EDITORIAL COMMENT

The Benefits of Glucose-Insulin-Potassium for Acute Myocardial Infarction (and Some Concerns)*

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An important study by van der Horst et al. (1) from the Netherlands reported in this issue of the *Journal* presents the results of the largest prospectively randomized trial of glucose-insulin-potassium (GIK) treatment for acute myocardial infarction (AMI) ever done (940 patients) and the first to be done in concert with rapid, successful percutaneous transluminal coronary angioplasty (PTCA). The most important result was that GIK increased survival impressively in the 91% of patients who presented without heart failure (HF) (Killip class 1), reducing the 30-day mortality risk from 4.2% in the control group to 1.2% in the GIK group (p < 0.01, relative risk reduction of 72%). In diabetics, there was a non-significant trend toward reduced mortality with GIK.

However, 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 the Estudios Cardiologicos Latinoamerica (ECLA) study (2), and caused a 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. But the small sample sizes preclude any definite conclusions about the effects of GIK in AMI patients with HF.

The results in the patients with HF are a dilemma of interpretation. Despite the small sample size and lack of statistical significance, because of their potential clinical importance, the non-significant trends cannot be completely ignored. Some insight may be gained by comparing the infusion rates and results of the current Dutch study with other large, randomized trials of GIK in AMI patients with HF.

The ECLA experience. In 1998, the ECLA group randomized 407 AMI patients, 62% of whom received reperfusion therapy, to GIK or control treatment. There was a remarkable 66% reduction in the relative in-hospital mortality risk when GIK was added to reperfusion (2,3). The absolute mortality risk decreased from 15.2% in the control group to 5.2% in the GIK group.

A comparison of the Dutch and ECLA studies reveals areas of agreement and disagreement. In both trials, more than 85% of the AMI patients presented without signs of congestive heart failure (CHF). Glucose-insulin-potassium in combination with reperfusion (which was done by thrombolysis in 95% of cases in the ECLA study and solely by PTCA in the Dutch study) was highly beneficial in such non-CHF cases; the relative reductions in mortality risk conferred by GIK were 72% and 66% in the Dutch and ECLA studies, respectively.

However, the ECLA results in patients who presented with HF are in the opposite direction to those of the present Dutch study. In the ECLA study there was a non-significant trend towards a lower mortality risk in the HF and shock patients who received GIK. An important treatment difference, and a possible explanation of the different results between these two studies, was the intravenous rate of volume loading, which was twice as high in the Dutch study as in the ECLA study (3 vs. 1.5 ml/kg/h). Thus, in the Dutch study, an 80-kg patient with CHF received approximately 2 l of fluid in the first 8 h.

The potential of GIK to influence mortality risk in the Killip class 3 and 4 cases in the Dutch study was also limited by the relatively low rate of successful reperfusion in these cases. Only 50% of the Killip class 3 and 4 cases had successful reperfusion; the ECLA results suggest the GIK is beneficial only in concert with reperfusion (2). 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.

Texas Heart Institute experience. Also discrepant with the Dutch study are results from Taegtmeyer et al. (4) in 322 consecutive patients with refractory HF immediately after cardiac surgery who were randomly treated with “standard care” or “standard care + GIK.” The addition of GIK to the standard regimen of inotropic drugs and intra-aortic balloon counterpulsation reduced in-hospital mortality by 34% (from 26.6% to 17.6%, p < 0.02); the infusion rates were 0.5 to 1.0 ml/kg/h, 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 (5), consistent with the Taegtmeyer results.

Considered together, these studies suggest that GIK may be potentially beneficial in AMI and post-cardiac surgery patients with HF and/or shock, but that GIK’s metabolic benefit can be outweighed by excessive volume loading. In the presence of HF or shock, a reasonable strategy might employ a more concentrated GIK solution with a lower infusion rate as was done in the ECLA and Texas Heart Institute studies.

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Institute studies. Placement of a central line and careful hemodynamic monitoring would be advisable in such cases.

**Timing and duration of GIK relative to the onset and duration of ischemia.** The different time frames of GIK treatment in the ECLA and Dutch studies raise some interesting clinical issues. In the former study, the time from onset of symptoms to hospital admission was 10 to 11 h; this was only 2.5 h in the latter study. Thus, in these two studies, GIK reduced AMI mortality risk similarly in non-CHF cases, despite a wide range of duration of ischemia before treatment. Furthermore, in both studies GIK had an impressive protective effect despite its being “on board” 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 h before hospital admission; assuming that thrombolysis was given promptly, and resulted in reperfusion within 2 h of arrival at hospital, GIK was infused for only approximately 15% (2 of 13 h) of the pre-reperfusion ischemic time. Similarly, in the Dutch study, ischemia had been present for 2.5 h before admission, and the admission-to-PTCA time was approximately 45 min. Assuming GIK was infused for 30 of those 45 min, the GIK would have been given for only 15% (30 of 195 min) of the ischemic pre-reperfusion period.

The fact that GIK was effective, despite being present for only a relatively brief period before reperfusion, suggests several possibilities. The GIK may protect against “reperfusion injury” or provide important metabolic support during reperfusion (6), and/or the GIK may be able to reverse some of the ischemic injury that has occurred before its being administered. Also, there is clearly a potential for increasing the benefits of GIK by its earlier administration. Thus, there is a clear need for further research.

**Mechanisms of mortality reduction by GIK.** In the current Dutch study, GIK appeared to decrease mortality by preventing the development of HF; 91% of the study population presented without HF (Killip class 1); the subsequent development of HF was responsible for 67% of the deaths in the Killip class 1 patients who did not receive GIK. Glucose-insulin-potassium treatment may prevent HF by reducing infarct size (cell death from both ischemia and reperfusion injury) and by providing an additional energy substrate that supports the non-infarcted myocardium’s ability to cope with a sudden mechanical load.

GIK’s metabolic actions against ischemic-reperfusion injury and necrosis. During an AMI, plasma free fatty acid (FFA) levels rapidly increase because of the lipolytic effects of catecholamines and/or heparin. The increased FFA levels are toxic to ischemic myocardium and are associated with increased membrane damage, arrhythmias, metabolic inefficiency, and decreased cardiac function. Glucose-insulin-potassium decreases FFA toxicity by decreasing circulating FFA levels and myocardial FFA uptake and oxidation (7–9).

Shifting myocardial oxidative metabolism from FFA to glucose oxidation makes the myocardium more “oxygen efficient”; approximately 11% more adenosine triphosphate (ATP) is synthesized per mole of oxygen when glucose is oxidized rather than FFA, and left ventricular (LV) function relative to oxygen consumption is improved when glucose, rather than FFA, is the major oxidative substrate (10,11). Despite a coronary occlusion, substantial oxidative ATP synthesis occurs in an acute infarct region because a significant degree of residual perfusion is almost always present (12); thus GIK has the potential to improve oxidative metabolic efficiency in the ischemic and infarcting regions.

The effect of GIK to increase glycolytic ATP synthesis is also important. During low-flow ischemia, with perfusion levels comparable to those in the infarct region in patients with AMI, provision of high glucose and insulin caused a small but significant increase in ischemic glycolytic ATP production, with consequent attenuation of both the ischemia-induced decreases in ATP and phosphocreatine and the reciprocal increases in inorganic phosphate (P) and adenosine diphosphate (ADP) levels (13–15). The resulting combination of a higher [ATP] and lower [P] and [ADP] resulted in a higher calculated free energy yield from ATP hydrolysis for all cellular adenosine triphosphatase reactions.

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 (16–20). A high glucose substrate level also increases myocyte resistance to the toxic effects of the increase in cell calcium levels that occurs during hypoxia (21).

Insulin alone exerts beneficial metabolic and functional effects during ischemia (22,23). Also, insulin given during early reperfusion reduced infarct size, possibly by reducing reperfusion apoptosis (24). The net effect of these GIK actions is the reduction of cellular injury from ischemia and reperfusion, and improved ischemic and post-ischemic systolic and diastolic function (13).

**Metabolic support for the acutely loaded non-infarct region.** An AMI acutely mechanically overloads the non-infarct region of the ventricle in proportion to myocardial infarct (MI) size, and the functional response of the non-infarct region may determine whether HF occurs. Recent elegant work from Liao et al. (25) has shown that normal myocardium is metabolically limited in its ability to adapt to an acute mechanical overload. After aortic banding, wild-type mice had a decreased high-energy phosphate profile, developed rapid LV failure, and had a mortality rate of 40% at eight 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, normal LV function, and had a very low mortality rate. Thus, enhanced cellular glucose uptake appears to be essential to the func-
tion 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.

Renewed interest in myocardial metabolism, lessons learned, and future questions. The current Dutch study contributes importantly to the clinical revival of metabolic support for the ischemic myocardium that began in the 1970s with the pioneering studies from the Rackley group (26), a meta-analysis of GIK treatment of AMI (27,28), and the Diabetes Mellitus, Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (29,30). The meta-analysis reviewed all previous randomized trials of GIK for AMI (these were all done in the pre-thrombolytic era). The majority of such trials were very poorly designed, often giving small amounts of GIK or starting therapy too late to be useful. In the nine randomized trials involving 1,932 patients, where GIK was given intravenously and started at an adequate dosage within 48 h of symptoms, GIK reduced relative in-hospital AMI mortality by 28%; furthermore, in the four studies in which GIK was administered at high concentrations to maximally suppress plasma FFA levels, relative AMI mortality risk was reduced by 48%. The Swedish DIGAMI study tested an insulin–glucose infusion, followed by multidose insulin treatment, in diabetics with AMI. The insulin–glucose treatment resulted in relative mortality decreases of 29% and 25% at one and three years of follow-up, respectively. These results, and those from the subsequent ECLA study and the current Dutch study, all support the principle that cardiac energy metabolism is an area deserving further research for the treatment of myocardial ischemia.

However, the results from the Dutch and ECLA studies should not be considered conclusive; before GIK is added to the therapeutic canon, larger trials are needed. Both trials were relatively small, and in each study a statistically significant reduction in mortality occurred only in a subgroup, not in the total population studied. In the ECLA study, GIK reduced AMI mortality significantly in the subgroup that received concomitant reperfusion treatment. In the Dutch study, the statistically significant mortality reduction occurred in the non–CHF subgroup. Even though these subgroups were prospectively defined and represented the majority of patients in each study, a conclusion based on a subgroup result is not as convincing as a result from the entire study population.

Whether GIK is beneficial in all patients with AMI is a crucial issue to resolve. Approximately 1.1 million MIs occur each year in the U.S. The Dutch results suggest that approximately one million present initially without CHF and that GIK has the potential to reduce their absolute mortality risk by 3%, saving the lives of approximately 30,000 such patients each year.

Whether GIK is beneficial in AMI patients with CHF and/or shock is an equally crucial issue to resolve. Although such patients comprise a relatively small percentage of the total AMI population, they have the highest mortality risk, but are also the least tolerant of a large volume infusion. Extrapolation from the Dutch study suggests that approximately 99,000 AMIs of Killip class 2 or higher occur annually in the U.S., with a mortality risk of 26.5%, resulting in 26,235 deaths per year despite rapidly available PTCA. A trial of a relatively concentrated GIK solution with low infusion rates, such as was used by Taegtmeyer et al. (4), would seem appropriate in such cases. Because patients with CHF and shock comprise a relatively small percentage of the total AMI population, a multicenter trial is probably required to resolve this issue.

Is GIK treatment for AMI beneficial in the general community outside of specialized centers? Would its benefits be increased by starting treatment as early as possible after the onset of symptoms and giving it during transport to a hospital site of revascularization? All these issues need to be resolved. The stakes are high; although such research is costly, treatment with GIK is cheap and the potential benefits are large.

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