Commentary
Is insulin an endogenous cardioprotector?
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Abstract

Stress hyperglycemia and diabetes mellitus with myocardial infarction are associated with increased risk for in-hospital mortality, congestive heart failure, or cardiogenic shock. Hyperglycemia triggers free radical generation and suppresses endothelial nitric oxide generation, and thus initiates and perpetuates inflammation. Conversely, insulin suppresses production of tumor necrosis factor-α and free radicals, enhances endothelial nitric oxide generation, and improves myocardial function. It is proposed that the balance between insulin and plasma glucose levels is critical to recovery and/or complications that occur following acute myocardial infarction and in the critically ill. Adequate attention should be given to maintaining euglycemia (plasma glucose ≤110 mg/dl) in order to reduce infarct size and improve cardiac function while using a glucose–insulin–potassium cocktail.

Keywords cardiac failure, cardioprotection, diabetes, free radicals, glucose, hyperglycemia, insulin, nitric oxide, tumor necrosis factor, septicemia, septic shock

Patients with acute myocardial infarction (AMI) exhibit raised blood glucose concentrations [1–3]. In addition, a positive association between hyperglycemia and mortality from AMI has been reported [4], although the exact reason for this association is not clear. Intensive treatment with insulin to lower plasma glucose concentrations decreases overall mortality in patients with diabetes mellitus who have AMI. In a prospective, randomized, controlled study involving adults admitted to surgical intensive care units and receiving mechanical ventilation [5], intensive insulin treatment reduced mortality and morbidity. Intensive insulin treatment reduced the number of deaths from multiple organ failure with sepsis. Markers of inflammation were found to be abnormal less frequently in the intensive insulin treatment group. This suggests that hyperglycemia is harmful, whereas insulin therapy is beneficial not only in AMI but also in critical illness with or without diabetes mellitus. It is likely that lack of insulin associated with hyperglycemia causes a decrease in glycolytic substrate and an increase in free fatty acids. This induces a reduction in myocardial contractility, and promotes cardiac failure and arrhythmias [6], leading to poor outcomes in such patients.

Hyperglycemia is proinflammatory whereas insulin is anti-inflammatory

Capes and coworkers [7] showed that patients with stress hyperglycemia but without diabetes mellitus at the time of AMI are at increased risk for in-hospital mortality and congestive heart failure or cardiogenic shock. Although the exact cause for the poor prognosis is not clear, it was suggested that hyperglycemia (an indirect reflection of relative insulin deficiency) increases circulating free fatty acids, which are toxic to myocardium and induce arrhythmias [6]. Hyperglycemia causes osmotic diuresis, and the resulting volume depletion may further compromise myocardial function.

Both in animal models of diabetes and in patients with diabetes mellitus, increased production of reactive oxygen species and consequent lipid peroxidation were noted [8–10]. Hyperglycemia increases the production of reactive oxygen species inside cultured aortic endothelial cells [11]. Superoxide anion inactivates both endothelial nitric oxide (NO) and prostacyclin produced by endothelial cells, which are potent vasodilators and platelet antiaggregators [12,13].

AMI = acute myocardial infarction; CCF = congestive cardiac failure; GIK = glucose–insulin–potassium; MIF = macrophage migration inhibitory factor; NADPH = nicotinamide adenine dinucleotide phosphate (reduced); NF-κB = nuclear factor-κB; NO = nitric oxide; TNF = tumor necrosis factor.

Thus, free radicals induce endothelial dysfunction. Normalizing levels of mitochondrial reactive oxygen species was reported to prevent glucose-induced activation of protein kinase C, formation of advanced glycation end-products, sorbitol accumulation, and nuclear factor-κB (NF-κB) activation [10]. Glucose challenge stimulated reactive oxygen species generation and levels of p47phox (a key protein of the enzyme nicotinamide adenine dinucleotide phosphate [reduced; NADPH] oxidase), whereas α-tocopherol levels decreased significantly in polymorphonuclear leukocytes and monocytes, even in normal subjects [14]. High glucose concentrations induced inflammatory events in rats, as evidenced by increased leukocyte rolling, leukocyte adherence, leukocyte transmigration through mesenteric venules associated with attenuation of endothelial NO release, and increased expression of P-selectin on endotheial surfaces [15]. Local application of insulin attenuated these proinflammatory effects. Insulin infusion inhibited reactive oxygen species generation, p47phox and NF-κB in mononuclear cells, and reduced soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 production by increasing NO synthesis [16–20]. These findings suggest that hyperglycemia has proinflammatory whereas insulin exhibits anti-inflammatory actions.

The exact mechanism by which glucose stimulates proinflammatory events is not clear, although indirect evidence suggests that it does so possibly by stimulating production of tumor necrosis factor (TNF)-α (a proinflammatory cytokine). A diet with a high glycemic load and hyperglycemia induced production of acute-phase reactants [21,22]. In experimental animal models of diabetes, the activity of NADPH-dependent oxidase and the levels of NADPH oxidase protein subunits p22phox, p67phox and p47phox were significantly increased [23], which accounted for the increased superoxide production in addition to decreased endothelial NO synthase activity. Similar to glucose, TNF-α also enhances free radical generation by augmenting polymorphonuclear leukocyte NADPH oxidase activity, activates NF-κB, and increases intercellular adhesion molecule-1 expression in endothelial cells [24]. This similarity in the actions of glucose and TNF-α, and the ability of former to enhance acute phase reactants suggests, but does not prove, that glucose may enhance TNF-α production and brings about its proinflammatory actions.

Tumor necrosis factor-α and myocardium

TNF-α is secreted by adipose tissue, macrophages and cardiac tissue, and plays roles in the pathogeneses of insulin resistance, type 2 diabetes mellitus, inflammation, and septic shock [13]. Release of TNF-α occurs early in the course of AMI and reduces myocardial contractility in a dose-dependent manner [25,26]. Using anti-TNF-α antibody can reduce TNF-α-induced myocardial injury and dysfunction [13,27]. Cardiac cachexia is believed to be due to an

increase in the circulating levels of TNF-α [28], and a direct correlation between the clinical features of congestive cardiac failure (CCF) and circulating levels of TNF have been reported. Following cardiac transplantation TNF-α levels decrease [13,25]. This suggests that TNF-α is an important mediator in the pathogenesis of CCF. In addition, it causes dysfunction and apoptosis of endothelial cells, and enhances generation of free radicals (including superoxide anion), which in turn quenches NO. Damage to endothelial cells triggers procoagulant activity and fibrin deposition [29]. These events are detrimental to the patient in the long run.

In CCF there is increased mesenteric venous pressure, which causes intestinal edema and increased bowel permeability. This causes an increase in endotoxin absorption from the gut. Increase in circulating levels of endotoxin activates macrophages and other cells to produce TNF-α [13]. In patients with CCF, CD14 concentrations (which are indicative of endotoxin–cell interaction) are raised in relation to the elevated levels of TNF-α and cachexia [30]. These findings suggest that methods designed to reduce TNF-α levels could be of significant benefit in inflammation, septicemia, and CCF.

Tumor necrosis factor-α and insulin

Both the American College of Cardiology and the American Heart Association recommended that intravenous glucose–insulin–potassium (GIK) be given to patients with AMI, especially those who are poor candidates for thrombolytic therapy and in whom the risk for bleeding is high [31], because the GIK regimen was beneficial in treating AMI [32–38]. It is generally believed that the GIK treatment improves the integrity and function of myocardial cells once glucose and potassium are transported in by insulin. Previously, I suggested that the GIK regimen in general and insulin in particular suppresses inflammation by inhibiting production of TNF-α, macrophage migration inhibitory factor (MIF) and superoxide anion, and by stimulating endothelial NO synthesis [16,26].

Satomi and coworkers [39] showed that exogenous insulin injection inhibited TNF-α production in a dose-related manner in animals after lipopolysaccharide challenge. Addition of insulin to cultures of peritoneal exudate cells from *Propionibacterium acnes* primed mice blocked TNF-α production, whereas in control animals it did not. Fraker and colleagues [40] reported that reduced food intake, decreased body weight gain, severe interstitial pneumonitis, periportal inflammation in the liver, and increases in the weights of the heart, lungs, kidney and spleen observed in TNF-α-treated animals reverted to normal levels when insulin was administered concurrently. The pneumonitis seen in these TNF-α-treated animals is somewhat similar to the adult respiratory distress syndrome that is seen in patients with septicemia and septic shock, conditions in which concentrations of interleukin-1, TNF-α, and MIF are elevated

[41,42]. In addition, insulin suppresses superoxide anion generation [43] and enhances the production of endothelial NO [44]. Thus, the ability of insulin to suppress TNF-α production, which decreases myocardial contractility, could be one mechanism by which the GIK regimen is beneficial in AMI.

Is it glucose or insulin that is critical to the heart?

Although several studies suggested that GIK regimen preserved systolic and diastolic function in ischemia and reperfusion [45] and protects the myocardium in patients undergoing open heart surgery [46,47], this is not without controversy [48–51]. Why did some studies give positive results whereas others failed to show a benefit from the GIK regimen? On closer examination, it is clear that not all studies were comparable to each other because the concentrations of glucose and insulin used in those studies were not uniform [45–51]. Studies in which higher concentrations of insulin were used showed better results than did those studies that employed a lesser dose. For instance, studies in which 33% glucose with 120 units of insulin [46] or 30% glucose with 300 units of insulin [47] was used yielded positive results. In contrast, the results reported by those studies that employed a lower dose (Bruemmer-Smith and coworkers [49] used 500 ml of 5% dextrose with 100 units of insulin, and Rao and colleagues [50] supplemented the cardioplegic solution with 10 units/l insulin) were less favorable. This is supported by the observation that stress hyperglycemia or even mild hyperglycemia with myocardial infarction is associated with increased mortality [7] and that intensive insulin treatment to maintain blood glucose levels between 80 and 110 mg/dl is highly beneficial and reduces morbidity and mortality among critically ill patients [5]. It is possible that the negative results obtained with GIK [49–51] were due to the low dose of insulin used; this invariably resulted in hyperglycemia, which is detrimental to the myocardium.

It has been known for several years that continuous intravenous infusion of insulin is superior to subcutaneous administration in terms of glycemic control, especially in patients with diabetes during the perioperative and postoperative periods [52]. During both the infusion period and the entire observation period (day of operation, and first and second postoperative days), GIK regimen resulted in lower blood glucose levels within the intended range of 90–180 mg/dl (5–10 mmol/l) as compared with conventional subcutaneous insulin administration. Improved diabetic control is believed to result in fewer wound infections and better wound healing. However, this view may be too simplistic. The beneficial effects of GIK regimen may extend beyond control of hyperglycemia alone [16,17]. As demonstrated recently [32,53], GIK infusion may salvage myocardium, improve cardiac function, and decrease mortality by an absolute 10%, provided that hyperglycemia is prevented. There is reasonable evidence to suggest that this beneficial effect may be independent of glucose [54–56].

These results are supplemented by those of a large trial conducted in a heterogeneous group of 1548 critically ill patients [5]. In that trial, intensive insulin therapy to avoid hyperglycemia (blood glucose was maintained below 110 mg/dl) in predominantly nondiabetic patients led to a decrease in morbidity and mortality as compared with less intensively treated patients (blood glucose maintained between 180 and 200 mg/dl). Those findings suggest that maintaining blood glucose concentrations at 110 mg/dl or less is critical in obtaining the benefits of insulin administration. This is supported by the observation that cardiac dysfunction induced by endotoxin administration was not related to arterial blood glucose concentrations [57,58]. Furthermore, infusions of insulin reversed cardiac failure and maintained normal performance in spite of wide ranges in glucose concentrations (5–120 mg/dl), suggesting that myocardial dysfunction is not precipitated or induced by the hypoglycemia of endotoxin shock.

The ability of insulin to improve myocardial performance may be related to its capacity to suppress TNF-α, MIF, and superoxide anion generation [13,16,17,59]. Therapeutic administration of high doses of insulin results in an accumulation of myocardial glycogen stores and improvement in glucose utilization. This leads to augmented myocardial adenosine triphosphate provision and maintains cellular energy charge during coronary ischemia, resulting in better tolerance to ischemia and improved myocardial protection [60].

Conclusion

It is evident from the preceding discussion that hyperglycemia is harmful whereas insulin treatment is beneficial. Even mild hyperglycemia is associated with poor neurologic outcome after brain injury and stroke [61], and burns or surgery in humans [62,63]. Animal studies revealed that hyperglycemia aggravates endotoxin shock and that insulin treatment decreases mortality [64]. What are the potential mechanisms by which insulin is able to bring about its beneficial actions?

Apart from its ability to lower blood glucose and to inhibit production of potentially dangerous proinflammatory cytokines (i.e. TNF-α, MIF, and superoxide anion), insulin has the following actions: it stimulates glucose uptake/glycolysis, pyruvate dehydrogenase and energy production; it increases muscle protein synthesis; it inhibits apoptosis and improves repair of damaged tissues; it promotes ischemic preconditioning and lessens ischemia/reperfusion damage (for review [59]); and it exhibits anti-inflammatory actions [16,17,65]. Because hyperglycemia induces apoptosis of myocardial cells [66], strict control of blood glucose is essential to preserve cardiac function both in diabetic and nondiabetic persons with stress hyperglycemia.

The ability of insulin to enhance endothelial NO synthesis is particularly significant when one considers its beneficial

action in AMI, stroke, and critical illness [16,17,59]. Recent studies [67–69] suggested that administration of L-arginine (the precursor of NO) improves postischemic recovery of endothelial and vascular smooth muscle functions after cold cardioplegic arrest, and enhances cardioprotection and postischemic functional recovery and reduces infarct size of the myocardium. Hence, some of the beneficial actions of insulin (and therefore those of the GIK regimen) in various conditions could be attributable to an increase in endothelial NO synthesis [16,44].

In summary, GIK regimen is useful in preserving the myocardium in septicemia and septic shock, and in patients with severe burn injury [16,17], provided that blood glucose levels are maintained at 110 mg/dl or below by employing an adequate insulin dose. Thus, insulin when present in appropriate amounts preserves myocardial integrity and function.

Competing interests

None declared.

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