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Blood urea nitrogen kinetics in the early postcardiac arrest phase are associated with clinical outcome

A retrospective cohort study

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Editor,

The postcardiac arrest syndrome (PCAS) features a global ischaemia–reperfusion injury that not only triggers the release of pro-inflammatory cytokines and a consecutive systemic inflammatory response but also organ dysfunction and haemodynamic instability.¹ The degree of the inflammatory response was reportedly associated with a poor outcome.¹ Furthermore, acute kidney injury (AKI), frequently occurring in PCAS, is a predictor of poor outcome.²

Urea plasma concentrations are a result of renal excretion and hepatic synthesis and most commonly quantified as blood urea nitrogen (BUN).^{3,4} Urea itself is a small, apolar molecule, which is freely filtered in the glomerulus and both secreted and reabsorbed in the tubular system with an overall higher net re-absorption.^{3,5} This latter is mainly mediated by urinary flow rate and vasopressin/antidiuretic hormone (ADH) activity. These hormones are also released during circulatory shock and cardiopulmonary resuscitation (CPR), and are responsible for the increased BUN-to-creatinine ratio in patients with pre-renal acute kidney injury.^{5,6} Interestingly, pro-inflammatory cytokines, mainly TNF- α , may increase hepatic BUN synthesis.⁴

In this context, we hypothesised that BUN plasma concentrations after cardiac arrest may reflect the extent of PCAS. However, absolute BUN concentrations may have relevant limitations, such as kidney function and nutritional status. Therefore, we hypothesised that the dynamic changes of BUN concentrations within the first hours after survived cardiac arrest may be a better marker

and so investigated their association with clinical outcome.

This study included 318 patients from the prospective Vienna Clinical Cardiac Arrest Registry⁷ of the Department of Emergency Medicine at the Medical University of Vienna between January 2013 and December 2018 ($n=1591$). The local independent Ethics Committee (Borschkegasse 8b/E06, 1090 Vienna, Austria) approved the study on 14 March 2018 (No. 1219/2018). It complies with the Declaration of Helsinki. Adults who survived (>24 h) nontraumatic cardiac arrest and had return of spontaneous circulation (ROSC) without extracorporeal CPR, and who had complete datasets for multivariate analysis were eligible. Patients with end-stage renal disease and renal replacement therapy before cardiac arrest and those requiring dialysis within 48 h of cardiac arrest were excluded (see Supplement, <http://links.lww.com/EJA/A593>).

The primary endpoint was neurological function at day 30, defined by the Cerebral Performance Category (CPC): good neurological outcome CPC 1/2, poor neurological outcome CPC 3/4/5 or persistent unresponsiveness because of sedation, or moribund before death.

As the main variable we calculated the difference in BUN concentration at 12 h from the BUN at admission (dBUN12h). We used binary logistic regression models (backward Wald procedure) to investigate potential associations with neurological outcome by odds ratio [odds ratio (OR), 95% CI]. Furthermore, we performed receiver-operating characteristic (ROC) curve analysis. Covariables for the multivariable models were included based on clinical reasoning and previous studies: age, sex, initial shockable rhythm, basic life support, witness status, number of shocks, cumulative adrenaline dose, lactate on admission, fluid balance, maximum noradrenaline dose ($\mu\text{g kg}^{-1} \text{min}^{-1}$), mean arterial blood pressure less than 65 mmHg (yes/no) (within 12 h after ROSC). A detailed description of the methods is presented in the supplement.

Baseline data are presented in Table 1. In univariate analysis, the crude OR for dBUN12h was 1.17 (95% CI, 1.11 to 1.23, $P < 0.001$) for poor neurological outcome. After multivariable adjustment, the adjusted OR of dBUN12h was 1.13 (95% CI, 1.07 to 1.20, $P < 0.001$). In ROC analysis, the area under the curve of dBUN12h was 0.72 (95% CI, 0.66 to 0.78, $P < 0.001$ compared with the reference line). There were no obvious cut-offs identifiable in ROC analysis (see Supplement, <http://links.lww.com/EJA/A593>). We dichotomised the population using the cut-off 0 mg dl^{-1} [AUC 0.64 (95% CI, 0.58 to 0.70, $P < 0.001$)] as it has a reasonable specificity of

Table 1 Baseline characteristics by outcome group and blood urea nitrogen group

	All (n=318)	Decreasing BUN (n=108)	Increasing BUN (n=210)	Good neurologic outcome (n=147)	Poor neurologic outcome (n=171)	P
Age	61 [49 to 71]	58 [47 to 69]	62 [50 to 73]	56 [46 to 68]	63 [53 to 73]	0.001
Female	95 (30)	33 (31)	62 (30)	42 (29)	53 (31)	0.638
Out of hospital cardiac arrest	280 (88)	96 (89)	184 (88)	130 (88)	150 (88)	0.649
Witnessed	265 (83)	89 (82)	176 (84)	130 (88)	135 (79)	0.014
BLS	193 (61)	70 (65)	123 (59)	98 (67)	95 (56)	0.043
Initial shockable rhythm	185 (58)	71 (66)	114 (54)	112 (76)	73 (43)	<0.001
No flow (min) ^a	0 [0 to 0]	0 [0 to 0]	0 [0 to 0]	0 [0 to 0]	0 [0 to 0]	0.869
Low flow (min) ^a	22 [12 to 33]	15 [9 to 21]	26 [15 to 38]	16 [10 to 26]	24 [17 to 34]	<0.001
Cardiac origin	216 (68)	73 (68)	143 (68)	115 (78)	101 (59)	<0.001
Immediate coronary revascularisation	103 (32)	36 (33)	67 (32)	56 (38)	47 (27)	0.054
Total dose of adrenaline (mg)	2 [0 to 3]	0 [0 to 2]	2 [1 to 4]	1 [0 to 2]	2 [1 to 4]	<0.001
Number of shocks applied ^b	3 [1 to 5]	2 [1 to 3]	4 [2 to 6]	3 [1 to 5]	3 [1 to 5]	0.002
Targeted temperature management	283 (89)	95 (88)	188 (90)	128 (87)	155 (91)	0.370
pH	7.18 [7.06 to 7.27]	7.25 [7.18 to 7.30]	7.13 [7.02 to 7.24]	7.25 [7.15 to 7.29]	7.12 [7.01 to 7.22]	<0.001
Lactate (mmol l ⁻¹)	6.7 [4.2 to 9.7]	5.0 [3.3 to 6.9]	8.1 [5.2 to 10.8]	5.1 [3.4 to 7.7]	7.9 [5.7 to 10.8]	<0.001
Creatinine at admission (mg dl ⁻¹)	1.2 [1.0 to 1.5]	1.1 [0.9 to 1.3]	1.3 [1.1 to 1.5]	1.1 [0.9 to 1.3]	1.3 [1.1 to 1.6]	<0.001
BUN at admission (mg dl ⁻¹)	17.1 [13.3 to 21.3]	17.0 [14.0 to 21.4]	17.1 [12.7 to 21.1]	15.8 [12.5 to 19.4]	17.3 [13.9 to 22.2]	0.001
Fluid balance (ml 12 h ⁻¹)	1910 [1075 to 2750]	1795 [1135 to 2560]	1946 [1050 to 2880]	1590 [950 to 2370]	2240 [1280 to 3050]	<0.001
Maximum noradrenaline dose (µg kg ⁻¹ min ⁻¹)	0.11 [0.05 to 0.27]	0.06 [0.03 to 0.13]	0.15 [0.06 to 0.35]	0.07 [0.02 to 0.15]	0.18 [0.08 to 0.44]	<0.001
MAP <65 mmHg in 12 h	116 (37)	34 (32)	82 (39)	34 (23)	82 (48)	
BUN change 12 h (mg dl ⁻¹)	2.6 [-1.2 to 5.9]	-2.3 [-4.1 to -1.0]	4.5 [2.6 to 8.0]	0.1 [-2.3 to 2.8]	4.3 [1.3 to 7.8]	<0.001
CPC 1/2	147 (46)	72 (67)	75 (36)	147 (100)	0 (0)	
Mortality day 30	113 (36)	17 (16)	96 (46)	0 (0)	113 (66)	

Good neurological outcome was defined as Cerebral Performance Category 1 to 2, poor neurological outcome as Cerebral Performance Category 3 to 5. Data are given as median [IQR] or n (%). BLS, basic life support; BUN, blood urea nitrogen; CPC, Cerebral Performance Category; MAP, mean arterial pressure. ^aData only for witnessed cardiac arrests available. ^bData only for patients receiving at least one shock.

85% (sensitivity 44%) and it is easy for clinicians to use. The crude, unadjusted OR for the increasing BUN group was 3.60 (95% CI, 2.21 to 5.87, $P < 0.001$) for poor neurological outcome whereas the adjusted OR was 2.73 (95% CI, 1.56 to 4.79, $P < 0.001$).

Several sensitivity analyses were performed in which results remained stable. In patients with a cardiac cause of cardiac arrest ($n = 216$), we included another covariate, the occurrence of acute kidney injury according to modified Kidney Diseases Improving Global Outcomes (KDIGO) criteria, truncated at 48 h because of data availability. Then, to exclude a form of selection bias, we performed univariate analysis of all patients with available data on dBUN12h ($n = 953$) (see Supplement, <http://links.lww.com/EJA/A593>).

Interestingly, dBUN12 h correlated moderately with the time to ROSC ($r = 0.41$, $P < 0.001$), with the cumulative adrenaline dose ($r = 0.49$, $P < 0.001$), with lactate concentration at admission ($r = 0.42$, $P < 0.001$) and with noradrenaline dose ($r = 0.42$, $P < 0.001$).

To our knowledge, this is the first analysis of BUN kinetics after cardiac arrest. Interestingly, in spite of a positive fluid balance in all of the included patients (median 1.9 l), BUN concentrations increased in two-thirds of the patients within 12 h after hospital admission, regardless of the occurrence of AKI.

Stress hormones, including adrenaline or cortisol, may increase urea production in the context of protein

catabolism.⁴ In a rat model, urea synthesis was upregulated within 3 h after administration of TNF- α . As pro-inflammatory cytokines play a crucial role in PCAS, this mechanism may in part explain our results.⁴ In the kidney, BUN is reabsorbed in an ADH-dependent manner.³ ADH's primary role is to maintain osmotic homeostasis but it is also released during haemodynamic instability and increases within minutes after circulatory arrest.^{4,6} In line, we observed correlations with various markers of haemodynamic instability and duration of CPR.

AKI frequently occurs after cardiac arrest.² Expectedly, the increase in BUN concentrations was more pronounced in patients with AKI. We included this covariate in the multivariate analysis but could not identify a relevant impact on effect sizes.

This study's limitations include its single-centre design, exclusion of a relatively large number of patients because of missing data, no data on TNF- α or ADH concentrations, and the use of modified, truncated KDIGO AKI criteria. Furthermore, it needs to be acknowledged that our study findings cannot guide treatment or decisions on treatment withdrawal in cardiac arrest survivors. Further research is required to determine the clinical value and applicability of BUN kinetics after successful resuscitation.

In conclusion, increasing BUN concentrations in the early postcardiac arrest phase are associated with poor neurological function at 30 days.

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References

- 1 Jou C, Shah R, Figueroa A, *et al.* The role of inflammatory cytokines in cardiac arrest. *J Intensive Care Med* 2020; **35**:219–224.
- 2 Storm C, Krannich A, Schachtner T, *et al.* Impact of acute kidney injury on neurological outcome and long-term survival after cardiac arrest - a 10year observational follow up. *J Crit Care* 2018; **47**:254–259.
- 3 Schrier RW. Blood urea nitrogen and serum creatinine: not married in heart failure. *Circ Heart Fail* 2008; **1**:2–5.
- 4 Thomsen KL. Regulation of urea synthesis during the acute phase response in rats. *Dan Med J* 2013; **60**:B4617.
- 5 Kato TS, Nakamura H, Murata M, *et al.* The effect of tolvaptan on renal excretion of electrolytes and urea nitrogen in patients undergoing coronary artery bypass surgery. *BMC Cardiovasc Disord* 2016; **16**:181.
- 6 Oshima K, Aoki M, Murata M, *et al.* Levels of catecholamines in the plasma of patients with cardiopulmonary arrest. *Int Heart J* 2019; **60**: 870–875.
- 7 Schrieffl C, Mayr FB, Poppe M, *et al.* Time of out-of-hospital cardiac arrest is not associated with outcome in a metropolitan area: a multicenter cohort study. *Resuscitation* 2019; **142**:61–68.

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