Stress Hyperglycaemia in Patients with Acute Coronary Syndrome

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Abstract: *Objective*: Stress hyperglycaemia is a prognostic marker in non-diabetic patients with acute coronary syndrome indicating increased mortality. However, there are conflicting results on the benefit of achieving near-normoglycaemia in these patients.

Methods: A prospective open-label cohort study including non-diabetic patients with acute coronary syndrome admitted to the medical intensive care unit of a tertiary care hospital. In patients with stress hyperglycaemia intravenous insulin treatment was initiated to achieve normoglycaemia, and prognosis (death, myocardial reinfarction, revascularisation, kidney failure, congestive heart failure) and the importance of inflammatory cytokines and cortisol were assessed.

Results: Overall 94 non-diabetic patients were included in the study, 48 patients with normoglycaemia and 46 patients with hyperglycaemia on admission. After 12 hours of intravenous insulin treatment patients with stress hyperglycaemia achieved plasma glucose levels similar to the normoglycaemic patients. The mean insulin dose was 36.5 $\pm$ 18.7 Units/24 hours, and there were no severe hypoglycaemic events. There was no difference in mortality or myocardial reinfarction, or new onset of renal insufficiency between the two groups, ($p=0.36$ and $p=0.31$, resp.), but congestive heart failure was significantly more common in patients with stress hyperglycaemia ($p=0.011$). Plasma cortisol levels were significantly increased in patients with stress hyperglycaemia and correlated to glucose concentrations ($r=0.426$, $p<0.001$).

Conclusions: Our findings suggest that in patients with acute coronary syndrome an increased stimulation of the cortisol axis contributes to stress hyperglycaemia and to the worse outcome.

Keywords: Stress hyperglycaemia, acute coronary syndrome, plasma cortisol, congestive heart failure, insulin resistance.

INTRODUCTION

Stress hyperglycaemia refers to elevated blood glucose levels in acutely ill patients without diabetes mellitus, and correlates to increased morbidity and mortality in patients with acute coronary syndrome (ACS) [1, 2]. Factors involved in the formation of stress hyperglycaemia are varied and include stress hormones like cortisol and adrenaline [3], lipotoxicity leading to increased levels of free fatty acids [4], and stimulated inflammatory pathways *via* cytokines like TNF-α, IL-1 and IL-6 resulting in impaired insulin secretion and sensitivity [5]. Treatment with insulin inhibits inflammatory mediators, and has beneficial effects on elevated free fatty acids that are toxic to the ischaemic myocardium and cause endothelial dysfunction [6].

Whereas mortality is almost two-fold increased in hospitalized patients with pre-existing type 2 diabetes and ACS compared to those without diabetes mellitus, there is an even 3.9-fold higher risk of cardiac death in patients with newly diagnosed stress hyperglycaemia and ACS [1, 7]. In non-diabetic patients with ACS glucose concentrations at hospital admission of > 6.1 mmol/l are associated with a rise in 30-day mortality [8, 9]. Strict glycaemic control targeted to near-normoglycaemia (glucose levels of 4.4 to 6.1 mmol/l) demonstrated to improve the clinical outcome in critically ill patients with and without diabetes mellitus [10, 11]. However, according to other studies the intensive insulin treatment and tight glucose control provided no survival benefit and resulted in a high incidence of hypoglycaemia [12, 13]. Nevertheless, recent guidelines recommend glucose target levels of 4.4 to 7.8 mmol/l for ICU patients with ACS and cardiac disorders particularly emphasizing the need to avoid hypoglycaemia [14, 15].

The purpose of our study was to assess stress hyperglycaemia in patients with ACS without pre-existing diabetes mellitus i.e. to identify factors contributing to stress hyperglycaemia in these patients, and to determine the benefit of intensive insulin treatment in these patients compared to normoglycaemic patients with ACS.

METHODS

Participants

From June 2008 to May 2009 a prospective, single-centre, open-label cohort study has been undertaken in

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a tertiary care hospital including non-diabetic patients with ACS who where admitted to the medical ICU. Patients were eligible for inclusion according to the following criteria: age 18 to 80 years, diagnosis of an acute coronary syndrome i.e. chest pain in the preceeding 24 hours and/or new ST-segment deviations in two or more leads, and/or elevated cardiac enzymes, and angiographically confirmed coronary heart disease; HbA1c in the normal range (< 5.7%), and elevated fasting (plasma glucose $\geq$ 5.6 mmol/l) and/or elevated random/postprandial plasma glucose ($\geq$ 7.8 mmol/l) corresponding to impaired fasting glucose and impaired glucose tolerance, respectively.

Exclusion criteria were pre-existing diabetes mellitus and/or a history of prediabetes, i.e. fasting plasma glucose concentrations $\geq$ 5.6 mmol/l and/or of a random or postprandial plasma glucose $\geq$ 7.8 mmol/l, cardiogenic shock/resuscitation, seizures, chronic glucocorticoid treatment, chronic kidney disease, i.e. elevated plasma creatinine concentrations above the upper normal limit or a glomerular filtration rate (GFR) less than 60 ml/min/1.73m^2 (estimated creatinine clearance rate using the Cockcroft-Gault formula).

Hypoglycaemia was defined as plasma glucose levels < 3.9 mmol/l, and as symptomatic hypoglycaemia if autonomic or neuroglycopenic symptoms were present, and as severe hypoglycaemia with plasma glucose concentrations < 2.5 mmol/l.

The study was approved by the local institutional review committee, and informed consent was obtained from all participants.

Procedures

At hospital admission a venous blood sample was obtained including random plasma glucose, HbA1c, troponin T, creatine kinase, creatinine, triglycerides, cholesterol, basal plasma cortisol, interleukin-1 β, interleukin-6, and TNF-α. In patients with stress hyperglycaemia an infusion with normal insulin (Actrapid®) was initiated according to an institutional infusion protocol with the objective to keep plasma glucose concentration $\leq$ 6.1 mmol/l according to the guidelines of the European Society of Cardiology and the European Association for the Study of Diabetes.[14] During the intravenous insulin treatment blood glucose was recorded every 30 to 60 minutes according to the infusion protocol in order to adjust the insulin infusion dose. Thereafter, and in patients without insulin treatment fasting plasma glucose was obtained after 6, 12, 24, 48 hours, on the day of discharge, and three months after the hospital stay.

HbA1c was analyzed by immuno-turbidimetric assay (TINIA, Cobas® 6000, Roche Diagnostics, Mannheim, Germany) on whole blood with an upper normal limit of 5.9% (42 mmol/l/mol Hb IFCC). The coefficient of variation was < 1.5 percent. Plasma glucose was measured by hexokinase method (Gluco-quant®, Boehringer Mannheim, Germany) with a normal range 3.9 to 6.4 mmol/l and a coefficient of variation of < 2.5%; and serum potassium was measured by indirect potentiometry with ion-selective electrode (ISE, Cobas 6000) and CV < 2%. Troponin T was determined by an electro-chemiluminescence immunoassay (ECLIA, Roche Diagnostics, Elecsys 2010) with cross reactivity to skeletal muscle troponin T of less than 0.01%. Plasma cortisol was measured by fluorometric enzyme-immunoassay (Dade Stratus ®, AHS, Merz + Dade, Munich, Germany). The intra-assay and inter-assay coefficients of variation were 5.1% and 4.1%, respectively. The sensitivity of the assay was 7.2 nmol/l with very low reactivity to other glucocorticoids. To convert values for plasma cortisol concentrations from nanomoles per litre to micrograms per decilitre, multiply by 0.036. Interleukin-1 β and Interleukin-6 were measured by an enzyme immunoassay (EIA, Quantikin human IL-1 beta and IL-6, RD Research and Diagnostics System, Minneapolis, USA) with the normal range of 0.0 to 3.1pg/ml. TNF-α was measured by an enzyme immunoassay (Quantikin HS human TNF-α, RD Research and Diagnostics System, Minneapolis, USA) with the normal range 0.0 to 6.3 pg/ml. Acute renal insufficiency was defined by an increase of the creatinine concentrations to $\geq$ 1.5x the upper normal range. Left ventricular ejection fraction was determined by ventriculographiy during coronary angiography and/or by echocardiography.

Analysis of Data

All statistical analyses were performed using IBM SPSS, version 15. The results are given as means $\pm$ SD, unless stated otherwise. T-tests were used for continuous variables, and chi-square analysis for categorical variables for comparison of the study groups. Relationships between variables were analyzed by linear regression analysis and Pearson product-moment correlation coefficient. $P < 0.05$ was considered as the limit of statistical significance.

RESULTS

A total of 94 non-diabetic patients with ACS were included in our study with a mean random plasma

Table 1: Baseline Characteristics of Participating Patients with Acute Coronary Syndrome (n=94) (NG=normoglycaemia, SHG=stress hyperglycaemia)

	Patients with NG (n=48)	Patients with SHG (n=46)	p
Age (years)	64.8	68.3	0.45
Gender (M/F)	38/10	34/12	0.36
BMI (kg/m^2)	26.5	27.3	0.39
Dyslipidemia	32 (66%)	33 (71%)	0.28
Time to admission (min)	272 ± 154	281 ± 244	0.46
Hypertension	31 (64%)	31 (67%)	0.77
Smokers	18 (37%)	20 (43%)	0.34
Claudication	3 (6%)	4 (8%)	0.20
Treatment with			
Betablockers	20 (41%)	23 (50%)	0.67
Statins	11 (22%)	13 (28%)	0.35
Aspirin	22 (45%)	25 (54%)	0.68
ACE-I/sartans	12 (25%)	10 (21%)	0.13

glucose concentration of 7.9 ± 2.7 mmol/ (range 4.4 to 18.4 mmol/l): 48 patients were classified as normoglycaemic at admission, and 46 patients as exhibiting stress hyperglycaemia, and they were allocated for intravenous insulin treatment. Patients were well matched with respect to baseline characteristics (Table **1**). The mean random plasma glucose in normoglycaemic patients was 6.0 ± 0.6 mmol/l, and in patients with stress hyperglycaemia 9.8 ± 2.6 mmol/l, respectively (p<0.001). Plasma glucose concentrations 6 hours after admission were 5.6 ± 2.1 mmol/l in normoglycaemic patients, and 9.1 ± 3.4 mmol/l in patients with stress hyperglycaemia, respectively (p<0.001), and 12 hours after admission 6.4 ± 1.3 mmol/l in normoglycaemic patients and 7.5 ± 2.1 mmol/l in patients with stress hyperglycaemia, respectively, and no longer of statistically significant difference (p=0.07; 95% CI -2.9 to 27.7). The course of glucose control in the both groups during hospitalization is shown in Figure **1**. The mean insulin dose in patients with stress hyperglycaemia was 36.5 ± 18.7 U/24h, and the mean duration of intravenous insulin treatment was 29 ± 13 hours. Mild hypoglycaemia i.e. blood glucose concentrations below 3.9 mmol/l, occurred in 8 patients (17%), symptomatic hypoglycaemia in 4 patients (8%), and there were no severe hypoglycaemic events. Coronary angiography was performed in 89 patients (92%) and stent placement in 70 patients (74%). Creatine kinase levels in normoglycaemic and hyperglycaemic patients reached a maximum after 6 hours at 704 ± 771 U/l, and 1203 ± 963 U/l, respectively (p=0.25), and troponin T levels peaked after 24 hours at 1.2 ± 2.9 ng/ml, and 2.5 ± 3.0 ng/ml, respectively (p=0.13). Table **2** displays further laboratory findings at admission: IL-6 levels were elevated in both groups, whereas IL-1β and TNF-α were in the normal range, but there were no significant differences between the two groups. Cytokines i.e. interleukin-1 β(p=0.56, r=0.14), interleukin-6 (p=0.10, r=0.39), and TNF-α (p=0.22, r=0.29) did not correlate significantly to plasma glucose and insulin dose, respectively. However, plasma cortisol levels were significantly higher in patients with stress hyperglycaemia and correlated to glucose concentrations (r=0.426, p<0.001) (Figure **2**). Clinical outcomes are presented in Figure **3**: there were no statistically significant differences in mortality or myocardial reinfarction, or new onset of renal insufficiency between patients with normoglycaemia and hyperglycaemia on admission (p=0.36 and p=0.31, resp.). However, congestive heart failure was significantly more common in patients with stress hyperglycaemia (p=0.011), also after correction for cardiovascular risk factors (i.e. hypertension, smoking, and valvular heart disease).

Of the 46 patients with elevated blood glucose on admission, 4 patients (8%) had antidiabetic treatment with metformin when discharged. Three months after discharge 2 patients were treated with metformin and one patient with metformin and bedtime insulin glargine.

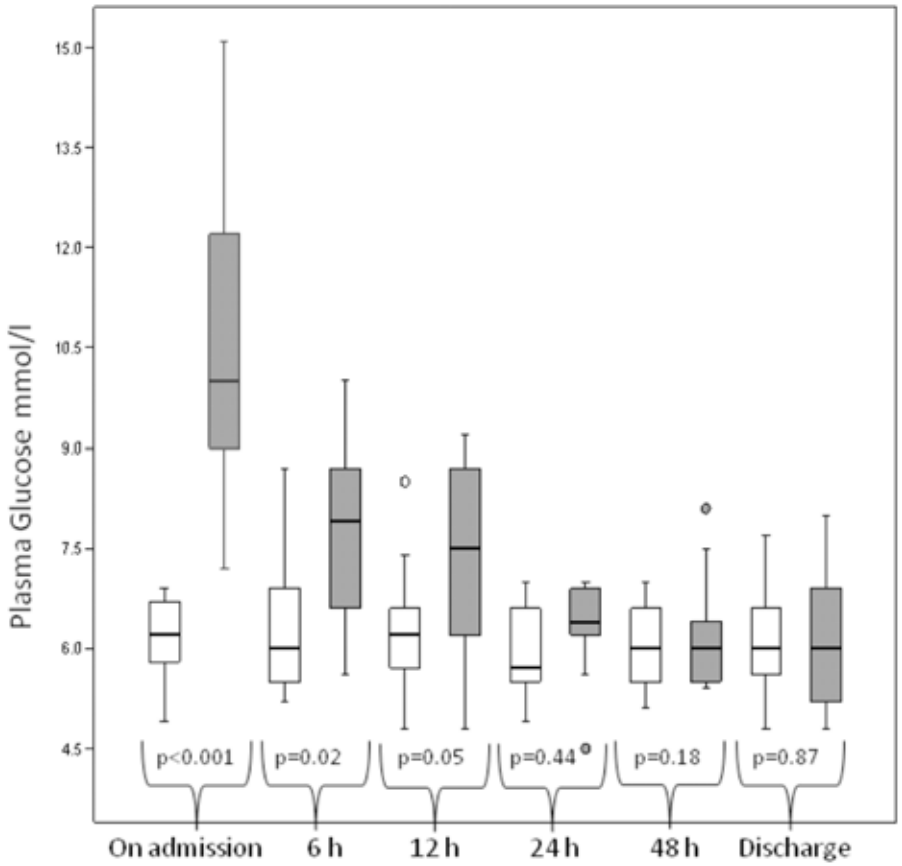

Figure 1: Course pf plasma glucose in 94 patients with ACS during hospitalization: white box plots represent patients with normoglycaemia on admission (n=48), grey boxes patients with hyperglycaemia (n=46). Box plots show mean ± SD, the whiskers indicate the 5% and 95% percentiles, and outliers are plotted as individual points.

Table 2: Laboratory and Clinical Findings in Patients with Acute Coronary Syndrome at Randomization (n=94) (NG=normoglycaemia, SHG=stress hyperglycaemia)

	Patients with NG (n=48)	Patients with SHG (n=46)	p
FPG (mmol/l)	6.0 ± 0.6	9.8 ± 2.6	<0.001
Plasma glucose after 12h	6.4 ± 1.3	7.5 ± 2.1	0.07
Creatinine (μmol/l)	104 ± 21	112 ± 32	0.18
Troponin T (μg/l)	0.17 ± 0.32	0.34 ± 0.67	0.52
Creatine kinase	171 ± 191	390 ± 623	0.14
Cholesterol (mmol/l)	5.9 ± 1.2	5.8 ± 0.8	0.71
HDL-Cholesterol (mmol/l)	1.4 ± 0.3	1.3 ± 0.4	0.95
Trigycerides (mmol/l)	2.0 ± 1.7	2.3 ± 1.4	0.44
Cortisol (nmol/l)	523 ± 281	791 ± 372	0.009
Interleukin-1β (pg/ml)	1.8 ± 1.9	1.9 ± 1.7	0.92
Interleukin-6 (pg/ml)	5.3 ± 3.1	7.7 ± 3.4	0.49
TNF-α (pg/ml)	2.2 ± 1.4	2.2 ± 2.3	0.97
Systolic BP (mm Hg)	137 ± 22	140 ± 25	0.66
LVEF (%)	58 ± 16	46 ± 17	0.11

FPG = fasting plasma glucose; BP = blood pressure; LVEF = left ventricular ejection fracture.

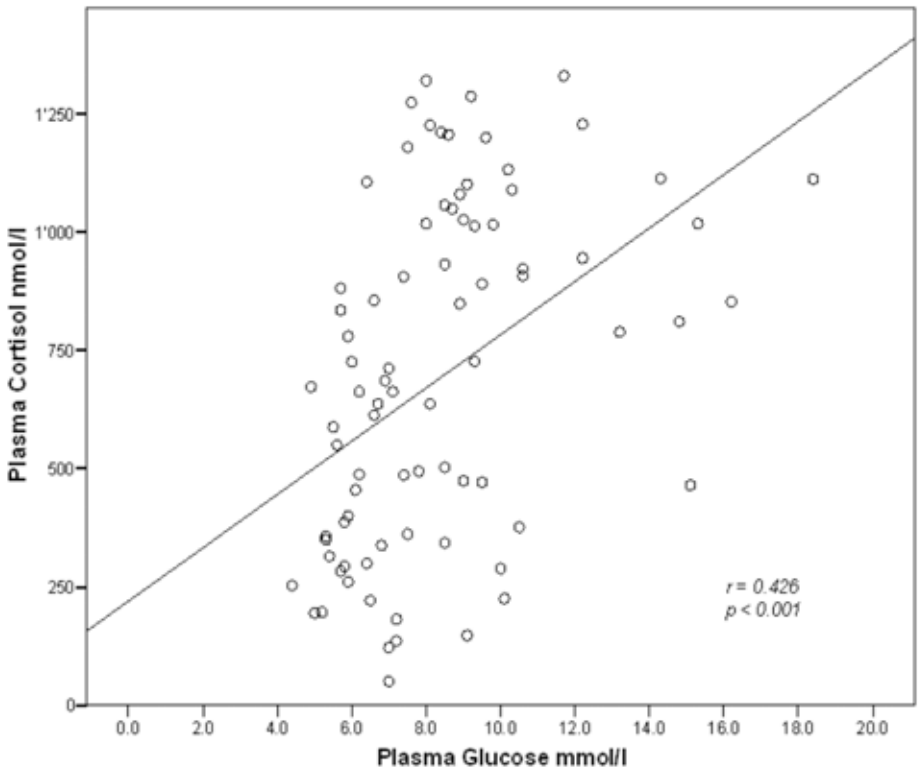

Figure 2: Correlation of plasma cortisol concentrations and plasma glucose levels on admission in 94 patients with ACS.

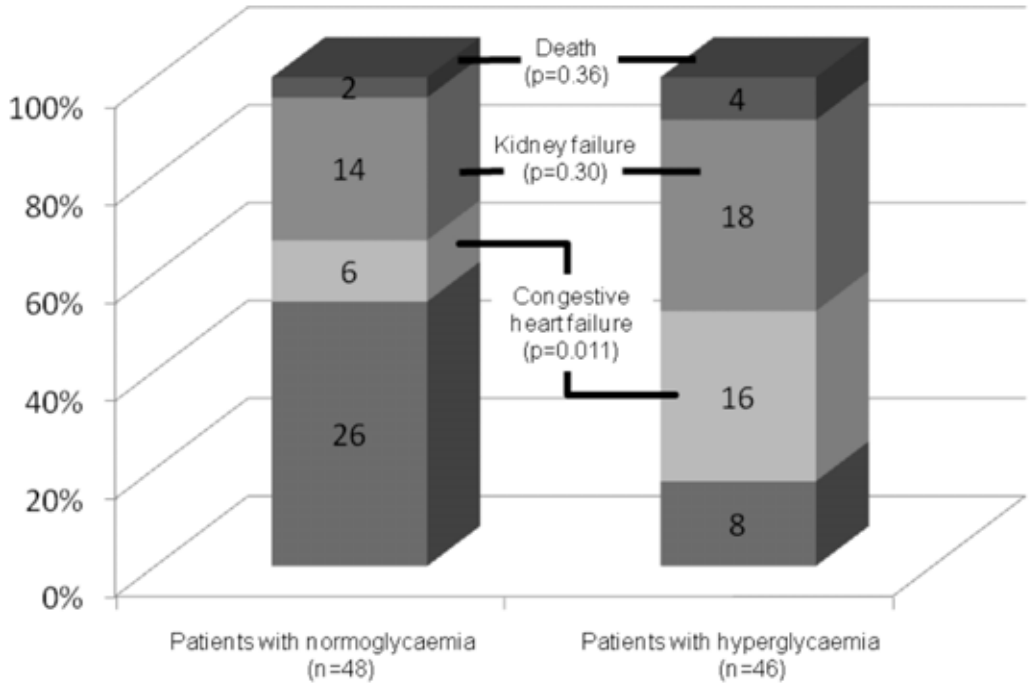

Figure 3: Clinical outcome in patients with ACS and normoglycaemia (n=48), and stress hyperglycaemia (n=46), respectively.

DISCUSSION

Stress hyperglycaemia is diagnosed in about 25% of non-diabetic patients with ACS admitted to our emergency unit. In our study patients with stress hyperglycaemia compared to normoglycaemic patients with ACS, there was clear evidence of an increased stimulation of the hypothalamic-pituitary-adrenal (or cortisol stress) axis with close correlation to the glucose concentration indicating a principal and initial

role of cortisol in the formation of stress hyperglycaemia. On admission, cytokines were either in the normal range like IL-1β and TNF-α, or equally elevated in both groups like IL-6; the clinical and laboratory characteristics of insulin resistance were balanced between the two groups, and the markers of myocardial damage and left ventricular function were similar in patients with stress hyperglycaemia and normoglycaemia, further supporting the predominant role of cortisol which has a well known prognostic role in critical illness [16].

Poor outcome related to stress hyperglycaemia has been described for a variety of disease states [1, 2, 4, 17] with particular emphasis on cardiovascular mortality, e.g. there are data indicating that mortality in non-diabetic patients in the ICU begins to increase when mean glucose concentrations exceed 7.8 mmol/l [18]. However, the identification of stress hyperglycaemia is complex, and a heterogeneous population of hyperglycaemic patients are usually analysed e.g. hospital inpatients with underlying yet undiagnosed diabetes, or patients with a high proportion of persisting type 2 diabetes after discharge [19, 20]. Furthermore, there are no specific guidelines addressing treatment intensity in stress hyperglycaemia [21] and there is some controversy about stress hyperglycaemia as a risk-marker or treatment target in patients with ACS [22]. However, recent clinical data underscore the importance of acute hyperglycaemia in non-diabetic patients with ACS and normal HbA1c with respect to prognosis: in large cohorts of patients with ST-segment elevation myocardial infarction those with stress hyperglycaemia and normal HbA1c had the highest mortality and risk for adverse cardiovascular events, and, in particular, a significantly higher incidence of in-hospital stent thrombosis [25, 26].

In our study patients with stress hyperglycaemia after 12h of intravenous insulin treatment near-normoglycaemic plasma glucose concentrations were achieved and were similar to the glucose levels in the normoglycaemic patients throughout the hospital stay without risk of severe hypoglycaemia. There were no significant excess death, recurrent myocardial infarction or kidney failure in the insulin treated patients with stress hyperglycaemia, however, congestive heart failure was significantly more common in these patients.

Considering the role of activated mineralocorticoid receptors on myocardial remodelling and their deleterious effect on heart failure on one side [23]. and the crossreactivity of the much higher concentrated plasma cortisol on mineralocorticoid receptors on the other side, which has already been demonstrated in experimental models of myocardial infarction [24], we assume a causative role of the elevated cortisol levels in these patients, not only by inducing insulin resistance and thus stress hyperglycaemia, but also by stimulating myocardial mineralocorticoid receptors. Therefore, based on our data we rather deem stress hyperglycaemia the consequence of an increased stimulation of the cortisol axis. Given the fact that even after abolishing stress hyperglycaemia there is a worse outcome in these patients may point to the over activated cortisol axis as a main contributor to the bad prognosis in patients with ACS and stress hyperglycaemia.

In summary, the activated cortisol axis constitutes a main cause of stress hyperglycaemia, and, through the activation of mineralocorticoid receptors, may contribute to heart failure independently of the myocardial infarct size. Further studies are needed to determine whether plasma cortisol may be a useful marker in patients with ACS and stress hyperglycaemia, and whether early inhibition of the mineralocorticoid receptors in these patients may prove beneficial.

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COMPETING INTERESTS

There are no competing interests reported by the authors of the study.

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