

# Changes in central venous to arterial carbon dioxide gap (PCO<sub>2</sub> gap) in response to acute changes in ventilation

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## ABSTRACT

**Background** Early diagnosis of shock is a predetermining factor for a good prognosis in intensive care. An elevated central venous to arterial PCO<sub>2</sub> difference ( $\Delta$ PCO<sub>2</sub>) over 0.8 kPa (6 mm Hg) is indicative of low blood flow states. Disturbances around the time of blood sampling could result in inaccurate calculations of  $\Delta$ PCO<sub>2</sub>, thereby misrepresenting the patient status. This study aimed to determine the influences of acute changes in ventilation on  $\Delta$ PCO<sub>2</sub> and understand its clinical implications.

**Methods** To investigate the isolated effects of changes in ventilation on  $\Delta$ PCO<sub>2</sub>, eight pigs were studied in a prospective observational cohort. Arterial and central venous catheters were inserted following anaesthetisation. Baseline ventilator settings were titrated to achieve an EtCO<sub>2</sub> of 5±0.5 kPa (V<sub>T</sub> = 8 mL/kg, Freq = 14 ± 2/min). Blood was sampled simultaneously from both catheters at baseline and 30, 60, 90, 120, 180 and 240 s after a change in ventilation. Pigs were subjected to both hyperventilation and hypoventilation, wherein the respiratory frequency was doubled or halved from baseline.  $\Delta$ PCO<sub>2</sub> changes from baseline were analysed using repeated measures ANOVA with post-hoc analysis using Bonferroni's correction.

**Results**  $\Delta$ PCO<sub>2</sub> at baseline for all pigs was 0.76±0.29 kPa (5.7±2.2 mm Hg). Following hyperventilation, there was a rapid increase in the  $\Delta$ PCO<sub>2</sub>, increasing maximally to 1.35±0.29 kPa (10.1±2.2 mm Hg). A corresponding decrease in the  $\Delta$ PCO<sub>2</sub> was seen following hypoventilation, decreasing maximally to 0.23±0.31 kPa (1.7±2.3 mm Hg). These changes were statistically significant from baseline 30 s after the change in ventilation.

**Conclusion** Disturbances around the time of blood sampling can rapidly affect the PCO<sub>2</sub>, leading to inaccurate calculations of the  $\Delta$ PCO<sub>2</sub>, resulting in misinterpretation of patient status. Care should be taken when interpreting blood gases, if there is doubt as to the presence of acute and transient changes in ventilation.

## INTRODUCTION

For patients in the intensive care unit (ICU), measurements of blood gases are used for the assessment of acid–base and oxygenation status. Many of these patients suffer from sepsis, estimated to affect over 30 million people each year and contributing significantly to the number of hospital deaths.<sup>1</sup> One

## Key messages

- ▶ Can acute changes in ventilation influence the PCO<sub>2</sub> (cv-a) gap?
- ▶ Acute increases or decreases in ventilation can alter the PCO<sub>2</sub> (cv-a) gap by as much as 50%, in comparison to the values before the change.
- ▶ This novel study examines the effect of simulated hyperventilation and hypoventilation on the PCO<sub>2</sub> (cv-a) gap, with rapid simultaneous arterial and central venous sampling (every 30 s).

of the main factors predetermining the prognosis of a patient with sepsis is the presence of septic shock.<sup>2 3</sup> In the last decade, much research in this area has been focused on the early detection of shock.<sup>4–6</sup> An elevated CO<sub>2</sub> gap, measured by the difference in central venous ('cv') and arterial ('a') PCO<sub>2</sub> ( $\Delta$ PCO<sub>2</sub>) has been used as an early indicator of shock. Furthermore, the ratio of  $\Delta$ PCO<sub>2</sub> to the arterial-venous difference in oxygen content  $\Delta$ PCO<sub>2</sub>(cv-a)/ $\Delta$ tO<sub>2</sub>(a-cv) has been used to guide and assess the response of fluid resuscitation strategies.<sup>4 7–10</sup>

Previous studies have illustrated that significant changes in  $\Delta$ PCO<sub>2</sub> can be due to circulatory effects,<sup>4 6</sup> focussing on how venous blood could be modified due to, for example, reduced tissue perfusion and the CO<sub>2</sub> stagnation phenomenon. However, there are other situations that could alter the blood gas parameters in an ICU setting, including spontaneous breathing and/or adjustment of ventilator settings.<sup>11 12</sup> Disturbances around the time of blood sampling could result in inaccurate calculations of  $\Delta$ PCO<sub>2</sub> and other related parameters. The isolated effects of a disturbance in ventilation on the CO<sub>2</sub> gap have however, not been investigated.

In this study, we hypothesise that acute changes in ventilation affects arterial blood faster than central venous blood and that this may result in clinically significant changes



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in the  $\Delta\text{PCO}_2$ . The aim of this study was, therefore, to determine and quantify the influences of acute changes in ventilation on the  $\Delta\text{PCO}_2$ , concluding on the clinical significance of these changes when interpreting values of  $\Delta\text{PCO}_2$ .

## METHODS

This study was designed to investigate changes in ventilation on  $\Delta\text{PCO}_2$  without the concurrent effects of modification of this gap due to altered tissue perfusion, inclusive of microcirculatory functional shunting. As such, it was decided to study animals (pigs) without cardiovascular or respiratory disease, thus reflecting a more normal physiology. This study was conducted from June 2019 to April 2020 in the Biomedicine Laboratory at Aalborg University Hospital North, Aalborg, Denmark. Eight female Danish Landrace pigs were used for the study. The methods were in line with the Utstein recommendations for uniformity in animal studies.<sup>13</sup>

## Protocol

All pigs were anaesthetised for the duration of the study. The anaesthesia was performed according to local protocols, with total intravenous anaesthesia for the duration of the study, and the presence of indwelling arterial and central venous catheters for blood sampling. The location of the catheters was checked by measurement of the respective blood pressures. Each pig was subjected to both *hyperventilation* and *hypoventilation*, with the order of the change in ventilation being randomised.

### 1. Blood sampling

Simultaneous blood sample pairs were taken by two trained individuals from the arterial and central venous catheters. Samples were taken at baseline, and at 30, 60, 90, 120, 180, 240s after the acute change in ventilation. Syringes were capped and air bubbles removed, immediately after sampling. A third person helped ensure synchronisation of the sampling and assisted with the capping of the syringes. All samples were analysed immediately after, in the order they were taken, arterial before venous, on the same ABL800 blood gas analyser (Radiometer, Copenhagen, Denmark).

### 2. Ventilator settings

Mechanically ventilated patients are often on assist mode of ventilation, with spontaneous breathing.<sup>14</sup> For these patients, a sudden increase or decrease in respiratory rate is not uncommon,<sup>15</sup> the former if the patient becomes stressed and the latter if ventilator support levels are increased and respiratory drive

suppressed.<sup>16</sup> This study was designed to reflect similar sudden changes in ventilation by varying respiratory frequency. Ventilator settings at baseline and for hyperventilation and hypoventilation are detailed in [table 1](#). Baseline ventilator settings were titrated to achieve a baseline end tidal  $\text{CO}_2$  ( $\text{EtCO}_2$ ) of  $5\pm 0.5$  kPa. The changes in ventilation corresponded to modifications of respiratory frequency to a high level (28 breaths/min), or a low level (7 breaths/min) which corresponded to an increase of 100% and a decrease of 50% in alveolar ventilation (a dead space of 150 mL was assumed for calculations). The first ventilatory change lasted for 4 min after which it was reverted to baseline for at least 30 min before the pig was subjected to a second change in ventilation.  $\text{EtCO}_2$  and  $\text{SpO}_2$  were measured throughout the study.

## Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

## Statistical analysis

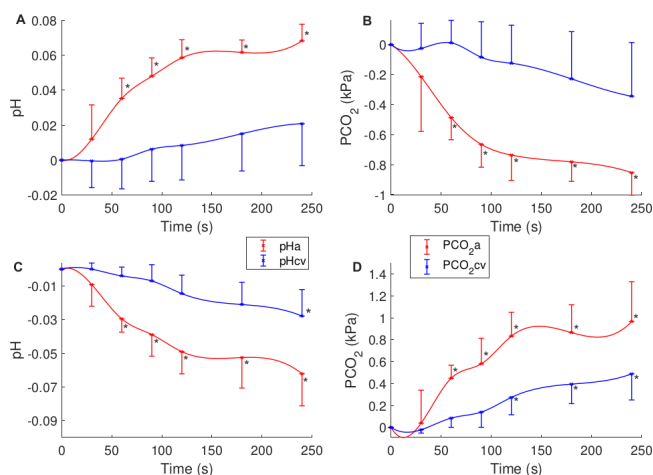
Eight pigs were studied with each one being subjected to both hyperventilation and hypoventilation. The data from the two changes in ventilation are presented as a change from baseline for pH and  $\text{PCO}_2$ .  $\Delta\text{PCO}_2$  was calculated using the difference between  $\text{PCO}_{2,\text{cv}}$  and  $\text{PCO}_{2,\text{a}}$ . Normality of data was tested using Shapiro Wilk's test and data were found to be normally distributed. Statistical comparisons of the timed arterial blood samples were compared using a repeated measures analysis of variance (ANOVA) followed by a post-hoc analysis comparing the average at each time point to the average at baseline using Bonferroni's correction. Similar analyses were conducted for central venous blood and  $\Delta\text{PCO}_2$  following hyperventilation and hypoventilation changes. All results are presented as mean $\pm$ SD, with  $p < 0.05$  considered statistically significant. Statistical analysis was conducted on SPSS V.25 (SPSS IBM Corp.).

## RESULTS

The eight pigs weighed an average of  $34.0\pm 8.7$  kg, and had mean values of pH and  $\text{PCO}_2$  at baseline of  $7.478\pm 0.050$  and  $5.34\pm 0.61$  kPa ( $40.1\pm 4.6$  mm Hg) for arterial blood, and  $7.440\pm 0.048$  and  $6.10\pm 0.70$  kPa ( $45.8\pm 5.3$  mm Hg) for central venous blood, respectively.

**Table 1** Ventilatory settings during baseline, hyperventilation and hypoventilation

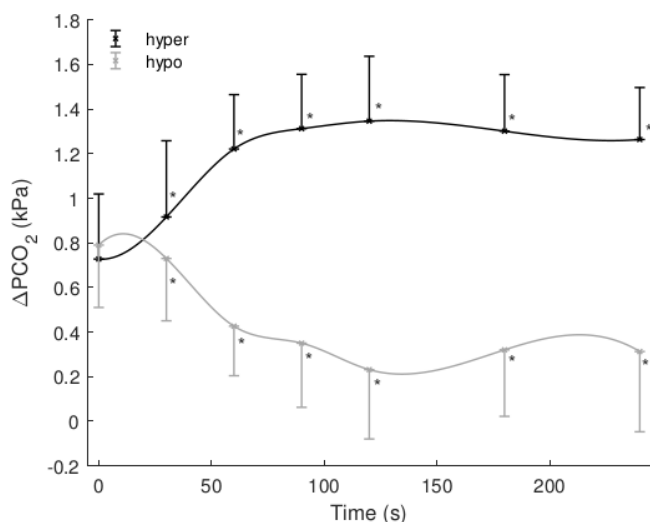
Parameters	Baseline	Hyperventilation	Hypoventilation
Tidal volume ( $V_T$ )	8 mL/kg	8 mL/kg	8 mL/kg
Respiratory frequency	$14\pm 2$ breaths/min	$28\pm 4$ breaths/min	$7\pm 1$ breaths/min
Criteria for termination		$\text{EtCO}_2 < 1.5$ kPa	$\text{SpO}_2 < 88\%$ $\text{EtCO}_2 > 6.5$ kPa



**Figure 1** Changes in arterial and central venous pH and  $\text{PCO}_2$  (kPa) following an acute change in ventilation. Changes from baseline in arterial (red, 'a') and central venous (blue, 'cv') pH and  $\text{PCO}_2$  (kPa) in response to acute hyperventilation (A, B) and hypoventilation (C, D). Presented as mean and SD (one sided error bars).  $n=8$ . \*Statistically significant when compared with baseline using a repeated measures analysis of variance and a post-hoc analysis with Bonferroni's correction ( $p<0.05$ ).

### Responses to hyperventilation and hypoventilation

Changes in pH and  $\text{PCO}_2$  from baseline at each sampling time are depicted in [figure 1](#) for both arterial and central venous blood. Following acute hyperventilation ([figure 1A,B](#)), values of arterial pH and  $\text{PCO}_2$  changed faster than venous and were significantly different from baseline at 60s ( $p<0.005$ ). The maximum arterial difference was observed at 120s with  $\text{pH}=0.059$  and  $\text{PCO}_2=-0.74$  kPa (5.5 mm Hg). There was no statistically



**Figure 2** Response of  $\Delta\text{PCO}_2$  to acute changes in ventilation. Changes in  $\Delta\text{PCO}_2$  (kPa) in response to acute hyperventilation (black) and hypoventilation (grey).  $n=8$ . \*Statistically significant when compared with baseline using a repeated measures analysis of variance and a post-hoc analysis with Bonferroni's correction ( $p<0.05$ ).

significant response observed in the central venous blood over the 4 min.

Following acute hypoventilation ([figure 1C,D](#)), there was a similar response in the arterial blood as with hyperventilation, with a rapid and statistically significant difference in values of pH and  $\text{PCO}_2$  seen 60s after the change in ventilation ( $p<0.005$ ). Central venous blood was significantly different from baseline at 120s for  $\text{PCO}_2$  ( $p<0.05$ ), while there appeared to be a statistically significant response in pH at 240s ( $p=0.035$ ). Oxygenation did not change for the duration of the study, where the pigs also had a stable and constant  $\text{FiO}_2$  and  $\text{SpO}_2$ .

### Effects on $\Delta\text{PCO}_2$

[Figure 2](#) illustrates the average changes in  $\Delta\text{PCO}_2$  following acute changes in ventilation. The average  $\Delta\text{PCO}_2$  at baseline was  $0.76\pm 0.29$  kPa ( $5.7\pm 2.2$  mm Hg). Following acute hyperventilation, there was a rapid increase in the  $\Delta\text{PCO}_2$ , with a maximal change of  $1.35\pm 0.29$  kPa ( $10.1\pm 2.2$  mm Hg). There was a corresponding decrease in the  $\Delta\text{PCO}_2$  following an acute hypoventilation, decreasing maximally to  $0.23\pm 0.31$  kPa ( $1.7\pm 2.3$  mm Hg). Changes in  $\Delta\text{PCO}_2$  in response to both changes in ventilation achieved statistical significance 30s following an acute change in ventilation ( $p<0.05$ ).

### DISCUSSION

The insertion of a central venous and arterial catheter is common practice for patient management in the intensive care setting, be it for monitoring, fluid and drug administration or blood sampling. Circulatory status of the patient can be assessed by calculation of various parameters using central venous and arterial blood gases, commonly  $\Delta\text{PCO}_2$ .<sup>17</sup> However, especially on assisted ventilation, acute changes in respiratory frequency and/or tidal volume can influence blood acid–base parameters. Previous studies have assessed the effects of circulatory changes on  $\Delta\text{PCO}_2$ .<sup>46</sup> This study is the first to assess the isolated effects of changes in ventilation on  $\Delta\text{PCO}_2$ . The study has demonstrated that  $\Delta\text{PCO}_2$  responds rapidly to acute changes in ventilation, with these changes due to the influences of ventilation on arterial blood, which are observed without delay, in comparison to central venous blood.

This study shows that acute changes in ventilation can result in  $\Delta\text{PCO}_2$  changes of  $\pm 0.6$  kPa. Normal values of  $\Delta\text{PCO}_2$  have previously been shown to be 0.8 kPa, with patients considered to have insufficient perfusion of the tissues if  $\Delta\text{PCO}_2$  is above this value.<sup>18</sup> Values of  $\Delta\text{PCO}_2$  have shown to be elevated to the range of 1.6 to 2 kPa (12–15 mm Hg) for patients with septic shock.<sup>19</sup> The  $\text{PCO}_2$  gap has been used in the intensive care departments as a surrogate to identify the onset of anaerobic metabolism, a measure of microcirculatory perfusion and to gauge fluid responsiveness during resuscitation for patients in shock.<sup>20</sup> A measurement of  $\Delta\text{PCO}_2$  concomitant with hypoventilation or hyperventilation

resulting in  $\Delta\text{PCO}_2$  changes of  $\pm 0.6$  kPa is therefore clinically significant, and may result in misclassification of patient state. A clinical example for this could be in the event of hyperventilation in response to metabolic acidosis secondary to tissue hypoxia<sup>21</sup> in patients with intact respiratory drive, which could acutely affect the  $\Delta\text{PCO}_2$ , causing even higher values than the low flow state of tissue hypoxia itself, leading to misinterpretation of patient prognosis.<sup>3</sup> The interpretation of this parameter becomes particularly tricky when narrow cut-off values of  $\Delta\text{PCO}_2$  or similar indices, for example, the  $\Delta\text{PCO}_2/\Delta\text{tO}_2$  ratio, are used. The  $\Delta\text{PCO}_2/\Delta\text{tO}_2$  ratio has been shown to be a good marker for global anaerobic metabolism and fluid responsiveness.<sup>8–10</sup> A high  $\Delta\text{PCO}_2/\Delta\text{tO}_2$  ratio, with cut-offs of  $\geq 1.8$ ,  $\geq 1.6$  or  $\geq 1.68$  mm Hg/mL have been associated with a worse prognosis.<sup>8–10</sup> Although the routine use of this ratio in critical care is controversial,<sup>22</sup> the narrow difference in the cut-offs make it imperative to understand the various influences on blood gas parameters, to be applied during clinical interpretation.

In interpreting these results, it is important to understand the degree to which transient changes in ventilation are seen in these patients, and of what magnitude. Around 80% of sepsis patients admitted into an ICU require ventilatory support, primarily due to the development of acute lung injury and acute respiratory distress syndrome.<sup>23</sup> For these patients, an initial short period of deep sedation, muscle paralysis and full ventilator control, typically less than 48 hours, is usually followed by the onset of assisted ventilation to preserve respiratory muscle function.<sup>14</sup> Spontaneous breathing with too little support or asynchrony often results in rapid shallow breathing with high respiratory frequency, similar to that applied in this study.<sup>15</sup> In contrast, over assistance from the mechanical ventilator has been shown to suppress drive and reduce respiratory frequency, with over assistance associated with values of respiratory frequency lower than 12 breaths/min.<sup>16</sup> It is therefore possible that the rapid changes in  $\Delta\text{PCO}_2$  of  $\pm 0.6$  kPa shown here are present in the usual treatment of critically ill patients.

### Limitations

Due to the differences in measurement of oxygen saturation in this animal model, it was not possible to measure oxygenation and therefore calculate changes in  $\Delta\text{PCO}_2/\Delta\text{tO}_2$ . As inspired oxygenation levels were not changed in this study, and oxygenation is relatively insensitive to ventilation volume, it is likely that  $\Delta\text{tO}_2$  was constant, and that these results apply similarly to that ratio.

### CONCLUSION

This study has shown that important clinical variation in  $\Delta\text{PCO}_2$  can be due to acute changes in ventilation, which may result in patient misclassification. Care should be taken when measuring  $\Delta\text{PCO}_2$  to ensure that ventilation

is stable, particularly in patients ventilated with assist modes of ventilation.

**Contributors** LS, SER and LPT conceptualised the study. LS, BK and LPT were involved in data collection and analysis. All authors contributed to the interpretation of results and writing the manuscript.

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**Competing interests** SER was a previous shareholder of OBI Medical A/S.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not required.

**Ethics approval** The study was approved by the Animal Experiments Inspectorate (no. 2018-0201-01392), and the animals were reused the same day for educational purposes and sacrificed.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data analysed in this study are available from the corresponding author upon reasonable request.

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