

# Clinical implication of relative hypoventilation in resuscitated cardiac arrest patients.

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# Introduction

- Current guidelines recommend **mild hypoventilation (PaCO<sub>2</sub> 40-45mmHg)**
- However, **hyperventilation is a physiological response** if there is significant metabolic acidosis
- Hypoventilation can lead to significant **unadjusted metabolic acidosis** which can lead to **hemodynamic instability**

# Hypothesis

Relative hypoventilation exposure (RHE) is associated with poor neurologic outcome because of its impact on MAP.

1. RHE is more closely associated with neurologic outcome compared to Absolute hypoventilation exposure (AHE)
2. RHE is an independent risk factor of poor neurologic outcome.
3. RHE is associated with MAP.
4. MAP mediate the impact of RHE on neurologic outcome.

# How we defined relative hypoventilation

$$\text{pH} = 6.1 + \log_{10} \left( \frac{[\text{HCO}_3^-]}{0.0307 \times p_{\text{CO}_2}} \right)$$

- Relative pCO2 excess =

Current pCO2 - (Bicarbonate/0.03)/10^(target pH - 6.1)

# RHE and AHE in this study

- **RHE: Time-weighted average of the difference** between current pCO<sub>2</sub> level and calculated pCO<sub>2</sub> level to achieve neutral pH (7.4)
- **AHE: Time-weighted average of the difference** between current pCO<sub>2</sub> level and normal pCO<sub>2</sub> level (40mmHg)

# Methods

- Hypothesis 1: RHE vs. AHE
  - Significance of difference in C-statistics
- Hypothesis 2: RHE is an independent risk factor of poor n. outcome.
  - Backward stepwise regression using BIC
- Hypothesis 3: RHE is associated with MAP.
  - Random effect model (treating individual difference as random effect)
- Hypothesis 4: MAP is a key mediator
  - Mediation analysis

# Population

- OHCA patients survived more than 24 hours after sustained ROSC
  - Used **all** measurements within 24 hours post-ROSC
- Exclusion criteria
  - Age < 18
  - ECMO
  - Patients not survived more than 24 hours
- 232 patients were included.

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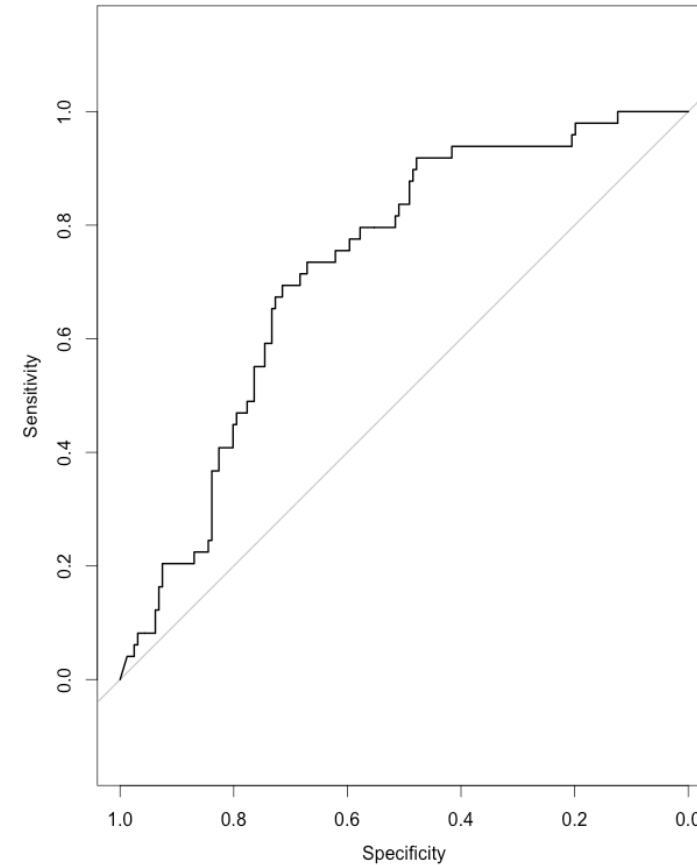
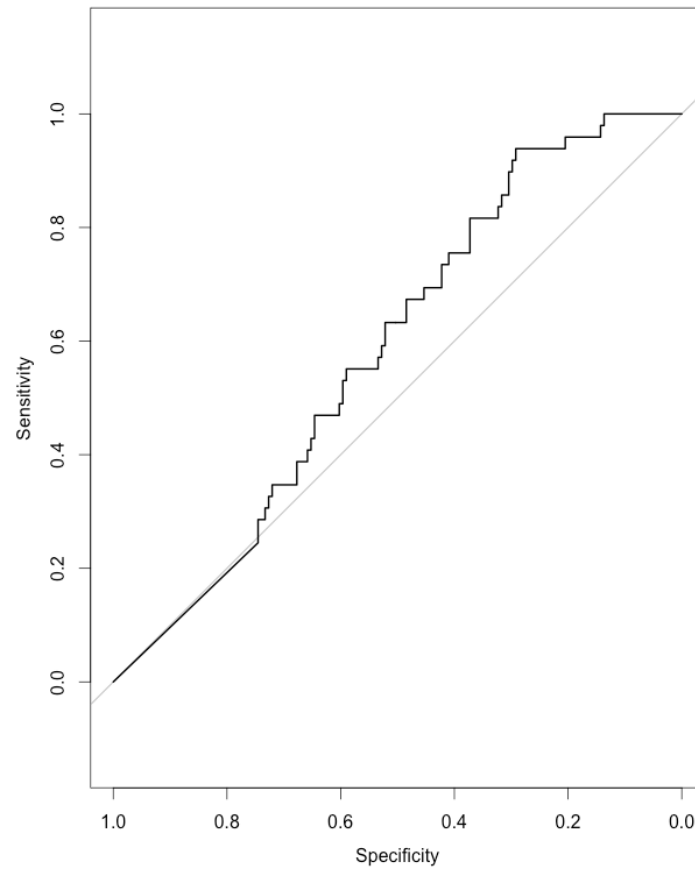




# Univariable logistic regression

	Estimates	p-value
age	-0.04	0.000
male	0.92	0.010
wit_bys	-0.05	0.871
wit_emt	0.34	0.366
pub_place	1.19	0.000
cardiac	1.88	0.000
shockable	2.79	0.000
byst_compr	0.70	0.020
pCO2_e	-0.14	0.020
pCO2_d	-0.03	0.403
pCO2_re	-0.16	0.000
pCO2_rd	0.06	0.505
pO2_e	0.00	0.717
pO2_d	-0.03	0.191
HCO3_a	0.19	0.000
Hct	0.08	0.001
WBC	0.01	0.612
PLT	0.01	0.001
c_Cr	-0.20	0.173
BUN	-0.03	0.029
Bilirubin	-0.51	0.168
Albumin	1.39	0.000
PTINR	-2.20	0.002
CRP	-0.20	0.014

# Comparison between RHE and AHE



C-statistics 0.589 vs. 0.726,  $p < .001$

# Multivariable models

- Used only variables with  $p$ -value $<0.1$  in univariable logistic regression
  - pCO2\_re (time-weighted exposure)
  - HCO3\_a (time-weighted average)
  - Age, male, pub\_place, cardiac, shockable, byst\_compr,
  - Hct, PLT, BUN, Albumin, PTINR, CRP

# Model 1: RHE and HCO<sub>3</sub>

- Multivariable logistic regression

Coefficients:

	Estimate	Std. Error	z value	Pr(> z )	
(Intercept)	-2.75940	1.11238	-2.481	0.01311	*
a_pCO <sub>2</sub> _re	-0.12638	0.03869	-3.267	0.00109	**
a_HCO <sub>3</sub> _a	0.13629	0.05439	2.506	0.01221	*

# Model 2: RHE + HCO3 + O2 exposures

- Multivariable logistic regression

Coefficients:

	Estimate	Std. Error	z value	Pr(> z )	
(Intercept)	-2.530998	1.237120	-2.046	0.04077	*
a_pCO2_re	-0.123351	0.039128	-3.152	0.00162	**
a_HCO3_a	0.136625	0.055563	2.459	0.01394	*
a_pO2_e	-0.001361	0.004809	-0.283	0.77715	
a_pO2_d	-0.026374	0.029021	-0.909	0.36347	

# Model 3: Full model

- Backward stepwise elimination using BIC criteria

Coefficients:

	Estimate	Std. Error	z value	Pr(> z )	
(Intercept)	1.86434	0.94026	1.983	0.04739	*
a_pCO2_re	-0.12504	0.04655	-2.686	0.00722	**
age	-0.05939	0.01510	-3.934	8.34e-05	***
cardiac	1.53815	0.55135	2.790	0.00527	**
shockable	1.34688	0.49190	2.738	0.00618	**

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# Random effect model (Univariable)

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	162.8830	12.763	
	pCO2_re	0.2333	0.483	-0.25
Residual		217.1201	14.735	

Number of obs: 1596, groups: id, 209

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t )
(Intercept)	88.68159	1.12347	177.06000	78.936	< 2e-16 ***
pCO2_re	-0.30861	0.06681	123.73000	-4.619	9.52e-06 ***

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Signif. codes: 0 '\*\*\*' 0.001 '\*\*' 0.01 '\*' 0.05 '.' 0.1 ' ' 1





# Adjusted for spot pO2 and HCO3

Random effects:

Groups	Name	Variance	Std.Dev.	Corr
id	(Intercept)	158.3743	12.5847	
	pCO2_re	0.2126	0.4611	-0.21
	Residual	224.4577	14.9819	

Number of obs: 1244, groups: id, 200

Fixed effects:

	Estimate	Std. Error	df	t value	Pr(> t )	
(Intercept)	8.106e+01	3.351e+00	9.750e+02	24.192	< 2e-16	***
pCO2_re	-2.498e-01	7.266e-02	1.154e+02	-3.438	0.000816	***
pO2	8.651e-04	8.415e-03	1.228e+03	0.103	0.918137	
HCO3	4.178e-01	1.547e-01	1.095e+03	2.700	0.007040	**

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# Mediation analysis

- The possible impact of increased RHE may be partially mediated (27.7%) by exposure to low MAP (<80 mmHg)

## Causal Mediation Analysis

### Quasi-Bayesian Confidence Intervals

	Estimate	95% CI Lower	95% CI Upper	p-value
ACME (control)	-0.00689	-0.01280	-0.00160	0.01
ACME (treated)	-0.00684	-0.01283	-0.00159	0.01
ADE (control)	-0.01880	-0.03665	-0.00613	0.00
ADE (treated)	-0.01875	-0.03660	-0.00611	0.00
Total Effect	-0.02564	-0.04206	-0.01173	0.00
Prop. Mediated (control)	0.27847	0.06165	0.56416	0.01
Prop. Mediated (treated)	0.27645	0.06224	0.56231	0.01
ACME (average)	-0.00687	-0.01282	-0.00160	0.01
ADE (average)	-0.01878	-0.03663	-0.00612	0.00
Prop. Mediated (average)	0.27746	0.06205	0.56235	0.01

# Conclusion

- RHE was an independent risk factor for poor outcome in OHCA patients.
- Increased RHE was associated with MAP level.
- The association between RHE and long-term outcome might be partially explained by the mediation effect of MAP