



From the Editor

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Two years ago this journal was founded by the Servier Research Group with the educational aim to impart information and create awareness among cardiologists of basic myocardial metabolism, metabolic imaging and metabolic therapy. This remains an excellent goal since over the last 10 years cardiac metabolic imaging has become a valuable clinical tool with the use of positron emission tomography (PET) and single photon emission computed tomography (SPECT). Also, metabolic interventions specifically aimed at the heart are now a clinical reality. Because of these new applications we need to upgrade our knowledge of cardiac metabolism. Therefore, the editorial board has opted for a systematic coverage of all major aspects of each issue.

The *main article* will discuss an important clinical problem and will involve review articles and guidelines on diagnosis, prevention, treatment and epidemiology; in short, on the state of cardiology today. The remaining articles will highlight various metabolic aspects related to the subject of the main clinical article. The *basic metabolism* section aims to give more insight into the basic aspects of metabolism; the section on *new therapeutic strategies* will discuss potential and existing metabolic therapy in relation to the clinical topic covered in the main article. Finally, each issue will contain an article on *cardiac metabolic imaging*, and, if space permits, *case reports* will also be presented. In this way we hope to present you with new and challenging data on the clinical implications of cardiac metabolism. We hope that our new-look journal will receive a positive response from you.

In this issue the potential beneficial effects of metabolic therapy using glucose-insulin-potassium (GIK) infusion in the acute stage of myocardial infarction are discussed by one of the ECLA authors, Dr Rafael Díaz. The ECLA authors showed that GIK intervention, especially with a high dose of glucose and insulin in the acute stage of myocardial infarction, is feasible and safe. More importantly, this metabolic therapy may be beneficial for acute infarction patients.

In the section on new therapeutic strategies,

Dr Carl Apstein looks critically at the ECLA data and compares them with previous data, in particular the meta-analysis of acute infarction interventions by Fath-Ordoubadi. The clinically most important question of whether we are ready for routine GIK use is answered in the negative by both contributors. However, the ECLA study was merely a pilot study and the ECLA II study is currently underway with adequate power to definitively prove whether this simple and cheap metabolic intervention is indeed beneficial for patients with acute myocardial infarction. Other international studies are also being planned or performed to support the preliminary data, so keep an eye out for future developments.

The basic metabolism article by Dr Michael Allard and colleagues gives some background for understanding the uptake and oxidation of glucose in normal and ischaemic myocardium and how very important insulin is for this process. Also the mechanisms by which GIK is beneficial following ischaemia are discussed. The evidence for GIK in both the basic research and the clinical setting shows the importance of metabolic changes in cardiac function and the interest of the metabolic approach to ischemic heart disease.

The importance of insulin for glucose imaging is shown on the front cover images provided by Dr Lucas Klein. One fluorodeoxyglucose (FDG) PET image is from a patient without insulin resistance, the second is from a patient with insulin resistance. Clearly, FDG uptake is better in the patient without insulin resistance, with a 'sharper' myocardial delineation and a better heart: background ratio.

In the cardiac metabolic imaging section, Professor Paolo Camici describes the myocardial uptake patterns of FDG under normal and ischaemic conditions. These patterns are important for optimizing metabolic conditions during FDG imaging and for the clinical interpretation of these images.

In summary, this issue gives an overview of the clinical applications of glucose in the diagnosis and treatment of ischaemic heart disease. I hope you will enjoy reading it as much as I did.

Metabolic effects of glucose-insulin-potassium on the heart

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Glucose-insulin-potassium (GIK) was first proposed as a metabolic intervention to treat acute myocardial infarctions almost 40 years ago by Sodi-Pallares et al.¹ In the last 3 years there has been a marked resurgence of interest in the use of GIK to treat ischemic heart disease. This has been stimulated by recent clinical successes with GIK treatment of acute myocardial infarction,² as well as the publication of a meta-analysis of previous trials showing a 28% reduction in in-hospital mortality using GIK.³ In this issue of *Heart and Metabolism*, articles by Dr Rafael Díaz and by Dr Carl Apstein review the clinical evidence supporting the use of GIK therapy following an acute myocardial infarction. The purpose of this 'basic metabolism' article is to describe some of the possible mechanisms by which GIK may exert these beneficial effects. In order to do this, it is important to first provide an overview of the metabolic actions of insulin on the heart. How GIK may modify metabolism in the heart, and how this may account for its clinical benefits are then discussed.

Insulin control of glucose metabolism in the heart

Cardiomyocytes oxidize fatty acids derived from both the plasma and the breakdown of intracellular triacylglycerol stores, while pyruvate is derived from either lactate dehydrogenase or glycolysis. The rates of these metabolic pathways are tightly coupled to the rate of contractile work, and conversely, contractile work is coupled to the supply of oxygen and the rate of oxidative phosphorylation.

Studies in animals and humans have shown that after an overnight fast the heart extracts free fatty acids (FFA), lactate and glucose from the blood, and that if one assumes complete oxidation of extracted substrates, fatty acids

are the major oxidative fuel for the heart (60–80% of the oxygen consumption), with a lesser contribution from lactate and glucose (10–20% from each) (see references 4 and 5 for reviews). The regulation of myocardial metabolism is complex in that it is linked to plasma substrate and hormone levels, coronary flow, inotropic state and the nutritional status of the tissue. GIK infusion has profound effects on myocardial metabolism that are mediated by the hyperglycemia, the direct effects of insulin on the cardiomyocytes, and by the indirect action of insulin on circulating FFA levels.

Regulation of glucose uptake

The uptake of extracellular glucose is regulated by the transmembrane glucose gradient and the concentration and activity of glucose transporters in the plasma membrane. Two isoforms from the glucose transporter family have been identified in the myocardium: GLUT-1 and GLUT-4, with GLUT-4 being predominant. Both transporters are located in the sarcolemmal membrane and in intracellular microsomal vesicles (*Figure 1*). The capacity of the cell to take up glucose is dependent upon the fraction of the glucose transporters that reside in the plasma membrane. Insulin results in translocation of GLUT-1 and GLUT-4 from the intracellular site into the sarcolemmal membrane, which results in an increase in the membrane capacitance for glucose transport.^{6,7} With regard to GIK, it is particularly relevant to note that the effects of insulin and moderate severity ischemia on glucose transporter translocation and glucose uptake are additive.⁷ Thus, treatment of ischemic patients with hyperinsulinemia will result in greater glucose uptake in the ischemic myocardium.

The rate of glucose uptake by the heart is

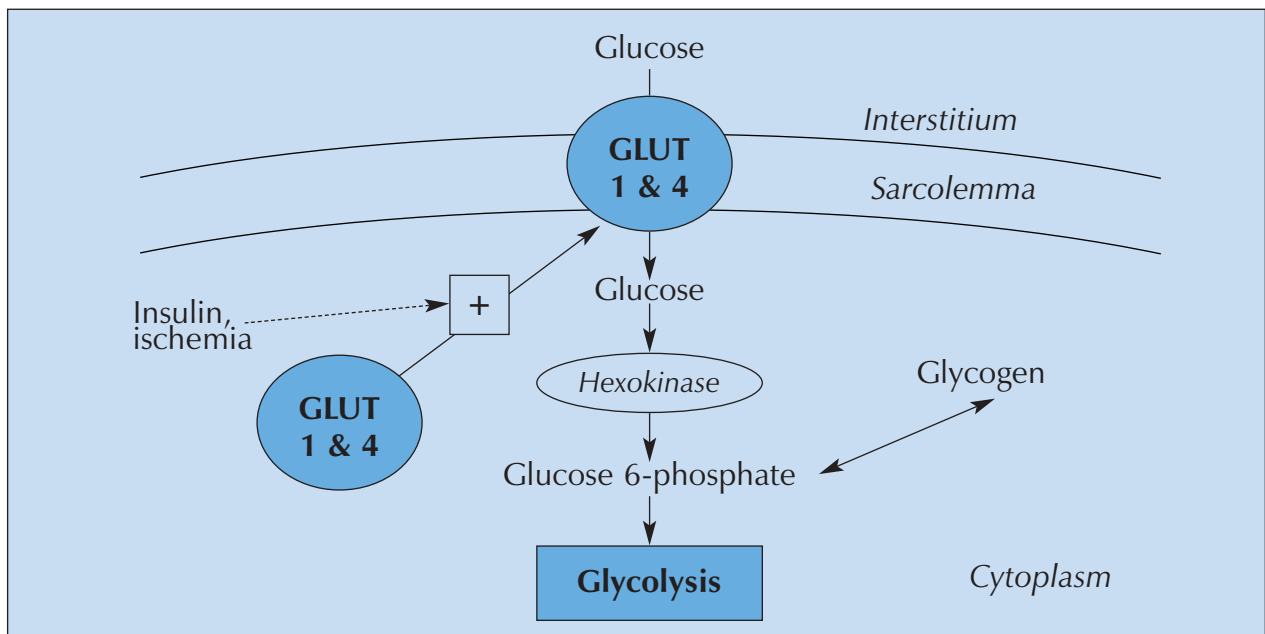


Figure 1. Insulin control of glucose uptake in the heart.

also very dependent upon the concentration of glucose in the interstitial fluid outside the cardiomyocyte. The interstitial glucose concentration is the major determinant of the transmembrane glucose gradient and, thus, the driving force for glucose transport across the plasma membrane. There is very little free glucose in the cell. The interstitial glucose concentration is a function of the arterial glucose concentration and blood flow. During myocardial ischemia there is a fall in interstitial glucose levels in proportion to the decrease in the rate of glucose delivery to the tissue.⁸ Thus a reduction in coronary blood flow increases the cell membrane's ability to transport glucose, but at the same time less glucose outside the cell is available to be transported into the cell. If the severity of myocardial ischemia is extremely severe there will be almost no blood flow and, thus, no glucose uptake. In human ischemia, even with acute myocardial infarction, there is residual myocardial blood flow due to incomplete blockage of the artery, and/or blood flow from collateral coronary arteries. Studies in swine show that acute hyperglycemia during myocardial ischemia results in a profound increase in interstitial glucose and greater glu-

ucose uptake by the heart, even in the absence of an increase in plasma insulin.⁹ Thus, the hyperglycemia that can occur with GIK therapy results in greater glucose uptake by increasing interstitial glucose in the myocardium. Upon entering the cell, free glucose is rapidly phosphorylated by hexokinase to form glucose 6-phosphate, thus, rendering the carbon skeleton of glucose impermeable to the cell membrane.

In addition to its effects on glucose transport, insulin also results in stimulation of hexokinase and glycogen synthetase activities, resulting in increased glucose phosphorylation and glycogen synthesis; the mechanism for this effect in heart is unclear, but could be at least partially due to the increase in glucose and glucose 6-phosphate that occurs secondary to insulin-stimulated glucose transport.

Regulation of glucose oxidation

After glucose enters the cell and is phosphorylated to glucose 6-phosphate, it proceeds down the glycolytic pathway to pyruvate. Under normal aerobic conditions, pyruvate enters the mitochondria and is decarboxylated

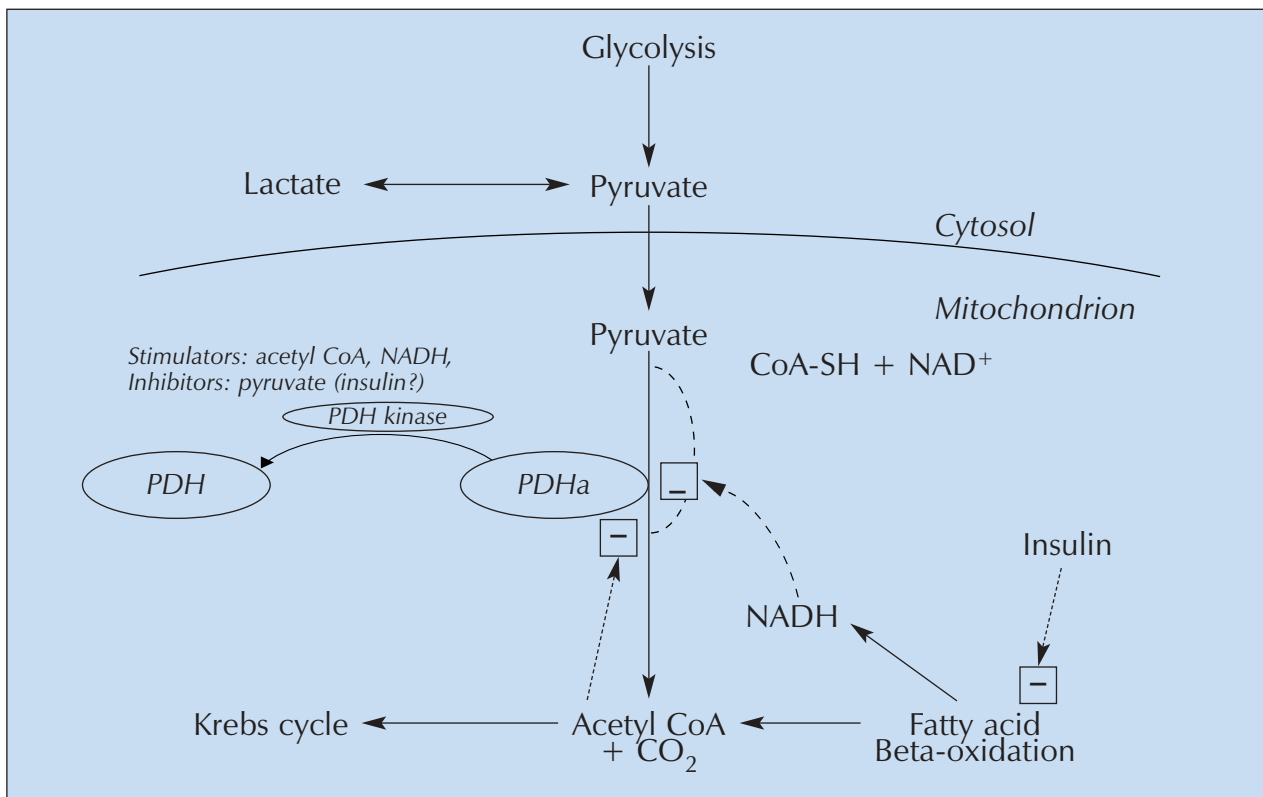


Figure 2. Insulin control of glucose oxidation in the heart. CoA-SH, Coenzyme A; NAD⁺, oxidized form of nicotinamide dinucleotide; NADH, reduced form of nicotinamide adenine dinucleotide.

to acetyl coenzyme A (CoA). Under ischemic conditions pyruvate is reduced in the cytosol to lactate. Pyruvate decarboxylation is the key irreversible step in carbohydrate oxidation and is catalyzed by pyruvate dehydrogenase (PDH). PDH is a multi-enzyme complex located in the mitochondrial matrix. The activity of PDH is regulated by a variety of mechanisms: in particular, it is inactivated by phosphorylation by a specific PDH kinase (Figure 2). The rate of pyruvate oxidation is very dependent on the degree of phosphorylation of PDH, and also on the concentrations of its substrates and products in the mitochondria, as these control flux through the active dephosphorylated form of the enzyme.^{10,11}

GIK therapy increases the oxidation of pyruvate by PDH. Pyruvate oxidation and the activity of PDH in the heart are enhanced by suppression of FFA oxidation induced by a decrease in plasma FFA levels. The high plasma insulin levels that occur during GIK treat-

ment will suppress the release of FFA from subcutaneous fat stores, rapidly lower plasma FFA concentration, and decrease the rate of fatty acid oxidation by the heart. This will relieve fatty acid-induced inhibition of pyruvate oxidation. High rates of fatty acid oxidation elevate the concentrations of nicotinamide adenine dinucleotide (NADH) and acetyl CoA in the mitochondrial matrix, and result in activation of PDH kinase and inhibition of PDH and pyruvate oxidation. Insulin lowers plasma FFA levels and the rate of fatty acid oxidation and, thus, removes NADH and acetyl CoA activation of PDH kinase activity. This results in activation of PDH and a greater rate of pyruvate oxidation. Thus, GIK therapy activates PDH indirectly through suppression of fatty acid oxidation. It has long been thought that insulin may act through a second messenger to activate PDH by inhibiting PDH kinase, though a mechanism for this effect has not yet been identified.

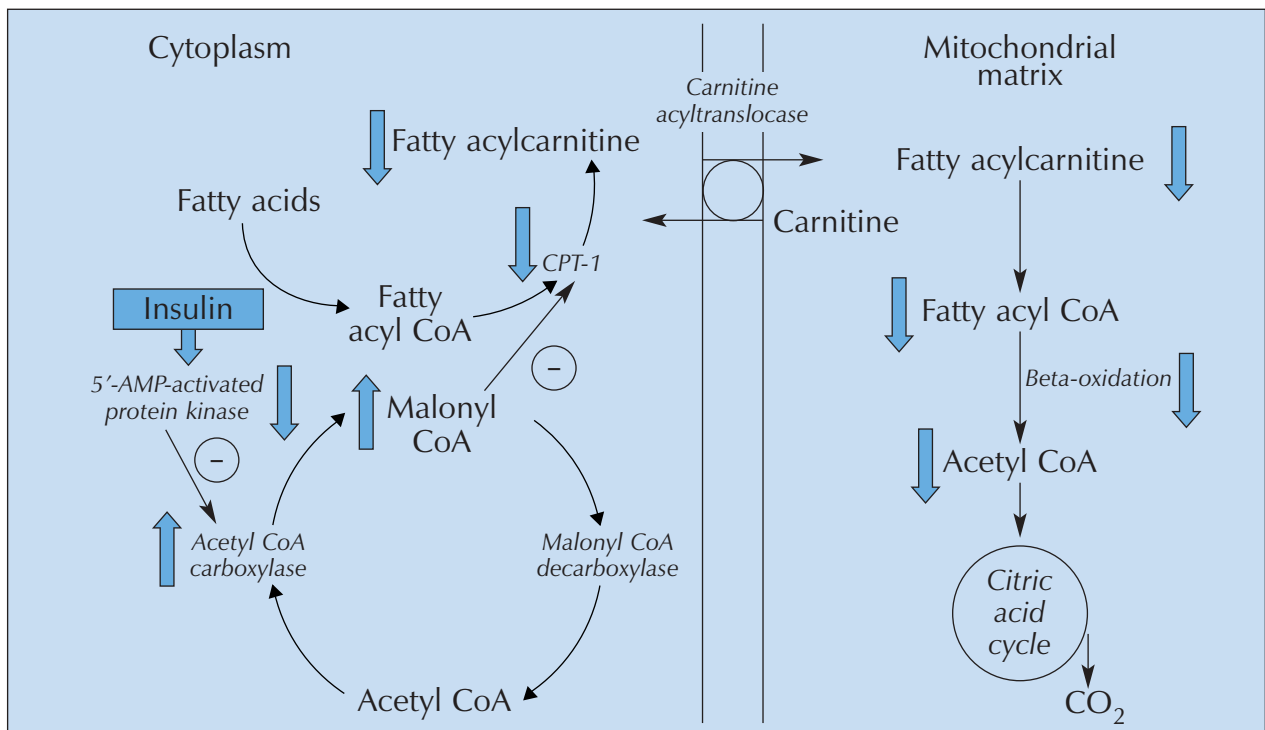


Figure 3. Insulin control of fatty acid oxidation in the heart.

Insulin control of fatty acid metabolism in the heart

Under most conditions, plasma FFA levels are the primary regulator of myocardial glucose and lactate oxidation. High plasma FFA levels (>0.8 mM) inhibit both the uptake and oxidation of glucose and lactate in human myocardium, while pharmacologically lowering plasma FFA levels (<0.3 mM) results in an increase in myocardial glucose and lactate uptake. This is primarily related to the release of product inhibition on PDH and glycolysis as FFA concentration decreases in the perfusate.

In addition to its effect on circulating FFA, insulin also has direct effects on fatty acid oxidation in the heart. A key site at which myocardial fatty acid oxidation is controlled is at the level of mitochondrial uptake of fatty acids. A key enzyme in this process is carnitine palmitoyltransferase (CPT)-1 (Figure 3). CPT-1 is the first committed step of fatty acid oxidation, and transfers the fatty acid moiety from acyl CoA to carnitine to form long chain acylcarnitine, which is then transported into the mitochondria.¹² A potent inhibitor of

CPT-1 and, therefore, of fatty acid oxidation, is malonyl CoA, which is produced by acetyl CoA carboxylase (ACC).¹³ ACC is in turn regulated by AMP-activated protein kinase (AMPK), which can phosphorylate and inhibit cardiac ACC activity (Figure 3).^{14,15} AMPK is very active in heart tissue¹⁴ and appears to act as a 'fuel gauge'.¹⁵ As such, AMPK is activated by increased energy demand as occurs during increased contractile activity or ischemia. By way of effects on ACC and malonyl CoA levels, activation of AMPK upregulates fatty acid oxidation, while a decrease in AMPK activity functions to decrease fatty acid oxidation rates in times of low demand. We recently demonstrated that insulin inhibits AMPK activity in the heart.^{16,17} Therefore, AMPK may function to downregulate fatty acid oxidation in response to the increase in glucose metabolism that occurs following insulin administration. This provides an attractive mechanism by which fatty acid oxidation and glucose metabolism in the heart can be coordinated. It is therefore, possible that one of the additional beneficial effects of GIK therapy is to inhibit

AMPK activity (*Figure 3*), thereby increasing malonyl CoA levels and inhibiting fatty acid uptake into the mitochondria.

Potential mechanisms by which GIK is beneficial during and following myocardial ischemia

The potential mechanisms responsible for the beneficial effects of GIK are most clearly understood by considering those that occur during ischemia separately from those that occur during reperfusion. During the development of an acute myocardial infarction, coronary blood flow to the infarcting myocardium is markedly reduced but still present.¹⁸ This feature of acutely infarcting myocardium is of critical importance in explaining the beneficial effects of insulin during ischemia because it indicates that some degree of substrate delivery and metabolite washout occurs at this time. During ischemia, oxidative metabolism is reduced and anaerobic glycolysis becomes a major source of myocardial ATP production.⁴ Despite an increased reliance on anaerobic glycolysis for ATP production, delivery of glucose to the myocardium is significantly reduced during ischemia because of the reduction in coronary flow.

Beneficial effects of GIK on glucose uptake and glycolysis during ischemia

One mechanism to account for the beneficial effects of GIK is increased provision of glucose, the substrate for glycolysis. Insulin and ischemia both increase the capacity of the myocardium to take up glucose because both stimulate translocation of GLUT-1 and GLUT-4 to the sarcolemma.^{6,19} Importantly, the effects of insulin and ischemia have been shown to be additive in terms of glucose transporter translocation and glucose uptake.⁷ By way of effects on glucose uptake and enzymes of glycolysis, GIK therapy acts to increase anaerobic glycolytic flux and, thereby, myocardial ATP production during ischemia.⁵ This increase in ATP production is beneficial because it helps maintain critical membrane functions such as

sodium and calcium ion homeostasis.²⁰ Additionally, the enhanced production of energy may delay and/or reduce the extent of ischemic myocardial necrosis, a situation that accounts in part for the beneficial effects of GIK.^{5,20} The fact that residual coronary flow occurs in the region of the acute infarct is important because it allows for removal of glycolytic products (lactate, protons) that could be detrimental if they accumulated.

Beneficial effects of GIK on glucose and fatty acid oxidation during reperfusion

During reperfusion, myocardial oxidative metabolism quickly recovers.⁶ Fatty acid oxidation, in particular, recovers and dominates as a source of myocardial energy production during reperfusion.^{5,21} Fatty acid oxidation becomes dominant at this time for several reasons. First, circulating fatty acid levels rise as a result of elevated endogenous catecholamines.^{22,23} Heparin administered therapeutically also likely contributes to the rise in fatty acid levels seen with an acute myocardial infarction.²⁰ These high levels of fatty acids lead to an increase in the rate of myocardial fatty acid uptake and oxidation. Second, myocardial fatty acid oxidation is directly stimulated during reperfusion. Myocardial malonyl CoA, a key regulatory intermediate, decreases at this time, relieving inhibition of CPT-1-mediated mitochondrial fatty acid uptake²¹ (*Figure 3*). Malonyl CoA is reduced because AMPK is stimulated in ischemic reperfused myocardium and phosphorylates to inactivate ACC, the enzyme responsible for malonyl CoA synthesis.²¹

Even though a rapid return of oxidative metabolism is required for full recovery of contractile function, the nature of the energy substrates used is a critical determinant of the extent of functional recovery.⁵ The dominance of fatty acid oxidation during reperfusion leads to a reduction in glucose utilization by the myocardium. Importantly, glucose oxidation is suppressed to a greater extent than glycolysis.⁵ As a result, there is an uncoupling of glycolysis from glucose oxidation that is substantially greater than normal. This increased

uncoupling leads to accelerated proton production. Accelerated proton production is considered to be an important contributor to the myocardial dysfunction and decreased contractile efficiency observed during reperfusion.⁵ In support of this viewpoint, stimulation of glucose oxidation, either directly or by inhibiting fatty acid oxidation, has been shown to significantly improve myocardial function and contractile efficiency.⁵ Thus, high rates of fatty acid oxidation contribute to myocardial dysfunction and contractile inefficiency during reperfusion by decreasing glucose utilization, particularly by reducing rates of glucose oxidation, and by increasing proton production from glucose metabolism.

During reperfusion, a major beneficial effect of GIK therapy is a reduction in circulating fatty acid levels^{5,20} (Figure 4). As a result, myocardial fatty acid uptake and oxidation are reduced. The importance of this effect is demonstrated by observations that the greatest clinical benefit of GIK therapy occurs with therapeutic regimens that maximally suppress circulating fatty acid levels.²⁴ Insulin may also

directly decrease myocardial fatty acid oxidation during reperfusion by inhibiting AMPK¹⁶ (Figure 3). A corollary of the GIK-induced reduction in fatty acid oxidation is that myocardial glucose use in general, and glucose oxidation in particular, are increased during reperfusion, an effect that leads to improved coupling of glycolysis to glucose oxidation, decreased proton production, and, thereby, increased myocardial function and contractile efficiency. In addition to indirectly stimulating glucose use by way of effects on fatty acid oxidation, GIK also directly stimulates glucose uptake during reperfusion.²⁵

Other potential beneficial effects of GIK

Depletion of citric acid cycle intermediates has been proposed as a major cause of impaired energy production by the heart during reperfusion.²⁶ Citric acid cycle intermediates are replenished by a process termed anaplerosis.^{20,26} Carboxylation of pyruvate is a major mechanism of anaplerosis in the

heart.²⁰ Importantly in this regard, GIK therapy increases pyruvate production by increasing glucose uptake and glycolytic flux. Therefore, an additional benefit of GIK therapy may be rapid replenishment of the depleted citric acid cycle intermediate pool.

Recently, insulin-like growth factor-I and insulin have been shown to protect against hypoxia- and ischemia-induced apoptosis.^{27,28} The high concentrations of insulin achieved with GIK therapy may activate these receptors and reduce apoptotic myocardial cell loss

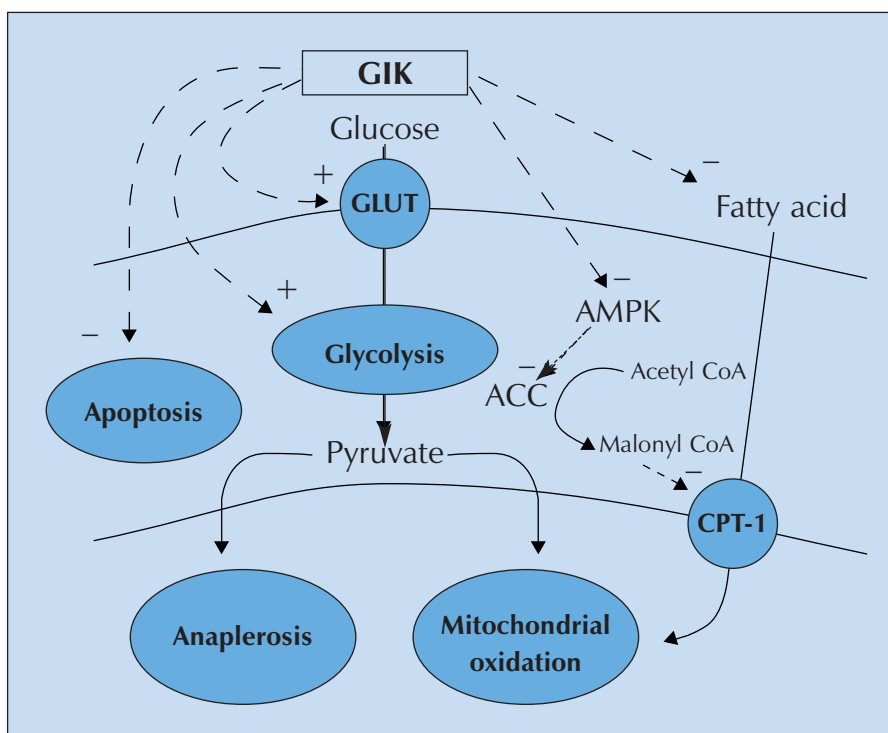


Figure 4. Potential mechanisms by which GIK protects the heart during ischemia.

associated with ischemia and reperfusion. This may be another mechanism by which GIK therapy favorably influences post-infarct remodeling.

Several other potentially important mechanisms may also contribute to the beneficial effects of GIK therapy. By way of its effects on the vasculature,¹⁹ insulin may improve myocardial perfusion and decrease peripheral vascular resistance. Additionally, insulin may have a direct inotropic effect on the myocardium.²⁹ As originally proposed, GIK therapy may reduce ventricular ectopy by increasing K⁺ reuptake through stimulation of the sarcolemmal Na⁺,K⁺-ATPase.¹

Pharmacological agents with actions similar to GIK

Numerous clinical and experimental studies have now convincingly demonstrated that ischemic heart disease can be treated by optimizing energy metabolism (see reference 30 for review). One approach used clinically is to inhibit fatty acid oxidation in the heart, an action that may partly explain the benefits of GIK. As discussed, during and following ischemia, high levels of circulating fatty acids effectively compete with glucose as a source of energy. This results in an accelerated acidosis in the muscle and an increase in energy requirements for non-contractile purposes (i.e. a decrease in cardiac efficiency). Inhibiting fatty acid oxidation and stimulating glucose oxidation can significantly improve cardiac efficiency (cardiac work/oxygen consumed). A number of pharmacological approaches can be used to achieve this, including altering fatty acid and glucose uptake into the heart muscle, directly inhibiting fatty acid oxidation, or directly stimulating the rate-limiting enzyme involved in glucose oxidation, PDH.³⁰ Agents that have been shown to produce these effects include dichloroacetate, trimetazidine, etomoxir, ranolazine, L-carnitine, and propionyl L-carnitine.^{30,31} Presently, the only pharmacological agent clinically used on a widespread basis to treat ischemic heart disease is trimetazidine, which acts by directly inhibiting fatty acid oxidation.³² This inhibition of fatty

acid oxidation is accompanied by a significant increase in PDH activity and an increase in glucose oxidation.³² This results in a decreased production of acidosis in the myocardium, which appears to account for the cardioprotective effects of trimetazidine observed in many experimental and clinical studies. As a result, optimizing energy substrate preference is emerging as a novel and effective approach to treating cardiovascular disease.

Conclusion

GIK has a number of actions on cardiac energy metabolism. These include increasing glucose uptake and glucose oxidation, while directly and indirectly inhibiting fatty acid oxidation. Additional actions on mitochondrial tricarboxylic acid cycle activity, apoptosis and direct effects on vascular function may also contribute to the beneficial effects of GIK. Combined with studies using pharmacological agents that act by optimizing energy metabolism, GIK therapy highlights the potential of metabolic modulation in the treatment of ischemic heart disease. ■

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Metabolic modulation of acute myocardial infarction: novel concepts underlying old strategies

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Acute myocardial infarction (AMI) continues to be the most frequent cause of death in the developed world. Despite tremendous improvement in the management of AMI during the last 20 years,^{1–4} the continuing high morbidity and mortality rates stimulate the intensive search for different therapeutic options.⁵

Reperfusion strategies (i.e. thrombolytic drugs or primary percutaneous transluminal coronary angioplasty) associated with aspirin, beta-blockers and angiotensin-converting enzyme inhibitors are core treatments of AMI^{6,7} and are a good example of therapy guided by evidence-based medicine.

Ischemia is essentially a metabolic event⁸ and basic research has reliably demonstrated that manipulation of different metabolic pathways can ameliorate the final outcome of viable myocardium.⁹ The concept of improving cardiac energy metabolism of the ischemic myocardium and its optimization may have considerable promise as a new approach to the treatment of cardiovascular disorders.

Cardiac metabolism in normal, ischemic and reperfusion conditions

Contractile function is sustained by the hydrolysis of adenosine triphosphate (ATP), produced by the metabolism of both carbohydrates and fatty acids.¹⁰ During fasting, fatty acids are the preferred fuel, and when oxidized, glucose oxidation is inhibited and the glucose taken up is converted to glycogen. Conversely, during the fed state, when levels of glucose and insulin are high, the circulating fatty acid levels are suppressed, their uptake decreases, the inhibition of glycolysis by fatty acids is removed, and glucose oxidation increases (*Figure 1*).¹¹

During ischemia, severe reductions in blood flow (like in AMI) result in reductions in glu-

cose uptake (extraction is related to coronary flow), greater rates of lactate accumulation, glycogen breakdown, complete contractile dysfunction and, finally, myocardial necrosis and infarction.

Circulating free fatty acid (FFA) levels rise dramatically during and following episodes of ischemia.^{13–15} This high plasma FFA concentration increases the severity of ischemic damage due to its direct toxic effects¹⁶ and in part due to the inhibitory effects on pyruvate oxidation by inhibiting the pyruvate dehydrogenase (PDH) complex.^{17,18}

Upon reperfusion, mitochondrial oxidative phosphorylation returns to pre-ischemic levels. However, mechanical contractile work remains transiently impaired, gradually recovering to a pre-ischemic level. This phenomenon, called ‘stunning myocardium’, is characterized by an increased level of oxygen consumption for a specific level of work developed.¹²

During myocardial reperfusion there is an overshoot of fatty acid metabolism,^{17,19,20} impaired pyruvate oxidation and an increase in glycolysis.²¹ High rates of FFA beta-oxidation inhibit pyruvate oxidation via inhibition of the PDH complex. Uncoupling of the accelerated glycolysis and pyruvate oxidation is the major source of net hydrogen ion (H⁺) production during reperfusion.^{22,23}

Metabolic intervention with glucose-insulin-potassium (GIK) in AMI

Different metabolic interventions have been proposed for the treatment of heart disease and they are all directed at shifting the source of energy towards a carbohydrate substrate by: (1) increasing glycolytic flux; (2) decreasing FFA oxidation and indirectly increasing glucose oxidation and flux through the PDH

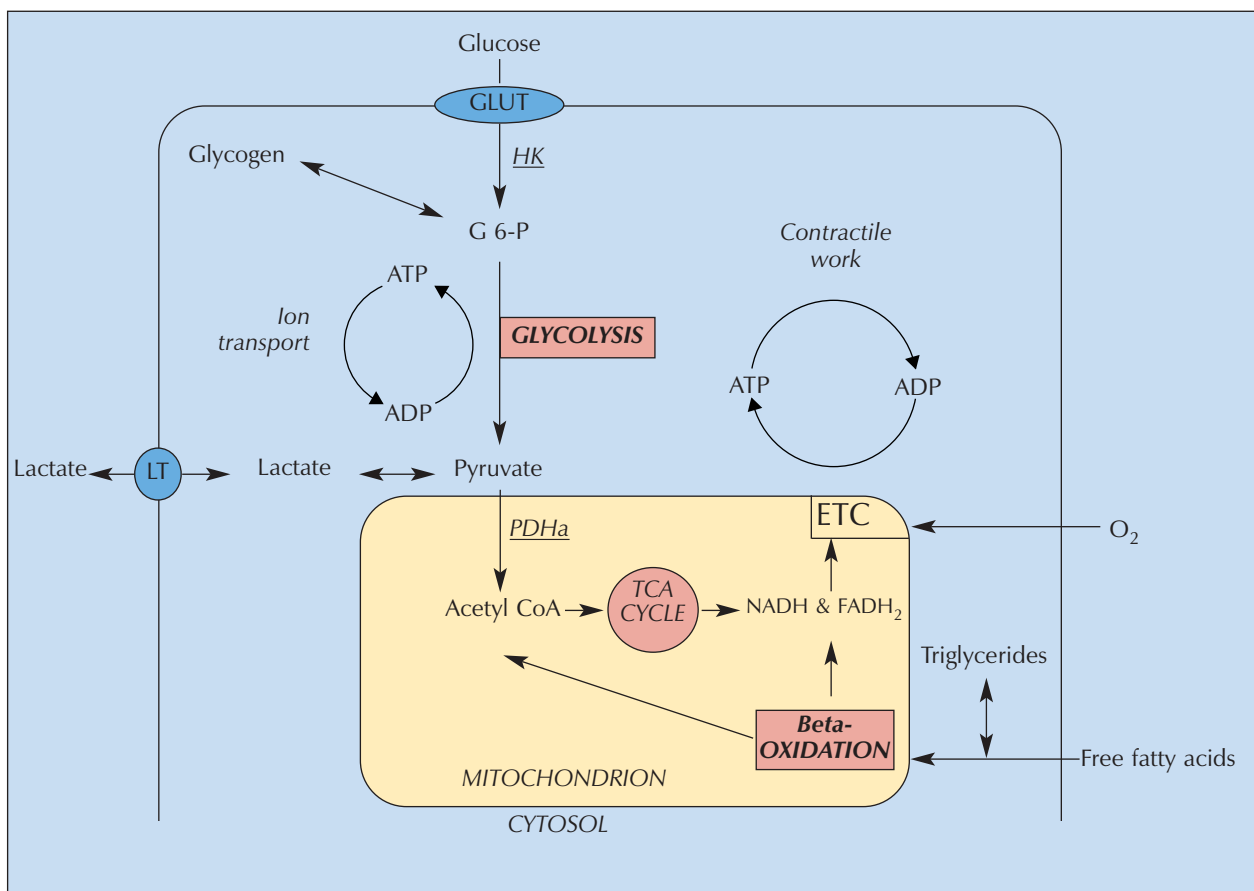


Figure 1. Schematic description of myocardial substrate metabolism. GLUT, glucose transporter; HK, hexokinase; G 6-P, glucose 6-phosphate; ADP, adenosine diphosphate; LT, lactate transporter; PDHa, activate dephosphorylated pyruvate dehydrogenase; ETC, electron transport chain; O₂, oxygen; Acetyl CoA, acetyl coenzyme A; TCA, tricarboxylic acid; NADH, nicotinamide adenine dinucleotide; FADH₂, flavine adenine dinucleotide.¹²

complex; and (3) directly activating the PDH complex, thereby increasing glucose oxidation.¹²

One simple method of stimulating glycolysis and decreasing fatty acid oxidation is by infusing high doses of glucose with insulin. High plasma glucose concentrations and insulin stimulate the uptake of glucose and glycolysis, and produce a marked decrease in circulating FFA, therefore reducing FFA oxidation (dramatically increased during the hyperacute phase of AMI, due to high levels of circulating catecholamines and, occasionally, the use of heparin).²⁴

Mechanism of action of GIK

The high glucose concentration and the addition of insulin produce an immediate shift in the source of metabolic substrate. Glucose uptake increases as it is related to its blood concentration, blood flow and the expression of its carrier GLUT1 and GLUT4 (stimulated by insulin).²⁵⁻²⁷ High glucose and activated transporters enhance the glycolytic flux to produce pyruvate. Due to the indirect stimulation of PDH (via the inhibition of FFA beta-oxidation), pyruvate is transformed to acetyl coenzyme A (CoA) that restarts the oxidative metabolism during reperfusion. The decrease in FFA levels and FFA beta-oxidation has salutary effects, avoiding their direct and indirect

toxic myocardial effects in the context of ischemia/reperfusion.¹⁹

In summary, the beneficial metabolic effects of high doses of glucose and insulin can be due to: (1) an increase in glycolysis and glycolytically derived ATP; (2) an increase in PDH complex activity due to a decreased plasma FFA and elevated insulin levels, resulting in less lactate and H⁺ accumulation; and (3) lower accumulation of noxious fatty-acyl CoAs due to lower FFA levels.¹²

Limiting the effects of glucose-insulin-potassium (GIK) to exclusively metabolic ones is a somewhat narrow perspective. Potassium itself reverses intracellular ion loss during extreme ischemia. High glucose concentration would produce favorable osmolar changes; fluid volume overload can contribute to a better hemodynamic performance; and insulin effects beyond the metabolic effect (coagulation, apoptosis) can also contribute to the potential beneficial effects of GIK in AMI.¹⁶

Clinical experience with GIK

Since it first appeared in the literature in 1962,²⁸ GIK infusion for the treatment of AMI has been empirically adopted by most cardiologists mainly based on its property of avoiding arrhythmias and accelerating the process of ST resolution. However, its impact on clinical outcomes has never been clearly demonstrated. Furthermore, clinical trials during this period did not fulfill the methodological statements accepted by the conceptual model of clinical research which emerged during the 1980s. Trials were done using different inclusion criteria, different dosages and durations of infusion, and different routes of administration, and these were reasons for the conflicting results between different trials, hiding the potential benefit of this approach. Furthermore, meta-analysis was not used until later as a common research tool to collect data and formulate hypotheses. The lack of any trial showing strong and convincingly positive results, and probably also due to the absence of any commercial support, are plausible reasons why the cardiovascular community aban-

doned GIK during the late 1970s.

In 1997, a meta-analysis of prior GIK trials in AMI was published.²⁹ The authors, using appropriate techniques, analyzed only studies that had been properly randomized, excluding those with unacceptable methodological pitfalls. The results showed a 28% (CI: 10–43) reduction of in-hospital mortality, from 21 to 16.1%, $P = 0.004$). Despite the intrinsic weaknesses and limitations of meta-analysis, the results were the first published data to show the impact of GIK on clinical outcomes in AMI. Most of the studies had been performed before the widespread use of reperfusion. An accompanying editorial called for a large, prospective trial with GIK in the setting of proven treatments and methodological modern standards.³⁰

In the context of the reperfusion era, three small trials were performed using GIK for the treatment of AMI. The DIGAMI trial used a GIK infusion followed by the long-term administration of subcutaneous insulin in diabetic patients with AMI and showed a trend towards a lower in-hospital mortality and a statistically significant reduction in mortality at 1-year follow-up.³¹ The Polish GIK trial in AMI patients within 24 h from the onset of symptoms was prematurely stopped due to a non-significant increase in all-cause in-hospital mortality in the GIK group³² and the ECLA GIK Pilot Trial.

The ECLA GIK Pilot Trial

In 1994, our group initiated the first step of a large project using metabolic support as an adjunctive therapy for AMI. The first part of this project was published in 1998, called the ECLA GIK Pilot Trial.³³ As a pilot trial, the study was designed to look for safety and feasibility. Patients randomized into the trial were to be recruited within 24 h of symptom onset. Ancillary treatments were left to the discretion of the physician responsible, including the choice of reperfusion therapy. Patients were allocated to GIK or control in a ratio of 2:1. Two GIK concentrations were selected: a high dose that had proved in the past to maximally suppress FFA levels, and a low dose (in an attempt to improve the practical use of this infusion).

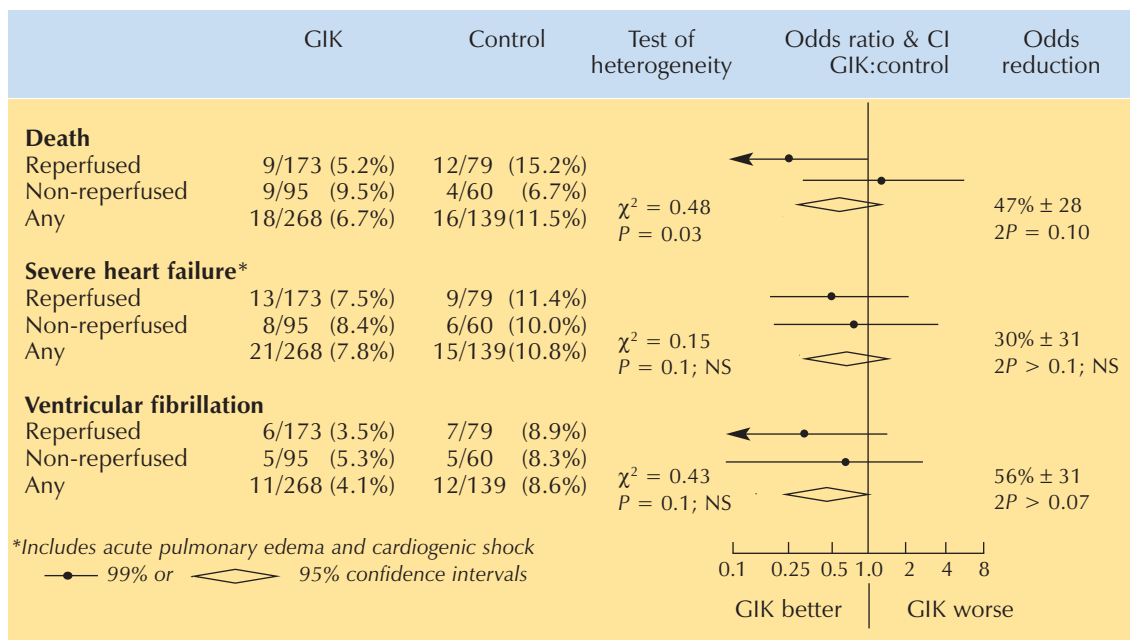


Figure 2. Major in-hospital events stratifying the population into reperused and non-reperused patients. Note the statistically significant P-values ($P = 0.03$) for the heterogeneity test for death, reinforcing the concept that GIK might have more pronounced effects in patients submitted to a reperfusion strategy.³³

GIK was shown to have minor, non-life-threatening and easily managed side effects. Mild phlebitis was more often reported in GIK patients (16.8%) than in controls. However, severe phlebitis occurred in only 2% of GIK patients (most of the population [83%] received the infusion via a peripheral line). Mild increases in glucose and potassium serum concentrations were observed in the GIK group, but in no case did these lead to an increase in morbidity or mortality.

Patients allocated to receive GIK (high or low concentrations) showed a non-significant in-hospital trend towards lower mortality, severe heart failure, ventricular fibrillation and a statistically significant decrease in the rate of electromechanical dissociation. The combined endpoint of death — non-fatal severe heart failure and non-fatal ventricular fibrillation — was significantly reduced from 20.1% in the control group to 12.1% in the GIK group (relative risk [RR] 0.56, CI 0.37–0.94, $2P = 0.03$). When analyzing the population of those who received and those who did not receive reperfusion therapies (as specified in the protocol), the mortality reduction trend observed in the

overall population reached a statistically highly significant value (RR 0.34, CI 0.15–0.77, $2P = 0.008$).

Using a more specific method of analyzing the data and focusing on hard events, we stratified the endpoints of death, severe heart failure and ventricular fibrillation in the non-reperused and reperused populations. A 47% non-significant reduction in all deaths was observed ($2P = 0.10$). Using the 99% CI, the lower limit of mortality reduction in reperused patients was still below the unit (RR 0.27, 99% CI 0.08–0.96), being the heterogeneity test significant ($\chi^2 = 4.68$, $P = 0.03$), probably reinforcing the concept that GIK produces different outcomes in patients who do or do not undergo a reperfusion strategy. A 30% non-significant reduction in any severe heart failure was observed, which was more pronounced in reperused patients, and a 56% borderline ($P = 0.07$) reduction in ventricular fibrillation was detected both in reperused and non-reperused patients (Figure 2).

As a pilot trial, the ECLA trial was underpowered to assess clinical outcomes, so the efficacy analyses should be cautiously inter-

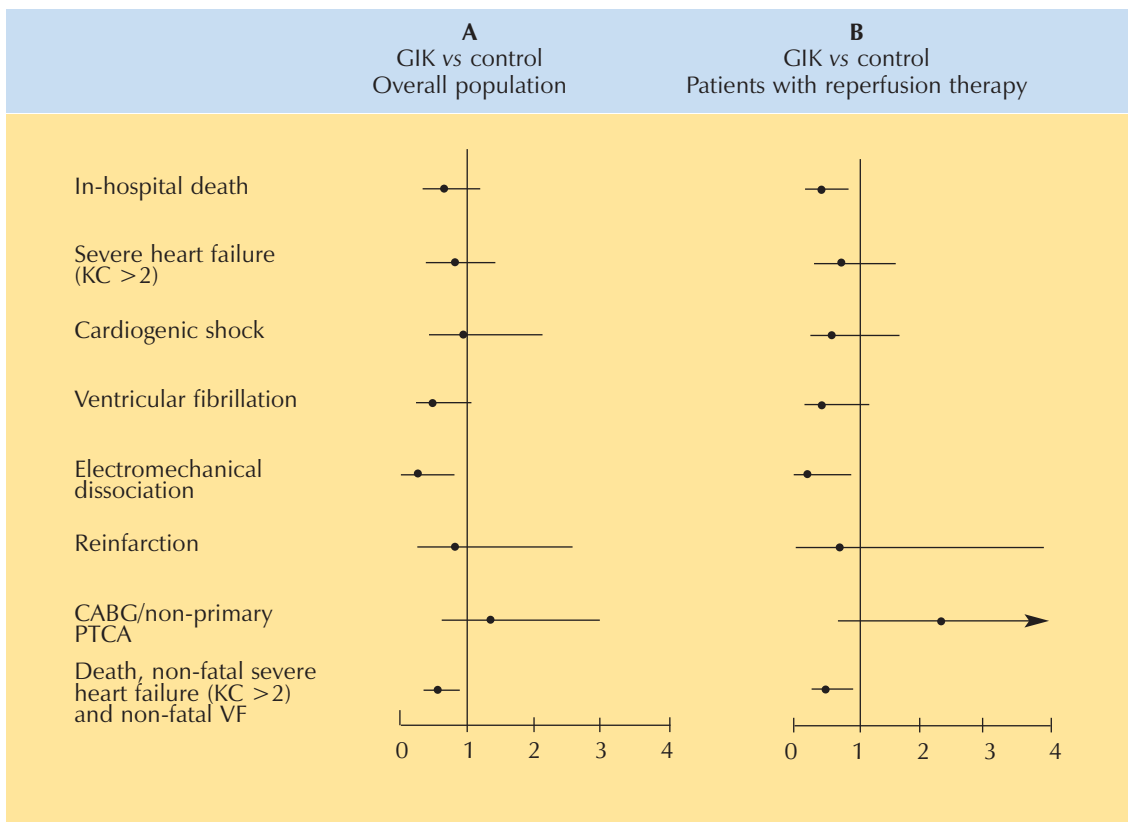


Figure 3. Relative risk of in-hospital events in the overall population (A) and in the subgroup of patients who received a reperfusion strategy (B). Note the consistent direction of the effect towards a benefit in those events potentially influenced by the GIK infusion, reaching a statistically significant P-value ($P = 0.008$) for death in the reperfused population. CABG, coronary artery bypass graft; PTCA, percutaneous transluminal coronary angioplasty; KC; killip classification VF, ventricular fibrillation.³³

preted and used merely as exploratory data. Figure 3 shows the relative risk of in-hospital events in the overall population and in the subgroup of patients who received a reperfusion strategy. Notwithstanding the impressive magnitude of the effect observed in hard end-points such as mortality, probably more important is the direction of the impact of GIK in different clinical outcomes. The benefit (towards a reduction) is evident in all variables that can be affected by a metabolic strategy (death, severe heart failure and severe arrhythmias), and more pronounced in the subgroup of patients treated with reperfusion therapies.

How should the ECLA GIK Pilot Trial be interpreted?

First, the pilot trial was part of a project developed to test a simple therapy that can modulate the metabolic derangement that occurs during the first hours of an AMI. The project is not finished and therefore we should not jump to hasty conclusions. Second, the pilot nature of the GIK trial should only be seen as a platform from which to carry out exploratory analyses of efficacy to formulate hypotheses. With this concept in mind, different conclusions can be reached:

- the safety of a GIK infusion during the early hours of an AMI has been proved;
- a high-dose infusion of GIK is applicable;
- the beneficial trend in outcomes observed in our pilot trial is consistent with previously

reported data and strongly supports the rationale for exploring GIK as an adjunctive strategy for the treatment of AMI;

- the target population for a large-scale trial using this therapeutic approach should comprise reperfused AMI patients; however, we cannot abandon the possibility that GIK could have an impact in non-reperfused patients.

Future directions

A novel concept using old therapies has emerged during recent years. During most of the last decade, research was focused on the improvement of reaching and maintaining patent related arteries, aimed at modifying the current natural history of AMI. Myocardial damage after an acute ischemic insult is the final determinant of immediate and long-term prognosis. Looking beyond the occlusive/thrombotic process and optimizing the energy transfer by manipulating the metabolic pathways soon after an AMI, would probably have a promising impact in limiting myocardial damage. The tremendous amount of basic research knowledge plus the promising results of limited clinical experience together comprise the rationale for a precise methodological endeavor to reliably answer a critical and relevant scientific question. The GIK 2 International Trial has already started and aims to determine the mortality impact of GIK in the current AMI scenario. This non-industry-supported challenge requires the mobilization of hundreds of cardiologist worldwide motivated by scientific curiosity. More than 1000 patients have been randomized to date. We believe this is the best way of testing this hypothesis in order to definitively establish the role of this simple, cheap and potentially life-saving therapy. ■

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Glucose-insulin-potassium for acute myocardial infarction: a perspective

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Glucose-insulin-potassium (GIK) as metabolic therapy for acute myocardial infarction (MI) has received renewed interest after several clinical reports reported reduced mortality rates, and experimental studies have provided basic mechanisms that explain its beneficial clinical effects. These developments constitute the latest chapter in the long history of this therapy.

The long and controversial history of GIK

The slow recognition of GIK for metabolic treatment of acute MI is distressingly reminiscent of the sad history of streptokinase as thrombolytic therapy. First introduced in the late 1950s, the efficacy of streptokinase was not finally appreciated for three decades, too late for the many preventable acute MI deaths that occurred in the interim.

The use of GIK in acute MI has been inhibited by a history of inconclusive clinical trials, basic science controversies, and pharmaceutical industry indifference to sponsoring research without likelihood of patents and profits. In 1962, in a small, non-randomized trial, Sodi-Pallares et al.¹ reported that GIK improved some of the ECG abnormalities associated with acute MI, reduced ventricular arrhythmias, and improved early survival. Over the next 35 years inconclusive results were reported from clinical trials which were often of very poor design. Several trials initiated therapy as late as 48 h after the onset of chest pain, a timing too late to influence MI size. Others used oral glucose and subcutaneous injections of insulin or relatively low concentrations of glucose, which did not achieve the glucose and insulin plasma levels required to maximally decrease plasma free fatty acid levels. It is not surprising that such studies showed no benefit.²

Consideration of the glycolytic pathway raised concerns that GIK could starve the cell of energy (glucose phosphorylation requires ATP), and/or worsen ischemic injury by intensifying myocardial acidosis as a result of increased lactate production.³ These concerns have been alleviated by recent quantitative perfusion imaging studies showing that substantial collateral flow provides significant residual perfusion in the acute MI region of most patients.^{4,5} This residual flow appears adequate to support a significant level of oxidative metabolism and prevent excessive lactate accumulation from inhibiting glycolysis; direct measurements of ATP content and intracellular pH during a comparable degree of low-flow ischemia in isolated hearts have shown that a high glucose-insulin substrate increases ATP levels and the free energy status, and does not worsen tissue acidosis.⁶⁻⁸ This observation is consistent with the analysis that during ischemia, proton generation from the hydrolysis of ATP exceeds that contributed by lactate;⁹ thus by maintaining a higher level of ATP the glucose-insulin inhibited the development of acidosis. Furthermore, experimental studies of isolated hearts exposed to acute MI perfusion conditions have consistently shown improved function when high levels of glucose-insulin were provided as metabolic support.^{6-8,10}

A resurgence of clinical interest in GIK

Interest in GIK was stimulated by the 1997 publication of a meta-analysis type of overview of randomized placebo-controlled acute MI trials.² Trials were included for analysis only if GIK (or placebo) was started within 48 h of chest pain. In nine such trials, involving 1932 patients, in-hospital mortality was reduced by 28% by the GIK therapy ($P = 0.004$). In the four studies in which the GIK

was administered intravenously at high doses, the in-hospital mortality was reduced by 48% relative to the placebo group. However, the strength of these results was diminished by the intrinsic weaknesses and limitations of the retrospective meta-analysis technique. In addition, current relevance was potentially reduced because all of the cited studies were done before the advent of thrombolytic and percutaneous transluminal coronary angioplasty (PTCA).

Early GIK and subsequent reperfusion for acute MI

The benefits of GIK have now been demonstrated in two large, prospective, randomized, acute MI trials where GIK was given prior to subsequent urgent reperfusion.

In the Swedish DIGAMI trial¹¹ half of the patients received thrombolytic therapy for acute MI and were randomized to receive either glucose-insulin followed by multi-dose insulin therapy or standard care. In the glucose-insulin group there was a trend towards a decrease in mortality at 3 months post-MI, and this became significant at 1 year post-MI (29% relative mortality reduction, $P = 0.027$).

Although the DIGAMI trial specifically enrolled diabetics, its results may be applicable to non-diabetics as well, because the most dramatic benefit of the glucose-insulin therapy was seen in the patients with only 'borderline' or mild diabetes, i.e. patients who did not require insulin prior to their hospitalization for acute MI. In this subgroup of patients the in-hospital mortality was reduced by glucose-insulin by 58% ($P < 0.05$) and the 1-year mortality was reduced by 52% ($P < 0.02$).

The strongest evidence for the benefits of GIK in the treatment of acute MI in the era of emergent reperfusion therapy comes from the recent ECLA (Estudios Cardiológicos Latinoamericana) study.^{12,13} This was the largest prospective, randomized trial of GIK for the treatment of acute MI ever carried out. Relative to reperfusion alone, there was a remarkable 66% reduction ($2P = 0.008$) in the relative in-hospital mortality risk when GIK was given prior to reperfusion (95% of those

reperfused had thrombolysis, 5% had primary PTCA); the absolute mortality risk decreased from 15.2 to 5.2% when GIK was part of the treatment.

Optimal GIK dosage

The ECLA study also compared high-dose GIK (the Rackley regimen¹⁴) with a lower dose. During the 1-year follow-up period the high-dose GIK group had a statistically significant survival advantage relative to the control group, but the low-dose GIK group did not, suggesting a greater degree of myocardial salvage by the high-dose GIK. There was no difference in the in-hospital mortality risk between the high- and low-dose GIK groups, but this result is not conclusive because the small group sizes ($n = 133$ – 135), with 8–10 deaths per group, provided little statistical power for ruling out a dose-related difference.

The superiority of the high-dose GIK in the ECLA study is consistent with the recent meta-analysis of GIK usage in acute MI. In the nine trials that used a variety of GIK regimens, the acute MI mortality risk was reduced by 28% by GIK relative to controls, but in the four trials which used high-dose GIK (i.e. the Rackley regimen), the relative acute MI mortality reduction was 48%.² Furthermore, a recent Polish study of low-dose GIK for acute MI showed no beneficial effect.^{15,16} This study's regimen delivered only approximately 15% of the glucose of the Rackley regimen. Thus the Rackley GIK regimen appears to be the current best choice.

Reservations about the ECLA study

Some unusual aspects of the ECLA study suggest that its conclusions be considered cautiously. There was a relatively long gap of 10–11 h between the onset of symptoms and the initiation of treatment. Whether such a long delay favors the finding of a beneficial effect of GIK is not known. Since the initiation of acute MI therapy is often faster, it is important to determine the relative benefits of GIK when treatment is started more quickly than

in the ECLA study. For example, in experimental studies, there was no difference in glycolytic flux rates between the control and glucose-insulin groups during the early ischemic period; a difference emerged only with more prolonged ischemia. During relatively brief periods of ischemia, myocardial glycogen stores may be able to provide a level of substrate adequate to support maximal glycolytic flux, and glucose-insulin may become important only after glycogen is depleted.⁶

The control (non-GIK) patients who underwent reperfusion in the ECLA study had a relatively high mortality risk of 15.2%, approximately twice as high as many recent large trials of thrombolysis for acute MI.¹⁷ The relatively long time to treatment may partially account for this higher mortality risk in the ECLA study. Nonetheless, the dramatically beneficial result with GIK relative to the control group may have been partly due the surprising and unusually high mortality risk of the control group.

Also surprising is the result that the non-reperfused, non-GIK patients had a mortality risk of only 6.7%. In other words, the non-GIK reperfused patients had more than twice the mortality risk (15.2%) of the non-reperfused patients, a result which is not consistent with numerous randomized trials of thrombolytic therapy of acute MI.¹⁷ A likely explanation for this surprising result is the small subgroup size and the fact that selection of patients for reperfusion therapy was not randomized, but left to the physician's discretion; thus it is likely that the reperfusion group comprised sicker patients. Nonetheless, these unusual aspects of the ECLA study suggest caution, and argue for replication, before the GIK results on mortality reduction can be accepted definitively.

GIK-reperfusion interaction

An important interaction between GIK and reperfusion therapy for acute MI was observed in the ECLA study.^{12,13} The reduction of acute MI mortality by GIK was observed only in the group of 252 patients who received reperfusion therapy; the patients not

reperfused received no benefit from GIK. However, this result is not conclusive because the ECLA study's non-reperfused group contained only 155 patients of whom 13 (8.4%) died; this sample size and mortality rate provided little statistical power. However, consistent with this ECLA result are ischemia-reperfusion experiments in isolated hearts. In these studies glucose-insulin had a relatively small beneficial effect on function during ischemia, but a large effect to improve post-ischemic recovery.^{6,10} This result suggests that GIK may slow the rate of ischemic necrosis, so that reperfusion can salvage a larger amount of tissue; however if reperfusion does not occur, the potential benefits of GIK may not be observed.

In contrast with ECLA, the meta-analysis of pre-thrombolytic era trials of GIK for acute MI included 1932 patients, and demonstrated a 28–48% reduction in acute MI mortality by GIK.² Thus, while the ECLA results might argue for a strategy of using GIK only in patients destined for reperfusion therapy, the meta-analysis results derived from a 10-fold larger sample size lead to an opposite, statistically stronger conclusion. A possible explanation for the discrepancy between the ECLA and meta-analysis regarding the differing GIK effects in the non-reperfused patients may lie in the phenomenon of spontaneous reperfusion. Spontaneous thrombolysis and reperfusion occur in a significant fraction of acute MI patients who do not receive pharmacologic thrombolytic therapy. If GIK were beneficial in such patients, such an effect might be observed in a large sample size, such as that considered in the meta-analysis overview,² but it might not be observed in the smaller sample size of the ECLA study. Clearly, more studies are required to resolve the important question of whether GIK is beneficial for acute MI patients in the absence of reperfusion therapy.

Future directions in cardiac metabolic therapy

Limitations of GIK therapy are the requirement of intravenous administration and the

restriction to a relatively short course of treatment. Several pharmacologic agents that can be taken orally and chronically also have the potential to favorably alter cardiac energy metabolism. These compounds include trimetazidine, ranolazine, etomoxir, dichloroacetate, carnitine and propionyl-L-carnitine. Future studies in cardiac energy metabolism should compare such agents to GIK and also determine whether a given drug's effects are additive to those of GIK.

Conclusion

What should the clinician do now? I am frequently asked whether the results reported to date constitute adequate evidence to justify the routine use of GIK for acute MI. I believe that they do not; more trials are needed, and quickly. Hopefully, the ECLA II study will soon provide the necessary information. ■

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Metabolic conditions stimulating FDG uptake in the heart

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Background

Recently, there has been a reawakening of interest in the patterns of glucose metabolism in the heart as a result of the use of radiolabelled deoxyglucose to evaluate myocardial utilization of exogenous glucose. Early studies of myocardial metabolism showed that the oxidation of glucose did not account for the major part of the oxygen uptake of the isolated heart-lung preparation. Rather, non-glucose fuels such as free fatty acids (FFA) were the most important substrate of the myocardium in the fasting state. In hypoxia, however, glucose extraction increased concurrently with the formation of lactate, showing that hypoxia could accelerate the pathways of glycolysis. On the basis of these observations, it may be expected that glucose extraction by the ischaemic heart should be accelerated, thereby allowing increased uptake of the tracer ^{18}F -2-fluoro-2-deoxyglucose (FDG), an event that can be imaged non-invasively by means of positron emission tomography (PET).

Glucose and FDG uptake by the normal heart

A small but consistent net uptake of circulating glucose by the heart is normally demonstrable in the fasting state. The reported arteriovenous differences range from 0.15 to 0.23 mmol/l, which correspond to a fractional uptake of only 3%.¹ This is consistent with the low myocardial FDG uptake ($0.11 \pm 0.04 \mu\text{mol/g per min}$) that has been demonstrated by PET in normal volunteers studied after overnight fasting.²

Feeding induces a set of metabolic changes in the whole body that have important effects on myocardial metabolism. Although the composition of the diet can be drastically altered in experimental models designed to assess specific nutritional influences, the mixed diet

of the average adult generates rather consistent substrate and hormonal signals. Of these, by far the most important is the increase in the circulating levels of insulin. Concomitant with insulin-induced stimulation of glucose metabolism is a drastic reduction in FFA delivery to tissues due to the inhibition of adipose tissue lipolysis by insulin. Therefore, the shift in myocardial substrate utilization occurring with feeding is the result of a concerted action of insulin at the whole body level. Since feeding is also associated with hyperglycaemia of a variable degree, the stimulatory action of insulin is coupled with increased glucose supply; hyperinsulinaemia and hyperglycaemia thus work synergistically to promote glucose disposal. The absolute rates of myocardial glucose uptake in man can be estimated at about $60 \mu\text{mol}/100 \text{ g per min}$, which is in the range of the values found in the isolated rat heart.¹ Similar rates of myocardial glucose utilization ($0.71 \pm 0.14 \mu\text{mol/g per min}$) have been reported in normal volunteers using FDG and PET during a euglycaemic-hyperinsulinaemic glucose clamp, a condition which closely mimics the postprandial state.³

Patterns of substrate uptake by the human myocardium therefore show marked oscillation between (1) the fasting state, with low rates of uptake of carbohydrate in contrast to the high rates of uptake of lipids such as FFA and sometimes triglyceride, and a low respiratory quotient of 0.74; and (2) the fed state, with high rates of uptake of glucose and lactate, accounting for virtually all of the concurrent oxygen uptake and with a respiratory quotient of nearly 1.0.¹

Glucose metabolism during myocardial ischaemia

The basic control mechanisms operative during myocardial ischaemia have been defined in ani-

mal experimental models. The two basic changes are increased glycogen breakdown and increased glucose uptake; both feed their products into the pathways of glycolysis which are accelerated by anaerobiosis (Pasteur effect). In the dog heart with coronary artery ligation, tissue glycogen is the major source of lactate released into coronary venous blood within the first 60 min after ligation, but thereafter circulating glucose becomes the major source. Non-invasive metabolic imaging of ischaemia using FDG and PET basically relies on the simple observation that glucose utilization by the myocardium is increased during ischaemic conditions. By using FDG, the process of glucose transport into the cell and its phosphorylation by hexokinase can be monitored non-invasively.¹

FDG uptake in patients with stable angina pectoris

In patients with angiographically proven coronary artery disease and stable angina on exercise studied at rest after overnight fasting, myocardial FDG uptake is very low and matches the distribution of coronary flow (*Figure 1*). Under these circumstances, patients are not distinguishable from normal volunteers studied under the same conditions.⁴ To study the effects of exercise on myocardial metabolism, patients with effort angina were subjected to maximal bicycle ergometric exercise in the supine position within a PET camera. In all patients the stress test induced typical chest pain and ECG signs of ischaemia that were accompanied by regional abnormalities of perfusion. An increase in myocardial glucose utilization was observed during the stress test. This increase, however, was not regionally homogeneous: glucose utilization in the non-ischaemic areas (i.e. those showing an increase in perfusion during exercise compa-

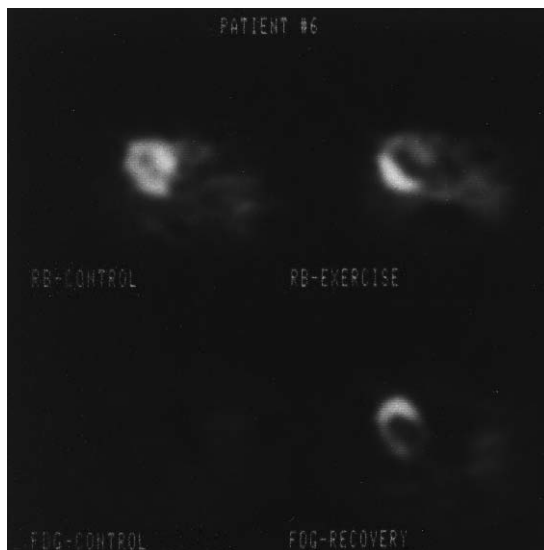


Figure 1. PET images of the chest of a patient with stable angina. In each image the left ventricle free wall is in the 6 to 10 o'clock position, the anterior wall and septum are in the 10 to 3 o'clock position, and the remaining open area is the plane of the mitral valve. Myocardial uptake of rubidium-82 (RB) at rest (top left) is homogeneous, while during exercise (top right), cation uptake is severely reduced in the anterior wall. When FDG was injected at rest (bottom left) after overnight fasting, myocardial tracer uptake was very low, the heart profile being barely detectable. In this patient FDG was also injected during recovery from the stress test when all signs of ischaemia had disappeared. Under these conditions (bottom right) the region of previous ischaemia was clearly identifiable, tracer uptake in the anterior wall being 1.75 times higher than that in non-ischaemic myocardium.



Figure 2. PET images of rubidium-82 (RB) and FDG uptake in the left ventricle of a patient with stable angina. Myocardial uptake of RB at rest (top left) is homogeneous, while during exercise (top right), cation uptake is severely reduced in the anteroseptal myocardium. When FDG was injected during the exercise (bottom left), tracer concentration in the ischaemic region was 0.75 times lower than in the non-ischaemic tissue (free wall) even though FDG in the ischaemic zone was in excess of perfusion. The scan recorded following an injection of FDG in the recovery phase, when RB had normalized (bottom right), shows a higher (1.90 times) tracer concentration in the previously ischaemic region in comparison with the non-ischaemic tissue (free wall). For figure orientation see legend to Figure 1.

rable with that in normal subjects) increased more than in the ischaemic regions (i.e. those developing flow defects during exercise), even though FDG uptake in the ischaemic zone was in excess of perfusion (Figure 2).⁵

Post-ischaemic FDG uptake

When glucose utilization is measured in the recovery period after exercise when all the indices of ischaemia, including myocardial perfusion, have normalized, a persistently increased FDG uptake can be demonstrated in the post-ischaemic myocardium (Figure 2). Taking enhanced FDG uptake as a sign of metabolic ischaemia, this post-exercise change could be termed a persistent metabolic abnormality that apparently occurs in the absence of symptoms or signs of frank ischaemia. The increased glucose uptake is not sustained by ischaemia, since coronary flow was comparable to that of control values, and could reflect either an increased glycolytic flux and/or an increased rate of glycogen synthesis due to depletion of the polysaccharide induced by ischaemia. The latter hypothesis is supported by experiments performed in the isolated perfused working rat heart where glycogen breakdown and synthesis were measured before and after a period of total global ischaemia.⁶ In addition, preliminary results obtained with ¹¹C-glucose and PET in patients with stable angina who showed increased uptake of FDG in the post-ischaemic myocardium, seem further to support the above hypothesis.⁵

FDG uptake in patients with unstable angina pectoris

Patients with unstable angina, characterized by frequent repeated episodes of spontaneous ST-segment depression, without evidence of acute infarction, were studied using FDG and PET after an overnight fast, at rest, and in the absence of symptoms and signs of myocardial ischaemia at the time of PET.⁷ Myocardial FDG uptake in these patients was different from that observed in normals and patients

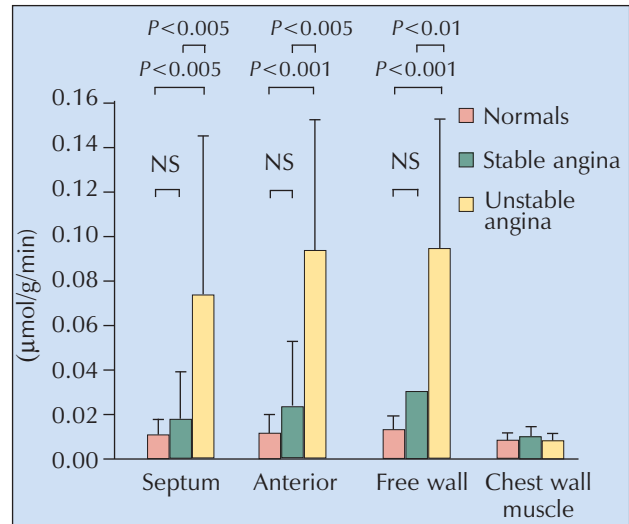


Figure 3. Myocardial (septal, anterior and free wall of the left ventricle) and skeletal muscle glucose uptake were measured using FDG and PET in normal volunteers and patients with stable or unstable angina, at rest and after overnight fasting. Glucose uptake was similarly low in normal subjects and patients with stable angina, but was significantly increased in patients with unstable angina despite the absence of symptoms and signs of myocardial ischaemia at the time of PET. It should be noted that the increase in FDG uptake was confined to the heart, as shown by the similar uptake in skeletal muscle in the three groups. This suggests that local, rather than systemic mechanisms, are likely to be responsible for the increased glucose utilization in patients with unstable angina (LC = 1).

with stable angina. In fact, FDG uptake was regionally or globally increased (Figure 3). This change occurred most often in the absence of perfusion abnormalities. It might be hypothesized that this pattern of FDG uptake represents a chronic adaptation of myocardial metabolism to repetitive ischaemia. The validity of the latter hypothesis was, at least in part, confirmed by further studies in these patients which proved that reduction of the number of ischaemic episodes, achieved by intensive medical treatment, was associated with normalization of the pattern of myocardial FDG uptake.⁸⁻¹⁰ ■

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Pharmacological optimization of cardiac metabolism in ischemic heart disease

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Diabetes will be one of the most challenging health problems of the 21st century,¹ and the cardiologist is certain to have a central role in caring for these patients. Heart disease in diabetics is a modern epidemic which requires a coordinated approach and the close attention of the cardiologist. In a recent health survey, 22% of diabetic patients reported they had seen a cardiologist in the preceding 12 months.² It is now well established that diabetics are at increased risk of coronary heart disease (CHD) and congestive heart failure,² and that they have a 1.5–3 times greater risk of death or reinfarction.³ Furthermore, the existence of a separate diabetic cardiomyopathy, independent of ischemic heart disease or hypertension, is now recognized.²

In diabetics, a strategy of strict glycemic control, as shown in the UKPDS which involved over 5000 patients with a median follow-up of 10 years, is associated with a 16% reduction in the incidence of acute myocardial infarction,⁴ which nearly attains statistical significance ($P = 0.052$). Further, and perhaps stronger, evidence in favor of strict glycemic control has come from the DIGAMI study in the setting of acute ischemia.⁵ In this study, all patients admitted with acute myocardial infarction and a blood glucose 11 mmol/l were randomized to an intensive regimen of glucose-insulin-potassium (GIK) or to control. The result was an astonishing overall 1-year 27% reduction in relative mortality in the GIK group compared with the control group.

How can these results with GIK be explained? In non-diabetics under non-ischemic conditions, fatty acid metabolism provides 60–80% of the ATP production, while glucose metabolism provides 40–60%. Diabetics are even more dependent on fatty acid metabolism than are non-diabetics, deriving at times more than 90% of their ATP from fatty acid metabolism.⁶ Furthermore, diabetes is characterized by an increase in circu-

lating free fatty acids. It has been known for over 20 years that fatty acids are deleterious in ischemia.⁶ GIK has a number of beneficial effects on myocardial metabolism in diabetics in ischemia, including, as shown by Rackley et al. nearly 20 years ago,⁷ a decrease in fatty acid metabolism compared with glucose metabolism.

Applying metabolic concepts to ischemic heart disease in diabetics

The results with GIK provide strong corroboration of what has now become recognized as the importance of metabolic interventions in cardiac disease. Metabolic agents, which include trimetazidine, ranolazine, dichloroacetate and etomoxir, act on specific metabolic processes, and are now attracting great interest for their potential value in treating ischemic heart disease. Trimetazidine, which directly inhibits fatty acid beta-oxidation and secondarily stimulates glucose oxidation, has anti-ischemic and anti-anginal properties.^{8, 9}

This metabolic mechanism of action explains the rationale for trimetazidine in diabetes. The hallmarks of the metabolic abnormalities in the diabetic heart are impaired glucose oxidation and an increase in dependence on fatty acid oxidation for energy production.¹⁰ The increased use of fatty acids causes an increased use of myocardial oxygen and enhanced intracellular accumulation of metabolic intermediates, leading to intracardiac conduction disturbances, arrhythmias, ion pump dysfunction, calcium overload, and contractile dysfunction. Furthermore, lactic acid accumulation further promotes the degradation of fatty acids.² These metabolic abnormalities are now thought to be an important contributing factor in the increased morbidity and mortality of ischemic heart disease (IHD) in diabetes.

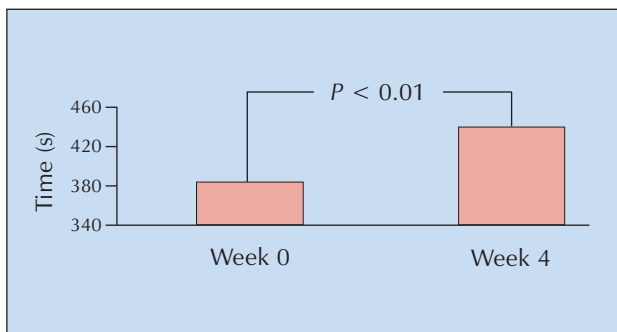


Figure 1. Exercise duration in diabetic patients after 4 weeks of trimetazidine.¹¹

By shifting the energy substrate away from fatty acids and towards glucose metabolism, trimetazidine optimizes cardiac metabolism in ischemia. In a clinical trial in 50 diabetic patients with stable angina pectoris, the addition of trimetazidine 20 mg t.i.d. to baseline monotherapy with a beta-blocker, calcium channel antagonist or long-acting nitrate led to a statistically significant improvement in terms of both clinical and ergometric parameters after 4 weeks of study treatment.¹¹ Average time to 1 mm ST-segment depression was increased by 52 s in these patients ($P < 0.01$), and time to onset of angina by 162 s. Total exercise duration increased by 57 s ($P < 0.01$) (Figure 1) and total work, on average, increased from 8.67 to 9.39 METs ($P < 0.01$). In terms of clinical parameters, mean weekly anginal frequency decreased by 36% from 4.79 to 3.06 ($P < 0.01$) and short-acting nitrate consumption decreased by 45% from 4.2 to 2.29 per week ($P < 0.01$).

These results demonstrate the usefulness of a metabolic approach to treating ischemic heart disease in diabetics. Interestingly, 98% of patients assessed the tolerability of trimetazidine as good or excellent.

Importance of metabolic management in all patients with CHD

The anti-anginal properties of the metabolic agent trimetazidine have been previously confirmed in numerous clinical studies in both monotherapy^{8,12,13} and in combination therapy with conventional hemodynamic drugs.^{14–16}

A double-blind, randomized, placebo-controlled trial in 227 patients with stable angina pectoris taking metoprolol was presented at the last ESC congress in Barcelona.¹⁷ Patients were randomized to receive trimetazidine or placebo. After 12 weeks, trimetazidine significantly improved all ergometric and clinical parameters compared with placebo. Time to 1 mm ST-segment depression was increased by 68 s ($P < 0.01$ compared with placebo) (Figure 2). This study adds a further example of the benefits of a metabolic intervention in all coronary patients.

There is also an increasing understanding of the role played by metabolic changes in ischemic cardiomyopathy,¹⁸ and there are some very good data about the effect of trimetazidine on both stress-induced left ventricular dysfunction and on hibernating myocardium. In a study by Lu et al.,¹⁹ 15 patients with stress-induced ventricular dysfunction were randomized to receive either trimetazidine or placebo for 15 days and then crossed over to the alternative treatment for another 15 days. Dobutamine stress echocardiography was performed at baseline and at the end of both treatment periods. Trimetazidine significantly reduced the wall motion score index (WMSI) from 1.40 to 1.34 at rest ($P < 0.013$) and from 1.71 to 1.61 at peak

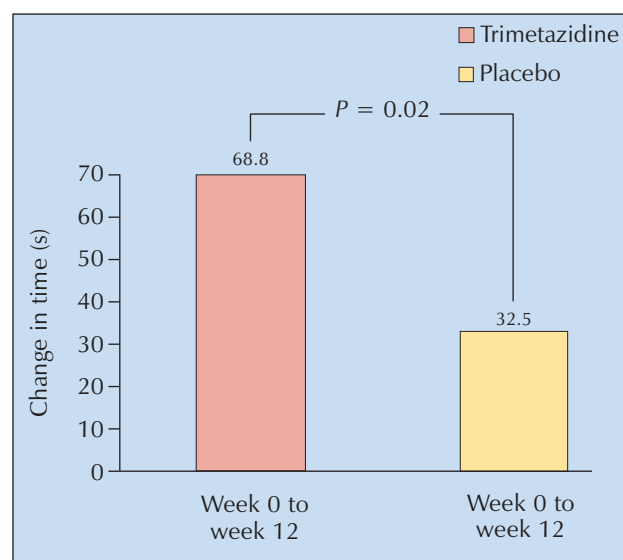


Figure 2. Increase in time to 1 mm ST-segment depression with trimetazidine.¹⁷

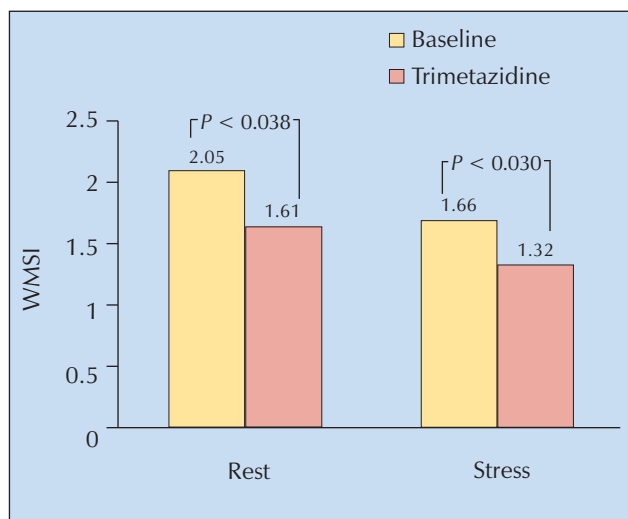


Figure 3. Trimetazidine decreases the wall motion score index (WMSI) at rest and at peak stress in patients with chronic left ventricular dysfunction and hibernating myocardium.²⁰

stress ($P < 0.018$). It is important to recognize that trimetazidine also delayed the onset of the ischemic threshold, as shown by significant increases in dobutamine infusion dose and time. Thus the WMSI was actually improved, even at a greater myocardial stress.

Equally interestingly, another study has shown that trimetazidine significantly improves the WMSI at rest and peak stress in patients with chronic ischemic left ventricular dysfunction.²⁰ Twenty-two patients with documented viable or hibernating myocardium, as determined by dobutamine stress echocardiography, were randomized to receive either trimetazidine 20 mg t.i.d. or placebo. In this population, all patients had a history of myocardial infarction, and mean baseline left ventricular ejection fraction was 33%. At rest, compared with placebo, trimetazidine caused a reduction in WMSI from 2.05 to 1.61 ($P = 0.038$ compared with placebo). At peak dobutamine infusion, trimetazidine decreased the WMSI from 1.66 to 1.32 ($P = 0.030$ compared with placebo) (Figure 3). Trimetazidine also increased mean ejection fraction from 41 to 51% at peak dobutamine infusion ($P = 0.008$ compared with placebo).

The improvement in the WMSI with trimetazidine seems to be at least comparable to that observed after percutaneous translumi-

nal coronary angioplasty in patients with viable myocardium.²¹

Conclusion

The importance of metabolic abnormalities in the pathophysiology of heart disease — including CHD, heart failure and diabetic cardiomyopathy — is now being recognized, in part because of the successes of metabolic therapy. The metabolic agent, trimetazidine, by shifting energy metabolism away from fatty acids towards the glucose pathway, has been demonstrated to be an effective anti-anginal and anti-ischemic agent in patients with stable angina pectoris and in those with other ischemic syndromes. ■

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