The role of glucose-insulin-potassium therapy in the current management of acute myocardial infarction

NARBEH MELIKIAN, FARZIN FATH-ORDOUBADI

Abstract

Glucose-insulin-potassium (GIK) therapy addresses the metabolic changes of ischaemia secondary to acute myocardial infarction. These changes include elevated plasma free fatty acid concentration and glucose intolerance.

A meta-analysis of trials from the pre-thrombolysis era showed a significant reduction in the number of deaths in the GIK group in comparison to placebo (16.1% *vs.* 21% respectively, p=0.004). High-dose GIK therapy was found to be of particular benefit.

Three randomised trials in the post-thrombolysis era have been published, with variable results. The DIGAMI study (in diabetics) and the ECLA pilot trial had positive results: in the latter there was a 60% reduction in in-hospital mortality in patients who received GIK therapy plus reperfusion. By contrast, the Pol-GIK trial was negative.

Outstanding questions include the usefulness of GIK therapy and beta blockade in the presence of thrombolysis or primary angioplasty. GIK therapy and beta blockade might act in complementary fashion to antagonise the metabolic changes of ischaemia while thrombolysis or angioplasty improve early reperfusion and limit infarct size. Patients with acute coronary syndrome might benefit more from GIK therapy since they have some coronary flow.

Key words: myocardial infarction, ischaemia, glucose-insulin-potassium therapy, GIK therapy, metabolic changes.

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Introduction

Ischaemia secondary to acute myocardial infarction (AMI) leads to major myocardial metabolic changes. The cornerstone of current treatment for AMI is restoration of myocardial blood flow and includes administration of antiplatelet agents (such as aspirin), thrombolysis and primary angioplasty. Alternative approaches directly address the metabolic changes and hence can theoretically exert a myoprotective effect until restoration of blood flow is achieved and the oxygen deficit reversed. Glucose-insulin-potassium (GIK) therapy is one such approach. Both *in vitro* and *in vivo* studies have identified several mechanisms by which GIK therapy may exert its beneficial effect.

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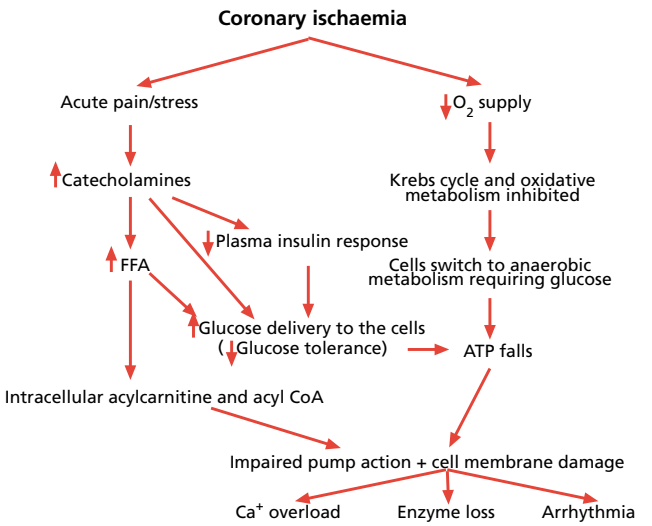
Molecular aspects

The normal heart can metabolise a variety of substrates in order to produce adenosine triphosphate (ATP). During acute myocardial infarction or ischaemia there is an increase in sympathetic activity with catecholamine release,[1] elevation in plasma free fatty acid (FFA) concentration,[2] low glucose availability secondary to poor perfusion and glucose intolerance. The net result is a cascade of events including increased myocardial oxygen demand as FFAs are metabolised in preference to anaerobic glycolysis, impairment of calcium homeostasis[3] and production of free radicals.[4] Hence, the outcome in ischaemic but still viable myocardium is adversely affected, with an increase in the incidence of fatal arrhythmias, propagation of the area of insult and depression of myocardial mechanical activity and contraction.[5-7] GIK therapy may be able to protect against these insults for up to 10 hours or more prior to restoration of adequate myocardial perfusion.[8]

At the molecular level the myoprotective effects of GIK therapy are multiple. During ischaemia exogenous glucose is a more efficient fuel than either FFA or glycogen.[9] Insulin lowers the concentration of plasma FFAs by inhibiting lipolysis and promotes intracellular uptake and utilisation of glucose;[10] there is also restoration of intracellular potassium.[11] The hyperosmolar effect of GIK infusion can lead to reduction in tissue oedema and can promote tissue healing.[12] Furthermore, insulin can decrease thromboxane-A production and plasma plasminogen activator inhibitor-1 activity, facilitating spontaneous thrombolysis.[13,14] The protective effects may also extend into the post-reperfusion period. Reduction of the myocardial ischaemic insult also limits reperfusion-induced myocardial injury. The protection of cell membranes, smooth muscle cells and endothelial cells reduces cell swelling and microvascular compression, thus protecting against the 'no reflow' phenomenon (figure 1).[8]

Figure 1. Metabolic changes during acute coronary ischaemia



There has been clinical interest in GIK therapy for AMI for almost half a century; it antedates the thrombolysis era.

The pre-thrombolysis era

The first controlled trial to investigate clinical mortality was published by Mitra in 1965.[15] The results were promising, showing a fall in mortality at 14 days in the GIK treatment group. There have been many trials over the subsequent decades but no one trial has been large enough and powered sufficiently to show a significant difference between the control and GIK therapy groups. A meta-analysis of the pre-thrombolysis trials was published in 1997.[16] A total of 14 trials were identified, but five trials were excluded because of poor randomisation techniques. A total of 1,932 patients from the remaining nine trials were included in the meta-analysis, 956 patients in the GIK arm and 976 patients in the placebo arm. Statistical analysis revealed a significant reduction in the number of deaths in the GIK group in comparison to the placebo group (154 deaths [16.1%] *vs.* 205 deaths [21%] respectively; p=0.004), with an odds ratio of 0.72 (95% CI 0.57–0.90). The proportional mortality reduction was 28% (95% CI 10.0–43.0%), with an estimated 49 lives saved per 1,000 patients with AMI.

To achieve adequate suppression of plasma FFA Rackley and colleagues have advocated the use of high-dose intravenous GIK therapy (30% glucose, 50 IU insulin and 80 mmol potassium infused at the rate of ≥1.5 ml/kg/hr).[17] Of the nine trials included in the meta-analysis discussed above[16] only four complied with the high-dose GIK infusion regime, with a total of 288 patients. Analysis of the pooled results from this subgroup indicated a 6.5% mortality rate in the GIK arm as opposed to 12% in the placebo arm. Although proportional reduction in mortality with GIK treatment was 48%, the small number of patients meant that the confidence intervals only just exceeded unity (odds ratio 0.52, 95% CI 0.25–1.07, p=0.17).[16]

The post-thrombolysis era

To date there have been three randomised trials of GIK therapy in the post-thrombolysis era.[18-20] The results have been variable.

The DIGAMI study[18] and subgroups of the ECLA pilot trial[19] yielded positive results. The DIGAMI study enrolled 620 diabetic patients, with 306 patients randomised to receive GIK therapy and 314 patients randomised to placebo. All patients received thrombolysis and beta blockade if they were not contraindicated. At one year there were 57 (18.6%) and 82 (26.1%) deaths in the GIK therapy and control arm respectively. This gave a relative mortality reduction of 29%, p=0.027.

The ECLA pilot trial enrolled 407 patients: some 268 were allocated randomly to receive GIK therapy (135 high-dose GIK and 133 low-dose GIK) and 139 received placebo. The major outcome of the study was a 60% reduction in relative risk of in-hospital mortality in patients who received a combination of GIK therapy and a reperfusion strategy (95% received thrombolysis and 5% underwent primary angioplasty) (2p=0.008). The absolute mortality risk also decreased from 15.2% to 5.2% in the GIK-reperfusion group. Furthermore, a survival benefit persisted over one-year follow-up in the high-dose GIK-reperfusion patients.[19]

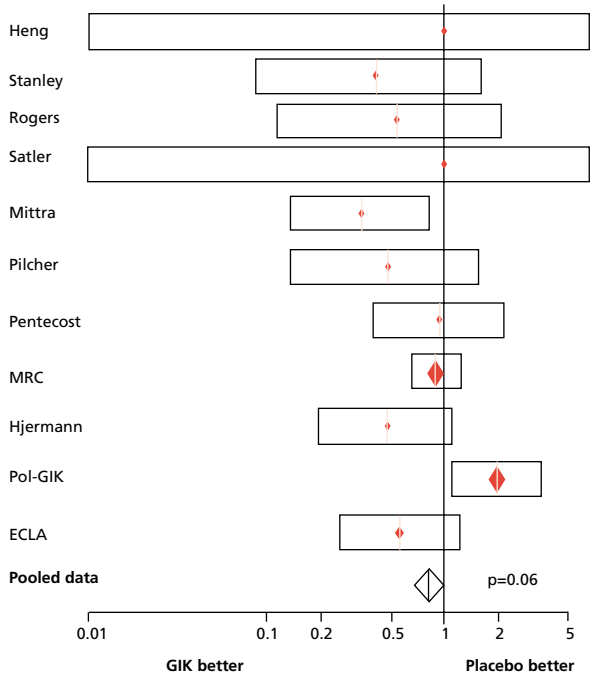
The positive results of the DIGAMI and ECLA studies are in accord with the meta-analysis of the pre-thrombolysis trials for both benefit and use of high-dose GIK therapy.

The third trial of the post-thrombolysis era, Pol-GIK, was negative.[20] Nine hundred and fifty-four patients with AMI were randomised to receive low-dose GIK therapy (494 patients) or placebo (460 patients). At 35-day follow-up there was no significant difference in cardiac mortality between the two arms of the study, and total mortality was higher in the GIK arm (8.9% *vs.* 4.8% respectively, odds ratio 1.95, 95% CI 1.12–3.47, p=0.01). The study design has attracted criticism, in particular with reference to recruitment of only low-risk cardiac patients and administration of low-dose GIK.[21] In addition, there was a very high proportion of non-cardiac death in the GIK group versus placebo (2.4% *vs.* 0.2%, respectively).

A second meta-analysis, which includes the results of the Pol-GIK and ECLA pilot trials, has now been performed (figure 2).[22] Despite the negative impact of the Pol-GIK trial the overall result still remains positive in favour of GIK therapy, with the upper limit of the confidence intervals just reaching unity (odds ratio 0.82, 95% CI 0.67–1.007). Similarly, the pooled results of all the high-dose GIK trials (including the ECLA pilot study) reveal a proportional mortality reduction of 44% and there is a trend toward statistical significance (odds ratio 0.56, 95% CI 0.31–1.01, p=0.07).

More recently, Dr Zijlstra presented his 940-patient study on GIK therapy in ST segment elevation MI in the hotline session of the European Society of Cardiology congress 2002. High-dose GIK therapy was used in this study but once again relatively low-

Figure 2. Meta-analysis of randomised prospective placebo-controlled trials of GIK therapy in acute myocardial infarction



Adapted from Fath-Ordoubadi F, Beatt KJ. *Lancet* 1999;**353**(9168):1968.[22]

risk patients were recruited. There was a non-significant reduction in all-cause 30-day mortality (4.8% *vs.* 5.8%). Interestingly, when patients with symptoms of heart failure (Killip class >1) were excluded both 30-day mortality (1.2% *vs.* 4.2%, p=0.01) and major adverse cardiac events (4.2% *vs.* 8.4%, p=0.01) were significantly lower in the GIK group.

Conclusion

In an era where the majority of patients with AMI are treated with thrombolysis or primary angioplasty and beta blockade, the role of GIK therapy needs further clarification. Emerging trends need confirmation and outstanding issues must be addressed. The benefit of high-dose GIK therapy, which has the potential to result in the greatest suppression of FFA levels, needs clarification. The recommended time frame for treatment needs to be studied further. The combined action of GIK therapy and beta blockade in the presence of thrombolysis or primary angioplasty is as yet unclear. Potentially GIK therapy and beta blockade could act in a complementary fashion to antagonise the metabolic changes of ischaemia (by reductions in catecholamine and FFA concentration, lowering the incidence of arrhythmias and improving glucose delivery and utilisation), whilst thrombolytic therapy or primary angioplasty markedly improve the chances of early reperfusion and limit infarct size. Theoretically patients with acute coronary syndrome (non-Q-wave MI, non-ST segment elevation MI and unstable angina) where the culprit artery is not necessarily completely occluded might benefit more from GIK therapy: in these patients the presence of coronary flow enables both better glucose and insulin delivery to jeopardised cells and better wash-out of metabolic by-products.

The evidence to date is positive and provides a strong indication that GIK therapy may have a role in the treatment of AMI. There is a sound theoretical rationale for its direct myoprotective action and its complementary role in the presence of beta blockade and thrombolysis or primary angioplasty. Further studies are still indicated to address the outstanding issues. However, with the low mortality rates achieved today in management of in-patient AMI, large studies will be required to ensure sufficient power. Such studies should address both short- and long-term outcome, and should be extended to study patients with acute coronary syndrome as well as those with ST segment elevation infarction.

Key messages

- GIK therapy may be able to exert a myoprotective effect in ischaemia secondary to acute myocardial infarction
- High-dose intravenous GIK therapy is advocated in order to achieve adequate suppression of plasma free fatty acids
- The pooled results of all the high-dose GIK trials reveal a proportional mortality reduction of 44%
- There is a sound theoretical rationale for its direct myoprotective action and its complementary role in the presence of beta blockade and thrombolysis or primary angioplasty

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