Acute hyperglycemia is a common feature during the early phase after acute myocardial infarction (AMI), regardless of diabetes status. Numerous studies have demonstrated that patients with AMI and hyperglycemia on admission have high rates of mortality. It has been reported that there is a linear positive relation between admission blood glucose levels and mortality after AMI. However, recent studies showed that the relationship is U-shaped in patients with a history of diabetes. Diabetic patients with moderate hyperglycemia (glucose 9–11 mmol/L) had the lowest mortality and not only severe hyperglycemia (glucose ≥11 mmol/L) but also euglycemia (glucose <7 mmol/L) was associated with higher mortality. Although it has been debated whether acute hyperglycemia is causally related to adverse outcomes after AMI or is simply an epiphenomenon of severely damaged myocardium, multiple physiological studies have demonstrated that hyperglycemia has a direct detrimental effect on ischemic myocardium through several mechanisms, including oxidative stress, inflammation, apoptosis, endothelial dysfunction, hypercoagulation, platelet aggregation and impairment of ischemic preconditioning. Current guidelines recommend the use of an insulin-based regimen to achieve and maintain glucose levels <10.0 mmol/dl, and emphasize the avoidance of hypoglycemia. However, the optimal management goal of glucose levels for patients with acute hyperglycemia remains uncertain. Further studies are warranted into the appropriate management in patients with AMI and acute hyperglycemia. (Circ J 2012; 76: 563–571)

**Key Words:** Diabetes mellitus; Glucose; Myocardial infarction

Definition of Acute Hyperglycemia

Acute hyperglycemia is common among patients with AMI. The prevalence of acute hyperglycemia in prior studies varies from <10% to >80%. It mostly depends on the definition of acute hyperglycemia, which is differs from study to study. Threshold glucose concentration used to define acute hyperglycemia has ranged from 6.1 mmol/L (1 mmol/L=18 mg/dl) to 11.0 mmol/L. As discussed later, there is a linear correlation between the blood glucose level on admission and mortality after AMI. Therefore, there is no clear cut-off value of blood glucose to predict mortality and no consensus about the appropriate definition of acute hyperglycemia for patients with AMI. In most of the recent studies, 10.0 mmol/L or 11.0 mmol/L of blood glucose on admission is used to define acute hyperglycemia.

Previous Studies Investigating the Relationship Between Admission Glucose and Mortality After AMI

In 2000, Capes et al performed a meta-analysis of 15 studies reporting in-hospital mortality or congestive heart failure after AMI.
AMI in relation to blood glucose level on admission. When patients did not have a history of diabetes, blood glucose ≥6.1–8.0 mmol/L was associated with a 3.9-fold higher risk of death, and glucose >8.0–10.0 mmol/L with increased risk of congestive heart failure or cardiogenic shock. In patients with diabetes, blood glucose ≥10.0–11.0 mmol/L was associated with a modestly increased risk of death, with relative risk of 1.7. This meta-analysis, however, included mostly older studies from the pre-reperfusion era or in the thrombolysis era.

The Cooperative Cardiovascular Project is the largest study to investigate the relationship between admission glucose level and mortality after AMI. They reviewed 141,680 patients aged ≥65 years with AMI, and showed that the 30-day and 1-year mortality rates were linearly increased as the admission blood glucose level increased. Interestingly, higher glucose levels were associated with greater risk of mortality in patients without known diabetes compared with diabetics. However, that study included patients from 1994 to 1996, and most of them did not receive reperfusion therapy. Thrombolysis was performed in 18.2% and percutaneous coronary intervention (PCI) only in 9.9%.

**Findings From the Japanese Acute Coronary Syndrome Study (JACSS)**

JACSS is a retrospective and multicenter observational study that finally included 5,325 consecutive patients hospitalized within 48 h of the onset of AMI at 35 medical institutions across Japan between 2001 and 2003. PCI was performed in 80% of the patients, mostly with stenting, and approximately 90% of the treated patients had successful coronary recanalization during the acute phase of AMI. JACSS, reviewing 1,253 patients during the first year of the entry, first investigated the clinical implication of the admission blood glucose level on in-hospital outcomes in patients with AMI who were...
mostly treated with PCI. The major finding was that there was a linear relation between blood glucose level on admission and in-hospital mortality in the entire study group, including both patients with and without diabetes (Figure 1). An increase of 1 mmol/L in blood glucose was associated with an increase in mortality risk of 12% in the univariate analysis and 10% in the multivariate analysis. In patients with acute hyperglycemia that was defined as admission glucose >11.0 mmol/L had a significantly higher in-hospital mortality than those without (16% vs. 6%, P<0.001) (Figure 2). However, there was no significant difference in mortality between patients with a history of diabetes and those without (8% vs. 9%, P=0.54).

Although diabetes was shown to predict morbidity and mortality after AMI in the thrombolysis era, recent progress in the treatment of patients with AMI has improved the short-term outcome of diabetic patients. PCI is similarly successful in diabetic and non-diabetic patients and is more effective than thrombolytic therapy in diabetic patients with AMI. Indeed, recent studies have reported that diabetes did not increase the short-term mortality rate of patients with AMI undergoing PCI, especially non-insulin-requiring patients with diabetes.

It is still debatable, however, that mortality rates are similar between diabetic and non-diabetic patients, because acute hyperglycemia is more frequent in diabetic patients than in non-diabetic patients. To clarify this issue, the influence of diabetes status on the relationship between admission glucose and mortality was investigated in 3,750 patients from JACSS. In patients without a history of diabetes, there was a linear relation between admission blood glucose level and in-hospital mortality, as in the original report (Figure 3). Non-diabetic patients with glucose <6 mmol/L had the lowest mortality (2.5%). As admission glucose increased by 1 mmol/L, mortality increased by 17% (P<0.001). In patients with a history of diabetes, however, there was a U-shaped relationship between blood glucose level and mortality. Diabetic patients with glucose 9–10 mmol/L had the lowest mortality (1.9%), and not only severe hyperglycemia (glucose ≥11 mmol/L; 9.1%, P<0.001) but also euglycemia (glucose <7 mmol/L; 9.4%, P=0.009) was associated with higher mortality as compared with moderate hyperglycemia (glucose 9–11 mmol/L; 3.2%).

In patients with mild to moderate hyperglycemia, there was no significant difference in the mortality of diabetic and non-diabetic patients. However, when they had severe hyperglycemia on admission, in-hospital mortality was significantly higher in patients without diabetes than in patients with diabetes (P=0.02). As will be discussed later, acute fluctuation of the blood glucose level increases oxidative stress, exaggerates inflammation and promotes apoptosis. Because the blood glucose level before AMI is usually higher in diabetic patients, the threshold glucose level to induce such deteriorating effects might have been increased. Another possible explanation is a paradoxical resistance of diabetic hearts to ischemic challenge. It has been reported that the activity of the sodium proton exchanger and calcium uptake, which play important roles in reperfusion injury, are decreased in the diabetic heart. Also, decreased glycolytic rates observed in diabetics lead to less intracellular proton accumulation, which may be beneficial to the heart, especially in circumstances of high plasma glucose concentration.

Another important finding is that diabetes is associated with significantly higher mortality not only in patients with severe hyperglycemia but also in patients with euglycemia. The major substrates of normal heart metabolism are glucose and free fatty acids. Free fatty acids produce more adenosine triphosphate (ATP) per molecule but require more oxygen than glucose. In the ischemic myocardium, where lack of oxygen in-
duces a shift to anaerobic metabolism, glucose assumes a central role for energy production. In the diabetic heart, however, uptake of glucose to myocytes, which is regulated by glucose transporter, is impaired. Also, high levels of circulating and endogenous free fatty acids markedly decrease myocardial glucose use. These changes may decrease the use of glucose below a critical level necessary to maintain cellular function, even with normal plasma glucose concentration and increased rates of delivery of free fatty acids, which are potentially harmful to the ischemic myocardium. In addition, diabetic patients with euglycemia may have a potential risk of hypoglycemia. Although the precise mechanism remains unknown, it is noteworthy that diabetic patients with euglycemia, but not hypoglycemia, have a higher mortality rate than those with mild to moderate hyperglycemia.

**Different Influence of Acute Hyperglycemia and Diabetes on Mortality After AMI**

As discussed earlier, in the contemporary PCI era acute hyperglycemia is a predictor of short-term mortality after AMI, but a history of diabetes is not. However, diabetes is still an important determinant of long-term outcomes in patients with AMI. The influence of acute hyperglycemia and diabetes on outcomes after AMI differs and is time dependent. My group reviewed 802 consecutive patients with AMI who underwent emergency coronary angiography at Hiroshima City Hospital from 1996 to 2000 (Figure 4). PCI was performed in 90% of the patients. Acute hyperglycemia was associated with a significantly higher 30-day mortality rate (8.4% vs. 2.4%, P<0.001), but there was no significant difference in the 30-day mortality rate between diabetic and non-diabetic patients (5.7% vs. 3.9%, P=0.29). Conversely, diabetes significantly increased mortality from 30 days to 3 years (10.0% vs. 5.5%, P=0.03), but acute hyperglycemia did not (8.4% vs. 5.9%, P=0.19). Acute hyperglycemia is associated with short-term mortality, whereas diabetes increases long-term mortality after convalescence in patients with AMI.

Reviewing 4,176 patients without known diabetes undergoing primary PCI for STEMI, Timmer et al recently reported similar findings. Both elevated glucose and elevated HbA1c levels measured on admission were associated with 1-year and long-term mortality. An elevated glucose level, but not an elevated HbA1c, was associated with larger infarct size. In turn, HbA1c, but not glucose, was associated with long-term mortality after exclusion of early mortality (within 30 days) or after multivariate analysis. Both the admission glucose and HbA1c level reflect different patient populations, and their association with outcome is related to different mechanisms.

**Does Acute Hyperglycemia in Non-Diabetic Patients Represent Previously Undiagnosed Diabetes?**

Abnormal glucose tolerance is common among patients with AMI who have no previous diagnosis of diabetes. Norhammar et al performed the oral glucose tolerance test (OGTT) in non-diabetic patients with AMI at hospital discharge and showed that 31% and 35% of the patients were diagnosed with diabetes and impaired glucose tolerance (IGT), respectively. Some previous investigators had confused acute hyperglycemia in non-diabetic patients with previously undiagnosed diabetes, and have regarded non-diabetic patients with acute hyperglycemia as having diabetes. To assess this issue, my group performed the OGTT in 200 patients with AMI and no history of...
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20 OGTT identified diabetes in 27% and IGT in 39% of the patients. When patients were divided into 3 groups according to blood glucose level on admission, the prevalence of abnormal glucose tolerance was similar (Figure 5). The relationship of fasting glucose ($r^2=0.50$, $P<0.001$) and HbA1c ($r^2=0.34$, $P<0.001$) to 2-h post-load glucose was significant, but there was no significant relation between admission glucose and 2-h post-load glucose ($r^2=0.02$, $P=0.08$). Therefore, it is clear that acute hyperglycemia on admission in non-diabetic patients with AMI does not represent previously undiagnosed abnormal glucose tolerance.

Is Acute Hyperglycemia a Cause or a Consequence of Severe Myocardial Damage?

Previous studies have clearly demonstrated that acute hyperglycemia is associated with higher mortality rates, larger infarct size and impaired left ventricular (LV) function after AMI. However, there is debate whether acute hyperglycemia is causally related to large infarct and impaired LV function after AMI or is simply an epiphenomenon of the severe disease conditions. Indeed, increased blood glucose level at admission is associated with more comorbid factors, including higher Killip class and large infarct. These findings suggest that hyperglycemia may be at least in part a reflection of greater disease severity. To assess this issue, my group investigated the association between acute hyperglycemia and LV function in 529 patients with a first anterior wall AMI (Figure 6). Contrast Left ventriculography was performed before reperfusion therapy and before hospital discharge. There was a small but significant difference in acute LV ejection fraction (EF): patients with acute hyperglycemia had lower LVEF before reperfusion ($46\pm12\%$ vs. $48\pm10\%$, $P=0.026$). However, the difference was more pronounced before hospital discharge. Patients with acute hyperglycemia had a significantly lower predischarge LVEF than those without ($51\pm15\%$ vs. $56\pm15\%$, $P=0.001$).
The improvement in LVEF was significantly smaller in patients with acute hyperglycemia (4.8±11.2% vs. 8.0±13.8%, P=0.022). Multivariable analysis showed that there was a significant correlation between higher glucose and impaired pre-discharge LVEF, even after adjustment of acute LVEF. These findings suggest that, although acute hyperglycemia is in part a reflection of severely damaged myocardium at the time of hospital admission, acute hyperglycemia is causally associated with further deterioration of LV function after reperfusion.

**Mechanisms by Which Acute Hyperglycemia Exacerbates Myocardial Damage**

Previous experimental and clinical studies have shown that acute hyperglycemia causes several unfavorable effects that contribute to the poor outcomes of patients with AMI (Table). Oscillating hyperglycemia acutely increases oxidative stress and exaggerates inflammation. Esposito et al. measured circulating levels of cytokines, including interleukin (IL)-6, IL-18 and tumor necrosis factor-α in subjects with normal or IGT during 3 consecutive pulses of intravenous glucose separated by a 2-h interval. The plasma cytokine levels increased as the blood glucose level increased but immediately returned to normal as glucose returned to normal levels. Interestingly, when the first elevation in the blood glucose level was maintained by subsequent continuous intravenous glucose infusion, plasma cytokine concentrations gradually returned to normal levels. Such responses of cytokines to acute elevation of blood glucose were completely prevented by an infusion of the antioxidant glutathione. These findings suggest that acute hyperglycemia, not sustained elevation of the blood glucose level, exaggerates inflammation by the oxidative mechanism.

Oscillating hyperglycemia also induces apoptosis of cells. Risso et al reported that intermittent high glucose enhanced apoptosis of human endothelial cells that were incubated in media containing different glucose concentrations. Apoptosis, which was studied by viability assay, cell cycle analysis, DNA fragmentation, and morphological analysis, was enhanced in human umbilical vein endothelial cells exposed to intermittent, rather than constant, high glucose concentrations.

Endothelial dysfunction is caused by acute hyperglycemia. Williams et al. assessed endothelium-dependent vasodilation through brachial artery infusion of methacholine chloride in non-diabetic subjects. They showed that hyperglycemia significantly attenuated the forearm blood flow response to methacholine, but did not reduce endothelium-independent vasodilation to verapamil. Azuma et al. reported that repetitive fluctuations in blood glucose level enhanced monocyte adhesion to the endothelium of rat thoracic aorta. Kersten et al. showed in a canine model that hyperglycemia decreases retrograde coronary collateral blood flow by adversely affecting nitric oxide availability.

Hyperglycemia also stimulates coagulation and platelet aggregation. It has been reported that hyperglycemia elevates coagulant activation markers, including thrombin antithrombin complexes and soluble tissue factor, whereas hyperinsulinemia inhibits fibrinolysis. Sakamoto et al. examined alternation of platelet aggregability during the OGTT. Platelet aggregability, defined as the number of small platelet aggregations, was measured with a laser-light scattering method. During the OGTT, platelet aggregability increased in parallel with the glucose level. Small aggregates correlated positively with glucose levels at 60 min post-load but not with insulin levels.

**Hyperglycemia and Ischemic Preconditioning**

Hyperglycemia also interferes with ischemic preconditioning. Ischemic preconditioning is a potent endogenous cardioprotective mechanism that is promoted by the brief transient isch-
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Among patients with AMI and acute hyperglycemia, persistent hyperglycemia is associated with worse LV function and higher mortality. Several studies have investigated whether continuous insulin infusion to normalize the glucose level will improve the outcome of patients with AMI. However, the results have been inconsistent, and there is no consensus on the safety and efficacy of glucose control using continuous insulin infusion for patients with AMI. There are 2 major questions about this issue. First, which of glucose control by insulin infusion or metabolic modulation by glucose-insulin-potassium (GIK) infusion is preferable for the management of acute hyperglycemia in patients with AMI? Second, what is the optimal management goal of the blood glucose level for patients with AMI?

The Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) Study randomized 620 patients with diabetes or admission glucose ≥11 mmol/L to ≥24-h insulin-glucose infusion followed by subcutaneous insulin or routine anti-diabetic therapy. Blood glucose levels were similar before randomization, at approximately 15.5 mmol/L, and became significantly lower in patients receiving the insulin-glucose in fusion (9.6±3.3 mmol/L) than in the controls (11.7±4.1 mmol/L, P<0.0001). Mortality during the 3.4 years was 33% in the insulin-glucose group and 44% in the control group (P<0.011). The mortality reduction by insulin-glucose infusion was most obvious in the highest tertile of baseline glucose level (≥16.5 mmol/L). In contrast, the Glucose-Insulin-Potassium Infusion on Mortality in Patients With Acute ST-Segment Elevation Myocardial Infarction (CREATE-ECLA), the largest scale international study that randomized 20,201 patients to GIK intravenous infusion for 24 h or usual care, showed that high-dose GIK infusion had a neutral effect on mortality, cardiac arrest, and cardiogenic shock in patients with acute ST-elevation MI. The baseline blood glucose level was 9.0 mmol/L, and most of the patients did not have hyperglycemia. The dose of GIK infusion was fixed and hypoglycemia rarely occurred: only in 0.4% of the GIK group and 0.1% of the control group. By 24 h after randomization, the mean glucose level was 8.6 mmol/L in the GIK group and 7.5 mmol/L in the control group. These 2 studies, as well as the other previous studies, suggest that blood glucose control using insulin, but not metabolic modulation by GIK, is important to improve the outcomes of patients with AMI and acute hyperglycemia.

The second question is what is the optimal blood glucose level for the management of patients with AMI and hyperglycemia? Prior guidelines, for example, the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, until revised in 2009, recommended insulin infusion to normalize blood glucose level in patients with ST-elevation MI as Class I in patients with complicated course, and Class IIa in patients without a complicated course. However, a recent meta-analysis of the 7 largest randomized trials, including more than 11,000 patients, in 6 of which the target glucose level was 80–110 mg/L, showed that intensive insulin therapy provided no survival benefit, but rather was associated with a higher incidence of hypoglycemia and increased morbidity. Hypoglycemia triggers and deteriorates cardiovascular events by exaggerating inflammation. It also induces increased platelet and neutrophil activation. The sympathetic activation during hypoglycemia increases adrenaline secretion that may induce arrhythmias and increase cardiac workload. Underlying endothelial dysfunction leading to decreased vasodilation may also contribute to cardiovascular risk. Desouza et al reported, using continuous glucose monitoring, that hyperglycemia is more likely to be associated with cardiac ischemia than hyperglycemia in diabetic patients with coronary artery disease. It has been shown that both hyperglycemia on admission and hypoglycemia during hospitalization are independently associated with mortality in diabetic patients with acute coronary syndrome.

The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study randomly assigned 6,104 patients admitted to the intensive care unit (ICU) to undergo either intensive glucose control, with a target blood glucose range of 4.5–6.0 mmol/L or con-

Management of Acute Hyperglycemia

Among patients with AMI and acute hyperglycemia, persistent hyperglycemia is associated with worse LV function and higher mortality. Several studies have investigated whether continuous insulin infusion to normalize the glucose level will improve the outcome of patients with AMI. However, the results have been inconsistent, and there is no consensus on the safety and efficacy of glucose control using continuous insulin infusion for patients with AMI. There are 2 major questions about this issue. First, which of glucose control by insulin infusion or metabolic modulation by glucose-insulin-potassium (GIK) infusion is preferable for the management of...
ventional glucose control, with a target of \(\leq 10.0\) mmol/L. The 90-day mortality was significantly higher in the intensive-control group than in the conventional-control group (27.5% vs. 24.9%, \(P=0.02\)). The difference in mortality between the 2 treatment groups was still significant after adjustment for the predefined baseline risk factors (adjusted odds ratio, 1.14; 95% confidence interval 1.01–1.29, \(P=0.04\)). Severe hypoglycemia (defined as a blood glucose level \(\leq 2.2\) mmol/L) was recorded more frequently in the intensive-control group. After these studies, recent guidelines revised their recommendation from intensive glucose control to mild glucose control, avoiding hypoglycemia. The current AHA/ACC guideline was updated in 2009 and recommends the use of an insulin-based regimen to achieve and maintain a blood glucose level \(<10.0\) mmol/dl, avoiding hypoglycemia in patients with STEMI with either a complicated or uncomplicated course. Similarly, the guideline from the American College of Physicians that was published in 2011 recommends not using intensive insulin therapy to strictly control blood glucose or to normalize blood glucose in non-surgical or medical ICU patients with or without diabetes. It recommends a target blood glucose level of 7.8–11.1 mmol/L if insulin therapy is used. However, there is no clear evidence whether such target-driven glucose control in AMI has meaningful clinical benefits.

Although continuous insulin infusion is the currently recommended first-line treatment for patients with AMI and acute hyperglycemia, it takes time to achieve optimal glucose levels by the time of reperfusion. Several adjunctive therapies to reperfusion to limit infarct size have been investigated. Of these, nicorandil, the only clinically available \(K_ATP\) opener, has shown cardioprotective effects that mimic ischemic preconditioning. Ishii et al. randomized patients with AMI to intravenous infusion of 1 mg nicorandil over 20 min just before PCI or saline. They showed that intravenous nicorandil prevented microvascular dysfunction, assessed by TIMI frame count and ST-segment resolution, and improved event-free survival. These beneficial effects of nicorandil were most pronounced among patients with admission blood glucose level \(\geq 10.0\) mmol/L. Such adjunctive therapy may also be beneficial for patients with AMI and acute hyperglycemia. Further studies are warranted into the appropriate management in patients with AMI and acute hyperglycemia.

Disclosures

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References


