Mechanism by Which Hyperglycemia Plays a Role in the Setting of Acute Cardiovascular Illness

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Acute hyperglycemia is associated with excess morbidity and mortality in acute cardiovascular illness in both diabetic and nondiabetic patients. Hyperglycemia is associated with altered myocardial energetics, but abnormalities in glucose oxidation and glycolysis do not fully account for this excess risk. Hyperglycemia leads to a pro-oxidative/proinflammatory state that is associated with endothelial dysfunction, diminished coronary vasodilatory reserve, and a prothrombotic state. Hyperglycemia negates the protective effect of ischemic preconditioning and, most importantly, appears to interfere with the salutary effects of insulin in acute cardiovascular illness. Aggressive therapy with continuous infusion of insulin seems to improve a host of metabolic and physiologic effects associated with acute hyperglycemia and appears warranted if euglycemia can be maintained.

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Individuals with diabetes mellitus (DM) have a 2- to 4-fold increased risk of cardiovascular (CV) disease, as well as nearly twice the mortality rate from acute myocardial infarction (AMI), as compared to nondiabetic (non-DM) individuals.[1,2] This increased risk extends to non-DM patients who present with elevated plasma glucose levels on admission for AMI.[3] Acute hyperglycemia is common in patients with AMI even in the absence of overt DM. The association of glucosuria with AMI was first noted over 70 years ago,[4] and hyperglycemia is

documented in up to half of all AMI patients, whereas previously diagnosed DM is present in only 20% to 25% of AMI patients.[5] Cardiologists need to be cognizant of the hazards associated with hyperglycemia and AMI, given the noticeably increased prevalence of diabetes and the epidemic of obesity and associated insulin-resistant states such as impaired glucose tolerance and metabolic syndrome.

Elevated admission plasma glucose and glycosylated hemoglobin (HbA1C) levels are recognized as independent prognosticators of in-hospital and long-term CV events after AMI in patients both with and without known DM.[3,6] A recent study of 808 diabetic patients with AMI found that glucose concentration at time of admission was the single most significant independent predictor of in-hospital mortality.[7] Although HbA1C level correlated with admission glucose concentration, it did not independently predict mortality, suggesting that acute hyperglycemia adds risk above and beyond the known effects of chronic hyperglycemia. In a retrospective study with prospective follow up, AMI patients without known DM had a continuous risk for mortality over the entire range of admission glucose levels (4% increase in mortality for every 18 mg/dL increase in glucose).[8] Patients with a glucose level greater than 200 mg/dL had a mortality rate similar to those with previously diagnosed DM.

Acute hyperglycemia in non-DM patients is associated with a nearly 4-fold increased risk of death after AMI as compared to a nearly 2-fold increased risk of death in diabetic individuals.[3] The presence of hyperglycemia is also associated with increased morbidity and mortality in critically ill patients and those undergoing cardiothoracic surgery.[9] A recent analysis of over 200,000 intensive care unit (ICU) admissions found a relationship between mean hyperglycemia and risk-adjusted mortality that began with very mild levels of hyperglycemia (111-145 mg/dL).[10] The odds ratio for mortality approached 3 with severe hyperglycemia (200-300 mg/dL) and jumped to over 4 in the cohort of cardiac ICU patients with severe hyperglycemia. Once again the magnitude of risk was more striking in patients without DM as compared to those with DM.

Although recommendations for strict glucose management are being developed for hospitalized patients,[11] current AMI risk indices do not include glucose determinations and AMI guidelines do not set specific targets for glycemic control. A recent sampling of over 140,000 elderly patients with AMI showed that a substantial proportion of patients (26%) with severe hyperglycemia (> 240 mg/dL) did not have previously recognized diabetes.[12] These patients were more than 3 times less likely to receive insulin during their hospitalization than diabetic patients with similar levels of hyperglycemia. Hyperglycemia was associated with a graded increase in risk-adjusted mortality at all glucose levels in elderly non-DM patients, whereas mortality was adversely affected by only severe hyperglycemia in DM patients. Because the study controlled for clinical indicators of disease severity, it is unlikely that a greater degree of stress and catecholamine release from a more extensive MI accounted for the excess mortality, as had been previously postulated in uncontrolled studies.

Although stress hyperglycemia correlates well with prognosis in AMI, correspondence between admission glucose levels with infarct size as measured by myocardial enzyme release has not been universal.[8] Additionally, lowering plasma glucose with insulin reduced short- and long-term mortality in AMI,[13] suggesting that hyperglycemia is not just a passive byproduct of the stress response. Thus, excessive stress-mediated release of counter-regulatory hormones (catecholamines, glucagon, and cortisol) due to a greater degree of myocardial damage cannot fully account for hyperglycemia in AMI.

So what are some of the alternate mechanisms that may explain the excess mortality in AMI patients with acute hyperglycemia? One proposed explanation for the frequent occurrence of hyperglycemia in AMI and its relationship to prognosis is the link between obesity, insulin resistance, metabolic syndrome, diabetes, and CV disease. Insulin resistance is associated with a host of CV risk factors, both traditional (obesity, hypertension, glucose intolerance, microalbuminuria, atherogenic euglycemia dyslipidemia) and novel (endothelial dysfunction and a proinflammatory, pro-oxidative, and prothrombotic state characterized by

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abnormal levels of circulating adhesion molecules, cytokines, and adipokines, such as high-sensitivity C-reactive protein [CRP], tumor necrosis factor [TNF]-α, and adiponectin) which are associated with an adverse prognosis in AMI. Insulin resistance is associated with approximately twice the risk of developing CV events, even when adjusted for known CV risk factors.

The majority of AMI patients with hyperglycemia are insulin resistant and are more prone to hyperglycemia in the setting of stress. Hyperglycemia in AMI is due to relative insulin deficiency, which is mediated in part by a decreased pancreatic beta cell secretion of insulin and increased hepatic glycogenolysis.[14] The prevalence of insulin resistance increases with age, with metabolic syndrome affecting approximately 40% of older Americans. In the Rancho-Bernardo study[15] of predominantly white Americans of European ancestry with a mean age of 70 years, after excluding subjects with known DM or fasting hyperglycemia, previously undiagnosed diabetes was present in 16% of men and 11% of women in the general population. Recent data have shown that the prevalence of DM or impaired glucose tolerance may be as high as 65% in AMI patients without prior diabetes.

In 181 consecutive non-DM patients with AMI,[16] two thirds of patients were diagnosed with DM or impaired glucose tolerance by oral glucose tolerance testing. Previously undiagnosed DM accounted for one half of AMI patients with an abnormal glucose metabolism. Interestingly, only one third of all patients fulfilling the criteria for DM on oral glucose tolerance testing had a fasting blood glucose concentration over 126 mg/dL. Although a blood glucose test at the time of admission for AMI may not be reliable in making the diagnosis of DM, concern that the diagnosis of impaired glucose tolerance or DM was erroneous in the acute setting due to stress hyperglycemia appears unwarranted as the results of glucose tolerance testing performed at the time of AMI were similar to those performed 3 months later.

Thus, patients with hyperglycemia may be at higher risk in part because they have previously undiagnosed and untreated diabetes, impaired glucose tolerance, or metabolic syndrome. Metabolic syndrome is associated with increased cardiovascular mortality, even when known diabetics are excluded. Metabolic syndrome is present in nearly 50% of AMI patients and is associated with adverse in-hospital outcomes.[17] Analysis of the predictive value of each of the 5 metabolic components in AMI reveals that hyperglycemia was the most predictive of congestive heart failure (odds ratio 3.3). As hyperglycemia affects prognosis to a greater extent in non-DM than DM patients, hyperglycemia appears to be more than just a marker of patients at higher risk due to the presence of a greater clinical risk profile.

Acute hyperglycemia itself is associated with a myriad of adverse metabolic and CV effects that may contribute to a poor outcome in AMI (Table 1). Exaggerated metabolic responses to ischemia may play a crucial role in myocardial energetics. Hyperglycemia is a reflection of relative insulinopenia, which is associated with increased lipolysis and free fatty acid (FFA) generation, as well as diminished myocardial glucose uptake and a decrease in glycolytic substrate for myocardial energy needs in AMI. Catecholamine release with stress further stimulates the release of FFAs, which may contribute to myocardial damage by increasing oxygen demand and arrhythmia risk. Although glucose metabolism is a major myocardial energy source, it is important to recognize that oxidation of FFAs is the preferred source of energy in the resting aerobic state. During myocardial ischemia, fatty acid oxidation rates decrease, but remain an important source of energy. During reperfusion fatty acid oxidation again dominates as a source of energy.

Table 1
Acute Effects of Hyperglycemia in Acute Myocardial Infarction

Endothelial dysfunction
Platelet hyperreactivity
Increased cytokine activation
Increased lipolysis and free fatty acid levels
Reduced glycolysis and glucose oxidation
Osmotic diuresis – potentially reduced cardiac output
Increased oxidative stress (? increased myocardial apoptosis)
Impaired microcirculatory function ("no reflow" phenomenon)
Impaired ischemic preconditioning
Impaired insulin secretion and insulin stimulated glucose uptake

Myocardial ischemia results in an increased rate of glycogen breakdown and glucose uptake via translocation of glucose transporter (GLUT)-4 receptors to the sarcolemma.[18] This adaptive mechanism is important because glucose oxidation requires less oxygen than FFA oxidation in order to maintain adenosine triphosphate (ATP) production. Thus, myocardial energetics are more efficient during the increased dependence on glucose oxidation with ischemia. With relative insulinopenia (insulin resistance or frank DM), exacerbated by

the stress of AMI, the ischemic myocardium is forced to utilize FFAs more than glucose for an energy source, as myocardial glucose uptake is acutely impaired. Thus, despite acute hyperglycemia, a metabolic crisis many ensue as the hypoxic myocardium becomes less energy efficient in the setting of frank DM or insulin resistance, as fatty acid oxidation results in the generation of fewer ATP molecules per molecule of oxygen as compared to glucose oxidation.

Insulin augments the translocation GLUT-1 and -4 receptors to the sarcolemma and can diminish FFA release from adipocytes.[19] Thus, to the extent that the myocardium expresses an intact response to insulin, therapeutic augmentation of oxidative glucose metabolism via exogenous insulin or improved insulin sensitivity may play a useful role for improving outcomes in patients with hyperglycemic and relative insulinopenia. The concept of a metabolic cocktail to stabilize cell membranes through potassium influx, promote glucose oxidation, and reduce FFAs to protect the ischemic myocardium dates back to Sodi-Pallares and colleagues.[20] Early studies yielded promising results with a subsequent meta-analysis suggesting that therapy with glucose-insulin-potassium (GIK) may reduce mortality in AMI.[21]

In the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial,[13] acute treatment for at least 24 hours with continuous intravenous GIK until blood sugar was controlled, coupled with subsequent aggressive treatment with subcutaneous insulin, resulted in a 29% relative reduction in 1-year mortality in a cohort of predominately type II–DM patients. Subsequent studies of intensive insulin therapy in the medical and surgical ICU settings were associated with improved morbidity and mortality, especially in patients requiring a prolonged ($\geq$ 3 day) ICU stay.[9,22] However, 2 recent trials showed no benefit of GIK in large numbers of AMI patients, dampening the enthusiasm for aggressive use of a metabolic cocktail in AMI.[23,24]

A major difference between the successful and unsuccessful studies was the degree of glycemic control. In earlier studies on the effects of GIK and intensive insulin therapy in AMI, critically ill and post-operative cardiothoracic patients' outcome benefits were associated with improvement in glucose levels toward the euglycemia range. However glucose control was either no better with more intensive therapy than controls (DIGAMI-2) or actually worsened at 6 hours in the intensively treated group (from 162 mg/dL to 187 mg/dL) as compared to improved glycemia (from 162 mg/dL to 148 mg/dL) in controls (CREATE-ECLA [The Clinical Trial of MEtabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Estudios Cardiologicos Latinoamerica]). In the latter study, patients in the highest tertile of glucose levels had over twice the mortality rate (14% vs 6.6%) of patients with the lowest levels of glucose on admission. Additionally, the metabolic actions of GIK are felt to be greatest in preserving ischemic-yet-viable myocardium when given early and prior to reperfusion strategies. The relatively late administration of GIK, which was given after reperfusion therapy in the majority of patients, may have limited its effectiveness in these trials. Finally, the frequent crossover of control patients to receive additional insulin injections (41%) and continuous insulin infusion (14%) in DIGAMI-2 may have biased the trial results against the aggressive insulin arm. The most recent compilation of studies comparing GIK to placebo in AMI patients found the use of high-dose GIK reduced 30-day mortality whereas no benefit was observed with low-dose GIK (Figure 1).[25-36] We look forward to the results of the ongoing Glucose-Insulin-Potassium Study (GIPS)-2, which is evaluating the effect of GIK as an adjunct to reperfusion therapy in AMI.

These studies suggest that the salutary effects of insulin may be offset by the presence of continued hyperglycemia. Recent evidence confirms that the vasodilatory effect of insulin is inhibited in the presence of hyperglycemia. In a novel study of patients with type I diabetes,[37] myocardial blood flow was measured at baseline and then after vasodilatation with adenosine, both under baseline metabolic conditions and during either hyperinsulinemic-euglycemic clamp or hyperinsulinemic-hyperglycemic clamp. Under baseline conditions vasodilatory reserve with adenosine was similar in both clamp groups, but vasodilatory reserve was reduced in the presence of hyperglycemia. Conversely, myocardial blood flow increased during hyperinsulinemia when glucose levels were maintained in the euglycemia range (Figure 2). Similarly, postprandial hyperglycemia is associated with reduced myocardial blood flow and perfusion defects in diabetic subjects without known macrovascular disease, whereas the postprandial state is associated with increased myocardial perfusion in normal subjects.[38] Thus, acute hyperglycemia impairs the beneficial effects of insulin on coronary vasodilatory reserve, which may outweigh the potential beneficial effects of acute insulin administration on cardiac metabolism.

Recent evidence further suggests that insulin therapy improves

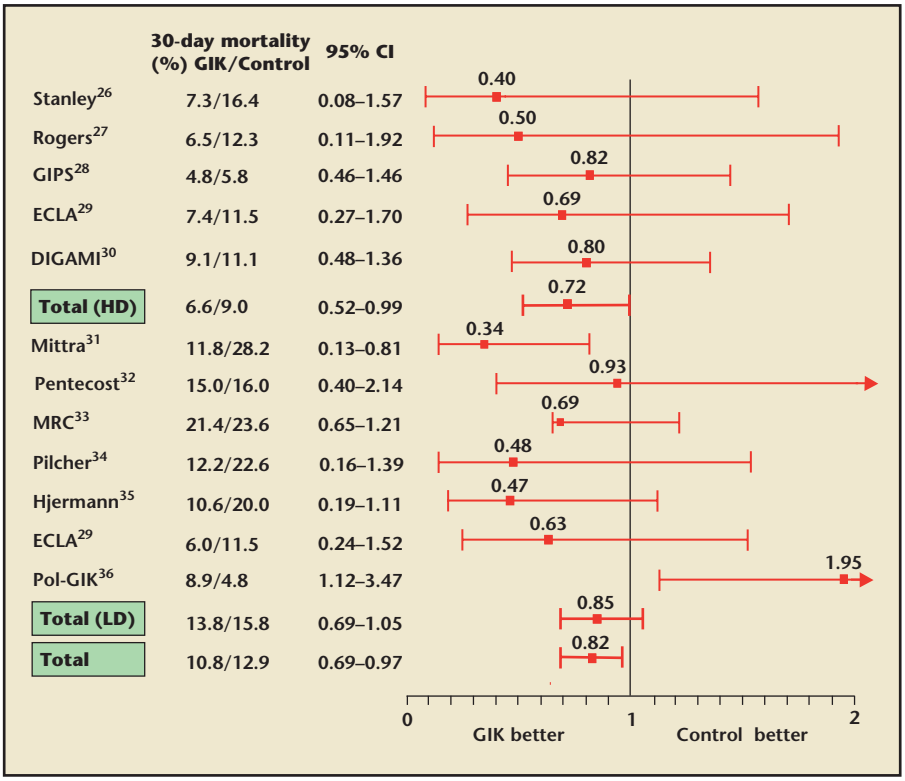

Figure 1. *Meta-analysis of glucose-insulin-potassium (GIK) in acute myocardial infarction. HD, high-dose GIK; LD, low-dose GIK. Reprinted with permission from van der Horst IC et al.[25]*

functional recovery after myocardial ischemia by mechanisms distinct from improving myocardial energetics.[39] Low-flow ischemia was induced in Sprague-Dawley rats and functional recovery and cardiac efficiency were measured under controlled conditions as compared to high-dose glucose and insulin infusion or dichloroacetate infusion (a direct activator of carbohydrate oxidation). Although dichloroacetate had a greater impact on augmenting glucose oxidation than did glucose/insulin infusion, only high-glucose/insulin infusion improved functional myocardial recovery. Furthermore, high-glucose/insulin infusion increased glycolytic lactate efflux during both ischemia and reperfusion. The discordance between improved carbohydrate oxidation and functional recovery suggests that methods other than improved myocardial energy efficiency are responsible for the beneficial effects of glucose and insulin therapy in acute ischemia. Myocardial protection via insulin administration at the time of reperfusion has been previously shown to be independent of effects on glucose metabolism and was associated with activation of cell survival signaling pathways in experimental models.[40] This observation was translated to humans where insulin infusion at the time of reperfusion was shown to have a profound anti-inflammatory effect and reduced infarct size as measured by cardiac enzymes, presumably through improved myocardial perfusion or an anti-inflammatory/anti-apoptotic mechanism.[41]

Although multiple pathways are known to be involved in hyperglycemia-induced micro- and macrovascular damage (ie, increased advanced glycation end products and activation of protein kinase C and nuclear factor [NF]-κB), a unifying theory developed by Brownlee[42] suggests that activation of oxidative stress and overproduction of superoxide radicals by the mitochondrial electron transport chain is responsible. Oxidative stress and inflammatory cytokine release are acutely increased with acute hyperglycemia and are likely candidates for linking hyperglycemia with circulatory dysfunction and excess cardiovascular events. TNF-α is known to interfere with insulin cell signaling, impair glucose uptake, and impair endothelial-dependent

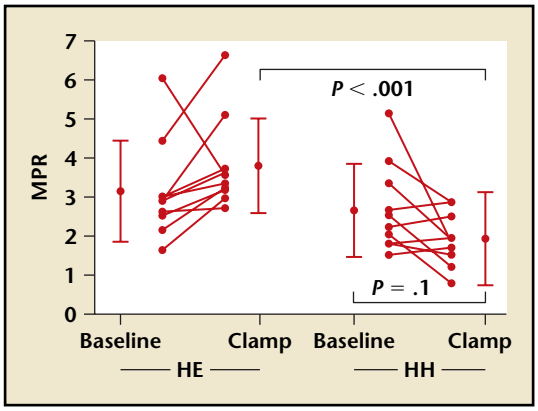

Figure 2. *Hyperglycemia outweighs the beneficial effects of hyperinsulinemia on coronary vasodilation. Myocardial perfusion rate (MPR) measured by positron emission tomography at baseline and with either HE (hyperinsulinemia/euglycemia) or HH (hyperinsulinemia/hyperglycemic clamp). Reprinted with permission from Srinivasan M et al.[37]*

vasodilatation in response to insulin in healthy volunteers and likely plays a role in both the development of insulin resistance and the link between hyperglycemia and endothelial dysfunction.[43] Within several hours of inducing hyperglycemia in control subjects' plasma levels of interleukin (IL)-6, TNF-α, and IL-18 rise significantly.[44] The duration and degree of cytokine release is exaggerated in subjects with impaired glucose tolerance. During AMI hyperglycemia is associated with increased inflammatory markers (CRP, IL-18), enhanced expression of cytotoxic T cells, and reduced T cell activation, which appear to be associated with larger infarct size as measured by troponin I and reduced ejection fractions.[45]

Postprandial hyperglycemia or a 75-gram glucose challenge markedly increases superoxide generation in leukocytes, which react with nitric oxide to produce metabolic byproducts that cause endothelial dysfunction.[46] Acute hyperglycemia rapidly suppresses flow-mediated vasodilatation, likely through increased production of oxygen-derived free radicals.[47] Hyperglycemia-induced abnormalities of endothelial-dependent vasodilatation are accentuated in patients with impaired glucose tolerance or diabetes and in the presence of hypertriglyceridemia.[48] Elevated levels of FFAs associated with insulin-resistant states lead to up-regulation of inflammatory pathways upstream of NF-κB, contributing to endothelial dysfunction that is worsened in the setting of further increases of FFAs during myocardial ischemia. It is, therefore, not surprising that impaired microvascular function is found in both obesity subjects and lean subjects with insulin resistance.[49,50] Hyperglycemia increases intranuclear NF-κB binding, as well as other proinflammatory transcription factors, which increases the expression of matrix metalloproteinases, tissue factor, and plasminogen activator inhibitor-1. Activation of oxidative stress appears to correlate more closely with acute glucose fluctuations than with sustained chronic hyperglycemia.[51] Using measurements of urinary isoprostanes as a surrogate for oxidative stress, it was recently shown that acute glycemic excursions and postprandial glycemia correlated better with oxidative stress as compared to mean glucose levels and HbA1C levels in diabetic subjects (Figure 3). Therefore, acute hyperglycemia was additive to the risk posed by chronic hyperglycemia. Similar glycemic excursions in lean non-DM subjects produced dramatic free radical–induced reductions of prostacyclin synthetase activity.[52] Thus, acute hyperglycemia is a potent inducer of an oxidative state both in subjects with and without chronic hyperglycemia.

Microcirculatory impairment leading to reduced coronary blood flow appears to play a major role in the adverse prognosis associated with acute hyperglycemia. A post hoc analysis of a major primary percutaneous coronary intervention (PCI) study in ST segment-elevation MI revealed that hyperglycemia was present on admission in 70% of patients, was associated with reduced TIMI (Thrombolysis In Myocardial Infarction) grade 3 flow prior to intervention (12% vs 28% in patients without hyperglycemia; $P < .001$), and was the most important predictor of absence of coronary reperfusion before primary PCI (odds ratio 2.6; 95% confidence interval, 1.5-4.5).[53] Despite similar post-procedural TIMI grade 3 flow rates after PCI, diabetic patients have reduced myocardial blush grades and diminished ST segment resolution consistent with diminished microvascular perfusion as compared to non-DM patients.[54] Iwakura and colleagues[55] reported that acute hyperglycemia was associated with impaired microcirculatory function as manifest by "no reflow" on myocardial contrast echocardiography after PCI. Preexisting HbA1C levels and diabetes status did not differ between subsets with and without no reflow, suggesting that acute but not chronic hyperglycemia was the precipitating factor. Subjects with no reflow subsequently had larger infarcts, as measured by myocardial enzyme release, and lower wall motion scores both acutely and at 6 months despite similar clinical profiles to subjects with intact microcirculatory function.

The well known adverse effects of diabetes and hyperglycemia on

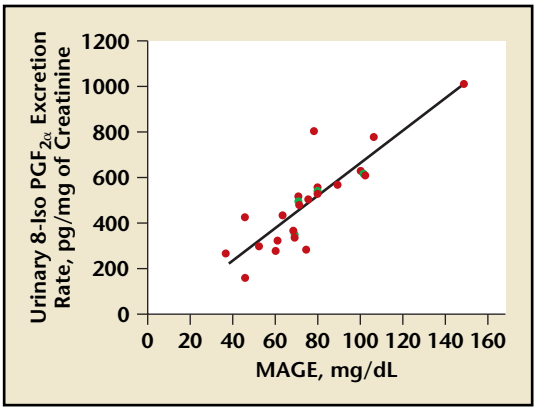

Figure 3. *Activation of oxidative stress by acute glucose fluctuations. 8-Iso $PGF_{2\alpha}$, F_2 isoprostane formed directly from free radical–mediated oxidation of arachidonic acid); MAGE, mean amplitude of glucose excursions. Reprinted with permission from Monnier L et al.*[51]

platelet function, fibrinolysis, and coagulation[56] likely play a significant role in the adverse effects of acute hyperglycemia. Hyperglycemia potentiates collagen-induced platelet aggregation through superoxide production.[57] Hyperglycemia also activates the tissue factor pathway,[58] with resultant increases in clotting factors and thrombin generation. Finally, hyperglycemia is associated with reduced fibrinolytic function mediated through increased plasminogen activator inhibitor-1 levels.

The importance of acute alterations in clotting factors, platelet aggregation, and fibrinolytic function in the setting of hyperglycemia is amplified in the setting of insulin resistance. Basal markers of thrombosis and altered fibrinolytic function are present in the metabolic syndrome and are associated with increased cardiovascular events.[59] Excess CV risk persisted in non-DM subjects with metabolic syndrome as compared to those without metabolic syndrome even when adjusted for the increased prevalence of atherosclerosis, as measured by carotid intimal media thickness.

Altered ischemic preconditioning may also play a role in the adverse AMI outcomes noted with hyperglycemia. In animal and human models, repetitive episodes of ischemia prior to coronary occlusion result in limitation of infarct size. In the setting of experimental ischemic preconditioning, acute hyperglycemia reversed the salutary effect of prior ischemia on infarct size. Similarly, non-DM patients with a history of prodromal angina had smaller infarcts, enhanced myocardial function, and improved survival after their first anterior MI as compared to subjects without prior angina.[60] However, the prodromal angina had no effect on infarct size and outcomes in DM patients, despite similar times to reperfusion, TIMI grade 3 flow scores with PCI, and collateral scores.

Conclusion

Hyperglycemia appears to interfere with the salutary effects of insulin in acute CV illness. Aggressive therapy with continuous infusion of insulin appears to improve a host of metabolic and physiologic effects associated with acute hyperglycemia and seems warranted if euglycemia can be maintained. Whether the hyperglycemia associated with acute cardiovascular conditions such as AMI should be treated with intensive insulin treatment to achieve normoglycemia remains an open question. While waiting for randomized clinical trials to help answer this question, it is prudent to know that intensive insulin therapy has shown benefit in critically ill patients. Cardiologists, who direct the care of acutely ill patients such as those with AMI, will need to become familiar with continuous insulin infusion protocols in order to achieve optimal glucose levels. ■

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Main Points

- Hyperglycemia is associated with excess morbidity and mortality after acute myocardial infarction (AMI) in both diabetic and non-diabetic patients.
- Excessive stress-mediated release of counter-regulatory hormones (catecholamines, glucagon, and cortisol) cannot fully account for hyperglycemia in AMI. Hyperglycemia can cause a pro-oxidative/proinflammatory state leading to endothelial dysfunction, diminished coronary vasodilatory reserve, and a prothrombotic state.
- Hyperglycemia negates the protective effect of ischemic preconditioning and seems to interfere with the salutary effects of insulin in acute cardiovascular illness. Aggressive therapy with continuous infusion of insulin appears to improve many metabolic and physiologic effects associated with acute hyperglycemia and may be warranted if euglycemia can be maintained.
- Whether the hyperglycemia associated with AMI should be treated with intensive insulin treatment remains an open question; however, it is prudent to be aware that intensive insulin therapy has shown benefit in critically ill patients.

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