Glucose-Insulin-Potassium
Much More Than Enriched Myocardial Fuel
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As in many other medical specialties, cardiac surgery is exploring its boundaries. The patient population scheduled for cardiac surgery is aging, and the surgical procedures are becoming more complex, leading to significant comorbidity. In addition, the myocardium is often poorly functioning; cardiac remodeling resulting from myocardial ischemic events or longstanding volume and/or pressure overload often results in low ejection fractions and increases the risk of low cardiac output in the early postoperative period of cardiac surgery. One example is aortic valve replacement for critical aortic stenosis with significant left ventricular hypertrophy. Many techniques aiming to optimize myocardial protection are used with variable success. Composition, temperature, and delivery route of cardioplegia are still matters of debate among cardiac surgeons; pharmacological interventions and the use of biocompatible materials to modulate the inflammatory response, evoked by surgery and cardiopulmonary bypass, are part of ongoing research projects. Interventions aiming to reduce the ischemia/reperfusion injury face difficulty translating their promising results from experimental settings into daily clinical practice; thus, the search for simple, inexpensive techniques to improve myocardial protection and outcome continues.

Metabolic intervention made up of glucose-insulin-potassium (GIK) began in cardiology and cardiac surgery two decades ago. Despite intensive research during this time, GIK remained a controversial and doubtful cardioprotective intervention. Initially, GIK was mainly considered an antiarrhythmic solution, reducing the incidence of cardiac rhythm disorders in ischemic hearts, and a metabolic cocktail, fueling the heart with an energy-saving substrate and increasing myocardial oxygen efficiency. Suppression of lipolysis, reduction of free fatty acid levels, and enhancement of glucose influx into the myocardium rendered cardiac metabolism more efficient, which was particularly important in ischemic myocardial tissue. Later, the properties of insulin as a signal for activation of survival pathways, as a suppressor of myocardial apoptosis in the setting of myocardial ischemia/reperfusion injury, and as a modulator of inflammation came into focus. More recent data suggest that tight glycemic control with intensive insulin therapy significantly reduces morbidity and mortality in cardiac surgical patients, and this effect is maintained for at least 4 years after the intervention.

In this issue of Circulation, Howell et al report on the results of the Hypertrophy, Insulin, Glucose and Electrolytes (HINGE) trial. More than 200 patients with critical aortic stenosis and significant left ventricular hypertrophy were randomly assigned to placebo or GIK in addition to standard myocardial protection. GIK treatment was associated with a significant reduction in the incidence of low cardiac output syndrome, with a significant reduction in the use of inotropes in the early postoperative period, and with an increased need for vasoconstrictors. Furthermore, the authors demonstrated a substantial increase in myocardial 5′ adenosine monophosphate-activated protein kinase and serine/threonine protein kinase Akt phosphorylation in left ventricular biopsies, as well as a significant increase in O-linked β-N-acetylgalcosamidation (O-GlcNAcylation) of selected protein bands, at least partially explaining the beneficial effects of GIK.

In contrast to previous trials studying the effects of GIK, the authors demonstrated a significant beneficial effect of GIK therapy. One explanation for this positive trial result is the inclusion of a very homogeneous patient population with a well-known risk for low cardiac output syndrome (critical aortic stenosis and severe left ventricular hypertrophy). An important merit of the HINGE trial is that, apart from looking at straightforward clinical outcome parameters, the authors also explored some of the potential molecular mechanisms explaining the effect of GIK, as previously reported in various animal and few clinical experiments.

Insulin, probably the most important component of GIK, exerts its effect via the phosphatidylinositol-3-kinase–AKT–endothelial nitric oxide synthase signaling pathway. As a result, the generated nitric oxide protects the myocardium. Indeed, insulin, given at the time of myocardial reperfusion in animal models, has been shown to reduce myocardial ischemia/reperfusion injury, partially via attenuation of apoptosis. This antiapoptotic effect of insulin in ischemia/reperfusion is mediated via phosphatidylinositol-3-kinase, the subsequent phosphorylation of endothelial nitric oxide synthase, and the concurrent local increase in nitric oxide production. Because there was no difference in troponin release between the 2 groups in the HINGE trial and no difference in the degree of myocardial necrosis, the significant reduction in low cardiac output syndrome can be explained by a reduction in posts ischemic myocardial stunning, which is consistent with the reported experimental data. Moreover, animal experiments...
clearly demonstrated that hyperglycemia, present at the time of myocardial reperfusion, blunts or abolishes the cardioprotective effects of insulin. In this regard, the HINGE investigators missed a unique opportunity to demonstrate in a standardized clinical situation the additional effects of insulin and tight glycemic control on both clinical outcome parameters and the underlying mechanisms. Indeed, many GIK trials in patients with acute myocardial infarction failed to demonstrate a protective effect because of the concurrent hyperglycemia caused by the high dose of glucose infusion and insulin resistance.

Insulin not only provides myocardial protection through its effect on the PI3-kinase–Akt–endothelial nitric oxide synthase signaling pathway but also exerts an antiinflammatory effect. We recently demonstrated a significant effect of GIK in combination with tight glycemic control on the release of C-reactive protein and the proinflammatory cytokines interleukin-6 and interleukin-8 in neonates undergoing congenital heart surgery. In the reported HINGE trial, the authors did not investigate the effects of GIK on the inflammatory response evoked by surgery and cardiopulmonary bypass. One can only speculate that the reported beneficial effects on outcome can be partially explained by modulation of the inflammatory response. Undoubtedly, this issue needs to be investigated in future trials.

Finally, the authors lift a part of the veil regarding the role of GIK in a posttranslational modification process of proteins by O-linked β-N-acetylglucosamine (O-GlcNAc). The concept and hypothesis of enhanced O-GlcNAcylation of proteins involved in the cardioprotective effects of GIK are based on the experimental findings that acutely increasing the presence of O-GlcNAc levels on intracellular proteins is related to enhanced cell survival and that increased O-GlcNAc levels could represent an endogenous recruitable mechanism of cardioprotection.10 In experiments with mouse hearts, for example, pharmacological augmentation of O-GlcNAc levels was associated with improved cardiomyocyte survival. In contrast, however, increased levels of O-GlcNAc have been implicated in the pathogenesis of cardiovascular complications of diabetic patients. In the HINGE trial, O-GlcNAcylation of proteins in left ventricular biopsies was more prominent in the GIK-treated patients. One could speculate that during short-term GIK treatment, insulin increases intracellular glucose influx, acutely increases O-GlcNAcylation of proteins, and contributes to the myocardial protective effect of GIK. This potential mechanism needs to be elucidated in future experiments and clinical trials.

The HINGE trial puts GIK in the spotlight of cardiovascular research again, but the observed underlying mechanisms definitely need confirmation from large multicenter trials in different patient populations at risk for low cardiac output syndrome. Not only should clearly defined clinical outcome parameters be measured, but also the different proposed underlying mechanisms involved in myocardial protection and cell survival should be assessed. Furthermore, the effects of insulin with or without tight glycemic control should be addressed. My hope is that the results of future well-designed clinical trials will elucidate the precise role of GIK in cardiovascular medicine, >45 years after the introduction of this simple, cheap, and intriguing therapeutic strategy.

Disclosures

None.

References


Key Words: Editorials acute cardiac care glucose insulin myocardial stunning surgery
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*Circulation*. 2011;123:129-130; originally published online January 3, 2011;
doi: 10.1161/CIRCULATIONAHA.110.002709

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/123/2/129

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