GIK in Cardiac Surgery

J.

Boldt

Gießen

Prof. Dr. Joachim Boldt, Abteilung für Anästhesiologie und operative Intensivmedizin, Justus-Liebig-Universität Gießen
Klinikstraße 29, D-35392 Gießen (Germany)

In 18-78% of patients undergoing coronary artery bypass grafting (CABG), evidence of myocardial ischemia is diagnosed after finishing cardiopulmonary bypass (CPB) [1-3]. In addition to various cardioplegic solutions, several pharmacological approaches have been proposed in the prebypass period of cardiac surgery patients to reduce the incidence of peri-operative myocardial ischemia, to avoid or reverse myocardial ischemia/reperfusion injury, and to improve myocardial function after CPB. Nitroglycerin [4], Ca^{++} channel blockers [5], acadesine [6], and other pharmacological compounds have been recommended to attenuate the sequelae of ischemia in these patients. Infusion of glucose/insulin in combination with potassium (GIK) is another technique for improving myocardial preservation at this time [7-9]. Since its first description by Sodi-Palares et al. [10] in 1965, we have gained a massive increase in knowledge related to the mechanisms of GIK: An increase in intracellular cardiac glycogen results in an increased glycolytic reserve and an improved resistance to ischemia most likely due to an enhanced glycolytic and anaerobic ATP production [11]. Additional beneficial effects of GIK include a reduction in circulating free fatty acids (FFAs), which are reported to have deleterious effects on myocardial function and metabolism during ischemia [12]. GIK was able not only to protect the ischemic myocardial cell, but also to improve global and segmental function of the myocardium, particularly in patients with impaired ventricular function [13]. The paper of Wistbacka et al. [14] published in this issue of INFUSIONSTHERAPIE und TRANSFUSIONSMEDIZIN also deals with the effects of GIK infusion prior to CPB in patients undergoing coronary artery bypass grafting (22 GIK-treated versus 22 nontreated patients). Aspartate/glutamate was added to the GIK infusion in this study, which is suggested to improve myocardial energy metabolism during and after ischemia [15]. Markers of reduced myocardial ischemia and/or improved myocardial function in the paper of Wistbacka et al. were CK-MB enzyme plasma levels and various hemodynamic data. The authors concluded from their results that GIK/ aspartate/glutamate infusion prior to CPB was associated with beneficial effects in cardiac function thereafter. In spite of some potential value of this technique, it has produced conflicting results varying from enthusiastic to discouraging reports, which even dispute any positive effect. Interestingly, Wistbacka and his group published a paper in 1992 dealing with the use of GIK in 32 elective coronary artery bypass patients [16]. Looking at CK-MB enzyme fraction, ECG and hemodynamic changes, they concluded in that paper that prebypass infusion of GIK entailed no clinical benefit in comparison to a control group, who had received Ringer's acetate. Inotropic support, incidence of arrhythmias, and duration of intensive care stay were not different between these two groups either. Thus the question arises whether this technique can be recommended in cardiac surgery

patients. In the study of Wistbacka et al published in this issue of *INFUSIONSTHERAPIE* und *TRANSFUSIONSMEDIZIN* [17], hemodynamics after CPB were sufficient in both groups (the GIK-treated and the nontreated control group), the control patients did not need more inotropic support, did not show more arrhythmias, and outcome was similar in both groups -thus the author's conclusion of the beneficial effects of an aspartate/glutamate-enriched GIK infusion is not very convincing. It has to be doubted whether hemodynamic data such as cardiac index (CI) or left ventricular stroke work index (LVSWI) allow such enthusiastic judgment. In Wistbacka's paper, percentage changes of hemodynamics are given, which may feign beneficial effects (e. g. when the PCWP increases from 10 to 12 mmHg this is an increase of 20%!! – what, however, is the [clinical] value? – or CI increases from 3.0 to 3.5 l/min·m² [+17%!!]). In this study, CI in the verum group increased by 28.8 ± 22.4% from pre-induction to decanulation and slightly decreased (-3.0 ± 26.2%) in the untreated control patients. Mean CI, however, was greater than 2.5 l/min · m² in the control group. Is it necessary to improve upon the already good? Is a CI of > 2.5 l/min · m² after CPB considered to be a better outcome than a CI of 2.5 l/min·m²? GIK-treated and untreated patients did not differ with regard to inotropic support in the post-CPB period and during their stay in the intensive care unit indicating no differences in myocardial function between the two groups. Standard serologic markers of ischemia (e.g. CK-MB enzyme plasma levels) were also without differences between the two groups. Unfortunately, new (more sensitive) markers of (minor) myocardial tissue damage in patients undergoing CABG (e.g. troponin T or troponin I) were not measured.

The benefit of adding aspartate/glutamate to the GIK regime can also be doubted. In the study of Wistbacka et al, an aspartate/glutamate-enriched cardioplegic solution was used in both groups, and rather high levels of aspartic acid and glutamic acid were found in the circulating blood in all patients. Thus it

© 1995 S. Karger GmbH,

Freiburg

is very difficult to separate the effects of GIK from the possible effects of aspartate/glutamate. In the studies dealing with GIK, there is a wide variation with respect to patient population (CABG versus valve patients), glucose/insulin ratios, infusion rates, and the optimal time when GIK should be started in cardiac surgery patients. In some reports, previous infusion times have been longer (i.e. even 12 h before start of CPB [18]), the kind of insulin varies (human or animal-derived insulin), GIK infusion was started before, during or even after ischemia – thus a comparison between the different studies is difficult. Nevertheless, it is a matter of highest urgency to emphasize the possible risks when a GIK regime is used (with or without addition of aspartate/glutamate) in cardiac surgery patients [19]. In a study in 50 patients undergoing elective aorto-coronary bypass grafting, GIK (using 50 g of glucose with either 50 or 100 IU of insulin along with 70 mmol potassium) was infused in the pre-ischemic (pre-bypass) period [20]. Blood glucose concentrations and various endocrine parameters were studied before, during and after CPB. In accordance with Wistbacka et al, inotropic support after CPB was not different in GIK-treated and untreated patients, and it was concluded that in patients with preoperative normal left ventricular function and only moderate ischemic period GIK is without benefit. Another major finding of this study was that the incidence of severely reduced (< 50 mg/dl) or elevated blood glucose level (> 300 mg/dl) was significantly higher in GIK-treated than in nontreated patients. Severely reduced glucose levels should be urgently avoided in anesthetised patients due to the risk of (undetected) convulsion. Some studies have warned of the consequences of hyperglycemia, which may enhance the effects of ischemia, particularly in the

brain [21, 22]. Thus it was suggested that glucose solutions should be completely eliminated from operations with CPB to prevent hyperglycemia [23]. As hyperglycemia appears to be a risk factor of cerebrovascular accidents, it was recommended to keep blood glucose levels even below 200 mg/dl [23, 24]. When GIK is used, high doses of insulin (e. g. 100 IU) are necessary. One reason to avoid (subsequent) high plasma insulin concentrations can be derived from a study by Hunt and McGiven [25] who demonstrated that increased plasma insulin levels can promote formation of small and relatively unstable hormone-antibody complexes, which easily disintegrate and serve as insulin depots with the risk of late, uncontrolled hypoglycemia in the postoperative period. In the study of Wistbacka et al., '... no hypoglycemic episodes and hyperglycemia were seen ...'. This is most likely due to extensive blood sugar and electrolyte monitoring as well as additional infusion of glucose in the GIK patients. This makes the procedure of GIK/aspartate/glutamate infusion even more expensive and problematical. It can be summarized that the complexity of the pathogenesis of myocardial ischemia in cardiac surgery may offer a large number of opportunities for cardioprotective measures. The anesthesiologist cannot influence duration of ischemia, the quality of anastomoses, and the quality of cardioplegic preservation – factors that markedly influence myocardial integrity and function after CPB. Infusion of GIK alone or enriched with glutamate/aspartate may have some beneficial effects on the myocardium as demonstrated recently in an animal experiment [26]: In isolated animal hearts, GIK decreased infarct size and increased ATP and creatine phosphate levels thus preserving cellular function and improving myocardial perfusion. However, extrapolation from animal models to the critically ill must always be used with caution! It has become increasingly evident that the pathophysiological characteristic of animal models does not always reflect the human condition. When using GIK with or without addition of aspartate/glutamate we have to be aware that it may produce severe derangement of glucose homeostasis and electrolytes. Thus extensive (and costly) monitoring is imperative. The risk/benefit and cost/benefit ratio of this technique must be viewed with some skepticism – particularly in patients undergoing elective first-time aorto-coronary bypass grafting and with sufficient myocardial function (21 out of 44 patients from Wistbacka's study had a left ventricular ejection fraction [LVEF] of greater than 50%). Whether this technique is of benefit in more critically ill cardiac surgery patients with severely reduced ventricular function or preoperative acute ischemia warrants further extensive clinical (outcome) studies.

References

- Slogoff S, Keats AS: Further observations on peri-operative myocardial ischemia. *Anesthesiology* 1986; 65:539-542.
- Dorman BH, Zucker JR, Verrier ED, Gartman DM, Slachman FN: Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1992;6:344-359.
- Knight AA, Hollenberg M, London MJ, Tubau J, Verrier E, Browner W, Mangano DT: Perioperative myocardial ischemia: Importance of the preoperative ischemic patterns. *Anesthesiology* 1988;68:681-688.
- Davies ME, Jones CJH, Feneck RO, Walesby RK: The effects of intravenous nitroglycerin and isosorbide dinitrate on hemodynamics and myocardial metabolism. *J Cardiothorac Anesth* 1989;3:712-719.

Seitelberger R, Zwölfer W, Binder T, Huber S, Peschl F, Spatt J, Schwarzacher S, Holzinger C, Coraim F, Weber H, Wolner E: Infusion of nifedipine after coronary bypass grafting decreases the incidence of early postoperative myocardial ischemia. *Ann Thorac Surg* 1990;49:61-68.

Boiling SF, Groh MA, Mattson AM, Gringae RA, Gallagher K: Acadesine (AICA-Riboside) improves postischemic cardiac recovery. *Ann Thorac Surg* 1992;54:93-99.

Haider W, Eckersberger F, Wollner E: Preventive insulin administration for myocardial protection in cardiac surgery. *Anesthesiology* 1984;60:422-429.

Hess ML, Okabe E, Poland J, Warner M, Steward JR, Greenfield LJ: Glucose, insulin, potassium protection during the course of hypothermic global ischemia and reperfusion: A new proposed mechanism by scavenging of free radicals. *J Cardiothorac Pharmacol* 1983; 5:35-43.

9v Bormann B, Scheld HH, Podzuweit T, Boldt J, Kling D, Hempelmann G: Enhancement of myocardial energy potentials in man by glucose-insulin treatment before and after ischemic heart arrest. *J Cardiovasc Surg* 1985;26:182-186.

72

Boldt

GIK in Cardiac Surgery

Sodi-Palares D, Testelli MD, Fisleder BL: Effects of an intravenous infusion of potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. *Am J Cardiol* 1965;9:165-169.

Scheuer J, Stezoski SW: Protective role of increased myocardial glycogen stores in cardiac anoxia in the rat. *Circ Res* 1979;27:835-840.

Henderson AH, Most AS, Parmeley WW: Depression of myocardial contractility in rats by free fatty acids during hypoxic periods. *Circ Res* 1970;26: 439-444.

Whitlow PL, Rogers WJ, Smith LR: Enhancement of left ventricular function by glucose-insulin-potassium infusion in acute myocardial infarction. *Am J Cardiol* 1982;49:811-816.

Wistbacka JOM, Lepojärvi MVK, Karlqvist KEV, Koistinen J, Kaukoranta PK, Nissinen J, Peltola T, Rainio P, Ruokonen A, Nuutinen LS: Amino acid-enriched glucose-insulin-potassium infusion improved hemodynamic function after coronary artery bypass surgery. A double-blind study in patients with unstable angina and/or compromised left ventricular function. *Infusionsther Transfusionsmed* 1995;22:82-90.

Rosenkranz ER, Okamoto F, Buckberg GD, Robertson JM, Vinten-Johanson J, Buguyi HI: Safety of prolonged aortic clamping with blood cardioplegia. III: Aspartate enrichment of glutamate blood cardioplegia in energy-depleted hearts after ischemia and reperfusion injury. *J Thorac Cardiovasc Surg* 1986;91:428-435.

Wistbacka JOM, Kaukoranta PK, Nuutinen LS: Pre-bypass glucose-insulin infusion in elective non-diabetic coronary artery surgery patients. *J Cardio-thorac Vasc Anesth* 1992;6:521-527.

Wistbacka JOM, Lepojärvi MVK, Karlqvist KEV, Koistinen J, Kaukoranta PK, Nissinen J, Peltola T, Rainio P, Ruokonen A, Nuutinen LS: Amino acid-enriched glucose-insulin-potassium infusion improves hemodynamic function after coronary artery bypass surgery. A double-blind study in patients with unstable angina and/or compromised left ventricular function.

Infusionsther Transfusionsmed 1995;22:82-90.

Oldfield GS, Commerford PJ, Opie LH: Effects of preoperative glucose-insulin-potassium on myocardial glycogen levels and on complications of mitral valve replacement. J Thorac Cardiovasc Surg 1986; 91:874-879.

Böhrer H, Fleischer F, Krier C: Hyperkalemic cardiac arrest after cardiac surgery following high-dose glucose-insulin-potassium infusion for inotropic support. Anesthesiology 1988;69:949-953.

Boldt J, Knothe C, Zickmann B, Dunnes S, Dapper F, Hempelmann G: Influence of different glucose-insulin-potassium regimes on glucose homeostasis and hormonal response in cardiac surgery patients. Anesth Analg 1993;76:233-238.

Lanier W, Slangland Scheithauer BW, Milde JH, Michenfelder JD: The effects of dextrose infusion and head position on neurological outcome after complete ischemia in primates: Examination of a model. Anesthesiology 1987;66:39-48.

Steward DJ, daSilva CA, Flegel T: Elevated blood glucose levels may increase the danger of neurological deficits following profoundly hypothermic cardiac arrest. Anesthesiology 1988;49:655.

McKnight CK, Elliot MJ, Pearson DT: The effects of four different crystalloid bypass pump priming fluids upon the metabolic response to cardiac operations. J Thorac Cardiovasc Surg 1985;89:97-106.

Sieber FE, Smith DS, Traystman RJ, Wollman H: Glucose: A reevaluation of its intraoperative use. Anesthesiology 1987;67:72-81.

Hunt JS, McGiven AR: Immunological Investigation of Renal Disease. Edinburgh, Churchill Livingstone, 1980, pp 50-59.

Lazar HL: Enhanced preservation of acutely ischemic myocardium using glucose-insulin-potassium solutions. J Card Surg 1994;9(suppl 3): 474-478.

Kryotec Bahrenfelder Chaussee 65 D-22761 Hamburg Hans-S. Schroder GmbH
BLUTPLASMA-QUARANTANE-LAGER

Preiswert – Anwenderfreundlich – Sicher Doppelkühlanlage – FCKW-Frei – Energiesparend
Modulsystem – Umbau und Erweiterungsfähig Ausgeklügeltes Teleskop-Schubladensystem von
1800 bis 54000 Plasmen Lagerkapazität

-40°C

-40°C

-40°C

-40°C

BLUTPLASMA-SCHOCKEINFRIERGERÄT-80°C

BLUTPLASMA SCHOCKGEFRIEREN MIT-80°C ULTRA KALTER LUFT!

Nur Luft, der physiologisch wohl unbedenklichste Kälteträger, kontaktiert den einzufrierenden Plasmabeutel.

KPE 04/70 (4 Beutel) = 48 bis 52 Beutel Kapazität in 8 Stunden KPE 12/70 (12 Beutel) = 144 bis 156 Beutel Kapazität in 8 Stunden KPE 18/70 (18 Beutel) = 216 bis 234 Beutel Kapazität in 8 Stunden

Das Einfrieren kann wahlweise mit oder ohne Karton erfolgen. Jede Charge Plasma wird in 30 Minuten auf -40°C Kerntemperatur gebracht. Die Kryotec Blutplasmaeinfriergeräte benötigen zum Betrieb nur eine 220 V Steckdose. Die Einfriergeräte arbeiten luftgekühlt.

FERNER IM PROGRAMM: BLUT- UND PLASMALAGERSCHRANKE FÜR DIE
EIGENBLUTSPENDE UND BLUTBANK

73