Targeting Glucose in Acute Myocardial Infarction: Has GIK missed the target?

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Introduction
Pro-inflammatory mechanisms may contribute to hyperglycemia associated adverse outcomes in acute myocardial infarction (AMI)(1-3). Insulin exerts anti-inflammatory effects in STEMI and CABG patients(4-6). Inflammation plays an important role in the pathogenesis of atherosclerosis and thrombosis(7; 8). Thus, insulin infusion in AMI should be beneficial. However Glucose –Insulin –Potassium (GIK) infusion was neutral in its benefit in the CREATE-ECLA study (9).

The GIK regimen (fixed combination of 1 liter 25% dextrose with 50units of regular insulin and 80meq/l of potassium) used in CREATE-ECLA is known to lower serum free fatty acid (FFA) concentrations(10) and to reduce mortality by 30% in AMI as reviewed previously(11). However, the infusion of 30grams/hr of glucose without titration of glucose or insulin in CREATE-ECLA led to a significant increase in blood glucose concentrations. The authors suggested that the adverse effect of GIK induced hyperglycemia may have neutralized any potential benefit of insulin in the GIK. However, the magnitude of the potential contribution of hyperglycemia to neutralize benefits of GIK was not commented upon. Since admission hyperglycemia was predictive of mortality in AMI in CREATE-ECLA, we have estimated the potential effects of GIK induced hyperglycemia on mortality in this study.

Methods
Based on the admission blood glucose related mortality rates in controls in the CREATE-ECLA, we have constructed a model 

\[ \%\text{mortality (30 day)} = 100 \times (1 - c \times \exp (-d \times \text{BG})) \]

predicting 30-day mortality as a function of admission blood glucose (BG). The constants c and d were estimated using a regression involving 3 points from this constructed curve. This model was then applied to the BG at admission, 6 and 24 hours for both the GIK and control groups, assuming that the relationship between glycemia and mortality is maintained even after admission in AMI. This assumption is probably valid because (a.) for every 0.6mmol/l reduction in glucose post admission, there is a 8% reduction in mortality in patients with AMI(12) and (b.) Glucose levels after admission predict mortality in AMI (13; 14).

The projected mortality at 0, 6 and 24 hrs (table 1) yielded trapezoids whose areas were calculated. After dividing by 24h, the following weighted average formula for mortality was obtained:

\[ \%\text{mortality (average)} = (0.125) \times \%\text{mortality at 0h} + (0.5) \times \%\text{mortality at 6h} + (0.375) \times \%\text{mortality at 24h}. \]

Results
In our model, the estimated 30-day mortality for controls based on blood glucose achieved during the 24 hours is 9.9%, which is similar to the observed mortality of 9.7% for the controls in CREATE-ECLA. However, the estimated mortality rate for the GIK group on the basis of the GIK induced hyperglycemia during the 24 hrs was 12.2%, which was 2.2% higher than the observed mortality of 10% for the GIK group.

Discussion
We suggest that the insulin in the GIK infusion used in CREATE ECLA might have neutralized the 2.2% (12.2% [expected] -10% [observed]) increase in mortality that should have been observed in the GIK group due to the effect of hyperglycemia induced by this infusion. Thus, if hyperglycemia was not induced by the GIK infusion used in CREATE-ECLA, the administration of insulin in this trial could have resulted in a 2.2% absolute and 22% relative reduction in mortality in the GIK group. Indeed, the CREATE-ECLA investigators have recently reported an excess mortality and congestive cardiac failure in the GIK group in the first three days when GIK induced hyperglycemia was present and probably had its maximal effect. In contrast, there was a reduction in mortality and congestive cardiac failure between 4 and 30
days(15) when glucose levels had probably approximated the levels in the control group. In a canine model of AMI, low dose insulin alone reduced the infarct size while glucose and potassium(16) caused hyperglycemia and increased infarct size. These findings and the pro-inflammatory, prothrombotic effects of hyperglycemia may explain how GIK induced hyperglycemia can neutralize the potential benefits of insulin(2).

A limitation of our study is that our analysis is based on the published data. In CREATE-ECLA. In the absence of detailed data and the derivational nature of our methodology which arrives at 12.2% expected mortality we are not in position to provide a p value or standard errors. However, based on the level of the expected precision in a large study like CREATE-ECLA a potential absolute reduction in mortality of 2.2% or relative reduction of 22% would be statistically significant and well outside the confidence bounds (9.4%, 10.6%) of the observed mortality of 10% for the GIK. Although our model accurately predicted the death rate for the controls, it is possible that we could have overestimated the death rate for the GIK patients. We have also speculated that the adverse effects of the reactive hyperglycemia observed following AMI are equivalent to the iatrogenic hyperglycemia induced by the GIK infusion. Iatrogenic hyperglycemia is known to induce proinflammatory cytokines and to endothelial dysfunction(17; 18). These mechanisms may be responsible for the adverse cardiovascular outcomes associated with hyperglycemia. The important point for discussion is not whether the model is fundamentally wrong, but whether “if these assumptions are essentially correct”. Is there then a factor (insulin) which protected the GIK patients from the toxic effects of hyperglycemia? Using the model based on the observations in CREATE-ECLA, the answer is probably in the affirmative.

Thus, hyperglycemia needs to be avoided when designing studies investigating whether insulin administration is beneficial in AMI. We have now designed a trial to test the hypothesis that insulin is cardioprotective in AMI due to its anti-inflammatory, profibrinolytic, antioxidant, antiapoptotic, vasodilatory and antiaggregatory actions and that these effects are enhanced by lowering of glucose into the normoglycemic range. We are using IV insulin infusion to lower glucose to 90-130mg/dl (IG) in STEMI patients. To allow us to infuse a minimal dose of 2.5 units/hr (the anti-inflammatory dose of insulin) in this trial, approximately 7 grams/hr of dextrose will be infused simultaneously to maintain euglycemia (19). At this infusion rate the anti-inflammatory and the potential cardioprotective effect of insulin is likely to be observed.
References
Table 1: Hyperglycemia related mortality in CREATE ECLA based on relationship of admission glucose to mortality in controls.

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<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>GIK</th>
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<tbody>
<tr>
<td></td>
<td>BG (mmol/l)</td>
<td>% Mortality</td>
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<tr>
<td>0</td>
<td>9</td>
<td>11.4</td>
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<tr>
<td>6h</td>
<td>8.2</td>
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<td>24h</td>
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