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VALUE OF ISCHEMIC PRECONDITIONING IN PATIENTS WITH FIRST NON-ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Thesis

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List of Abbreviations

Abbreviation	Meaning
A Fib	Atrial Fibrillation
ACE_i	Angiotensin converting Enzyme inhibitors.
AP-2	Adaptor protein 2
ARBs	Angotensin receptor blocker
BAD	Proapoptotic Bcl-2 family member.
B. Blockers	Beta receptor adrenergic blocker
Ca^{2+}	Calcium ion.
Ca^{2+} channel blocker	Calcium channel blocker.
CABG	Coronary artery bypass Grapft.
cGMP	Cyclic guanosine monophosphate.
CGRP	Calcitonin gene related peptide.
CHF	Congestive heart failure**.**
eNOS	Endothelial nitric oxide synthase.
ERK	Extracellular regulated kinase.
GPCRs	G protein coupled Receptor(s)
GSK	Glucose synthase kinase.
GSK3β	Glucose synthase kinase 3.
HIF-1a	Hypoxia inducible factor**.**
IPC	Ischemic preconditioning
JNK	One of the mitogen activated kinases.
LMWH	Low molecular weight heparin.
LVWMSi	Left ventricular wall motion score index.
MAPK	Mitogen activated protein kinases.
MPT	Mitochondrial permeability transition pore
mTOR	Mammalian target of rapamycin.
Na^+	Sodium ion.

List of Abbreviations (Cont.)

Abbreviation	Meaning
NCX	Sodium calcium exchange.
NOS	Nitric oxide synthase.
PACs	Premature atrial contractions.
PC	Preconditioning
PDK 1	Phosphoinositide-dependent protein kinase 1
PI3K	Phosphoinositide 3-kinase.
PIP3	Phosphatidyl inositol 3, 4, 5, triphosphate
PKA	Protin Kinase A.
PKC 139	Protein kinaae C139
PKC	Protein kinase C.
PKG	Protein Kinase G.
PTCA	Percutaneous trasluminal coronary Angioplasty
PVCs	Premature ventricular contractions.
RIP	Remote ischemic preconditioning.
ROS	Reactive oxygene species.
RSK	Ribosomal S6 kinase.
VDAC	Voltage-dependent anion channel.

INTRODUCTION

Several studies have demonstrated the protective effects of pre-infarction angina in setting of Q wave myocardial infarction, implicating the role of ischemic preconditioning (IPC) but this role remains uncertain in patients with NSTEMI. Subendocardial viability in NSTEMI patients is thought to be less dependent on collateral circulation and thus more likely to be protected by other mechanisms such as preconditioning ***(Christodoulos et al., 2003).***

Since the phenomenon of ischemic preconditioning (IPC) was first described by ***Murry et al., (1986)*** demonstrating a significant limitation of infarct size in the preconditioned myocardium, several studies have been designed in order to bring to light all aspects of this novel protective mechanism, which was considered as the most powerful intervention to reduce infarct size other than reperfusion ***(Kloner et al., 1998).***

For both logistic and ethical reasons, no clinical study can meet the strict conditions of experimental studies on (IPC) in which infarct size is the endpoint. Thus surrogate endpoints that have been used, including contractile function, echocardiographic ischemic changes or bio-chemical evidence of cell damage cannot always be accurately quantified. These have to be taken into consideration in the evaluation of clinical studies on (IPC) as the mechanism of such form of

preconditioning may differ from those involved in the reduction of infarct size in the experimental models ***(Tomi et al., 1999).***

Myocardial cell death due to ischemia-reperfusion is a major cause of morbidity and mortality. In the past few decades, it has become clear that the myocardial response to ischemia-reperfusion can be manipulated to delay injury, which has motivated intense study of the mechanisms of cardioprotection.

The cardioprotective strategy of (IPC), first described by Murry et al in 1986, provided an indication of the magnitude of the possible cardioprotective effect and stimulated considerable research into the mechanisms involved.

Over the past two decades, we have learned a detail about the signaling pathways involved in (IPC). More recently, activation of signaling kinases at reperfusion, either by agonist addition or by postconditioning, has been shown to be cardioprotective ***(Zhao et al. 2003, Hausenloy et al., 2005)***.

In spite of the identification of these signaling pathways, the precise mechanism by which these pathways reduce cell death is only beginning to be understood. In parallel with the intense study of cardio-protective mechanisms, the past few decades have also seen intense research into mechanisms involved in regulating apoptosis and necrosis (it has recently been appreciated that necrosis is also regulated and can be inhibited by many "anti-apoptotic" agents ***(Hausenloy et al., 2005; Zong et al.,2006).***

AIM OF THE WORK

The aim of this study is to evaluate the effect of pre-infarction angina in the clinical setting of Non-ST segment elevation myocardial infarction (Non-STEMI).

PRECONDITIONING AND THE HEART

Episodes of ischemia as short as 5 minutes followed by reperfusion protects the heart from subsequent longer periods of coronary artery occlusion by markedly reducing the amount of necrosis that results from the test episode of ischemia. This phenomenon has been observed in each species in which it has been studied, and has a powerful cardio-protective effect. This novel phenomenon is first described by Murry et al., 1986 and it is called preconditioning (IPC) ***(Kloner et al., 2001)***.

Consequences of brief ischemia:

Brief episodes of transient myocardial ischemia are tolerated by myocytes. Although there is no cell death results from ischemia the myocytes are damaged. In canine heart, total proximal coronary artery occlusions up to 15 minutes result in reversible injury and beyond that irreversible injury. The 15-minute period of ischemia, however, induces marked change in the high-energy phosphates and the adenine nucleotide pool, depletion of glycogen, accumulation of lactate and H^+ and mild intracellular edema observed on ultrastructure: but once blood flow is reestablished, the myocytes eventually recover, the clinical counterparts to brief periods of transient ischemia include angina, unstable angina, coronary vasospasm and

transient ischemia induced by inflation of an angioplasty balloon in the coronary arteries. Patients with coronary artery disease may experience episodes of transient ischemia on daily basis without developing myocardial necrosis ***(Kloner et al., 2001)***.

Over the past 25 years, both in the experimental laboratory and in clinical realm, the brief episode of ischemia is considered to influence the myocardium in both positive and negative ways and this influence may last for days. Brief episodes of ischemia induce both stunned myocardium and (IPC) ***(Kloner et al., 2001).***

Physiological and biological changes found in reversibly injured myocardium:

Effect of Ischemia:

Jennings et al., (1990) reported that Sudden occlusion of major branch of a coronary artery in large animal heart such as the dog heart is followed by physiological and biological changes that appear within seconds of the cessation of coronary flow; for example, energy metabolism shifts from aerobic (mitochondrial) metabolism to anaerobic glycolysis after only 8 seconds of reduced arterial flow.

This shift occurs as soon as the O_2 trapped in the tissues as oxhemoglobin and oxmyoglobin is consumed. Simultaneously,

with the shift in metabolism, effective contractions diminish and then cease and the myocardium stretches rather than shortens with each systole. The membrane potential decreases and ECG changes appear. Because the demand of the myocytes for energy far exceeds the supply from anaerobic glycolysis and from reserves of high-energy phosphates (HEP), tissue ATP decreases and ADP begins to accumulate. Creatine phosphate, a major reserve source of HEP, decreases very quickly about 90% exhausted after 30 seconds of ischemia, whereas ATP declines more slowly. Late in the reversible phase of ischemia 75% to 80% of the ATP present at the onset of ischemia has disappeared ***(Jennings et al., 1985).***

Anaerobic glycolysis provides 80% of the new (HEP) produced in zones of sever or total ischemia. Because little glucose is trapped in the extracellular fluid, anaerobic glycolysis utilizes glucose-1-p from glycogenolysis as its substrate. In this process, 3μmole HEP is generated per each μmol glucose-1 p converted to twoμmol lactate. The lactate and its associated H^+ accumulate. After only 10 minutes of ischemia, the intracellular PH decreases to (5.8 to 6.0) and the load of intracellularly osmotically active particles, lactate, inorganic phosphate, creatine, etc. increase markedly ***(Jennings et al., 1986).***

This osmotic load, however, causes only a modest increase in intracellular H_2O, because relatively little H_2O is available in the extracellular space of severely ischemic tissue to support the swelling process. This edema is visible on transmission electron microscopy; however, it appears as an increase in the sarcoplasmic space.

Tissue glycogen decreases and products of anaerobic glycolysis, such as (glucose 1-P, glucose 6-P, α-glycophosphate and lactate) increase ***(Jennings et al., 1986; Jennings et al., 1990).***

The adenine nucleotide pool is degraded as the ADP formed from the action of ATPase accumulates, because ADP is being formed quickly, whereas rephosphorlation of ADP to ATP via anaerobic glycolysis is slowed by acidosis and lactate ***(Rovelto et al., 1975).***

The HEP of ADP is captured for use via the action of adenylate cyclase; in this process, AMP is formed and accumulates intracellularly, where it is degraded to adenosine. Adenosine diffuses to the extracellular fluid and is lost from the adenine nucleotide pool. In the extracellular fluid, the adenosine is further degraded to insoine and hypoxanthine; both metabolites accumulate. The result of these reactions is the reduction of the nucleotide pool (Σ Ad), i.e. Σ (ATP + ADP + AMP) late in the

reversible phase of ischemia it falls to 30%-40% of its initial level ***(Jennings et al., 1985).***

A variety of substances, such as bradykinin opioids norepinephrine and angiotensin are released into the extracellular fluid during the first few minutes of ischemia. These substances join adenosine as agents that can bind to receptors on myocytes and thereby stimulate the intracellular signaling systems. These reactions occur quickly, for example, phosphorylase is activated only a few seconds after the onset of ischemia by the norepinephrine that is released from the intra-myocardial sympathetic nerve endings as a response to ischemia ***(Wall et al., 1994; Schultz et al., 1995).***

There is evidence in vitro isolated perfused hearts that intracellular ionic Ca^{2+} rises slightly late in the reversible phase This has been difficult to confirm in vivo but seems likely to occur, because the rise of intracellular hydrogen (H^+) of ischemia causes intracellular Na^+ to rise via (Na^+/H^+) exchange. The increase in intracellular Na^+ should serve to drive Ca^{+2} intracellularly via (Na^+/Ca^{+2}) exchange. Conversely, no increase in the total tissue Ca^{+2} or in the specific activity of Ca^{+2} accumulated in the tissue from the plasma reperfusing the myocardium can be seen after 15 minutes of ischemia and 0.5, 3 or 20 minutes of reperfusion ***(Jennings et al., 1985; Steenbergen et al., 1987).***