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Original Article

Association between early arterial pH, base excess and lactate and 24-h mortality and neurological outcomes after cardiac arrest and cardiopulmonary resuscitation: a translational study

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Abstract

Aim: We aimed to assess the translational relevance of blood gas-derived acid-base parameters measured in rat and pig models of cardiac arrest and cardiopulmonary resuscitation, evaluating their potential as predictors of mortality and poor neurological outcome.

Methods: Seventy-seven rats, 83 pigs and 61 patients who experienced cardiac arrest of proven or suspected cardiac origin were retrospectively analyzed. Blood gas analyses were performed 4 h after return of spontaneous circulation. Neurological recovery was assessed using Neurological Deficit Score in rats, overall performance category in pigs, and cerebral performance category in patients. Nonlinear associations between blood gas-derived acid-base parameters and outcomes were analyzed using a generalized additive model. Receiver operating characteristics curve analyses were performed.

Results: In a multivariate regression analysis area under the curve, considering pH, base excess and lactate, for prediction of mortality were respectively: 0.796 (95%CI: 0.635–0.956), 0.980 (95%CI: 0.946–1.000), 0.959 (95%CI: 0.896–1.000) in rats; 0.908 (95%CI: 0.826–0.990), 0.933 (95%CI: 0.863–1.000), 0.798 (95%CI: 0.588–1.000) in pigs; and 0.830 (95%CI: 0.724–0.936), 0.832 (95%CI: 0.731–0.933), 0.839 (95%CI: 0.738–0.940) in patients. Area under the curve, considering pH, base excess and lactate, for prediction of poor neurological outcome were respectively: 0.673 (95% CI: 0.515–0.831), 0.724 (95%CI: 0.576–0.872), 0.900 (95%CI: 0.760–1.000) in pigs; and 0.835 (95%CI: 0.734–0.937), 0.835 (95%CI: 0.735–0.936), 0.884 (95%CI: 0.793–0.945) in patients.

Conclusion: Arterial pH, base excess and lactate were early independent predictors of both 24-h mortality and neurological outcome following cardiac arrest in animal models and in humans. BE showed the highest predictive value for mortality, while lactate was the strongest predictor for poor neurological outcome.

Keywords: Base excess, Lactate, Survival, Neurological outcome, Cardiac arrest

Introduction

Cardiac arrest (CA) remains a major health burden.[1] Even when return of spontaneous circulation (ROSC) is achieved, long-term prognosis remains poor.[2] Accurately predicting the clinical trajectory of patients after successful resuscitation remains inherently challenging.[3] Early physician prognostications sometimes inadequately capture the true progression of the disease,[4] possibly resulting in the premature withdrawal of treatments.[5] Conversely, the persistence of aggressive life-sustaining interventions may cause unnecessary suffering and unjustifiable costs if not aligned with the

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patient's goals of care.[6] Reliable prognostic models combining objective parameters and multiple predictive factors are essential to guide accurate and ethically sound decision-making.[7,8] Among the available laboratory parameters, pH, base excess (BE) and lactate are routinely measured in most hospital settings and reflect the duration and severity of tissue hypoxia.[8,9] In acute care settings, several studies have consistently demonstrated their association with survival across various pathologies, including multiple trauma, sepsis, pneumonia and immune system disorders.[10–12] After CA and cardiopulmonary resuscitation (CA/CPR) growing evidence indicates that pH and lactate levels serve as reliable predictors of survival and neurological outcome in humans.[12–18] For instance, arterial pH has been proposed as a component of a multimodal evaluation for early assessment of neurological prognosis, due to its strong discriminatory ability for poor neurological outcomes and high specificity and positive predictive value.[19] Evidence also indicate an association between BE and neurological outcome in clinical populations. However, although pre-hospital venous BE measured at the beginning of CPR has been independently associated to neurological outcome,[20,21] the overall evidence supporting the predictive value of these parameters remains limited. Furthermore, no data are currently available regarding their predictive performance in animal model of CA/CPR. This observational retrospective study aims to evaluate the translational relevance of value of arterial blood gas (ABG)-derived acid-base parameters measured shortly after resuscitation in rat and pig models of CA/CPR, and to compare these results with corresponding ABG measurements obtained in human patients after resuscitation.

Materials and methods

This study was a retrospective analysis of data acquired from earlier prospective investigations.[22–29] All procedures involving animals and their care conformed with national and international laws and policies. Approval of the original studies were obtained from the institutional review board and governmental institution (Ministry of Health approval no. 683/2023-PR, for rat model of CA/CPR; no. 84/2014-PR, 72/2014-PR, 657/2020-PR, 1129/2020-PR for pig model of CA/CPR). The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Study 1: rat model of CA/CPR

The experimental design is illustrated in Fig. 1A. Detailed methods for animal preparation, CA/CPR procedure, and measurements are provided in Supplemental Material.

Experimental procedures

Male Sprague- Dawley ex-breeder rats (weight, 464 ± 32 g; $n = 77$) (Envigo) were used for the study. Animals were anesthetized and instrumented for hemodynamic measurements and induction of CA, as previously reported.[30] An established model of electrically induced CA/CPR was used, as described in the Supplemental Methods.[30] Animals underwent 8 min of untreated ventricular fibrillation (VF) followed by 8 min of mechanical chest compressions and ventilation prior to defibrillation. After successful resuscitation, animals were invasively monitored for 4 h before being returned to their cages. Blood gas analyses were assessed at baseline, 2- and 4-h post-ROSC. Neurological recovery was assessed 24 h after resuscitation using Neurological Deficit Score (NDS) ranging from 0 (brain death) to 500 (normal), as described in the Supplemental Material (Table 4A).[31] Scoring was performed by collaborators. Animals that achieved ROSC ($n = 58$) were retrospectively classified according to their 24 h survival status, resulting in two groups: survivors ($n = 26$) and non-survivors ($n = 32$). In this species, neurological outcomes were assessed only through correlation analyses, as no validated NDS cut-off exists to distinguish favorable from unfavorable outcomes. This lack of a standardized threshold prevented the development of a predictive model for neurological prognosis.

Study 2: pig model of CA/CPR

The experimental design is illustrated in Fig. 1B. Detailed methods for animal preparation, CA/CPR procedure, and measurements are provided in Supplemental Materials.

Experimental procedures

Male domestic pigs (weight, 39 ± 4 kg; $n = 83$) were used for the study. Animals were anesthetized and instrumented for hemodynamic measurements and induction of CA, as previously reported.[27] An established model of ischemically induced CA/CPR was used, as described in the Supplemental Methods.[24,26] Briefly, animals underwent 12–14 min of ischemic VF followed by 5 min of mechanical chest compressions and ventilation prior to defibrillation. After successful resuscitation, animals were invasively monitored for 4 h before being returned to their cages. Blood gas analyses were assessed at baseline, 2- and 4-h post-ROSC. Neurological recovery was assessed at 96 h post-ROSC according to the overall performance category (OPC), as described in the Supplemental Material (Table 4B).[32] Scores were assessed by veterinarians.[26] Animals that achieved ROSC ($n = 64$) were first retrospectively classified according to their 24 h survival status, resulting in two groups: survivors ($n = 49$) and non-survivors ($n = 15$). The same cohort was then further evaluated and stratified based on 96-h neurological outcome, categorized as good (OPC 1–2, $n = 31$) or poor (OPC 3–5, $n = 33$).

Study 3: patient cohort

This retrospective, observational cohort study included all adult patients with out-of-hospital and in-hospital CA who were admitted to the ICU of the IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico in Milan (Italy), over a 4-year period (August 8th, 2020–June 6th, 2023).[29] The study complies with the Declaration of Helsinki and was approved by the Regional Ethics Committee "Lombardia 3" (approval no. OSMAMI25/07/2024-0029769-U) and registered on ClinicalTrials.gov (NCT06608771). Written informed consent was waived in accordance with local regulations on retrospective study design. Detailed methods for eligibility criteria and measurements are provided in Supplemental Material. Adult patients admitted to the ICU following in-hospital and out-of-hospital CA due to a presumed cardiac cause, were included. Arterial blood gas analyses were assessed at ICU admission. Functional recovery was evaluated at ICU discharge according to cerebral performance category (CPC), as described in the Supplemental Material (Table 4C).[33] In the present analysis, included patients ($n = 61$) were first classified according to their ICU survival status as survivors ($n = 40$) and non-survivors ($n = 21$). The same cohort was further evaluated and stratified based on neurological outcome, categorized as good (CPC 1–2, $n = 33$) or poor (CPC 3–5, $n = 28$).

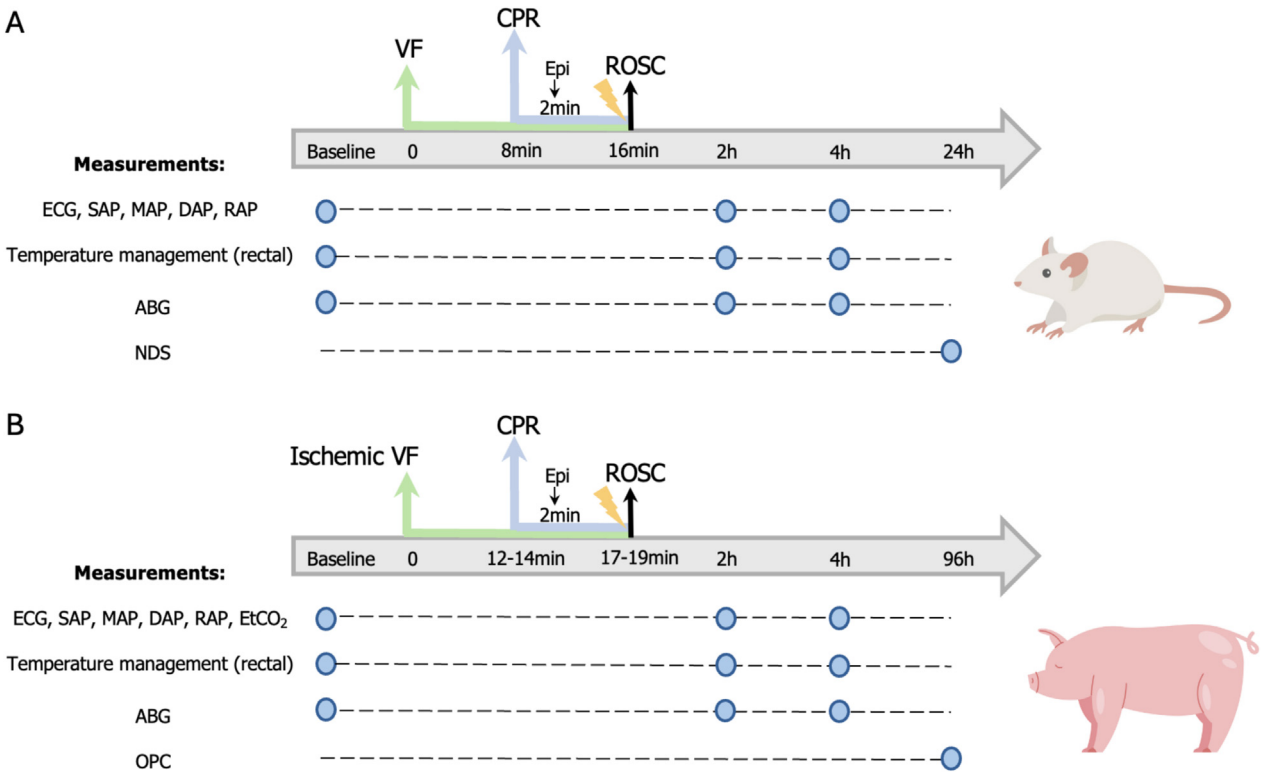

Fig. 1 – Experimental designs. Experimental designs adopted for rat model (A) and pig model (B).
ABG indicates arterial blood gas; CPR, cardiopulmonary resuscitation; DAP, diastolic arterial pressure; ECG, electrocardiogram; Epi, epinephrine; $EtCO_2$, end-tidal carbon dioxide; MAP, mean arterial pressure; NDS, neurological deficit score; OPC, overall performance category; RAP, right atrial pressure; ROSC, return of spontaneous circulation; SAP, systolic arterial pressure; VF, ventricular fibrillation.

Statistical analysis

Statistical analyses were performed using R Studio (v2024.12.1 +563) and GraphPad Prism v10.5.0 (GraphPad Software, San Diego, CA, USA). Continuous and categorical data were expressed as means (standard deviation) and frequency (percentage), respectively. Normality of continuous variables was assessed using the D'agostino & Pearson test. Differences between groups were assessed using the Wilcoxon rank-sum test for continuous data and Fisher's exact test for categorical data. Nonlinear associations between ABG-derived acid-base parameters and outcomes were modeled using multivariate generalized additive model (GAM)[34,35] including relevant covariates (age, coronary perfusion pressure (CPP), number of shocks and time to ROSC for animal models and age, gender, body weight, initial presenting rhythm, CPP and time to ROSC for patient cohort) as adjustment terms. Each parameter (pH, BE and lactate levels) was added separately to the adjusted model to evaluate its incremental predictive value for 24 h mortality and poor neurological outcome. Model discrimination was compared by the area under the receiver operating characteristic curve (AUC) and the DeLong test. The model fitting effects were evaluated using Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Generalized Cross-Validation (GCV) and Coefficient of Determination (R^2/*R*-squared). Optimal cutoff values were determined using the Youden index (J = sensitivity + [specificity − 1]). Correlations between variables were explored using linear regression analysis, and the degree of association was reported using the Spearman's rank correlation coefficient. Statistical significance was set at p-value <0.05.

Results

Study1: rat model of CA/CPR

24 h mortality

Comparing with survivors, non-survivors were older ($p < 0.05$) and showed a lower pH ($p = 0.001$), a worse BE ($p < 0.001$) and a higher lactate ($p < 0.001$) at 4 h post-ROSC (Table 1A). pH, BE and lactate were subsequently entered into the adjusted model individually to assess their incremental predictive contribution to 24-h mortality. ROC curves were plotted (Fig. 2A), and the corresponding AUCs were 0.796 (95%CI: 0.635–0.956) for pH, 0.980 (95%CI: 0.946–1.000) for BE, 0.959 (95%CI: 0.896–1.000) for lactate. A statistically significant difference in AUCs was observed only between pH and BE ($p = 0.035$). pH, BE and lactate levels measured 4 h after resuscitation were independent predictors of 24 h mortality, with the most accurate predictive model incorporating BE, followed by lactate and pH. This model emerged as the most reliable predictor based on the lowest AIC, BIC and GVC values, alongside the highest AUC and R^2 values (Fig. 2A and Table 2A). The optimal BE cut-off value to predict 24 h mortality was ≤ -10.5 mmol/L (sensitivity 100%, specificity 77.3%); for lactate, it was ≥ 1.995 mmol/L (sensitivity 93.8%, specificity 92.9%) and for pH the threshold was ≤ 7.315 (sensitivity 81%,

Table 1 – Subjects characteristics of rat model of CA/CPR (A), pig model of CA/CPR (B, C) and patient cohort (D, E). (A) Subjects characteristics for rat model of CA/CPR stratified according to 24-h mortality status (survivor vs. non-survivors). (B) Subjects characteristics of pig model of CA/CPR stratified according to 24-h mortality status (survivor vs. non-survivors) and (C) according to neurological outcome at 96 h post resuscitation (good-OPC vs. poor-OPC). (D) Patient cohort stratified according to hospital mortality status (survivor vs. non-survivors) and (E) according to neurological outcome at ICU discharge (good-CPC vs. poor-CPC). BE indicates base excess; BL, baseline; CPC, cerebral performance category; CPP, coronary perfusion pressure; OPC, overall performance category; ROSC, return of spontaneous circulation.

A

		24-h mortality		
Variables	***n***	**Non-survivors *n* = 32[a]**	**Survivors *n* = 26[a]**	***p*-value[b]**
Age (weeks)	46	30.1 (3.5)	27.6 (3.7)	0.008
CPP	52	25.6 (4.6)	24.0 (5.2)	0.3
Time to ROSC (s)	58	972 (15)	967 (13)	0.085
n shocks	58	2 (1)	2 (1)	0.6
pH BL	52	7.44 (0.04)	7.45 (0.02)	0.4
pH 2 h	54	7.26 (0.10)	7.35 (0.05)	0.001
pH 4 h	43	7.09 (0.65)	7.37 (0.11)	0.001
$paCO_2$ BL	51	38.0 (5.1)	37.1 (4)	0.6
$paCO_2$ 2 h	54	33 (9)	38 (6)	0.01
$paCO_2$ 4 h	43	26 (9)	35 (10)	0.01
BE BL (mmol/L)	52	1.77 (3.24)	2.00 (2.17)	0.7
BE 2 h (mmol/L)	54	−11.2 (5.2)	−4.7 (2.9)	<0.001
BE 4 h (mmol/L)	44	−16.0 (7)	−5.0 (3)	<0.001
Lactate BL (mmol/L)	27	1.95 (1.78)	1.25 (0.63)	0.060
Lactate 2 h (mmol/L)	33	4.54 (2.63)	1.44 (0.68)	<0.001
Lactate 4 h (mmol/L)	30	4.80 (3.10)	1.27 (0.46)	<0.001

B

		24-h mortality		
Variables	***n***	**Non-survivors *n* = 15[a]**	**Survivors *n* = 49[a]**	***p*-value[b]**
Adrenaline	59			0.047
1 mg		7 (47%)	34 (77%)	
2 mg		5 (33%)	8 (18%)	
3 mg		3 (20%)	2 (5%)	
CPP	59	35 (14)	36 (15)	>0.9
Time to ROSC (s)	64	1270 (220)	1122 (195)	0.004
n shocks	64	21 (19)	13 (20)	0.019
pH BL	64	7.45 (0.05)	7.48 (0.06)	0.090
pH 2 h	64	7.26 (0.08)	7.35 (0.05)	<0.001
pH 4 h	56	7.31 (0.10)	7.41 (0.06)	<0.001
$paCO_2$ BL	64	37.83 (2.48)	37.28 (2.67)	0.5
$paCO_2$ 2 h	64	41.9 (7.6)	40.1 (4.4)	0.8
$paCO_2$ 4 h	56	40.2 (9.1)	40.6 (5.0)	0.5
BE BL (mmol/L)	64	2.1 (3.1)	4.0 (3.5)	0.034
BE 2 h (mmol/L)	63	−8.7 (3.0)	−3.3 (5.1)	<0.001
BE 4 h (mmol/L)	56	−6.0 (5.5)	1.4 (3.9)	<0.001
Lactate BL (mmol/L)	26	2.87 (2.50)	1.86 (0.67)	0.5
Lactate 2 h (mmol/L)	25	7.31 (1.65)	8.18 (4.25)	<0.9
Lactate 4 h (mmol/L)	19	6.05 (4.08)	4.55 (3.33)	0.5

C
Poor neurological outcome

Variables	*n*	Good-OPC *n* = 31[a]	Poor-OPC *n* = 33[a]	*p*-value[b]
Adrenaline	59			0.6
1 mg		22 (76%)	19 (63%)	
2 mg		5 (17%)	8 (27%)	
3 mg		2 (7%)	3 (10%)	
CPP	59	38 (11)	34 (12)	0.4
Time to ROSC (s)	64	1121 (165)	1191 (241)	0.8
n shocks	64	15 (21)	15 (18)	0.8
pH BL	64	7.48 (0.06)	7.46 (0.06)	0.2
pH 2 h	64	7.37 (0.07)	7.29 (0.09)	<0.001
pH 4 h	56	7.42 (0.05)	7.36 (0.10)	0.014
$paCO_2$ BL	64	37.12 (2.77)	37.68 (2.48)	0.3
$paCO_2$ 2 h	64	39.4 (3.6)	41.5 (6.4)	0.4
$paCO_2$ 4 h	56	40.6 (3.9)	40.5 (7.7)	0.4
BE BL (mmol/L)	64	3.8 (3.8)	3.3 (3.3)	0.6
BE 2 h (mmol/L)	63	−2.5 (5.0)	−6.4 (4.8)	0.003
BE 4 h (mmol/L)	56	1.7 (3.7)	−1.9 (5.8)	0.027
Lactate BL (mmol/L)	26	1.92 (0.76)	2.52 (2.13)	0.7
Lactate 2 h (mmol/L)	25	6.87 (4.54)	8.47 (2.40)	0.048
Lactate 4 h (mmol/L)	19	3.56 (2.64)	6.82 (3.85)	0.079

D
ICU mortality

Variables	*n*	Non-survivors *N* = 21[a]	Survivors *N* = 40[a]	*p*-value[b]
Age	61	65 (13)	59 (14)	0.027
Gender	61			0.4
Female		3 (14%)	3 (8%)	
Male		18 (86%)	37 (93%)	
Body weight	61	77 (21)	80 (14)	0.6
Rhythm	61			0.057
Shockable rhythm		13 (62%)	34 (85%)	
Non-shockable rhythm		8 (38%)	6 (15%)	
Adrenaline	59			0.017
0 mg		2 (10%)	15 (38%)	
1 mg		2 (10%)	12 (31%)	
2 mg		4 (20%)	3 (8%)	
3 mg		3 (15%)	2 (5%)	
4 mg		4 (20%)	3 (8%)	
5 mg		1 (5%)	2 (5%)	
6 mg		1 (5%)	1 (3%)	
7 mg		1 (5%)	1 (3%)	
8 mg		2 (10%)	0	
Time to ROSC (min)	61	33 (20)	21 (14)	0.01
n shock	59	2 (2)	3 (3)	0.3
pH	61	7.32 (0.10)	7.36 (0.09)	0.2
$paCO_2$	61	38 (8)	39 (9)	0.8
BE (mmol/L)	61	−6.0 (4.5)	−3.6 (4.0)	0.023
Lactate (mmol/L)	61	4.43 (2.59)	2.52 (1.79)	<0.001

(*continued on next page*)

Table 1 (continued)

		E Poor neurological outcome		
Variables	***N***	**Good-CPC *N* = 33[a]**	**Poor-CPC *N* = 28[a]**	***p*-value[b]**
Age	61	59 (14)	64 (13)	0.035
Gender	61			0.4
Female		2 (6%)	4 (14%)	
Male		31 (94%)	24 (86%)	
Body weight	61	80 (13)	78 (20)	0.5
Rhythm	61			0.14
Shockable rhythm		28 (85%)	19 (68%)	
Non-shockable rhythm		5 (15%)	9 (32%)	
Adrenaline	59			0.005
0 mg		14 (43%)	3 (12%)	
1 mg		11 (33%)	3 (12%)	
2 mg		3 (9%)	4 (15%)	
3 mg		1 (3%)	4 (15%)	
4 mg		3 (9%)	4 (15%)	
5 mg		1 (3%)	2 (8%)	
6 mg		0	2 (8%)	
7 mg		0	2 (8%)	
8 mg		0	2 (8%)	
Time to ROSC (min)	61	18 (13)	33 (19)	0.001
n shock	59	2 (2)	3 (3)	0.4
pH	61	7.37 (0.08)	7.32 (0.11)	0.10
$paCO_2$	61	38 (8)	39 (10)	>0.9
BE (mmol/L)	61	−3.3 (3.3)	−5.7 (5.0)	0.007
Lactate (mmol/L)	61	2.09 (1.30)	4.46 (2.51)	<0.001

[a] Mean (SD); *n* (%).
[b] Wilcoxon rank sum test; Fisher's exact test.

specificity 72.7%). Analyses performed at 2 h post-ROSC are detailed in the Supplemental Methods.

Poor neurological outcome

At 4 h post-ROSC we observed a positive correlation of pH ($r = 0.460$, $p < 0.005$, 95%CI: 0.155–0.685) and BE ($r = 0.817$, $p < 0.0001$, 95%CI: 0.670–0.902), and a negative correlation of lactate ($r = -0.777$, $p < 0.0001$, 95%CI: −0.892 to −0.566) with NDS assessed at 24 h after resuscitation (Fig. 2B). Analyses performed at 2 h post-ROSC are detailed in the Supplemental Methods.

Sudy2: pig model of CA/CPR

24 h mortality

Comparing with survivors, non-survivors showed a longer time to ROSC ($p < 0.005$), a higher number of shocks ($p < 0.05$), lower pH ($p < 0.001$) and a worse BE ($p < 0.001$) at 4 h post-ROSC (Table 1B). ROC curves were plotted (Fig. 3A); and the corresponding AUCs were 0.908 (95%CI: 0.826–0.990) for pH, 0.933 (95%CI: 0.863–1.000) for BE, 0.798 (95%CI: 0.588–1.000) for lactate. The comparison of AUCs revealed no statistical difference among the three parameters. pH, BE and lactate levels measured 4 h after resuscitation were independent predictors of 24 h mortality, with the most accurate predictive model incorporating BE, followed by lactate and pH. Evaluation of model performance indicated that this model was the most robust predictor, combining the lowest GCV with the highest AUC and R^2 values (Fig. 3A and Table 2B). The optimal BE cut-off value to predict 24 h mortality was ≤ -3.5 (sensitivity 89.1%, specificity 70%); for lactate, it was ≥ 3.58 mmol/L (sensitivity 58.3%, specificity 71.4%) and for pH the threshold was ≤ 7.36 (sensitivity 82.6%, specificity 80%). Analyses performed at 2 h post-ROSC are detailed in the Supplemental Methods.

Poor neurological outcome

Compared with those in good-OPC group, pigs in poor-OPC group showed a lower pH ($p < 0.05$) and a worse BE ($p < 0.05$) at 4 h post ROSC (Table 1C). ROC curves were plotted (Fig. 3B); and the corresponding AUCs were 0.673 (95%CI: 0.515–0.831) for pH, 0.724 (95%CI: 0.576–0.872) for BE, 0.900 (95%CI: 0.760–1.000) for lactate. A statistically significant difference in AUCs was observed only between pH and BE ($p = 0.039$). pH, BE and lactate levels measured 4 h after resuscitation were independent predictors of poor neurological, with the most accurate predictive model incorporating lactate, followed by BE and pH. Among the models tested, this one proved the most reliable, as reflected by its minimal AIC, BIC values and maximal AUC and R^2 values (Fig. 3B and Table 2C). The optimal lactate cut-off value to predict poor neurological outcome was ≥ 3.58 mmol/L (sensitivity 77.8%, specificity 70%); for BE, it was ≤ -3.5 mmol/L (sensitivity 40%, specificity 93.5%) and for pH the threshold was ≤ 7.36 (sensitivity 52%, specificity 90.3%). Analyses performed at 2 h post-ROSC are detailed in the Supplemental Methods.

Study3: patient cohort

ICU mortality

Compared with those of survivors, patients in non-survival group showed a higher age ($p < 0.05$), a longer time to ROSC ($p < 0.01$),

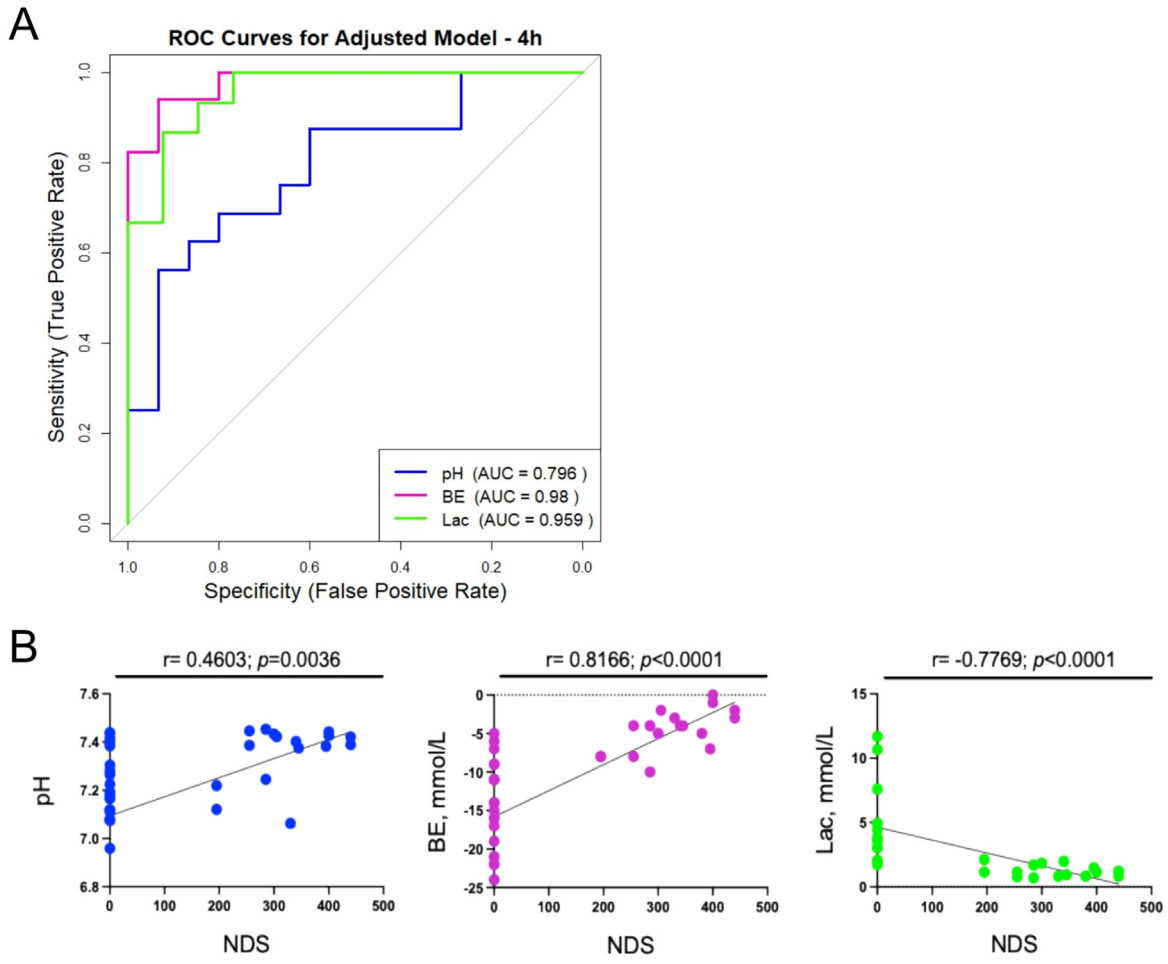

Fig. 2 – Rat model of CA/CPR: ROC curves of pH, BE and lactate measured at 4 h post-ROSC (A) and correlation between pH, BE and lactate measured 4 h post-ROSC with NDS assessed at 24 h after resuscitation (B). (A) The multivariate regression models were adjusted for age, CPP and time to ROSC. (B) Scatter plot illustrating the relationship between pH, BE and lactate measured at 4 h post-ROSC with NDS assessed 24 h after resuscitation. Spearman's correlation coefficient plots.

AUC indicates area under the curve; BE, base excess; Lac, lactate; NDS, neurological deficit score; ROC, receiver operating characteristics.

a worse BE ($p < 0.05$) and a higher lactate ($p < 0.001$) at ICU admission (Table 1D). ROC curves were plotted (Fig. 4A); and the corresponding AUCs were 0.830 (95%CI: 0.724–0.936) for pH, 0.832 (95%CI: 0.731–0.933) for BE, 0.839 (95%CI: 0.738–0.940) for lactate. The comparison of AUCs revealed no statistical difference among the parameters. pH, BE and lactate levels measured at ICU admission were independent predictors of mortality, with the most accurate predictive model incorporating BE, followed by lactate and pH. This model emerged as the slightly superior predictor based on the lowest AIC, BIC and GVC and highest R^2 values, despite lowest AUC values (Fig. 4A and Table 2D). The optimal BE cut-off value to predict mortality was ≤ -5.4 mmol/L (sensitivity 80%, specificity 57.1%); for lactate, it was ≥ 2.75 mmol/L (sensitivity 72.5%, specificity 81%) and for the threshold was ≤ 7.293 (sensitivity 82.5%, specificity 38.1%).

Poor neurological outcome

Compared with those of good-CPC, patients in poor-CPC group showed a higher age ($p < 0.05$), a longer time to ROSC ($p < 0.001$), a worse BE ($p < 0.05$) and a higher lactate ($p < 0.001$) at ICU admission (Table 1E). ROC curves were plotted (Fig. 4B); and the corresponding AUCs were 0.835 (95%CI: 0.734–0.937) for pH, 0.835 (95%CI: 0.735–0.936) for BE, 0.884 (95%CI: 0.793–0.945) for lactate. The comparison of AUCs revealed no statistical difference among the parameters. pH, BE and lactate levels measured at ICU admission were independent predictors of poor neurological outcome, with the most accurate predictive model incorporating lactate, followed by BE and pH. Among the models tested, lactate proved the most reliable, as reflected by its minimal AIC, BIC and GCV values and maximal AUC and R^2 values (Fig. 4B and Table 2E). The optimal lactate cut-off value to poor neu-

Table 2 – Comparison of predictive models in rat model of CA/CPR (A), pig model of CA/CPR (B, C) and patient cohort (D, E). (A)Comparison of predictive models for 24-h mortality in rat model of CA/CPR. The multivariate regression models were adjusted for age, CPP and time to ROSC. (B) Comparison of predictive models for 24-h mortality and (C) for poor neurological outcome in pig model of CA/CPR. The multivariate regression models were adjusted for CPP, number of shocks and time to ROSC for pH and BE; while for CPP and time to ROSC for lactate. (D) Comparison of predictive models for ICU mortality and (E) for poor neurological outcome in patient cohort. The multivariate regression models were adjusted for age, gender, body weight, initial presenting rhythm CPP, and time to ROSC. AIC indicates Akaike information criterion; AUC, area under the Receiver operating characteristics curve; BE, base excess; BIC, Bayesian information criterion; CPP, coronary perfusion pressure; GCV, generalized cross-validation; ICU, intensive care unit; ROSC, return of spontaneous circulation; lac, lactate; NPV, negative predictive value; PPV, positive predictive value, R^2, R-squared/coefficient of determination.

A

***Adjusted model* for age, CPP and time to ROSC**

	n surv	*n* non-surv	PPV	NPV	AUC	AIC	BIC	GCV	R^2
Time point: 4 h									
pH	21	22	0.74	0.80	0.796	51.441	60.045	0.297	0.035
BE	22	22	0.82	1	0.980	24.062	32.856	0.120	0.606
Lac	16	14	0.94	0.93	0.959	35.637	43.630	0.202	0.357

B

***Adjusted model* for CPP, *n* shock and time to ROSC**

	n surv	*n* non-surv	PPV	NPV	AUC	AIC	BIC	GCV	R^2
Time point: 4 h									
pH	46	12	1	0.53	0.908	39.049	50.400	0.126	0.260
BE	46	12	1	0.53	0.933	33.851	45.202	0.113	0.335
Lac	15	9	1	0.64	0.798	31.008	35.731	0.284	0.088

C

***Adjusted model* for CPP, *n* shock and time to ROSC**

	n good	*n* poor	PPV	NPV	AUC	AIC	BIC	GCV	R^2
Time point: 4 h									
pH	31	25	0.65	0.71	0.673	78.347	89.938	0.264	0.035
BE	31	25	0.90	0.71	0.724	73.778	85.368	0.242	0.118
Lac	10	9	0.75	1	0.900	28.485	33.217	0.249	0.254

D

***Adjusted model* for age, gender, body weight, initial presenting rhythm and time to ROSC**

	n surv	*n* non-surv	PPV	NPV	AUC	AIC	BIC	GCV	R^2
Time point: ICU admission									
pH	40	21	0.91	0.62	0.830	80.811	97.698	0.216	0.166
BE	40	21	0.87	0.67	0.832	79.509	96.396	0.212	0.184
Lac	40	21	0.88	0.65	0.839	80.370	97.260	0.215	0.172

E

***Adjusted model* for age, gender, body weight, initial presenting rhythm and time to ROSC**

	n good	*n* poor	PPV	NPV	AUC	AIC	BIC	GCV	R^2
Time point: ICU admission									
pH	33	28	0.83	0.76	0.835	85.639	102.53	0.234	0.180
BE	33	28	0.86	0.75	0.835	85.073	101.96	0.232	0.187
Lac	33	28	0.81	0.90	0.884	80.342	97.229	0.215	0.248

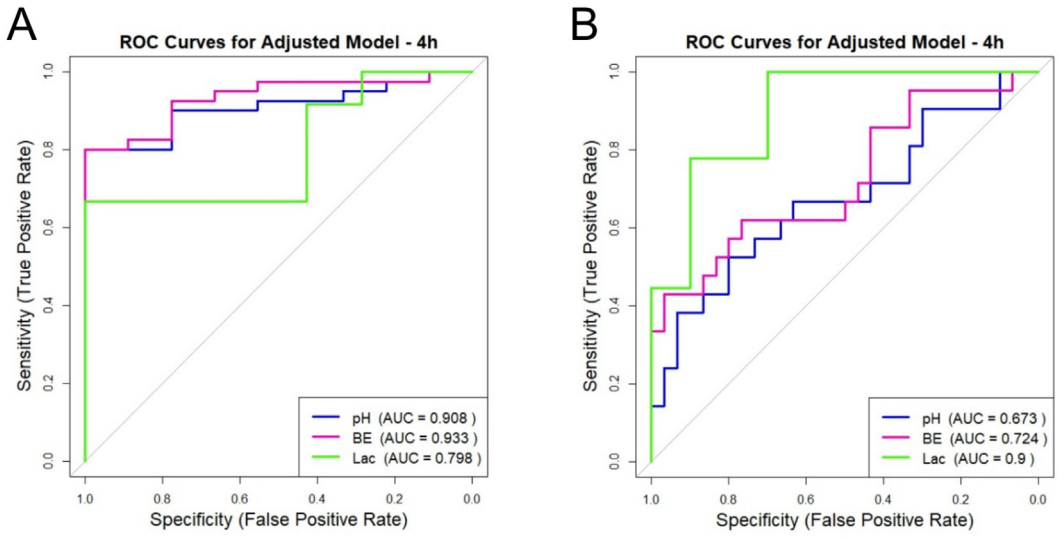

Fig. 3 – Pig model of CA/CPR: ROC curves of pH, BE and lactate measured 4 h post-ROSC for 24-h mortality (A) and for poor neurological outcome (B).

The multivariate regression models were adjusted for CPP, number of shocks and time to ROSC for pH and BE; while for CPP and time to ROSC for lactate.

AUC indicates area under the curve; BE, base excess; Lac, lactate; ROC, receiver operating characteristics.

rological outcome was ≥2.75 mmol/L (sensitivity 78.6%, specificity 81.8%); for BE, it was ≤−5.4 mmol/L (sensitivity 60.7%, specificity 84.8%) and for pH the threshold was ≤7.388 (sensitivity 82.1%, specificity 42.4%).

Discussion

Our study evaluated the prognostic value of ABG-derived acid-base parameters for predicting mortality and neurological outcomes across two animal experimental models of CA/CPR. A predictive model based on pH, BE and lactate was developed for the first time in animals and further validated in human CA patients. Our findings were consistent across species, supporting the translational relevance of the results and the importance of continued use of animal models in cardiac arrest research. In our study, BE emerged as the strongest predictor of 24-h mortality across all three cohort. The optimal BE cut-off value were ≤−10.5 mmol/L in rat model, ≤−3.5 mmol/L in pig model and ≤−5.4 mmol/L in patients. BE quantifies the amount of base required to return the pH of a liter of fully oxygenated arterial blood to the physiological value of 7.40 under standard conditions (37°C, $PaCO_2$ of 40 mmHg).[36] In the context of CA, the abrupt interruption of circulation results in widespread tissue hypoxia, leading to the accumulation of acidic metabolic byproducts and the development of significant metabolic acidosis. While elevated lactate levels are commonly used to assess the severity of tissue hypoxia, they only partially explain the degree of metabolic acidosis observed following CA.[20] BE offers a more integrated measure, encompassing both lactate-dependent and lactate-independent components of metabolic disturbance.[37] A previous study reported a significant association between BE levels measured at the start of advance CPR and survival with favorable neurological outcome at 30-day after CA. Specifically, lower BE values were associated with decreased likelihood of survival with good neurological outcome.[20] Although previous studies reported only an association between BE and outcomes, we advanced these findings by developing a predictive model. This model establishes the prognostic value of BE for survival prediction after CA.

Once discussed survival outcomes, we proceed to discuss the implications of our findings for neurological outcomes. In our study, lactate was identified as the most reliable predictor of poor neurological outcome in both pig model and human patients. The optimal cut-off values were ≥3.58 mmol/L in pig model and ≥2.75 mmol/L in patients. Lactate is a key biomarker of impaired tissue oxygenation and altered cellular metabolism.[14] In the context of CA, its elevation reflects the profound metabolic disturbance caused by global ischemia during the no-flow period, followed by the injury associated with reperfusion. The initial increase in lactate levels is primarily driven by anaerobic glycolysis due to the lack of oxygen delivery during CA.[38] This is further exacerbated by the systemic inflammatory response triggered by reperfusion. After ROSC, persistently elevated lactate levels may result from a combination of factors (tissue hypoperfusion, myocardial dysfunction, mitochondrial injury and the continued presence of the underlying cause of arrest).[39] Several studies have identified lactate levels as predictor of long-term neurological outcome following CA, typically assessed several months post-event.[40–42] One study reported that lactate levels were predictive of neurological prognosis with an AUC of 0.735.[43] In the rat model, the assessment of neurological outcome was limited to correlation analyses, as no validated cut-off value for the NDS exists to dichotomize neurological outcomes as favorable and unfavorable. This lack of a standardized threshold prevented the development of a predictive model for neurological prognosis in this species. Despite this limitation, our results demonstrate a statistically significant correlation between NDS and both BE and lactate levels.

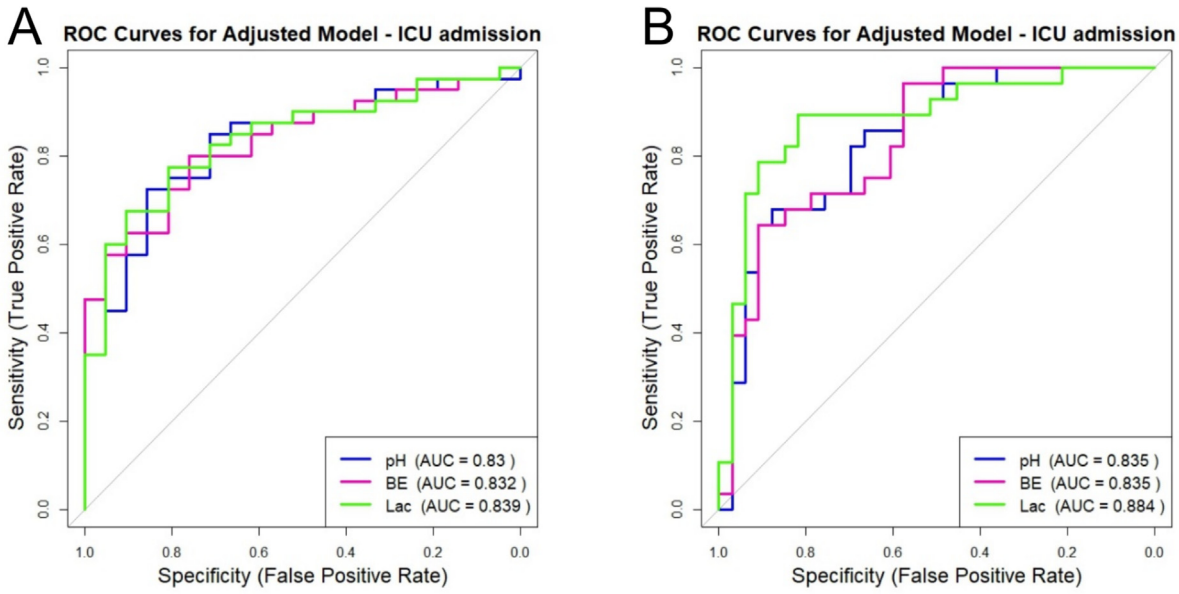

Fig. 4 – Patient cohort: ROC curves of pH, BE and lactate measured at ICU admission for hospital mortality (A) and for poor neurological outcome (B).
The multivariate regression models were adjusted for age, gender, body weight, initial presenting rhythm, CPP and time to ROSC.
AUC indicates area under the curve; BE, base excess; ICU, intensive care unit; Lac, lactate; ROC, receiver operating characteristics.

Limitations

This study has several limitations that should be acknowledged. First and foremost, it should be emphasized that this is a retrospective study and was not originally designed specifically for the purposes addressed here. Second, no validated cut-off value for the NDS currently exists to allow a dichotomous classification between favorable and unfavorable neurological outcomes. This lack of a standardized threshold prevented the development of a predictive model for neurological prognosis in rats. Third, the timing of ABG sampling differed between animal models and patients. Although small animals have a higher metabolic rate and may reach acid–base stabilization earlier, ICU admission remains a practical and clinically relevant time point, representing the earliest standardized opportunity to obtain ABG measurements after cardiac arrest. Fourth, since BE reflects both metabolic and respiratory components, changes in ventilation or CO_2 levels, frequently observed after ROSC[44–46] could partially confound its association with outcomes. Finally, there may be differences in treatment between ROSC and ABG sampling, including administration of intravenous fluids,[47] vasopressors, or other interventions (ventilation with Argon and administration of Esmolol[27,28]), may have influenced acid–base parameters and the observed associations.

Conclusion

In conclusion, our study demonstrates that pH, BE and lactate are independent early predictors of both 24-h mortality and neurological outcome following CA/CPR in experimental animal model in different species and in patients. BE showed the highest predictive value for mortality, while lactate was the strongest predictor for poor neurological outcome.

Data sharing

The datasets is available upon request of the corresponding author.

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CRediT authorship contribution statement

Francesca Callegari: Writing – original draft, Investigation, Formal analysis, Data curation. **Daria De Giorgio:** Investigation, Data curation. **Giulia Merigo:** Investigation, Data curation. **Marianna Cerrato:** Investigation, Data curation. **Ornella Tinelli:** Formal analysis. **Aurora Magliocca:** Investigation, Data curation. **Elisa R. Zanier:** Supervision. **Giuseppe Ristagno:** Supervision, Investigation, Conceptualization. **Francesca Fumagalli:** Supervision, Investigation, Conceptualization.

Declaration of competing interest

GR is member of the editorial board of Resuscitation Plus; AM is associate editor of Resuscitation Plus. All other authors declare no conflict.

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Not applicable.

Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.resplu.2026.101228.

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