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METABOLIC ACIDOSIS MODIFIES CARBOXYHEMOGLOBIN-SERUM POTASSIUM LINK IN CO POISONING: A CROSS-SECTIONAL STUDY

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Abstract

This study aimed to investigate whether metabolic acidosis modifies the association between carboxyhemoglobin (COHb) and serum potassium in acute carbon monoxide (CO) poisoning patients. A cross-sectional analysis was conducted on 124 patients. Serum potassium was the outcome, COHb saturation the exposure, and metabolic acidosis was defined as a standard base excess (SBE) < -3 mmol/L. The interaction was analyzed using multiple linear regression. The interaction between COHb and metabolic acidosis on serum potassium was significant ($\beta = -0.0184$, 95% CI: -0.0362 to -0.0005, $P = 0.044$). Subgroup analysis showed a stronger effect in patients with SBE < -4 mmol/L ($\beta = -0.0269$, $P = 0.002$). In conclusion, metabolic acidosis significantly enhances the negative association between COHb and serum potassium in acute CO poisoning, with the effect intensifying with acidosis severity. This highlights the need for integrated assessment of blood gas and electrolyte indicators, particularly in patients with moderate to severe acidosis, to mitigate the risk of a pronounced COHb-driven decrease in potassium.

Key words: acute carbon monoxide poisoning, carboxyhemoglobin, metabolic acidosis, hypokalemia, interaction

Introduction. Acute carbon monoxide (CO) poisoning is a globally common cause of accidental poisoning. Its primary toxicity arises from the high affinity

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of CO for hemoglobin. The formation of carboxyhemoglobin (COHb) compromises oxygen transport and impedes oxygen dissociation, leading to systemic tissue hypoxia and multi-organ damage, making it a frequent critical condition in emergency departments [1–3].

Electrolyte disturbances are common complications of acute CO poisoning. Among these, hypokalemia frequently occurs in emergency acute medical inpatients and is an independent risk factor for short-term adverse outcomes. It is closely associated with fatal events such as malignant cardiac arrhythmias and myocardial injury [4,5]. The systemic stress and metabolic disturbances triggered by CO poisoning can further increase the risk of hypokalemia. However, the factors influencing serum potassium changes in CO-poisoned patients have not been fully elucidated. While hyperkalemia is recognized as a marker of severity and prognosis in acute CO poisoning, hypokalemia also commonly occurs and poses arrhythmia risks. This study focuses on whether metabolic acidosis modifies the association between COHb and serum potassium (particularly hypokalemia risk), to identify high-risk subsets for electrolyte disturbance.

COHb is the key indicator for diagnosing CO poisoning and assessing the severity of intoxication. However, its correlation with clinical symptoms and the degree of organ damage is not entirely linear, suggesting that other factors may modify its pathophysiological effects. Metabolic acidosis is a direct consequence of tissue hypoxia following CO poisoning. Previous studies have confirmed that initial blood lactate levels in acute CO poisoning patients are significantly positively correlated with COHb concentration and poisoning severity. CO poisoning can elevate organic acids such as lactate and pyruvate, inducing metabolic acidosis [6,7]. Standard base excess (SBE) is a specific indicator of metabolic acid-base imbalance, excluding interference from respiratory factors. It can more accurately quantify the severity of acidosis compared to blood pH and has been proven to be closely associated with disease severity and poor prognosis in various critical illnesses [8,12].

Acid-base balance is central to the regulation of potassium homeostasis. The effect on serum potassium differs fundamentally between types of acidosis: inorganic acidosis often leads to hyperkalemia through H^+-K^+ transmembrane exchange; whereas organic acidoses, such as lactic acidosis and ketoacidosis, cannot establish an effective transmembrane H^+ gradient, thus do not trigger K^+ efflux and may even lower serum potassium [13]. This pattern has been corroborated in studies on toluene poisoning [14]. However, no studies have yet investigated the modifying effect of metabolic acidosis on the association between COHb and serum potassium. Therefore, this study retrospectively analyzed the clinical data of acute CO poisoning patients to explore this modifying effect, aiming to provide a basis for the early identification of high-risk individuals for hypokalemia and the optimization of electrolyte management.

Methods. This study was approved by the Ethics Committee of Bozhou People's Hospital (Approval No. BoYi Lun Shen 2025 No. 263). With a waiver of informed consent, this retrospective study analyzed the records of 124 patients with acute carbon monoxide poisoning admitted between December 2021 and December 2024. Inclusion required both arterial blood gas and venous electrolyte tests within 1 hour of arrival. Patients with other poisonings, end-stage renal disease, dialysis, or recent use of potassium-affecting drugs were excluded.

Participants were categorized by standard base excess (SBE) into a metabolic acidosis group (MA, SBE < -3 mmol/L, $n = 72$) and a non-acidosis control group (non-MA, $n = 52$), matched for age and sex. Data collected included demographics, comorbidities, and laboratory values (COHb, potassium, SBE, lactate, creatinine, white blood cell count) and heart rate. Arterial blood was analyzed immediately on a Radiometer ABL90 FLEX analyzer; serum tests were performed centrally.

Statistical analysis. Analyses used R 4.4.2. Data are presented as median (IQR) or n (%). Group comparisons used Mann–Whitney U, Chi-square, or Fisher's exact tests. The association of mean-centred COHb with serum potassium and its interaction with acidosis was tested via multiple linear regression. Robustness was assessed through subgroup analyses (varying SBE cutoffs) and Bootstrap resampling. A two-sided $P < 0.05$ was significant.

Results. A total of 124 patients were ultimately enrolled, comprising 72 in the metabolic acidosis group and 52 in the non-acidosis group. A comparison of the baseline characteristics between the two groups is presented in Table 1. The two groups were well-balanced in terms of demographic features (age, sex) and comorbidities (hypertension, diabetes) (all $P > 0.05$). Compared to the non-acidosis group, patients in the acidosis group had significantly higher levels of COHb, lactate, serum creatinine, white blood cell count, and heart rate, alongside a significantly lower SBE (all $P < 0.05$). There was no statistically significant difference in serum potassium levels between the two groups ($P = 0.493$).

Univariable analysis showed a significant negative correlation between centred COHb and serum potassium ($\beta = -0.0216$, 95% CI: -0.0304 to -0.0128, $P < 0.001$), with no significant association found for other variables. After adjusting for covariates, the multivariable model (Table 2) confirmed this association ($\beta = -0.0251$, 95% CI: -0.0339 to -0.0164, $P < 0.001$) and revealed a significant interaction between COHb and metabolic acidosis ($\beta = -0.0184$, 95% CI: -0.0362 to -0.0005, $P = 0.044$). This indicates that in patients with acidosis, each 1% increase in COHb additionally lowers serum potassium by 0.0184 mmol/L. The model showed good fit ($R^2 = 0.2756$, adjusted $R^2 = 0.2319$), with no severe multicollinearity (all VIF < 3) and satisfactory residual diagnostics (normality $P = 0.127$; homoscedasticity $P = 0.356$).

Subgroup analysis (Table 3) revealed that this modifying effect was strongest at an SBE cutoff < -4 mmol/L ($\beta = -0.0269$, $P = 0.002$) and was not significant

Table 1

Comparison of baseline characteristics in patients with acute CO poisoning

Characteristic	Overall (n=124)	Non-acidosis group ($n = 52$)	Acidosis group ($n = 72$)	P value
Age (years)	56.00 (46.75, 70.00)	56.00 (48.00, 67.00)	56.00 (46.75, 72.00)	0.713
Male, n (%)	65 (52.42)	26 (50.0)	39 (54.17)	0.642
COHb (%)	25.50 (14.02, 33.75)	23.60 (13.10, 31.93)	27.65 (15.30, 36.20)	0.195
Serum K^+ (mmol/L)	3.88 (3.54, 4.24)	3.87 (3.65, 4.14)	3.91 (3.54, 4.39)	0.493
SBE (mmol/L)	−3.60 (−7.12, −1.40)	−1.15 (−2.15, 0.43)	−5.90 (−9.80, −4.18)	< 0.001
Lactate (mmol/L)	3.00 (1.80, 5.17)	2.00 (1.40, 3.23)	3.75 (2.27, 6.35)	< 0.001
Creatinine (μmol/L)	59.50 (47.98, 76.33)	56.45 (46.07, 68.85)	65.15 (50.25, 89.08)	0.013
WBC ($\times 10^9$/L)	11.29 (8.85, 15.91)	9.72 (7.90, 13.19)	12.59 (9.37, 17.49)	0.003
Heart rate (bpm)	87.50 (78.00, 100.50)	81.50 (76.75, 97.25)	92.00 (78.75, 108.00)	0.010
Hypertension, n (%)	35 (28.23)	17 (32.69)	18 (25.00)	0.348
Diabetes, n (%)	12 (9.68)	4 (7.69)	8 (11.11)	0.525
Hypokalemia, n (%)	28 (22.58)	12 (23.08)	16 (22.22)	1.000

Note: Data are presented as median (IQR) or n (%). COHb – carboxyhemoglobin; SBE – standard base excess; WBC – white blood cell count; K^+ – potassium; bpm – beats per minute.

Table 2

Multivariable linear regression analysis of factors influencing serum potassium in patients with acute CO poisoning

Variable	β Coeff.	Std. Error	P value	95% CI Lower limit	95% CI Upper limit
Intercept	4.4169	0.2935	< 0.001	3.8356	4.9982
Centred COHb	−0.0251	0.0071	< 0.001	−0.0339	−0.0164
Acidosis	0.1641	0.1078	0.131	−0.0494	0.3776
Age	−0.0060	0.0033	0.071	−0.0124	0.0005
Sex (Female)	−0.1046	0.1046	0.319	−0.3118	0.1026
Hypertension (Absent)	0.2334	0.1373	0.092	−0.0386	0.5054
Diabetes (Absent)	−0.3491	0.1950	0.076	−0.7354	0.0372
COHb × Acidosis	−0.0184	0.0090	0.044	−0.0362	−0.0005

Note: CI – confidence interval; COHb – carboxyhemoglobin.

at SBE < −2 mmol/L. Sensitivity analyses (Table 4) confirmed the robustness of the interaction when using different covariate sets or treating COHb as a categorical variable, but it was non-significant when acidosis was defined by pH < 7.35.

Discussion. This study is the first to confirm via retrospective analysis of clinical data from patients with acute CO poisoning that metabolic acidosis can potentiate the serum potassium-lowering effect of elevated COHb, and this modifying effect exhibits a clear dose-dependent relationship: the more severe the acidosis quantified by SBE, the more significant the potassium-lowering effect of COHb, with the strongest effect observed at SBE < −4 mmol/L and no statistical

Table 3

Subgroup analysis of the interaction between COHb and acidosis under different SBE cutoffs

SBE Cutoff (mmol/L)	Cases with Acidosis (n)	β coefficient	95% CI Lower limit	95% CI Upper limit	P value
SBE < -2	86	−0.0144	−0.0333	0.0045	0.134
SBE < -3	72	−0.0184	−0.0362	−0.0005	0.044
SBE < -4	56	−0.0269	−0.0440	−0.0098	0.002
SBE < -5	46	−0.0221	−0.0396	−0.0046	0.014

Note: SBE – standard base excess; β – regression coefficient; CI – confidence interval.

Table 4

Sensitivity analysis of the interaction effect between COHb and acidosis in acute CO poisoning patients

Test type	β Coeff.	95% CI Lower limit	95% CI Upper limit	P value	Result judgment
Primary Analysis (Reference)	−0.0184	−0.0362	−0.0005	0.044	Significant
Expanded Covariate Adjustment	−0.0204	−0.0387	−0.0021	0.03	Robust
Minimal Covariate Adjustment	−0.0205	−0.0384	−0.0026	0.025	Robust
COHb as Categorical Variable	−0.4452	—	—	0.037	Robust
Bootstrap (1000 Replicates)	−0.0184	−0.0375	−0.0002	0.048	Robust
Redefined Acidosis (pH<7.35)	−0.0062	−0.0235	0.0111	0.478	Non-significant
Logistic Regression (Binary Outcome)	−0.0215	−0.0489	0.0059	0.577	Non-significant

Note: COHb – carboxyhemoglobin; β – regression coefficient; CI – confidence interval. For the categorical variable analysis, a single 95% CI is not applicable, and its β coefficient is on a different scale.

significance at SBE > -2 mmol/L. Additionally, this effect remained robust when metabolic acidosis was defined solely by SBE but not by blood pH, highlighting the clinical value of SBE in assessing metabolic acid-base imbalances [12]. This finding not only explains the significant heterogeneity in serum potassium levels among patients with similar COHb levels in clinical practice but also addresses the gap in existing research that neglects the interactions between variables.

The study provides direct clinical evidence for the specific effect of organic acidosis on serum potassium in the CO-poisoned population. Its results are consistent with the classic 1981 study by Perez et al. [13] (inorganic acidosis is associated with hyperkalemia, while uncomplicated organic acidosis alone does not induce hyperkalemia) and the clinical characteristics of severe hypokalemia associated with organic acidosis in toluene poisoning [14], which verifies the common role of organic acidosis in potassium regulation and supplements the clinical evidence for the association between organic acidosis and hypokalemia. It also remedies the

deficiency of previous CO poisoning research that separately explored the correlations between acidosis and poisoning severity, and between COHb and electrolyte disturbances [6, 7], enriching the understanding of the network of relationships among clinical indicators in the acute phase of CO poisoning.

The differential results obtained when using SBE versus pH to define acidosis can be attributed to the fact that blood pH is influenced by both respiratory and metabolic factors, and compensatory hyperventilation in CO-poisoned patients can mask the severity of metabolic acidosis. SBE, however, can exclude the interference of respiratory factors and accurately reflect the actual degree of metabolic acid-base disturbance.

This study suggests that in acute CO poisoning with metabolic acidosis, elevated COHb levels may specifically increase the risk of hypokalemia. Therefore, beyond recognizing hyperkalemia as a prognostic marker, clinicians should consider combined assessment of COHb and SBE to identify patients at heightened risk for COHb-driven hypokalemia, particularly when SBE < -3 mmol/L, and implement proactive potassium monitoring and management as needed [15, 16].

This study has certain limitations. First, as a single-centre cross-sectional study with a relatively small sample size, it inherently carries risks of an increased probability of false-positive results and limited generalizability of conclusions, requiring further validation by large-sample multicentre studies. Second, the cross-sectional design precludes causal inferences regarding the relationships among metabolic acidosis, COHb, and serum potassium. Third, potential confounding and modifying factors such as the time from poisoning to admission, specific treatment regimens, and lactate levels were not analyzed. Fourth, nonsignificant results in some sensitivity analyses indicate that the applicability of the study conclusions must be interpreted cautiously in specific clinical scenarios.

Conclusion. Metabolic acidosis significantly enhances the negative association between COHb and serum potassium. In patients with concomitant acidosis, vigilance for COHb-driven hypokalemia is warranted. Combined monitoring of COHb and SBE can aid in risk-stratified electrolyte management.

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