

Intraoperative Glucose-Insulin-Potassium for Increased Myocardial Protection in Coronary Surgery in Man

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Myocardial Protection with GIK — Hurless

A topic of interest to extracorporeal technologists and great practicality for patients having cardiac surgery is how best to protect the myocardium from ischemic injury during cardiopulmonary bypass. Two methods of protection—profound local myocardial hypothermia and maintenance of mean systemic arterial pressure at prebypass levels— have gained acceptance.^{1, 2}

Cardiac surgery today in terms of mortality and morbidity has a proven record of safety. On the other hand, is cardiac surgery safe enough? We believe the answer is no. While survival after cardiac surgery is the rule, the published figures for perioperative myocardial infarction of 10 to 20%, occurring ironically during coronary artery by-pass operations done to prevent myocardial infarctions, demonstrate that technics for protecting the myocardium are imperfect.³⁻¹⁴ Improved methods for protecting myocardial cells during all cardiac operations should be identified and put into practice.

In dog experiments, glucose-insulin-potassium (GIK) administration decreased the size of induced myocardial infarctions.^{15, 16} Experiments with GIK in humans who have sustained a medical myocardial infarction have yielded disappointingly conflicting results.¹⁷⁻¹⁹

To test the hypothesis that an intraoperative GIK perfusate would offer additional myocardial protection during aortocoronary bypass grafting a prospective experiment was carried out.²⁰ Matched patients undergoing myocardial revascularization operations were randomly given either a GIK or a control group, Normosol-R[®], perfusion. Patients were matched, and subgroups compared, according to number of bypass grafts. Blood levels of glucose, insulin, potassium, and the three myocardial enzymes, SGOT, total CPK, and CPK-MB isoenzymes²¹⁻²³ were monitored serially to 24 hours postoperatively.

This report presents (1) the results of the study, (2) observation made about GIK perfusion, and (3) types of future studies that could further determine whether GIK was beneficial, and if beneficial why.

METHODS

Patients undergoing myocardial revascularization, including single to quadruple grafting, were considered eligible for the study. Excluded were patients who had myocardial revascularization and concomitant resection of a ventricular aneurysm or valve replacement. Patients with diabetes mellitus were not excluded. All patients gave informed consent prior to participating.

Matching of patients was considered important because a patient undergoing a triple coronary artery bypass was felt not comparable to the patient undergoing a single bypass. Patients were matched according to the number of bypass grafts. This matched patients with like severity of coronary artery disease as well as severity of the intraoperative aortic cross-clamping ischemic insult.

The GIK perfusate contained 1.6 gm glucose, 2.1 U insulin, and 1.7 mEq KCl per kilo patient body weight. The control group perfusate was Normosol-R® (pH 7.4). The latter perfusate contained no glucose or insulin, and 4 mEq of potassium per liter. In the latter group additional potassium was given during the operation by the anesthesiologist depending on the serum potassium level.

The GIK was mixed in an intravenous bottle, with sodium bicarbonate added to render the pH 7.4. The solution was infused after bypass was instituted and while cooling was in full force. Administration of the GIK mixture took from three to five minutes and was complete prior to the first aortic cross-clamping which was done when the temperature reached 30°C.

Conduct of cardiopulmonary bypass was standardized with (1) a bubble oxygenator and roller pumps, (2) systemic hypothermia to 30°C, (3) high flow perfusion, 70 cc/kilo, (4) hemodilution, 16 cc of Normosol-R® /kilo, and (5) maintenance of mean arterial pressure at the preoperative level.

Standard conduct of operation included (1) local myocardial hypothermia with iced Ringer's slush placed in the pericardial cavity, (2) aortic cross-clamping for the performance of each distal anastomosis, (3) three-minute periods of cold coronary perfusion following aortic cross-clamping, (4) all distal anastomoses were made prior to the proximal anastomoses, and (5) warming was effected during the last aortic cross-clamping and while the proximal anastomoses were performed with aid of a nonocclusive aortic clamp.

During a GIK perfusion Dextrostix® were used half hourly as a spot check of blood glucose levels in the operating room. Standard chemical determination of blood glucose levels were also made. When blood glucose fell below 1,000 mg%, 25 gm of glucose was given intravenously. An additional 50 U of insulin was given by vein every half hour unless blood glucose level was below 400 mg%. Potassium levels were checked every half hour. When the potassium level rose above 7 mEq/100 mg of Lasix and 25 cc of sodium bicarbonate were given intravenously.

Serum glucose was determined by glucose oxidase method using Beckman Glucose Analyzer. Potassium was determined on a flame photometer. Total creatinine phosphokinase (CPK) was determined by method of Rosalki²⁴ and serum glutamic-oxalacetic transaminase (SGOT) by method of Reitman and Frankel.²⁵ Immunoreactive insulin (IRI) levels were determined by radioimmunoassay using a Schwarz/Mann kit.²⁶ Quantitative CPK-MB isoenzyme was determined fluoro-

metrically after cellulose acetate electrophoresis using materials from Helena Laboratories.²⁷

RESULTS

A) Patients Studied

There were few patients in the single bypass graft group; therefore, they are not reported here. Included in this report are 31 control group patients and 25 GIK group patients. Of patients receiving two grafts, eight were control, five, GIK; of those with three grafts, 14, control and 13, GIK; of those with four grafts, nine control and seven, GIK.

B) Chemical Determinations

1) Glucose and Insulin

The glucose/insulin relationship in control group patients appears in Figure 1, while the relationship in GIK-treated patients is seen in Figure 2. Early in the control group operation the immunoreactive insulin (IRI) levels dropped to a mean of 12.1 U/ml while the plasma glucose level was 267 mg%. IRI fell to inappropriately low levels during surgery and then rebounded to a higher level when bypass was discontinued. Even at this time IRI values were commensurate with glucose levels in only half the patients. In the other half the insulin values remained suppressed. In contrast in the GIK group glucose levels were 2½ times these in the control group. The IRI levels were greatly elevated during the GIK surgical procedure but fell rapidly after the procedure. There was no statistically significant difference between IRI levels in control and GIK group six hours after operation.

2) Potassium

The potassium values seen during a typical control compared to a typical GIK bypass are seen in Figure 3. Potassium was high initially in the GIK patients but fell to normal or low-normal levels at the end of bypass. In contrast potassium levels in control patients remained normal throughout bypass. In two patients with preoperative renal insufficiency hyperkalemia was noted postoperatively. The serum potassium values were alarmingly high but both patients had a benign postoperative course.

SERUM GLUCOSE AND INSULIN LEVELS IN CONTROL GROUP

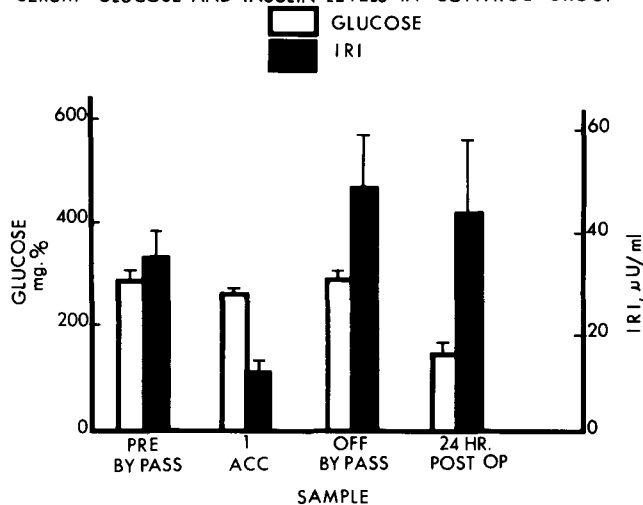


Figure 1 — Serum glucose and insulin levels in control group during myocardial revascularization. ACC refers to first aortic cross-clamping.

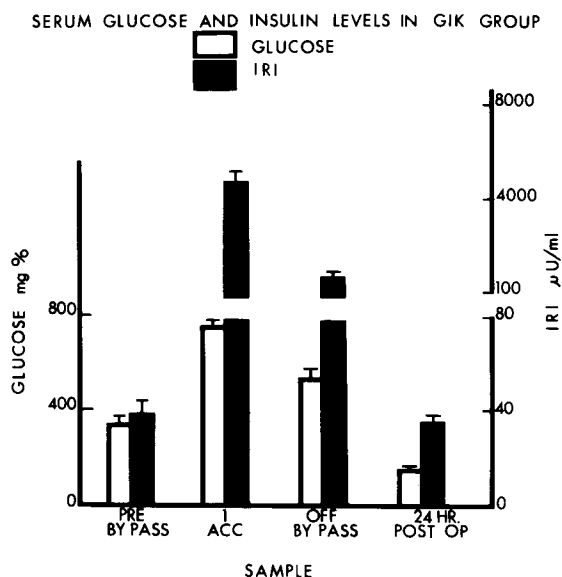


Figure 2 — Serum glucose and insulin levels in GIK group.

3) Cardiac Enzymes; SGOT, CPK, CPK-MB Isoenzyme

Enzymatically two distinct groups of patients could be identified, those with myocardial infarctions and those without. The most specific of the cardiac enzymes, CPK-MB, best differentiated the two different groups of patients. Our definition of myocardial infarction was a 24 hour CPK-MB isoenzyme value of 100 IU/1 or greater. Six patients had such a value (11%) and were said to have had myocardial infarcts. Table I shows the distribution of this group of patients in respect to the number of bypass grafts and whether they had a GIK bypass or a control group bypass. Four of the six (13%) had a control group bypass. Two of the six infarct patients (8%) had a GIK bypass. The GIK patient with a double graft who had an infarct did so because of technical difficulty arising during an attempted graft to the superior obtuse marginal branch of the circumflex. This graft had to be abandoned. Therefore, the difference in myocardial infarction rate between the two groups was 13% for control patients and 4.2% for the GIK group.

Of the six patients identified with a myocardial infarction, three had new and persistent Q-waves in their postoperative electrocardiogram and three did not. Four of the six had SGOT's at 24 hours postoperative over 100 (180, 111, 121, 152) but two had 24 hour SGOT's which were below that (68 and 78). None of the six myocardial infarction patients had a stormy postoperative course; all are surviving to date. The only death in the entire group of patients occurred in a GIK-treated triple graft patient who had massive fatal pulmonary embolus 12 days postoperatively (mortality 1.8%).

In the non-infarct group of patients (89%) there was a similar level of cardiac enzyme elevation in GIK and control group which increased progressively from the two graft to the four graft subgroup of patients. The time course of enzyme elevation was accelerated in the four graft group as compared to the three graft. Administration of GIK did not appear to alter this distinct background level of release of cardiac enzymes from the level observed in the control group.

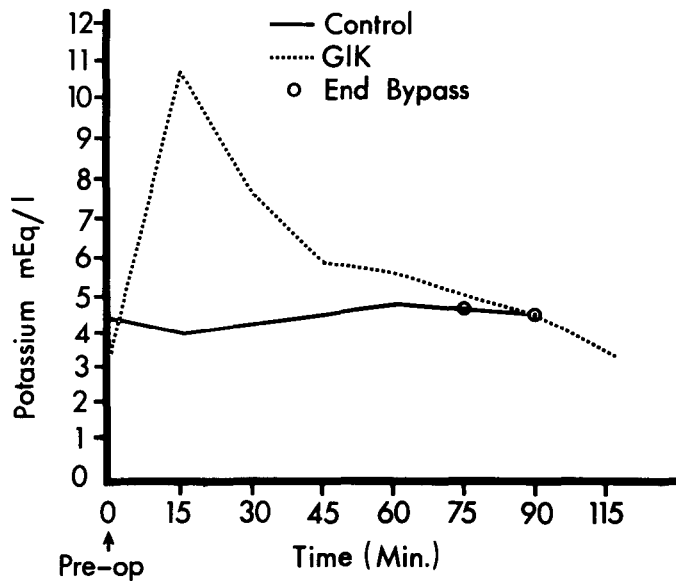


Figure 3 — Potassium levels in control and GIK group patients.

C) Osmolality Observations

Osmolality determinations were made in 17 patients. The average preoperative osmolality was 301 milliosmoles/kg. In GIK-treated patients the average intraoperative increase in osmolality was 11% and the highest osmolality was 346 milliosmoles/kg. In control group patients the average intraoperative increase was 3.5% and the highest osmolality was 333 milliosmoles/kg. The osmolality of Normosol-R® was 303 and of the GIK mixture in the intravenous bottle prior to its being administered was 2,620 milliosmoles/kg.

D) Clinical Observations Made During GIK Bypass

In the first several patients studied the GIK mixture was administered quite rapidly, just prior to the first aortic cross-clamping for the performance of the first distal anastomosis. When GIK was administered in this fashion the heart abruptly stopped. Because we were uncertain of the desirability of this potassium-induced

TABLE I

SPONTANEOUS DEFIBRILLATION

	Control Group	GIK Group
2 Grafts	13% (1/8)	40% (2/5)
3 Grafts	0% (0/14)	46% (6/13)
4 Grafts	11% (1/9)	14% (1/7)
TOTAL	7% (2/31)	36% (9/25)

arrest, thereafter, the GIK solution was added slowly over 3-5 minutes. Potassium cardioplegia did not occur then.

Early in the experience it was noted that GIK patients frequently defibrillated spontaneously at the end of the revascularization procedure. These data are given in Table I. In the control group only two patients out of a total of 31 (7%) exhibited

spontaneous defibrillation. In the GIK group nine out of a total of 25 (36%) had spontaneous defibrillation.

In the control group after cardiopulmonary bypass had begun, additional volume from the pump, usually 500 to 800 cc had to be administered to maintain a CVP of 3 to 10 mm Hg, the desired CVP at our institution. During GIK cardiopulmonary bypass a different phenomenon was observed. There was an initial, quite large venous return to the oxygenator of 500 to 1,200 cc at a CVP of 3 to 10 mm Hg. This initial venous return was stored in the reservoir and returned to the patient before bypass was discontinued. Before this observation was made GIK-treated patients had higher than desirable CVP readings.

When additional 25 gm doses of glucose were administered too rapidly transient arterial hypotension occurred. The added glucose given over 40 to 60 seconds did not produce hypotension.

E) Safety of GIK Bypass

We were initially concerned about the safety of GIK bypass. To our knowledge no similar experiment had been done and, therefore, no precedent existed. For this reason the experiment was carried out without blinding any of the observers.

The course of the 25 GIK patients and 31 control group patients was reviewed in respect to various organ systems; central nervous system, kidney, pulmonary, cardiovascular, and endocrine. Pre- and postoperative EEG's were done in both groups of patients and the incidence of postoperative Grade II dysrhythmia was not different. Two GIK patients had marked but clinical benign postoperative elevations of serum potassium to a level of 8 mEq/l. This decreased over 36 hours. In both an element of preoperative renal dysfunction, with elevated BUN and creatinine, had existed. We postulate that these patients were not able to adequately clear the administered load of potassium because of their renal insufficiency. In neither did this potassium level cause either cardiovascular instability, EKG changes, or arrhythmia. The reason their elevated serum potassium was benign may have been that their serum to cellular transmembrane potassium ratio was relatively normal. Nevertheless, renal insufficiency should be viewed as a relative contraindication to GIK therapy. Hyperosmolar solutions are known to cause pulmonary edema in patients not on cardiopulmonary bypass because large increments of extravascular volume are mobilized to the intravascular compartment. In no patient in this series was intraoperative or postoperative pulmonary edema encountered. On the other hand deliberate attempts to maintain a low central venous pressure and store the mobilized extravascular volume into the oxygenator were followed. Cardiovascular instability of any sort was not observed in GIK-treated patients. Diabetic patients treated with GIK did not differ from their nondiabetic GIK-treated counterparts.

COMMENT

This experiment was begun with two hypotheses; first, that GIK would decrease the infarction rate in matched patients undergoing myocardial revascularization; second, that we would be able to detect this diminished cardiac damage by observing an overall diminution in the efflux of cardiac enzymes in GIK-treated patients.

In respect to GIK's diminishing the infarct rate the data presented here is not conclusive because the number of patients with myocardial infarctions is small, and we have made a new and quite arbitrary definition of myocardial infarction. When one excludes the one technical error infarct in a GIK double graft patient, the difference in infarction rate, 13% for control patients and 4.2% for GIK patients, suggests that GIK may be of benefit. Obviously more patients must be studied.

In respect to the second hypothesis, we were surprised to see that GIK did not cause any diminution in a distinct background level of cardiac enzyme elevation which (a) was progressively greater, the more grafts placed, (b) rose more rapidly, the more grafts placed, and (c) was the same in control and GIK group patients.

Note should be taken of the arbitrariness of the experimental and operative protocol which prevailed during the time when the experiment was being conducted. For instance, the dosage of the GIK mixture was purely arbitrary. A different dosage schedule might have been preferable. We allowed three-minute periods of coronary perfusion between each aortic cross-clamping. A case has recently been made for performing all distal anastomoses during a single aortic cross-clamping.²⁸ The method of administering the GIK and supplementing the glucose and insulin during the operation was also arbitrary. While an effort was made to maintain mean systemic arterial pressure at prebypass levels this was not always successful.⁷ GIK therapy was not continued in the postoperative period. There is evidence that postoperative GIK therapy can increase the cardiac output.²⁹ Whether alterations in the experimental or operative protocol might have given different results is not known.

We now believe that enzyme measurements may be a rather crude, or possibly even inaccurate, measurement of the protective effect afforded by GIK perfusate.³⁰ An electron microscopical study of trephine punch biopsies of the left ventricular myocardium taken before and after all aortic cross-clampings is underway. No firm data is available now concerning this aspect of the study. It is interesting to note, however, that Maroko and Braunwald in their electron microscopical study of ventricular biopsies taken from dogs given experimental myocardial infarctions and treated with GIK found that GIK promoted preservation of the mitochondrion, the intracellular powerplant.¹⁶ If the same could be shown in human hearts one might have the anatomic explanation for the more frequent spontaneous defibrillation observed in the GIK-treated patients.

The present surgical study could serve as a human model for other experiments designed to reduce infarct size in patients sustaining medical myocardial infarctions. Because the surgical group of patients lend themselves to invasive studies more readily, additional data including biopsies of the ventricle could be performed. The effects of steroids, osmotic agents, i.e. Mannitol, or other chemicals could be studied.

The present GIK study raises more questions than it answers. If GIK is beneficial, how does it work? Postulated mechanisms of action include (1) increased anaerobic glycolysis, (2) increased glycogen reserves, (3) increased stability of the cell membrane, (4) prevention of cell swelling with maintenance of the Na⁺/K⁺ cell wall pump or hyperosmolar effect of GIK.

Also, since GIK is a mixture of three potent agents, which of the three is the most critical or are all three necessary? Recent work by Gay and Ebert has raised the question whether potassium-induced cardioplegia might not be protective against anoxia.³¹ The work of Austen et al showed ten years ago that glucose loading of the heart afforded additional protection against ischemia.³² Insulin levels during cardiopulmonary bypass are known to be low, seemingly depressed.^{33,34} Perhaps the addition of insulin is the most critical aspect of the GIK regimen.

Several broader implicatons of the study are suggested by the results. (1) Each aortic cross-clamping, whether in GIK or control patients, incurs an added increment of myocardial damage, despite the three-minute coronary perfusion allowed between aortic cross-clampings. (2) Some surgeons euphemistically refer to postoperative surgical myocardial infarctions as occurring in the perioperative period. These should

probably be more properly labeled intraoperative myocardial infarctions. (3) There remains the distressing and central paradox of incurring a measure of cardiac damage during operations solely designed and performed to correct already existing cardiac dysfunction.

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