A landmark study is reported in this issue of *Circulation*, continuing the rediscovery of glucose-insulin-potassium (GIK) treatment of acute myocardial infarction (AMI) that began in this journal last year with a meta-analysis and editorial.\(^2,3\) That meta-analysis considered all prior randomized trials of GIK for AMI (these were all done in the prethrombolytic era) and concluded that GIK had the potential to reduce AMI mortality by 28% to 48% depending on dosage and timing of therapy initiation relative to symptom onset. An accompanying editorial called for a modern large-scale trial of GIK in combination with thrombolyis for AMI. Such a prospective trial is now reported by the ECLA (Estudios Cardiologicos Latinoamerica) Collaborative Group, and the results are dramatic.

**Comparison of ECLA With Prior Meta-Analysis**

The ECLA result of a 66% relative decrease in AMI mortality by GIK is consonant with both the meta-analysis (28% to 48% relative mortality decrease) and the recent DIGAMI (Diabetes-Insulin-Glucose in Acute Myocardial Infarction) trial that reported a decreased relative mortality risk of 29% to 58% (depending on subgroup) in diabetic patients with AMI who were treated with glucose and insulin.\(^4\) The ECLA results are also in accord with the meta-analysis regarding the optimal GIK dosage but show disagreement regarding the effect of GIK in patients who were not acutely reperfused.

**Optimal GIK Dosage**

High-dose GIK was superior to the lower dose when 2 doses were compared in the ECLA study. During the 1-year follow-up period, the high-dose GIK group had a statistically significant survival advantage relative to the control group, and the low-dose GIK group did not, which suggests a greater degree of myocardial salvage by 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 of 133 to 135, with 8 to 10 deaths per group, provided little statistical power for ruling out a dose-related difference.

The decision by the ECLA group to use a high-dose GIK regimen was based on the pioneering work of Rackley and coworkers, whose dose-response studies determined the glucose and insulin infusion rates that achieved maximal suppression of arterial free fatty acid (FFA) levels and myocardial FFA uptake rates, as well as minimal increases in myocardial glucose uptake.\(^5\) The superiority of high-dose GIK in the ECLA study is consistent with the recent meta-analysis of GIK usage in AMI. In the 9 trials that used a variety of GIK regimens, the AMI mortality risk was reduced by GIK by 28% relative to controls, but in the 4 trials that used high-dose GIK, (ie, the Rackley regimen), the relative AMI mortality reduction by GIK was 48%.\(^2\) Thus, the Rackley GIK regimen appears to be the current best choice.

**GIK-Reperfusion Interaction**

An important interaction between GIK and reperfusion therapy for AMI was observed in the ECLA study, but this result was not consistent with the meta-analysis.\(^2\) In the ECLA study, the reduction of AMI mortality by GIK was

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observed only in the group of 252 patients who received concomitant reperfusion therapy; the patients not reperfused received no benefit from GIK. However, this result is not conclusive because the nonreperfused group in the ECLA study contained only 155 patients, of whom 13 (8.4%) died; this sample size and mortality rate provided little statistical power. In contrast, as noted above, the meta-analysis of prethrombolytic era trials of GIK for AMI included 1932 patients and demonstrated a 28% to 48% reduction in AMI mortality by GIK. Thus, whereas the ECLA results might argue for a strategy of using GIK only with concomitant reperfusion therapy, the meta-analysis results derived from a >10-fold larger sample size lead to an opposite, statistically stronger conclusion.

A possible explanation of the discrepancy between the ECLA and meta-analysis results regarding the differing GIK effects in the nonreperfused patients may lie in the phenomenon of spontaneous reperfusion. Spontaneous thrombolysis and reperfusion occur in a significant fraction of AMI patients who do not receive pharmacological 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, 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 AMI patients in the absence of concomitant reperfusion therapy.

Unusual Aspects of the ECLA Study
Some unusual aspects of the ECLA report also require further clarification by additional study. There was a relatively long gap of 10 to 11 hours between the onset of symptoms and initiation of treatment. Whether such a long delay favors the finding of a beneficial effect of GIK is not known. Because the initiation of AMI 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.

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 AMI. The relatively long time to treatment may partially account for this higher mortality risk in the ECLA study; nonetheless, the ECLA control group has an unusually high mortality risk value compared with the mortality risk of the GIK group. The high mortality risk of this control group argues for caution in accepting the dramatically beneficial result with GIK.

Also surprising is the result that the nonreperfused, 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 nonreperfused patients, a result that is not consistent with numerous randomized trials of thrombolytic therapy of AMI. 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 was 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 the need for caution and argue for replication before the GIK results on mortality reduction can be accepted definitively.

A Controversial Clinical and Scientific History of GIK
GIK therapy of AMI has a long and controversial history. Since the first report by Sodi-Pallares et al., clinical trials have yielded mixed results. However, the recent meta-analysis has greatly clarified the historical record. Discarded in the meta-analysis were those studies that were not randomized, or in which small amounts of GIK were given, or in which GIK was started too late to be useful. Included in the meta-analysis were only randomized trials in which adequate doses were given and therapy was initiated relatively early. The combined results of these well-done, prethrombolytic era studies suggested that GIK was highly likely to reduce AMI mortality. The DIGAMI and ECLA trials now demonstrate AMI mortality reduction by GIK in the thrombolytic era.

Experimental studies of the effects of increased glycolytic substrate on ischemic myocardium have also been controversial. This controversy can be attributed in part to results of experiments in which isolated hearts were subjected to zero-flow ischemia, a condition with dire metabolic consequences and in which therapeutic metabolic manipulation is impossible. However, recent elegant measurements of myocardial perfusion during the initial hospital presentation of patients with AMI have demonstrated that the acute infarct region is one of low-flow, not zero-flow, ischemia. The recognition that AMI results in a region of low-flow ischemia, with a level of residual perfusion adequate for substrate delivery and lactate washout, provides a rationale for GIK intervention in the AMI setting. Moreover, experimental studies of glucose and insulin during low-flow ischemia of comparable severity to that of the clinical AMI setting have shown highly beneficial effects of increased glycolytic substrate availability.

Mechanisms of GIK Protection
Several metabolic mechanisms are probably responsible for the beneficial effects of GIK in AMI. GIK decreases both circulating levels of FFAs and myocardial FFA uptake. Increased FFA levels are toxic to ischemic myocardium and are associated with increased membrane damage, arrhythmias, and decreased cardiac function. The anti-FFA effects of GIK may be especially beneficial in patients with high circulating levels of catecholamines or those receiving heparin because both of these agents increase serum FFA levels.

The early rationale for GIK was the stimulation of myocardial K+ reuptake by insulin’s stimulation of Na+,K+ ATPase and provision of glucose for glycolytic ATP production. The significance of the relatively small increase in ischemic glycolytic ATP production that results from increased provision of glycolytic substrate has been questioned. Nonetheless, the increase in glycolytic flux resulting from increased glucose and insulin during low-flow ischemia attenuated the ischemia-induced decrease in ATP and phosphocreatine, prevented the increase in inorganic phosphate (P), and decreased ischemic ADP levels. The combination of a higher [ATP] and lower [P] and [ADP] resulted in
a significantly higher calculated free energy yield from ATP hydrolysis in the presence of the G+I substrate. This increase in free energy is available to all cellular ATPase reactions, whether fueled by ATP synthesized by oxidative metabolism or by glycolysis. Thus, the increase in ischemic glycolytic ATP synthesis, even if relatively small, has the consequence of acting as a “trap” for inorganic phosphate and ADP, with a resulting amplification of free energy yield beyond that contributed by the increase in glycolytic ATP synthesis per se.

Moreover, the intracellular location of glycolytic enzymes may provide glycolytic ATP with particular value in the maintenance of critical membrane functions such as calcium and sodium homeostasis. Recent work from our laboratory has also shown that a high glucose substrate increases myocyte resistance to the toxic effects of the increase in cell calcium concentration that occurs during hypoxia. Thus, there is now strong clinical and scientific evidence to support the use of GIK in AMI.

Possible Future Directions: A Renewed Interest in Clinical Myocardial Bioenergetics? It is hoped that the ECLA study will generate renewed clinical interest in the potential of therapeutic metabolic manipulation in ischemic heart disease (see Reference 21 for recent monograph and review of this topic). In addition to AMI, there are other clinical settings, such as cardiogenic shock or myocardial preservation during cardiac surgery, in which GIK has the potential to improve myocardial bioenergetics and clinical outcome.

There are also specific patient subgroups in which GIK may be particularly beneficial in the AMI setting. For example, in experimental studies, glycolytic activity and stimulation was of greater benefit to hypoxic or ischemic hypertrophied myocardium than to nonhypertrophied tissue; thus, patients with left ventricular hypertrophy who sustain an AMI may constitute a subgroup especially likely to derive clinical benefit from GIK.

Assuming that GIK slows the rate of ischemic necrosis after a coronary occlusion, patients who receive primary angioplasty as therapy for AMI may be another subgroup to particularly benefit. If a GIK infusion was started at the moment a patient with suspected AMI was first seen by a medical personnel, eg, when picked up by an ambulance, the consequences of a relative delay to angioplasty might be negated. In other words, a GIK infusion might “buy time” or increase the time window in which successful salvage can be achieved by subsequent reperfusion. These possibilities warrant further study.

Conclusions

The remarkable results of the ECLA study affirm the great potential of GIK to reduce AMI mortality when it is added to acute reperfusion therapy. But the ECLA results should not be considered conclusive; before GIK is added to the therapeutic canon, the reported beneficial result needs to be replicated in a larger trial. Despite its being the largest prospective randomized trial of GIK to date, the ECLA study is still only 1 trial of GIK, and it is small in comparison with contemporary randomized trials of various thrombolytic agents for AMI. Furthermore, a statistically significant reduction in mortality occurred only in the subgroup that received concomitant reperfusion treatment. Even though this subgroup was prospectively stratified and represented 62% of the total number of patients studied, a conclusion based on a subgroup result is not as convincing as a result from the entire study population. Especially when such a result is so dramatically beneficial, it needs to be confirmed before it becomes standard practice.

References


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