Glucose, Insulin, and Potassium for Metabolic Support in Acute Myocardial Infarction: Is the Jury Still Out?

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During ischemic and cardiomyopathic conditions, carbohydrate (glucose) metabolism in cardiomyocytes predominates over use of free fatty acids. The shift to glucose metabolism is a physiologic response to ischemia, which in many patients, particularly diabetics or those who are insulin-resistant, is blunted. Free fatty acid metabolism during ischemia produces higher levels of lactate and hydrogen ions within the ischemic cells. This in turn degrades myocardial contractility, induces diastolic dysfunction, and reduces the arrhythmogenic threshold of the cardiomyoctye. Suppression of free fatty acid uptake and oxidation by any means will increase myocardial glucose substrate utilization in ischemia. Theoretically, then, an insulin-glucose solution that can augment GLUT-1 and GLUT-4 translocation to the sarcolemmal membrane can assist cardiomyocyte survival during ischemia; however, study results have not supported metabolic therapy. It is essential for any investigation of glucose, insulin, potassium therapy to separate out the effect of hyperglycemia and glucose toxicity to make any meaningful comment on the effectiveness of metabolic support in myocardial infarction.
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Glucose, insulin, and potassium (GIK) is a metabolic cocktail that has been under investigation since the mid 1960s, when Sodi-Pallares began researching its effects as a "polarizing agent" in acute myocardial infarction (AMI). As a point of reference, other therapies, such as the use of aspirin or beta-blockers for thrombolysis, were not being investigated. Since the early studies by Sodi-Pallares evaluating the effect of GIK intravenous infusions on

the electrocardiography findings in AMI, we have developed more questions than answers on the potential application of GIK in patients presenting with acute coronary syndromes.[1] The first clinical trial of GIK in AMI by Mittra was published in 1965.[2] This fueled interest among clinical investigators, leading to a number of studies performed during the 1970s and 1980s. Unfortunately, trial designs were underpowered to show significant effects of mortality and did not show consistent results, which did not allow for conclusions. Soon the focus of clinical investigation moved on to new and exciting developments such as those previously mentioned. With that came the loss of momentum in evaluating GIK as a therapy for AMI.

There were some researchers who still supported its investigation and proceeded with basic physiologic experiments. They identified some intriguing concepts that would justify the use of GIK as a metabolic support for ischemic myocardium during AMI as well as the volume loading that often accompanies ischemia. From the 1970s on, investigators such as Lionel Opie and Carl Apstein began to better understand the mechanisms of cardiomyocyte energetics prompting GIK back into the realm of clinical trials.

The Metabolic Theory

As illustrated by Apstein and colleagues, human cardiomyocytes use 2 primary sources of energy: free fatty acids (FFA), and carbohydrate (glucose). Fetal cardiomyocytes rely on glucose as an energy source. At birth there is a metabolic switch that occurs, and in the postnatal period, FFA metabolism begins to predominate. This schema continues throughout normal adult life, with FFA metabolism accounting for 60% to 90% of the energy generated, versus 10% to 40% for glucose metabolism.[3,4]

In normal physiologic conditions, FFA is an abundant and effective source of energy. FFA metabolism is somewhat expensive in an energetic sense as compared to glucose metabolism. Ten percent to 15% more oxygen is required to produce an equivalent amount of energy from FFA as compared to glucose.[5] As a measure to optimize energy expenditure during ischemic and cardiomyopathic conditions, the energy metabolism profile switches back to the fetal profile with carbohydrate metabolism becoming more prominent.[4] FFA metabolism during ischemia produces higher levels of lactate and hydrogen ions within the ischemic cells. This in turn degrades myocardial contractility, induces diastolic dysfunction, and reduces the arrhythmogenic threshold of the cardiomyoctye.[6-9]

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This mechanistic switch to carbohydrate metabolism is caused by the translocation of the GLUT-1 and GLUT-4 receptors to the sarcolemmal membrane.[10-12] GLUT-1 and GLUT-4 translocation is initiated by ischemia and by insulin.[13] Insulinopenia or insulin resistance is a characteristic of diabetes mellitus. This relative deficiency of insulin and/or resistance hampers myocardial glucose uptake, causing reliance on FFA metabolism. These actions may make the cardiomyocytes more susceptible to the adverse effects of ischemic metabolism of FFA with the associated metabolic and mechanical derangements.[10]

The shift therefore to carbohydrate metabolism is a physiologic response to ischemia, which in many patients, particularly diabetics or those who are insulin resistant, is blunted. Opie suggests that suppression of FFA uptake and oxidation by any means will increase myocardial glucose substrate utilization. Theoretically, then, an insulin-glucose solution that can augment GLUT-1 and GLUT-4 translocation to the sarcolemmal membrane can assist cardiomyocyte survival during ischemia.[6]

The Role of Glucose

Perhaps the Achilles' heel of GIK therapy is the role of hyperglycemia. Although not directly cardiotoxic, hyperglycemia promotes thrombosis, platelet reactivity, is pro-inflammatory, and causes endothelial dysfunction. Hyperglycemia is associated with elevated C-reactive protein levels, and activation of NF-kappa-B–regulated pathways. Inflammatory cytokines, including tumor necrosis factor–alpha, are elevated in this setting.[14] Hyperglycemia promotes a hypercoagulable state with elevated levels of clotting factors, platelet activation, and inhibition of the fibrinolytic system. Hyperglycemia also promotes endothelial dysfunction by enhancing the elaboration of angiotensin II and vascular endothelial growth factor. Hyperglycemia is also associated with a characteristic dyslipidemia

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with elevated triglycerides and small dense low-density lipoprotein, and decreased overall low-density lipoprotein and high-density lipoprotein levels.

In a landmark study by Leuven and colleagues, the role of glucose control and critically ill patients in the intensive care unit was examined. The study population consisted primarily of surgical patients, but included a large proportion of high-risk cardiac patients post–coronary artery bypass grafting (CABG). Reduction of the blood glucose level below 110 mg/dL significantly reduced in-hospital mortality. Furthermore, in a retrospective analysis, there was a direct linear correlation between the degree of hyperglycemia and the risk of death.[15,16]

When looked at in the setting of AMI, in addition to hyperglycemia's own intrinsic effects, it is also a marker for preexisting diabetes mellitus. Approximately half of all patients with ST elevation-MI (STEMI) present with hyperglycemia, many of whom are diabetic. Hyperglycemia observed on hospital admission then places the patients at risk for all of its diabetes-concomitant comorbidities.

Patients who have DM tend to have a higher incidence of multivessel coronary artery disease and renal insufficiency, and their early and late mortality after AMI is 2 to 4 times that of non-diabetics.[10] In a post-hoc analysis of the Cardinal study, Goyal and colleagues analyzed 1469 patients who presented with STEMI and found that hyperglycemia at admission was associated with a higher 30-day and 180-day mortality. The change in glucose level over the first 24 hours of admission was also an independent prognostic factor for adverse outcome.[17]

Early Studies Testing the Metabolic Theory

In a meta-analysis by Fath-Ordoubadi and Beatt of 15 studies examining GIK in AMI published between 1966 and 1996, only 9 were found to be adequate for their analysis. The others were excluded for poor randomization processes and 1 because it only looked at diabetics. Therefore, 9 trials and 1932 patients were included for this analysis.[18]

Unfortunately, as is the case in most meta-analyses, there was a significant variance in methods among these different studies, which were difficult to completely compensate for in this analysis. Some of these differences in trial designs included important factors such as the concentration of the GIK solution used, intravenous infusion rates, time from symptom onset to administration, method of administration, and adjunctive therapies allowed for in the trial. Of these studies, 4 used the high-dose GIK that was shown by Rackley and colleagues to suppress FFA levels and prevent their uptake by cardiomyocytes.[19] Analysis of the 9 studies showed an in-hospital mortality rate of 16.1% in the GIK group, and 21% in the control group. The reduction in mortality was 28%, with a CI of 0.57 to 0.90. In the 4 studies with high-dose GIK, the mortality was 6.5% in the GIK group and 12% in control. The relative reduction in mortality was 48% with a CI of 0.25 to 1.07.[18] This hypothesis generating analysis reignited interest in GIK as a treatment for AMI and called for further randomized controlled clinical trials.

Around this time, a number of pilot studies were initiated to determine whether GIK reduces mortality in STEMI. These pilot studies wound up raising more questions regarding GIK therapy. Three of the important trials were the Diabetes and Insulin-Glucose infusion in AMI (DIGAMI) trial, the Glucose-Insulin-Potassium Study (GIPS) trial, and the ECLA-GIPS trial. Each of these trials was followed by a subsequent study to clarify results.

DIGAMI Study

The DIGAMI randomized 620 patients with diabetes presenting with acute STEMI to an insulin-glucose infusion followed by multidose subcutaneous insulin for 3 or more months or conventional therapy. In this study, insulin administration resulted in a decrease in serum glucose level from a baseline of 211 mg/dL to 173 mg/dL. In-hospital mortality was reduced from 11.1% to 9.1%. This extended to a significant 29% reduction of 1-year risk mortality from 26.1% versus 18.6% ($P = .0273$). The mortality reduction was most significant (52%) in patients with a low cardiovascular risk profile or no previous insulin therapy. Only 10% of patients had insulin discontinued due to hypoglycemia and there was no associated morbidity. These results seemed to support glucose control in diabetes mellitus, but could not be extrapolated to support GIK in patients with AMI.[20]

In an attempt to answer this question, the same study coordinators initiated DIGAMI-2, a prospective, randomized, controlled, open label trial comparing GIK + intensive insulin control, GIK + standard blood glucose (BG) control, and standard care. In the intensive insulin control group, the trialists attempted to keep the fasting BG level at 5 to 7 mmol/L, and the non-fasting BG below 10 mmol/L via subcutaneous insulin (3 or more times daily). A significant shortcoming of the study was that the BG goal for the intensive therapy group was missed, with less than 50% of the patients receiving the multi-dose insulin, and in the standard BG control and standard care, the BG levels were lower than anticipated. In fact, the BG levels in all 3 groups were not significantly different: 9.1 mmol/L, 9.1 mmol/L,

and 10.0 mmol/L, respectively. There were no differences in outcomes observed among the 3 different groups. Although funding difficulties and the aforementioned findings led to an early conclusion of the study, one can interpret the results that show that the mortality benefit seen in DIGAMI-1 with no benefit in DIGAMI-2 was more likely due to reduced glucose levels than the GIK infusion itself.[21]

GIPS Study

The GIPS Study compared a high-dose GIK infusion to control in 940 patients who presented with STEMI. The primary endpoint was 30-day mortality. In the GIK group, 30-day mortality was 4.8% versus 5.8% in the control. The difference was not statistically significant, with a CI of 0.46 to 1.46. Subgroup analysis showed that in the patients who were Killip class 1, or without heart failure, the GIK group had a mortality of 1.2% versus 4.2% in the control group. This was statistically significant with a CI of 0.1 to 0.75. In patients with heart failure, or Killip class 2 or greater, mortality was not significantly different (36% in the GIK group and 26.5%; CI of 0.65 to 3.22).[22] Admission BG was the same between the experimental groups at 8.5 mmol/L. However, 16 hours after admission there was a trend for a lower BG in the GIK-treated group (7.7 vs 8.1 mmol/L).

This study is often pointed to as the benchmark for GIK trials.[9,23] The GIK was initiated early and before reperfusion. Reperfusion was achieved early and primarily by percutaneous coronary intervention. So the therapeutic approach to STEMI was contemporary as the trial site locations were in Western centers with control mortality rates comparable to rates in the United States. This trial provided much optimism for proponents of the metabolic theory. GIK seemed to reduce mortality, with the exception of patients who presented with heart failure and who may not have been able to tolerate the volume load required with the GIK infusion. The study failed to reach statistical significance in its primary endpoint because it was underpowered, with mortality rates lower than expected. In addition, the subgroups were not prespecified, and corrections for multiple subgroup analysis were not performed. The authors then embarked on a follow-up study to determine whether they could show a difference with GIK in patients who present with STEMI and no heart failure (Killip class 1).[24]

The GIPS II study enrolled 889 patients from August of 2003 to December of 2004 before termination. The study showed a 30-day mortality of 2.8% in the GIK group, and 1.8% in the control group. There was no statistically significant difference between groups with a *P* value of .27, with a trend toward increased mortality in the GIK group. When compared to the GIPS I study, it is interesting that the difference between trials is most significant for a decrease in mortality in the control group (4.2% vs 1.8%). Multivariate analysis showed that elevated glucose on admission, as well as unsuccessful reperfusion and anterior infarction, were predictors of 30-day mortality.[25]

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ECLA Study

The ECLA study randomized 407 patients with acute myocardial infarction to either GIK therapy (high or low dose) versus control. The study was conducted in 29 centers throughout 6 Latin American countries. Because of the small number of patients enrolled, the high- and low-dose GIK groups were combined for analysis purposes. When combining high- and low-dose GIK, in-hospital mortality was 6.7% in the GIK group versus 11.5% in control (CI of 0.30 to 1.10; *P* = NS); 61.9% of patients underwent reperfusion therapy, which was predominantly thrombolysis. In this subgroup, the mortality in the GIK group was 5.2%, compared to 15.2% in control (*P* = .01; CI of 0.15 to 0.77).[26] This seems to us most likely a statistical phenomenon, however, as reperfusion should not increase mortality in acute myocardial infarction (11.5% in control population, 15.2% in control with reperfusion). In this study, there was a trend toward lower presenting BG levels in the GIK group. During the infusion of GIK, there was a bump in the serum glucose levels, giving the GIK group a higher serum glucose than control at 6 and 24 hours. By 48 hours, with the infusion completed, the BG levels again were lower in the GIK group.

The CREATE-ECLA Randomized Controlled Trial randomized 20,201 patients in 470 centers worldwide to high-dose GIK (25% glucose, 50 U/L of regular insulin, and 80 mEQ of KCL, infused at 1.5 mL/kg per hour for 24 hours) versus control. The 30-day mortality in the GIK group was 10.0% versus 9.7% for control (*P* = .45). There were no significant differences in any of the prespecified subgroups including heart

failure, diabetes, time to presentation, or reperfusion therapy.[27]

Proponents of the metabolic theory, Apstein and Opie, point out some of the flaws in this trial. First, they speculate that the location of the trial centers was problematic and described by the investigators themselves as "resource poor," where reperfusion therapies were varied and inconsistently applied. In the reperfusion arm, there was no consistency in the selection of lytic agents, with a high percentage of streptokinase and urokinase. Only a small minority of patients underwent primary percutaneous coronary intervention. The duration of symptom onset to presentation and treatment was longer than what was observed in the GIPS 1 trial. They also point out other flaws in the trial design, which may have hampered the effectiveness of GIK in protecting the myocardium from ischemia. In particular, the GIK solution was started late—a median of 4.7 hours following symptom onset, and 1 hour post-median reperfusion time of 3.85 hours. For the theoretical benefits of GIK to be effective, it ideally should be initiated before reperfusion, and the reperfusion therapy should be effective. It is unclear whether the CREATE-ECLA trial was able to achieve this.[9]

Despite these criticisms, the use of adjunctive agents appears to be comparable to what we see in Western centers: aspirin was used in 97% of patients, intravenous nitrates in 74%, angiotensin-converting enzyme 1 in 70%, beta blockade in 70%, and lipid-lowering therapy in 67%. Further, in analysis of the CREATE-ECLA data, there were 1437 patients who received GIK before reperfusion, and 6900 patients who received GIK after reperfusion. The 30-day mortality was 12.2% in patients who received GIK before reperfusion and 8.2% in patients who received GIK after reperfusion, compared to 8.7% in patients who received reperfusion therapy without GIK.

It is unclear how each of these factors may have affected the outcome of the trial; however, the mortality rate noted in the CREATE-ECLA trial of 10% is significantly higher than what we have observed in the contemporary STEMI trials. A direct comparison of 30-day mortality in the CREATE-ECLA trial to the GIPS 1 for patients who present with STEMI who are not in heart failure (Killip class 1) is 7.1% versus 1.2%. Apstein and Opie point out that in the CREATE-ECLA trial, the patients who underwent percutaneous coronary intervention had a trend toward reduced mortality by 25% with GIK versus control (4.8% vs 6.3%; CI of 0.51 to 1.11).

In CREATE-ECLA, there was no additional provision made for BG modulation with supplemental insulin. Baseline BG levels in this study were equivalent between study groups at 162 mg/dL (9 mmol/L), but diverged with treatment. In the GIK group, BG increased to 187 mg/dL, whereas in the control group, BG decreased to 148 mg/dL. Furthermore, a retrospective analysis of the data on presenting glucose levels shows that presenting BG level correlated with mortality. In the lowest one third of patients, mortality was 6.6% in comparison with 8.5% in the middle tertile, and 14.0% in the highest tertile.

With the results of the CREATE-ECLA study, enrollment into OASIS-6, a randomized controlled study comparing GIK to control, was halted. Analysis of its 2000 enrolled patients showed no difference in death (GIK group 7.6% vs 6.7% for the control group), heart failure (GIK group 10.6% vs 12.2% for control), or a composite of death and heart failure at 30 days (GIK group 14.3% vs 15.4% for control).[28]

Future Direction

The metabolic theory in relation to cardiac ischemia is an intriguing one that has a storied history, but has thus far had little success in demonstrating conclusively any benefit of GIK in the setting of AMI. Early studies that were promising have failed to be duplicated in follow-up studies. Benefits in specific subgroups analysis, which generated hypotheses and new trials, failed to be confirmed on further testing. The failure to show any benefit with metabolic support in the form of GIK could be understood by a few explanations. This could reflect an incomplete understanding of the physiology of the cardiomyocyte. Perhaps FFA metabolism is not as crucial as is postulated. Or it could reflect an underestimation of glucose toxicity that appears to be rampant in the GIK study populations and a significant determinant of patient outcomes in these studies. This failure could reflect a flaw in our way of designing clinical trials and our inadequacy in controlling for factors such as blood glucose values and the time to initiation of infusion.

Carl Apstein, a strong supporter of the metabolic theory and the pioneer of much of the basic science behind it, helped design a clinical trial that he thought would give GIK its best chance to demonstrate an ability to improve mortality in STEMI. The Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care (IMMEDIATE) trial enrolled patients to early GIK versus control. The primary hypothesis is that early GIK will reduce 30-day and 1-year mortality. Major secondary hypotheses posit that GIK will reduce pre- or in-hospital cardiac arrest,

progression of unstable angina to AMI, and, by limiting MI size, the propensity for heart failure. Treatment will be initiated by emergency medical services upon first contact with the patient in the field.[29] These patients will then be taken to a center where they will be eligible for primary percutaneous coronary intervention. They will be randomized to receive a 12-hour IV infusion of either GIK or placebo. The intervention GIK solution will consist of 1 L of 30% dextrose mixed with 80 mEq of potassium chloride, and 50 units of regular insulin (for use in the ambulance). This will provide these patients with what Apstein thought necessary for GIK to be effective—early initiation after symptom onset, and effective revascularization.[30] Of interest will be the blood glucose levels achieved in the GIK-treated patients compared to the control population. The results of this trial may hinge not only on the early introduction of GIK in these patients with STEMI, but also the blood glucose levels achieved during the infusion periods in both groups.

Or perhaps GIK has a future, albeit not in STEMI. The physiology of STEMI is primarily of flush occlusion of an epicardial coronary artery. Although collateral vessels occasionally form to feed ischemic myocardium, these often take time to develop. According to the metabolic hypothesis, the GIK solution must be delivered to the ischemic myocardium, and a flush total occlusion is not the ideal setting to achieve that. NSTEMI is often related to a subtotal occlusion of an epicardial coronary artery, and carries with it a mortality that is equivalent to, if not higher than, STEMI. This may then be a better setting for GIK to provide evidence in support of the metabolic hypothesis. Regardless of the setting for future GIK trials, it will be essential for any investigation of GIK to separate out the effect of hyperglycemia and glucose toxicity to make any meaningful comment on the effectiveness of metabolic support in myocardial infarction. We eagerly await these studies to assist in our understanding of these pathophysiologic phenomena. ■

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Main Points

- During ischemic and cardiomyopathic conditions, carbohydrate (glucose) metabolism in cardiomyocytes predominates over use of free fatty acids.
- Free fatty acid metabolism during ischemia produces higher levels of lactate and hydrogen ions within the ischemic cells. This in turn degrades myocardial contractility, induces diastolic dysfunction, and reduces the arrhythmogenic threshold of the cardiomyoctye.
- Theoretically, then, an insulin-glucose solution that can augment GLUT-1 and GLUT-4 translocation to the sarcolemmal membrane can assist cardiomyocyte survival during ischemia; however, study results have not supported this theory.
- Hyperglycemia promotes thrombosis and platelet reactivity, is pro-inflammatory, and causes endothelial dysfunction.
- The effects of hyperglycemia and glucose toxicity in glucose-insulin-potassium therapy must be separated out to make any meaningful comment on the effectiveness of metabolic support in myocardial infarction.

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