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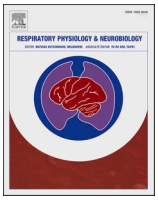

Short communication

Respiratory rate responses to both hypercapnia and acidaemia are modified by age in patients with acidosis

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ABSTRACT

Objective: To explore the associations between arterial pO_2, pCO_2 and pH and how these are modified by age.
Methods: An analysis of 2598 patients admitted with a diagnosis of Covid-19 infection to a large UK teaching hospital.
Results: There were inverse associations for arterial pO_2, pCO_2 and pH with respiratory rate. The effects of pCO_2 and pH on respiratory rate were modified by age; older patients had higher respiratory rates at higher pCO_2 ($p = 0.004$) and lower pH ($p = 0.007$) values.
Conclusions: This suggests that ageing is associated with complex changes in the physiological feedback loops that control respiratory rate. As well as having clinical relevance, this may also impact on the use of respiratory rate in early warning scores across the age range.

1. Introduction

Respiratory physiology underpins much of pulmonary medicine, and measures of oxygen (O_2), carbon dioxide (CO_2) and acidity in arterial blood samples are commonly used in patients with respiratory failure to assist clinical management. Breathing is regulated by the brainstem with inputs from peripheral and central chemoreceptors, augmented by cortical control (Vaporidi et al., 2020). The main feedback mechanism that is used to respond to changes in arterial blood gases and pH is the respiratory rate; which increases in response to acute reductions in arterial O_2 or higher blood CO_2 or acidaemia (West, 2000).

However, there are no epidemiological studies of the association of these arterial gases with respiratory rate in populations of unventilated patients with a broad range of respiratory failure of a single aetiology outside the intensive care unit setting. Neurone loss and decreased brain function are associated with aging (Mattson and Arumugam, 2018), and it is likely that other activities and reflexes that involve the brain will also change as patients get older. We hypothesised that age would be an independent risk factor that modified the association between arterial oxygen, carbon dioxide levels and pH with respiratory rate in patients who had either confirmed or clinically suspected Covid-19 infection.

2. Methods

A database of all patients admitted to Nottingham University Hospital with suspected and confirmed COVID infection between 21 February 2020 and 31 December 2021 (Crooks et al., 2022) was constructed that included all adult (>18 years) patients with an arterial blood gas sample and respiratory rate recorded within 30 min of each other. Patients with blood alkalosis defined as a pH of greater than 7.45 were excluded to permit linear modelling through the normal and acidotic ranges as these are of the greatest clinical importance. Patients who recorded respiratory rate greater than 50bpm were excluded. Data were not available from patients who were on intensive care units.

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We assessed the association between respiratory rate and the eligible arterial pO_2, pCO_2, and pH measurements corrected for temperature. These associations were adjusted by age and sex using a linear mixed effects regression model with a random intercept for each patient to adjust for repeated measurements. Data analysis was performed using R version 4.2.2 (R Core Team, 2022).

3. Results

2598 patients had eligible paired arterial blood gas and respiratory rate measurements (a total of 4533 paired measurements were available, Table 1). After adjustment for age and sex, all three outcomes of interest, arterial pO_2, pCO_2 and pH were inversely associated with respiratory rate (Table 2).

Linear coefficients for the blood gas associations combined with the interaction term were calculated for 18, 40, 60, and 80-year olds. These showed that for pCO_2 ($p = 0.004$) there was a reduction in the inverse association with respiratory rate as age increases (Table 3, Supplementary Table). This association decreased for pH ($p = 0.007$) with increasing age.

4. Discussion

This is the first analysis to explore the association between respiratory rate and blood oxygen, carbon dioxide and pH levels in a large population of patients with a broad range of respiratory failure with a common aetiology. Inverse associations were observed between all three exposures of interest and respiratory rate, with effect modification of these associations with pCO_2 and pH by age.

The analysis confirmed clinical experience in demonstrating inverse associations between arterial O_2, CO_2 and pH, with respiratory rate. Central chemosensation responds to small changes in pH with high gain in order to maintain arterial pCO2 within tight bounds (Guyenet et al., 2010). In this real-world sample, acidaemia (due to either metabolic or respiratory acidosis) is therefore likely to be the primary driver of increased respiratory rate, with resulting reductions in pCO2 being a consequence of increased respiratory drive. This would explain the inverse association between pCO2 and respiratory rate shown here, as distinct from experimental manipulations of pCO2 that induce tachypnoea in a laboratory setting.

The observation that age is an important modifier of the associations with regard to CO_2 and pH has not been reported previously. A hypothetical male patient aged 20 years old with acidosis of pH 7.25 would be predicted as having a respiratory rate of 23.5 bpm, while his 90-year old male counterpart would have an equivalent rate of 25.5 bpm. Possible explanations for this might include increased chemosensory

Table 1
Description of study population.

Patients (n)	2598
Paired measurements (n)	4533
Gender (Male) n (%)	2398 (53%)
Age (years): < 30 years	132 (3%)
Age (years): 30–39 years	229 (5%)
Age (years): 40–49 years	347 (8%)
Age (years): 50–59 years	566 (12%)
Age (years): 60–69 years	1044 (23%)
Age (years): 70–79 years	1158 (26%)
Age (years): > 79 years	1057 (23%)
Median Respiratory Rates (breaths per minute) (IQR)	22 (19,28)
Median Temperature Corrected pO2, kPa (IQR)	8.88 (7.13–11.3)
Median Temperature Corrected pCO2, kPa (IQR)	5.68 (4.71–7.38)
Median pH, (IQR)	7.379 (7.316–7.421)
Median H+ (10^{-7} mmol)	4.178 (3.793–4.831)
Median HCO3, mmol/L (IQR)	25.3 (21.2–30.2)

Arterial Measurements collected within 30 min of Respiratory Rate measurement.
IQR = interquartile range.

Table 2
Association between arterial oxygen, carbon dioxide and pH measurements and respiratory rate adjusting for age and sex.

Variable	Respiratory rate in breaths per minute for each unit change in variable (95% confidence intervals)			
Age at admission, years	+ 0.01 (−0.01 to +0.02)	+ 0.01 (−0.01 to +0.02)	+ 0.01 (−0.01 to +0.02)	+ 0.01 (−0.01 to +0.02)
Female sex	-0.44 (−0.94 to +0.06)	-0.38 (−0.88 to +0.12)	-0.47 (−0.97 to +0.03)	-0.46 (−0.95 to +0.04)
Absolute arterial blood gas values per unit increment				
Arterial pO2, kPa	-0.05 (−0.08 to −0.02)			
Arterial pCO2, pKa		-0.14 (−0.24 to −0.04)		
Arterial pH			-5.42 (−7.68 to −3.16)	
H+ (10^{-7} moles)				+ 0.35 (+0.18 to +0.53)
Scaled arterial blood gases per standard deviation increment				
Arterial pO2, standardised kPa	-0.32 (−0.51 to −0.14)			
Arterial pCO2, standardised kPa		-0.33 (−0.57 to −0.09)		
Arterial pH, standardised			-0.49 (−0.69 to −0.28)	
H+ ,standardised moles				+ 0.41 (+0.21 to +0.61)

Statistical analysis using linear mixed effects model fitted with random intercept for patient to adjust for repeated measures.

Table 3
Contrast in mixed effects model with an interaction between blood gas measure and age as a continuous variable adjusted for sex.

	Change in respiratory rate in breaths per minute for each unit increase in arterial blood gas output (95% confidence intervals)
pO2, kPa x1	p value (Likelihood ratio test for interaction term) = 0.16 *
in 18-year old	-0.11 (−0.20 to −0.02)
in 40-year old	-0.07 (−0.11 to −0.03)
in 60-year old	-0.05 (−0.08 to −0.02)
in 80-year old	-0.03 (−0.07 to +0.00)
pCO2, kPa x1	p value (Likelihood ratio test for interaction term) = 0.004 *
in 18-year old	-0.83 (−1.32 to −0.35)
in 40-year old	-0.43 (−0.65 to −0.21)
in 60-year old	-0.22 (−0.34 to −0.11)
in 80-year old	-0.02 (−0.15 to +0.11)
pH, x1 unit	p value (Likelihood ratio test for interaction term) = 0.007 *
in 18-year old	+ 8.08 (−1.97 to +18.13)
in 40-year old	+ 0.03 (−4.52 to +4.58)
in 60-year old	-4.00 (−6.47 to +1.52)
in 80-year old	-8.02 (−10.96 to −5.07)
H+ , x10^{-7}moles	p value (Likelihood ratio test for interaction term) = 0.015 *
in 18-year old	-0.56 (−1.32 to +0.20)
in 40-year old	-0.01 (−0.35 to +0.33)
in 60-year old	+ 0.26 (+0.07 to +0.45)
in 80-year old	+ 0.54 (+0.31 to +0.77)

Age stratified coefficients from a linear combination of coefficients and interaction, for example linear coefficient for pCO2 in 40 year olds = $\beta_{[ArterialpCO2\_TTempcorrected]} + 40 * \beta_{[ArterialpCO2\_TTempcorrected]:[AGE\_AT\_ADMISSION]}$
Linear mixed effects model fitted with random intercept for patient to adjust for repeated measures.
*Generalised likelihood ratio test p value shown comparing model with interaction between age and blood gas measurement with nested model without interaction.

sensitivity with age, modification of the peripheral and central physiological feedback loops that control respiratory rate or reduced gas exchange efficiency necessitating a higher respiratory rate as compensation (Schaeffer et al., 2021).

The strengths of this analysis include the fact that data were available from all patients admitted to a single busy teaching hospital with a clinical diagnosis of Covid-19 infection. The study population included a broad range of ages of patients with differing degrees of severity of respiratory failure, which allowed the hypotheses of interest to be tested.

The limitations of these data are that as they are from the real world, they are not randomly sampled. However, this is unlikely to make the associations that have been reported invalid, as we have been able to explore the associations of interest across a broad spectrum of respiratory failure severity. Although measurement error exists with regard to respiratory rate (Fogarty et al., 2022), it is unlikely to be related to age and hence would not bias the analysis. One confounding factor that we were unable to adjust for was the use of medications that suppress respiratory drive such as opiates. Finally, we have generated linear models that incorporate age from a population with a median age of 69 years, and estimates for younger patients were inevitably based on less data than in older individuals.

5. Conclusions

As such, these data set the scene and highlight the need for further studies to clarify if these observations are generalisable to other populations, and especially if this is an observation that extends beyond patients with Covid-19 infection. They have implications for furthering our understanding of the broader effects of aging and emphasise that defining what can be considered a normal physiological response in the context of respiratory failure is likely to vary across the life course, and hence has implications for both clinical care and also the use of early warning scores across the age range (Vardy et al., 2022).

Clinical governance and approvals from regulatory bodies

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CRediT authorship contribution statement

AF and DS developed the hypothesis. JW, TC, CC, SB, JM, IJ, MS, SC, SH-P developed the database. CC did the statistical analysis. The first draft of the manuscript was written by AF and CM and edited by all of the manuscript's authors.

Declaration of Competing Interest

There are no competing interests for any author.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.resp.2023.104098.

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