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Prediction of mortality with unmeasured anions in critically ill patients on mechanical ventilation

Predviđanje mortaliteta neizmerenim anjonima kod kritično obolelih na mehaničkoj ventilaciji

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Abstract

Background/Aim. Acid-base disorders are common within critically ill patients. Physicochemical approach described by Stewart and modified by Figge gives precise quantification method of metabolic acidosis and insight into its main mechanisms, as well as influence of unmeasured anion on metabolic acidosis. The aims of this study were to determine whether the conventional acid-base variables are connected with survival rate of critically ill patients at Intensive care unit; whether strong ion difference/strong ion gap (SID/SIG) is a better predictor of mortality rate comparing to conventional acid-base variables; to determine all significant predictable parameters for the 28-day mortality rate at intensive care units. **Methods.** This retrospective observational analytic study included 142 adult patients requiring mechanical ventilation, survivors (n = 68) and nonsurvivors (n = 74). Apparent strong ion difference (SIDapp), effective strong ion difference (SIDeff) and SIG values were calculated with the Stewart-Figge's quantitative biophysical method. Descriptive and analytical statistical methods were used in the study [*t*-test, Mann-Whitney U test, χ^2-test, binary logistic regression, Reciever operating characteristic (ROC) curves, calibration]. **Results.** Age, Na^+, acute physiology and chronic health evaluation (APACHE II), Cl^-, albumin, SIG, SID app, SIDeff, and aninon gap (AG) were statistically significant predictors. AG represented a model with imprecise calibration, i.e. a model with little predictive power. APACHE II had *p*-value more than 0.05 if it was near it, and therefore it could be considered potentially unreliable for outcome prediction. SIDeff and SIG represented models with well-defined calibration. ROC analysis results showed that APACHE II, Cl^-, albumin, SIDeff, SIG i AG had the largest area bellow the curve. By creation of logistic models with calibration methods, we found that outcome depends on SIG and APACHE II score. **Conclusion.** Based on our data, unmeasured anions provide prediction of mortality of critically ill patients on mechanical ventilation, unlike the traditional acid-base variables which are not accurate predictors of the 28-day mortality rate.

Key words:
critical illness; acid-base imbalance; intensive care units; mortality.

Apstrakt

Uvod/Cilj: Acidobazni poremećaji su uobičajeni kod kritično obolelih. Fizičko-hemijski pristup koji je opisao Stewart a modifikovao Figge omogućava precizan način kvantifikovanja metaboličke acidoze i pruža uvid u njene glavne mehanizme, kao i doprinos neizmerenih anjona metaboličkoj acidozi. Ova studija imala je za cilj da utvrdi: da li su konvencionalne acidobazne varijable povezane sa mortalitetom kritično obolelih u jedinici intenzivne nege; da li su snažna jonska razlika/snažni jonski gap (SID/SIG) bolji prediktori mortaliteta od konvencionalnih acidobaznih varijabli; sve značajne prediktivne faktore acidobazne ravnoteže za 28-dnevni mortalitet u jedinicama intenzivne nege. **Metode.** Ovom retrospektivnom opservacionom analitičkom studijom bila su obuhvaćena 142 odrasla bolesnika na mehaničkoj ventilaciji od kojih je preživelo 68 i umrlo 74. Vrednosti očigledne snažne jonske razlike (SIDapp), efektivna snažna jonska razlika (SIDeff) i SIG izračunavane su pomoću Stewart's-Figge kvantitativnog biofizičkog metoda. Korišćene su deskriptivne i analitičke statističke metode [*t*-test, Mann-Whitney *U*-test, χ^2-test, binarna logistička regresija, (*Receiver operating characteristic* – ROC) krive, kalibracija]. **Rezultati.** Univarijantna analiza ukazuje da su starost, Na^+, APACHE II, Cl^-, albumin, SIG, SIDapp, SIDeff i anjonski gap (AG) statistički značajni prediktori. AG se pokazao kao model sa lošom kalibracijom, odnosno model sa malom prediktivnom moći. APACHE II imao je *p* vrednost neznatno veću od 0,05, pa se i on može smatrati potencijalno sumnjivim za predikciju ishoda. SIDeff i SIG su se pokazali kao modele sa dobrom kalibracijom. ROC analiza je ukazala da APACHE II, Cl^-, albumin, SIDeff, SIG i AG imaju najveću površinu ispod krive. Kreiranjem logističkih modela metodom kalibracije pronašli smo da ishod zavisi od SIG i APACHE II skora. **Zaključak.** Dobijeni podaci pokazuju da neizmereni anjoni omogućavaju predviđanje mortaliteta kritično obolelih na mehaničkoj ventilaciji, za razliku od tradicionalnih acidobaznih varijabli koje nisu precizni prediktori 28-dnevnog preživljavanja.

Ključne reči:
kritična stanja; acidobazna ravnoteža, poremećaji; intenzivna nega, odeljenja; mortalitet.

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Introduction

Acid-base disorders are common in critically ill patients [1]. Traditional measurements which allow partial quantification of metabolic component of acid-base disorders are the following: pH, anion gap (AG), standard bicarbonates (SB), and standard base excess (SBE) [2]. Anion gap is the term used for apparent lack of anions compared to cations. This anion shortage in healthy persons is only apparent because only electrolytes of vital importance (sodium, potassium, chlorides and bicarbonates) are measured. If wider an anion gap, it indicates the presence of additional anions in plasma, such as: ketones, lactates, acid interproduct in salicylic acids, methanol or paraldehyde poisoning. In other words, anion gap widening is an indication for acidosis [3].

Numerous studies show, however, that conventional parameters of metabolic status have limited accuracy in predicting the outcome of treatment and the percent of mortality of critically ill patients [4–7]. The reasons for limited precision probably originate in different mechanisms involved in acid-base disorders formation: cumulative effect of hypoalbuminemia (values less than 35g/L), influence of various metabolites of unmeasured anions, the presence of various types of acidosis, the degree of hyperlactatemia (lactates values more than 2 mmol/L) [4, 7, 8]. The physicochemical approach described by Stewart [9] and modified by Figge et al. [10] gives a precise quantification method of metabolic acidosis. Also, it gives insight into its main mechanisms, as well as the influence of unmeasured anion on metabolic acidosis. This approach emphasizes that changes in blood pH are regulated by three independent variables: pH, strong ionic difference (SID) and total weak acids concentration [9, 10].

The partial pressure of carbon-dioxide ($PaCO_2$) provides some information about the respiratory component of acid-base disorders. However, the interpretation of metabolic component is far more complex. Apparent strong ion difference (SIDapp) is a difference between the sum of all strong cations and strong anions measured [9, 10]. Effective strong ion difference (SIDeff) represents the effect of corrected $PaCO_2$, weak acids (albumins), and inorganic phosphates on electric charge balance in plasma [10]. The difference between SIDapp and SIDeff measured represents a strong ion gap (SIG) [11]. The SIG value for healthy people is zero, while within critically ill patients high SIG is defined by the values ≤ 2 and indicates accumulation of unmeasured anions (sulfate, keto acids, citrate, pyruvate, acetate, gluconate, etc.) [8, 10–14]. Unmeasured anions are a sign of acidosis that must be included to account for the measured pH [14–19].

The aim of this study was to determine whether the conventional acid-base variables are connected with survival rate of critically ill patients at intensive care units (ICU), whether SID/SIG is a better predictor of mortality rate comparing to conventional acid-base variables, as well as to determine all significant predictable parameters for the 28-day mortality rate at Intensive care unit.

Methods

This retrospective observational analytic study involved subpopulation of critically ill patients on mechanical ventilation, admitted to the Intensive Care Unit, during the period January 2012–October 2012. The study was approved by the institutional ethical commitee.

Inclusion criteria in the study were the following: patients who needed mechanical ventilation and intensive monitoring of vital parameters (ECG monitoring, body temperature, arterial blood pressure). It was necessary that arterial gas analyses and biochemical analyses were done on admission date at Intensive Care Unit (electrolytes, albumins, haematocrit, leukocytes, and creatinine). Exclusion criteria were: patients under 18, patients admitted due to various poisoning, and patients diagnosed with cancer. According to the outcome, patients were divided into two groups: survivors and nonsurvivors. Fluid resuscitation was performed with crystalloids, colloids and blood products, according to the diagnosis of critically ill. All the patients were monitored during a 28-day period from the moment of admission to Intensive Care Unit in order to establish mortality rate [13].

Demographic data, admission diagnosis, APACHE II score values within the first 48 hours of admission (Acute Physiology And Chronic Health Evaluation), and treatment outcome (survivors and nonsurvivors) were collected from case histories and discharge notes of patients involved in the study. Venous blood was collected through a cannula introduced for therapy application. Different veins in forearm were drawn. Arterial blood was sampled from radial artery. Arterial puncture was done with syringe and needle (24–26 G) which were covered with heparin as anticoagulant. All samples were analysed with a gas analyser (GEM Premier 3000, Instrumentation Laboratory, Italy). Biochemical parameters were analysed by biochemical analyser (Ilab 600, Instrumentation Laboratory, Italy).

AG values were calculated with the following formula: $AG = [Na^+ + K^+] - [Cl^- + HCO_3^-]$, (concentrations are in mmol/L) [2, 3].

SIDapp, SIDeff and SIG values were calculated with the Stewart-Figge's quantitativebiophysical method using the following formulas:

$SIDapp = [Na^+ + K^+ + Ca^{2+}] - [Cl^- + \text{lactate}]$, (my concentrations are in mmol/L) [9, 10].

$SIDeff = 2.46 \times 10^{-8} \times PaCO_2/10^{-pH} + [\text{albumin}] \times (0.123 \times pH - 0.631) + (0.309 \times pH - 0.469)$ [10]. In this equation, PaCO2 is measured in kPa, albumin in g/L.

$SIG = SIDapp - SIDeff$ [11].

The minimum data required by a calculator of unmeasured anions is: pH, $PaCO_2$, Na^+, K^+, Cl^- and albumins [13].

The following descriptive methods were used: absolute and relative numbers, central trend measures (arithmetic mean and median), and dispersion measures (SD – standard deviation). Comparison tests (*t*-test, Mann-Whitney *U*-test, χ^2-test), and correlation analysis (binary logistic regression) were used as analytical methods. Receiver operating characteristic (ROC) curves were created in order to estimate which variables analysed have mortality discriminating prediction,

as well. Any analyses with $p < 0.05$ were considered relevant. The accuracy of treatment outcome prediction with prognostic model was shown by the calibration Hosmar-Lemeshow test (H-L test). This test assesses whether or not the observed event rates match the expected event rates in the subgroups of the model population [15]. SPSS 12.0 software package (Chicago, Illinois) was used for statistical analysis.

Results

There were 142 subjects included in the study, 67 men and 75 women. The patients were divided into two categories according to the 28-day survival rate: survivors (n = 68) and nonsurvivors (n = 74). The average age in the survivors group was 56.43 ± 17.45 years and nonsurvivors 64.05 ± 15.77 years. Detailed information about the average values and the results of logistic regression for survivors and nonsurvivors groups are given in Table 1. Univariate analysis showed that the following predictors are statistically significant: age, Na^+, APACHE II, Cl^-, albumin, SIG, SID app, SIDeff and AG. Nevertheless, for all the models it is important to emphazise that AG is a model with poor calibration, or a little predictive power. APACHE II had *p*-value more than 0.05 if it was near it, and therefore it could be considered potentially unreliable for outcome prediction. On the other hand, SIG was a model with well-defined calibration. The results of ROC analysis (Table 2) shoed that statistically significant predictors were as follows: age, Na^+, APACHE II, Cl^-, albumin, SIDeff, SIG and AG. The largest

Table 1

Demographic data, variables used for acid-base evaluation Glasgow Coma Score (GCS) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, average values and the results of logistic regression

Variables	Survivors (n = 68)	Nonsurvivors (n = 74)	*p*-value	OR (95% CI)
Age (years), $\bar{x} \pm SD$	56.43 ± 17.45	64.05 ± 15.77	0.009	1.028 (1.007–1.050)
Sex (male), n (%)	36 (53.7)	31 (46.3)	0.189	1.560 (0.804–3,029)
Hct (%), $\bar{x} \pm SD$	0.315 ± 0.06	0.310 ±0.07	0.649	0.321 (0.002–42.516)
Le ($n \times 10^9$/L), $\bar{x} \pm SD$	13.751 ± 5.76	13.689 ± 6.60	0.952	0.998 (0.947–1.053)
Na^+ (mmol/L), $\bar{x} \pm SD$	138.000 ± 5.32	142.35 ± 11.13	0.007	1.065 (1.017–1.114)
K^+ (mmol/L), $\bar{x} \pm SD$	3.824 ± 0.78	3.991 ± 0.82	0.221	1.297 (0.855–1,967)
PaO_2 (kPa), $\bar{x} \pm SD$	11.865 ± 2.81	11.699 ± 4.63	0.797	0.989 (0.908–1,077)
pH, $\bar{x} \pm SD$	7.374 ± 0.07	7.354 ± 0.12	0.259	0.152 (0.006–3.994)
SB (mmol/L), $\bar{x} \pm SD$	22.666 ± 4.82	22.046 ± 6.38	0.515	0.981 (0.925–1.040)
SBE mEg/L, $\bar{x} \pm SD$	1.235 ± 3.84	-0.153 ± 7.50	0.177	0.962 (0,909–1,018)
Lactates (mmol/L), $\bar{x} \pm SD$	1.732 ± 1.43	2.319 ± 2.49	0.106	1.171 (0.967–1.417)
Cl^- (mmol/L), $\bar{x} \pm SD$	101.540 ± 5.46	103.62 ± 6.44	0.043	1.060 (1.002–1.122)
Ca^{2+} (mmol/L), $\bar{x} \pm SD$	1.261 ± 0.370	1.225 ± 0.38	0.562	0.769 (0.316–1.870)
$PaCO_2$ (kPa), $\bar{x} \pm SD$	6.152 ± 1.61	5.835 ± 2.04	0.312	0.910 (0.759–1.092)
Albumin (g/L), $\bar{x} \pm SD$	27.88 ± 5.51	25.31 ± 6.54	0.015	0.932 (0.880–0.986)
SIDapp mEg/L, $\bar{x} \pm SD$	42.094 ± 7.60	44.566 ± 8.61	0.078	1.040 (0.996–1.085)
SIDeff mEg/L, $\bar{x} \pm SD$	34.568 ± 5.67	32.253 ± 8.35	0.061	0.956 (0.911–1.002)
SIG mEg/L, $\bar{x} \pm SD$	7.513 ± 7.15	12.352 ± 9.47	0.001	1.071 (1.027–1.116)
AG mEg/L, $\bar{x} \pm SD$	14.350 ± 6.86	17.427 ± 8.95	0.026	1.050 (1.006–1.095)
APACHE II, $\bar{x} \pm SD$	13.28 ± 6.10	18.93 ± 5.50	< 0.001	1.180 (1.103–1.262)
GCS, $\bar{x} \pm SD$	11.87 ± 3.42	10.88 ± 4.06	0.121	0.932 (0.853–1.019)

OR – odds ratio; CI – confidence interval; Hct – hematocrit; Le – leucocytes; MAP – mean arterial pressure; PaO_2 – partial pressure of oxygen; pH – Potential of hydrogen; SB – standard bicarbonates; SBE – standard base excess; $PaCO_2$ – partial pressure of carbon-dioxide; SIDapp – apparent strong ion difference; SIDeff – effective strong ion difference; SIG – strong ion gap; AG – anion gap; GCS – Glasgow Coma Score; APACHE II – Acute Physiology and Chronic Health Evaluation II.

Table 2

Receiver operating characteristics (ROC) curve analysis

Variables	Area under ROC curve	95% CI		*p* value	Cut-off value	Sn / Sp (%)
		Lower	Upper			
APACHE II	0.756	0.677	0.834	< 0.001	> 14	79.7/60.3
pH	0.496	0.400	0.591	0.927	<= 7.21	13.5/98.5
SB	0.483	0.387	0.578	0.724	<= 15.6	14.9/97.1
SBE	0.421	0.326	0.517	0.106	<= -3.3	32.4/91.2
Lactates	0.580	0.485	0.674	0.102	> 1.1	63.5/51.5
$PaCO_2$	0.426	0.332	0.521	0.131	<= 4.9	40.5/80.9
Albumin	0.370	0.279	0.462	0.008	<= 24	54.1/72.1
SIDapp	0.555	0.460	0.650	0.261	> 40.8	71.6/42.6
SIDeff	0.395	0.301	0.488	0.030	<= 31.8	54.0/69.1
SIG	0.651	0.561	0.742	0.002	> 10.6	56.7/73.5
AG	0.615	0.522	0.707	0.019	> 21	37.8/86.8

CI – confidence intervals; APACHE II – Acute Physiology and Chronic Health Evaluation II; SB – standard bicarbonates; SBE – standard base excess; $PaCO_2$ – partial pressure of carbon-dioxide; SIDapp – apparent strong ion difference; SIDeff – effective strong ion difference; SIG – strong ion gap; AG – anion gap; Sn – sensitivity; Sp – specificity.

area bellow the curve had: SIDeff, SIG, AG and APACHE II (Figure 1). It is important that *p* value is as far as possible from 0.05.

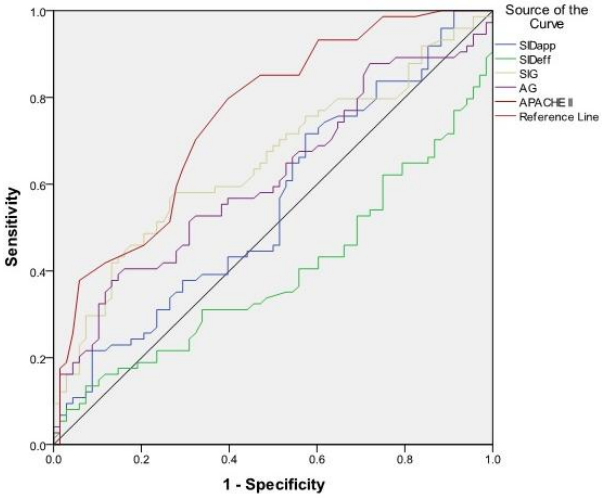

Fig. 1 – Receiver operating characteristic (ROC) curves of apparent strong ion difference (SIDapp), effective strong ion difference (SIDeff), strong ion gap (SIG), anion gap (AG) and Acute Physiology and Chronic Health Evaluation II (APACHE II) score.

Next, logistic models were made (Table 3). The first logistic model was a model to which predictors with $p < 0.1$ were added. The model was well-calibrated (H-L $p = 0.626$). This model indicated that the only significant predictor was the APACHE II score. However, we consider the model created with ENTER not adequate enough due to a disproportion between the sample size and the results of importance and the number of variables present in this model. Therefore, an additional model was created and predictors processed with the Forward method. It can be seen that at the first step APACHE II was a variable introduced as a statistically significant predictor with the least *p*-value. However, in this case the results of H-L test was $p = 0.072$, which indicated that APACHE II model was not enough for outcome prediction. In the step 2 SIG as a statistically significant predictor was added, and the result of HL test was $p = 0.274$. It indicated a well-calibrated model with good predictive capabilities.

Table 3

Results of logistic regression using the Enter and Forward method

Predictor	*p* value	OR	95% CI	
			Lower	Upper
Enter method				
Age	0.514	1.009	0.983	1.036
Na+	0.100	1.102	0.981	1.238
APACHE II	0.002	1.130	1.045	1.221
Cl^-	0.829	0.987	0.878	1.110
Albumin	0.174	0.950	0.882	1.023
SIDapp	0.550	0.503	0.053	4.802
SIDeff	0.593	1.850	0.194	17.658
SIG	0.525	2.080	0.218	19.870
AG	0.298	1.077	0.937	1.237
Forward method				
APACHE	< 0.001	1.180	1.103	1.262
APACHE II	0.000	1.171	1.093	1.255
SIG	0.012	1.062	1.013	1.114

OR – odds ratio; CI – confidence interval; SIDapp – apparent strong ion difference; SIDeff – effective strong ion difference; SIG – strong ion gap; AG – anion gap; APACHE II – Acute Physiology and Chronic Health Evaluation II.

Discussion

The present study show that the only reliable predictors of the 28-day survival rate in critically ill patients are SIG and APACHE II scores. It should be mentioned that this study is the first one focused on critically ill patients on mechanical ventilation exclusively, unlike the majority of similar studies [1, 5, 7, 12, 16]. Numerous studies have examined the predictive capability of standard and acid-base variables derived from the Stewart-Figge's quantitative biophysical method [1, 4, 12, 17, 18]. It has been noticed that the traditional acid-base variables (pH, AG, SB, and SBE) could be unsuccessful in complex acid-base disorders identification in critically ill patients.

If contradictory results from the literature on this phenomenon were taken into consideration, there would be unreliability regarding prognostic usefulness of some acid-base variables, and therefore their biological significance would be questionable. Although the severity of metabolic acid-base disorders or lactic acidosis in critically ill patients can predict the outcome of treatment, there are many inconsistencies regarding clinical relevance of these variables. Gunnerson et al. [1] analysed a possible discrepancy between SIG in healthy volunteers and stable patients before discharge from intensive care units. It was shown that stable patients at discharge had significantly higher levels of undetected anions comparing to healthy volunteers. This finding is explained with occult acid-base disorders, which cannot be identified by the standard metabolic status interpretation. The study conducted by Maciel and Park [4], shows that different anion proportions which cause aci-

dosis at admission to intensive care units are similar for survivors and nonsurvivors. At paediatric population of critically ill patients, Balasubramanyan et al. [5] have indicated that unmeasured anions can be used for lactate values prediction and that they predict mortality rate better than serum lactates. However, this discovery was contradictory to the study of Cusack et al. [16] conducted on adult population of critically ill patients. That study proved that initial pH and SBE had the best capability to predict treatment outcome among acid-base variables, while SIG had not significant prognostic power. On a narrow-selected patient population with serious vascular traumas, Kaplan et al. [19] found that SID/SIG methodology was a better 'tool' for estimation of potential mortality rate at patients than hypoperfusion markers and standard acid-base. Rocktaeschel et al. [14] in their study find that useful predictors of hyperlactatemia in adult general ICU patients are: BE, BEua (BE caused by unmeasured anions) and AG. Also, they find that in critically ill patients acid-base variables, calculated in four ways (AG, Agcorr-corrected anion gap, BEua, SIG), have a limited ability to predict hospital mortality. Therefore, they conclude that the nature, origin and true significance of unmeasured anions in critical illness remain unknown. Antonini et al. [20] conclude that despite the absence of acidaemia, progressive metabolic acidosis may be ongoing in the early phase of critical illness. However, metabolic acidosis determined by unmeasured anions is a clinically relevant phenomenon correlated with mortality.

In our study, ROC analysis indicates more potential predictors. It has been revealed by creation of logistic models with calibration methods [15], that outcome depends on SIG and APACHE II score. The arithmetic mean for SIG in the survivors group is significantly higher compared to the group of nonsurvivors. These values of SIG in the nonsurvivors group represent very large amount of undetected anions and indicate that organism is overloaded with acids. The results of this study support conclusions of other studies which claim that unmeasured anions, detected by the Stewart-Figge's methodology, identify a greater number of patients with acid-base disorders comparing to the conventional parameters (pH, AG, SB, SBE) [1, 4, 12, 18, 20, 21]. A great number of acidosis at critically ill patients were caused iatrogenically, by infusion solutions rich in chlorides and plasma expanders which act as weak acids [1, 8, 19]. However, unmeasured anions seem to represent heterogeneous set of various anions which is not always well-characterized because the anions come from many possible sources, and therefore future research should focus precisely on detecting their source. The scope of different diagnoses in this study is very heterogeneous, and it can be recommended that future studies on this phenomenon should focus on patients with clearly defined diagnosis (surgical, neurosurgical, neurological, internist etc.).

Conclusion

This study indicates that unmeasured anions if measured with quantitative biophysical method could have clinical implications, regarding not only the prognosis of critically ill treatment and its outcome, but also the early diagnostics of complex acid-base abnormality which cannot be detected with the traditional acid-base variables.

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