The effect of insulin on the heart

Part 2: Effects on function during and post myocardial ischaemia

L.J. Klein, F.C. Visser

Insulin infusion has been advocated in the treatment of myocardial ischaemia and myocardial infarction. There is evidence from experimental animal studies for a protective effect of high-dose insulin administration in myocardial ischaemia and myocardial infarction. In some relatively small study populations a reduction in mortality was reported in those patients who received glucose-insulin-potassium (GIK) during myocardial infarction, which was confirmed in two meta-analyses. However, it has not been possible to reproduce these positive results in large randomised clinical trials. (Neth Heart J 2010;18:255-9.)

Keywords: Cardiomyopathy; Founder Effect; Mutation; Myosin-binding Protein C

In this second part of the review of the cardiovascular effects of insulin, we focus on the potential protective effect of insulin in myocardial ischaemia and discuss the large clinical trials which have been performed with insulin administration in acute myocardial infarction.

Myocardial protection of insulin in (experimental) myocardial ischaemia

In vitro studies

In vitro studies applying ischaemia to rat,[1-4] guinea pig[5] and rabbit hearts[6-8] reported improvement in systolic[2-8] and diastolic function[2,6-8] when insulin was added to the perfusate after reperfusion. Two studies reported the best protection by insulin when it was added shortly before reflow was established after experimental occlusion.[1,8] Insulin led to (relative) preservation of high-energy phosphates in many studies,[4-6,8] as well as to a reduction in ultrastructural damage of the myocytes caused by ischaemia and anoxia,[6] but did not change the high-energy phosphate depletion caused by ischaemia in one study.[2] Also, addition of insulin to the perfusate preserved glycolytic flux during ischaemia[2,6-8] and increased lactate production, indicating increased anaerobic metabolism of glucose.[2,7,8] Mitochondrial function and glycogen storages were maintained.[3,5] A number of the observed effects correlated to each other: the left ventricular end-diastolic pressure (LVEDP) correlated strongly and negatively with the preserved adenosine triphosphate (ATP) content, lactate production and glucose uptake, myocardial glucose-uptake correlated positively with lactate production and ATP content.[8] In a study in which dog hearts were perfused with the aid of another dog, perfusion was interrupted for two hours after pretreatment with glucose-insulin-potassium (GIK). Systolic function was preserved and myocardial damage was less in pretreated dog hearts compared with dog hearts which were not pretreated with GIK, thus indicating a preservative effect of GIK.[9]

Finally, reduction of infarct size by insulin administration after coronary occlusion seemed to be dependent on time of administration: infarct size was reduced when insulin administration was started just before reperfusion (and continued for 15 or 120 minutes), but not if insulin administration was started ten minutes after reperfusion.[1] This may indicate protection against myocardial injury caused by reperfusion.

In vivo experimental studies

Insulin preserved systolic and diastolic function during ischaemia, or hearts from insulin-treated animals showed better recovery of function after reperfusion,[10-18] but others did not observe an effect of insulin on postischaemic function.[19-21] Interestingly, one of the positive studies infused insulin intracoronarily at a rate of 4 U/min in mongrel dogs

L.J. Klein
F.C. Visser
Department of Cardiology, VU Medical Centre, Amsterdam, the Netherlands

Correspondence to: L.J. Klein
Department of Cardiology, VU Medical Centre, PO Box 7057, 1007 MB Amsterdam, the Netherlands
E-mail: lucasklein@xs4all.nl

Table 1. Glucose-insulin-potassium (GIK) in myocardial infarction studies.

Study	Number, type of patients	Protocol	Insulin equivalent mU/kg/h	Results
DIGAMI[39, 40]	n=620 Known diabetes or high glucose at admission (>11.1 mmol/l)	Insulin 160 U/l + glucose 5% at 30 ml/h, rate adjusted for blood glucose, ≥24 hours; subsequent subcutaneous insulin for 3 months *vs.* standard care	64 †	Reduced one-year mortality in GIK + sc insulin treated patients (18.6 *vs.* 26.1%, p=0.027) Reduced mortality at 3.4 years FU (33 *vs.* 44%, p=0.011)
DIGAMI-2[41]	n=1253 Known type 2 diabetes or high glucose at admission (>11.1 mmol/l); trial terminated early because of slow recruitment	Insulin 160 U/l + glucose 5% at 30 ml/h, rate adjusted for BG ≥24 hours, ± subsequent subcutaneous insulin for 3 months *vs.* standard care *vs.* standard care	64 †	No effect of GIK on mortality (22-24%), reinfarction, stroke at 2 years FU
HI-5[42]	n=240 Known diabetes or hyperglycaemia at admission (>7.8 mmol/l)	Insulin 2 U/h + glucose 5% at 80 ml/h (heart failure: glucose 10% at 40 ml/h); insulin infusion adjusted according to BG, 24 hours *vs.* standard care	27 †	No effect of GIK *vs.* placebo on mortality at discharge (4.8 *vs.* 3.5%), at 3 months (7.1 *vs.* 4.4%), 6 months (7.9 *vs.* 6.1%) Reduction in heart failure (12.7 *vs.* 22.8%, p=0.04) and reinfarction (2.4 *vs.* 6.1%, p=0.05) at 3 months
REVIVAL[43]	n=312 Reperfusion therapy	Insulin 40 U/l + glucose 200 g/l + KCl 64 mmol/l at 1.8 ml/kg/h, 24 hours *vs.* standard care	72	No effect on 6-month mortality (5.6 *vs.* 6.4%) No effect on infarct size (salvage index in GIK 0.5, in placebo 0.48, with initial infarct size of 22% of LV) In diabetics (n=72) significant difference in myocardial salvage (mean difference 0.19; 95% CI 0.01-0.37)
ECLA pilot[44]	n=407 Controls Low-dose GIK High-dose GIK	Insulin 50 U/l + glucose 250 g/l + KCl 80 mmol/l at 1.5 ml/kg/h, 24 hours *vs.* Insulin 20 U/l + glucose 100 g/l + KCl 40 mmol/l at 1.0 m/kg/h, 24 hours *vs.* Standard care	75 20	No effect on in-hospital mortality One year survival in patients with high-dose GIK and reperfusion better than in controls and low-dose GIK
Pol-GIK[45]	n=954 Early termination, 2650 planned patients	Insulin 32 U/l (later 20 U/l) + glucose 100 g/l + potassium 6g/l at 42 ml/h, 24 hours *vs.* saline 0.9 % at 42 ml/h, 24 hours	17.9 Later 11.2	Trial stopped because of excess mortality in GIK treated group at 35 days after index event
GIPS[46]	n=940 Primary PCI	Glucose 200 g/l + KCl 160 mmol/l at 3 ml/kg/h + insulin variable rate according to BG, 8-12 h *vs.* standard care	Variable (actual rate not reported)	Overall: no difference in 30-day mortality (GIK: 4.8%; controls: 5.8%) Patients with Killip 1 at presentation: 30-day mortality 1.2% (GIK) *vs.* 4.2% (controls), p=0.01, RR 0.27, overall mortality at 1-year FU: 6.5 *vs.* 8.2%, p=NS
GIPS-2[47]	n=889 (of 1044 planned) Killip class I, primary PCI	Glucose 200 g/l + KCl 80 mmol/l at 2 ml/kg/h + insulin variable rate according to BG, 12 h *vs.* standard care	Variable (actual rate not reported)	No difference on mortality (GIK 5.3%, controls 3.9%), revascularisation and reinfarction at 1-year FU
CREATE-ECLA[48]	n=20,201 Patients with STEMI <12 h	Insulin 50 U/l + glucose 250 g/l + KCl 80 mmol/l at 1.5 ml/kg/h, 24 hours *vs.* standard care	75	No difference in 30-day mortality (GIK: 9.7%; controls: 10%)
Oasis-6[49]	n=2748 (8000 planned) Patients with STEMI Early termination because of negative results CREATE-ECLA	Insulin 50 U/l + glucose 250 g/l + KCl 80 mmol/l at 1.5 ml/kg/h, 24 hours *vs.* standard care	75	No difference in 6-month mortality (GIK: 10.8; controls 10.4 %)

† estimated for a person of 75 kg. BG=blood glucose, FU=follow-up, GIK=glucose-insulin-potassium, LV=left ventricle, NS=not significant, PCI=percutaneous coronary intervention, RR=relative risk, sc=subcutaneous, STEMI=ST-elevation myocardial infarction.

of 15 to 30 kg (130 to 260 mU/kg/min) without systemic effects.[12] Intracoronary insulin infusion increased myocardial glucose uptake more than intravenous insulin but effects on function were not different from insulin administered intravenously (4 U/min, 130 to 260 mU/kg/min).[12] The rate of insulin perfusion in this study was extraordinarily high compared with human studies (see below). Insulin administration during ischaemia relatively preserved high-energy phosphates,[15,19,22-24] but showed no effect on high-energy phosphates in other studies.[11,13] Histological and ultrastructural damage was limited in GIK administration during ischaemia compared with controls.[19,25] Scar size and the amount of apoptosis were reduced,[17,18,26] but in some studies scar size was not able to show an effect on scar or apoptosis.[10,20] The area of necrosis was smaller if GIK was started during the induced ischaemia which was followed by reperfusion than when started at reperfusion; however, the reduction when started at reperfusion was still larger than in the control group.[17]

Conflicting results were also obtained with regard to the ST deviation, with a reduction of ST deviation during ischaemia and concurrent GIK administration[10,21,22] but no difference was observed by others.[11,24,27] Ventricular fibrillation occurred less frequently[17] or as often as in controls.[27]

Glucose-insulin-potassium in acute myocardial infarction

In 1962, Sodi-Pallares et al. used potassium-glucose-insulin (so-called polarising solution) in ten patients with acute myocardial infarction and 20 patients with chronic coronary insufficiency.[28] In three patients, the signs of acute ischaemia decreased, in two patients they worsened. In patients with chronic coronary insufficiency, alterations in repolarisation were observed as well. Ventricular arrhythmias almost disappeared and reoccurred when the infusion was stopped.

After the initial report by Sodi-Pallares, studies were performed applying GIK infusions, subcutaneous insulin in combination with glucose infusion or subcutaneous insulin and oral glucose and potassium as adjunctive therapy to myocardial infarction, a number of them with the aim to reduce in-hospital mortality.[29-37] Fath-Ordoubadi and Beatt performed a meta-analysis of these studies, leaving out studies without a proper design.[38] All these studies were performed in the prethrombolysis era. From the pooled data, a proportional mortality reduction of 28% (95% CI 10 to 43%) was calculated in favour of insulin administration in the setting of acute myocardial infarction.[38] However, interpretation of the results of this meta-analysis is difficult, since the studies included in the meta-analysis have important methodological differences. Furthermore, the results can hardly be extrapolated to date, because the studies were mainly performed in the prereperfusion era.

After the publication of the meta-analysis by Fath-Ordoubadi and Beatt,[38] a number of new studies have been published, which are summarised in table 1.[39-49]

In contrast to the meta-analysis of Fath-Ordoubadi,[38] the conclusion from the overview in table 1 is that GIK administration does not reduce mortality in patients with acute myocardial infarction. There are only three studies with a true positive result: the DIGAMI study (patients with known diabetes or high glucose at admission),[39,40] the pilot ECLA study (mainly in patients with reperfusion therapy by thrombolysis)[44] and the GIPS study for patients with Killip class 1.[46] However, the DIGAMI-2,[41] GIPS-2,[47] the CREATE-ECLA trial[48] and the OASIS-GIK[49] did not show a reduction in mortality and are the largest trials on GIK in myocardial infarction ever performed.

The different regimens of insulin administration used in the trials are a point of concern.[50] From data with experimental ischaemia in animals but also from those studies focusing on myocardial function in humans (see part 1 of this review),[51] it is probably more important to give a high dose of insulin than to administer glucose and adjust insulin infusion rate. Furthermore, the applied dose of insulin in patients is generally much lower than in experimental animal studies.

In studies in patients with myocardial infarction not focusing on mortality, no effects were observed on oxidative stress[52] or only a trend towards a larger amount of salvaged myocardium was observed.[53]

Summary and conclusion

In experimental studies with myocardial ischaemia and myocardial infarction, glucose-insulin administration has a protective effect on myocardial function and reduces infarct size. The lack of effect in clinical studies (no effect on mortality in acute myocardial infarction) does not exclude a positive effect of high-dose insulin infusion on myocardial function. ■

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