Changes in central venous to arterial carbon dioxide gap (PCO₂ gap) in response to acute changes in ventilation

Lisha Shastri, Benedict Kjærgaard, Stephen Edward Rees, Lars Pilegaard Thomsen

ABSTRACT

Background Early diagnosis of shock is a predetermining factor for a good prognosis in intensive care. An elevated central venous to arterial PCO₂ difference (∆PCO₂) 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 ∆PCO₂, thereby misrepresenting the patient status. This study aimed to determine the influences of acute changes in ventilation on ∆PCO₂ and understand its clinical implications.

Methods To investigate the isolated effects of changes in ventilation on ∆PCO₂, 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 EtCO₂ of 5±0.5 kPa (V̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̇̄

Key messages

► Can acute changes in ventilation influence the PCO₂ (cv-a) gap?
► Acute increases or decreases in ventilation can alter the PCO₂ (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 PCO₂ (cv-a) gap, with rapid simultaneous arterial and central venous sampling (every 30 s).

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. One of the main factors predetermining the prognosis of a patient with sepsis is the presence of septic shock. In the last decade, much research in this area has been focused on the early detection of shock. An elevated CO₂ gap, measured by the difference in central venous (‘cv’) and arterial (‘a’) PCO₂ (∆PCO₂) has been used as an early indicator of shock. Furthermore, the ratio of ∆PCO₂ to the arterial-venous difference in oxygen content ∆PCO₂(cv-a)/∆O₂(a-cv) has been used to guide and assess the response of fluid resuscitation strategies.

Previous studies have illustrated that significant changes in ∆PCO₂ can be due to circulatory effects, focussing on how venous blood could be modified due to, for example, reduced tissue perfusion and the CO₂ 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. Disturbances around the time of blood sampling could result in inaccurate calculations of ∆PCO₂ and other related parameters. The isolated effects of a disturbance in ventilation on the CO₂ 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.
in the ΔPCO₂. The aim of this study was, therefore, to
determine and quantify the influences of acute changes
in ventilation on the ΔPCO₂, concluding on the clinical
significance of these changes when interpreting values of
ΔPCO₂.

METHODS
This study was designed to investigate changes in ventilation
on ΔPCO₂ 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 physi-
ology. 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.13

Protocol
All pigs were anaesthetised for the duration of the study.
The anaesthesia was performed according to local proto-
col, with total intravenous anaesthesia for the duration of
the study, and the presence of indwelling arterial and
central venous catheters for blood sampling. The loca-
tion 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 ve-
 nous 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 as-
sisted with the capping of the syringes. All samples were
analysed immediately after, in the order they were tak-
en, 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.14
For these patients, a sudden increase or decrease in
respiratory rate is not uncommon,15 the former if the
patient becomes stressed and the latter if ventilator
support levels are increased and respiratory drive
suppressed.16 This study was designed to reflect simi-
lar sudden changes in ventilation by varying respira-
tory 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 CO₂ (EtCO₂) of 5±0.5 kPa.
The changes in ventilation corresponded to modifi-
cations 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 subject-
ed to a second change in ventilation. EtCO₂ and SpO₂
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 PCO₂. ΔPCO₂ was calcu-
lated using the difference between PCO₂ cv and PCO₂ 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 base-
line using Bonferroni’s correction. Similar analyses were
conducted for central venous blood and ΔPCO₂ following
hyperventilation and hypoventilation changes. All results
are presented as mean±SD, with p<0.05 considered statis-
tically significant. Statistical analysis was conducted on
SPSS V.25 (SPSS IBM Corp.).

RESULTS
The eight pigs weighed an average of 34.0±8.7 kg,
and had mean values of pH and PCO₂ at baseline of
7.478±0.050 and 5.34±0.61 kPa (40.1±6.5 mm Hg) for
arterial blood, and 7.440±0.048 and 6.10±0.70 kPa
(45.8±5.3 mm Hg) for central venous blood, respectively.

| Table 1 Ventilatory settings during baseline, hyperventilation and hypoventilation |
|---------------------------------|----------------|----------------|----------------|
| Parameters                      | Baseline       | Hyperventilation | Hypoventilation |
| Tidal volume (Vt)               | 8mL/kg         | 8mL/kg          | 8mL/kg          |
| Respiratory frequency           | 14±2 breaths/min | 28±4 breaths/min | 7±1 breaths/min |
| Criteria for termination        | EtCO₂ <1.5 kPa | SpO₂ <88%       | EtCO₂ >6.5 kPa  |

Responses to hyperventilation and hypoventilation

Changes in pH and PCO₂ 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 PCO₂ changed faster than venous and were significantly different from baseline at 60 s (p<0.005). The maximum arterial difference was observed at 120 s with pH=0.059 and PCO₂=−0.74 kPa (5.5 mm Hg). There was no statistically 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 PCO₂ seen 60 s after the change in ventilation (p<0.005). Central venous blood was significantly different from baseline at 120 s for PCO₂ (p<0.05), while there appeared to be a statistically significant response in pH at 240 s (p = 0.035). Oxygenation did not change for the duration of the study, where the pigs also had a stable and constant FiO₂ and SpO₂.

Effects on ∆PCO₂

Figure 2 illustrates the average changes in ∆PCO₂ following acute changes in ventilation. The average ∆PCO₂ at baseline was 0.76±0.29 kPa (5.7±2.2 mm Hg). Following acute hyperventilation, there was a rapid increase in the ∆PCO₂, with a maximal change of 1.35±0.29 kPa (10.1±2.2 mm Hg). There was a corresponding decrease in the ∆PCO₂ following an acute hypoventilation, decreasing maximally to 0.23±0.31 kPa (1.7±2.3 mm Hg). Changes in ∆PCO₂ in response to both changes in ventilation achieved statistical significance 30 s 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 ∆PCO₂. 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 ∆PCO₂. This study is the first to assess the isolated effects of changes in ventilation on ∆PCO₂. The study has demonstrated that ∆PCO₂ 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 ∆PCO₂ changes of ±0.6 kPa. Normal values of ∆PCO₂ have previously been shown to be 0.8 kPa, with patients considered to have insufficient perfusion of the tissues if ∆PCO₂ is above this value. Values of ∆PCO₂ have shown to be elevated to the range of 1.6 to 2 kPa (12–15 mm Hg) for patients with septic shock. The PCO₂ 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. A measurement of ∆PCO₂ concomitant with hypoventilation or hyperventilation
resulting in ΔPCO2 changes of ±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 hypoxia25 in patients with intact respiratory drive, which could acutely affect the ΔPCO2, causing even higher values than the low flow state of tissue hypoxia itself, leading to misinterpretation of patient prognosis. The interpretation of this parameter becomes particularly tricky when narrow cut-off values of ΔPCO2 or similar indices, for example, the ΔPCO2/ΔtO2 ratio, are used. The ΔPCO2/ΔtO2 ratio has been shown to be a good marker for global anaerobic metabolism and fluid responsiveness.8 10 A high ΔPCO2/ΔtO2 ratio, with cut-offs of ≥1.8, ≥1.6 or ≥1.68 mm Hg/mL have been associated with a worse prognosis.8–10 Although the routine use of this ratio in critical care is controversial,22 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.25 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.14 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.15 In contrast, over assistance from the mechanical ventilator has been shown to supress drive and reduce respiratory frequency, with over assistance associated with values of respiratory frequency lower than 12 breaths/min.16 It is therefore possible that the rapid changes in ΔPCO2 of ±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 ΔPCO2/ΔtO2. As inspired oxygenation levels were not changed in this study, and oxygenation is relatively insensitive to ventilation volume, it is likely that ΔtO2 was constant, and that these results apply similarly to that ratio.

**CONCLUSION**

This study has shown that important clinical variation in ΔPCO2 can be due to acute changes in ventilation, which may result in patient misclassification. Care should be taken when measuring ΔPCO2 to ensure that ventilation is stable, particularly in patients ventilated with assist modes of ventilation.

**References**