_{ATP}) and reduction in mitochondrial calcium overload [8]. Delayed preconditioning, although responding to similar agonists, likely involves activation of nuclear factor-kappa-B and transcription of several mediators, such as B-cell lymphoma 2 (Bcl-2), that maintain the mitochondrial transition pore in its closed conformation [9].

The foregoing experimental and clinical studies provide a background for reports of improved outcome in AMI patients who experience angina preceding the infarction. Compared with those without antecedent angina, patients with angina had lower mortality, pump failure, arrhythmias, and peak cardiac serum enzyme levels as well as enhanced recovery of cardiac contractile function. In these studies, pre-infarction angina has occurred within 24 to 72 hours of AMI, consistent with the temporal relations of early and delayed preconditioning [10-13].

AIM OF THE WORK

In this study we aim to assess the impact of history of angina prior to first attack of acute ST segment elevation anterior wall myocardial infarction on in-hospital outcome after primary percutaneous coronary intervention (PPCI).

Chapter 1
ACUTE MYOCARDIAL INFARCTION AND PRE-INFARCTION ANGINA

Acute Myocardial Infarction

- ***Definition of acute myocardial infarction***

Myocardial infarction can be defined from a number of different perspectives related to clinical, electrocardiographic, biochemical and pathologic characteristics. It is accepted that the term myocardial infarction reflects death of cardiac myocytes caused by prolonged ischemia. The electrocardiography (ECG) may show signs of myocardial ischemia, specifically ST and T changes, as well as signs of myocardial necrosis, mainly changes in the QRS pattern [(14)].

- ***Universal definition of acute myocardial infarction*** [(14)]

The term acute myocardial infarction (AMI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions the following criteria meets the diagnosis for AMI:

Detection of a rise and/or fall in cardiac troponin with at least one value above the 99th percentile of the upper reference limit (URL) and with at least one of the following:

- Symptoms of ischemia.
- New or presumed new significant ST-segment–T wave changes or new left bundle branch block.

- Development of pathological Q waves in the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
- Identification of an intracoronary thrombus by angiography or autopsy.

Pathogenesis of acute myocardial infarction

An acute coronary syndrome is nearly always caused by a sudden reduction in coronary blood flow caused by atherosclerosis with thrombosis superimposed, with or without concomitant vasoconstriction *(15).*

ST-segment elevation myocardial infarction (STEMI) is the clinical correlate of full thickness ischemia and infarction of myocardium and is the result of sudden thrombotic occlusion of its blood supply. The transition from a diseased but patent coronary artery to one that is occluded by thrombus begins with either rupture or erosion of a coronary atherosclerotic plaque *(16).*

In fact, the majority of ST segment elevation myocardial infarction evolve from mild to moderate stenosis. However, severe stenosis is more likely to undergo plaque events leading to infarction than mild ones *(17).*

Plaque disruption results in exposure of its lipid-rich core to the lumen and adherence of platelets to the arterial sub-endothelium. The platelets become activated and develop high affinity for fibrinogen, causing their cross-linking and

degranulation [18]. Simultaneously, the release of tissue factor from the lipid-rich core results in activation of the coagulation cascade and generation of thrombin [19]. The result is a luminal thrombus consisting of aggregated platelets, cross-linked fibrin strands, and entrapped red blood cells, the enlarging thrombus can interrupt blood flow and lead to an imbalance between oxygen supply and demand that if severe and persistent, causes transmural infarction of the myocardium (Figure 1) [20].

It is now believed that the stability of the atherosclerotic plaque and the risk for the development of acute myocardial infarction are variable. It is now appreciated that the risk is related more to the composition and "Vulnerability" of the plaque, than to the degree of vessel stenosis. Risk factors can be categorized as abnormalities of the vessel wall, blood flow or thrombogenicity, or as local versus systemic effects [21].

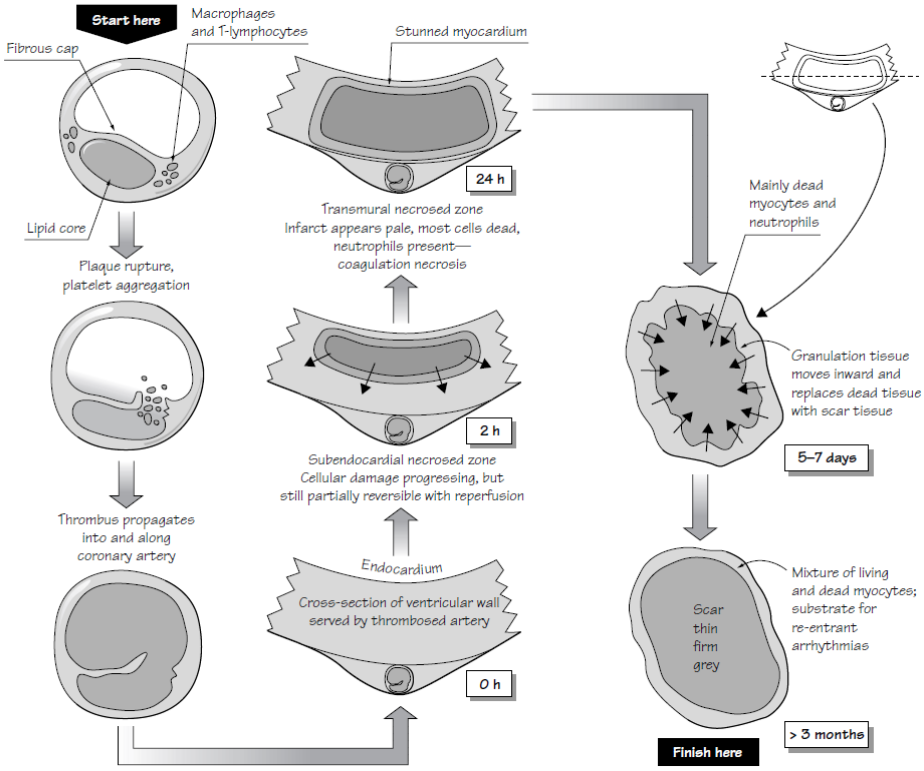

Figure (1): Pathogenesis of acute myocardial infarction [(20)].

Myocardial infarction caused by complete coronary artery occlusion begins to develop after 15–30 minutes of severe ischemia (no forward or collateral flow) and progresses from the sub-endocardium to the sub-epicardium in a time-dependent fashion (the wave-front phenomenon) [(20)].

Reperfusion, including recruitment of collaterals, may save myocardium at risk from undergoing necrosis; suboptimal but persistent flow may extend the time-window for achieving myocardial salvage by complete reperfusion [(17)].

Pre-infarction angina

Definition:

The term "pre-infarction angina" has come to encompass a spectrum of symptoms suggestive of deterioration in the balance between oxygen supply and demand in a coronary circulation compromised by obstructive arterial disease [(1)].

Potential Mechanisms of Cardio-protection by Previous Angina

In humans, pre-infarction angina is associated with improved prognosis after acute myocardial infarction, several mechanisms may explain this benefit such as enhanced collateral circulation towards the ischemic myocardium, increased sensitivity to thrombolysis or myocardial ischemic preconditioning [(10,12,22,23,24)].

Brief episodes of myocardial ischemia prior to experimental infarction are associated with decreased infarct size and improved wall motion recovery [(4,25)].

Reperfusion-induced myocardial injury is markedly reduced by experimental pre-infarction ischemia [(26,27)].

Improved perfusion of the area at risk after coronary recanalization may be related to ischemic preconditioning of the myocardium. In humans, micro-vascular injury following ischemia and reperfusion results in myocardial no-reflow (reduced myocardial perfusion despite complete epicardial coronary recanalization) [(28)].

Hirai et al observed that patients who experienced angina for more than 1 week before coronary occlusion had higher left ventricular ejection fraction and better wall motion in the infarct-related zone compared with patients without angina. The authors concluded, however, that this improvement in left ventricular function was a secondary consequence of increased collateral perfusion in patients with previous angina [29].

Matsuda et al and Cortina et al also reported better preservation of left ventricular function in patients with a history of angina before myocardial infarction. In the study of Matsuda et al, this was not due to increased collaterals whereas in the study by Cortina et al, collaterals appeared to play a role [30, 31].

Some studies have suggested that patients with prior angina have more collaterals [32]. But results have not been consistent [30].

Muller et al showed that patients with a history of angina for more than 1 week before acute myocardial infarction had a lower rate of re-occlusion after thrombolysis and a nonsignificant trend toward lower in-hospital mortality (4.6% versus 7.2%) [33]. Several factors were implicated to play a role in the benefit of prior angina, including enhanced collateralization, ischemic preconditioning, prior antianginal medicines, or intrinsic differences in the thrombolytic systems between the two groups.

In a preliminary report, Ottani et al. described smaller infarct sizes (determined by CK) and a smaller number of hypokinetic segments (assessed by left ventricular angiography)

in patients with prodromal angina within 24 hours of the onset of myocardial infarction, and they postulated that prodromal angina may have preconditioned these infarcts [(34)].

Brief ischemia 24 hours before sustained coronary occlusion has also been shown to reduce infarct size and may be related to expression of heat shock protein; this delayed protection implies that the heart may become more resistant to prolonged ischemia even when this dose of brief ischemic preconditioning occurred at a remote previous time. The mechanism whereby heat shock and expression of heat shock proteins provide longer protection of the heart is still under investigation. Thus, it appears that brief periods of ischemia provide endogenous protection to the heart [(35)].

Importance of angina for development of collateral circulation

When myocardial ischemia is caused by severe stenosis of a coronary artery it stimulates the development of collateral vessels between major coronary arteries [(36)]. Some workers have attempted to relate the extent of the development of collateral channels to pre-infarction angina, which is indicative of myocardial ischemia [(37)]. Collateral perfusion will be less when the diseased arteries are not completely obstructed [(38)]. In these circumstances, even if there are well developed collateral vessels, collateral flow and corresponding imaging of the collateral channels may be reduced, thus collateral development in patients with myocardial infarction can only be evaluated accurately when the diseased coronary arteries are occluded [(39)].

Chapter 2

PRECONDITIONING AND POSTCONDITIONING

Ischemic preconditioning

Definition:

A series of short ischemic periods separated by brief reperfusion.

Timing of preconditioning:

Infarct size can be limited by endogenous mechanisms applied at three major time points:

1. **Before the ischemic event (Cardio-protective treatments):**

a) ***Early preconditioning or first window of preconditioning:***

Applied immediately before the ischemic event.

b) ***Delayed preconditioning or second window of preconditioning:***

Applied 24 hours before the ischemic event [(4)].

2. **Endogenous mechanisms applied during the ischemic event [(40)].**
3. **At reperfusion:**

E.g. by thrombolysis, percutaneous coronary intervention (PCI), or surgery [(41)].

o Mechanisms of Preconditioning and Postconditioning:

Any fully cardio-protective strategy applied at the time of reperfusion must provide protection against the known mediators of lethal reperfusion injury, which include cellular and mitochondrial calcium overload, a burst of oxidative stress, endothelial dysfunction, and reduced nitric oxide production. It is now possible to protect the reperfused myocardium by activating prosurvival kinase signaling pathways (reperfusion injury salvage kinase - RISK pathway) [(42)].

Both pre- and postconditioning activate the same key pathways, which include phosphatidylinositol 3-kinase-Akt and extracellular signal–regulated kinase [(42, 43)] (figure 2).

Upstream may be activation of G-protein coupled receptors, and the many downstream events include key phosphorylations of endothelial nitric oxide synthase and inhibition of the apoptosis promoters.

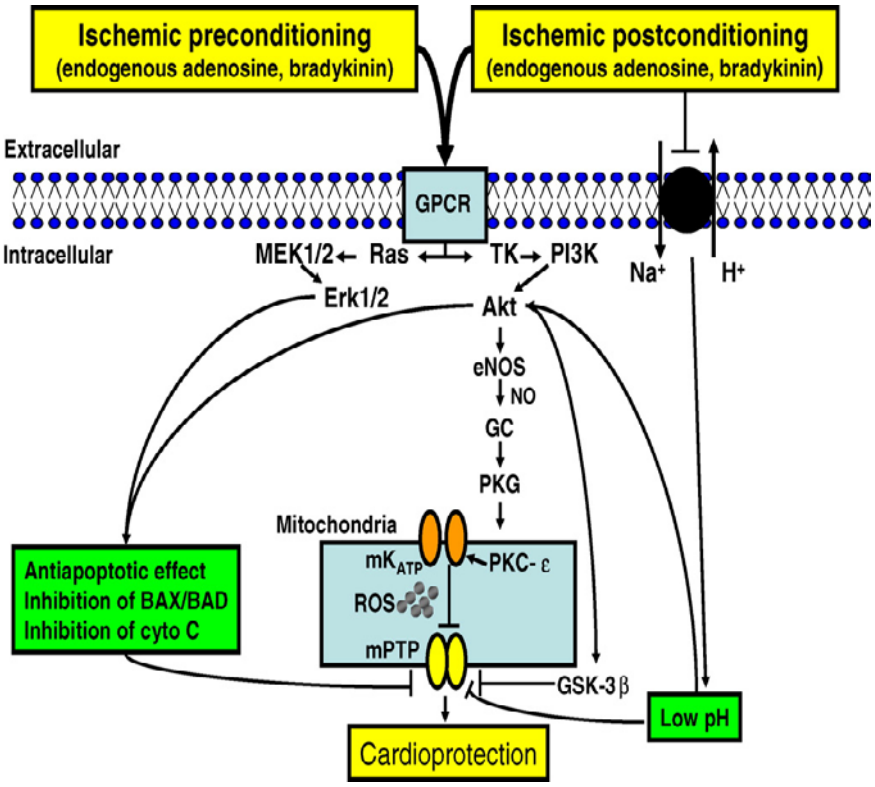

Figure (2): Schematic diagram for ischemic preconditioning (IPC) and ischemic postconditioning (IPOC) cardio-protective pathways, it demonstrates how the different components of the common cardio-protective pathway recruited specifically at the time of myocardial reperfusion by both IPC and IPOC mediate their cardio-protective effect. Many of the signal transduction pathways converge on mitochondrial permeability transition pore mPTP which appears to be the end-effector of cardio-protection in IPC and IPOC. Abbreviations: GPCR, G-protein coupled receptor; TK, tyrosine kinase; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; GC, guanylate cyclase; PKG, protein kinase G; PKC-ε, protein kinase C; mK^{+}_{ATP}, mitochondrial adenosine triphosphate potassium channel; ROS, reactive oxygen species; mPTP, mitochondrial permeability transition pore; GSK-3β, glycogen synthase kinase-3β; Na^{+}, sodium ion; H^{+}, hydrogen ion; Ras, rat sarcoma; MEK, Mitogen activated protein extracellular signal regulated kinases; Erk, Extracellular signal regulated kinase; BAX, Bcl-2 associated X protein; BAD, Bcl-2 associated death promoter; cyto C, cytochrome C [(44)].

As in the case of ischemic preconditioning (IPC), protective pathways activated by postconditioning (IPOC) appear to converge on the mitochondria, in particular the mitochondrial permeability transition pore (m-PTP). This opens during the first few minutes of reperfusion, in response to mitochondrial calcium overload, oxidative stress, and adenosine triphosphate depletion [45, 46,47].

Furthermore, the protective effect of postconditioning may directly or additionally be related to beneficial antioxidant effects, decreased extracellular levels of noxious metabolites such as protons and lactate or delayed washout of adenosine, a well-established mediator of preconditioning[48, 49]. Stimulation of any G protein-coupled receptor (GPCR) has been shown to trigger preconditioning and a similar involvement of GPCR is being revealed for postconditioning [6]. These GPCRs include adenosine, bradykinin, norepinephrine, and opioids' receptors and may include protease-activated receptor type 2 (PAR2) at least for postconditioning.

The involvement of these receptors must satisfy several criteria:

1) The receptors must be present in the target tissue (myocytes, endothelium and inflammatory cells) and active during ischemia and/or reperfusion;

2) The stimulating ligand must be endogenously produced and elevated during either ischemia (preconditioning or index) or reperfusion;

3) The endogenous ligand-receptor interaction can be blocked pharmacologically or the protective effects not observed in animal models in which the specific receptor has been knocked out or the endogenous ligand has been knocked down by Small interfering ribonucleic acid (siRNA) approaches; and

4) The exogenous ligand can mimic the effects of IPC and IPOC. Adenosine is released during ischemia and reaches high interstitial and intravascular levels [(50)].

Adenosine is also rapidly washed out during reperfusion, with high concentrations being detected in coronary perfusate during the early minutes of reflow [(48)]. There are four adenosine receptor subtypes: A1, A2A, A2B, and A3. Blockade of the A1 receptor abolished IPC's cardio-protection [(25)], while exogenous application of selective A1-receptor agonists prior to the index ischemia reduces infarct size which suggests that stimulation of the A1 receptor by adenosine released during the preconditioning stimulus exerts protection before the index ischemia is imposed[(51)]. Zhao and colleagues found that endogenously released adenosine also exerts cardio-protection during reperfusion and that the A2 receptor, rather than the A1 receptor is involved in modulating infarction during reperfusion [(52)]. In