Editorial

Metabolic Management of Acute Myocardial Infarction Comes to the Fore and Extends Beyond Control of Hyperglycemia

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A cute myocardial infarction (AMI) is an acute metabolic stress, as has been recognized for at least 40 years.1,2 Its components include a rapid rise in plasma catecholamines, plasma free fatty acids, and blood glucose within the first 1 to 2 hours of onset of symptoms.3 Recent attention has focused on the possible adverse effects of hyperglycemia,4 now thought to have adverse effects in its own right, such as formation of oxygen free radicals5 and consequent adverse inflammatory response.6,7 Therefore, the level A recommendation of the American Heart Association (AHA) Diabetes Committee is that glucose levels should be measured in all patients with suspected or confirmed acute coronary syndromes (ACS). There follows, perhaps with a little less conviction (level of evidence B), the proposal that intensive glucose control may be considered if plasma glucose is >180 mg/dL (10 mmol/L) or even if the degree of hyperglycemia is less (level C). The recommendation to use intravenous insulin is based on extrapolation from other patient populations in acute intensive care,8,9 and a wise call is made for further studies to define the best approach to glucose control in patients with ACS.

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These recommendations raise several challenges, each of which merits closer examination. This Editorial will argue the case for a broader view of the relationship between glucose metabolism and ACS, with particular analysis of the proposal that it is the high adrenergic mediated levels of free fatty acids (FFAs or nonesterified fatty acids [NEFAs]) that may be the major lethality of the general metabolic reaction of which glycemia is but a marker. Thus, there could be 2 apparently discordant metabolically based therapeutic strategies: (1) rectification of hyperglycemia, versus (2) amelioration of adverse effects of excessive circulating FFAs on the ischemic tissue as it undergoes infarction. Additional therapeutic aims could be direct protective effects on ischemic tissue by insulin-mediated glucose uptake and decreased reperfusion-induced myocardial injury.

Causes of Glycemia

AMI is diabetogenic, not only at the time of the AMI but thereafter with delayed onset.10 But what is diabetes mellitus? The definition of diabetes mellitus is veering away from clear cutoff glycemie thresholds to a sliding scale of probabilities of risks.11 Thus, glycemia during AMI could be but a marker of multiple metabolic abnormalities, which in their turn may influence the outcome of acute myocardial ischemia. Acute catecholamine release in AMI could be regarded as the basic metabolic problem in that the consequences include changes that predictably worsen ischemic damage, such as rapid elevation of plasma FFA. The initial pain-related burst of catecholamine discharge (1) acts on adipose tissue to mobilize FFAs, (2) acutely inhibits the release of insulin from the pancreas, and (3) causes hyperglycemia.3 The elevated plasma FFAs are preferentially oxidized by skeletal and cardiac muscle, hence inhibiting the uptake and oxidation of glucose12 and directly contributing to insulin resistance,13,14 thereby increasing the probability of glycemia. Hence, glycemia is the consequence both of the high circulating FFAs and catecholamine discharge, the latter additionally promoting hepatic glycogenolysis. Sustained β-adrenergic stimulation also directly promotes insulin resistance by inhibition of insulin signaling at the level of protective kinases.15 To tackle the fundamental β-adrenergic stimulation that causes both FFA elevation and insulin resistance would logically require early β-blockade, a procedure known to reduce plasma FFA uptake by the failing myocardium16 and to lessen fatty acid accumulation in the ischemic-reperfused heart.17 However, routine early intravenous β-blockade may have adverse hemodynamic consequences including cardiogenic shock and hypotension.18 Giving β-blockade later, once hemodynamic stability has been attained, would miss the crucial first 3 hours when reduction of infarct size is most likely to be achieved.19 A metabolically oriented trial of early β-blockade is ideally required but unlikely to be achieved in the wake of the potential hemodynamic problems.18 That moves the focus to other methods of controlling the high FFAs, currently a neglected aim in the metabolic management of AMI, in that the AHA Scientific Statement concentrates on the dangers of hyperglycemia.4

Potential Adverse Effects of High Circulating FFAs in AMI

When circulating FFAs are high enough to exceed the tight binding sites on the albumin and are therefore loosely bound with an increased FFA:albumin ratio, perhaps at an FFA concentration of about 1200 mEq/L,20 with an FFA-albumin
molar ratio of about 2.5 or more, adverse effects on the ischemic myocardium include increased enzyme release,21 which by current definitions reflects an increase in irreversibly damaged cells. Such FFA levels are reached in the early hours of AMI.22,23 The leading mechanisms to explain such effects are the membrane-damaging detergent properties of FFAs24 and an increased oxygen demand, especially in the context of experimental diabetes mellitus.25 Both these mechanisms are expected to increase the extent of ischemic damage. Such metabolic inefficiency may lead to contractile abnormalities and adverse left ventricular remodelling.25 Although a total switch from carbohydrate to fatty acid metabolism by the normal heart only increases the oxygen demand by about 11%, that does not allow for the increased oxygen demand due to catecholamine stimulation or diabetes mellitus.26 In diabetic hearts perfused with high FFA concentrations (1.4 mmol/L), unloaded oxygen consumption increases by an extraordinary 86%27 and is associated with “pronounced oxygen wastage” coupled with decreased cardiac efficiency. These changes are in part the probable result of mitochondrial uncoupling,27 which underlies the FFA-induced increase in myocardial oxygen consumption28 and local heat production.29 At a mitochondrial level, excess FFAs induce low ratios of ATP production/oxygen consumption and excess production of electrons, which are transferred to molecular oxygen without ATP production.14 The increased free radicals thus produced can inactivate the insulin receptor at IRS-1 by phosphorylating serine residues, thereby directly promoting insulin resistance.14 FFAs also stimulate receptor-mediated proinflammatory signaling by activating cytokines including tissue necrosis factor α (TNF-α) and interleukins 1β and 6.14

**Lipid-Induced Myocardial Dysfunction**

Excess circulating FFA may also increase myocardial triglyceride and myocardial diastolic dysfunction.30 Data from a mouse knockout model with deficiency of adiposocyte triglyceride lipase suggest that it is the FFA rather than excess myocardial triglyceride that promotes cardiac insulin resistance.31 Such lipid loading of the heart is an important component of the newly postulated cardiomyopathy of insulin resistance.13 Thus, there could be 2 major consequences of excess circulating FFA on the infarcting myocardium, namely, increased ischemic damage and impaired myocardial mechanical function. Increasing contractile failure is likely further to promote insulin resistance.26

**Therapy Aimed at Reducing Circulating FFA**

How could FFA be reduced to test these multiple postulated adverse effects? Having already dismissed β-blockade as having too many potential hemodynamic side effects for routine use, 2 alternatives remain, namely nicotinic acid or its derivatives and insulin. In the intact dog heart, FFA-induced “oxygen-wastage” was reduced by about 40% either by nicotinic acid or by intravenous glucose.28 Antilipolytic therapy given to patients with early-phase AMI by a nicotinic acid analog brought down FFA levels and lessened electrocardiographic signs of ischemia32 but was not subjectively acceptable because of the high incidence of flushing and hypotension. Glucose-insulin-potassium (GIK) infusions given to patients decreased FFA levels substantially,33 with less dramatic FFA-lowering effects when low-dose GIK was used.23 A similar result was obtained with intravenous glucose.22 Ideally, circulating FFA should be reduced to levels sufficiently low to reach the estimated threshold for myocardial FFA uptake of about 200 μmol/L.33 However, in a baboon model of early AMI, reduction of FFA from about 600 to 700 to about 300 μmol/L by GIK24 reduced pathologically assessed infarction.35 In a perfused rat heart with coronary ligation, decreasing the perfusate FFA from 1.5 to 0.5 mmol/L without any added glucose or insulin reduced enzyme release by about half,21 thus demonstrating that it is not essential to reduce FFA levels down to the hypothetical threshold for FFA uptake by the myocardium; and reduction of FFA by itself lessens cellular ischemic damage. As neither β-blockade nor nicotinic acid analogs are ideal strategies to reduce plasma FFA in patients, that leaves insulin, which can be given either directly (covered by glucose) or as part of GIK. Note that this rationale for the use of GIK is totally different from the original “repolarizing” concept.

**Increased Glycolysis Versus Decreased Glycemia**

Besides reducing circulating FFA, insulin may directly protect the ischemic zone from developing into infarction by several means: promoting glycolytic flux and protective signaling and protecting against reperfusion damage. To maximize myocardial glycolytic flux would require both high insulin and high circulating glucose as in GIK (strategy 1), whereas another and contrasting major aim of insulin therapy would be to reduce inflammatory provoking glycemia (strategy 2) (Table).

**Maximizing Myocardial Glycolytic Flux (Strategy 1)**

This concept dates back to at least 197036 and has solid experimental support in studies on ischemic rat, dog, and baboon hearts.31,34,37 The basic benefit of glycolytic flux appears to be 2-fold: first, the membrane protection afforded by increased flux and production of glycolytic ATP,38,39 and second, the enhanced oxidation of pyruvate with decreased production of harmful protons40,41 and lessened mitochondrial oxidation of harmful FFA.42 Consequently, the production of free energy from ATP hydrolysis is increased.43 In the setting of experimentally severe ischemia, Apstein’s group showed that both an increased glucose concentration and added insulin help to promote protective glycolytic flux.44 Furthermore, in humans hyperglycemia and hyperinsulinemia inhibit the rate of fatty acid entry into mitochondria.45

**Reduction of Glycemia (Strategy 2)**

Several major studies link an increased baseline blood glucose value in AMI to poor prognosis.4,6,46,47 As one study concludes, “The most important issue is whether elevated glucose is a direct mediator of adverse outcomes or a marker of greater disease severity.”44 Strong arguments suggest that the glycemia in itself could have harmful prooxidative and proinflammatory effects,6,48,49 so that normalizing the blood glucose would become the major aim of intensive insulin
negate the benefits of GIK infusion.34 Furthermore, GIK and glucose to mean values of 380 mg/dL in baboons did not adverse outcomes in AMI. Experimentally, a 1-hour elevation harmful hyperglycemia. However, no clear evidence exists to major theoretical problem is the production of potentially treatment as outlined in the AHA document.4 One current trial follows this strategy, comparing intensive insulin infusion with standard glycemic control,50 with cardiac magnetic resonance imaging as end point.

### Problems With Each Strategy

**Strategy 1** is epitomized in the Immediate Metabolic Myocardial Enhancement During Initial Assessment and Treatment in Emergency care (IMMEDIATE) GIK trial.55 The major theoretical problem is the production of potentially harmful glycemia. However, no clear evidence exists to link short-term elevation of antiinflammatory markers with adverse outcomes in AMI. Experimentally, a 1-hour elevation of glucose to mean values of 380 mg/dL in baboons did not negate the benefits of GIK infusion.34 Furthermore, GIK and reduction of FFA should both decrease oxidative stress.52,53 Overall, the present author favors the view that increased glucose uptake by the ischemic tissue is metabolically protective by increasing glycolysis and inhibiting the adverse effects of high free fatty acids,21,38,45 thus outweighing any longer-term potential detrimental effects of hyperglycemia. The early timing of IMMEDIATE is crucial. A major aspect of all experimental studies with GIK, or glucose or insulin, has been in the setting of acute ischemia, at the most within 3 hours of coronary occlusion,19,54 which is before infarction has fully developed. Earlier studies such as the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI)55 and the multicenter GIK trial,34 although pointing the way, did not meet this essential requirement defined by the experimental studies. The major problems with strategy 2 are the potentially late onset of intensive insulin therapy and hypoglycemia.

**Benefits of Insulin Common to Both Strategies**

**Protective Signaling**

Insulin in the absence of glucose protects from hypoxia-induced apoptosis in neonatal cardiomyocytes by inhibiting the activity of p38 mitogen-activated protein kinase.15 This mechanism may explain why, even in the absence of glucose, insulin decreases ischemic cell damage in the isolated rat heart with coronary ligation.21

**Reduction of FFA**

Insulin inhibits release of FFA from adipose tissue and rapidly reduces circulating FFA. As already argued, high FFAs are directly injurious to ischemic tissue. In addition, high FFAs have proinflammatory effects.53

**Protection From Reperfusion Damage**

Another potential beneficial mechanism, unrelated to any effects on glycemia or FFA, tests the potential therapeutic role of insulin when on board at the time of reperfusion, the “window of opportunity for cardioprotection.”57 Extensive animal work strongly suggests that reperfusion damage can be limited at that time by the protective reperfusion-ischemia survival kinases (RISK) such as Akt and extracellular signal-regulated kinase (ERK), as stimulated by insulin58,59 and with a major reduction (45%) in infarct size.60

**Problems of Extrapolating From Non-ACS Intensive Care Studies**

In the absence of direct data supporting the concept of intensive insulin therapy for ACS, the AHA scientific statement draws on studies in non-ACS intensive care units,4 citing evidence on other patient populations as level B evidence in favor of strict glycemic control. In the case of noncardiac patients in a medical intensive care unit (ICU), a 2006 study by Van den Berghe et al8 suggested that intensive insulin therapy reduced morbidity (weaning from mechanical ventilation) but not mortality, whereas their earlier (2001) study on patients in a surgical ICU had found decreased mortality.61 In patients with severe sepsis, intensive insulin reduced glycemia without effect on mortality or on organ failure but at the cost of increased severe hypoglycemia and

### Table. Comparison of 2 Major Ongoing Trials

<table>
<thead>
<tr>
<th></th>
<th>Strategy 1: IMMEDIATE</th>
<th>Strategy 2: INTENSIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypothesis</strong></td>
<td>Start GIK urgently before cells die</td>
<td>Intensive insulin limits harmful glycemia (BG &lt;130 mg/dL) and has benefits independent of glucose control</td>
</tr>
<tr>
<td><strong>Patients, n</strong></td>
<td>15 450</td>
<td>700</td>
</tr>
<tr>
<td><strong>Entry point</strong></td>
<td>Acute chest pain; All ACS</td>
<td>Glycemia (&gt;140 mg/dL) plus anterior STEMI within 6 hours of onset</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Prehospital EMS (ambulance); or ED arrival</td>
<td>ED/Cath lab</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo infusion</td>
<td>Standard glycemic care BG &gt;180 with sliding scale</td>
</tr>
<tr>
<td><strong>Estimated BG</strong></td>
<td>&gt;11 μmol/L (&gt;200 mg/dL)*</td>
<td>5–7.2 μmol/L (90–130 mg/dL)</td>
</tr>
<tr>
<td><strong>Mechanistic</strong></td>
<td>Ischemic damage: Insulin protects; glycolytic flux decreases; FFA increases</td>
<td>Inflammation &amp; oxidative stress: Insulin protects, glycemia increases</td>
</tr>
<tr>
<td><strong>Risks</strong></td>
<td>Hyperglycemia</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td><strong>Reduction of reperfusion injury</strong></td>
<td>If PCI undertaken; likely in most</td>
<td>PCI routinely; insulin should reduce</td>
</tr>
<tr>
<td><strong>End point</strong></td>
<td>↓ 30-day and 1-year mortality</td>
<td>↓ MRI-determined infarct size</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndromes; BG, blood glucose; EMS, emergency medical services; ED, emergency departments; Cath lab, catheter laboratory; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; ICU, intensive care unit; and MRI, magnetic resonance imaging. Data on IMMEDIATE provided by Dr Harry Selker; data on INTENSIVE provided by Dr Paresh Dandona.

*Lower in modified GIK.
serious adverse events that stopped the trial. More directly relevant is an observational study showing a U-shaped relationship between mean blood glucose and mortality, whereby optimal blood glucose values in nearly 17 000 patients appeared to lie between 80 and 120 mg/mL (4.4 and 6.6 mmol/L), with, however, hypoglycemia (<70 mg/dL) increasing mortality, leaving 90 to 120 mg/dL (5.0 to 6.6 mmol/L) as the ideal. Note, however, that the higher glucose values may have reflected larger myocardial infarcts.

Confounding Factors
In metabolic studies on the outcome of acute coronary syndromes or myocardial infarction, several potential confounding factors are present. Going back to the classic study by the Braunwald group in 1971, “We conclude that the hemodynamic status and neurohumoral background at the time of occlusion and for up to 3 hours thereafter can alter the extent and severity of myocardial ischemic injury and myocardial necrosis.” Neurohumoral inhibitors that reduce experimental infarct size include propranolol, captopril, quinapril, and candesartan. Thus, early administration of neurohumoral inhibitors as often given to patients with ACS is likely to modify infarct size and outcome, irrespective of any metabolic manipulation.

What Can Be Learned From Trials Already or Soon to Be Initiated?

Testing Strategy 1
IMMEDIATE tests the hypothesis that very early GIK, started in the ambulance, will protect ischemic cells from infarction by promoting the metabolism of glucose and inhibiting that of FFA. Additional benefit should be derived by insulin-mediated protection from reperfusion injury. These advantages are thought to outweigh the theoretical danger of hyperglycemia-induced oxidative stress, which may be limited by the short-term duration of the infusion and by the anti–free radical properties of GIK. The end point of IMMEDIATE is mortality, for which a large number (>15 000) of patients would be needed.

Testing Strategy 2
This strategy, as represented by the Intensive Insulin Therapy and Size of Infarct as a Visual End-Point by cardiac magnetic resonance imaging (INTENSIVE) trial, would respond to the proinfarctial issues raised by the AHA document and would apply lessons learned from non-ACS but acutely ill patients in medical ICUs. The aim would be intense insulin therapy to achieve euglycemia while giving enough glucose to avoid hypoglycemia. The comparator is current standard therapy to achieve euglycemia while giving enough glucose to avoid hypoglycemia. These are trials that must still be undertaken. A small trial was positive, but the GLP was only started after reperfusion.

Conclusions
Metabolic therapy for AMI rests on amelioration of the metabolic changes that are the consequences of acute stress-induced catecholamine stimulation, namely increased blood FFA levels, insulin resistance, and hyperglycemia. Only about 3 hours are available from the onset of ischemic pain during which metabolic or pharmacological manipulation can influence infarct size, with the “earlier the better” being the rule of thumb. Logically, the fundamental therapy should consist of β-adrenergic blockade but potentially major hemodynamic risks are involved. Nicotinic acid and its analogs are not well tested. That leaves insulin therapy, which should correct all the major metabolic changes and reduce infarct size if initiated early enough. The 2 major strategies of insulin administration would be, first, as GIK, which is aimed at reducing FFA levels, relieving the insulin resistance, and increasing glycolytic flux to protect the threatened ischemic myocardium; and, second, intense insulin aimed at reducing the blood glucose without causing hypoglycemia, thereby relieving proinflammatory oxidative stress. Two trials currently under way (Table) test the metabolic therapy of AMI by aiming at these apparently different hypotheses. As certain mechanisms are common to both trials, especially the multiple beneficial effects of insulin, the information gained is likely to be complementary.

Disclosures
Dr Opie is a member of the steering committee of the National Institutes of Health–supported IMMEDIATE trial.

References


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