Cardiac energy metabolism

The normal human heart requires a huge amount of energy. Adenosine triphosphate (ATP) delivers the energy required for contraction, relaxation, and ion homeostasis. A normal heart weighing 300 g synthesizes and utilizes approximately 15 times its weight (5 kg) of ATP each day. However, the heart contains only about 750 mg of ATP and, therefore, this critical but small ATP pool completely “turns over,” (ie, is utilized and resynthesized) every few seconds. Any reduction in ATP synthesis quickly results in systolic and diastolic dysfunction that is soon followed by irreversible injury.

The metabolic energy source for this large amount of ATP synthesis comes primarily from the uptake and oxidation of glucose and fatty acids (usually referred to as free fatty acids [FFAs] because they are not esterified). The heart is metabolically dependent on an adequate supply of these substrates and an abundant supply of oxygen for their oxidation. Thus, the heart is as much a furnace as it is a pump; it oxidizes hydrocarbon fuel (glucose and FFAs) to obtain the energy necessary for its function. Like a furnace or a hybrid engine, the heart can run on either or both of these two energy sources. Under well-oxygenated conditions, there is no apparent advantage to either substrate and when both are available, the heart utilizes both. However, during ischemia, when oxygen availability is limited, glucose is a better substrate (the reasons are discussed in detail below). A summary of glucose and FFA metabolism is shown in Figure 1.

Effects of infarction and ischemia on cardiac energy metabolism

During acute MI, the heart is composed of several regions with important metabolic differences. In the non-ischemic region, workload is increased to compensate for the loss of function in the ischemic region. To accomplish a greater workload, the non-ischemic region requires an increased rate of ATP synthesis and, therefore, a higher rate of substrate oxidation. However, in the ischemic region, ATP synthesis is markedly reduced due to the lack of oxygen and washout of metabolic products. Furthermore, the extent and consequences of the metabolic alterations depend importantly on the severity of the ischemic state.

During acute MI, residual or collateral flow usually provides at least 10% of the normal perfusion to a significant portion of the ischemic myocardium. This decrease in perfusion markedly reduces ATP synthesis. However, this small amount of oxygen still supports a level of oxidative ATP synthesis that greatly exceeds that produced from anaerobic glycolysis. Moreover, a level that is 10% of normal perfusion appears to provide an adequate washout of tissue lactate and a concomitant increase in ATP synthesis by GIK. In sub-regions, with more severe ischemia, anaerobic glycolysis becomes a progressively more important source of energy for a limited amount of ATP, which may or may not suffice to support the most essential cellular functions. Thus, during an acute MI, a mixture of both oxidative and anaerobic metabolism supports the myocardium.

Glycogen is rapidly mobilized during ischemia and reduced glycogen concentrations impair force development, calcium release, and contractile function. Key intermediates of the Krebs cycle also become depleted and may further impair ATP synthesis. Overall, the ischemic myocardium is metabolically characterized by:

- decreased synthesis of ATP with resultant reduced levels of ATP and creatine phosphate (CrP), and a corresponding increase in adenosine diphosphate (ADP) and inorganic phosphate (Pi)
- intracellular acidosis secondary to the proton generation from ATP breakdown, production of lactate from any anaerobic glycolysis, and the reduced washout level of the ischemic state
- increased cellular levels of calcium and sodium as ion homeostasis deteriorates
- depleted levels of Krebs cycle intermediates.
Acylcarnitine inhibits the sarcoplasmic reticular Ca^2+ metabolism such as acylcarnitine and acyl Co-A that have toxic effects, resulting in increased intracellular accumulation of intermediary FFA and myocardial FFA uptake, and FFA toxicity.

Shift from FFA to glucose uptake and utilization

Because of differences in the two overall pathways, approximately 11% more ATP is generated through the glycolytic pathway. Conversely, a high level of plasma glucose and insulin, stimulates the glycolytic pathway and decreases myocyte FFA uptake. Because of differences in the two overall pathways, approximately 11% more oxygen is required to generate an equivalent amount of ATP from FFA than from glucose; thus, glucose is a more oxygen-efficient way of generating ATP.

**Basic mechanisms of GIK protection**

**Shift from FFA to glucose uptake and utilization**

The “Rackley” GIK regimen was developed to maximize myocardial glucose uptake and decrease arterial FFA levels, myocardial FFA uptake, and FFA toxicity. It consists of a solution of 30% glucose (300 gm/L), 50 units of regular insulin per liter, and 80 mEq of KCl/L, given intravenously at 1.5 mEq/kg/hour, or approximately 100 ml per hour for a 70 kg patient. This regimen increases myocardial glucose uptake by 250% and reduces FFA uptake by 90%. The substrate shift from FFA to glucose has several beneficial effects.

- Better oxygen-efficient oxidative ATP synthesis with glucose: oxidative ATP synthesis is 11% more oxygen-efficient for glucose than for FFA oxidation; i.e., the oxidative synthesis of equivalent amounts of ATP requires 11% more oxygen if FFA is the substrate.
- Anti-FFA actions of glucose: GIK has important anti-FFA effects. High circulating levels of glucose and insulin both depress plasma levels of FFA and decrease myocardial FFA uptake at any given plasma FFA level, thereby minimizing intracellular FFA toxicity. Consequently, high glucose and insulin levels minimize the inhibition of glycolysis by FFA.
- Increased glycolytic ATP synthesis and cellular energy status: In addition to more efficient oxidative ATP synthesis, high glucose (G) and insulin (I) levels during low-flow ischemia also increase glycolytic ATP synthesis, thereby improving the high energy phosphate status of the myocardium by maintaining higher ATP and phosphocreatine levels, and lower inorganic phosphate (Pi), and ADP levels. The combination of a higher [ATP] and lower [Pi] ADP results in a significantly higher calculated free energy yield from ATP hydrolysis. Thus, the increase in ischemic glycolytic ATP synthesis acts as a “trap” for inorganic phosphate and ADP with a resulting amplification of free energy yield, which is available to all cellular ATPase reactions.
- Effects on ion homeostasis: Glycolytic ATP protects membranes, drives the transport of Ca^2+ into the sarcoplasmic reticulum, improves sodium homeostasis of ischemic myocardium, and regulates ATP-sensitive K^+ channels. A high glucose substrate increases myocyte resistance to the toxic effects of the increase in cell calcium concentration that occurs during hypoxia.
- Benefits during reperfusion: GIK may also improve cardiac function and efficiency during reperfusion by several mechanisms. GIK can accelerate the replenishing of depleted levels of Krebs cycle intermediates, processes called anaplerosis. An increased glycolytic flux generates more pyruvate which, in turn, generates Krebs cycle intermediates.

The glycolytic pathway itself may also be important in ischemia-reperfusion transitions. In isolated working hearts that were made ischemic and then reperfused, glycolysis was a highly adaptive emerg

**GIK toxicity during MI**

During an AMI, plasma FFA levels are increased in most patients secondary to the lipolytic action of endogenous or therapeutically-administered catecholamines and/or heparin. High levels of plasma FFA increase myocyte FFA uptake and depress myocardial contractility, inhibit glycolytic flux, increase cyclic AMP levels, accumulate as intracellular toxic fatty acid derivatives, cause membrane damage and arrhythmias, and increase myocardial oxygen consumption without a concomitant increase in myocardial work (oxygen wasting effect of FFA). Ischemia decreases the oxidation of FFA to carbon dioxide, resulting in increased intracellular accumulation of intermediary FFA metabolites such as acylcarnitine and acyl Co-A that have toxic effects. Acylcarnitine inhibits the sarcoplasmic reticular Ca^2+ pump and the sarcolemmal Na^+/Ca^2+ exchanger and Na^+ pump and can also activate Ca^2+ channels and increase cyclic AMP levels. These actions can lead to cell calcium overload, oxygen wasting, and arrhythmia generation.

**Increased potential of GIK in the hypertrophied and/or chronically infarcted heart**

An acute MI often occurs in patients with cardiac hypertrophy from chronic hypertension and/or prior chronic infarction. Hearts with pressure-overload hypertrophy are more sensitive to ischemic injury and derive greater anti-ischemic protection from increased glycolytic substrate than non-hypertrophied hearts. In hearts with chronic infarction, the energy reserve of the non-infarcted myocardium...
is substantially impaired, increasing susceptibility to acute metabolic stress. Myocardial metabolic support with GIK may be particularly beneficial in these settings.

Role of insulin
Insulin is a critical component of the GIK regimen. The combination of glucose and insulin is more effective than either alone in stimulating glycolysis under ischemic conditions. Insulin may also stimulate pyruvate dehydrogenase and increase pyruvate entry into the citric acid cycle, increase glycogen synthesis, and have direct ionic and inotropic effects. In studies of low-flow ischemia, insulin improved contractile function and myocardial metabolic efficiency without alterations of ATP, PCr, or Pi levels. Furthermore, in a model of ischemia and reperfusion, the inotropic and metabolic effects of insulin and epinephrine were additive and resulted in improved functional recovery in association with enhanced glucose uptake and utilization. Insulin may also protect the myocardium by activating "innate cell survival pathways" such as Akt. In clinical practice, however, administration of insulin without glucose in nondiabetics can cause hypoglycemia. Therefore, combined glucose and insulin administration is the practical clinical regimen.

Metabolic support for the acutely loaded non-infarct region
An acute MI mechanically overloads the non-infarct region of the ventricle in proportion to MI size and the functional response of the non-infarct region may determine whether heart failure occurs. Normal myocardium is metabolically limited in its ability to adapt to an acute mechanical overload. In a study of aortic banding in mice, wild-type animals had a decreased high-energy phosphate profile, developed rapid LV failure, and had a mortality rate of 40% at 8 weeks. In contrast, transgenic mice with a cardiac-specific overexpression of the glucose transporter, GLUT-1, had a markedly increased level of glucose uptake, maintained a normal high energy phosphate profile and normal left ventricular (LV) function, and had a very low mortality rate. Thus, enhanced cellular glucose uptake appears critical for the function and survival of acutely overloaded myocardium. By increasing glucose availability and uptake, GIK may provide important metabolic support to the acutely overloaded non-infarct region.

Role of residual blood flow for efficacy of GIK
With very severe ischemia, glycolytic stimulation by GIK could potentially increase myocardial acidosis from lactate accumulation. Approximately 10% of normal myocardial perfusion is required to prevent severe tissue lactate accumulation. When coronary flow was reduced by 90%, GIK doubled the glycolytic flux, prevented contracture during ischemia and reperfusion, increased post-ischemic contractile function, decreased ultrastructural damage, and increased high energy phosphate levels (Figure 2). Since the acute infarct region retained >10% of normal perfusion in most cases of acute MI, it appears to be above the perfusion level required for adequate lactate washout and successful stimulation with GIK. Importantly, even with more severe degrees of ischemia, although a high G4+ substrate was ineffective in affording protection in some studies, it did not cause more injury than the control glucose levels.

Clinical use of GIK for AMI
Limitations of early trials
Early clinical trials of GIK for acute MI yielded conflicting and inconclusive results because of several factors (eg, inadequate sample size, poor design, methodological differences including varying times to the start of GIK and the use of different GIK regimens). Many trials continued recruitment longer than 48 hours after the onset of chest pain, a timing too late to influence MI size. Several trials used oral glucose therapy with subcutaneous insulin injections or inadequate amounts of glucose, and did not achieve the glucose and insulin plasma concentrations required to significantly decrease plasma FFA concentrations. Moreover, none of these early trials had an adequate sample size and, therefore, lacked the statistical power to rigorously assess GIK. It is not surprising that such studies showed inconsistent results.

Pre-thrombolytic era trials
A 1997 review identified 9 GIK placebo-controlled mortality trials for acute MI in which GIK (or placebo) was started within 48 hours of chest pain (Table 1). Patients in these trials did not receive reperfusion therapy (thrombolysis or percutaneous coronary intervention [PCI]). In these trials involving 1932 patients, GIK significantly reduced in-hospital MI mortality (16% versus 21% for placebo). The number of lives saved was 49 per 1000 patients treated. In the 4 studies in which GIK was administered at high concentrations (see the "Rackley GIK regimen" above), the relative reduction in in-hospital mortality was even greater (6.5% versus 12%). The review concluded that GIK was highly likely to reduce mortality risk in acute MI.

Benefits of GIK with reperfusion therapy for acute MI
Three major, randomized, placebo or “standard care” controlled trials of GIK for acute MI have been conducted in concert with reperfusion therapy, with either thrombolytic drugs or percutaneous transluminal coronary angioplasty (PTCA): the DIGAMI, ECLA, and Dutch studies. All have shown impressive benefits of GIK treatment for acute MI, but none are conclusive enough to provide a definitive recommendation for the use of GIK.
The DIGAMI study

In the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) trial, 620 patients with diabetes and acute MI were randomly assigned to intensive insulin therapy (insulin-glucose infusion for 24 hours followed by subcutaneous insulin 4 times daily for at least 3 months) or standard treatment. Therapy was initiated at an average of 7 hours after symptom onset. Approximately half the patients received thrombolytic therapy and the treatment and control groups had similar rates of revascularization procedures.

In the intensive insulin group, there was a significant reduction in mortality at 1 year (19% vs. 26%) and at 3.4 years (13% vs. 21%). The benefit of intensive therapy was most pronounced in patients without prior insulin use and at low cardiovascular risk. In this subgroup, in-hospital mortality was significantly reduced (5% versus 12% for standard therapy). Thus, the DIGAMI results indicate that an insulin-glucose infusion via a peripheral intravenous catheter can significantly reduce acute MI mortality in diabetics; this may reflect the benefit of improved post-MI glycemic control, as well as the acute administration of insulin and glucose.

The ECLA study

The ECLA (Estudios Cardiologicos Latinoamerica) group randomly assigned 407 patients to high- or low-dose GIK or placebo; 62% received a thrombolytic agent. The ECLA study is summarized in Figure 3. For the entire group, GIK therapy was associated with a trend towards reduced in-hospital mortality (6.7% vs. 11.5% for placebo) and a trend towards a lower incidence of CHF in the GIK group. Among the patients treated with a thrombolytic agent, GIK markedly and significantly reduced in-hospital mortality (5.2% vs. 15.2%). Reperfused patients who received high-dose GIK had a significant 37% reduction in mortality at 1 year follow-up. Adverse effects of GIK treatment were minimal: 17% developed mild phlebitis and only 2% developed severe phlebitis, even though the majority of patients received the infusion via a peripheral intravenous catheter.

In the ECLA study, patients treated with thrombolytics alone (without GIK) had a relatively high mortality risk of 15.2%, slightly more than twice that of many recent large trials of thrombolysis for MI. Furthermore, patients not treated with thrombolytics or GIK had a mortality risk of only 6.7%. This finding of a higher mortality risk with reperfusion is not consistent with numerous randomized trials of thrombolytic therapy for acute MI. Probable explanations for this unusual result include small subgroup size; the fact that the selection of patients for reperfusion therapy was not randomized, but left to the physician’s discretion; it is therefore likely that sicker patients comprised the reperfusion group; and the relatively long time from symptom-onset to treatment initiation (average =11 hours) that may have contributed to the relatively high mortality rate in the non-GIK groups. Nonetheless, the relatively high mortality rate in the non-GIK reperfused group argues for caution before accepting the dramatic mortality reduction in the GIK group.

The Dutch study

The Dutch study was the largest prospectively randomized trial of GIK treatment for acute MI and the first to be done in concert with rapid, successful primary PCI (Table 2). The 940 acute MI patients were randomly assigned to GIK infusion for 8-12 hours or no infusion. For the entire patient group, the primary endpoint of 30-day mortality was not significantly reduced by GIK (4.8% versus 5.8% for the control group). However, among the 856 patients who presented without signs of heart failure (HF), GIK reduced mortality by 70% (P<0.01; Table 3). In diabetics, there was a non-significant trend towards reduced mortality with GIK.

GIK was not beneficial in patients who presented with HF, possibly because the GIK was infused at a relatively high rate (twice as high as in the ECLA study) and may have caused volume overload. In the 4% of patients who presented with mild HF (Killip class 2), GIK treatment was neither beneficial, nor harmful. In the 5% who presented with severe HF (Killip classes 3 and 4), the mortality risk was higher in the GIK group than in the control group. However, the small sample sizes preclude reaching definite, statistically significant, conclusions about the effects of GIK in MI patients with HF.

Comparison of the Dutch and ECLA studies

In both the ECLA and Dutch trials, more than 85% of the acute MI patients presented without signs of HF. In these non-HF patients, GIK in combination with reperfusion markedly reduced mortality risk in both studies, by 70% (P<0.01) and 66% (P<0.004) in the Dutch and ECLA studies, respectively.

However, the interaction between HF and GIK were not concordant in the ECLA and Dutch studies. In the ECLA study, there was a non-significant trend towards a lower incidence of HF in patients who received GIK. An important treatment difference and possible explanation of the different results between these two studies was the intravenous rate of volume loading that was twice as high in the Dutch study as in the ECLA study (3 vs 1.5 mL/kg/hr). Thus, any beneficial metabolic effects of GIK in the HF patients in the Dutch study may have been outweighed by the high level of volume loading, whereas the lower rate of volume loading in the ECLA study allowed the metabolic benefits of GIK to manifest.

In the Dutch study, the potential for GIK to influence mortality risk in advanced HF was also limited by the relatively low rate of volume loading in the non-GIK reperfused group argues for caution before accepting the dramatic mortality reduction in the GIK group.

Table 1: Summary of the major clinical trials of GIK for AMI

<table>
<thead>
<tr>
<th>Study/clinical condition</th>
<th>Sample size</th>
<th>Mortality decrease (subgroup benefit)</th>
<th>In-hospital mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIK meta-analysis* +**</td>
<td>1932</td>
<td>28% (P=0.004)</td>
<td></td>
</tr>
<tr>
<td>DIGAMI* +**</td>
<td>620</td>
<td>58% (P=0.05; Low risk subgroup only)</td>
<td></td>
</tr>
<tr>
<td>ECLA* +**</td>
<td>252</td>
<td>66% (P=0.004; Reperfusion subgroup only)</td>
<td></td>
</tr>
<tr>
<td>Post-op cardiogenic shock*</td>
<td>322</td>
<td>34% (P=0.02)</td>
<td></td>
</tr>
<tr>
<td>Dutch trial* +**</td>
<td>940</td>
<td>72% (P&lt;0.05; Killip 1 + PTCA only)</td>
<td></td>
</tr>
</tbody>
</table>

* NSTEMI=STEMI **STEMI only AMI = acute myocardial infarction

Table 2: Summary of the Dutch study of GIK for AMI

| • Prospectively randomized GIK vs. control |
| • N = 940; STEMI only; primary angioplasty |
| • Largest GIK for AMI trial to date |
| • Symptoms to admission: 150 min. |
| • Door to balloon: 45 min. |
rate of successful reperfusion in these patients. Only 50% of Killip class 3 and 4 cases had successful reperfusion. The ECLA results suggest that GIK is beneficial only in concert with reperfusion. In the entire Dutch study of 940 patients, only 23 Killip class 3 and 4 patients had successful reperfusion; such a small sample precludes any definite conclusions regarding the effects of GIK in acute MI in patients with HF.

Texas Heart Institute experience

There is also a discrepancy between the Dutch study’s HF results and the Texas Heart Institute results where 322 consecu- tive patients with refractory HF immediately post-cardiac surgery were randomly treated with standard care or standard care plus GIK. The addition of GIK to the standard regimen of inotropic drugs and intra-aortic balloon counterpulsation was associated with a significant reduction in in-hospital mortality (17.6% vs. 26.6%); the infusion rates were 0.5 to 1.0 mL/kg/hr, maximally, only one-third of the rate used in the Dutch study. In an experimental model of cardiogenic shock induced by multiple coronary occlusions, GIK substantially increased short-term survival, consistent with the Texas Heart Institute results.

Considered together, these studies suggest that GIK may be potentially beneficial in MI and post-cardiac surgery patients with HF and/or shock, but that the metabolic benefit of GIK can be outweighed by excessive volume loading. In the presence of HF or shock, a reasonable strategy might be to employ a more concentrated GIK solution. Placement of a central line and careful hemodynamic monitoring would be advisable in such cases.

Timing and duration of GIK

The different timeframes of GIK treatment in the ECLA and Dutch studies raise some interesting clinical issues. In the ECLA study, the time from onset of symptoms to hospital admission was 10 to 11 hours compared to only 2.5 hours in the Dutch study. Thus, in these 2 studies, GIK reduced AMI mortality risk similarly in non-HF cases, despite a wide range of duration of ischemia prior to treatment.

Furthermore, in both studies, GIK had an impressive protective effect despite being administered for a relatively small fraction of the ischemic pre-reperfusion period. For example, in the ECLA study, ischemia had been present for 10 to 11 hours prior to hospital admission. Assuming that thrombolysis was given promptly and resulted in reperfusion within 2 hours of arrival at hospital, GIK was infused for only approximately 15% (2 of 13 hours) of the pre-reperfusion ischemic time. Similarly, in the Dutch study, ischemia had been present for 2.5 hours prior to admission, and the admission-to-PCI time was approximately 45 minutes. Assuming GIK was infused for 30 of those 45 minutes, GIK would have been given for only 15% (30 of 195 minutes) of the ischemic pre-reperfusion period.

The fact that GIK was effective despite being administered for only a relatively brief period prior to reperfusion suggests several possibilities. GIK may protect against “reperfusion injury” or provide important metabolic support during reperfu-