

Original Article

Effects of stress hyperglycemia on cardiac function and prognosis in critical patients of ICU

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Abstract: Background: This study explored effects of stress hyperglycemia (SHG) on cardiac function and prognosis in critical patients of ICU. Methods: We analyzed 80 critical non-diabetic patients admitted to ICU. Based on blood glucose levels, patients were divided into normal group with normal blood glucose level (conventional treatment) and SHG group. SHG patients were further divided into control group (conventional treatment) and strengthen group (intensive insulin therapy). Cardiac function parameters of patients were monitored by the Swan-Ganz catheter, including right atrial pressure (RAP), pulmonary artery pressure (PAP), pulmonary artery wedge pressure (PAWP); cardiac output (CO), cardiac index (CI), brain natriuretic peptide (BNP), hydrogen ion concentration (PH), partial pressure of oxygen in artery (PaO₂), and partial pressure of carbon dioxide in artery (PaCO₂). Results: SHG patients showed higher RAP, PAP, PAWP, BNP levels, and lower CO, CI, PaO₂ and PaCO₂ levels than normal group. Intensive insulin therapy significantly decreased RAP, PAP, PAWP, BNP, and increased CO, CI, PaO₂, and PaCO₂. Moreover, ICU length of stay, the number of patients using ventilator, duration of mechanical ventilation and mortality were all significantly decreased in strengthen group. Conclusion: SHG had a significant effect on cardiac function in patients admitted to ICU, resulting in exacerbation and poor prognosis. Intensive insulin therapy markedly improved cardiac function of patients with SHG.

Keywords: Stress hyperglycemia (SHG), ICU, cardiac function, prognosis, intensive insulin therapy

Introduction

Stress hyperglycemia (SHG) refers to previous sharp rise in blood glucose levels of diabetes patients or patients without diabetes history by stimulation, such as, severe trauma, infection, cardiovascular, cerebrovascular accidents and major surgery. For patients without diabetes history, if a random blood glucose levels ≥ 11.1 mmol/L or fasting blood glucose levels ≥ 7.0 mmol/L two more times, it can be diagnosed as SHG [1]. Different with diabetes, SHG has the following characteristics [2, 3]: (1) acute or a short time hyperglycemia and blood glucose back to normal with primary disease cured; (2) increasing serum insulin and C-peptide; (3) the outstanding "insulin resistance" performance; (4) associated with high metabolism, mainly in gluconeogenesis.

According to blood glucose recorded, the occurrence of SHG in ICU patients is very common. For most critically ill patients admitted to the

ICU, even with no previous history of diabetes, blood glucose often rise and the occurrence rate is about 50%, which is of a great danger [4]. According to recent studies on non-diabetic or diabetic patients, SHG is an independent risk factor causing cardiovascular disease [5]; Hyperglycemia on admission state can significantly affect the prognosis of patients with cardiovascular disease. Compared to patients with diabetes, a higher mortality occurs in 2030 cases of hyperglycemia patients [6]. Blood glucose level reflects the strength of the body's stress response, and the persistent high blood glucose level is positively correlated with critical illness severity and prognosis [4]. Intensive insulin therapy can significantly improve blood glucose level to strengthen lung function and correct acid-base imbalance [7]. Though the impact of diabetes on cardiac function has been studied very thoroughly, the mechanism of SHG on cardiac function is an urgent clinical problem to be solved.

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In this study, 80 cases of critically ill patients admitted to the ICU were recruited. Cardiac function was measured by the Swan-Ganz catheter and BNP blood tests. All patients were divided into normal group with normal blood glucose level (conventional treatment) and SHG group. SHG patients were further divided into control group (conventional treatment) and strengthen group (intensive insulin therapy). To explore the effects of SHG on cardiac function and clinical prognosis of the critical patients from ICU, we analyzed hospitalized situation and prognosis of patients in three groups. Furthermore, cardiac function differences were also analyzed before and after intensive insulin therapy.

Material and methods

Subjects

This prospective study was approved by the ethics committee of the 254 Hospital of Chinese People's Liberation Army, and written informed consent was obtained from all patients before enrollment. All patients admitted to the ICU of our hospital without previously known diabetes were screened for development of hyperglycemia during December 2010 to September 2014. Patients for this study were recruited using the following inclusion criteria: (1) patients without previously known diabetes, insulinoma, or glucose metabolic disorders; (2) patients with normal glycated hemoglobin levels after admission; (3) patients in their first hyperglycemia period; (4) the critical ill patients with normal glucose level. The exclusion criteria were: (1) Patients with acute myocardial infarction; (2) Patients with diabetic ketoacidosis, or with hyperosmolar nonketotic diabetic coma; (3) Patients with hepatic and renal disorders; (4) Patients with severe arrhythmia; (5) Patients with active rheumatic heart disease; (6) Patients with valvular stenosis or insufficiency; (7) Patients with severe pulmonary arterial abnormality or pulmonary hypertension; (8) Patients implanted with cardiac pacemaker. Finally, a total of 80 critically ill patients with normal glucose or hyperglycemia were recruited into this study. Twenty patients were diagnosed with acute cardiac insufficiency, 18 with acute respiratory distress syndrome (ARDS), 11 with septic shock, 19 with cerebrovascular accidents, and 10 with cardiopulmonary-cerebral resuscitation. Patients were divided into normal group (normal glucose; con-

ventional treatment) and SHG group according to their glucose levels. The latter was further divided into control group (conventional treatment) and strengthen group (intensive insulin therapy).

Hyperglycemia was defined as 2 fasting glucose values of at least 140 mg/dL or a random glucose of at least 200 mg/dL, which was adapted from the definition outlined in a consensus statement regarding inpatient glucose control by the American Diabetes Association [8].

Data collection

Blood glucose measurements were recorded using a portable glucometer (Johnson & Johnson) during the 28 days of ICU admission. Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated to evaluate illness severity [9]. Hepatorenal function, myocardial enzyme, glycosylated hemoglobin (HbA_{1c}), and brain natriuretic peptide (BNP) were monitored. Swan-Ganz catheterization was performed to monitor cardiac function variables, including central venous pressure (CVP), pulmonary arterial pressure (PAP), pulmonary artery wedge pressure (PAWP), cardiac output (CO), and cardiac index (CI). Arterial blood samples were drawn for blood gas analyses using the GEM Premier 3000, Instrumentation Laboratory, Lexington, MA, USA). Patients in strength group were infused with insulin (1 u/mL) at 0.1 U/kg/h in addition to the conventional therapy. Duration of ICU stay and mechanical ventilation, number of patient using ventilator, and the mortality of the patients 28 days after ICU admission were recorded.

Statistical analysis

Statistical analysis was performed using SPSS (version 17.0). Data were expressed as means \pm standard deviation (SD). Comparisons between groups were conducted using χ^2 tests or Student *t* test as appropriate. A *P* value, *P* \leq 0.05, was considered as statistically significant.

Results

Clinical data of patients with normal blood glucose or SHG

To figure out the patient's health status, we analyzed clinical data of patients including sex,

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Table 1. Comparison of information from the three group patients

Group Type	n	Male/ Female	Age	APACHE II Score
Normal group	24	12/12	63.2±10.9	20.0±4.2
Control group	28	15/13	65.7±9.5	21.2±4.8
Strengthen group	28	16/12	64.5±10.1	21.5±4.5

APACHE II: Acute Physiology and Chronic Health Evaluation II.

Table 2. Measurement of the related cardiac function parameters in ICU patients

Index	Normal group (n=24)	SHG group (n=56)
RAP (mmHg)	5.9±3.7	9.6±5.8*
PAP (mmHg)	27.4±10.8	33.9±15.3*
PAWP (mmHg)	8.9±6.7	15.6±7.2*
CO (L/min)	5.9±3.2	3.2±2.4*
CI (L/min·m ²)	2.75±0.52	1.85±0.25*
BNP (pg/mL)	184.3±54.2	476.9±243.6*
PH	7.39±0.20	7.42±0.13
PaO ₂ (mmHg)	68.21±14.56	54.85±10.52*
PaCO ₂ (mmHg)	38.63±2.71	17.35±6.64*

RAP: Right atrial pressure; PAP: Pulmonary artery pressure; PAWP: Pulmonary artery wedge pressure; CO: Cardiac output; CI: Cardiac index; BNP: Brain natriuretic peptide; PH: Hydrogen ion; PaO₂: Partial pressure of oxygen in artery; PaCO₂: Partial pressure of carbon dioxide in artery; *P < 0.05 vs. normal group.

age and APACHE II score in the first 24 h of admission (**Table 1**). There was no significant difference among sex and age ($P > 0.05$). As we know, APACHE II is a good system to evaluate the severity of the disease. Normal group showed the lowest APACHE II score. Strength group showed the highest APACHE II score.

Measurement of the related cardiac function parameters of patients in the first 24 h of admission

To further gain insight into the patient cardiac function, the related cardiac function parameters, including RAP, PAP, PAWP, CO, CI, BNP, PaO₂, and PaCO₂, were measured by the Swan-Ganz catheter (**Tables 2 and 3**). RAP, PAP, PAWP and BNP indexes in SHG group were significantly higher than normal group. RAP and PAWP in SHG patients were 1.5 times more than normal group. BNP was 2.5 times more than normal group. And CO, CI, PaO₂ and PaCO₂ indexes in patients with SHG were significantly lower than

those with normal blood glucose. CO, CI, PaO₂ and PaCO₂ in SHG patients were decreased by 45.76%, 32.73%, 19.59%, 55.09%, respectively. The difference was statistically significant ($P < 0.05$).

Characterization of the related cardiac function parameters from patients of SHG

To investigate how intensive insulin therapy affected cardiac function and prognosis in critical patients of ICU, patients in the SHG group were randomly divided into control group and strength group. Intensive insulin therapy was exclusively applied to strength group, with the regular insulin (40 mL, 1 u/mL) administered by a syringe. The parameters related to cardiac function (RAP, PAP, PAWP, CO, CI, BNP, PaO₂ and PaCO₂) were measured using the Swan-Ganz catheter technique.

As shown in **Table 3**, there was no significant difference in RAP, CI, BNP levels, between strengthen group and control group before treatment. Intensive insulin therapy resulted in significant lower levels of RAP, PAP, PAWP and BNP index in strengthen group, while significantly higher CO, CI, PaO₂, pH and PaCO₂ indexes when compared with the control group. Thirdly, we compared the parameter differences of strengthen group before and after intensive insulin therapy. As we expected, RAP, PAP, PAWP, BNP in patients were decreased significantly after intensive insulin therapy; and CO, CI, PaO₂ and PaCO₂ index were increased significantly. The difference was statistically significant ($P < 0.05$).

Analysis of related prognostic parameters

To fully understand the hospitalization of three group patients, we analyzed ICU stay, the ventilator utilization, duration of mechanical ventilation, and mortality (**Table 4**). Compared with normal group, ICU stay, the number of patients using ventilator, duration of mechanical ventilation, and mortality of patients were all higher in SHG group. After intensive insulin therapy, the length of ICU stay, the number of patients using ventilator, duration of mechanical ventilation, and the mortality were significantly decreased in strength group than that in the control group, although still significantly higher than normal group ($P < 0.05$).

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Table 3. Parameters comparison of strengthen group before and after intensive insulin therapy

Index	Control group	Strengthen group	
		Before treatment	After treatment
RAP (mmHg)	9.2±6.0	9.6±5.8	7.9±2.3* [#]
PAP (mmHg)	30.1±7.7	33.9±15.3	22.0±3.6* [#]
PAWP (mmHg)	14.9±8.1	15.6±7.2	9.9±5.4* [#]
CO (L/min)	2.9±2.3	3.2±2.4	5.0±3.1* [#]
CI (L/min·m ²)	1.95±0.80	1.85±0.25	2.53±0.32* [#]
BNP (pg/mL)	436.9±273.6	466.9±293.3	206.7±60.3* [#]
PH	7.39±0.19	7.42±0.13	7.40±0.15 [#]
PaO ₂ (mmHg)	52.45±10.54	57.85±8.52	69.21±13.63* [#]
PaCO ₂ (mmHg)	20.23±7.74	17.35±6.64	37.63±3.71* [#]

RAP: Right atrial pressure; PAP: Pulmonary artery pressure; PAWP: Pulmonary artery wedge pressure; CO: Cardiac output; CI: Cardiac index; BNP: Brain natriuretic peptide; PH: Hydrogen ion; PaO₂: Partial pressure of oxygen in artery; PaCO₂: Partial pressure of carbon dioxide in artery; **P* < 0.05 vs. control group; [#]*P* < 0.05 vs. strengthen group before treatment.

Table 4. Comparison of hospitalizations and prognosis

Index	Normal group (n=24)	Control group (n=28)	Strengthen group (n=28)
ICU length of stay (d)	7.28±3.94	14.66±2.54*	10.56±3.46* [#]
Ventilator n (%)	10 (41.7)	22 (78.6)*	18 (64.3)* [#]
Mechanical ventilation (h)	56.86±10.43	124.08±15.64*	84.48±12.63* [#]
Mortality n (%)	3 (12.5)	13 (46.43)*	8 (28.57)* [#]

**P* < 0.05 vs. normal group; [#]*P* < 0.05 vs. control group, *P* ≤ 0.05.

Discussion

Stress hyperglycemia (SHG) is common in critically ill patients admitted to ICU and it seriously affects cardiac function and prognosis of patients [4, 8, 10, 11]. SHG was mainly caused by several factors [12], as follows: (1) Stress hormones imbalances: neuroendocrine system is activated by infection, trauma, shock, surgery, acute myocardial infarction, heart failure or other factors, leading hypothalamic-pituitary-adrenal axis (HPA) over-excited, stress hormones glucagon, catecholamines, glucocorticoids, growth hormone increased. Then the body showed insulin secretion relative lack, insulin/glucagon imbalance, glycogen breakdown. Finally, insulin resistance appeared and cause neuroendocrine dysfunction. The body appeared relatively inadequate insulin secretion, and thereby stimulated to break down glycogen and resist insulin [13-16]; (2) Inappropriate secretion of cytokines: under stress, monocytes and cells from different tissues

secreted various cytokines, such as, TNF- α , IL-1, IL-6, which affected insulin signaling pathway and caused high blood glucose [15, 17, 18]. (3) Other factors: elderly, bedridden, obesity and excessive intake of sugar during the treatment [19-21]. All aspects seriously resulted in glucose production exceeded glucose clearance in SHG patients.

In this study, we analyzed general information of critically ill patients admitted to ICU. There was no significant difference in sex and age among three groups, thus illustrating our results objective and reliable. Some studies have shown that age was closely related to SHG, and plasma insulin level was not proportional to age [20]. In a study of trauma patients, hypoglycemia incidence of the old over 60 years old was far higher 38% than the young 0%

[21]. Our selected patients were all over 60 years old. Under insulin resistance stress, insulin deficiency played a very important role in SHG of elderly. APACHE II, a severity of disease classification system, can be used to evaluate the use of hospital resources and compare the efficacy of intensive care in different hospitals or over time [9, 10, 22]. An APACHE II score over 21 was associated with 94% mortality [23]. A significantly positive correlation existed between APACHE II score and mortality. Our results also indicated that an APACHE II score over 21 had a higher mortality.

Recent studies have demonstrated that SHG produced by various stress reactions involved in many diseases [4, 11, 24]. Thus blood glucose level could reflect the reaction of the body to stress [25]. The parameters related to cardiac function were measured through the Swan-Ganz catheter technique. The results showed that RAP, PAP, PAWP and BNP in SHG patients were all higher than normal group, and that CO,

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CI, PaO₂, PaCO₂ were all lower. It indicated that patients in SHG group had worse cardiac function than normal group. Especially, PaCO₂ level in SHG patient was significantly low compared with normal group, which was decreased by 55.09%. This can be explained by the decreasing body hypoxia and heart function, accompany by breathing faster and increasing carbon dioxide emission. As the important indicative factors to reflect acid-base balance in respiration, PaCO₂ and PaO₂ levels were all decreased to normal group, suggesting SHG involved in regulation of acid-base balance. Cardiac function caused by SHG was decreased with alveolar ventilation dysfunction, pulmonary diffusion dysfunction, myocardial hypoxia aggravated.

It was reported that intensive insulin therapy significantly improved lung function and corrected acid-base imbalance. PaO₂ level elevated and oxygen metabolism improved in patients with heart failure and high blood glucose after intensive insulin therapy [7]. This clarified that intensive insulin therapy provided a good treatment for SHG. In addition, we analyzed the effect of intensive insulin therapy on cardiac function and prognosis of the patients. All indexes were improved after treatment. For critically ill patients of SHG, hemodynamic parameters measured by the Swan-Ganz catheter technique, such as, RAP, PAP, PAWP, CO, CI, PaO₂, PaCO₂ and BNP, were all improved significantly. BNP can be a quantitative marker of heart failure [26]. Compared with BNP in control group, strengthen group showed that BNP was decreased by 52.69% after intensive insulin therapy. Compared with BNP before intensive insulin therapy, strengthen group showed that BNP was decreased by 55.73% after intensive insulin therapy. All results declared that intensive insulin therapy could protect cardiac function and improve the prognosis. At the same time, we need closely monitor blood glucose levels of critically ill patients to reduce the incidence of adverse events. Intensive insulin therapy may cause blood glucose level too low some time, and thus leading heart or brain ischemia further aggravated, even death [27, 28].

Studies have shown that SHG, an independent prognostic factor, made primary disease progression, delayed the disease recovery, and thereby resulted in a variety of serious complications or even death in critically ill patients [1,

29]. It has been reported that blood glucose levels elevated along with the relative lack of insulin secretion and increased plasma free fatty acids, which resulted in membrane damaged, calcium overload, myocardial contractility reduced. Moreover, hyperglycemia can prompt pump failure and trigger arrhythmias [30, 31]; In addition, hyperglycemia can change osmotic pressure of cell, suppress the immune, increase pro-inflammatory cytokines, impair mitochondrial function, and increase oxygen free radicals, which all promoted damage in tissues and organs [32, 33]; In our study, for SHG critically ill patients, length of ICU stay, the number of patients using ventilator, duration of mechanical ventilation and mortality were all higher than normal group, consistent with the results of Langouche's study [29]. The mortality of patients in strengthen group and control group was 3.3 and 2.3 times than normal group, respectively. Compared with control group, these parameters in strengthen group were decreased a lot after intensive insulin therapy, such as, mortality decreased by 38.5%, average duration of mechanical ventilation decreased by 31.9%. Future study is required to clearly understand the effect mechanism of SHG on cardiac function and prognosis, and to better use of intensive insulin therapy to reduce the mortality of the patients.

In summary, our study showed that SHG had a significant influence on cardiac function of critically ill patients from ICU, resulting in exacerbations and poor prognosis. The blood glucose level at the acute phase can be one of the important parameters for evaluating the severity and prognosis. The effect of SHG on cardiac function is complex. It is strongly suggested that intensive insulin therapy be taken to control the blood glucose levels, and to protect the cardiac function. Meanwhile, it is essential to closely monitor of blood glucose levels to prevent hypoglycemia. Intensive insulin therapy paves an important way for SHG to reduce blood glucose levels. Future study is still required on reducing blood glucose of severe medical field.

Disclosure of conflict of interest

None.

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