

Myocardial Metabolism : Pharmacological Manipulation in Myocardial Ischaemia

B Mitra*, M Panja**

Abstract

Acute myocardial ischemia may result in diverse outcomes ranging from asymptomatic episodes to frank myocardial infarction. Reperfusion therapy becomes the mainstay of treatment of patients with evolving MI and provide practical approach for salvage of ischemic myocardium. Favorable modulations of metabolic events during and after ischemia results in increased myocardial salvage in reperfused myocardium. The use of GIK showed great advantage in enhancing myocardial salvage in patients with AMI. Use of other metabolic agents show great promise in experimental studies and merits further evaluation in human trials. Metabolic modulation of ischemic myocardium continues to be a unique and untapped approach to favorably effect ischemic myocardium. Metabolic adjuncts can be employed to lessen ischemic injury and thereby enhance the salutary effects of reperfusion. The use of metabolic manipulations which enhance glycolytic pathways and inhibit potentially noxious fatty acid intermediates may also offer a noble approach for the protection of transiently ischemic myocardium in patients with coronary artery disease. And one thing is certain, that is - agents that modify myocardial metabolism in disease states have definitely enhanced the therapeutic armamentarium to fight the problem and improve the well being of the patients. ©

INTRODUCTION

Acute myocardial ischemia may result in diverse outcomes ranging from asymptomatic episodes to frank myocardial infarction. Reperfusion therapy either by direct angioplasty or thrombolytic therapy has become the mainstay of treatment of patients with evolving MI and provide practical approach for salvage of ischemic myocardium. But benefit of reperfusion is influenced by various factors like duration, severity of ischemia, prior reperfusion, adequacy of reflow, presence of restenosis and coronary reocclusion. Furthermore reperfusion triggers specific biochemical, functional and ultra structural changes which may limit maximum myocardial salvage.

An alternative or adjunctive treatment for myocardial ischemia is to optimize energy metabolism in the ischemic myocardium and thus reduce the production of angina producing stimulus (that is H⁺ and adenosine). Unlike with traditional approach, this alternative approach does not have any direct effects on coronary blood flow, heart rate and after load, instead this agent modify the metabolism of the ischemic tissue so that there is less accumulation of lactate and lesser fall in intracellular pH and the level of ATP.

Varieties of pharmacological adjuncts have been proposed to minimize ischemic injury and there by maximize the myocardial salvage, than those achieved by reperfusion. This brief review will present the biochemical and physiological rationale of various strategies to protect ischemic myocardium depending on modified substrate metabolism as an adjunct to treatment of myocardial ischemia and evolving infarction. The maximum benefit can be achieved when these metabolic adjuncts are used with reperfusion therapy. Myocardial ischemia occurs when there is imbalance between the delivery of oxygenated blood to the myocardium and the normal cardiac demand for the inotropic and chronotropic state. Traditional therapies for ischemia are aimed at restoring the balance between oxygen delivery and the myocardial demand of oxygen.

Cardiac work is supported by high rate of combustion of carbon fuel and oxygen consumption. In healthy heart, fatty acid is the main fuel, supply 60-80% of energy. Balance of energy comes from oxidation of glucose and lactate. ATP is broken down to fuel contractile work, it also resynthesised in mitochondria by using energy from oxidation of fatty acid, glucose and lactate. Myocardial ischemia dramatically alters fuel metabolism. Myocardial ischemia occurs when there is imbalance between the delivery of oxygenated blood to the myocardium and the normal cardiac demand for the inotropic and chronotropic state. When coronary blood flow reduces by 30-60% of normal there is a proportional decrease in the rate of oxygen consumption, ATP

*Resident, Department of Internal Medicine; **Head of Department, Department of Cardiology, Institute of Post Graduate Medical Education and Research, SSKM Hospital, Kolkata.

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production and increase in glucose uptake by heart. However unlike under normal aerobic conditions, the glucose taken up by the ischemic myocardium is not readily oxidized in mitochondria but rather converted to lactate and there is switch from uptake of lactate by the heart to lactate production. This leads to disruption of cell homeostasis, ATP content decreases; there is accumulation of lactate and H⁺, a fall in intracellular pH and decrease in contractile work. Paradoxically, the ischemic tissue continues to drive most of its energy (50-70%) from the oxidation of fatty acids despite there being a high rate of lactate production. This ischemia induced disruption of cardiac metabolism can be minimized by metabolic agents that decrease oxidation of fatty acids and increase the rate of combustion of glucose and lactate, resulting in clinical benefit to the ischemic patients.¹

REVIEW OF MYOCARDIAL METABOLISM

In normoxic condition: Substrate Metabolism, consumption of oxygen and synthesis of ATP

Heart is an intrinsically aerobic organ, constantly requiring and producing energy to meet the needs of contraction and maintenance of ionic homeostasis. It utilizes various substrates to produce high energy compound Adenosine Triphosphate (ATP) for the contractile function. Their production depends on arterial level of substrates, oxygen, hormones, coronary blood flow, and ionotropic state. Among the various substrates most important are long chain free fatty acid and glucose, others are lactate ketone bodies.

Under normal fasting state long chain fatty acid is the preferred fuel as they are abundant in arterial blood and provide significant amount of ATP for each mole of fatty acid oxidation. ATP is broken down to ADP and inorganic phosphate by myosin ATPase and the energy, that is released, drives the movement of actin and myosin filaments. ATP is also used by the Ca⁺⁺-ATPase on the sarcoplasmic reticulum (SR) to pump Ca⁺ into the sarcoplasmic reticulum (SR) at the end of systole and allow diastolic relaxation. Approximately two-third of ATP used by the heart goes to contractile shortening and remaining used for uptake of calcium into SR. ATP is constantly regenerated from ADP and inorganic phosphate in mitochondrium by oxidative phosphorylation^{2,3} which is driven by electron transport chain which takes energy from oxidation of fatty acid, glucose, lactate primarily via reduced nicotinamide adenine dinucleotide (NADH) and pumps H⁺ out of mitochondrial matrix. By oxidative phosphorylation ATP is resynthesized when H⁺ reenters the matrix and oxygen is consumed. Cardiac muscle requires a constant high rate of carbon substrate oxidation to generate NADH for electron transport chain and drive formation of ATP by oxidative phosphorylation.^{2,3} In healthy heart the processes of ATP synthesis and breakdown are

exquisitely matched so that there is never a significant fall in ATP concentration, even with increase in cardiac output, like in exercise.

Under normal state long chain fatty acid is the preferred fuel, supplying 60-80% of energy requirement. The balance of energy comes from the oxidation of glucose and lactate in equal proportions. Fatty acid uptake by heart is determined by plasma fatty acid concentration level, whose level depends on triglyceride breakdown (Lipolysis) in subcutaneous adipocytes. Lipolysis is inhibited by insulin, and stimulated by catecholamines. Thus under fasting condition and in diabetes (where insulin is low, catecholamines are elevated) plasma concentration of fatty acid increases and rate of fatty acid oxidation increases. After a meal when insulin level is high, the fatty acid oxidation rate falls.

Carbohydrate metabolism is entirely controlled by the rate of fatty acid oxidation, which strongly inhibits the rate of glucose and lactate uptake and oxidation. Myocardial glucose uptake is regulated by transmembrane glucose gradient and glucose transporter GLUT-1, GLUT-4. In myocardium glucose is either stored as glycogen or broken down by glycolysis to pyruvate in cell cytosol.

Oxidation of lactate also produces pyruvate, which is transported into mitochondrial matrix and metabolized to acetyl-coenzyme-A. It is also produced by fatty acid oxidation and is thus the confluence of metabolism of carbohydrate and fatty acid. The rate of flux of pyruvate to acetyl-CoA is determined by multi-enzyme complex. This rate of conversion is determined by amount of active enzyme in tissue and concentration of substrate (Co-A, NAD⁺, Pyruvate) and products (acetyl-CoA, NADH). High rate of fatty acid oxidation causes elevation of NADH:NAD⁺ and acetyl Co-A: free CoA ratios which in turn inhibit the flux through the active enzyme. The active enzyme amount is also under allosteric control of PDH Kinase, which phosphorylates and inhibits PDH.³ PDH kinase activity is stimulated by increase in the NADH: NAD and acetyl-coA: CoA ratios. So high rates of fatty acid oxidation stimulate PDH



Fig. 1 : Myocardial energy metabolism under normal aerobic condition. Heart extracts oxygen, fatty acid, glucose, lactate from the blood and combusts them to CO₂, water and heat, releasing the energy that produces mechanical work.

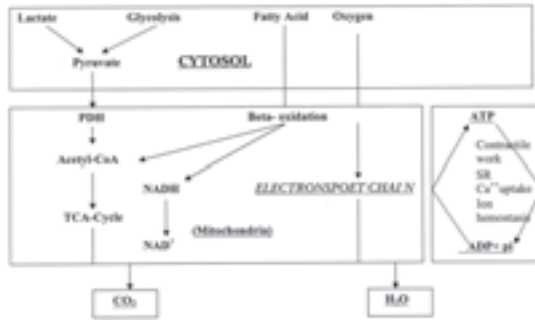


Fig. 2 : Myocardial energy metabolism under normal aerobic condition. Fatty acids are the primary source of energy for ATP synthesis. The balance comes from oxidation of pyruvate formed from lactate oxidation and glycolysis. Only a trivial amount of ATP is resynthesized by glycolysis via substrates level phosphorylation, Coenzyme-A, PDH, NADH, reduced nicotinamide adenine dinucleotide. SR : Sarcoplasmic reticulum.

kinase and decrease the rate of glucose and lactate oxidation by the heart.

Substrate metabolism during ischemia and the rationale for metabolic protection

In ischemia, lack of oxygen cause shift to anaerobic metabolism with rapid stimulation of glucose uptake, glycogenolysis and glycolytic flux. Moderate reduction in blood flow and oxygen supply result in increased glucose extraction and glycolysis with no change in glucose uptake. As severity of ischemia increases, myocardial glucose uptake, glucose extraction, and glycolysis increase more significantly.

Following ischemia, glucose transporter GLUT-4 and GLUT-1 are recruited from intracellular stores to plasma membrane. Depending on severity and duration of ischemia, their transcription also gets modified. During ischemia stimulation of glucose transport is reflected by increased glycolytic flux. There is a decrease of ATP, which causes activation of phosphofructokinase-1 (PFK-1) by c-AMP that increases glycolytic flux. Prolong ischemia inhibits glycolysis due to increased level of lactate and protons, and decreases availability of NAD+.

Myocardial ischemia alter fuel metabolism. when coronary blood flow decreases upto 30-60% of normal, there are proportional reductions in the rate of oxygen consumption and production of ATP.^{2,3} Glycolysis is stimulated and there is an increase in uptake of glucose by the heart and breakdown of tissue glycogen stores.^{2,3} However, unlike under conditions of normal blood flow, during ischemia, pyruvate produced by glycolysis is not so readily oxidized in the mitochondria, but rather is reduced to lactate in the cytosol.

This causes dramatic disruption in cell homeostasis, and a decrease in contractile work. ATP concentration decreases, ADP, inorganic phosphate (Pi), Adenosine, lactate and H⁺ accumulates, intracellular pH falls. As ATP levels fall, the ADP that is formed accumulates and is converted to adenosine,⁴ this adenosine leaves the myocyte and stimulates adenosine A1 receptors on

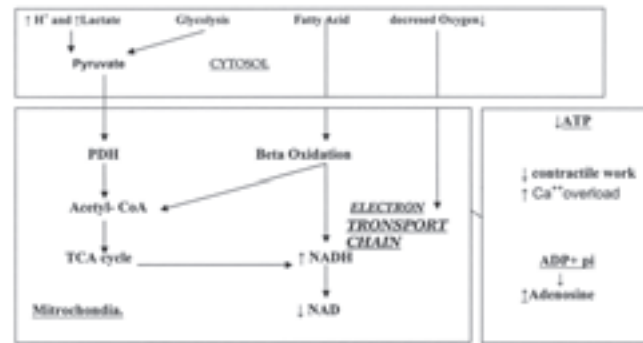


Fig. 3 : Cardiac energy metabolism during moderate ischemia (40% of normal blood flow). The arrow pointing up and down indicate the change compared to normal aerobic conditions. Relative to aerobic conditions transient ischemia results in an increase in glycolysis without an increase in rate of pyruvate oxidation, thus resulting in lactate accumulation in the cell. Despite this acceleration of glycolysis and lactate production, the relatively high rate of residual oxygen consumption is fuelled primarily by the oxidation of fatty acids, Co-A : Co Enzyme A, NADH : reduced nicotinamide adenine dinucleotide, PDH : Pyruvate dehydrogenase, pi : inorganic phosphate.

cardiac afferent sensory neurons, causing anginal pain.⁵

Fall of intracellular pH affect the cardiac myocyte to use the energy released from the breakdown of ATP to perform contractile work and to maintain Ca⁺⁺ homeostasis. The concentration of Ca⁺⁺ for a given amount of force generation is greater at low pH, so higher cytosolic Ca⁺⁺ concentration is required during systole to produce a giving amount of mechanical power.⁶ The amount of ATP required by SR Ca⁺⁺ pump increases when pH falls.⁶ Thus for a given rate of synthesis and breakdown of ATP at low pH, more of energy released from ATP breakdown goes to the chemical work of regulating Ca⁺⁺ content in the cytosol and less to contractile work. In addition, the efflux of H⁺ from myocyte in exchange for Na⁺ has been shown to lead to a greater Na⁺/Ca⁺⁺ exchange across the cell membrane, and so further wasting of ATP to maintain Ca⁺⁺ homeostasis.⁷

Paradoxically, the residual consumption of oxygen during moderate myocardial ischemia is supported by fatty acid oxidation.^{2,3} During ischemia there is an impairment of oxidation of pyruvate that contributes to the biochemical and mechanical dysfunction that occur in face of continued high rate of fatty acid oxidation. In myocardial ischemia, particularly in infarction, there is high level of plasma free fatty acid level (>1mmol/L) due to peripheral sympathetic nervous system activation, which greatly inhibit flux through PDH.

During ischemia, low rate of pyruvate oxidation appears to be due to build up of NADH and a rise in NADH: NAD ratio in mitochondria, which feedback and inhibit flux through PDH via product inhibition.³ The build up of NADH during ischemia is the result of decrease in consumption of oxygen and oxidative phosphorylation, resulting backup of NADH at electron

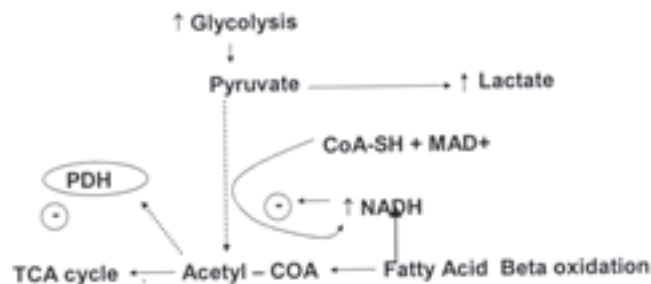


Fig. 4 : Regulation of pyruvate oxidation during moderately deoxygenating myocardial ischemia. The acetyl-Coenzyme A (CoA) and reduced nicotinamide adenine dinucleotide (NADH) generated by fatty acid oxidation inhibit the oxidation of pyruvate by pyruvate dehydrogenase. Pharmacologically inhibiting the rate of fatty acid oxidation removes inhibitions of flux through pyruvate dehydrogenase by NADH and acetyl-CoA, and results in more pyruvate oxidation and less lactate production.

transport chain and fall in NAD content.

Various studies suggest that, during ischemia, impairment of pyruvate oxidation is not due to deactivation of enzyme but rather to inhibition of production by an increase in the NADH: NAD⁺ ratio; in addition there might be an increase in the acetyl-CoA: free CoA ratio owing to relatively high fatty acid oxidation rate.⁸

In 1960, Oliver and colleagues first demonstrated that high serum fatty acid concentration is related with morbidity and mortality in patients presenting with acute coronary syndrome. High levels also causes dysrhythmia and sudden death compared to those with low level of fatty acid. They hypothesized that these may be due to the high levels of circulating catecholamine, and they suggested - the use of beta-blocker, blocking fatty acid release from fat by nicotinic acid, and supplying the heart with increased glucose. The concept is that, ischemic myocardium could be protected by reducing fatty acid levels and increasing the availability of alternative fuel substrate.

There are so many convincing studies that demonstrate that use of glycolytic metabolism by ischemic myocardium can preserve viability and delay ischemic contracture, (which is the hallmark of glycolytic failure) and prevent irreversible cell damage. Glycolysis specifically support the cell membrane function, maintaining sodium and calcium homestasis. The protection of myocardium from ischemia by modifying myocardial metabolism, prevents ischemic injury and improves functional recovery upon reperfusion.

There are various approaches that can decrease fatty acid level and enhance glycolysis. The most widely tested and direct approach is to increase glucose metabolism by exogenous glucose with or without exogenous insulin. Glucose metabolism can be stimulated by reduction of serum fatty acid level by glucose-insulin - potassium (GIK) infusion and drugs such as oxfenicin, etomoxir, carnitine, congeners of niacin, and nicotinic

acid.

Ischemia induced disruption of cardiac metabolism can be minimized by metabolic agents that decrease fatty acid oxidation and increases oxidation of pyruvate by PDH in mitochondria.³ Increasing the oxidation of pyruvate decreases the lactate production, fall of pH, and ATP breakdown and results in clinical benefit in ischemic patients. Studies showed that during ischemia lactate production can be decreased by inhibiting myocardial fatty acid oxidation or by directly activating PDH.³ Use of PDH activators or inhibitors of fatty acid oxidation is optimally suited for conditions under which there is sufficient delivery of oxygen to the myocardium to support pyruvate oxidation. It is therefore important that there be a sufficient rate of acetyl CoA oxidation and oxygen consumption so that increasing the rate of pyruvate oxidation has a meaningful effect on the rate of lactate production.

Metabolic interventions should work best with demand induced ischemia (e.g.; exercise induced angina) or during post ischemic reperfusion.

Changes during reperfusion

With reperfusion, mitochondrial oxidative phosphorylation returns to normal rapidly. PET (Positron Emission Tomography) scan revealed that following prompt thrombolytic therapy, recovery of oxidative metabolism occurs over a period of weeks. Even after brief periods of ischemia, like balloon inflation during angioplasty, contractile functions take some time to recover, even when blood flow is completely restored- a phenomenon called myocardial stunning. On PET scan, contractically dysfunctioning myocardial segments may in fact be manifesting myocardial stunning from repetitive episodes of ischemia followed by spontaneous reflow. Thus adjunct metabolic therapy may not only benefit in patients with acute coronary syndrome, but also those with chronic coronary artery disease- and perhaps even those with non ischemic cardiomyopathy.

Some studies suggested that after reperfusion, fatty acid metabolism is reduced. Regarding glucose metabolism, there are so many controversies. Thus no single metabolic pathway clearly appears to supervene following reperfusion. Oxidative metabolism, either from glycolytic or fatty acid oxidation is required for ultimate recovery of contractile function.

Reperfusion injury

Early reperfusion limits myocardial necrosis and salvages ischemic myocardium. Principal mediators of reperfusion injury are neutrophils, and reactive oxygen species (ROS) [Oxygen centered free radicals]. Normally ROS are generated in small amounts and inactivated by scavenger enzyme systems. Reperfusion of ischemic myocardium produces ROS, which overwhelm cellular scavenger enzymes and induce tissue damage. ROS, is

produced by mitochondrial respiration, neutrophil activation, and xanthine oxidase activities. In ischemia xanthine accumulates, mitochondrial redox potential is altered, producing ROS on reperfusion. The evidence that ROS causes myocardial injury in humans is still lacking, so trials of ROS scavengers have yielded disappointing results.

In post ischemic myocardium, neutrophils become activated and attached to endothelial surface and migrate in the tissues. These activated neutrophils release ROS and a proteolytic enzyme that causes tissue necrosis, block capillaries, reducing blood flow. They also release platelet-activating factor, thromboxane, and leucotrienes which cause inflammation and further increase neutrophil and platelet activities in reperfused area. The interventions that reduce neutrophil activation in reperfused areas have shown to reduce reperfusion injury, but their clinical application is subjected to further evaluation.

PROTECTION OF ISCHEMIC MYOCARDIUM WITH GLUCOSE-INSULIN-POTASSIUM

Experimental study by Opie *et al* proposed the therapeutic role of glucose in protecting ischemic myocardium.^{9,10} A number of studies demonstrated that infusion of glucose-insulin potassium have various effects. It decreases infarct size, reduces ultra structural damage, improves contractile function, reduces frequency and duration of ventricular arrhythmia, improves cardiac function and survival of patients after myocardial infarction, especially when administered with thrombolytics.

Several recent trials support the complimentary role of GIK and reperfusion therapy.¹¹⁻¹³

It has been estimated that GIK therapy has the potential to protect ischemic myocardium before reperfusion for 10 hours or even longer,¹⁴ thus lengthening the period during which effective myocardial salvage is possible with reperfusion strategies such as thrombolytics or primary angioplasty. Through the reduction of extent of ischemic myocardial damage and suppression of FFA levels, GIK therapy helps to prevent reperfusion injuries that may occur after successful revascularization.¹⁵ Protection of cell membrane of ischemic myocyte, endothelial and vascular smooth muscle may also improve reflow after reperfusion and protect against no-reflow phenomenon by reducing cell swelling and micro vascular compression.¹⁴ Coronary reperfusion may in turn add to the effectiveness of GIK therapy, as GIK treatment only delay the onset of irreversible myocardial damage and unless the blood flow is reestablished, myocardial necrosis will eventually occur. Reestablishment of blood flow by reperfusion strategies prevents accumulation of lactic acid and hydrogen ion that may inhibit glycolysis. In the diabetes mellitus insulin glucose infusion in acute

myocardial infarction (DIGAMI) study, diabetic patients with AMI receiving GIK treatment had 29% reduction of death at 1 year compared with patients not receiving GIK.⁹ In another recent study, patients with suspected AMI receiving GIK exhibit decreased mortality, heart failure, and arrhythmia compared with patients not receiving GIK. Results were most favorable in patients receiving thrombolytic therapy.

Mechanism of Action

Exogenous glucose has been shown to be a more efficient fuel than FFA or glycogen and is more likely to prevent ischemic myocardial injury.¹⁸ Glycolysis derived ATP preferentially supports cell membrane functions by protecting membrane ion transport, hence helps to preserve cell integrity.^{19,20} During myocardial ischemia, high concentrations of FFA provoked by sympathetic activity have been shown to lead to increase the myocardial oxygen requirement and depression of myocardial mechanical activity and contraction.²¹ They may also cause impairment of calcium homeostasis²² and production of free radicals, leading to an electrical instability and ventricular arrhythmia and ultimately to cell membrane damage (via detergent effect).²³ Insulin lowers the plasma concentration of FFA by inhibiting lipolysis. Other possible mechanisms of action of GIK are-

1. Preventing the ischemic contracture and improvement of myocardial performance at a lower oxygen consumption.¹³
2. Protection of ischemic coronary vasculature, resulting in preservation of low coronary resistance and myocardial perfusion.¹⁴ This may be important as recent studies have shown that ischemic myocardial injury can be reduced by very small increase in myocardial perfusion.²⁴
3. Restoration of intracellular potassium.
4. Promotion of wound healing and reduction of tissue edema (via its hyperosmolar effect).⁹
5. Facilitating spontaneous thrombolysis.

Several studies have shown that insulin treatment reduces thromboxane production and decreases plasma plasminogen activator inhibitor activity.²⁵

Short term GIK infusion has also been effectively used in patients with refractory left ventricular failure after revascularization surgery;²⁶ here GIK lowers plasma FFA, and decreases systemic vascular resistance. In those patients, the requirements of inotropic support as well as the time of intraaortic balloon pump and stay in invasive care unit were all significantly reduced.

Thus excellent clinical and experimental data support the concept that increase in the glycolytic flux, induced by exogenous glucose and reduced serum FFA, help in protecting the ischemic myocardium, and improving the survival and function after acute ischemic episode.

The ECLA Glucose-Insulin-Potassium pilot trial confirms that a metabolic modulation strategy in the 1st hours of an AMI is feasible, applicable worldwide and has mild side effects. The statistically significant mortality reduction in patients that underwent reperfusion strategies might have important implication for management of AMI patients.¹⁶

OTHER AGENTS THAT MODULATE MYOCARDIAL METABOLISM

Aldose reductase inhibitors

Various studies documented that in diabetic hearts as well as with ischemia there is increase glucose metabolism via polyol or aldose reductase pathway, where glucose is reduced to sorbitol by aldose reductase. Inhibition of aldose reductase conserves NADPH, NAD⁺, and glucose.

Experimental studies have demonstrated that aldose reductase inhibition reduces ischemic injury by lowering the elevated cytosolic redox state, and conserving NAD⁺, which improve glycolysis in both normoxic and ischemic myocardium,²⁷⁻²⁹ it also increases myocardial glucose oxidation.

Study in a small number of human subjects with AMI who were treated with aldose reductase inhibitor-Zopolrestat showed modest improvement in ejection fraction. Currently a large clinical trial is under way to test the efficacy of aldose reductase inhibitors in protecting patients with myocardial infarction.

Co Enzyme Q10: Role in angina

Co Enz Q10 (Ubiquinone) is fat soluble quinone with characteristics that are common to vitamins. Chemical structure is similar to vit-K. In humans, it is found mainly in heart, liver, kidney and pancreas.³⁰ It has antioxidant and membrane stabilizing properties, it acts as a mobile electron carrier in mitochondrial electron transfer process of respiration and coupled phosphorylation and has been demonstrated to scavenge free radicals³¹ produced by lipid peroxidation.³² It prevents mitochondrial deformity³³ during ischemia, and it has some ability to maintain the integrity of myocardial calcium ion channels during ischemic insult.

In recent years, there has been increased interest in the study of events that occur during reperfusion phase of myocardial ischemia by oxygen derived free radicals.

Possible therapeutic mechanism of Co Enz Q10 in cardiovascular disease.

1. Correction of Co -Q deficiency state.
2. Direct free radical scavenger via semiquinone species.
3. Direct membrane stabilizing activity due to phospholipids-protein interaction.
4. Correction of mitochondrial electron leaks during oxidative respiration.

5. Induction of DT diaphorase.
6. Possible effect on prostaglandin metabolism.
7. Inhibition of intracellular phospholipase.
8. Preservation of myocardial Na⁺, K⁺ ATPase activity.
9. Stabilization of integrity of Ca⁺⁺ dependent slow channels.

Several studies examining Co Q as a therapeutic agent indicate that its major mechanism of action is protection of ischemic tissue from reperfusion damage. Co-Q is anti oxidant and free radical scavenger. It appears to be capable of stabilizing cellular membranes and preventing the depletion of metabolites necessary for resynthesis of ATP. It also induces DT diaphorase, a potent inhibitor of free radical formation.³⁴

Scharde F *et al*³⁵ studied the effects of Co-Q on ischemic ECG ST segment depression in 15 patients with chronic stable angina. Patients were entered in a double blind cross-over study designed to compare the effect of 600mg oral Co-Q daily to placebo, and the combination of Pindolol (7.5 mg) and Isosorbide dinitrate (30 mg) daily. Treatment with Co-Q caused significant reduction in cumulative exercise induced ST segment depression when compared with placebo.

There was no difference observed in this parameter when comparing Co-Q treatment and combined Pindolol plus Nitrate therapy in the patients. In this study Co-Q caused reduction in exercise systolic BP compared to placebo values without an observable changes in diastolic BP or heart rate.³⁵

The mechanism for increase exercise capacity in patient with angina treated with Co-Q is poorly understood. Experimental studies showing protection of ischemic myocardium favor a role of Co-Q in maintaining oxidative phosphorylation. It has been proposed that Co-Q 's antianginal action results from either enhanced resynthesis of ATP, or by a direct membrane protection mechanism or through reduction of free radical species.³⁷

It is clear that Co-Q has action that differs from conventional antianginal agents, like nitrates or betablockers. It has not appreciable hemodynamic effects. Treatment with Co-Q may allow ischemic tissue to reach a higher level of energy expenditure prior to the onset of clinical manifestations or exercise induced ST changes. Currently Co-Q is being extensively studied in the United States. The trials are examining the antianginal effect of two Co-Q doses (150mg and 300mg) compared to placebo in patients with chronic stable angina. Preliminary results from the trials suggest a favorable effect of Co-Q on exercise tolerance with minimum adverse reactions.

Trimetazidine

Since high fatty acid oxidation rate markedly decreases glucose oxidation, one approach to increasing

glucose oxidation is, to inhibit fatty acid oxidation. Pharmacological agents that inhibit fatty acid oxidation include direct beta-oxidation inhibitors. These novel groups of compounds includes the 3-Ketoacyl-coenzyme A thiolase (3KAT) inhibitors -Trimetazidine and Ranolazine.

It is a metabolic anti-ischemic agent with cardio protective properties;³⁸ selectively inhibit the long chain 3-ketoacyl CoA thiolase (3-KAT) activity. This leads to reduction in fatty acid oxidation and stimulation of glucose oxidation that is independent of any hemodynamic adverse effects.³⁹ Various studies demonstrated that it inhibits mitochondrial oxidation of palmitoyl carnitine, thus only slightly altering oxidation of pyruvate and preserving mitochondrial oxidative functions.⁴⁷ It also stimulate PDH activity, the rate limiting enzyme for glucose oxidation. Stimulation of glucose oxidation improves the coupling of glycolysis to glucose oxidation, resulting in decreasing in proton production and in intracellular acidosis during ischemia.

In several double blind trials, trimetazidine has been shown to improve ergometric exercise duration and total work output of patients with effort angina, increasing the time to 1mm ST segment depression relative to placebo.^{45,46} Patients with chronic stable angina reported a greater than 50% decline in attack frequency and a reduction in nitroglycerine requirement while taking trimetazidine as well as displaying improved effort tolerance on ergometric testing. Multicentric trials of trimetazidine by European collaborative working group confirmed the anti anginal efficacy of trimetazidine. Its antianginal effect is equivalent to that of propranolol, nifedipine with out any reduction of cardiac rate-pressure product or coronary blood flow. Thus Trimetazidine is considered unique among anti anginal agents for its lack of vasodilator activities and has also been found to have beneficial effects in the acute ischemic changes associated with coronary angioplasty. It has been approved for clinical use worldwide.

It's direct cytoprotective effect on the myocardium was demonstrated in several studies.⁴⁰ Metabolic agents such as the 3KAT inhibitor Trimetazidine are currently quoted in the European and American guidelines for the management of stable angina.^{41,42} Exercise tolerance was improved after a single oral dose and this effect persisted following prolonged treatment. It also raises the threshold of stress-induced Echocardiographic signs of myocardial ischemia, decreases the severity of anginal pain sensation even sometimes up to complete disappearance of exercise induced anginal pain.

Carnitine

Fatty acids are transported to mitochondria by carnitine mediated shuttle. Carnitine also increases glucose oxidation by influencing pyruvate dehydrogenase (PDH) activity. Carnitine analogue Propionyl-Carnitine has similar effects on glucose

oxidation. It also influences the TCA cycle via anaplerosis.⁴³ A number of experimental studies have demonstrated protection of ischemic myocardium by both carnitine and propionyl carnitine. Clinically carnitine and its congeners have been shown to reduce ST depression and left ventricular end-diastolic pressure in patients with coronary artery disease,⁴⁴ as well as to improve exercise capacity and increase ejection fraction in patient with heart failure. In several trials, carnitine treatment early after acute MI was found to attenuate infarct size, decrease left ventricular dilatation, and favorably influences left ventricular remodeling.

Beta-blockers, Angiotensin-converting-enzyme-inhibitors

As we know, beta blockers are extremely useful adjunctive agents in the treatment of the MI due to its anti-arrhythmic, anti-ischemic and anti-hypertensive effect. It also decreases myocardial work, alters catecholamine environment, and causes membrane stabilization. Some studies demonstrate that it reduces adrenoceptor mediated lipolysis, and myocardial fatty acid uptake.⁴⁸⁻⁵⁰

ACE-Inhibitor exerts vasodilatation, inhibits renin-angiotensin-aldosterone system, augments kinin system; exerts anti-endothelial effect and inhibits growth of myocardial and vascular tissue.⁵¹

Experimental study demonstrates that it also stimulates glucose use by ischemic and reperfused myocardium, thus maintaining energy requirements and enabling the recovery of functions in reperfused myocardium.⁵² Thus their beneficial effect, may be mediated, in part by their metabolic effects.

Sodium Hydrogen Exchanger (NHE) inhibitors

In addition to the metabolic pathways described previously, recently a new ion exchange system has been discovered, which play an important role in the setting of reperfusion injury and cell necrosis. This is the Sodium Hydrogen Exchanger system, which was extensively studied by Frolich O *et al.*⁵⁶ This exchanger has six isoforms, ubiquitously distributed in tissues, but its NHE-1 isoform predominantly is found in the myocardium. The role of transmembrane sodium-hydrogen exchanger is to maintain myocardial intracellular pH integrity during myocardial ischemia, but paradoxically it can also cause cell necrosis.

During ischemia, it is rapidly activated as the accumulating hydrogen ion interact with the sensor side of exchange protein to promote electroneutral trans membrane exchange of H⁺ for sodium ion, promoting cell necrosis by calcium exchange for sodium ion.^{53,54}

Cariporide is a powerful and specific inhibitor of this exchanger, which was recently developed. It is a benzoylguanidine, with a molecular weight of 379.46 Da. It has cardio protective effect in various experimental models of ischemia-reperfusion. To asses the

effectiveness of NHE Inhibition in humans, the first large scale trial "GUARDIAN" trial was conducted. However the trial concluded that though there are no significant benefits of Cariporide across a wide range of clinical situations of risk, but proper inhibition of exchanger in settings of ischemia-reperfusion such as CABG could be beneficial. Furthermore NHE inhibition may be beneficial in unexplored situations such as evolving MI, cell hibernation and stunning.⁵⁵ Further trials with different study designs are required to investigate this important clinical issue.

CONCLUSIONS

It is clear that favorable modulations of metabolic events during and after ischemia results in increased myocardial salvage in reperfused myocardium. The use of GIK showed great advantage in enhancing myocardial salvage in patients with AMI. Use of other metabolic agents show great promise in experimental studies and merits further evaluation in human trials. Metabolic modulation of ischemic myocardium continues to be a unique and untapped approach to favorably effect ischemic myocardium.

Traditional treatments for ischemia and infarcted myocardium had been directed at increasing myocardial perfusion. Though these modalities of therapy are effective, they also have some drawbacks. One is the adverse effects, of which most important is hemodynamic alteration. This traditional agent may again not be effective in all situations of ischemia for symptom relief. Thus there may be situations where associated comorbidities preclude the use of these modalities, e.g. beta blocker in COPD patients.

It is important to restate that only with early, prompt, and full reperfusion is maximum myocardial recovery from acute ischemic events likely. Metabolic adjuncts can be employed to lessen ischemic injury and thereby enhance the salutary effects of reperfusion. The coming years are likely to see increasing trials of these agents for maximizing the efficacy of reperfusion therapy in the treatment of coronary artery disease. The use of metabolic manipulations which enhance glycolytic pathways and inhibit potentially noxious fatty acid intermediates may also offer a noble approach for the protection of transiently ischemic myocardium in patients with coronary artery disease. And one thing is certain, that is -agents that modify myocardial metabolism in disease states have definitely enhanced the therapeutic armamentarium to fight the problem and improve the well being of the patients.

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