A challenge to the metabolic approach to myocardial ischaemia

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The negative results of glucose-insulin-potassium (GIK) in the very large CREATE-ECLA trial that studied 20,201 patients with ST-elevation acute myocardial infarction (AMI), are disappointing and warrant thorough evaluation. We attempt to put the new data into perspective and uncover the serious flaws in the trial design, otherwise the whole metabolic concept will be disparaged. The crucial issue, developed from basic science data, is that GIK should be initiated very early, before, or at the time of reperfusion. Another problem with CREATE-ECLA is that the mortality in Killip class 1 reperfused patients was 7.1%, much higher than that of a recent Dutch study in which mortality was only 1.2%. Nonetheless, there was a strong trend towards a lower mortality in the sub-groups that received the best reperfusion therapy in CREATE-ECLA, as well as in the first of two rather small Dutch GIK trials. In the future, the ideal protocol to test would be if GIK were given in the ambulance as the patient is being transported to a specialized centre of percutaneous coronary intervention (PCI), with the aim of expanding the time window between pain onset and actual PCI.

Keywords
Metabolic therapy; Glucose-insulin-potassium; Acute myocardial infarction; Reperfusion

Introduction

At a time when the metabolic management of myocardial ischaemia and heart failure is coming to the fore, and there are substantial trials with agents that use the principle of metabolic manipulation for myocardial ischaemia (ranolazine and trimetazidine as antianginals), the negative results of the CREATE-ECLA trial, are disappointing and warrant thorough evaluation. The purpose of this article is to put the new data into perspective and uncover the serious flaws in the trial design. Otherwise there will be no further trials with glucose-insulin-potassium (GIK) and the whole metabolic concept will be disparaged. CREATE-ECLA studied 20,201 patients with ST-elevation acute myocardial infarction (AMI), mostly in India and China, who were randomly assigned to receive usual care or GIK infusion for 24 h. Major outcomes, including mortality, cardiogenic shock, and reinfarction at 30 days, were not different in the two groups. Although this was clearly an ambitious and well-intentioned trial, we will argue that crucial defects in the trial design of CREATE-ECLA and the high mortality rate mean that the possible benefit of metabolic therapy by GIK for AMI has not been settled for centres with contemporary western standards and much lower mortality rates.

Metabolic approach to acute myocardial ischaemia

The story of GIK it started with a simple clinical observation by Sodi Pallares. In 1944, his mother with heart failure seemed to be sodium overloaded and because of diuretic therapy was probably potassium depleted. His concept was ‘two kingdoms at war, sodium vs. potassium’. He
Timing of metabolic intervention

Theoretically, and based on strong experimental evidence, GIK should be given early and able to reach the ischaemic myocardium prior to reperfusion. Glucose and/or insulin, when present from the start of coronary ligation, gave protection from fatty-acid induced regional ischaemia in the isolated rat heart. As GIK reduces blood free fatty acids and increases glycolysis, this new metabolic approach renewed interest in the clinical application of GIK. However, in the next group of studies, GIK was often given late.

The CREATE-ECLA study: an ambitious failure?

The CREATE-ECLA study was an ambitious attempt to test the efficacy of GIK for AMI on a large international scale largely in underdeveloped countries. Unfortunately, the consequence was a study design that sacrificed the scientific principles outlined earlier, and minimized the potential for GIK to be effective. The negative conclusions of the CREATE-ECLA trial do not take into account the limitations of the trial, and hence the more general extrapolation decrying GIK as in the accompanying editorial is not justified. The GIK was given too late to be effective; an accurate conclusion would state that late administration of GIK, especially when given after reperfusion, is not effective therapy for AMI.

In the CREATE-ECLA study, 83% of patients had reperfusion therapy at a median time of 3.85 h after symptom onset. But randomization to GIK or control groups occurred almost 1 h later (median: 4.7 h post-symptom onset); then GIK was started mostly ‘within the next hour’. This late, often post-reperfusion, administration minimized GIK’s potential to reduce ischaemic injury. GIK protects ischaemic myocardium by increasing glycolysis and ATP, and decreasing free fatty acid (FFA) levels; this cannot occur instantaneously. GIK’s full potential can be assessed only when it is started early (ideally, within an hour) after the onset of ischaemia, and well before reperfusion; in CREATE-ECLA only 2.8% of patients were randomized within an hour, and then GIK was begun subsequently.

Also of concern, in CREATE-ECLA, the overall AMI mortality rate was relatively high, suggesting a lower level of general care, and/or ineffective reperfusion, which could obviate any benefit of GIK. Effective reperfusion is critical for exploiting GIK’s benefits. For example, in CREATE-ECLA, GIK did reduce mortality by 25% in the 9% of patients who had effective reperfusion with percutaneous coronary intervention (PCI) (CI: 0.51–1.11). Furthermore, in the subgroup subject to primary PCI or tPA, GIK reduced mortality by 28% (just short of the P < 0.05 level, with a hazard ratio 0.72; confidence intervals 0.51–1.01 (data presented at 2004 AHA Scientific sessions). In CREATE-ECLA the mortality rate of the Killip class 1 reperfusion cases was six-fold higher (7.1%) than in the Dutch trial (1.2%) (discussed subsequently). Such a high mortality rate in CREATE-ECLA cautions against applying results from trials in underdeveloped countries to modern American and European CCU settings with more effective reperfusion treatments.

The preceding weaknesses in CREATE-ECLA are further augmented by their failure to report separately results from the different regional subgroups. The ECLA cohort of CREATE-ECLA was apparently not a pre-specified subgroup, but arguably it should have been. This cohort was largely studied several years before the Asian cohort was begun, the genotypes and phenotypes of the ECLA and Asian populations were clearly different, and undoubtedly ‘standard care’ for AMI differed as well. The authors do their readership a disservice by not candidly and fully reporting any such trends which could provide mechanistic clinical insights into differences among the groups. Regional results are of particular interest and importance since the original ECLA study reported a significant reduction in AMI mortality by GIK in patients who received reperfusion treatment. Did the ECLA cohort of CREATE-ECLA completely refute the original ECLA study, or was a strong trend towards benefit with GIK in the ECLA cohort simply obfuscated by the much larger sample size of the Asian cohort where GIK had a neutral effect due to defects in design?
The way ahead: follow the Dutch?

The clinical study that apparently best incorporates the principles for maximizing GIK’s potential is the recent Dutch trial, which remains the benchmark study, and may be a good guide for GIK for AMI.\(^2\) GIK was given relatively early (2.5 h after symptom onset) and was followed by highly effective primary angioplasty (PCI) and documented reperfusion; GIK reduced mortality by 71\% (\(P < 0.01\)) in the pre-specified ‘no heart failure subgroup’ (\(n = 856\)) which actually comprised 91\% of the entire study population. In the Dutch study, the mortality rate for Killip class 1 patients treated with GIK prior to PCI was a remarkably low 1.2\%, suggesting to the power of early GIK and effective reperfusion to reduce AMI mortality. In contrast, the CREATE-ECLA study’s Killip class 1 GIK and reperfusion subgroup (91\% thrombolytics, streptokinase, urokinase, or alteplase of unspecified manufacture and of undocumented efficacy) had a six-fold higher mortality rate of 7.1\%.

However, the follow-up Dutch study, verbally presented to the American College of Cardiology in March 2005, failed to confirm any mortality benefit and was stopped. The dose of GIK was cut by one-third. While awaiting further details, we note that (i) there were more patients with anterior infarcts in the GIK group (\(P = 0.009\)), and that anterior infarcts are potentially more lethal; and (ii) combining Dutch 1 and 2 studies still appears to give a trend to a mortality reduction, albeit much diminished in its power. In neither of the Dutch studies were details given of any use of early \(\beta\)-blockade, which potentially has a GIK-like effect by shifting myocardial metabolism from adverse fatty acid uptake to glucose.\(^3\)

Future studies should follow the Dutch, but use an improved design by concentrating on GIK given much earlier than reperfusion and in a setting where Killip class 1 patients have the much better contemporary prognosis that they deserve, and had in the Dutch study, rather than the high mortality in CREATE-ECLA. Ideally the Dutch protocol should be expanded into a two by two factorial design, testing GIK vs. early \(\beta\)-blockade vs. otherwise standard treatment. A second testable hypothesis is whether the time window from onset of pain to PCI could be widened, because GIK, and \(\beta\)-blockade both resist ischaemia. Of note, the one positive finding in the CREATE-ECLA study was decreased ischaemia with GIK, at both 7 days and 30 days.

**Conclusion**

In conclusion, the very strong trends towards a reduced mortality with GIK in the sub-groups that received the best reperfusion treatment in CREATE-ECLA, as well as in those that received documented effective reperfusion in the first Dutch study, should not be dismissed and ignored, and certainly warrant further investigation. Ideally, GIK must be started as early as possible and before reperfusion, for example, in the ambulance as the patient is being collected for transport to a specialized PCI centre. Such a study is currently underway in the United States and pilot data indicate that most patients can receive GIK within 60 min of symptom onset.

**References**

