EDITORIAL COMMENT

Acute Myocardial Infarction, Hyperglycemia, and Insulin*

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The intravenous infusion of the glucose-insulin-potassium (GIK) or the GIK solution in patients with acute myocardial infarction (AMI) was started by Sodi-Pallares on the basis of the hypothesis that this treatment would drive potassium with glucose into the damaged myocardial cells under the influence of insulin (1). This, he believed, would lead to the repolarization of the damaged myocardium and thus sustain its viability and function. Although this regimen has been used intermittently and erratically for over 40 years, the results have largely been inconsistent (2). A similar GIK regimen was used by Rogers et al. (3) to suppress plasma free fatty acid concentrations, which are considered to be metabolically toxic to tissues in general and to the ischemic myocardium in particular. Again, this particular strategy was not able to improve clinical outcomes in spite of the reduction in free fatty acid concentrations (2).

A recent large (n = 20,201) and definitive prospectively randomized trial, meant to answer whether the infusion of GIK improves clinical outcomes, demonstrated that GIK infusion does not exert a beneficial effect in patients with AMI (4). However, this trial yielded a significant amount of additional information. First, it provided the best evidence to date that increasing concentrations of glucose at the time of admission for AMI are predictive of mortality. Thus, the rate of mortality in patients with the lowest tertile of glucose (<7 mmol/l) was 6.6%, the middle tertile (7 to 8 mmol/l) was 8.2%, and the highest tertile (>8 mmol/l) was 14%. Second, GIK infusion caused a significant increase in plasma glucose concentrations over the 24-h period after admission when compared with patients in the control arm in whom glucose concentrations fell spontaneously (post-randomization glucose of >144 mg/dl was seen in 62% of the GIK subjects vs. 38% of the control group). Further analysis also revealed that GIK therapy was associated with an increase in mortality and congestive cardiac failure in the first 3 days that was attributed to the hyperglycemia, positive fluid balance, and hyperkalemia induced by the GIK infusion, whereas between days 3 and 30 there was a significant decrease in the combined end point of mortality and congestive cardiac failure, suggestive of a beneficial effect of insulin (5). There was also the evidence that, for a given level of glycemia, there was an improvement in outcomes in the GIK group, with a 18% reduction in mortality in subjects with the highest tertile of post-randomization glucose (>144 mg/dl) (6). Therefore, the CREATE-ECLA (Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation–Estudios Clinicos Latino America) study demonstrated that elevated admission and post-randomization glucose concentrations are associated with increased mortality, and because GIK therapy induced hyperglycemia, it is possible that any potential benefit of insulin therapy might have been masked by the detrimental effects of hyperglycemia. This issue is clearly important, because any attempt to infuse insulin to improve clinical outcomes must ensure that hyperglycemia is not induced.

Most of the GIK regimens have used high rates of glucose infusion of 25 to 30 g/h, similar to that used in CREATE-ECLA and therefore are likely to have induced hyperglycemia even if the data on glucose levels have not been provided (2). An important lesson learnt from these trials is that future studies of insulin therapy in ST-segment elevation myocardial infarction (STEMI) should use a regimen that does not induce hyperglycemia and lowers blood glucose into the normoglycemic range.

Other studies have also shown that an increase in glucose concentrations after admission for AMI and the overall glycemic load after admission determine morbidity and mortality in this condition (7,8). Recent guidelines have suggested that glucose levels should be maintained below 140 mg/dl in subjects with STEMI (9).

Because atherothrombosis is a pro-inflammatory condition, it is important to describe the pro-inflammatory effects of glucose and the anti-inflammatory and other relevant effects of insulin that are independent of its glucose-lowering effect (10). Glucose induces reactive oxygen species generation, an increase in the expression of p47phox, as a marker of nicotinamide adenine dinucleotide phosphate oxidase, the enzyme that generates superoxide from molecular oxygen. In addition, glucose induces an increase in nuclear factor kappa B (NFκB) binding, a reduction in inhibitor κBα, an increase in activating protein-1 and matrix metalloproteinases, and an increase in early growth response-1 and tissue factor (10). In STEMI, acute hyperglycemia is associated with an increase in no reflow, increased platelet aggregation, and increased left ventricular remodeling (10). Insulin, in contrast, suppresses reactive
Oxygen species generation, p47phox, NFκB binding, early growth response-1 binding, tissue factor, and plasminogen activator inhibitor type 1 concentrations (10). More recently, insulin has been shown to suppress the expression of toll-like receptors (TLR), in particular, TLR-2 and -4 (11). Both are involved in the pathogenesis of insulin resistance, whereas TLR-2 is involved in the mediation of ischemia reperfusion injury and is thus particularly relevant in patients with AMI. In addition, insulin is a vasodilator, induces nitric oxide generation and the endothelial form of nitric oxide synthase expression, and inhibits platelet aggregability both in normal subjects and in patients with acute coronary syndromes (10). Because insulin infusion leads to a reduction in glucose concentrations in addition to exerting its own beneficial effects, an insulin infusion that maintains normal glucose concentrations is likely to improve clinical outcomes in AMI.

Chaudhuri et al. (12) first demonstrated, consistent with this concept, that an insulin infusion associated with glucose concentrations below 140 mg/dl was not only anti-inflammatory and pro-fibrinolytic but also potentially cardioproteective. They demonstrated that an insulin infusion leads to a marked reduction in plasma C-reactive protein and serum amyloid A concentrations by >40% at 24 and 48 h with concomitant reductions in plasminogen activator inhibitor type 1 and creatine kinase-myocardial band concentrations. In the HI-5 (Hyperglycemia Intensive Insulin Infusion in Infarction Study), lowering glucose with insulin led to a >50% reduction in the rates of re-infarction and congestive cardiac failure in addition to a >40% reduction in plasma C-reactive protein concentrations within 24 h of starting the insulin infusion (13). There was a delay in initiation of insulin (13 h after onset of chest pain), and the study lacked the power to demonstrate a reduction in mortality. A Serbian study that randomized patients with AMI within 3 h of chest pain to an insulin infusion demonstrated an 88% reduction in major adverse clinical events and an improvement in left ventricular ejection fraction (14). The DIGAMI-2 (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) study investigated whether lowering glucose with intravenous insulin in the first 24 h, followed by intensive multiple dose subcutaneous insulin therapy as outpatient, would be beneficial in diabetic subjects with myocardial infarction. This study failed to show a benefit of this approach; however, the targets for glucose control with intensive treatment were not achieved in this study (15).

In this context, the study by Marfella et al. (16) in this issue of the Journal is an important and timely contribution, because it provides for the first time data not only on the effect of insulin on clinical indexes but also on the histological features of the myocardium, including that on indexes of inflammation and apoptosis, the process that leads to the death of myocardial cells during ischemic injury.

This study shows that patients with AMI and blood glucose concentrations >140 mg/dl at admission have significantly larger infarcts as measured by ultrasonography and as reflected in higher creatine kinase and troponin concentrations than those with blood glucose concentrations <140 mg/dl. These patients also have lower ejection fraction, higher left ventricular end-diastolic pressure, and a higher rate of atrial fibrillation. Histologically, these patients have a higher expression of CD3, the marker for T cells; CD68, the marker of macrophage infiltration; p65, the key component of NFκB, a major pro-inflammatory transcription factor; tumor necrosis factor-α, a major pro-inflammatory cytokine; inducible nitric oxide synthase, the enzyme that generates nitric oxide during inflammation; nitrotyrosine, a product of nitrative stress; and caspase-3, a major mediator of apoptosis. Remarkably, the low-dose infusion of insulin that reduced the blood glucose concentrations from 208 to 126 mg/dl was associated with a reduction in the size of the infarct, a reduction in left ventricular end-diastolic pressure, an increase in ejection fraction, and a reduction in troponin concentrations. In addition, there was a reduction in the expression of CD3, CD68, p65 (NFκB), tumor necrosis factor-α, inducible nitric oxide synthase, nitrotyrosine, and caspase in the myocardium. The data obtained for the first time in the human myocardium in AMI are consistent with those from rat and dog models of AMI in which insulin has been shown to reduce apoptosis (17,18). Interestingly, the investigators infused 3 U of insulin/h, a dose similar to the one at which anti-inflammatory effects of insulin have been demonstrated by us in healthy obese subjects and in subjects with STEMI.

These data put into the appropriate context the INTENSIVE (EFFECT of Insulin Glargine and Apidra in Patients With Acute ST Elevation MI) study, which aims to investigate the effect of a continuous infusion of a low dose of insulin while maintaining blood glucose concentration <130 mg/dl in patients with an anterior STEMI and blood glucose concentrations >140 mg/dl (19). The primary end point is the size of the infarct as measured by magnetic resonance imaging at 60 days after the infarct. The secondary end points include major adverse cardiac event, myocardial blush grade, ST-segment resolution, and dysrhythmias as assessed by computerized electrocardiographic monitoring during 24 h after the infarct, left ventricular ejection fraction, and indexes of inflammation. In contrast, the IMMEDIATE (Immediate Myocardial Metabolic Enhancement During Initial Assessment and Treatment in Emergency Care Trial) study is examining the effect of an early infusion of the GIK solution into AMI patients, in the ambulances, to provide the benefit of this treatment as early as possible (20). However, it does not take into consideration the issue of the induction of hyperglycemia, because the rate of infusion of glucose is similar to that in the CREATE-ECLA study. It is likely that the rate and the magnitude of hyperglycemia will be of the same order as that observed in the CREATE-ECLA study, with its inevitable clinical consequences.
REFERENCES


