

Impact of Hyperglycemia on Inpatient Outcomes: A Therapeutic Target?

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Patient survival after acute myocardial infarction (AMI) has improved considerably during the last several decades as percutaneous coronary intervention (PCI), fibrinolytic therapy, and other advances have entered clinical practice. Despite these improvements, the likelihood of death soon after AMI remains much greater among individuals with diabetes than among nondiabetic patients. It was long believed that the relationship between diabetes and heart disease could be explained by risk factors common to the 2 conditions. However, a number of studies have shown that hyperglycemia is directly associated with worse clinical outcomes after AMI, even after controlling for other clinical factors that are associated with diabetes.^{1,2} Among nondiabetic patients, hyperglycemia at the time of AMI is associated with a high likelihood of death or heart failure, even when myocardial infarct sizes are relatively small. Acute hyperglycemia is also a significant predictor of long-term mortality after AMI. Several studies have demonstrated that there are abnormalities of myocardial blood flow in patients with diabetes and that hyperglycemia is associated with impairments of myocardial blood flow before and after PCI. Clinical studies that have investigated the therapeutic potential of insulin treatment in patients with AMI have produced conflicting results. In the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, insulin infusion improved clinical outcomes after AMI in patients with diabetes, especially among those with the highest baseline blood glucose levels. In the recent Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment E American Study Group (CREATE-ECLA), an infusion of a glucose-insulin-potassium (GIK) solution did not significantly improve clinical outcomes after AMI, although the treatment regimen used produced a significant increase in plasma glucose level from baseline soon after admission. The true benefit of insulin therapy for AMI and the best ways to incorporate insulin treatment into current treatment strategies require additional study.

DIABETES, HYPERGLYCEMIA, AND MYOCARDIAL INFARCTION

Patient survival after AMI has improved considerably over the last 50 years.¹ Until the 1960s, the in-hospital mortality rate after AMI was ~30% for all patients and 50% for those with diabetes.² By the late 1990s, advances such as fibrinolytic therapy and PCI had reduced the in-hospital mortality rate to <10%.¹ However, despite significant progress in the treatment of AMI, patients with diabetes still have nearly double the 30-day mortality rate of patients without diabetes.³

The persistence of this large gap in treatment outcomes between patients with and without diabetes suggests that the mechanisms by which diabetes increases heart disease risk remain poorly understood and are not adequately corrected by current treatment strategies for AMI.

Since at least the 1930s, clinicians have hypothesized that hyperglycemia increases the risk of coronary artery disease. It has long been recognized that diabetes significantly affects clinical outcomes after AMI in a number of ways. Autopsy studies of out-of-hospital deaths have found that patients with diabetes are much less likely than those without the disease to survive AMI long enough to reach a hospital.

Even when procedural outcomes are similar, patients with diabetes also have higher rates of early reinfarction, impaired coronary blood flow after PCI, increased reactivation of thrombosis after fibrinolytic therapy, increased risk of heart failure, and longer intensive care unit and hospital stays.⁴

Ischemic preconditioning, a phenomenon in which an initial ischemic episode confers protection from subsequent ischemic insults, is also attenuated in individuals with hyperglycemia.⁵

A number of studies have found that acute hyperglycemia at the time of hospital admission—sometimes referred to as stress hyperglycemia—is a significant predictor of increased mortality among patients with AMI.⁶ For example, the relationship between hyperglycemia and myocardial injury in AMI was examined by Oswald et al⁷ in 101 patients in the United Kingdom. Infarct size estimated using peak aspartate transaminase activity (a biological marker that is no longer used) of patients with AMI and without diabetes was plotted against plasma glucose levels. A statistically significant correlation was noted between infarct size and admission plasma glucose levels, although the magnitude of the correlation was small ($r = 0.26$; $P <$

0.005). Of particular interest was a subset of 7 patients who had high plasma glucose levels at baseline (>198 mg/dL) but small infarcts. Of these patients, 6 either died (4 patients) or developed heart failure (2 patients) during hospitalization. Thus, these patients tended to have poor clinical outcomes despite the fact that their infarcts were small. The poor outcome in these patients may have been a consequence of their high plasma glucose levels at the time of admission.

Such studies generated relatively little interest among cardiologists because they often did not control for potential confounding factors associated with diabetes. For many years, most cardiologists believed that heart disease and diabetes were indirectly linked by a set of common risk factors, rather than by a direct causal relationship between hyperglycemia and vascular disease. For example, patients with diabetes are more likely to have several factors that predict worse outcomes after AMI, such as a history of myocardial infarction (MI), congestive heart failure, older age, and more extensive multivessel disease.³ However, data from large clinical trials of patients with AMI suggest that diabetes remains an important predictor of poor clinical outcomes, even when controlling for these shared risk factors. In the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries clinical trial,³ which examined the efficacy of fibrinolytic therapy with streptokinase in patients with AMI, an angiographic substudy found that even after adjusting for clinical variables (age, sex, previous heart disease, admission systolic blood pressure) and angiographic measures (coronary blood flow after fibrinolysis, presence of multivessel disease), the likelihood of 30-day mortality associated with diabetes remained significantly elevated (odds ratio [OR], 2.0; $P = 0.02$).³ Similarly, in the Fragmin and Fast Revascularization During Instability in Coronary Disease Trial,⁸ which examined invasive versus conservative management of acute coronary artery disease and the efficacy of the low-molecular-weight heparin dalteparin, multivariate analysis found that the strongest independent risk factor for early mortality was a diagnosis of diabetes.⁹ The mortality risk ratio associated with a diagnosis of diabetes was 5.42 after controlling for other clinical variables ($P = 0.001$); multivessel disease was not a significant independent predictor of mortality in the multivariate analysis.

Examination of the time course of mortality in patients with AMI reveals that differences in outcome between patients with and without diabetes occur largely during long-term follow-up and not during the first 24 hours after treatment. For example, in the Munich AMI patient registry, a large hospital patient database, the 24-hour mortality in 1999 was 14% for patients with diabetes ($n = 126$) and 5% for patients without diabetes ($n = 205$) ($P = 0.01$).¹⁰ In 2001, after the adoption of more intensive care for patients with AMI and diabetes, 24-hour mortality was 4% for patients with and without diabetes. However, for in-hospital mortality beyond the first 24 hours, outcomes are still relatively poor for patients with diabetes. In the Munich registry in 1999, in-hospital mortality beyond the first 24 hours was 16% for patients with dia-

betes and 11% for those without. In 2001, these rates were 12% and 9% for patients with and without diabetes, respectively.¹⁰ This suggests that factors other than the success of immediate reperfusion and early treatment continue to affect outcomes in patients with diabetes.

Although these studies indicate that diabetes increases the risk of poor outcomes following AMI, they do not reveal the underlying pathophysiology of this relationship. Hyperglycemia and insulin resistance both exacerbate a large number of systemic factors that are known to increase the risk of coronary artery disease or to predict relatively poor clinical outcome following AMI. Some of these factors include matrix metalloprotease production, C-reactive protein, platelet aggregation, fibrinogen, von Willebrand factor, factor VII, factor VIII, tissue factor, and sympathetic nervous system activity. The impact of all of these factors on heart disease may be increased by the presence of insulin resistance and can then be further increased by hyperglycemia. For example, platelet function is abnormal in individuals who have insulin resistance but who have normal postprandial plasma glucose levels, and the addition of hyperglycemia further impairs platelet function. Diabetes is also associated with left ventricle abnormalities within the infarct zone that interfere with recovery following ischemia, including decreased fibrinolysis and collateral vessels and increased oxidative stress. Myocardial abnormalities of the noninfarct zone are also possible, including endothelial dysfunction, cardiomyopathy, "silent" infarction, and decreased production of adenosine triphosphate.

EFFECTS OF ACUTE HYPERGLYCEMIA ON CLINICAL OUTCOMES

A number of clinical studies have suggested that hyperglycemia may directly contribute to poor outcomes in patients with diabetes. Stranders et al¹¹ examined blood glucose levels as a risk factor for long-term mortality following AMI in patients with and without diabetes. The patients were divided into 4 groups. Groups 1, 2, and 3 were categorized by admission blood glucose levels of <141 mg/dL, 141 to 199 mg/dL, and ≥ 200 mg/dL, respectively. Group 4 consisted of patients with known type 2 diabetes mellitus at enrollment. In-hospital mortality was similar for groups 2, 3, and 4 (7.1%, 6.9%, and 4.6%, respectively) and was significantly lower for patients in group 1 (2.5%; $P = 0.02$). During long-term follow-up for up to 93 months (median, 50 months), the mortality rate of patients in group 3 (42.6%) was similar to that of patients with diabetes (43.1%). Long-term mortality rates for patients in groups 1 and 2 were 25.5% and 26.4%, respectively. Some of the patients in group 3 may have had undiagnosed diabetes or impaired glucose tolerance. Group 2 was the most interesting group in this study. During hospitalization, these patients had a higher mortality rate than patients with blood glucose levels <141 mg/dL, but over time the mortality rates for the 2 groups converged (**Figure 1**). This may represent the effects of true stress hyperglycemia (ie, acutely elevated blood glucose levels at the time of study

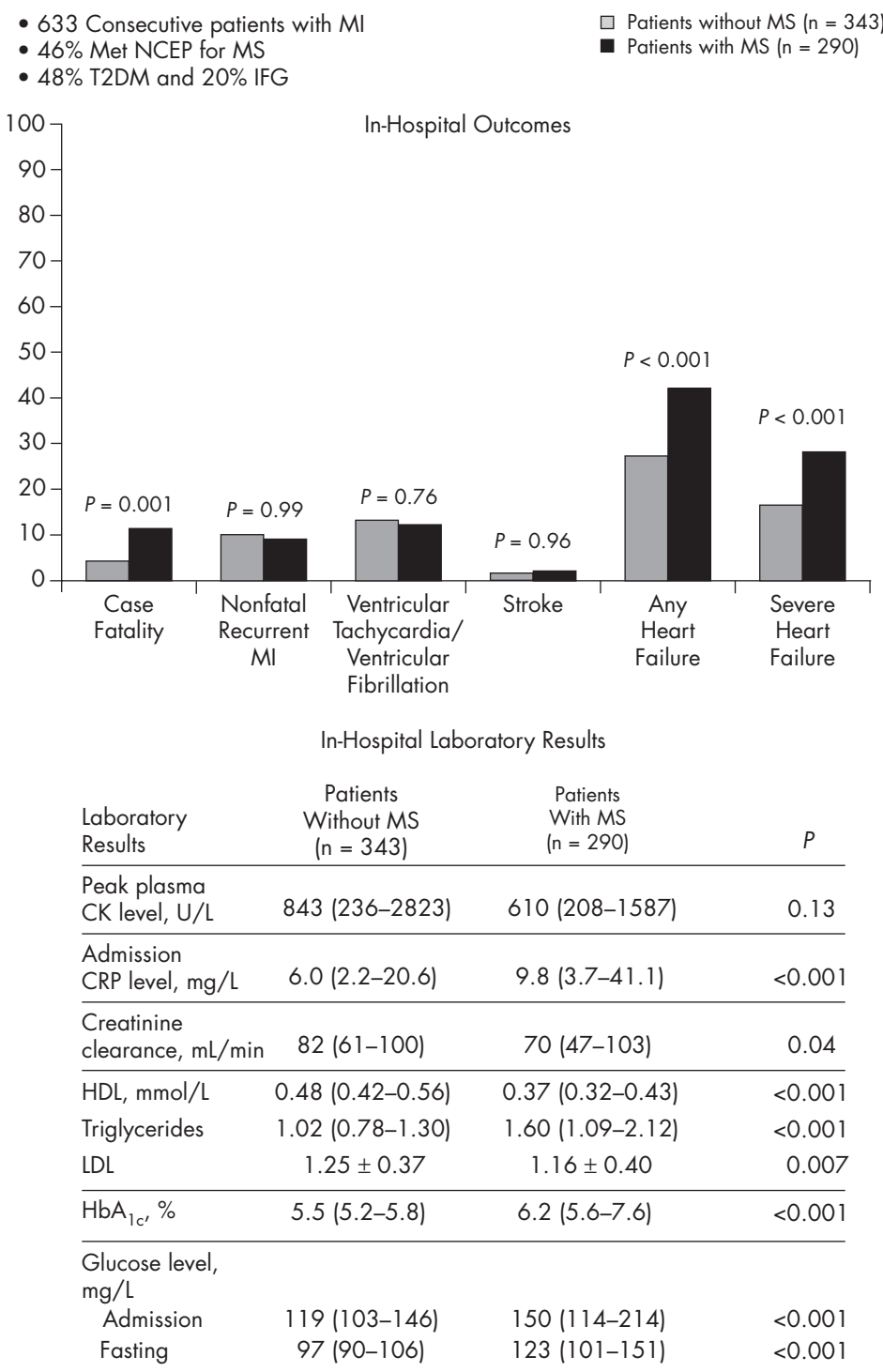


Figure 1. Metabolic syndrome (MS) is associated with increased risk for congestive heart failure and death in acute myocardial infarction (MI). NCEP = National Cholesterol Education Program; T2DM = type 2 diabetes mellitus; IFG = impaired fasting glucose; CK = creatine kinase; CRP = C-reactive protein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; HbA_{1c} = glycosylated hemoglobin. Data from Zeller M et al. Prevalence and impact of metabolic syndrome on hospital outcomes in acute myocardial infarction. *Arch Intern Med.* 2005;165:1192–1198; with permission. Copyright © 2005, American Medical Association. All rights reserved.

entry without extensive, ongoing insulin resistance). In these patients, early mortality is often due to heart failure. Similarly, Zeller et al¹² recently described the impact of hyperglycemia and other clinical variables in patients with metabolic syndrome and AMI. These investigators examined each of the 5 components of metabolic syndrome (hyperglycemia, low high-density lipoprotein cholesterol levels, high blood pressure, abdominal obesity, and elevated triglyceride levels) as a risk factor for severe heart failure. In a multivariate analysis, hyperglycemia was the strongest independent risk factor (OR, 3.31; $P < 0.001$).

Another study used a population-based approach to examine blood glucose levels, in-hospital mortality, and congestive heart failure in patients with AMI in Nova Scotia, Canada.¹³ Patients with or without diabetes were stratified by admission blood glucose levels (≤ 198 mg/dL or >198 mg/dL). The in-hospital mortality for patients with diabetes was similar for patients with elevated blood glucose levels (18.3%) and those without an elevated level (18.8%) at admission. Nondiabetic patients with elevated blood glucose levels had a mortality rate that was similar to that of the patients with diabetes (23.7%). In contrast, nondiabetic patients without elevated blood glucose levels at admission had a lower in-hospital mortality rate (8.1%; $P < 0.001$). For heart failure during hospitalization, outcomes were more closely related to admission blood glucose levels than to history of diabetes. Among patients with elevated blood glucose levels, heart failure occurred in 35.5% and 32.6% of those with and without diabetes, respectively. For patients without elevated blood glucose levels, heart failure was noted for 18.9% and 13.3% of patients with and without diabetes, respectively. These findings confirm that patients with hyperglycemia at admission are at high risk of cardiovascular events, independent of a diagnosis of diabetes. Finally, Meier et al¹⁴ recently reported the effects of plasma glucose levels at hospital admission on outcomes after a mean of 3.5 years among patients with AMI enrolled at a single medical center in Germany between 1991 and 1997. Data were examined from 227 patients with type 2 diabetes mellitus and 287 nondiabetic patients. The patients with diabetes had lower overall survival. However, in both groups, higher admission plasma glucose levels were associated with lower rates of long-term survival. Each increase in plasma glucose concentration of 50 mg/dL was associated with a relative risk of mortality of 1.42 in patients with diabetes ($P < 0.001$) and 1.54 in patients without diabetes ($P = 0.002$).

Similar findings have been described in animal-model studies. In 1 study, diabetes was induced in rats by injecting streptozotocin, and cardiac ischemia and reperfusion were induced by reversibly ligating the left anterior descending coronary artery.¹⁵ The mean infarct size was larger in diabetic rats than in nondiabetic controls when blood glucose level was maintained within an elevated range but not when it was maintained within the normal range. In an in vitro study, these investigators infused isolated ischemic hearts with a normal glucose solution, a high glucose solution, or a

high glucose solution that also included the antioxidant glutathione. Infusion of high-dose glucose alone, but not the combination of glucose and glutathione, significantly increased infarct size (Figure 2; $P < 0.05$).

CHANGES IN MYOCARDIAL BLOOD FLOW WITH HYPERGLYCEMIA

Together, these studies provide considerable support for the hypothesis that elevated plasma glucose levels, and not diabetes, is a principal determinant of myocardial injury following ischemia. The mechanism of this effect is not well understood, but a number of studies have shown that hyperglycemia is associated with abnormalities of myocardial blood flow.

Myocardial blood flow abnormalities in patients with diabetes have been examined by evaluating changes in blood flow after ingestion of a meal in healthy subjects and patients with diabetes.¹⁶ Ingestion of a meal results in a large increase in circulating glucose in individuals with insulin resistance. Myocardial blood flow decreases after ingestion of a meal in patients with diabetes, but not in healthy controls, and the degree of this decrease is greatest among those with the largest postprandial plasma glucose levels. Circulatory dysfunction in diabetes was also examined by measuring myocardial blood flow in response to the cold pressor test, in which immersion of the hand in very cold water increases heart rate, blood pressure, and myocardial blood flow.¹⁷ Myocardial blood flow in this setting was examined in 5 groups of patients that were selected to represent a spectrum of increasing insulin resistance and carbohydrate intolerance: normal insulin sensitivity, insulin resistance, impaired glucose tolerance, diabetes, and the combination of diabetes and hypertension. Compared with insulin-sensitive patients, the increase in myocardial blood flow in response to the cold pressor test was reduced by ~50% in patients with insulin resistance and decreased again by more than half in patients with impaired glucose tolerance or diabetes (Figure 3). Patients with diabetes and hypertension actually had a paradoxical decrease in myocardial blood flow, despite a large increase in myocardial oxygen demand. Thus, vascular injury begins to develop with insulin resistance and worsens with progressive glucose intolerance. Of note, insulin-resistant patients had clinical features that generally resembled those of patients with normal insulin sensitivity, including similar fasting plasma glucose levels. One significant difference between these 2 groups was body mass: patients with normal insulin sensitivity had a mean body mass index (BMI) of 25 kg/m² compared with a mean BMI of 33 kg/m² for patients with insulin resistance. This is a good example of how obesity alone can significantly affect myocardial function.

Hyperglycemia is also a specific and independent predictor of poor myocardial blood flow in patients undergoing PCI. In a study of patients undergoing primary PCI for AMI, Timmer et al¹⁸ found that hyperglycemia, but not diabetes, was independently associated with impaired blood flow

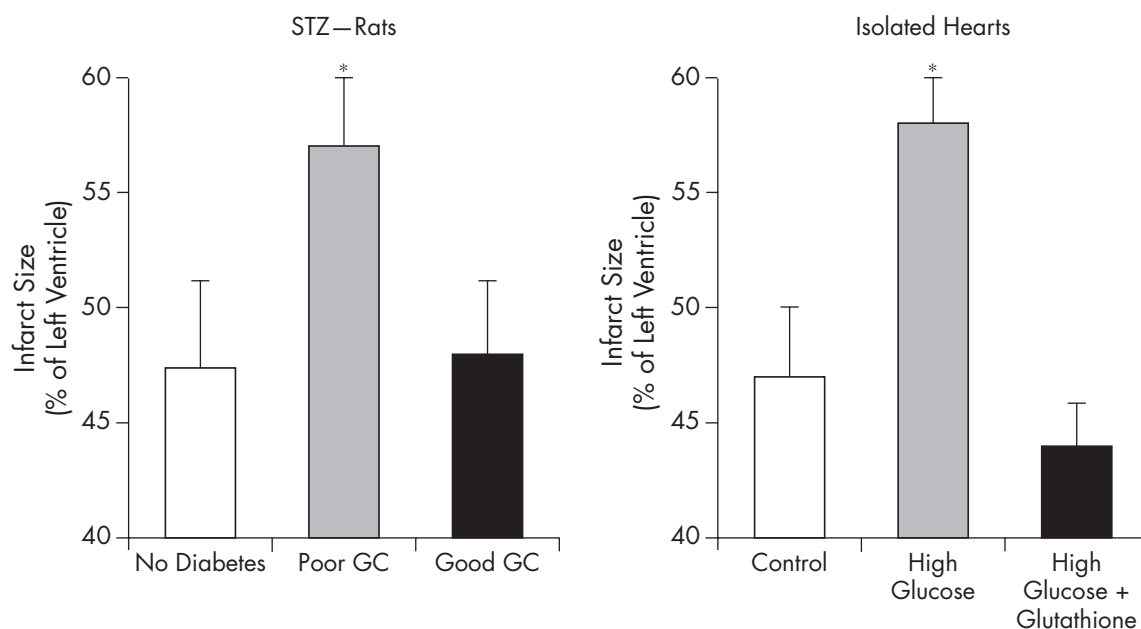
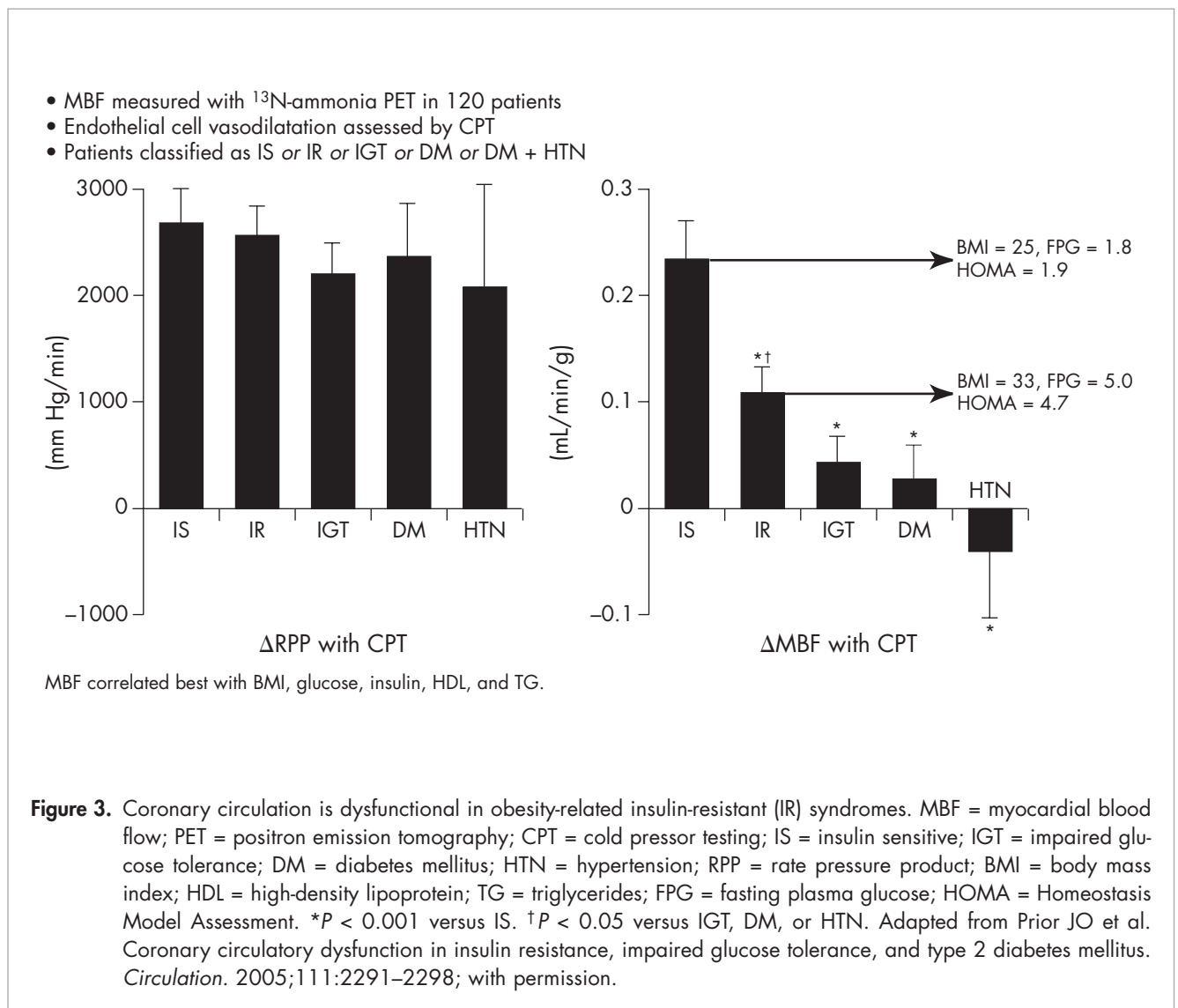


Figure 2. Myocardial infarction in diabetic rats: Role of hyperglycemia on infarct size. STZ = streptozotocin; GC = glycemic control. * $P < 0.05$. Adapted from Marfella R et al. Myocardial infarction in diabetic rats: Role of hyperglycaemia on infarct size and early expression of hypoxia-inducible factor 1. *Diabetologia*. 2002;45:1172–1181; with kind permission of Springer Science and Business Media.

before reperfusion in multivariate analysis. Hyperglycemia also influences outcome after PCI.¹⁹ When patients with AMI were evaluated 3 months after PCI, those with plasma glucose levels ≥ 160 mg/dL ($n = 75$) were more likely than those with lower plasma glucose levels ($n = 71$) to have no reflow (52% vs 14% of patients, respectively; $P < 0.001$). Patients with hyperglycemia also had significantly higher mean creatine kinase activity and less improvement in wall motion score after PCI than those without hyperglycemia ($P < 0.01$). Baseline glucose level was the most important of several predictive factors studied, including age, sex, cholesterol level, hypertension, MI location, heart rate, presence of collateral blood vessels, baseline wall motion score, time from symptom onset to treatment, and whether or not the patient received a stent. Again, diabetes was not a significant independent predictor of impaired blood flow in multivariate analysis. Prasad et al²⁰ examined the effects of diabetes on coronary reperfusion following PCI using postprocedural angiography. Blood flow was measured using blush grade, an angiographic measure of perfusion throughout the territory of a reperfused artery. The blush grade is rated on a scale of 0 to 3; higher scores indicate better blood flow and are associated with better long-term outcomes. Despite similar rates of success at establishing reperfusion of the occluded artery, patients with diabetes were significantly more likely to have lower blush grades. The effects of hyperglycemia were not investigated in this study.

Finally, are there data to show that interventions that target hyperglycemia improve outcomes in patients with AMI? The DIGAMI trial²¹ examined the effects of insulin treatment in 620 people with diabetes and AMI. Although primarily a study of type 2 diabetes mellitus, it should be noted that ~10% of the patients had type 1 diabetes mellitus. The patients were randomized to receive either an insulin-glucose infusion for 24 hours followed by SC insulin 4 times per day for at least 3 months, or treatment as usual. Rigorous guidelines were used to ensure that other treatments were the same for the 2 patient groups. The insulin-glucose infusion produced an early improvement in mortality that persisted across follow-up of up to 5 years. After a mean duration of follow-up of 3.4 years, the mortality rate was 44% with treatment as usual and 33% with insulin therapy ($P = 0.011$). The benefit was greatest among patients who had few cardiovascular risk factors and who were not taking insulin at baseline. A separate analysis of mortality by blood glucose level at enrollment found that mortality significantly increased with baseline glucose values in the control group ($P < 0.001$) but not in the insulin infusion group ($P = 0.1$). Thus, the difference between treated and control groups was greatest in the patients with the highest baseline glucose values.²² The recent CREATE-ECLA clinical trial examined the efficacy of a GIK infusion in >20,000 patients with AMI.²³ Patients presenting within 12 hours of symptom onset were randomly assigned to receive intravenous GIK infusion for



24 hours ($n = 10,088$) or usual care ($n = 10,107$). GIK infusion did not significantly improve treatment outcomes. The incidence of 30-day mortality was 9.7% for patients in the control group and 10.0% for patients who received insulin ($P = \text{NS}$). The 2 groups also had similar rates of other clinical outcomes, including cardiac arrest, cardiogenic shock, and mortality. One limitation of this study was that the GIK solution contained a large amount of glucose, and the mean glucose levels increased from 162 mg/dL at baseline to 187 mg/dL within 6 hours after beginning treatment. In the control group, the mean plasma glucose level decreased from 162 mg/dL at enrollment to 148 mg/dL at 6 hours. The increase in plasma glucose level in the insulin group may have offset any potential benefit of insulin administration. In addition, the GIK treatment also required the infusion of ~ 3 L of water. The mean net fluid gain by the end of the infusion was 1018 mL in the insulin group and 446 mL in the control group. Patients in the GIK group also had significantly greater likelihood of hyperkalemia >5.5 mEq/L (4.3% vs 1.6%; $P < 0.001$), significant

phlebitis (3.4% vs 0.2%; $P < 0.001$), and symptomatic hypoglycemia (0.4% vs 0.1%; $P < 0.001$).

CONCLUSIONS

Considerable evidence suggests that hyperglycemia is harmful in patients with AMI, and that administration of insulin may help to reduce myocardial injury. However, despite 4 decades of research into the role of hyperglycemia in heart disease, there are many unanswered questions, including the optimal dose of glucose and insulin, how soon after AMI onset the treatment must be administered, and for how long. The treatment of AMI is becoming more condensed, with patients increasingly leaving the hospital as early as 48 hours after AMI. This may limit the amount of time available for treatment. Additional research is required to determine whether insulin infusions improve outcomes in patients with AMI, the mechanisms of any therapeutic effect, and the practicalities of incorporating insulin infusion into current AMI treatment strategies.

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