Glucose and potassium derangements by glucose-insulin-potassium infusion in acute myocardial infarction

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Published in:
Netherlands Heart Journal

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Background. High-dose glucose-insulin-potassium infusion (GIK) has been suggested to be beneficial in acute myocardial infarction (MI). Recently new large trials have shown no effect of GIK on mortality. To investigate whether metabolic derangement could have negated the potential beneficial effect, we studied the relation between systemic glucose and potassium levels and outcome.
Methods. Patients with signs and symptoms of ST-segment-elevation MI and treated with primary percutaneous coronary intervention (PCI) were randomised to no infusion or high-dose GIK, i.e. 80 mmol potassium chloride in 500 ml 20% glucose at a rate of 3 ml/kg/hour and 50 units short-acting insulin in 50 ml 0.9% sodium chloride for 12 hours.
Results. A total of 6991 glucose values and 7198 potassium values were obtained in 476 GIK patients and 464 controls. Mean serum glucose was significantly higher in the GIK group (9.3±4.5 mmol/l vs. 8.4±2.9 mmol/l, p<0.001). Mean potassium level was significantly higher in the GIK group (4.2±0.5 mmol/l vs. 3.9±0.4 mmol/l, p<0.001). Incidence of hyperglycaemia (glucose >11.0 mmol/l) occurred in 70.8% of GIK patients and 33.8% of controls (p<0.001). Hypokalaemia was less common in the GIK group (23.5 vs. 41.2%, p<0.001). Incidence of hyperkalaemia and hypoglycaemia did not differ significantly between the two groups. In multivariate analysis age, previous cardiovascular disease, Killip class >1, unsuccessful PCI and mean glucose after admission were associated with increased one-year mortality.
Conclusion. In ST-segment-elevation MI patients treated with primary PCI, high-dose GIK induced hyperglycaemia and prevented hypokalaemia. Derangement of the glucose metabolism was related to one-year mortality.
(*Neth Heart J* 2006;14:89-94.)

Keywords: glucose, insulin, potassium, infusion, myocardial infarction, hyperglycaemia

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In the past three decades an extensive body of evidence has accumulated that underscores the importance of glucose metabolism during ischaemia and reperfusion of the heart. A meta-analysis involving nine early clinical studies with 1932 patients indicated that GIK might play an important role in reducing in-hospital mortality after acute myocardial infarction (MI).[1] In the four studies in which a higher dose was used, a reduction in mortality from 12% in the control group to 6.5% in the GIK group was observed.[2-5] In these studies high-dose GIK denoted an infusion of at least 30 grams of glucose, 50 units of insulin, and 80 mmol potassium per litre at a rate of 1.5 ml/kg/hour. This dose maximally suppressed arterial free fatty acids (FFA) levels and myocardial FFA uptake, and induced a maximal increase in myocardial glucose uptake.[6]

Table 1. Algorithm of insulin infusion rate in patients randomised to the GIK group. Starting dose and hourly adjustment.

Starting dose of insulin infusion rate		
Glucose (mmol/l)	**Additional action**	**Infusion rate (IU/hour)**
>15	8 IU short-acting insulin iv	30
11.0-15.0		30
10.0-10.9		24
9.0-9.9		18
8.0-8.9		12
7.0-7.9		6
<7		3
Hourly adjustment of insulin infusion rate based on hourly measured glucose		
Glucose level (mmol/l)	**Additional action**	**Infusion rate (IU/hour)**
>15	8 IU short-acting insulin iv	Increase by 6
11.0-15.0		Increase by 3
7.0-10.9		Leave unchanged
4.0-6.9		Decrease by 6
<4	1. Stop infusion for 15 minutes	
	2. Measure blood glucose level every 15 minutes until >6.9 mmol/l	
	3. Start infusion with infusion rate 6 ml/hour beneath rate before stop	
	4. If symptoms of hypoglycaemia are present than give 20 ml of glucose 30% i.v.	

Thereafter in the Estudios Cardiologicos Latinoamerica (ECLA) pilot trial the combination of reperfusion and GIK was related to a 10% 30-day mortality reduction (5.2 vs. 15.2%, p<0.001). In a randomised trial with 940 patients we studied whether primary percutaneous coronary intervention (PCI) with high-dose GIK was beneficial.[7] After 30 days the mortality rate in the overall population was 4.8% in the GIK group compared with 5.8% in the control group (p=0.50). The recently published CREATE-ECLA confirmed that GIK does not lower mortality.[8]

In two early studies involving 30 and 104 patients, the infusion of GIK in MI patients induced hyperglycaemia and hyperkalaemia.[9,10] We sought to determine the relation between metabolic derangements induced by GIK infusion and one-year mortality, in order to explain the absence of a clinically beneficial effect in the recently completed randomised trials.

Methods

Study population

Patients with symptoms and signs of ST-segment-elevation MI eligible for primary PCI were randomised to GIK or no infusion. GIK consisted of a continuous infusion of 80 mmol potassium chloride in 500 ml 20% glucose with a rate of 3 ml/kg/hour in a peripheral venous line and 50 units short-acting insulin in 50 ml 0.9% sodium chloride. The dose and adjustments of the insulin infusion were based on a modified algorithm, to obtain blood glucose levels between 7.0 and 11.0 mmol/l (table 1). The infusion was continued for a maximum of 12 hours. All patients went to the catheterisation laboratory where PCI was performed if the coronary anatomy was suitable. The research protocol was reviewed and approved by the medical ethics committee, and patients were included after informed consent.

Metabolic determinants

In all patients frequent measurements of glucose and potassium (Modular System, Roche/Hitachi, Basel, Switzerland) were obtained. We defined hyperglycaemia as a glucose level >11.0 mmol/l,[11] hypoglycaemia as a glucose ≤3.0 mmol/l,[12] hyperkalaemia as a potassium level of ≥5.5 mmol/l,[13] and hypokalaemia as a potassium level ≤3.5 mmol/l.[14] We compared the incidence of glucose or potassium derangements in the GIK and control group, and in addition determined the relation between these derangements and one-year mortality.

Statistical analysis

Data were expressed as means with standard deviation unless otherwise indicated. Previous cardiovascular disease (CVD) was defined as either previous myocardial infarction, previous angioplasty, previous coronary artery bypass grafting, or previous cerebrovascular accident. Unsuccessful PCI was defined as TIMI flow <3 or blush grade <2. Differences between group means at baseline were assessed with the two-tailed Student's t-test. Chi-square analysis was used to test differences between proportions. Survival was calculated by the

Table 2. Baseline characteristics of the Glucose Insulin Potassium Study.

Characteristics	GIK group	Control group
Age, years ± SD	59.9±11.9	60.8±12.0
Men	351 (73.7)	368 (79.3)
Referred patients	201 (42.3)	180 (38.8)
Body mass index	26.7±3.8	27.0±4.0
Previous MI	52 (10.9)	53 (11.4)
Previous PCI	22 (4.7)	24 (5.2)
Previous CABG	14 (2.9)	12 (2.6)
History of stroke	17 (3.6)	15 (3.2)
Diabetes mellitus	50 (10.5)	49 (10.6)
Hypertension	134 (28.2)	130 (28.0)
Dyslipidaemia	94 (19.7)	95 (20.5)
Currently smoker	225 (47.3)	237 (51.1)
Positive family history	195 (41.0)	179 (38.6)
Time to admission, min (IQR)*	150 (100-215)	150 (105-234)
Door to balloon time, min (IQR)	45 (31-64)	48 (34-69)
Killip class 1	426 (89.5)	430 (92.7)
Killip class 2	24 (5.0)	14 (3.0)
Killip class 3	14 (2.9)	14 (3.0)
Killip class 4	12 (2.5)	6 (1.3)
Anterior MI	250 (52.9)	224 (49.1)
Multivessel disease	249 (52.3)	242 (52.2)
PCI	436 (91.6)	424 (91.4)
Stent**	255 (58.5)	236 (55.7)
GP IIb/IIIa receptor blocker**	96 (22.1)	109 (25.7)
In-hospital CABG	19 (4.0)	19 (4.1)
TIMI 3 flow	459 (96.4)	435 (93.8)
Successful reperfusion†	394 (82.8)	384 (82.8)
Intra-aortic balloon pump	45 (9.5)	42 (9.1)
Mechanical ventilation	12 (2.5)	4 (0.9)

Data are number (%) unless otherwise indicated. MI=myocardial infarction, IQR=interquartile range, PCI=percutaneous coronary intervention, CABG=coronary artery bypass grafting. *Time to admission denotes time between onset of symptoms until admission. †In-hospital CABG=CABG defined as patients initially treated conservatively, followed by elective CABG within 7 days. †Successful reperfusion denotes TIMI 3 flow and blush grade 2 or 3. **Percentage defined as the percentage of the patients who underwent PCI.

Kaplan-Meier product-limit method. The log-rank test was used to evaluate differences in survival curves between the two treatment groups. The Cox proportional hazards regression model was used to estimate the independent association between glucose and potassium derangements and one-year mortality. Age, and mean glucose and potassium level were entered as continuous variables in this analysis. Differences were considered significant for a two-tailed p value <0.05. The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA; version 11.0.1) was used for statistical analysis.

Results

A total of 6991 glucose values and 7198 potassium values were analysed in 940 patients. Baseline characteristics of patients randomised to GIK (n=476) or no infusion (n=464) are represented in table 2. Mean glucose level was 9.3±4.5 mmol/l in the GIK group compared with 8.4±2.9 mmol/l in the control group (p<0.001) (table 3). The mean glucose values were significantly higher in the GIK patients between two and six hours after admission (figure 1). Hyperglycaemia occurred in 337 GIK patients and in 157 control patients (70.8 vs. 33.8%, p<0.001). A total of only ten patients developed hypoglycaemia, three patients in the GIK group vs. seven patients in the control group (0.6 vs. 1.5%, p=0.34).

Mean potassium level was 4.2±0.5 mmol/l in the GIK group vs. 3.9±0.39 mmol/l in the control group (p<0.001), (table 3). The potassium levels were significantly higher in the GIK group between 2 and 48 hours (figure 2). A total of 26 patients (5.5%) treated

Table 3. Metabolic data of GIK group and control group patients.

	GIK group	Control group	P value
Glucose			
- Level (mean±SD)	9.3±4.5	8.4±2.9	<0.001
- Range	2.2-39.0	1.7-41.0	
- 5-95% percentiles	5.3-18.9	5.6-13.9	
- Hyperglycaemia (>11%)	337 (70.8)	157 (33.8)	<0.001
- Hypoglycaemia (≤3%)	3 (0.6)	7 (1.5)	0.34
Potassium			
- Level (mean±SD)	4.2±0.5	3.9±0.4	<0.001
- Range	2.3-6.9	2.4-7.3	
- 5-95% percentiles	3.5-4.9	3.4-4.6	
- Hyperkalaemia (>5.5%)	26 (5.5)	15 (3.2)	0.11
- Hypokalaemia (<3.5%)	112 (23.5)	191 (41.2)	<0.001

with GIK vs. 15 patients (3.2%) who received no infusion had a potassium level of 5.5 mmol/l or higher (p=0.11). Hypokalaemia was observed less often in 112 patients (23.5%) in the GIK group vs. 191 patients (41.2%) in the control group (p<0.001).

Metabolic derangements and one-year mortality

In 494 patients with hyperglycaemia during admission, 48 patients (9.4%) died vs. 21 patients (4.7%) out of 446 patients without hyperglycaemia (RR 2.18 (1.28 to 3.70), p=0.004). The number of patients who died with hyperglycaemia in the GIK group was 28 (8.3%) out of 337 patients compared with 20 patients (12.7%) out of 157 controls (RR 0.62 (0.34 to 1.14), p=0.14). Only ten patients had a glucose level ≤3.0 mmol/l and two of these patients (20%) died. Both were randomised to infusion with GIK and both PCI procedures were unsuccessful. One died on day 2 and the other on day 4 after admission. The lowest glucose value was 2.8 mmol/l and 3.0 mmol/l in these patients.

A total of 41 patients had hyperkalaemia and 18 patients (43.9%) did not survive after one year. In the GIK group 26 patients had hyperkalaemia and nine patients (34.6%) died compared with nine patients (60%) out of 15 patients in the control group (RR 0.35 (0.10 to 1.31), p=0.19). Hypokalaemia was present in 303 patients and 30 patients (9.9%) died. In the GIK group ten patients (8.9%) out of 112 patients compared with 20 (10.5%) out of 191 control patients did not survive to one year (RR 0.84 (0.38 to 1.86), p=0.84).

To study the independent predictive value of glucose and potassium derangements on one-year mortality, multivariate regression analysis was performed including age, gender, diabetes, randomisation to GIK and all variables that were significant predictors in univariate analysis. Unadjusted predictors of one-year mortality were increased age, anterior MI, previous CVD, Killip class >1, multivessel disease, unsuccessful PCI, and mean glucose. After multivariate analysis, age (OR 1.05, 95% CI 1.02 to 1.08), previous CVD (OR 3.14, 95% CI 1.81 to 5.43), Killip class 2 (OR 3.62, 95% CI 1.52 to 8.61), Killip class 3 (OR 7.60, 95% CI

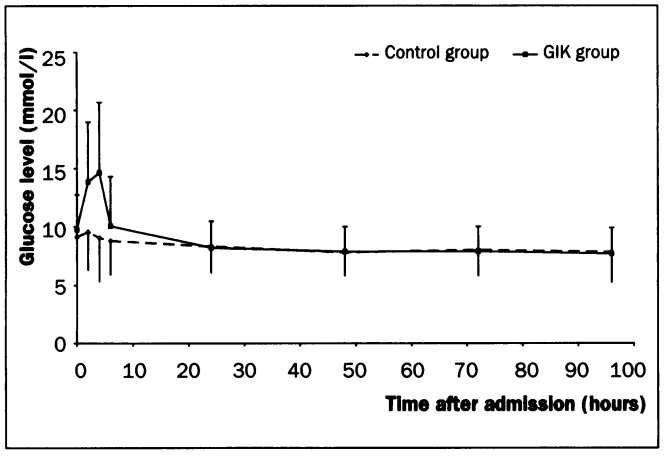

Figure 1. Mean ± SD glucose level over 96 hours after admission in patients in the GIK group and control group.

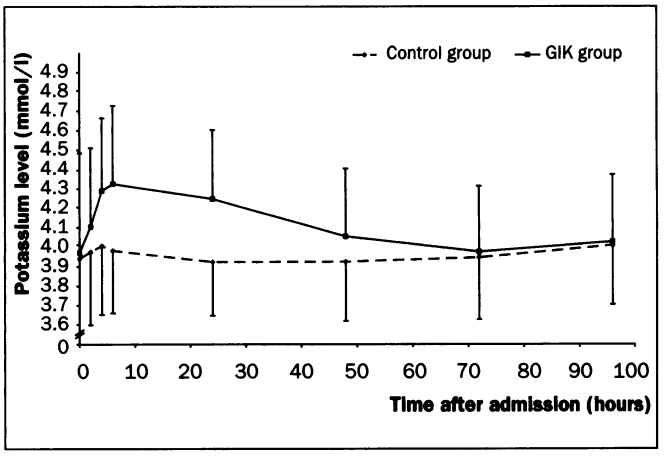

Figure 2. Mean ± SD potassium level over 96 hours after admission in patients in the GIK group and control group.

3.57 to 16.1), Killip class 4 (OR 18.6, 95% CI 8.23 to 41.8), unsuccessful PCI (OR 2.71, 95% CI 1.58 to 4.63), and mean glucose (OR 1.08, 95% CI 1.01 to 1.15) were independent predictors of long-term mortality.

Discussion

In ST-segment-elevation MI patients treated with primary PCI, infusion of high-dose GIK is related to significantly higher glucose levels during the first hours after admission. Hyperglycaemia was observed in at least seven out of ten patients treated with GIK. This is more than double the rate in patients who received no infusion. Patients with a higher mean glucose during hospital admission had worse one-year mortality independent of the existence of diabetes, and other risk factors such as age, anterior localisation of the infarction, multivessel disease and unsuccessful PCI. Age and mean glucose were entered as continuous variables into the analysis. For every 1.0 mmol/l increase in mean glucose level the risk increased by 8%.

The relation between GIK infusion and hyperglycaemia was found by others. Prather and colleagues found that the mean glucose values were higher in 18 patients treated with GIK compared with seven untreated controls during the infusion period of 48 hours.[9] A relation that was also present in a study by Sysoeva and colleagues comparing 56 patients treated with GIK with 48 controls.[10] In the low-dose Polish GIK (Pol-GIK) trial the mean glucose level in 494 GIK patients was even lower in 460 control patients after 24 hours (5.9 mmol/l vs. 6.2 mmol/l). In this study the amount of insulin infusion was decreased because of a glucose level <3.4 mmol/l in 35 (9.4%) out of 369 patients. In the CREATE-ECLA symptomatic hypoglycaemia was uncommon but more frequent in the GIK infusion group (0.4%) than in the control group (0.1%).[8] In our study the amount of GIK infused induced hyperglycaemia. It has been suggested that hyperglycaemia is related to impaired preconditioning, increased infarct size, and no reflow phenomenon.[15,16] Hyperglycaemia is related to stress-induced elevation of free fatty acids which may compromise myocardial function as they reduce contractility and increase ischaemic and reperfusion injury. Possibly the potential beneficial effect of GIK could be diminished by the induction of hyperglycaemia. Hypoglycaemia was uncommon, and only two patients with hypoglycaemia died, probably related to the sequel of unsuccessful reperfusion. In experimental studies hypoglycaemia induced myocardial damage.[17] In clinical studies it has been found that hypoglycaemia was related to increased in-hospital mortality.[18]

The infusion of potassium as part of the GIK infusion in our study had only a minor effect on the mean potassium level of the GIK group. That the differences in potassium levels between both groups persisted for 48 hours can be explained by the fact that potassium needs to be cleared by the kidneys. In the Prather study the mean potassium level was approximately 1.5 mmol/l higher in GIK patients after 24 hours until 96 hours after admission.[9] In the ECLA the potassium levels were also significantly higher (4.25 mmol/l vs. 4.04 mmol/l at 24 hours (p=0.0001) and 4.24 mmol/l vs. 4.08 mmol/l at 48 hours (p=0.0027)). The number of GIK patients with hyperkalaemia was somewhat higher and with hypokalaemia slightly lower. In the Pol-GIK trial four GIK patients (0.8%) had hyperkalaemia and three patients (0.7%) had hypokalaemia.[13] In the CREATE-ECLA hyperkalaemia (>5.5 mmol/l) was also more frequent in the GIK infusion group than in the control group (4.3 vs. 1.6%).[8] Further analysis of the subgroup with hyperkalaemia indicated more deaths at 30 days in the control group (23.6%) compared with the GIK infusion group (14.4%), suggesting that the hyperkalaemia associated with GIK use was not deleterious. The relation between hyperkalaemia and one-year mortality was especially present in the control group. Avoiding hypokalaemia is considered to be beneficial in several cardiovascular disease states including acute MI.[19] The relation between hypokalaemia and arrhythmias is found in some but not all studies.[14,20,21] Sodi-Pollares and colleagues were the first to suggest that GIK was beneficial in the treatment of ischaemic myocardial arrhythmias.[22]

Conclusion

This study shows that in ST-segment-elevation MI patients treated with primary PCI, infusion of high-dose GIK was related to both hyperglycaemia and hyperkalaemia, and prevention of hypokalaemia. The beneficial effect of GIK on mortality was possibly negated by the induction of these metabolic derangements, especially hyperglycaemia. Substantial experimental evidence underscores the potential beneficial effects of metabolic treatment with glucose, insulin, and potassium for the heart exposed to the injuries of ischaemia and reperfusion. ■

Acknowledgment

This study was supported by a generous grant from the Netherlands Heart Foundation (99.028). No other conflicts of interest or financial disclosure.

The Netherlands Heart Foundation had no role in any of the following items: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

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