Cardioprotective Effects of Insulin
How Intensive Insulin Therapy May Benefit Cardiac Surgery Patients

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Interest in the effects of insulin on the heart came with the recognition that hyperglycemia in the context of myocardial infarction is associated with increased risks of mortality, congestive heart failure, or cardiogenic shock.\textsuperscript{1,2} More recently, instigated by research findings on stress hyperglycemia in critical illness, this interest has been extended to the influence of insulin on clinical outcome after cardiac surgery. Even in nondiabetic individuals, stress hyperglycemia commonly occurs as a key metabolic response to critical illness, eg, after surgical trauma. It is recognized as a major pathophysiological feature of organ dysfunction in the critically ill. The condition stems from insulin resistance brought about by dysregulation of key homeostatic processes, which implicates immune/inflammatory, endocrine, and metabolic pathways.\textsuperscript{3} It has been associated with adverse clinical outcomes, including increased mortality, increased duration of mechanical ventilation, increased intensive care unit (ICU) and hospital stay, and increased risk of infection.\textsuperscript{5,6,8}

Hyperglycemia in critical illness is managed with exogenous insulin as standard treatment; however, there is considerable disagreement among experts in the field as to what target blood glucose level is optimal for the critically ill patient. Conventionally, the aim of insulin therapy has been to maintain blood glucose levels below the renal threshold, typically 220 mg/dL (12.2 mmol/L). In recent years, some have advocated tight glycemic control (TGC) with intensive insulin therapy (IIT) to normalize blood glucose levels to within the euglycemic range, typically 80 to 110 mg/dL (4.4−6.1 mmol/L).

Current evidence on the applicability of TGC to critical illness in general is inconclusive. Although early studies showed that IIT reduced mortality and morbidity in the ICU,\textsuperscript{9,10} more recent systematic studies and meta-analyses have largely failed to support some or all of these findings, with some suggesting that IIT may increase the risk of hypoglycemia.\textsuperscript{11} These differences in outcomes may be ascribed in part to differences in study design, including insulin administration protocol, target glycemic level, method of blood glucose measurement, and patient feeding. Alternatively, they may indicate that TGC may not be equally beneficial in all manner of critical illnesses, such that the heterogeneity of the study populations has made identification of outcome benefits difficult. Indeed, a meta-analysis of 26 studies has suggested that TGC appears to benefit surgical ICU patients but not those in medical ICU or mixed ICU settings.\textsuperscript{12} The present review focuses on the benefits that cardiac surgery patients may derive from TGC/IIT.

Evidence That Intensive Insulin Therapy Is Beneficial in the Context of Cardiac Surgery

Studies on TGC/IIT specific to the setting of cardiac surgery are limited in number and have varied greatly in methodology. Nevertheless, a recent meta-analysis of 7 randomized controlled trials concluded that TGC during or after cardiac surgery reduced mortality in the ICU (odds ratio 0.52, 95% confidence interval 0.30−0.91), postsurgical atrial fibrillation (AF; odds ratio 0.76, 95% confidence interval 0.58−0.99), use of epicardial pacing (odds ratio 0.28, 95% confidence interval 0.15−0.54), duration of mechanical ventilation (mean difference −3.69, 95% confidence interval −3.85 to −3.54), and length of stay in the ICU (mean difference −0.57, 95% confidence interval −0.60 to −0.55).\textsuperscript{14}

A significant number of studies, including 2 of the largest randomized controlled trials on TGC/IIT in critical illness (single-center Leuven study\textsuperscript{9} and the multicenter Normoglycaemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation [NICE-SUGAR] study\textsuperscript{15}), were excluded from the meta-analysis because they included noncardiac surgery patients. However, subgroup analysis for cardiac surgical patients was made available by some authors. In the Leuven study, in which 60% of the study population were cardiac surgical patients, subgroup analysis has revealed a particularly strong beneficial effect of IIT, with ICU and hospital mortality reduced by 60% and 56%, respectively, reduced duration of mechanical ventilation, reduced length of ICU/hospital stay, reduced inflammation, and lower risks of acute renal failure and acute illness polyneuropathy.\textsuperscript{16} Moreover, in the pediatric population, 75% of the 700 critically ill children included in another study, which demonstrated significantly reduced pediatric ICU stay and attenuated inflammation with IIT, underwent cardiac surgery.\textsuperscript{17}
with this, an association between perioperative hyperglycemia and poor clinical outcome has also been reported in adult and pediatric cardiac surgery patients.\textsuperscript{18,19}

The increased mortality seen with stress hyperglycemia has been ascribed to unresolved secondary complications, such as multiple organ failure or sepsis, rather than worsening of the primary illness.\textsuperscript{20} It has also been suggested that the outcome benefits of TGC/IIT, where observed, were largely attributable to the glycemic effects of insulin, but the relative importance of the glycemic and nonglycemic effects of insulin may be organ specific.\textsuperscript{21} The benefits seen in cardiac surgery patients suggest that a cardiac-specific mechanism may contribute toward improved clinical outcome in this patient group. To rationalize how IIT may improve clinical outcome for cardiac surgery patients, we review insulin signaling pathways and the cardioprotective effects of insulin in the following sections. These are summarized in Figure 1.

**Insulin Signaling Pathways**

Insulin is a pleiotropic hormone with various effects on glucose metabolism, the central nervous system, immune system, and cardiovascular system. It signals via the phosphatidylinositol 3-kinase (PI3K) pathway, the E3 ubiquitin-protein ligase CBL (Cbl)/Cbl-associated protein (CAP) pathway, and the mitogen-activated protein kinase pathway. The primary cardioprotective action of insulin is thought to occur through upregulation of components of both the PI3K and mitogen-activated protein kinase pathways, which are sometimes collectively referred to as the reperfusion injury salvage kinase (RISK) pathway.\textsuperscript{22}

Classic insulin signaling in glucose metabolism occurs via the PI3K pathway. The binding of insulin to insulin receptor kinases activates the insulin receptor substrate. This leads to the association of the insulin receptor substrate with PI3K, which in turn activates a number of downstream effectors, including Akt (alternatively known as protein kinase B), protein kinase C, and the mammalian target of rapamycin (mTOR). Activation of Akt and protein kinase C results in the translocation of the intracellular glucose transporter 4 (GLUT4) protein to the plasma membrane, which enhances peripheral glucose uptake, whereas mTOR activation promotes lipogenesis and protein synthesis.\textsuperscript{23,24} GLUT4 translocation to the plasma membrane is also instigated by the activation of the Cbl/CAP pathway. In cardiac and skeletal muscles, signaling via the Cbl/CAP pathway is achieved by the insulin-induced phosphorylation of Cbl and is compromised in both insulin resistance and insulin insufficiency.\textsuperscript{25,26} Meanwhile, Akt activation promotes glycogen synthesis by inhibiting glycogen synthase kinase-3, the enzyme that phosphorylates (and hence inactivates) glycogen synthase. The mitogen-activated protein kinase pathway is mitogenic and leads to protein synthesis.\textsuperscript{27}

The reperfusion injury salvage kinase pathway is responsible for mitigating reperfusion injury after cardiac ischemia. It can be particularly relevant in the context of cardiac surgery that may require aortic cross-clamping, a procedure that results in ischemia-reperfusion of the myocardium. The reperfusion injury salvage kinase pathway incorporates the so-called prosurvival kinases from the PI3K-Akt and the extracellular signal-regulated kinase 1 and 2 cascades and is universally mediated by a range of factors, including insulin and insulin-like growth factor-1, as well as ischemic preconditioning and postconditioning.\textsuperscript{22} The cardioprotective role of PI3K-Akt activation has been demonstrated in a number of studies. Transplantation of Akt-enriched mesenchymal stem cells into infarcted rat hearts limited infarct size and improved cardiac function in a manner dependent on the number of cells injected.\textsuperscript{28} Similarly, constitutive activation of Akt more than halved the infarct size and reduced apoptosis by up to 84% in a transgenic rat model of ischemia-reperfusion,\textsuperscript{29} and it enhanced myocardial contractility in transgenic mice.\textsuperscript{30} Activation of the mitogen-activated protein kinase pathway also has been shown to inhibit DNA damage and apoptosis.\textsuperscript{31}

**Cardioprotective Effects of Insulin**

In 1962, Sodi-Pallares et al\textsuperscript{32} introduced the glucose-insulin-potassium (GIK) infusion for the treatment of acute myocardial infarction. Since then, the effect of GIK on the heart has been studied extensively. Insulin is recognized as the central component of the GIK cocktail; glucose and potassium are
added to adjust for the secondary effects of glycemic alteration and hypokalemia caused by simultaneous cellular uptake of potassium with glucose. Although evidence for the clinical benefit of GIK has been mixed,33–37 many cardioprotective effects of insulin have been identified (Figure 2).

Counteracting Glucose Toxicity

Hyperglycemia leads to glucose toxicity by increasing oxidative stress, flux via the hexosamine pathway, and levels of advanced glycation end products, which are detrimental to the heart.38 In humans, hyperglycemia has been identified as an independent risk factor for ischemic heart disease and correlates with poor prognosis after acute myocardial infarction.1,39 Perioperative hyperglycemia has also been associated with increased mortality and morbidity in pediatric and adult patients undergoing cardiac surgery.18,19

Hyperglycemia may have a prothrombotic effect that augments inflammation.40 It has also long been known that hyperglycemia promotes free radical generation and oxidative stress in diabetes mellitus.41 In turn, reactive oxygen species may induce insulin resistance42 and hence perpetuate the hyperglycemia. Oxidative stress damages mitochondrial DNA and vital cellular proteins, which leads to mitochondrial dysfunction in cardiovascular disease and the metabolic syndrome.43,44 Evidence derived from diabetic patients suggests that oxidative stress may also result from increased NADPH oxidase activity. NADPH oxidase generates superoxides from intracellular NADPH.45 Elevated myocardial NADPH oxidase activity has been linked to cardiac failure.46 Oxidative stress is also closely associated with inflammation, apoptosis, and vascular dysfunction.47

In cardiomyocytes, hyperglycemia induces apoptosis and aggravates ischemia-reperfusion injury in cultured human and mouse cardiomyocytes.48–52 In cultured rat cardiomyocytes, it reduces intercellular contact and inhibits the formation of myofibrils via an oxidative mechanism.53 Importantly, the cardioprotective effects of ischemic and anesthetic preconditioning or postconditioning are negated by coexistent hyperglycemia in animal models.54–57 In aortic endothelium, hyperglycemia inhibits the cardioprotective effects of endothelial nitric oxide synthase (eNOS), the enzyme responsible for nitric oxide (NO) production, mediated via the PI3K-Akt cascade.58 Normalization of blood glucose levels with insulin may temper many of the damaging effects to the heart associated with hyperglycemia.

Positive Inotropic Effect

Visscher et al59 demonstrated that insulin increased cardiac contractility in isolated heart-lung preparations and increased arterial blood pressure in live animals. Others have later shown that in animal models and in isolated human myocardia, insulin possesses a direct positive inotropic effect that is independent of its modulation of glucose metabolism,60–63 although the effect may be species specific. The underlying mechanisms of insulin-induced positive inotropy remain incompletely understood. Using failing myocardia from heart failure patients, Lewinski et al64 reported that the positive inotropic effect of insulin was mediated by elevated intracellular Ca2+ concentrations. Compared with Ca2+ administration, insulin was associated with a greater increase in contractile force per unit increase in intracellular Ca2+ levels. Thus, insulin appears to sensitize cardiac muscles to the effects of intracellular Ca2+. Interestingly, in the
presence of 11.2 mmol/L glucose (ie, under hyperglycemic conditions), the increase in contractile force was correlated with insulin dose. With the inhibition of glycolysis, the dose dependence was abrogated, although significant positive inotropy was still observed.

In addition, insulin induces the phosphorylation of heat shock protein 27. Heat shock protein 27 has been shown to associate with actin microfilaments in adult cardiomyocytes and possibly plays an important role in maintaining the structure and function of the cells.65 Phosphorylated heat shock protein 27 is associated with improved myocardial contractility after ischemia-reperfusion injury.66

**Antioxidant Effect**

Impaired insulin signaling has been implicated in elevated oxidative stress and mitochondrial dysfunction in the murine heart.67 Insulin can prevent oxidative damage by reducing the formation of peroxynitrite (ONOO -) free radicals via the PI3K-Akt pathway after myocardial ischemia and reperfusion in the rat.68 In diabetic rat hearts, insulin restores the activity of glutathione peroxidase, a key antioxidant enzyme, correspondingly reduces the toxic process of lipid peroxidation, and increases eNOS expression.69,70

In humans, administration of the GIK cocktail during percutaneous coronary intervention has been reported to attenuate the increase in the activity of antioxidant enzymes (including superoxide dismutase, catalase, and glutathione peroxidase) in the myocardium otherwise seen in control subjects given isotonic saline infusion.71 Although the authors suggest that this reflects an association between GIK treatment and lower oxidative stress, the extent of oxidative stress was not directly compared between the groups, nor were the implications of the lower antioxidant enzyme activity on oxidative damage investigated.

**Antiapoptotic Effect**

One of the most studied modes of cardioprotection by insulin is the aversion of apoptotic cell death in the context of ischemia-reperfusion. In a rabbit model of ischemia-reperfusion, a high concentration (33 mmol/L) of glucose significantly increases both the infarct size and the proportion of apoptotic cardiac myocytes on reperfusion, whereas both parameters are normalized by the addition of insulin.72 Similarly, in the rat, insulin not only reduces the infarct size, plasma creatine kinase and lactate dehydrogenase (both markers of myocardial injury), and apoptosis (measured by the proportion of apoptotic cells and caspase 3 activity) 24 hours after ischemia, but it better preserves the structure and function of cardiac tissues 4 weeks afterward.73

The antiapoptotic effect of insulin is attributed to insulin signaling via the reperfusion injury salvage kinase pathway. Central to this effect are the mitochondrion and hexokinase. The translocation and binding of intracellular hexokinase to mitochondrial membranes is thought to lead to a number of antiapoptotic events. First, it suppresses free radical generation and hence reduces oxidative damage to the cell.74 Second, it inhibits the release of cytochrome c, which recruits caspases to promote cell death, from the mitochondrion into the cytosol.75 Third, it may prevent the opening of mitochondrial permeability transition pores. Dissociation of hexokinase from the mitochondrion causes the mitochondrial permeability transition pores to open,76 which greatly increases the permeability of the mitochondrial membrane, which leads to mitochondrial swelling and apoptosis.77 Hexokinase binding to mitochondria is mediated by Akt, and the activation of the PI3K-Akt cascade by insulin has been shown to inhibit the opening of mitochondrial permeability transition pores in rat cardiomyocytes.78 Because hexokinase translocation to mitochondria is induced both by insulin and by ischemic stimulation in the rat heart, it has been suggested that insulin may protect the human heart by averting apoptosis through mitochondrial hexokinase translocation in a manner similar to ischemic preconditioning.79 In relation to this, NO has been demonstrated to inactivate caspases in the mitochondrial apoptotic pathway.80 Upregulation of eNOS and NO by insulin may therefore inhibit apoptosis. In cultured rat cardiomyocytes, the activation of Akt by insulin also promotes the phosphorylation (and hence inactivation) of the proapoptotic protein, Bad.81

**Anti-Inflammatory Effect**

Hyperglycemia is proinflammatory, whereas insulin is anti-inflammatory.82 The anti-inflammatory effects of insulin are intimately linked to its antioxidant effects. In human subjects, acute hyperglycemia raises plasma levels of proinflammatory cytokines, including interleukin-6, interleukin-18, and tumor necrosis factor-α, an effect that is abrogated by glutathione administration and thus suggestive of an oxidative mechanism.83

In addition to limiting the proinflammatory effects of hyperglycemia, insulin exerts some direct anti-inflammatory effects. For instance, it inhibits interleukin-6 signaling via the mitogen-activated protein kinase pathway.84 Insulin also inhibits c-Jun N-terminal kinase (JNK), which mediates the proinflammatory effects downstream of tumor necrosis factor-α, via the mTOR pathway.85 In myocardial ischemia-reperfusion, insulin suppresses tumor necrosis factor-α through PI3K-Akt–mediated eNOS activation and NO production, which in turn reduce apoptosis in cardiomyocytes.86 Meanwhile, insulin inhibits nuclear factor-κ light chain enhancer of activated B cells (nuclear factor-κB) activity in the human aortic endothelium.87 Because a wide range of inducers of inflammation converge on nuclear factor-κB activation, insulin has the potential to avert a range of proinflammatory events. Additionally, inhibition of nuclear factor-κB may improve cardiac function independently of suppressing inflammation.88 Insulin has also been demonstrated to inhibit leukocyte adherence to the endothelium, in a manner dependent on Akt activation and downstream NO production.89 This is thought to prevent leukocyte accumulation in the myocardium and attenuate inflammation.

**Vascular Effects**

Insulin has been reported to cause coronary dilation and raise myocardial blood flow in dogs.90 In humans, insulin increased coronary sinus and myocardial blood flow and
reduced coronary resistance.91–93 Insulin-induced coronary vasodilation is related to NO production.94 Insulin facilitates endothelial production of NO by upregulating the expression of eNOS via the PI3K-Akt pathway, without inducing inducible NO synthase.95,96 In vitro studies using cocultures of endothelial cells and cardiomyocytes have suggested that endothelial cells are a paracrine source of NO, which protects cardiomyocytes from ischemia-reperfusion injury.97 The activation of eNOS and enhanced NO production have vasodilating effects, as well as antiapoptotic and positive inotropic effects.98,99

Additionally, the suppression of inducible NO synthase, albeit not specifically in the myocardium, has been suggested as the mechanism responsible for the protection of the vascular endothelium in the Leuven study.100 The analysis of liver and skeletal muscle biopsy samples from nonsurvivors revealed a significantly lower level of inducible NO synthase mRNA expression that concurred with lower levels of adhesion molecules, including intercellular adhesion module-1 and E-selectin, which facilitate leukocyte rolling in endothelium activation, in the IIT group.100

**Other Putative Effects**

A recent meta-analysis has concluded that TGC during or after cardiac surgery reduced the incidence of AF and the use of epicardial pacing.14 Meanwhile, diabetes mellitus is associated with an increased risk of AF.101 Whether insulin resistance leads to AF remains debatable.102 Although a positive effect of insulin on cardiac rhythm remains to be demonstrated empirically, a possible effect can be suggested on the basis of a study whereby PI3K activation was decreased in atrial appendages of AF patients and in a transgenic mouse model of AF, whereas enhanced PI3K activation in cross-bred transgenic mice reduced atrial fibrosis and PR intervals on the ECG.103 Atrial fibrosis and prolonged PR intervals both increase susceptibility to AF.104,105 PI3K activation by insulin may therefore avert AF and improve cardiac rhythm.

In addition, insulin may modulate AF by facilitating K⁺ uptake in the myocardium, which may help restore sinus rhythm and stabilize the myocardium.14 This hypothesis is in agreement with the reduced need for pericardial pacing identified in the meta-analysis.14 The enhancement of K⁺ uptake into tissues by insulin occurs independent of glucose uptake, and the rate of K⁺ uptake in diabetic subjects has been shown to be similar to that in healthy control subjects.106 However, a separate meta-analysis investigating the effect of perioperative GIK infusion on mortality and AF after coronary artery bypass grafting found no significant reduction in AF by perioperative GIK infusion,96 and insulin cardioplegia did not decrease the incidence of postoperative arrhythmias compared with placebo in another study.107

**Conclusions**

Insulin exerts cardioprotective effects via glucose-dependent and -independent mechanisms, including aversion of glucose toxicity; positive inotropy; the interrelated modulation of oxidative stress, inflammation, and apoptosis; and regulation of blood flow. These effects may account for the clinical benefits of IIT observed in cardiac surgery patients. Although there is no direct evidence yet that IIT confers cardioprotection, and indeed, the evidence on the clinical benefits of IIT in cardiac surgery is noteworthy but by no means conclusive, this discussion ought to provide the impetus and direction for future research into the potential benefits of IIT and the mechanism of any protection in cardiac surgery patients. Such studies may also provide valuable input into ascertaining the value of IIT in critical illness and identifying those patient groups who may benefit particularly from such treatment.

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