SPECIAL ARTICLE

The Glucose-Insulin-Potassium (GIK) Regimen in the Treatment of Myocardial Ischemia

By Norman Brachfeld, M.D.

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In 1959 Selye\(^1\) reported that myocardial resistance to cardiotoxic agents was reduced by intracellular hypokalemia and hypomagnesemia. Resistance was regained when this ionic imbalance was restored.

Obstruction of a coronary artery inevitably causes a heterogeneous mixture of normal well-oxygenated, ischemically injured, and dead cells. This zone is biochemically and electrically unstable. Its progressively changing proportions are determined by many factors including the location of the site of vascular insufficiency, the magnitude of the collateral circulation, the condition of the cell prior to injury, the level of endogenous glycogen stores, and possibly by successful therapeutic intervention. Early ischemic changes are potentially reversible. Survival and recovery of normal function has been demonstrated despite total cessation of flow for periods of 20 to 60 min. The metabolic behavior of this zone of ischemia (the sick cell) most often determines the clinical course of the patient.

Creatine phosphate (CP) and adenosine triphosphate (ATP) concentration fall rapidly after the onset of ischemia. There is an increase in intracellular adenosine diphosphate and inorganic phosphate (Pi), the latter diffusing through the plasma membrane. Metabolic feedback controls permit an enhancement of anaerobic glycolysis supported by an increase in glucose transport and phosphorylation and in glycogenolysis. Glycogen depletion begins almost immediately. There is a shift of glycolytic intermediates to a reduced redox state, a fall in lactate extraction and an increase in intracellular a-glycero-phosphate and lactate production.

The enzymic capacity of the glycolytic pathway in the mammalian heart is theoretically capable of supplying sufficient energy for normal stroke work. It can do so in the reptile but as yet unknown factors restrict mammalian glycolytic energy production to from 12% to 15% of total requirements. Glycolytic activity is near maximal in the ischemic cell during normoglycemia. Near maximal rates have been demonstrated at very low external glucose concentrations and little change in glucose uptake was seen when concentration was increased above 50 mg% in the presence of insulin.\(^2\) Thus significant enhancement of energy production by this pathway is probably unresponsive to stimulation by an increase in circulating glucose concentration. Optimal anaerobic energy production cannot meet the ATP requirements of the normally contracting myocardium.

Furthermore, anaerobic glycolysis is not an unmixed blessing. The accompanying increase in intracellular lactate and other acidic metabolic end products gradually exceeds the poor intrinsic buffering capacity of the myocardial cell, with a resultant fall in pH. Cellular acidosis progressively inhibits phosphofructokinase (PFK) activity and depresses glycolytic potential. Myocardium has proven extremely sensitive to such changes, and unless checked, they may ultimately prove lethal.\(^3\) A decrease in intracellular pH alone may reproduce most of the hemodynamic responses to ischemia despite normal tissue oxygenation. Thus cellular acidosis per se rather than the decrease in tissue PO\(_2\) may be responsible for the immediate hemodynamic response to ischemia.

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From the New York Hospital-Cornell Medical Center, New York, New York.

Address for reprints: Norman Brachfeld, M.D., The New York Hospital-Cornell Medical Center, 525 East 68th Street, New York, New York 10021.
The accompanying editorial by Dr. Leaf reviews the possible role of cell swelling in ischemic tissue damage. When myocardial hypoxia is severe or prolonged, autolytic breakdown of protein may lead to accumulation of additional osmotically-active molecules. Swelling and the development of a palpable firmness of the ventricular wall follows. High membrane tensions reduce cell pliability and mobility and undoubtedly contribute to a depression of contractility. Transitory ischemia may induce a persistent reduction in tissue perfusion. This "secondary" ischemia may potentiate the adverse effects of capillary endothelial swelling and contribute to the "no-reflow" phenomenon. Thus ischemia may beget further ischemia and impede both substrate and oxygen flux. Dilution of intracellular calcium may further depress the normal inotropic response to this ion already burdened by competition with H+ ions for contractile-binding sites.

Potassium egress following ischemia has been described in the human and in the experimental animal. It is a response to and not the cause of the biochemical lesion. Indeed, biochemical and histological lesions associated with well-oxygenated but hypokalemic cells are quite distinct from those discussed in the present context. Although efflux of potassium is reflected by negative arteriovenous differences, the specific pathways of this flux are unknown. Shifts in potassium between the intracellular and extracellular space may have significant electrical and hemodynamic sequelae. Leakage of potassium from injured cells increases its concentration in the extracellular fluid bathing the plasma membrane of adjacent normal cells. The resultant membrane hypopolarization and decrease in transmembrane resting potential may be responsible for ST-segment shifts in the electrocardiogram, and may potentiate the production of ectopic foci and potentially lethal dysrhythmias.

Sodi-Pallares et al., Larcan and others described a regimen for the early treatment of myocardial ischemia which consists of dietary regulation of sodium, potassium, and water intake and an intravenous infusion of 10% glucose containing 40 mEq of KCl, 20 units of regular insulin, and 10 mg of Heparin (Sodi-Pallares) or dibasic potassium phosphate, K+ and Mg2+ Aspartate, Heparin, Co-carboxylase and cytochrome-C (Larcan). Volume, duration, and rate of administration are determined by the severity of the episode and by serum potassium and glucose concentrations. Treatment was reported to decrease the frequency, duration, and severity of angina pectoris, dysrhythmias, congestive heart failure, fever, and shock. Electrocardiographic changes rapidly disappeared, contractility was enhanced, cellular metabolism returned to normal, and disturbances in intracellular water, sodium, and potassium balance were corrected.

Response to this therapy was attributed to a restoration of intracellular potassium concentration mediated by insulin stimulation of glucose transport. The impatient advocacy of its proponents provided an enthusiastic and hopeful reception to the idea of introducing "polarizing solutions," despite the lack of a convincing rationale for their use. Controlled clinical trials lacked comparability because of variations in criteria for patient selection. Data describing administration, metabolic, hemodynamic, and electrocardiographic controls were incomplete, and concurrent therapy and subgroup analysis of data were either inadequately reported or differed markedly within and/or between studies. Patient study populations varied from 13 to 986 subjects and rarely adhered to the regimen as described by its originator. Results of clinical trials have in general proven disappointing. Mittra reported one of the few large affirmative clinical studies. There was "spectacular improvement" in 370 trial and post trial patient evaluations. Unexplained is the fact that the reduction of a high control mortality of 37% to 9.7% was limited to males. In a study by Pilcher et al. a control group mortality of 41% in patients over 60 years of age was reduced to 13% with no change in the low control mortality of a younger patient population. Subgroup analysis of mortality based on severity of the clinical state was not presented in either study. Some perspective is gained when we consider that hospital mortality in most coronary care facilities for class I patients is approximately 6% and for class II patients about 17%.

A large multicenter controlled clinical trial of 13 hospitals and 986 patients conducted by the Medical Research Council of Great Britain employed a similar regimen as did a study reported by Pentecost. Routine monitoring was performed in only two centers. There was no significant difference in mean mortality between control and treated groups. Nevertheless, there was a significant variation in mortality between centers which variously reported figures of 12.2% to 35.4% for the control series and 9.7% to 33.7% for the GIK-treated group.

If one makes the disputable assumption that systemically-administered GIK actually does reach
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The ischemic zone of myocardium, it is difficult to understand why the solutions have proven ineffective when given by direct intracoronary infusion. A systemic response to the volume of fluid infused, its osmolality or the concentration of its components, either individually or in concert, may explain the experimental results reported by recent investigators. Each component of the GIK solution has rather wide-ranging metabolic effects. When used in combination their actual locus of action is difficult to determine. Reversing intracellular loss of potassium is certainly not the only possible mechanism by which such a regimen may affect the ischemic myocardium. Although only modest enhancement of glycolytic energy production during hypoxia can be expected by induction of hyperglycemia, intravenous infusions of glucose may significantly affect cellular carbohydrate metabolism in other ways.

The rapid oral or intravenous introduction of 10% to 20% glucose solution may rapidly depress circulating potassium levels. The fall can persist for 6-9 hr and may be severe enough to induce ECG changes. There is a simultaneous and quantitatively similar intracellular movement of inorganic phosphate. Experimental administration of orthophosphate to intact cells has been shown to markedly stimulate glycolysis and glycogenolysis by acting as substrate for glycogen phosphorylase and glyceraldehyde-3-phosphate dehydrogenase and as an allosteric effector of phosphofructokinase.

Other studies indicate that glucose in high concentration may have a direct effect on transmembrane action potential. It is unlikely that this action depends on an increase in energy production since it could be duplicated by the two nonmetabolized sugars xylose and deoxy glucose.

The multivalent actions of insulin on cell metabolism are now well recognized. This hormone may play a direct and independent role in myocardial ion transport. Insulin enhances inorganic phosphate uptake in the liver independent of its effect on glucose transport and may hyperpolarize the muscle cell membrane. An intracellular migration of potassium may thus accompany phosphate shifts. This activity is extremely sensitive and is independent of the translocation of glucose. Insulin may also directly stimulate contractility in the isolated heart, independent of the presence of glucose or of the anoxic state. This activity is probably mediated by a direct action on electrolyte transport. The insulin effects on glucose and potassium movements are probably independent, the latter being closely related to stimulation of the sodium "pump." Insulin may also enhance potassium retention by a direct renal effect.

It is difficult to assess the role of potassium in the ischemic myocardium. The ion is obviously irrevocably tied to conduction and membrane potential and shifts in its concentration undeniably related to the onset and termination of dysrhythmias. Electrocardiographic changes reflect shifts in intracellular/extracellular (IC/EC) concentration, however, and do not necessarily indicate myocardial redox state. When induced in the well-oxygenated heart, such shifts can reproduce "ischemic" changes. We may assume that negative myocardial arteriovenous (A-V) potassium differences are due to efflux of potassium from ischemic cells, but we have no experimental proof that these same cells regain potassium when positive balance is regained by the maneuvers discussed above. Potassium salts should certainly be given to the patient with demonstrable hypokalemia but egress of potassium following onset of ischemia suggests that myocardial extracellular potassium concentration is already elevated. Indeed, electrocardiographic ST-segment shifts and ectopic activity and response to potassium-oriented therapy may be caused not by changes in ischemic or necrotic cells but by shifts in IC/EC potassium ion gradients of the near normal cells in the heterogeneous zone of ischemia.

"Reflow" experiments suggest an additional mechanism of action of the GIK solutions. Here the presence of potassium and insulin is less important than the volume of fluid infused and the osmolar potential of the glucose it contains. Hyperosmolar solutions may enhance "reflow" and prevent extension of ischemia to adjacent areas. Compliance may be increased by restoration of low membrane tensions. An increase in serum osmolality may have other salutary effects on ischemic myocardial performance. A moderate increase may be sufficient to enhance myocardial tension development by as yet unknown mechanisms. Reduction of cell volume toward normal may also enhance contractility by a relative increase in intracellular calcium concentration. The antidysrhythmic effects of the GIK solutions were apparent only on intravenous infusion in experimental studies. The constituents of the solution appeared to be less important than its rate of infusion and osmolality. Hypertonic glucose, saline, and sucrose were all equally effective in treatment of dysrhythmias induced by ischemia and in reduction of potassium efflux.
The report by Maroko et al.\textsuperscript{10} indicates that cell viability and contractile potential appear to show a favorable response to infusions of GIK or hyper-tonic glucose. It seems doubtful that stimulation of anaerobic glycolysis was solely responsible for their findings.

Before GIK solutions are recommended for general use further laboratory and clinical investigation might well trace the metabolic pathways followed by the components of the solution singly and in combination. Potassium, inorganic phosphate and sodium flux, plasma volume and osmolality, urine output, oxygen consumption, glucose consumption and oxidation, lactate production and effects on free fatty acid metabolism should be described. The recent development of techniques for chronic coronary sinus sampling and flow determinations are well suited for evaluation of the transcoronary vs systemic effects of treatment. Efforts to confirm favorable experimental reports and to determine optimal solution composition, method, time, and duration of administration, as well as guidelines by which such therapy can be evaluated \textit{in vivo} and potentially toxic effects avoided, should be encouraged.

References

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NORMAN BRACHFELD

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