

Glucose-Insulin-Potassium Revived Current Status in Acute Coronary Syndromes and the Energy-Depleted Heart

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The oxidative metabolism of the human heart was first defined by Bing and colleagues¹ in a series of articles in the 1950s. Carbohydrates made up a relatively small part of the oxidative metabolism of the resting human heart. Focus on free fatty acids (FFAs) as a major myocardial fuel started with the finding in 1961 that FFAs inhibited glucose oxidation in the isolated heart.² The next year, Sodi-Pallares et al³ wrote their seminal article that stirred interest in the possible therapeutic benefit of the promotion of glucose metabolism by administration of glucose-insulin-potassium (GIK). These basic concepts are still being explored today, 50 years later. This article covers the historical buildup of studies and ideas (the Table), the concept of a glucose-fatty acid interaction in health and disease, and the evolution of GIK and its application in beneficially altering the metabolic patterns in early-phase myocardial ischemia (Figure 1) and in the energy-depleted heart.

Although there have been many clinical studies on GIK given to patients with acute myocardial infarction (AMI) with variable results, few have focused on 2 crucial aspects of the clinical and experimental data: timing and metabolism (the Table). In the original article by Sodi-Pallares et al,³ only 1 of the 7 patients was studied in the early acute phase of AMI. This 1 patient had early-phase ST-segment elevation, which abruptly decreased after an infusion of GIK. In the other 7 patients with nonacute MI, there were only minor ST- and T-wave changes after GIK. These results suggest that timing of GIK supply is crucial for any physiological benefit.

The inhibitory effects of FFAs on glucose metabolism² were substantially expanded by Randle and coworkers⁴ in their classic glucose-fatty acid cycle with rapid clinical application.⁵ However, such studies were not early enough after the onset of AMI. Kurien and Oliver⁶ found high plasma FFA levels in patients with AMI within 30 minutes of the onset of chest pain, and such levels could be reduced by GIK infusion.⁷ Very high FFA levels induced marked oxygen waste in the dog heart.⁸ Possible application of GIK to heart failure (HF) was mooted in 1971.⁹

Importantly, in 1972, in a pioneering laboratory study reported by Maroko et al,¹⁰ Braunwald's group found that GIK infusions started 30 minutes after experimental coronary occlusion in the dog had a protective effect against myocardial ischemia and reduced the extent of myocardial necrosis. In 1975, Opie and colleagues¹¹ reported that GIK given within the first hour of regional ischemia in the baboon model decreased circulating FFA levels and reverted tissue high-energy phosphate contents substantially toward normal, thus suggesting that GIK spared FFA-related cardiac oxygen waste in early ischemia. That the metabolic approach could also be applicable to humans was shown in the same year by Rackley's group and reported by Stanley et al.¹² Although they studied patients with stable coronary artery disease, the principles are relevant. Reduction of circulating FFAs by GIK decreased the arteriovenous difference of FFA across the human heart with highly significant decreases in the myocardial oxygen extraction. Subsequently, in 1983, Apstein et al¹³ showed that hyperglycemia and insulin increased glycolytic flux and prevented ischemic contracture in the acutely ischemic rabbit heart. In an influential meta-analysis, Kloner and Nesto¹⁴ found that even delayed GIK reduced 30-day patient mortality by $\approx 18\%$. Stimulation of glucose oxidation in rodent hearts decreased infarct size.¹⁵ The application of these concepts to humans has been taken further by the recent study in which myocardial biopsies from patients given left ventricular assist devices showed decreased levels of toxic lipid intermediates.¹⁶

Despite these results emphasizing the importance of timing of GIK supply during ischemia, over the years there has been only 1 clinical study, the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care (IMMEDIATE) Trial,¹⁷ covering administration in the first critical hours after the onset of symptoms in an acute coronary syndrome (ACS), a period when FFA levels are high.⁶ This study showed promising effects of GIK when started by paramedics very early in the course of ACS, in the ambulance during transport to the nearest hospital emergency department, and then continued for 12

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Table. Evolution of Major Studies1–17 Leading to Present Concepts of Benefits of Glucose-Insulin-Potassium or Components Thereof

Study	Study Design	Major Finding
Bing et al, ¹ 1954	Humans with HF; coronary sinus catheterization to measure arteriovenous transmural substrate and oxygen uptakes	Fats are the major fuel source in the human myocardium in the fasted overnight state
Shipp et al, ² 1961	Isolated rat hearts perfused with both glucose and FFAs	FFAs are preferentially oxidized in the heart and inhibit glucose oxidation when both substrates are present
Sodi-Pallares et al, ³ 1962	GIK administered to patients with AMI	GIK decreases ECG changes in the ischemic myocardium
Randle et al, ⁴ 1963	Isolated rat hearts perfused with both glucose and FFA; measured changes in glycolytic intermediates; studied fed and fasted states	Randle cycle describes competition between glucose and fatty acids for their metabolism in muscle and adipose tissue; insulin shifts muscle substrate use from FFAs to glucose
Mitra, ⁵ 1965	Patients within few days of onset of AMI	GIK lowers the incidence of arrhythmias and reduces mortality in patients with AMI
Kurien and Oliver, ⁶ 1966		Plasma FFAs are elevated at the onset of AMI
Opie group reported by Gupta et al, ⁷ 1969	Patients with recent AMI in coronary care unit given infusions of glucose	Glucose infusion reduces plasma FFA levels in AMI
Mjos, ⁸ 1971	Dog hearts subjected to very high FFA levels induced by intralipid/heparin	Substantial myocardial oxygen waste and functional impairment
Taylor and Majid, ⁹ 1971	Patients with HF given glucose and insulin	Provisional: GIK appeared to have beneficial effects in patients with HF
Braunwald group reported by Maroko et al, ¹⁰ 1972	Coronary ligation in dogs with epicardial ECG changes and tissue biopsies	GIK reduced tissue necrosis and epicardial ECG changes in ischemic zones
Opie et al, ¹¹ 1975	Coronary-ligated baboon heart	GIK infusions for 1 h reversed ATP loss
Rackley group reported by Stanley et al, ¹² 1975	GIK administered to patients with stable coronary artery disease	GIK lowered plasma FFA levels and caused a shift in cardiac metabolism from FFA to glucose oxidation
Apstein et al, ¹³ 1983	Moderate global ischemia in rabbit heart	Hyperglycemia and insulin doubled glycolytic flux, thereby preventing contracture
Kloner and Nesto, ¹⁴ 2008	Meta-analysis of clinical studies	GIK decreased 30-d mortality by ≈18%
Lopaschuk group reported by Ussher et al, ¹⁵ 2012	Ex vivo isolated working mice and rat hearts; demand-induced ischemia in pigs	Stimulation of glucose oxidation by PDH or MCD inhibition in knockout mice and by increased cardiac malonyl CoA activity, increases glucose oxidation, and decreases infarct size
Chokski et al, ¹⁶ 2012	Human cardiac biopsies before and after ventricular assist device implantation	Device lessens myocardial lipotoxicity (decreases diacylglycerol and ceramide)
IMMEDIATE Trial, ¹⁷ 2012	12-h infusion initiated in the prehospital setting to patients with ECG signs of ACS	GIK improves outcomes, including cardiac arrest or 30-d mortality in patients with AMI

ACS indicates acute coronary syndromes; AMI, acute myocardial infarction; FFA, free fatty acid; GIK, glucose-insulin-potassium; HF, heart failure; MCD, malonyl CoA decarboxylase; and PDH, pyruvate dehydrogenase.

hours.¹⁷ At a basic level, using the blood-perfused rat heart to simulate very early-phase AMI, Cave and colleagues¹⁸ found that glucose-insulin improved both ischemic systolic and diastolic function and postischemic recovery. Accordingly, we suggest that much of the clinical controversy relates to the studies reporting the late application of GIK at a variable time well after the onset of ACS symptoms, by when ischemia is more likely to have progressed to infarcted tissue and when beneficial effects on tissue metabolism are much less likely. Moreover, several of the studies were conducted before the advent of current coronary care or emergency care units.¹⁹

Metabolism of the Normal and Ischemic Heart

The heart has been called an omnivore because of its ability to metabolize different substrates, namely glucose and fatty acids, to produce energy in the form of ATP. Metabolism of glucose via the glycolytic pathway produces only 2 ATP mols per 1 mol glucose, whereas continued metabolism of glucose via oxidation in the mitochondria produces an extra 36 ATP mols per 1 mol glucose. Even in low-flow ischemia, some oxidative metabolism remains. Fatty acids and glucose compete

for oxidation in the heart because high concentrations of one inhibits the metabolism of the other via the Randle cycle.⁴ Besides the myocardial accumulation of toxic lipid intermediates,¹⁶ fatty acids inhibit pyruvate dehydrogenase (PDH), the enzyme that links glycolysis to subsequent glucose oxidation by converting pyruvate to acetyl coenzyme A (CoA) for entry into the tricarboxylic acid cycle (Figure 2).^{15,20} Conversely, increased glucose use inhibits fatty acid oxidation at the level of the enzyme carnitine palmitoyl transferase 1 (CPT-1), whereas increased malonyl-CoA levels produced by increased glucose flux potently inhibit this enzyme, thus providing a mechanism whereby high rates of aerobic glycolysis inhibit the oxidation of FFAs (Figure 3).^{15,20,21} Compared with glucose, the β -oxidation of 1 mol palmitate yields significantly more ATP (129 versus 38 ATP per 1 mol substrate) but consumes more oxygen.²² FFAs are therefore the preferred substrate for the heart under normal conditions, and their uptake and use are determined primarily by their circulating concentrations.²² Accordingly, myocardial oxygen demand is in part dictated by FFA oxidation. Experimentally, FFA-induced oxygen waste can increase the myocardial oxygen uptake by 48%.^{22,23}

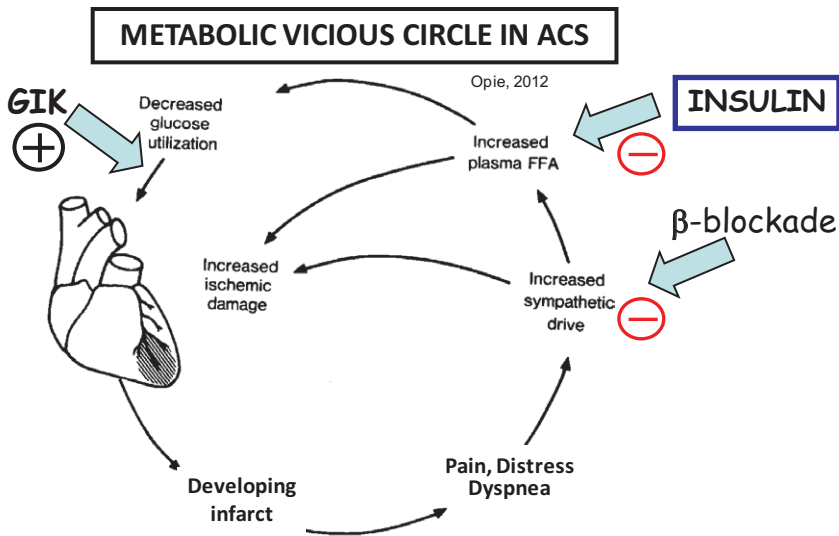


Figure 1. The metabolic vicious circle in acute coronary syndrome (ACS). In early-phase ACS, we hypothesize a metabolic vicious circle in which pain, distress, and dyspnea provoke increased sympathetic drive, which in turn increases myocardial ischemic damage via tachycardia and indirectly by increasing plasma free fatty acids (FFAs). The latter event increases ischemic damage both by lipid loading in the ischemic tissue (fatty acyl Co A in Figure 2) and indirectly by blocking protective glycolysis.

During ischemia, both glucose oxidation and fatty acid oxidation are reduced and anaerobic glycolysis is increased relative to the severity of flow deprivation.^{18,24,25} The metabolic patterns are shown in Figures 2 and 3. To maintain glycolytic flux, the heart breaks down endogenous glycogen stores and/or increases its extraction of circulating glucose.²⁶ Glycolysis produces protons and pyruvate; the latter is converted to lactate when unable to undergo subsequent oxidation.²⁶ Additionally, myocardial ischemia activates the neurohormonal stress response, resulting in a surge of catecholamines being released into circulation that stimulate lipolysis in adipose tissue.²⁴ The subsequent acute elevation in plasma FFAs increases their uptake by the heart.²² Although under aerobic conditions the uptake of FFAs is coupled to their successive breakdown by β -oxidation, decreased oxygen supply during ischemia impairs oxidative metabolism, leading to an adverse accumulation of fatty acids and their metabolites in the myocardium.²²

FFAs and Ischemic Injury

Cardiac steatosis, the accumulation of abnormal lipid intermediates in the myocardium, occurs when the supply of lipids to the heart exceeds their removal by oxidation and is found in conditions characterized by high circulating levels of fatty acids and impaired insulin response, including obesity, diabetes mellitus, and ACS.^{22,27} Excess lipids are toxic to the myocardium and are thought to contribute to the development of nonischemic cardiomyopathy and ventricular dysfunction in diabetes mellitus and obesity.^{22,28,29} During myocardial ischemia, acute elevations in systemic fatty acids have been shown to waste oxygen and reduce contractility,³⁰ to induce insulin resistance,³¹ to lead to dangerous arrhythmias,³² and to impair postischemic functional recovery.^{33–36}

Lipotoxic Arrhythmias

Although the exact mechanism of lipotoxic injury during ischemia remains to be clearly defined, experimental research has elucidated several possibilities, which are not mutually exclusive. High circulating FFAs and their derivatives are strongly

arrhythmogenic, probably in large part as a result of their actions on cellular membranes.³⁷ In patients with AMI, the unbound circulating FFA levels in particular are associated with adverse outcomes.³⁸ Fatty acids when esterified to CoAs or carnitine become amphipathic, thus acting as detergents breaking down membrane phospholipids and subsequently releasing arrhythmogenic lysophospholipids into the cell. Fatty acids can directly insert into the bilayer, disrupting membrane structure and function.³⁹ Incorporation of intracellular lipid intermediates, specifically acylcarnitine and lysophosphatidylcholine, into the sarcolemma during myocardial ischemia is postulated to alter membrane ion-channel activities, resulting in electrophysiological changes that induce dangerous arrhythmias.⁴⁰

Mitochondrial Damage

Another important target of lipid-mediated injury is the mitochondrion (Figure 3).^{16,27,41,42} Reduced β -oxidation in ischemia leads to an accumulation of fatty acyl-CoA and, to a lesser extent, acylcarnitine within the mitochondrial matrix, thereby uncoupling respiration,⁴³ inhibiting ATP synthesis, stimulating cytochrome c release, and depolarizing the mitochondrial membrane potential, actions that impair metabolism and increase the probability of the opening of the mitochondrial permeability transition pore, ultimately leading to apoptosis.^{42,44} Fatty acids also stimulate apoptosis by increasing the generation of reactive oxygen species, by disturbing endoplasmic reticulum structure,^{31,45} by undergoing conversion to toxic intermediates such as ceramide,^{16,27} and by acting as endogenous ionophores, leading to mitochondrial and cytosolic Na^+ and Ca^{2+} overload.⁴⁶

GIK in ACS: Metabolic Support for the Ischemic Heart

Anti-FFA Benefits

Reduction of circulating fatty acids has long been regarded as a key component of GIK-mediated cardioprotection during ischemia.^{24,47,48} Insulin inhibits peripheral lipase and decreases intracellular cAMP concentrations in adipose tissue, which

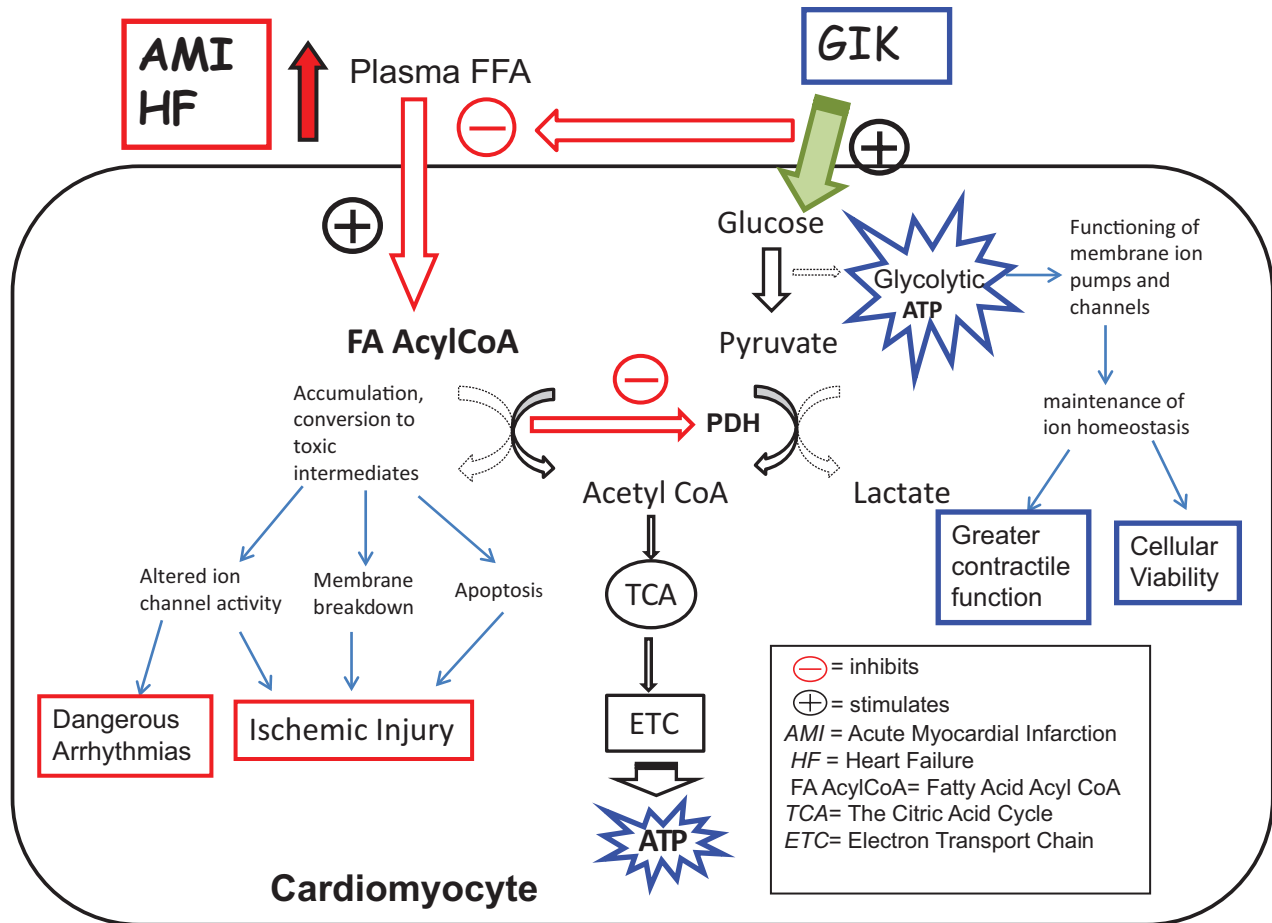


Figure 2. Metabolic pathways in the heart and metabolic support provided by glucose-insulin-potassium (GIK). **Left,** Adverse metabolic paths and consequences. **Right,** Beneficial glucose-related metabolic changes. The myocardial uptake of plasma free fatty acids (FFAs; **top left**) depends on their circulating concentrations and increases during catecholamine-driven elevations in plasma FFAs, such as that which occurs during stressful conditions like acute myocardial infarction (AMI) or heart failure (HF). Once within the cardiomyocyte, FFAs are converted to fatty acyl (FA) CoA, which has 2 adverse consequences. First, glucose oxidation and its protective benefits are suppressed by inhibition of the key enzyme pyruvate dehydrogenase. Second, the accumulation of toxic lipid intermediates leads to dangerous arrhythmias and increased ischemic injury. GIK (**top right**) decreases the levels of circulating FFAs and promotes the uptake of glucose, explaining its benefits in the Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency care (IMMEDIATE) Trial. ETC indicates electron transport chain; and TCA, tricarboxylic acid.

interferes with β -adrenergic signaling and attenuates catecholamine-stimulated lipolysis.⁴⁹ Subsequently, GIK infusion has been shown to lower plasma fatty acid levels in healthy patients¹² and during ischemia/reperfusion,^{47,48} thus reducing FFA availability for uptake by the heart. In the recent IMMEDIATE trial,¹⁷ GIK-treated patients had lower concentrations of plasma fatty acids measured over the first 12 hours, an effect that may have contributed to the significantly reduced occurrence of in-hospital cardiac arrest in this group because fatty acids are strongly associated with the development of ventricular fibrillation early in ischemia.^{34,50}

Stimulation of Glucose Metabolism

Sustained glycolytic flux is critical for maintaining cellular viability during ischemia and reperfusion.^{13,16,18,24,25,51-56} Glycolytic ATP preferentially supports membrane ATP-dependent ion pumps and channels, the proper functioning of which is essential for preserving ion homeostasis and membrane integrity.⁵⁷⁻⁶⁰ Moreover, because ATP synthesis by oxidative phosphorylation is reduced or inhibited by lack

of oxygen, the continued production of ATP by glycolysis is necessary to prevent total cellular ATP levels from falling below a critical threshold.²⁴ The cell is able to support enhanced glycolysis for a period by increasing its extraction of circulating glucose and breaking down endogenous glycogen stores; eventually, however, as the duration and severity of ischemia progress, glycolysis can become inhibited by buildup of its acidic byproducts or depletion of substrate.²⁶ Loss of glycolysis occurred simultaneously with the onset of ischemic contractures in experimental models,^{13,18,52,53} demonstrating its crucial role in slowing the progression of irreversible injury.

Conversely, administration of glucose-insulin during ischemia enhanced glycolytic flux^{13,18,51-56} and subsequently delayed or prevented the development of ischemic contracture.^{13,18,51-54} Glucose-insulin provision started at the onset of ischemia maintains high rates of glycolysis throughout extended periods of ischemia and for significantly longer durations than in control subjects.^{13,18,53,54} This increased and sustained production of glycolytic ATP slows the onset of irreversible injury,^{13,18,51,53,54} improves contractile

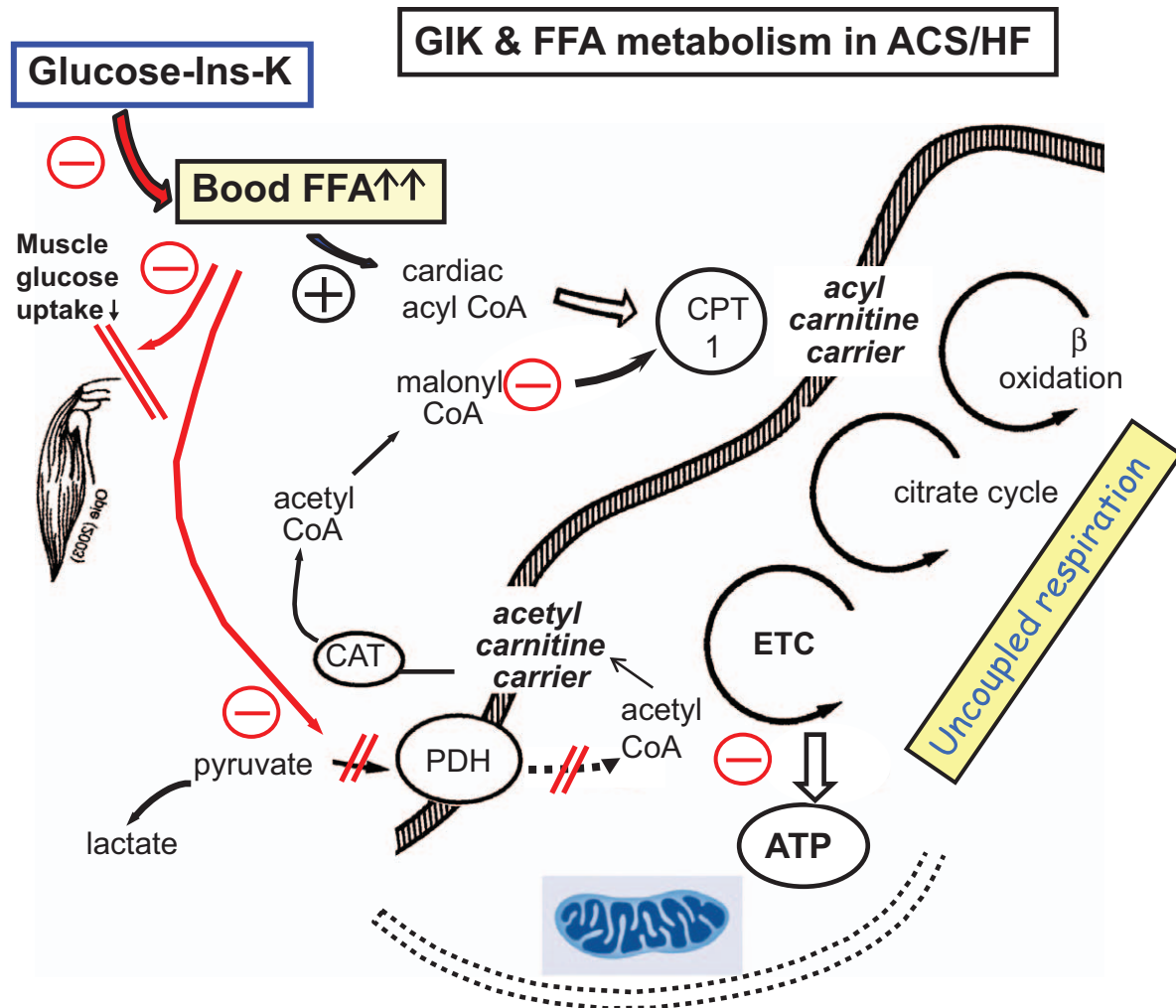


Figure 3. Cellular effects of glucose-insulin-potassium (GIK) on free fatty acid (FFA) metabolism in acute coronary syndromes (ACS)/heart failure (HF).²¹ Excess circulating FFAs have 3 major effects (from left to right): inhibition of skeletal muscle uptake, suppression of glucose oxidation by inhibition of pyruvate dehydrogenase (PDH), and elevation of cardiac cytosolic cellular acyl CoA levels. The result is uncoupled respiration, which can be ameliorated by GIK infusions. For details, see the text. CAT indicates carnitine-acetyl translocase; CPT, carnitine palmitoyl transferase; ETC, electron transport chain; and TCA, tricarboxylic acid. Reproduced from Opie²³ with permission. Copyright © 2004 L.H. Opie.

function during ischemia,^{13,25,53} and leads to greater recovery at reperfusion.^{13,16,18,51,53–55,59,60}

Enhanced glycolytic flux increases the concentrations of pyruvate, which stimulates PDH and drives its entry into the tricarboxylic acid cycle for subsequent oxidation.^{4,26} However, during ischemia/reperfusion, elevated FFAs inhibit PDH, subsequently uncoupling glucose oxidation from glycolysis.^{33–36} Unable to be oxidized, pyruvate is instead converted to lactate, producing H^+ as a byproduct that then stimulates an influx of Na^+ via the Na^+/H^+ exchanger.⁶¹ This Na^+ , in turn, activates reverse activity of the Na^+/Ca^{2+} exchanger, resulting in additional calcium influx during a critical period when the heart is trying to recover from calcium overload. By suppressing glucose oxidation, fatty acids impair recovery from acidosis and exacerbate the calcium burden, contributing to postischemic contractile dysfunction and reperfusion injury.^{33–36}

Provision of glucose-insulin, however, attenuates FFA inhibition of PDH by lowering plasma FFA concentrations, resulting in a beneficial switch from fatty acid to glucose metabolism that reduced oxygen consumption in patients with

stable coronary artery disease.¹² This beneficial metabolic switch also occurred with GIK administration to in vivo dogs during ischemia/reperfusion and was associated with greater postischemic recovery.⁶²

Normalization of Mitochondrial Metabolism

High circulating FFAs increase their uptake by cardiac tissue, with esterification to complex lipids inside the cytoplasm.¹⁶ Several actions are possible, including conversion to acyl carnitine by the enzyme CPT-1 and transfer across the mitochondrial membrane (hatched area in Figure 3). Inside the mitochondria, acyl carnitine is converted back to acyl-CoA by CPT-2 for subsequent entry into the fatty acid oxidation spiral. β -Oxidation of acyl-CoA forms acetyl CoA, which is oxidized in the tricarboxylic acid cycle, producing reducing equivalents that are delivered to the electron transport chain and stimulate ATP synthesis by oxidative phosphorylation. Excessive rates of FFA uptake and oxidation, however, disturb respiration by uncoupling electron transport from ATP synthesis, resulting in wasted oxygen, impaired ATP production, and reduced cardiac efficiency.^{8,16,30}

GIK helps to normalize intramitochondrial energy production by inhibiting the FFA-induced abnormalities. Increased flux of pyruvate through PDH produces excess acetyl CoA that can undergo oxidation in tricarboxylic acid or be transported out of the mitochondria as acetyl carnitine by acetyl-carnitine translocase. In the cytoplasm, this acetyl CoA undergoes conversion to malonyl CoA, a potent endogenous inhibitor of cardiac fatty acid oxidation²⁰ that suppresses CPT-1 (Figure 3), thereby lessening mitochondrial fatty acid–induced oxygen waste. The net outcome benefit is reduced infarct size.¹⁶

Clinical Implications

In early-phase ACS, we hypothesize a metabolic vicious circle (Figure 1) in which pain, distress, and dyspnea provoke increased sympathetic drive, which, in turn, furthers myocardial ischemic damage via tachycardia and indirectly by increasing FFAs. The plasma FFA level rises in relation to the measured size of the developing infarct.⁶³ Even in nondiabetic patients with ACS, blood glucose concentrations spontaneously rise,⁶⁴ but tissue glucose metabolism is impaired by insulin resistance.⁶⁵ Both high plasma FFA levels and insulin resistance are countered by provision of glucose-insulin as in GIK.

We recognize that in ACS restoration of flow by percutaneous coronary intervention or thrombolytics is undoubtedly the most effective way to salvage ischemic myocardium. However, because the outcome of ischemic injury is directly correlated with its duration and severity,⁶⁶ the ability of reperfusion to improve outcome is related to the time lapse between symptom onset and revascularization.⁶⁷ Reperfusion itself can also induce additional damage to the injured yet viable myocardium, a phenomenon called reperfusion injury.⁶⁸ Therefore, interventions that protect the heart during early ischemia and target molecular mediators that lessen reperfusion injury should increase myocardial salvage and improve clinical outcomes.

GIK, if given early enough in the course of ischemia, is one such intervention.^{69,70} By inhibiting fatty acids and promoting glucose metabolism, GIK enhances the metabolic state of the myocardium and slows the progression of ischemic injury.^{47,71–73} This lengthens the window of time that injured tissue remains viable and increases the amount of myocardium able to be recovered by reperfusion.⁶⁹ Additionally, there is evidence that GIK and/or insulin exerts specific cardioprotective effects during reperfusion such as reduced cell death and improved contractile function.^{62,74,75}

The timing of metabolic therapy is critical. Despite its success in many different experimental settings, GIK has yielded mixed benefit in clinical studies. We suggest that this is related to its late administration after the onset of symptoms of ACS. A 1997 meta-analysis of clinical studies performed in the pre-reperfusion era settled early debate by concluding that GIK reduces mortality in AMI,⁷⁶ reinforced by the more recent meta-analysis of 30-day mortality by Kloner and Nesto.¹⁴ Positive studies with GIK administration as an adjunct to thrombolytics or percutaneous coronary intervention have demonstrated a range of short- and long-term beneficial effects, including reduced myocardial damage,^{77,78} improved perfusion after revascularization,⁷⁹ decreased incidence of major

adverse cardiac events,⁸⁰ enhanced ventricular function,⁸¹ and lower mortality.^{82,83} However, several large studies have shown no benefit with GIK.^{84–86} A 2010 meta-analysis of 9 randomized trials that involved >28 000 patients did not reveal any mortality benefit with GIK therapy in ST-segment–elevation AMI.⁸⁷ However, all the studies examined AMI patients ≥ 3 hours after the onset of symptoms except for Glucose-Insulin-Potassium Study-1 (GIPS-1), which accounted for only 3% of the total population in the meta-analysis and had a relative risk of 0.83, whereas 70% of the meta-analysis population (>20 000 patients) were from 1 large trial, the Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Cardiológicos Latino America (CREATE-ECLA), in which the mean delay time was 4.7 hours.⁸⁷

In contrast, the recently completed IMMEDIATE trial showed benefit when GIK was instituted very early in the course of ACS as in the large-animal coronary ligation studies.^{10,11} Paramedics using ECG-based decision support gave GIK treatment in the ambulance at a median of 90 minutes after ischemic symptom onset to 871 patients in this randomized, placebo-controlled, double-blind effectiveness trial on patients with ACS in 13 US cities.¹⁷ Although the primary outcome of progression to completed infarction was not altered, there was a significant reduction in the prespecified secondary composite end point of cardiac arrest or in-hospital mortality; this occurred in 4.4% with GIK versus 8.7% with placebo (odds ratio, 0.48; 95% confidence interval, 0.27–0.85; $P=0.01$). Among 357 patients presenting with suspected ST-segment–elevation AMI, this composite was 6.1% with GIK versus 14.4% with placebo (odds ratio, 0.39; 95% confidence interval, 0.18–0.82; $P=0.01$). In the biological mechanism cohort ($n=143$), in those receiving GIK, the median infarct size was 2% of left ventricular mass compared with 10% of left ventricular mass with placebo ($P=0.01$). Among those with suspected ST-segment–elevation AMI, GIK infarct size was 3% of left ventricular mass versus 12% with placebo ($P=0.05$). With GIK, FFA levels were 367 versus 578 $\mu\text{mol/L}$ with placebo ($P<0.001$). Additional data from the 1-year results of IMMEDIATE are needed to make definitive conclusions; however, these results support the concept that GIK may beneficially affect clinical outcomes when started immediately after the onset of ischemic symptoms and then administered for a total of 12 hours during the course of ischemia.

GIK and Metabolic Therapy of HF and Other Energy-Poor Conditions

The metabolic phenotype of the failing myocardium is remarkably similar to ACS: energy deprivation, excess circulating FFAs, and increased insulin resistance.^{88–90} Both experimental and clinical studies have shown that the failing myocardium, like the ischemic myocardium, becomes relatively more dependent on glucose use for ATP production.⁸⁹ Importantly, an experimental study using transgenesis in the mouse heart failing as a result of pressure overload showed that increasing glucose use even further slowed the course of HF.⁹¹ Such experimental studies suggest that GIK therapy may have a beneficial effect on the failing myocardium and the acutely ischemic myocardium.

The principle of metabolic therapy for HF has been analyzed with benefits found from metabolically modulating drugs such as trimetazidine, ranolazine, and perhexiline, which act independently of decreasing circulating FFA levels.⁹⁰ Other studies have shown that β -blockade reduces circulating FFA levels⁹² and can change the metabolic pattern from the use of FFA to glucose.⁹³ The greater the β -receptor occupancy is in HF patients, the lower the FFA uptake is.⁹⁴ Maximum activation of protective glycolysis may be achieved by a combination of GIK, β -blockade, and activators of the regulatory enzyme PDH or of malonyl CoA dehydrogenase.^{22,95}

Although few in number, clinical reports using GIK therapy in several other non-ACS energy-poor conditions also suggest that it may be efficacious.^{96–98} In patients with chronic ischemic cardiomyopathy with left ventricular dysfunction, GIK infused over 4 hours improved wall motion score, peak systolic velocity, and end-systolic volume independently of effects on hemodynamics or catecholamines.⁹⁸ In patients with mitral valve replacement, preoperative GIK increased cardiac glycogen levels and provided a lower incidence of postoperative acute HF with hypotension, less serious postoperative arrhythmias, and overall fewer serious complications.⁹⁹ During aortic valve replacement for aortic stenosis in patients with left ventricular hypertrophy, GIK protected from episodes of low cardiac output.¹⁰⁰ GIK also reduced the morbidity and mortality of patients in cardiogenic shock after hypothermic ischemic arrest for aortocoronary bypass surgery.¹⁰¹ A small subset of these patients developed postoperative insulin resistance requiring treatment with supplemental insulin. Thus, meticulous glucose monitoring is required to avoid GIK-induced hyperglycemia.^{100,101}

Of interest, in advanced human HF, ventricular assist device implantation corrects myocardial lipotoxicity, decreases insulin resistance, and normalizes cardiac metabolism.¹⁶ Such metabolic changes are in line with those that could be expected from GIK, which remains to be tested in advanced chronic HF.

Summary

When a coronary artery becomes occluded, the threatened myocardium rapidly undergoes severe metabolic alterations that result in significant cellular dysfunction and injury. Stimulation of glucose metabolism and reduction of FFA in the ischemic tissue by treatment with GIK counters these metabolic derangements and remains a viable option in the therapy of ACS. Importantly, its major benefit can be expected when administration is started within the first hours of symptom onset. The failure or relatively weak benefit of almost all prior GIK studies when given for ACS is attributed to late onset of infusion when the heart has already incurred substantial irreversible damage. The concept of early GIK therapy in patients is supported by the recent results from the IMMEDIATE trial, which are consistent with the myocardial metabolic support that was envisioned 50 years ago for GIK. Ours is the only metabolic trial with outcome data initiated in the ambulance and the only trial in which GIK infusion was started within 1 hour of symptom onset.

Conversely, in the therapy of chronic HF, intense β -blockade may help to mediate the change from fatty acid to glucose metabolism. In acute HF in the postoperative phase, further

studies are warranted in light of the positive outcomes after GIK therapy during operations for aortic stenosis and mitral valve disease.

Disclosures

None.

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