Prognostic Value of Blood Glucose in Patients With Cardiogenic Shock

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Background  Although an elevated blood glucose has prognostic value in cardiovascular disease, few data are available regarding its prognostic value for patients across the spectrum of cardiogenic shock.

Method and Results  A total of 81 patients with cardiogenic shock whose blood glucose and adrenaline were measured on arrival at the emergency room (ER) were enrolled in this prospective study. The primary endpoint was death from any cause in hospital. The rate of death was 12.3% (10/81), and the glucose level was lower among patients who were discharged alive than among those who died (8.7±3.7 mmol/L vs 13.8±6.7 mmol/L, p<0.001). The unadjusted rate of death increased in a stepwise fashion among patients in increasing quartiles of glucose level (p<0.05). The blood glucose level of 9.2 mmol/L had the highest combined sensitivity and specificity for the identification of death. In the multiple logistic-regression analysis for the primary outcome, the adjusted odd ratio for a glucose level of 9.2 mmol/L or more was 5.8 (95% confidence interval, 1.0–32.8, p=0.047). There was a significant positive correlation between the glucose and adrenaline levels (R=0.726, p<0.0001).

Conclusion  The measurement of blood glucose level on ER arrival provides predictive information for use in risk stratification across the spectrum of cardiac emergencies complicated by cardiogenic shock. (Circ J 2006; 70: 1064–1069)

Key Words: Blood glucose; Cardiogenic shock; Prognosis

Ever since Cruikshank et al reported elevated blood glucose levels in nondiabetic patients with acute myocardial infarction (AMI) in 1931, there have been reports of elevated blood glucose levels in a variety of critically ill patients. Hyperglycemia associated with insulin resistance is common in critically ill patients, even those who have not previously had diabetes. It has been reported that pronounced hyperglycemia may lead to complications in such patients and increased risk of death. Moreover, therapy to maintain the blood glucose level improves the outcome. Several studies have also reported a correlation between elevated blood glucose level on admission for AMI and the eventual outcome. A meta-analysis by Capes et al reported that outcomes were adjusted for the identification of death. In the multiple logistic-regression analysis for the primary outcome, the adjusted odd ratio for a glucose level of 9.2 mmol/L or more was 5.8 (95% confidence interval, 1.0–32.8, p=0.047). There was a significant positive correlation between the glucose and adrenaline levels (R=0.726, p<0.0001).

Methods

Patients  A prospective clinical study was conducted. Patients who were transported directly by ambulance to the emergency room (ER) were enrolled when the following criteria were fulfilled: age 18 years or older and cardiogenic shock, defined as (1) evidence of hypoperfusion in the field and/or on ER arrival (cold clammy skin, especially the feet and hands, associated with peripheral cyanosis of the nail beds, disordered mentation) and systolic blood pressure (BP) <100 mmHg in the field and/or ER arrival, (2) evidence of a primary cardiac abnormality (LV dysfunction, RV dysfunction or serious arrhythmia). The diagnosis of cardiogenic shock was determined by attending cardiologists using clinical examination, electrocardiography, echocardiography, X-ray and blood examination during the primary care according to the American Heart Association (AHA) Guidelines. The hemodynamic findings were added to the diagnosis when a pulmonary artery catheter was placed to guide therapy.

Patients were excluded if they met any of the following criteria: cardiac arrest prior to arrival at the ER, shock from noncardiac causes (aortic disease, pulmonary embolism, drug overdose, exsanguination, cerebrovascular disease, trauma, etc), blood samples could not be taken before administration of any medication, history or treatment for diabetes mellitus before shock, glycol-hemoglobin (HbA1c)
on arrival at the ER of 5.9% or more, chronic renal failure with hemodialysis before shock, or refusal by patient or families to participate in the study.

Treatment of Cardiogenic Shock

Treatment was given in accordance with the guidelines 2000 for the management of cardiogenic shock. In cases of shock caused by a volume problem, such as RV infarction, large volumes of intravenous fluid were given rapidly, supplemented with vasopressors if circulatory collapse could not be corrected. In cases of shock because of a pump problem with LV dysfunction, vasopressors such as norepinephrine and dopamine were administered with reference to the systolic BP. In cases of shock because of a rate problem, tachyarrhythmias were treated promptly with an anti-arrhythmic drug or electric defibrillation. Bradyarrhythmias were treated with atropine and/or transvenous pacing if circulatory collapse could not be corrected. If circulatory collapse could not be corrected through these measures, then an assisted circulation device, such as intra-aortic balloon pumping or cardiopulmonary bypass, was used. Coronary reperfusion therapy was also initiated for any underlying conditions. If there were no contraindications, a bolus intravenous injection of mutant tissue-type plasminogen activator was commenced as soon as possible after ER arrival in cases of AMI with ST elevation or new bundle-branch block, then emergency coronary angiography for coronary reperfusion therapy was performed following intravenous thrombolysis. If TIMI grade 0, 1 or 2 flow was observed in the infract-related artery, emergency percutaneous coronary intervention (PCI) was immediately performed.

If hemodynamic improvement was not seen in cases of acute coronary syndrome (ACS) with ST depression, emergency coronary angiography was performed immediately, followed by PCI or coronary arterial bypass graft surgery if necessary. If hemodynamic improvement did occur in cases of ACS with ST depression, coronary angiography was performed 12–48h later, followed by PCI or coronary arterial bypass graft surgery if necessary.

Data Collection and Study Endpoints

On arrival at the ER, consent for emergency care was obtained from the patient, and blood taken for measurement of blood glucose, HbA1c and adrenaline. The immobilized glucose oxidase membrane method (GA-1160, Arkray Co, Kyoto, Japan) was used for determination of blood glucose levels, and high-performance liquid phase chromatography for determination of HbA1c and adrenaline levels (HbA1c: HA-8160, Arkray Co; adrenaline: L7485, Hitachi High-Technologies Ltd, Tokyo, Japan). The emergency life-saving technicians were asked to record the condition of each patient up until arrival at the ER, including vital signs. The primary endpoint was death from any cause in hospital. The secondary endpoint was the cause of death.

Data Analysis

Patients were divided into 4 groups according to quartiles of blood glucose level on ER arrival. The mean values and proportions of the baseline variables were compared among the 4 groups using a one-way analysis of variance for continuous variables, and the chi-square test for categorical variables. The chi-square test was also used to assess the relationship between blood glucose level and the study endpoints in patients who were divided into 4 groups according to quartiles of blood glucose level. Cut-off values to differentiate survival and death were calculated for blood glucose levels using receiver-operating characteristics (ROC) curves. A multiple logistic regression analysis was performed for independent predictors of the primary outcome of death in hospital, including age, gender, systolic BP (≥70 mmHg vs 71–90 mmHg vs ≥91 mmHg), primary problems of shock (rate problem vs pump problem vs volume problems), and blood glucose level (<9.2 mmol/L vs ≥9.2 mmol/L). Finally, the relationship between the blood glucose and adrenaline levels was analyzed using simple regression analysis. Values are expressed as mean±2SD, with p<0.05 as the level of statistical significance.

Results

Patient Characteristics

Of the 2,801 patients who were transported by ambulance to the ER during the 4-year period from January 2001 to December 2004, 1,154 were cardiogenic emergencies, including 140 that developed into cardiogenic shock. Of the 140 patients with cardiogenic shock, 81 met the criteria and were enrolled. The blood glucose level on ER arrival ranged from 2.4 to 26.1 mmol/L, with a mean (±SD) of 9.3±4.4 mmol/L, a median of 8.1 mmol/L, 25th percentile value of 6.7 mmol/L, and 75th percentile value of 10.1 mmol/L (Fig 1). There were 2 patients whose blood glucose level was less than 3.8 mmol/L; 1 had a long time interval from the onset of AMI to blood sample collection, and had not eaten and drunk after the onset of AMI, and the other had a medical history of gastrectomy for gastric cancer.

Table 1 shows the baseline characteristics of the patients according to the quartile of blood glucose level. No significant differences were observed among the 4 groups in age, gender, systolic BP at the scene and on ER arrival, cause of shock, HbA1c levels, and primary problems of shock, although there was a significant difference among the groups in pH at the initial arterial blood gas analysis.

Outcomes

The rate of death in hospital was 12.3% (10/81) and the blood glucose level was significantly higher in patients who died than in those who survived to hospital discharge.
The primary endpoint of death in all patients increased in a stepwise fashion across the increasing quartiles of blood glucose level (with quartile 1 at 5% vs quartile 2 at 5% vs quartile 3 at 10% vs quartile 4 at 30%, p=0.047). This association remained significant in the subgroups of patients whose shock was caused by a pump problem or ACS (Fig 2), although no significant difference was observed in the primary endpoint among each subgroup of patients whose shock was caused by a volume problem, rate problem or non-ACS.

The secondary endpoint of cause of death was as follows. Each patient in quartile 1 and 2 had a cardiac rupture complicating AMI on day 2 and day 3, respectively. Of the 2 deaths in quartile 3, 1 was from cerebral infarction on day 1, and the other from LV dysfunction complicating AMI on day 1. Of the 6 deaths in quartile 4, 3 were from LV dysfunction complicating AMI on day 1, 1 was refractory low output syndrome on day 5, 1 was papillary muscle rupture complicating AMI on day 1, and 1 was cardiac rupture complicating AMI on day 1. No significant difference was observed among the 4 groups for causes of death.

Cut-off Value of Blood Glucose Level for Death

The capacity of blood glucose level to differentiate death from survival was assessed with a ROC curve analysis (Fig 3). The area under the ROC curve when blood glucose level was used to differentiate death from survival was 0.75 (95% confidence interval (CI) 0.58–0.93; p=0.01). A blood glucose level of 9.2 mmol/L had a highest combined sensitivity and specificity for identifying death (sensitivity of 70%, specificity of 77.5%, accuracy of 76.5% for differentiating death from survival). In addition, higher values were associated with more accurate positive predictive values for differentiating death from survival (for a blood glucose level of 21.6 mmol/L, the positive predictive value was 100%). In a multivariate logistic regression analysis for independent predictors of death, including age, gender, systolic BP on ER arrival (≤70 mmHg vs 71–90 mmHg vs ≥91 mmHg), and primary problem of shock (rate, pump, volume), blood glucose level (<9.2 mmol/L vs ≥9.2 mmol/L), a blood glucose level of 9.2 mmol/L or more was the strongest prognostic indicator of death, with an adjusted odds ratio of 5.80 (95% CI 1.03–32.8, p=0.047). Age, gender, systolic BP on ER arrival, and the primary problem of shock were not independent predictors of death (Fig 4). When the initial arterial pH after ER arrival was entered into the multiple logistic analysis, the blood glucose level remained unchanged.

Blood Glucose Level and Adrenaline Concentration

The relationship between the blood glucose level and the plasma adrenaline concentrations is shown in Fig 5. There
was a significant positive correlation between them in patients with cardiogenic shock on ER arrival (R=0.726, \( p<0.0001 \)).

**Discussion**

We evaluated the prognostic implication of stress hyperglycemia across the entire spectrum of cardiogenic shock. In all types of cardiogenic shock, (volume, pump or rate problems), the blood glucose level on the ER arrival was an independent prognostic factor for the primary outcome of death in hospital. The rate of death increased in a stepwise fashion among the patients in increasing quartiles of the blood glucose level on ER arrival. The optimal cut-off point for death was a blood glucose level of 9.2 mmol/L and none of the patients with a blood glucose level 21.6 mmol/L or more survived to hospital discharge. Furthermore, a blood glucose levels of 9.2 mmol/L or more was the strongest prognostic indicator of death. Blood glucose levels also showed a significant positive correlation with levels of adrenaline, one of the stress hormones. These results show that the blood glucose level on ER arrival provides powerful information for use in risk stratification across the entire spectrum of cardiogenic shock.

The AHA guideline reported that cardiogenic shock consisted of volume problems caused by RV dysfunction, pump problems caused by LV dysfunction, and rate problems associated with tachyarrhythmias or bradyarrhythmias.
Correction of hyperglycemia through early administration of insulin may also improve the outcome in patients with cardiogenic shock by inhibiting the activation of the inflammatory response, progression of cell apoptosis, and platelet activation. We did not investigate the relationship between blood glucose control and cell damage, cytokines and immune function, or platelet activation, although blood glucose levels were controlled to less than 11.1 mmol/L during intensive care.

**Study Limitations**

First, this study was conducted at a single institution with a small number of patients with cardiogenic shock. A prospective multicenter study of cardiogenic shock is needed. Second, we were unable to thoroughly examine the relationship between blood glucose level and the time interval from the onset of cardiac disease to blood sample collection, or the relationship between the blood glucose level and the time interval from the onset of shock to blood sample collection, because those time intervals may contribute to hyperglycemia. Third, blood glucose level was measured in whole blood. If blood glucose is measured using plasma, the cut-off point and upper limit of the blood glucose level for death might change slightly. Finally, although the patients in this study were treated according to the standard guidelines, the precise managements of blood glucose level and body temperature may have influenced outcomes.

In conclusion, determination of blood glucose level using venous blood on arrival at the ER can be performed quickly and easily, and provides predictive information for use in risk stratification across the spectrum of cardiogenic shock.

**References**


