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The association of admission blood glucose level with the clinical picture and prognosis in cardiogenic shock – Results from the CardShock Study[☆]

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ABSTRACT

Background: Critically ill patients often present with hyperglycemia, regardless of previous history of diabetes mellitus (DM). Hyperglycemia has been associated with adverse outcome in acute myocardial infarction and acute heart failure. We investigated the association of admission blood glucose level with the clinical picture and short-term mortality in cardiogenic shock (CS).

Methods: Consecutively enrolled CS patients were divided into five categories according to plasma glucose level at the time of enrolment: hypoglycemia (glucose <4.0 mmol/L), normoglycemia (4.0–7.9 mmol/L), mild (8.0–11.9 mmol/L), moderate (12.0–15.9 mmol/L), and severe (≥16.0 mmol/L) hyperglycemia. Clinical presentation, biochemistry, and short-term mortality were compared between the groups.

Results: Plasma glucose level of 211 CS patients was recorded. Glucose levels were distributed equally between normoglycemia (26% of patients), mild (27%), moderate (19%) and severe (25%) hyperglycemia, while hypoglycemia (2%) was rare. Severe hyperglycemia was associated with higher blood leukocyte count (17.3 (5.8) E9/L), higher lactate level (4.4 (3.3–8.4) mmol/L) and lower arterial pH (7.23 (0.14)) compared with normoglycemia or mild to moderate hyperglycemia ($p < 0.001$ for all). In-hospital mortality was highest among hypoglycemic (60%) and severely hyperglycemic (56%) patients, compared with 22% in normoglycemic group ($p < 0.01$). Severe hyperglycemia was an independent predictor of in-hospital mortality (OR 3.7, 95% CI 1.19–11.7, $p = 0.02$), when adjusted for age, gender, LVEF, lactate, and DM.

Conclusions: Admission blood glucose level has prognostic significance in CS. Mortality is highest among patients with severe hyperglycemia or hypoglycemia. Severe hyperglycemia is independently associated with high in-hospital mortality in CS. It is also associated with biomarkers of systemic hypoperfusion and stress response.

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¹ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

1. Introduction

Critically ill patients often present with hyperglycemia, regardless of previous history of diabetes mellitus (DM) [1]. Hyperglycemia in acute illness partly reflects the activation of stress response mechanisms that are essential for survival [2,3]. Hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal system become activated in response to severe trauma, hemorrhage, sepsis as well as hypotension or shock of any cause, resulting in high release of stress mediators

such as catecholamines and cortisol. In addition to multiple changes in cardiovascular and immune systems, these stress mediators alter the carbohydrate metabolism by inducing gluconeogenesis, glycolysis and insulin resistance [2–5]. This in turn leads to hyperglycemia, a condition associated with adverse outcome among critically ill patients [5,6]. On the other hand, it has been argued that hyperglycemia is merely an indicator of severity of illness and not a harmful phenomenon as such [2].

Previous studies have shown the association between hyperglycemia and increased mortality in acute coronary syndrome (ACS) and acute heart failure [7,8]. However, data on the significance of blood glucose level in cardiogenic shock (CS) are sparse [9,10]. CS is the most severe form of acute heart failure and the leading cause of death in ACS, characterized by low cardiac output, hypotension and tissue hypoperfusion. Mortality rates in CS are as high as 40% to 50% [11]. In addition to hypoperfusion, there is increasing evidence regarding the role of neurohormonal activation and systemic inflammatory response in the development of CS [12].

The aim of this study was to investigate the association of blood glucose levels with patient characteristics and clinical presentation, and to assess the prognostic significance of admission blood glucose level in CS.

2. Methods

The CardShock study (NCT01374867 at www.clinicaltrials.gov) is a multicenter, prospective, observational study conducted between 2010 and 2012. The data were collected from nine tertiary hospitals in eight countries across Europe. We enrolled consecutive adult CS patients within 6 h of the detection of the shock, and both ACS and non-ACS etiologies were included. CS was defined as severe hypotension of acute cardiac cause (systolic blood pressure <90 mmHg despite adequate fluid resuscitation or need for vasopressor therapy to maintain systolic blood pressure >90 mmHg) and signs of hypoperfusion (altered mental status, cold periphery, oliguria (diuresis <0.5 ml/kg/h for previous 6 h) or plasma lactate >2 mmol/L). Patients presenting with on-going hemodynamically significant cardiac arrhythmia were excluded, as well as patients suffering from CS after cardiac surgery. The detailed design and main results of the CardShock study have been published previously [13].

Data on patient characteristics and medical history were collected. Echocardiography was performed, clinical parameters were evaluated, and blood was drawn at the time of enrolment. Blood leukocytes, hemoglobin, glucose, sodium, alanine aminotransferase (ALT), lactate, and arterial pH were analyzed locally. Creatinine, C-reactive protein (CRP), high-sensitivity troponin T (hsTnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP, Roche Diagnostics, Basel, Switzerland) were analyzed centrally from blood samples stored at -80°C . Estimated glomerular filtration rate (eGFR) was calculated from creatinine values using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation [14]. The investigation conforms to the principles outlined in the Declaration of Helsinki and the study was approved by local ethics committees.

For statistical analyses, we divided the study population into five different categories according to plasma glucose level at the time of enrolment: patients with hypoglycemia (glucose <4.0 mmol/L), normoglycemia (glucose 4.0–7.9 mmol/L, reference group), and mild (glucose 8.0–11.9 mmol/L), moderate (glucose 12.0–15.9 mmol/L), or severe hyperglycemia (glucose ≥ 16.0 mmol/L). The cut-off level of hypoglycemia and the range of normoglycemia were set according to a recent, clinically oriented review on glucose management in critically ill patients [15]. The same plasma glucose range of 3.9 mmol/L as in normoglycemic group was used to categorize the hyperglycemic patients into three distinct, clinically relevant groups. We compared the medical history, clinical presentation, biochemical variables, and short-term (in-hospital and 90-day) mortality between the five groups. Categorical variables are presented as numbers (n) and percentages (%), continuous variables as means with standard deviations (SD) or medians with inter-quartile ranges (IQR) for variables with a skewed distribution. Group comparisons were performed with chi-square test for categorical variables and with analysis of variances (ANOVA) or Kruskal-Wallis test for continuous variables, as appropriate. Correlations between two continuous variables were tested by using Spearman's rank correlation (ρ) due to the skewed distribution of the variables. We built uni- and multivariate logistic regression models to investigate the association of various baseline plasma glucose levels with in-hospital mortality, and normoglycemia was used as reference glucose level. In addition to glucose level, age, gender, and history of DM, the multivariate model included admission blood lactate and left ventricular ejection fraction (LVEF) for their prognostic value in critical illness in general and especially in CS, respectively [13, 16,17]. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Kaplan-Meier survival curves were used to illustrate differences in mortality between the groups. The end-point of interest was 90-day mortality. The threshold p-value for statistical significance was 0.05. Statistical analyses were performed by SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA).

3. Results

Plasma glucose level was recorded at the time of enrolment in 211 CS patients. Hypoglycemia occurred in five (2%) patients, normoglycemia in 55 (26%), mild hyperglycemia in 58 (27%), moderate hyperglycemia in 41 (19%), and severe hyperglycemia in 52 (25%) patients. Medical history and patient characteristics are shown in Table 1. There were no differences in age or gender between the groups. In contrast, there was a significant difference in the prevalence of diabetes mellitus ($p < 0.001$), hypertension ($p = 0.04$), and hyperlipidemia ($p = 0.002$). Severely hyperglycemic patients were the most likely to have an ACS etiology of CS ($p = 0.03$). They also had the highest body mass indices (BMI) ($p = 0.01$) and were the most likely to get intubated ($p < 0.001$).

The clinical presentation and biochemistry at the time of enrolment are shown in Table 2. There were no differences in systolic blood pressure, heart rate, LVEF, or presence of infection. In contrast, blood lactate level was significantly higher and arterial pH lower among severely hyperglycemic patients compared with patients with normoglycemia and mild or moderate hyperglycemia ($p < 0.001$ for all). Patients with severe hyperglycemia also had the highest blood leukocyte count ($p < 0.001$). The hypoglycemic patients presented with the highest levels of lactate, ALT and NT-proBNP, and the lowest arterial pH and LVEF, but the differences were statistically non-significant due to the small number of patients in this group. No differences in the levels of blood hemoglobin, plasma CRP, hsTnT, or eGFR were observed between the groups. Plasma glucose had a positive correlation with blood leukocyte count ($\rho = 0.33$, $p < 0.001$), lactate ($\rho = 0.33$, $p < 0.001$), creatinine ($\rho = 0.15$, $p = 0.03$) and hsTnT ($\rho = 0.17$, $p = 0.02$), and a negative correlation with arterial pH ($\rho = -0.31$, $p < 0.001$).

Both in-hospital and 90-day mortality differed significantly between the groups (Table 1). Mortality was highest among hypoglycemic and severely hyperglycemic patients with in-hospital mortality rates of 60% and 56%, respectively, in contrast to 22% among normoglycemic patients ($p = 0.005$). The Kaplan-Meier survival curves are shown in Fig. 1. Mean glucose level of in-hospital survivors was lower than that of non-survivors (11.6 (SD 6.3) vs. 14.4 (6.9) mmol/L, $p = 0.005$). In univariate logistic regression analysis for in-hospital mortality, higher baseline glucose level as a continuous variable (per 1 mmol/L increase) was associated with increased mortality (OR 1.06, 95% CI 1.02–1.11, $p = 0.005$). When the study population was categorized by the prior DM status, higher plasma glucose level was associated with adverse outcome in patients without DM (OR 1.10, 95% CI 1.03–1.16, $p = 0.005$) but not in patients with diagnosed DM (OR 1.02, 95% CI 0.95–1.09, $p = 0.6$). Similarly, there was a significant difference in mean glucose level among in-hospital survivors and non-survivors without DM (10.1 (SD 4.5) vs. 12.9 (6.8) mmol/L, $p = 0.008$), but not among those with diagnosed DM (16.3 (SD 8.5) vs. 17.4 (6.3) mmol/L, $p = 0.6$). When the small group of hypoglycemic patients was excluded from the analysis (due to its distinct pathophysiology), the association between increasing glucose level and in-hospital mortality was even accentuated among patients without DM (OR 1.12, 95% CI 1.05–1.19, $p = 0.001$), but not among those with diagnosed DM (OR 1.01, 95% CI 0.94–1.09, $p = 0.7$).

When glucose was considered a categorical variable and normoglycemia used as reference level, severe hyperglycemia was a strong predictor of in-hospital mortality (OR 4.5, 95% CI 1.9–10.5, $p < 0.001$), whereas mild (OR 1.7, 95% CI 0.75–4.1, $p = 0.2$) and moderate hyperglycemia (OR 1.9, 95% CI 0.75–4.6, $p = 0.2$) were not significantly associated with higher mortality. Hypoglycemia (OR 5.4, 95% CI 0.80–35.9, $p = 0.08$) also showed a trend towards increased mortality. In multivariate logistic regression analysis, severe hyperglycemia was independently associated with increased in-hospital mortality (OR 3.7, 95% CI 1.19–11.7, $p = 0.02$) after adjusting for age, gender, plasma lactate, LVEF, and history of DM (Table 3).

Table 1
Patient characteristics, medical history and mortality.

	All	Hypoglycemia	Normoglycemia	Mild hyperglycemia	Moderate hyperglycemia	Severe hyperglycemia	p value
N (%)	211	5 (2)	55 (26)	58 (27)	41 (19)	52 (25)	
Female	54 (26)	2 (40)	12 (22)	16 (28)	7 (17)	17 (33)	0.40
Age (SD), years	67 (12)	65 (10)	65 (13)	67 (13)	68 (12)	67 (10)	0.82
BMI, kg/m ²	26.7 (4.0)	27.0 (3.1)	25.8 (4.5)*	25.9 (4.1)†	27.0 (3.6)	28.3 (3.2)*†	0.01
ACS etiology	170 (81)	3 (60)	38 (69)	47 (81)	34 (83)	48 (92)	0.03
PCI	143 (68)	3 (60)	30 (55)	41 (71)	30 (73)	39 (75)	0.16
Resuscitation	59 (28)	1 (20)	13 (24)	11 (19)	14 (34)	20 (38)	0.16
Intubation	131 (64)	2 (40)	24 (44)	38 (67)	24 (60)	43 (86)	<0.001
<i>Medical history</i>							
Diabetes mellitus	58 (27)	1 (20)	4 (7)	11 (19)	15 (37)	27 (52)	<0.001
Hypertension	129 (61)	3 (60)	28 (51)	30 (52)	30 (73)	38 (73)	0.04
Hyperlipidemia	97 (46)	4 (80)	16 (29)	22 (38)	22 (54)	33 (63)	0.002
Coronary artery disease	72 (34)	3 (60)	16 (29)	16 (28)	13 (32)	24 (46)	0.15
Congestive heart failure	35 (17)	0 (0)	6 (11)	10 (17)	6 (15)	13 (25)	0.28
Previous MI	53 (25)	2 (40)	10 (18)	13 (22)	10 (24)	18 (35)	0.32
Asthma/COPD	18 (9)	1 (20)	6 (11)	4 (7)	2 (5)	5 (10)	0.70
<i>Mortality</i>							
In-hospital	77 (36)	3 (60)	12 (22)	19 (33)	14 (34)	29 (56)	0.005
90-day	85 (41)	3 (60)	14 (26)	22 (39)	15 (37)	31 (60)	0.008

BMI = body mass index, ACS = acute coronary syndrome, PCI = percutaneous coronary intervention, MI = myocardial infarction, COPD = chronic obstructive pulmonary disease. Categorical variables are presented as numbers (percentages), continuous variables as means (standard deviation) for normally distributed variables. P-values are for the differences between the groups (* and † indicate, between which two groups).

4. Discussion

In this prospective study of an unselected adult CS population, we have four main findings. First, blood glucose levels range widely from hypoglycemic to highly elevated values in CS. Patients can be clearly categorized according to their baseline blood glucose level into clinically relevant groups which have prognostic significance. Second, severe hyperglycemia is associated with biomarkers of systemic hypoperfusion and stress response. Third, both hypoglycemia and severe hyperglycemia are associated with high mortality in CS, whereas normoglycemia at presentation suggests a relatively favorable outcome. Prior DM status

modifies the prognostic value of admission blood glucose. Finally, severe hyperglycemia is an independent predictor of in-hospital mortality.

In this CS population, baseline glucose levels were distributed equally between the groups of normoglycemia as well as mild, moderate, and severe hyperglycemia. The medical history differed significantly between the groups and the prevalence of DM was highest among severely hyperglycemic patients and lowest among normoglycemic patients. High blood glucose levels among diabetic patients may be related to the excessive hepatic glucose production and peripheral insulin resistance that are constantly present and even accentuated during critical illness [1,18].

Table 2
Clinical presentation and biochemistry at the time of enrolment.

	All	Hypoglycemia	Normoglycemia	Mild hyperglycemia	Moderate hyperglycemia	Severe hyperglycemia	p value
N (%)	211	5 (2)	55 (26)	58 (27)	41 (19)	52 (25)	
Systolic BP; mmHg (SD)	77 (14)	74 (14)	79 (11)	80 (10)	74 (13)	76 (18)	0.19
MAP; mmHg	57 (11)	54 (7)	58 (9)	59 (10)	55 (10)	54 (12)	0.07
HR, beats/min	90 (28)	79 (17)	85 (29)	95 (24)	92 (31)	89 (31)	0.34
LVEF; %	33 (14)	26 (9)	34 (15)	32 (14)	36 (14)	31 (13)	0.43
Sinus rhythm, n (%)	154 (74)	3 (60)	43 (80)	49 (84)	26 (63)	33 (65)	0.05
Infection, n (%)	30 (14)	0 (0)	9 (17)	8 (14)	8 (20)	5 (10)	0.56
Lactate >2 mmol/L, n (%)	150 (72)	4 (80)	30 (56)	39 (67)	31 (78)	46 (90)	0.002
Confusion, n (%)	142 (68)	3 (60)	30 (55)	41 (73)	27 (68)	41 (79)	0.08
Cold periphery, n (%)	199 (95)	5 (100)	51 (94)	54 (93)	39 (95)	50 (96)	0.94
Oliguria, n (%)	115 (55)	3 (60)	23 (42)	35 (61)	21 (53)	33 (65)	0.14
<i>Biochemistry</i>							
Leukocytes; E9/L	14.4 (5.6)	13.8 (3.6)	11.9 (4.5)*	14.0 (5.5)†	14.5 (5.1)	17.3 (5.8)*†	<0.001
Hemoglobin; g/L	129 (22)	116 (11)	126 (25)	129 (22)	130 (23)	131 (18)	0.54
eGFR; ml/min/1.73m ²	63 (29)	59 (40)	63 (28)	69 (29)	66 (29)	56 (31)	0.30
Sodium; mmol/L	137 (5)	139 (5)	136 (6)	137 (5)	137 (4)	136 (6)	0.57
ALT; U/L	62 (29–159)	466 (74–801)	64 (25–158)	47 (30–132)	59 (32–129)	89 (39–207)	0.41
Glucose; mmol/L	10.7 (7.8–15.8)	3.2 (2.7–3.5)	6.9 (6.2–7.6)	9.4 (8.7–10.6)	13.4 (12.7–14.5)	20.8 (18.8–25.2)	<0.001
Lactate; mmol/L	2.8 (1.7–5.6)	8.3 (2.7–14.0)	1.8 (1.2–3.2)*	2.6 (1.8–4.8)†	2.6 (2.1–4.6)‡	4.4 (3.3–8.4)*†‡	<0.001
Arterial pH	7.30 (0.13)	7.19 (0.22)	7.35 (0.12)*	7.30 (0.11)†	7.31 (0.11)‡	7.23 (0.14)*†‡	<0.001
NT-proBNP; ng/L	2501 (608–9015)	26,300 (19,129–33,471)	3759 (550–9806)	2520 (647–8537)	2015 (563–8904)	2426 (601–7294)	0.33
hsTnT; ng/L	2120 (389–5417)	1052 (278–1828)	1717 (132–4925)	1485 (243–6462)	2616 (570–5244)	2629 (975–7842)	0.40
CRP; mg/L	15 (4–49)	61 (39–84)	22 (5–83)	9 (4–40)	18 (5–75)	12 (4–35)	0.24

BP = blood pressure, MAP = mean arterial pressure, HR = heart rate, LVEF = left ventricular ejection fraction, eGFR = estimated glomerular filtration rate, ALT = alanine aminotransferase, NT-proBNP = N-terminal prohormone B-type natriuretic peptide, hsTnT = high-sensitivity troponin T, CRP = C-reactive protein. Categorical variables are presented as numbers (percentages). Continuous variables are presented as means (standard deviation) for normally distributed variables and as medians (inter-quartile range) for variables with a skewed distribution. P-values are for the differences between the groups (*, † and ‡ indicate, between which two groups).

Fig. 1. Kaplan–Meier survival curves.

In contrast, CS patients rarely presented with hypoglycemia. Previous studies have shown the association of both mild and severe hypoglycemia with increased mortality in critically ill patients [19–21]. In the present study, excessive dose of insulin or some other DM medication was unlikely the cause of hypoglycemia, since only one out of five hypoglycemic patients had a diagnosis of DM. Instead, severe acute cardiac failure was especially evident among hypoglycemic patients, as evidenced by low LVEF and high NT-proBNP levels that were elevated up to ten-fold compared with other groups. In four out of five hypoglycemic patients, plasma ALT levels were also markedly elevated, suggesting hepatic congestion and hepatocyte injury [22,23]. This may partly inhibit the adequate response to stress mediators and induce hypoglycemia due to insufficient level of hepatic gluconeogenesis and glycolysis. Moreover, clearly acidotic pH values and high lactate levels indicated profound hypoperfusion among these patients. In addition to hypoperfusion, hepatic dysfunction as such may increase blood lactate levels, since liver is the major site of lactate clearance [24].

Acidosis and hyperlactatemia were prevalent not only among hypoglycemic patients but also among patients with severe hyperglycemia. In CS, low cardiac output and hypotension cause both hyperlactatemia due to insufficient tissue perfusion, and hyperglycemia due to stress response and subsequent rise in the concentrations of catecholamines and cortisol. In this study, plasma glucose levels correlated positively with lactate levels and negatively with arterial pH levels. In the presence of systemic hypoperfusion and insufficient oxygen supply, the carbohydrate metabolism is shifted towards anaerobic metabolism, resulting

in the increase of plasma lactate level. On the other hand, lactate can then be converted back to glucose through the Cori cycle in the liver. In addition, both endogenous and exogenous catecholamines induce accelerated aerobic glycolysis resulting in elevated lactate levels [25].

The strong endogenous stress response in severely hyperglycemic patients was also demonstrated by high blood leukocyte count. Moreover, plasma glucose correlated positively with blood leukocytes. Leukocytosis has been associated with increased mortality in ST-elevation acute myocardial infarction [26]. As a part of inflammatory response, leukocytes are mobilized from the bone marrow by soluble inflammatory mediators such as cytokines. Tissue necrosis stimulates the inflammatory response, and in this study plasma glucose also correlated positively with ACS etiology and hsTnT, a marker of myocyte necrosis. The use of percutaneous coronary intervention (PCI) for the treatment of patients with CS has increased considerably during the last decades [27]. Most patients with ACS underwent PCI also in this study. Despite the frequent use of PCI, elevated plasma glucose was common and associated with high mortality, suggesting that the endogenous stress response is not sufficiently attenuated by early revascularization alone.

Our study indicates, that the baseline blood glucose level has prognostic significance in CS patients. Both in-hospital and 90-day mortality were highest among hypoglycemic and severely hyperglycemic patients. In contrast, the prognosis of normoglycemic patients was relatively favorable, confirming the J-shape association curve of blood glucose concentrations and mortality generally detected in critically ill patients [15,28]. Glucose is an established, inexpensive and routinely monitored biomarker which therefore possesses broad utility and applicability as a risk marker. Many novel biomarkers have been studied in myocardial infarction and heart failure [29,30]. In CS, data on angiotensin-2, FGF-23 and GDF-15 have been published, but so far these biomarkers have not been incorporated in clinical decision making [31–33].

Interestingly, normoglycemic patients had only mild abnormalities in both arterial pH and plasma lactate, suggesting less severe hypoperfusion and a lesser stress response compared with other groups. Stress hyperglycemia has not only been associated with increased mortality in ACS, but also with an increased risk of developing heart failure or CS [7]. Thus, hyperglycemia is a warning sign of severely disturbed homeostasis. Multiple studies have shown the association of increasing lactate level and poor outcome in the critically ill [16,34,35] and it has been suggested that the prognostic value of hyperglycemia is modified by simultaneous hyperlactatemia [36]. Importantly, our study demonstrates that severe hyperglycemia is independently associated with increased in-hospital mortality. Highly elevated blood glucose as such may be harmful due to its influences on serum osmolality and fluid balance [37]. However, when the study population was dichotomized according to prior DM history, mean plasma glucose level of non-survivors was significantly higher among patients without DM, but not among patients with previous diagnosis of DM. Our results thus suggest, that the predictive value of plasma glucose on short-term mortality applies mainly to non-diabetic patients. In contrast, among diabetic patients there are multiple factors impacting the plasma glucose level during acute illness. These include the individual glycemic balance, the type of DM medication, and especially the pathophysiology of DM itself: insulin resistance and hepatic overproduction of glucose even in normal status. Our findings confirm the observations about the role of prior DM status on the prognostic value of glucose [1,6,10,28,38]. Hence, it has been suggested, that it is the relative rather than the absolute level of hyperglycemia that should be considered during acute illness [1,28,39].

Our study has certain limitations. First, no data on the DM medication or use of insulin treatment was available. However, as discussed above, the predictive value of glucose level is blurred by many factors in DM patients, and only one fourth of the study population were diabetics. Furthermore, as blood glucose level in this study was

Table 3
Multivariate regression analysis for in-hospital mortality.

	OR	95% CI	p value
Age, per 1 year increase	1.05	1.02–1.09	0.002
Male gender	0.67	0.29–1.5	0.35
Plasma glucose			
Hypoglycemia	1.8	0.16–20.0	0.64
Normoglycemia	Ref		
Mild hyperglycemia	1.5	0.52–4.4	0.45
Moderate hyperglycemia	2.9	0.90–9.1	0.08
Severe hyperglycemia	3.7	1.19–11.7	0.02
LVEF, per % increase	0.95	0.92–0.98	< 0.001
Plasma lactate, per 1 mmol/L increase	1.3	1.18–1.5	< 0.001
History of DM	0.59	0.25–1.4	0.22

OR = odds ratio, CI = confidence interval, LVEF = left ventricular ejection fraction, DM = diabetes mellitus.

measured at the time of enrolment, most likely few, if any, patients had received insulin therapy by the time of blood sampling.

Conclusions

Admission blood glucose level has prognostic significance in cardiogenic shock. Mortality is highest among hypoglycemic and severely hyperglycemic patients, whereas normoglycemia at presentation is associated with relatively favorable prognosis. Severe hyperglycemia is associated with biochemical findings of systemic hypoperfusion and stress response. Moreover, severe hyperglycemia is an independent predictor of in-hospital mortality. Hypoglycemic patients present with findings of profound hypoperfusion and hepatic congestion.

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References

- [1] A.M. Deane, M. Horowitz, Dysglycaemia in the critically ill – significance and management, *Diabetes Obes. Metab.* 15 (9) (Sep 2013) 792–801.
- [2] P.E. Marik, R. Bellomo, Stress hyperglycemia: an essential survival response! *Crit. Care* 17 (2) (Mar 6 2013) 305.
- [3] J.C. Preiser, C. Ichai, J.C. Orban, A.B. Groeneveld, Metabolic response to the stress of critical illness, *Br. J. Anaesth.* 113 (6) (Dec 2014) 945–954.
- [4] E. Barth, G. Albuszies, K. Baumgart, et al., Glucose metabolism and catecholamines, *Crit. Care Med.* 35 (9 Suppl) (Sep 2007) S508–S518.
- [5] K.M. Dungan, S.S. Braithwaite, J.C. Preiser, Stress hyperglycaemia, *Lancet* 373 (9677) (May 23 2009) 1798–1807.
- [6] M. Falciglia, R.W. Freyberg, P.L. Almenoff, D.A. D'Alessio, M.L. Render, Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis, *Crit. Care Med.* 37 (12) (Dec 2009) 3001–3009.
- [7] S.E. Capes, D. Hunt, K. Malmberg, H.C. Gerstein, Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview, *Lancet* 355 (9206) (Mar 4 2000) 773–778.
- [8] A. Mebazaa, E. Gayat, J. Lassus, et al., Association between elevated blood glucose and outcome in acute heart failure: results from an international observational cohort, *J. Am. Coll. Cardiol.* 61 (8) (Feb 26 2013) 820–829.
- [9] M.M. Vis, K.D. Sjaauw, R.J. van der Schaaf, et al., In patients with ST-segment elevation myocardial infarction with cardiogenic shock treated with percutaneous coronary intervention, admission glucose level is a strong independent predictor for 1-year mortality in patients without a prior diagnosis of diabetes, *Am. Heart J.* 154 (6) (Dec 2007) 1184–1190.
- [10] J.H. Yang, P.S. Song, Y.B. Song, et al., Prognostic value of admission blood glucose level in patients with and without diabetes mellitus who sustain ST segment elevation myocardial infarction complicated by cardiogenic shock, *Crit. Care* 17 (5) (Oct 3 2013) R218.
- [11] H. Thiele, E.M. Ohman, S. Desch, I. Eitel, S. de Waha, Management of cardiogenic shock, *Eur. Heart J.* 36 (20) (May 21 2015) 1223–1230.
- [12] A. Shpektor, Cardiogenic shock: the role of inflammation, *Acute Card. Care* 12 (4) (Dec 2010) 115–118.
- [13] V.P. Harjola, J. Lassus, A. Sionis, et al., Clinical picture and risk prediction of short-term mortality in cardiogenic shock, *Eur. J. Heart Fail.* 17 (5) (May 2015) 501–509.
- [14] A.S. Levey, L.A. Stevens, C.H. Schmid, et al., A new equation to estimate glomerular filtration rate, *Ann. Intern. Med.* 150 (9) (May 5 2009) 604–612.
- [15] D. Mesotten, J.C. Preiser, M. Kosiborod, Glucose management in critically ill adults and children, *Lancet Diabetes Endocrinol.* 3 (9) (Sep 2015) 723–733.
- [16] H. Khosravani, R. Shahpori, H.T. Stelfox, A.W. Kirkpatrick, K.B. Laupland, Occurrence and adverse effect on outcome of hyperlactatemia in the critically ill, *Crit. Care* 13 (3) (2009) R90.
- [17] L.A. Sleeper, H.R. Reynolds, H.D. White, J.G. Webb, V. Dzavik, J.S. Hochman, A severity scoring system for risk assessment of patients with cardiogenic shock: a report from the SHOCK Trial and Registry, *Am. Heart J.* 160 (3) (Sep 2010) 443–450.
- [18] S. Cornell, Continual evolution of type 2 diabetes: an update on pathophysiology and emerging treatment options, *Ther. Clin. Risk Manag.* 11 (Apr 16 2015) 621–632.
- [19] S. Finfer, B. Liu, D.R. Chittock, et al., Hypoglycemia and risk of death in critically ill patients, *N. Engl. J. Med.* 367 (12) (Sep 20 2012) 1108–1118.
- [20] J.S. Krinsley, M.J. Schultz, P.E. Spronk, et al., Mild hypoglycemia is independently associated with increased mortality in the critically ill, *Crit. Care* 15 (4) (Jul 25 2011) R173.
- [21] J.S. Krinsley, A. Grover, Severe hypoglycemia in critically ill patients: risk factors and outcomes, *Crit. Care Med.* 35 (10) (Oct 2007) 2262–2267.
- [22] S. Laribi, A. Mebazaa, Cardiohepatic syndrome: liver injury in decompensated heart failure, *Curr. Heart Fail. Rep.* 11 (3) (2014 Sep) 236–240.
- [23] M. Nikolaou, J. Parissis, M.B. Yilmaz, et al., Liver function abnormalities, clinical profile, and outcome in acute decompensated heart failure, *Eur. Heart J.* 34 (10) (Mar 2013) 742–749.
- [24] B. De Jonghe, C. Cheval, B. Misset, et al., Relationship between blood lactate and early hepatic dysfunction in acute circulatory failure, *J. Crit. Care* 14 (1) (Mar 1999) 7–11.
- [25] M. Garcia-Alvarez, P. Marik, R. Bellomo, Stress hyperlactatemia: present understanding and controversy, *Lancet Diabetes Endocrinol.* 2 (4) (2014 Apr) 339–347.
- [26] I.M. Seropian, C. Sonnino, B.W. Van Tassel, L.M. Biasucci, A. Abbate, Inflammatory markers in ST-elevation acute myocardial infarction, *Eur. Heart J. Acute Cardiovasc. Care* 5 (4) (2016 Aug) 382–395.
- [27] L. De Luca, Z. Olivari, A. Farina, et al., Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes, *Eur. J. Heart Fail.* 17 (11) (2015 Nov) 1124–1132.
- [28] J.S. Krinsley, M. Egi, A. Kiss, et al., Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study, *Crit. Care* 17 (2) (2013 Mar 1) R37.
- [29] C. Mueller, Biomarkers and acute coronary syndromes: an update, *Eur. Heart J.* 35 (9) (2014 Mar) 552–556.
- [30] E. Braunwald, Biomarkers in heart failure, *N. Engl. J. Med.* 358 (20) (2008 May 15) 2148–2159.
- [31] J. Poss, G. Fuernau, D. Denks, et al., Angiotensin-2 in acute myocardial infarction complicated by cardiogenic shock—a biomarker substudy of the IABP-SHOCK II-Trial, *Eur. J. Heart Fail.* 17 (11) (2015 Nov) 1152–1160.
- [32] G. Fuernau, J. Poss, D. Denks, et al., Fibroblast growth factor 23 in acute myocardial infarction complicated by cardiogenic shock: a biomarker substudy of the Intraaortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial, *Crit. Care* 18 (6) (2014 Dec 21) 713.
- [33] G. Fuernau, C. Poenisch, I. Eitel, et al., Growth-differentiation factor 15 and osteopontin in acute myocardial infarction complicated by cardiogenic shock: a biomarker substudy of the IABP-SHOCK II-trial, *Eur. J. Heart Fail.* 16 (8) (2014 Aug) 880–887.
- [34] D. Juneja, O. Singh, R. Dang, Admission hyperlactatemia: causes, incidence, and impact on outcome of patients admitted in a general medical intensive care unit, *J. Crit. Care* 26 (3) (2011 Jun) 316–320.
- [35] A.D. Nichol, M. Egi, V. Pettila, et al., Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study, *Crit. Care* 14 (1) (2010) R25.
- [36] K.M. Kaukonen, M. Bailey, M. Egi, et al., Stress hyperlactatemia modifies the relationship between stress hyperglycemia and outcome: a retrospective observational study, *Crit. Care Med.* 42 (6) (2014 Jun) 1379–1385.
- [37] G. Liamis, E. Liberopoulos, F. Barkas, M. Elisaf, Diabetes mellitus and electrolyte disorders, *World J. Clin. Cases.* 2 (10) (2014 Oct 16) 488–496.
- [38] M. Egi, R. Bellomo, E. Stachowski, et al., Blood glucose concentration and outcome of critical illness: the impact of diabetes, *Crit. Care Med.* 36 (8) (2008 Aug) 2249–2255.
- [39] G.W. Roberts, S.J. Quinn, N. Valentine, et al., Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio, *J. Clin. Endocrinol. Metab.* 100 (12) (2015 Dec) 4490–4497.