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High-dose glucose-insulin-potassium after cardiac surgery: a retrospective analysis of clinical safety issues

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Background: Metabolic treatment with insulin or glucose-insulin-potassium (GIK) has received attention in association with myocardial infarction, cardiac surgery and critical care. As a result of insulin resistance during neuroendocrine stress, doses of insulin up to 1 IU kg^{-1} b.w.*h are required to achieve maximal metabolic effects after cardiac surgery. The clinical experience with regard to safety issues of such a high-dose GIK regime in critically ill patients after cardiac surgery is reported.
Methods: Retrospective, observational study involving all patients treated with high-dose GIK after cardiac surgery during one year in a cardiovascular center at a University Hospital.
Results: Eighty-nine patients out of 854 adult patients undergoing cardiac surgery were treated with high-dose GIK. Mean age was 69 ± 1 years, Higgins score 5.3 ± 0.3. Preoperatively 31.4% had left ventricular function EF $\leqslant 0.35$ and 32.5% had sustained a myocardial infarct during surgery. Mortality was 5.6% and the average ICU stay was 3.7 ± 0.5 days. The main indication for GIK was intraoperative heart failure (69.7%). The average glucose infusion rate during the first 6 h was 4.22 ± 0.15 and 4.91 ± 0.14 mg kg^{-1} b.w.*min, respectively, in diabetic and non-diabetic patients ($P = 0.023$). Blood glucose and s-potassium control was acceptable.
Conclusions: The high-dose GIK regime allowed substantial amounts of glucose to be infused both in diabetic and critically ill patients with maintenance of acceptable blood glucose control. Provided careful monitoring, this regime can be safely used in clinical practice and deserves further evaluation for treatment of critically ill patients following cardiac surgery.

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Key words: Cardiac surgery; glucose; insulin; metabolic support; myocardial infarction; postoperative heart failure; potassium; safety.

As a result of encouraging reports in recent years, insulin treatment with or without glucose-potassium has gained increasing attention in association with myocardial infarction, cardiac surgery and surgical critical care (1–9). However, although glucose-insulin-potassium (GIK) was introduced in the sixties the ideal GIK regime remains to be established. Furthermore, the relative importance of insulin, glucose administration and strict blood glucose control for therapeutic gain remains unknown. With regard to substrate utilization it has been shown that carbohydrates provide a more beneficial oxygen economy for the heart compared with free fatty acids (10). In contrast to free fatty acids, carbohydrates have anaplerotic properties and thus may contribute to the recovery of mitochondrial oxidative capacity after severe ischemia (10).

In the setting of cardiac surgery, studies on systemic and myocardial metabolism have demonstrated a severe degree of insulin resistance early after cardiac operations (10–12). Although moderate doses of insulin suppress free fatty acid levels in plasma and control blood glucose, only doses of 1 IU kg^{-1} b.w. and hour or more have so far been documented to achieve desirable metabolic effects such as maximal systemic glucose uptake and a shift from myocardial free fatty acids (FFA) uptake to carbohydrate uptake (10–12).

Extremely high doses of insulin have been used in animal experimental models with promising results regarding preservation of myocardial viability and recovery of hemodynamic performance after severe ischemia (13, 14). However, such regimes have to our knowledge not been implemented in clinical practice presumably because of fear of pronounced vasodilatation and electrolyte shifts. In light of this, we have developed and implemented a high-dose GIK regime that should provide the desired metabolic effects in

most patients, without having the pronounced vasodilative properties of the 'hemodynamic doses' of insulin described in previous studies (15, 16).

To describe our clinical experience with particular reference to issues such as safety and possible differences in efficacy between diabetic and non-diabetic patients, the records of all patients treated with high-dose GIK during one year were scrutinized.

Methods

Patients

The records of all patients receiving high-dose GIK during one year (88 patients undergoing 89 procedures from a total of 854 adult cardiac surgical procedures) in a cardio-thoracic surgical unit at a university hospital, the only center serving a population of one million people in the South-east Health Region of Sweden, were investigated. A detailed systematic review according to a protocol for analysis of clinical outcome, adverse effects, blood glucose and electrolyte control was undertaken. Sixteen of these 89 high-dose GIK-treated cases were tablet- or insulin-treated type II diabetics. Demographic data are presented in Table 1.

High-dose GIK

During the timeframe of the study a 30% glucose solution, supplemented by 10 mmol Mg and 40 mmol of phosphate per liter, was infused in a central venous catheter. The infusion rate was determined by regular checks of blood glucose to achieve a stable blood glucose level between 7 and 12 mmol l^{-1}.

Insulin of a fast-acting type (Actrapid Novo®, Novo Nordisk A/S, Bagsuaerd, Denmark) was infused at a rate of 1 IU kg^{-1} b.w. and hour for 6 h. A bolus of 25 IU was injected intravenously 5 min after starting the glucose infusion to achieve an early steady-state metabolic effect. After the insulin infusion had been completed, the glucose infusion was maintained until the effect of the insulin had subsided, the infusion rate being gradually decreased according to the blood glucose level. This treatment constitutes a clinical application of a hyperinsulinemic glucose clamp; therefore, the blood glucose level in the short-term is influenced only by the rate of glucose infusion.

Potassium was infused separately but s-potassium was allowed to decrease to 3.5 mmol l^{-1} to avoid rebound hyperkalemia when the insulin infusion was stopped.

Clinical management

Details of clinical management regarding preoperative medication, anesthesia, cardiopulmonary bypass (CPB) and myocardial protection have been given previously (17).

Monitoring

A Swan-Ganz catheter was used for hemodynamic monitoring in 27 patients out of 89 cases. A surgically introduced epidural catheter through the outflow tract of the right ventricle into the pulmonary artery

Table 1

Preoperative data in high-dose-treated glucose-insulin-potassium cases (n = 89).	
Age (years)	69 ± 1
Age >70 years (%)	51.6
b.w. (kg)	75 ± 1.3
Length (cm)	171 ± 0.9
Female gender (%)	33.7
Diabetes mellitus (%)	18.0
Hypertension (%)	33.7
Peripheral vascular disease (%)	11.2
Preoperative serum-creatinine (μmol l^{-1})	109 ± 5
Preop s-creatinine >140 μmol l^{-1} (%)	9.5%
Unstable angina (%)	29.2
Left main stenos ⩾70% (%)	8.9
Preoperative heart failure (%)	39.3
Acute myocardial infarction <4 weeks (%)	11.2
LVEF	0.44 ± 0.02
LVEF ⩽0.35 (%)	31.4
NYHA class i.v.	39.3
Higgins score	5.3 ± 0.4

Results are given in percentages or mean ± SEM.
b.w.=body weight; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association.

was routinely used in the other patients for monitoring of pulmonary artery pressure and to take blood samples for mixed venous oxygen saturation (SvO_2) (17). The study was not designed to evaluate the hemodynamic efficacy of GIK and hence presentation of hemodynamic results was considered inappropriate.

Definitions

Mortality was defined as 30-day mortality. Complications presented refer to events occurring, or treated at our institution. Postoperative renal failure was defined as a postoperative increase of s-creatinine by more than 50% compared with preoperative values as suggested by Andersson *et al*. (18). Neurological complications include stroke or depression of consciousness associated with signs of cerebral injury on a CT-scan and transient ischemic attacks with focal neurological deficit. Perioperative myocardial infarction was diagnosed according to screening routines at our institution with aspartate amino transferase (ASAT) $\geqslant 3.0\ \mu kat\,l^{-1}$ on the first postoperative morning and alanine aminotransferase less than half of the ASAT value. Usually the diagnosis was supported by creatinine kinase MB isoenzyme $>70\ \mu g\,l^{-1}$ on the first postoperative morning.

Statistics

ANOVA repeated measures design and Tukey honest significant difference tests for post hoc analyses were employed for assessment of changes occurring over time and for comparison of intergroup differences. Results are presented as mean ± SEM. Statistical significance was defined as a $P<0.05$. Statistical analyses were performed with a computerized statistical package (Statistica 5.1, StatSoft Inc, Tulsa, OK).

Results

Indications for treatment with high-dose GIK

The decision to use a high-dose GIK was dependent on the individual anesthetist's/surgeon's clinical evaluation. According to the records, the indication was treatment of postoperative cardiac failure (69.7%), intraoperative ST changes suggesting severe myocardial ischemia (6.7%) or anticipated problems resulting from preoperative risk factors or complicated procedures (23.6%). In the majority of these cases the treatment was instituted after unclamping and before weaning from CPB but 25% received it after termination of CPB. Of the patients, 41.5% received additional metabolic support with an intravenous glutamate infusion.

Preoperative data

Almost one-third of the patients had severely compromised left ventricular function before surgery and 39.3% were in preoperative heart failure. More than half of the patients were older than 70 years and the average Higgins score was 5.3 ± 0.4. Detailed preoperative data are presented in Table 1.

Intraoperative data

Combined valve+coronary artery bypass graft procedures constituted 18.0%, redo-procedures 7.8%, double-valve procedures 6.7%, postinfarct ventricular septal defect 4.5% and surgery for acute dissection of the ascending aorta was 1.1%. Inotropes were used in 43.8% for weaning from CPB. In 5.5%, mechanical circulatory support was employed. Further details are given in Table 2.

Postoperative data

Postoperative data are given in Table 2.

Systemic glucose uptake and glucose control

The average infusion rate of glucose and blood glucose in all the high-dose GIK treated cases ($n = 89$) are presented in Fig. 1. After completion of the insulin infusion the glucose infusion rate was gradually decreased according to the blood glucose levels and was maintained for an average 21.9 ± 1.2 h from the beginning of the GIK treatment.

The average infusion rate of glucose during the first 6 h of the high-dose GIK treatment was somewhat lower in the diabetic compared with the non-diabetic patients (4.22 ± 0.15 vs. $4.91 \pm 0.14\ mg\,kg^{-1}$ b.w.*min; $P = 0.023$). It also tended to be lower in patients receiving simultaneous treatment with inotropes compared with those receiving only metabolic treatment (4.69 ± 0.14 vs. $4.99 \pm 0.23\ mg\,kg^{-1}$ b.w.*min; $P = 0.23$). The average rates of glucose infusion in diabetics and non-diabetics with or without inotropes are given in Fig. 2.

The average blood glucose levels in diabetics and non-diabetics with or without inotropic stimulation are presented in Fig. 3.

Blood glucose was recorded 2–3 times during the first hour and thereafter approximately once every hour. A blood glucose below $4\ mmol\,l^{-1}$ was found in 1.4% of the readings ($n = 1047$) and occurred at some stage during the first 16 h in 11.2% of the

Table 2

Intraoperative and postoperative data including data on circulatory support in high-dose-treated glucose-insulin-potassium patients (n = 89).

Intraoperative data	
Redo surgery (%)	7.8
CABG (%)	60.7
Valve+CABG (%)	18.0
Aortic valve replacement (%)	7.9
Double valve procedure (%)	6.7
Mitral valve procedure (%)	1.1
Postinfarct-VSD (%)	4.5
Acute aortic dissection (%)	1.1
Aortic crossclamp time (min)	76 ± 4
Cardiopulmonary bypass time (min)	144 ± 7
Operation time (min)	280 ± 10
Circulatory treatment	
Mechanical circulatory support (%)	5.5
Inotropes for weaning from CPB (%)	43.8
Inotropes used during the first 24 h (%)	70.8
Dobutamine $>4\ \mu g\,kg^{-1}$ b.w. and min (%)	28.1
Epinephrine $>40\ ng\,kg^{-1}$ b.w. and min (%)	22.5
Milrinone therapy (%)	20.2
Vasoconstrictive drug used total (%)	66.3
Neosynephrine (%)	11.2
Norepinephrine (%)	25.8
Angiotensin II (%)	40.4
Vasodilators used in total (%)	84.3
Nitroglycerine (%)	79.8
Nitroprusside (%)	51.7
Intravenous glutamate infusion (%)	41.5
Postoperative data	
PMI (%)	32.5
Atrial fibrillation (%)	48
Premature ventricular contractions (%)	41
VT (%)	13
VF (%)	0
Lidocain treatment (%)	7
Electrical cardioversion (%)	0
Maximum postop serum creatinine ($\mu mol\,l^{-1}$)	129 ± 6
Postoperative renal failure (%)	10.7
Hemodialysis (%)	0
Peritoneal dialysis (%)	2.3
Neurological complication (%)	7.8
Wound infection (%)	5.6
Mechanical ventilation time (h)	52 ± 12
ICU stay (days)	3.7 ± 0.5
Mortality (%)	5.6

Results are given in percentages or mean ± SEM.
Results on overall inotropic support include the use of milrinone.
Postoperative renal failure=increase of s-creatinine >50% compared with preoperative values.
CABG=coronary artery bypass graft; VSD=ventricular septal defect; PMI=perioperative myocardial infarction; ICU=intensive care unit; VT=ventricular tachycardia; VF=ventricular fibrillation.

patients. The lowest blood glucose value recorded was $3.1\ mmol\,l^{-1}$. Mild to moderate hyperglycemia was aimed at in all cases but pronounced hyperglycemia with blood glucose $>14.0\ mmol\,l^{-1}$ was found in 2.8% of the readings and was recorded at some stage within the first 16 h of treatment in 14.6% of cases. Diabetics comprised 18% of the study population and accounted for 46.2% of the patients with blood glucose recordings exceeding $14.0\ mmol\,l^{-1}$.

Potassium control

Serum-potassium control and potassium infusion are presented in Fig. 4. Serum potassium was recorded approximately once every hour. As low potassium levels were considered desirable a s-potassium $<3.5\ mmol\,l^{-1}$ was found in 14.9% of the readings (n = 987) and at least one episode of s-potassium $<3.5\ mmol\,l^{-1}$ within the first 16 h of treatment was observed in 67.4% of the patients. The lowest value

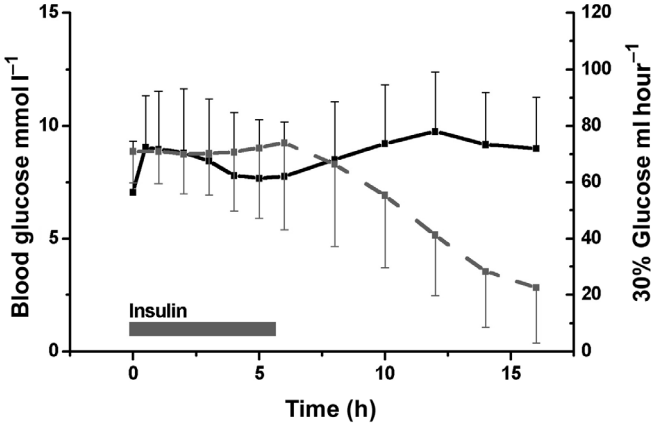

Fig. 1. Average blood glucose level (solid line; left axis; mmol l^{-1}) and infusion rate of 30% glucose (dashed line; right axis; ml h^{-1}) in all high-dose glucose-insulin-potassium-treated cases during 1994 (n = 89; mean ± SEM). The transverse bar indicates the duration of the insulin infusion.

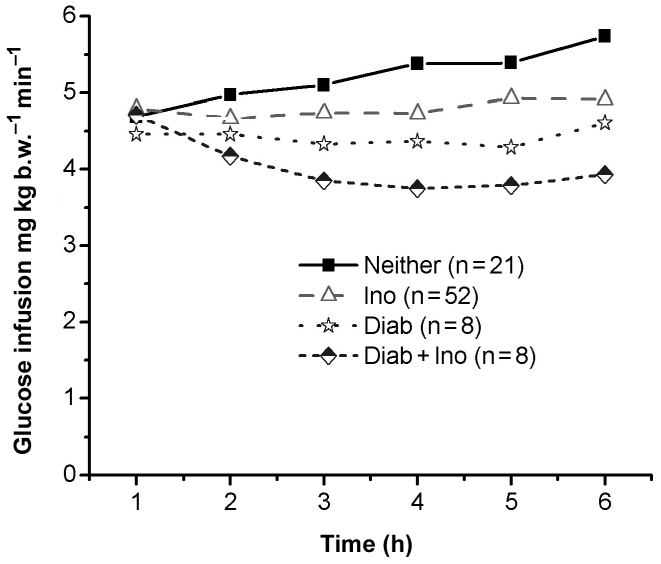

Fig. 2. Average rate of glucose infusion during high-dose insulin infusion in different subsets of patients depending on presence of diabetes or treatment with inotropes. Significant intergroup differences were observed (P = 0.049) as a result of differences between the groups 'Neither' and 'Diab+Ino' according to post hoc analyses (P<0.05).

recorded was 2.6 mmol l^{-1}. No case of ventricular fibrillation was observed. The incidence of ventricular tachycardia did not differ significantly between patients with s-potassium recording below 3.5 mmol l^{-1} and those without such episodes.

Hyperkalemia (s-potassium >5.0 mmol l^{-1}) appeared in 2.7% of the readings and was found in 7.9% of the cases at some stage. It was mild in all instances and usually occurred after stopping the

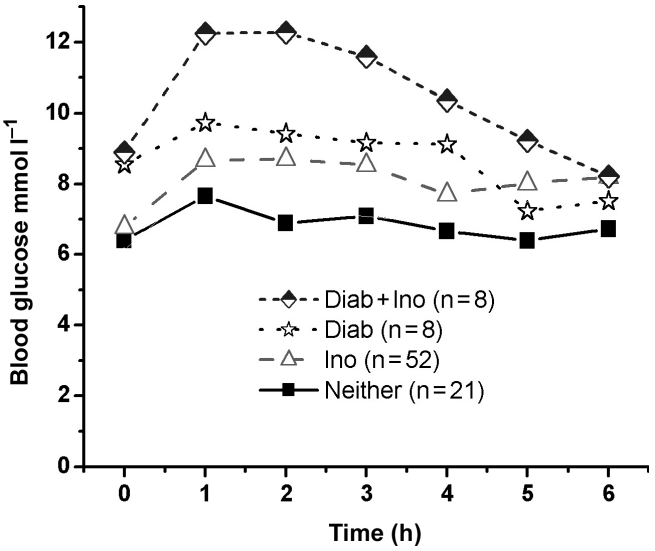

Fig. 3. Average blood glucose during high-dose insulin infusion in different subsets of patients treated with high-dose glucose-insulin-potassium because of clinical indication. Diab=diabetic patients, Ino=patients receiving inotropic drugs, Diab+Ino=diabetic patients receiving inotropic drugs, Neither=patients without diabetes or treatment with inotropic drugs. Significant intergroup differences were observed (P = 0.0059), with higher blood glucose levels in 'Diab' (P<0.05) and 'Diab+Ino' (P<0.05) compared with 'Neither' according to post hoc analyses.

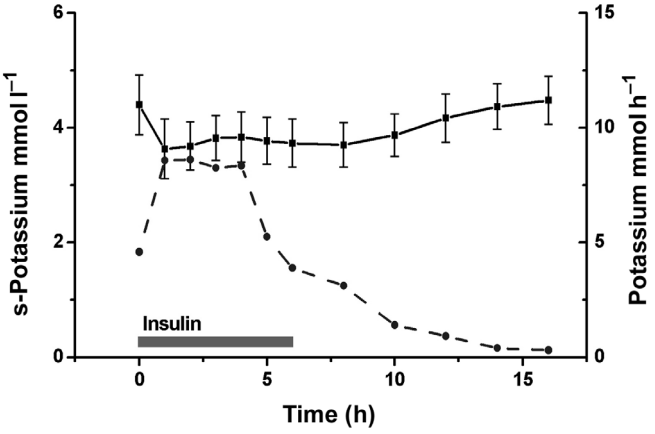

Fig. 4. Average serum potassium level (mean ± SEM; solid line; left axis; mmol l^{-1}) and the average infusion rate of potassium (mean; dashed line; right axis; mmol h^{-1}) in all high-dose glucose-insulin-potassium-treated cases during 1994 (n = 89). The transverse bar indicates the duration of insulin infusion.

insulin infusion. The highest value recorded was 5.9 mmol l^{-1}.

Pharmacological adjustment of peripheral vascular resistance

Nitroprusside was frequently used (51.7%) for afterload reduction during the early stages of treatment.

Phenylephrine (Neosynephrine®, Sanofi Winthrop) was used in 11.2% of the cases, mainly to treat vasodilatation during or immediately after CPB. In 58.4% of the patients, norepinephrine and/or angiotensin II was added to the treatment at some stage because of vasodilatation. The patients simultaneously treated with PDE III inhibitors (milrinone) received higher doses of norepinephrine ($P = 0.0003$) and angiotensin II ($P = 0.0057$) during the first 16 h. No case of refractory vasodilatation was observed.

Discussion

Our early clinical experience with metabolic interventions and the rationale behind our use of them in cardiac surgery have been given previously (6, 10). Since its introduction just over a decade ago high-dose GIK has been used in approximately 700 patients at our center without obvious side-effects. However, a detailed review with regard to blood glucose and serum-potassium homeostasis has not been carried out previously. In the present one-year series, high-dose GIK was used mainly to treat cardiac failure on weaning from CPB and in the early postoperative setting. The patients treated represented 10 percent of the most critically ill patients after cardiac surgery in an ICU caring for all patients undergoing cardiac surgery in the South-east region of Sweden. The decisions to use high-dose GIK were taken by the individual anesthetists and surgeons. In the ICU the treatment was managed and supervised by a nurse.

The dosage of insulin used in our protocol was based on available metabolic studies in association with cardiac surgery. Whereas moderate doses of insulin suffice to reduce plasma FFA levels, insulin doses up to 1 IU kg^{-1} b.w. an hour may be required to achieve full metabolic effects early after cardiac surgery (11, 12). Whether lower doses of insulin can cause a shift in myocardial substrate utilization from FFA to carbohydrates is not known, but currently only such doses have a documented effect on myocardial metabolism (10, 11). From a systemic metabolic point of view the effect of insulin is attenuated even at these supra-physiological doses and it is conceivable that this also applies to the effects on myocardial metabolism. To account for postoperative insulin resistance we have evolved a GIK regime employing a bolus of 25 IU to achieve an earlier steady-state insulin effect followed by an infusion of 1 IU kg^{-1} b.w. an hour. The duration of insulin treatment was originally set to 6 h to allow the effect to gradually subside, as available experience suggested that metabolic treatment provided an additional benefit for treatment of postoperative heart failure mainly during the first 12 h (7).

Management in general was satisfactory and stable blood glucose levels were routine. After the insulin infusion had been stopped, the glucose infusion was gradually decreased and maintained for approximately 22 h on average. Episodes of hypoglycemia were infrequent and mild. The incidence of hyperglycemia was higher mainly because of the protocol. Mild to moderate hyperglycemia was initially chosen for target blood glucose because it had been shown that systemic glucose uptake and presumably myocardial glucose uptake could be enhanced (19) and because initial concerns with this protocol mainly focused on the risk of hypoglycemia.

Basically the high-dose GIK protocol is a clinical application of a hyperinsulinemic glucose clamp. Thus, with the insulin doses employed, the blood glucose level in the short-term is influenced only by the rate of glucose infusion. A trend in blood glucose indicates that maximal systemic glucose uptake either exceeds or falls below the rate of glucose infused and, hence, the rate of infusion can be adjusted early before blood glucose is allowed to deviate from the target values. Therefore, high-dose GIK provides a means for strict blood glucose control. Target blood glucose for our high-dose GIK protocol is currently 7–10 mmol l^{-1}. Based on recently published data a further modification of target blood glucose to lower values seems warranted. First there is data showing that improved blood glucose control can reduce the incidence of wound infection in diabetics undergoing cardiac surgery and that treatment of hyperglycemia may attenuate the impact of stroke (20, 21). In a recent randomized trial, insulin treatment to keep blood glucose below 6.1 mmol l^{-1} (110 mg deciliter^{-1}) was reported to reduce in-hospital mortality of critically ill surgical ICU patients by 34% (1). Two-thirds of these patients were cardiac surgical patients and this subgroup had a 59% reduced risk (unadjusted) of dying in the ICU.

Although substantial amounts of glucose could be infused in these critically ill patients, it fell well below the 13 mg kg^{-1} b.w. and min found in preoperative studies using similar doses of insulin on patients undergoing elective coronary surgery for stable angina (12). On the other hand the amounts of glucose infused in our clinical experience was not markedly less compared with that infused in these stable elective patients after coronary surgery. Furthermore, we found only minor, albeit statistically significant,

differences in glucose requirements between diabetic and non-diabetic patients, illustrating the pseudo-diabetic state associated with postoperative neuroendocrine stress. Accordingly, blood glucose also tended to be higher and the need for glucose infusion lower if inotropes were used (Figs 2 and 3).

Apart from blood glucose control, vasodilatation and potassium control are central issues when high-dose GIK is used. Vasodilatation did not cause major problems. In fact, nitroprusside was used for afterload reduction in half of the patients at the early stage of treatment. As the treatment proceeded, some degree of vasodilation developed in most patients and nitroprusside was discontinued. A vasoconstrictor (angiotensin II or norepinephrine) was instituted in just over half of the GIK-treated patients at some stage to prevent hypotension. The need for vasoconstrictors was higher in those patients who were simultaneously treated with PDE III inhibitors, but no case of refractory vasodilatation was encountered. However, without access to angiotensin II we would not recommend combining high-dose GIK with a PDE III inhibitor.

Potassium was infused separately but s-potassium was allowed to decrease to approximately 3.5 mmol l^{-1} to avoid rebound hyperkalemia when the insulin infusion was stopped (Fig. 4). With this regime no episode of pronounced hyperkalemia was encountered. The limited problems posed by hyperkalemia after stopping the insulin infusion suggest that the protocol can be modified with a slight increase of target s-potassium. Mild hypokalemia was encountered in two-thirds of the patients. It cannot be excluded that hypokalemia during the insulin infusion contributed to premature ventricular contractions. However, the ventricular arrhythmias were generally benign and there was no need for electrical cardioversion. Furthermore, it is conceivable that the clinical condition of the patients, including a high proportion of patients with acute myocardial infarction, were responsible for a substantial proportion of these arrhythmias. The incidence of atrial fibrillation was also on level with what could be anticipated considering the mean age, which was close to 70 years, and the high proportion of complex procedures (22).

The incidence of neurological injury initially raised concerns, but according to the literature it was not unduly high considering the subset of patients (23). Furthermore, subsequent multivariate analysis of another cohort of patients at our institution revealed no indications that GIK was a risk factor for neurological complications (24). However, there are reports indicating that hyperglycemia may worsen outcome in stroke and thus depending on the quality of GIK management this treatment could potentially attenuate or promote such untoward effects (21).

The impact of GIK on hemodynamic performance and recovery has previously been documented in cardiac surgery (7, 8, 15, 16). Compared with dobutamine GIK was found to be a more economic way to improve myocardial function, as it did not increase oxygen consumption (8). For obvious reasons our study was not designed to evaluate the hemodynamic efficacy of high-dose GIK.

The relative importance of insulin, glucose administration and strict blood glucose control, respectively, remains to be established in the treatment of patients after cardiac surgery. With respect to infections and stroke, blood glucose control seems to be vital, but the other effects of the insulin required to achieve strict blood glucose control cannot be disregarded (1, 21). The high-dose GIK regime used in the present study has been shown to provide insulin levels sufficient to optimize the metabolic effects during conditions characterized by severe neuroendocrine stress (12, 25). In the present study it was found that it has the potential to achieve strict blood glucose control in conjunction with substantial glucose administration in critically ill patients including diabetics. It is currently the only GIK regime with a documented effect on myocardial substrate uptake after cardiac surgery and this effect has also been demonstrated in diabetic patients (11, 26).

Conclusions

The metabolic and physiological background, and the clinical safety of high-dose GIK in cardiac surgery with particular regard to blood glucose and serum potassium have been described. Provided careful monitoring, high-dose GIK can be safely employed in clinical practice after cardiac surgery. The high-dose GIK regime allowed substantial amounts of glucose to be infused both in diabetic and critically ill patients with maintenance of acceptable blood glucose control, but room for adjustment of target blood glucose and s-potassium has subsequently been identified. Although encouraging clinical and metabolic results have been obtained with high-dose GIK (6, 10, 11, 26) further studies including randomized trials are required to define the role of high-dose GIK in cardiac surgery and intensive care.

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