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BY
LISHA SHASTRI

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
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Dissertation submitted 2021

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CV

Dr. Lisha Shastri obtained her Bachelor of Medicine of and Bachelor of Surgery degrees in 2016 from St. John's Medical College, India. During her Bachelor education, she contributed to various peer reviewed researcher papers, being awarded the best speaker at the National Conference of the Nutritional Society of India and the HJ Metha award for best research paper. She further pursued her interest in physiology by obtaining an MSc in Space Physiology & Health with distinction in 2017 at King's College London, UK. For her master dissertation, Lisha was awarded the SAFE Europe Student of the Year Award. Furthermore, she has been an active member of the UK Space Environments Association since 2018.

She is currently enrolled as a PhD fellow under the supervision of Lars Pilegaard Thomsen and Stephen Edward Rees. The results of her work have been disseminated through peer reviewed papers and oral presentations at ESICM Lives 2021, BTS Winter Meet 2020 and ATS 2020 conferences. Lisha has been actively engaged in teaching tasks, including the supervision of bachelor projects and facilitating problem based learning for the Medicine and MedIS programmes. As a board member of both the PhD Association of Aalborg University (PAU) and the PhD Association Network of Denmark (PAND), she has been representing PhD students in Denmark at a local and national level.

English Summary

Arterial blood gases (ABGs) are the gold standard for assessment of blood acid-base status. However, an arterial puncture is painful and has many complications. Venous blood was proposed as a surrogate for arterial blood, but it differs based on sample location and is less reliable outside the normal physiological range. An alternative method has been developed involving physiology-based models, called v-tac™ which has been shown to transform peripheral venous values to their arterialised equivalents. It has been tested in patients in the emergency and pulmonary departments and has been shown to work well within clinically acceptable limits.

ABGs can be rapidly influenced by changes in ventilatory patterns. Such changes could be present at the time of blood sampling and could alter the results of the blood gas analysis. Similar responses of venous blood or v-tac to changes in ventilation have not yet been explored. In addition, differences between peripheral and central venous blood in terms of their responses to ventilatory changes or with respect to v-tac conversions has not been evaluated. This PhD project aimed to evaluate the responses of arterial, peripheral, and central venous blood to acute changes in ventilation, simulating the changes observed around the time of blood sampling. In addition, the use of v-tac following acute ventilatory changes was evaluated, as well as its ability to transform values of central venous blood to arterialised equivalents.

The results show that arterial blood responds rapidly to acute changes in ventilation, while venous blood displays a more delayed and dampened response. As a consequence of using the stable venous blood, v-tac was able to accurately calculate arterialised values, thereby better representing the steady-state/baseline arterial values, when compared to the rapidly changed acid-base parameters measured in the arterial blood. This means that if there is any suspicion of a change in ventilatory pattern when collecting an arterial blood sample, it might be prudent to draw a venous blood sample and use the v-tac converted values instead of the traditional ABG, to avoid risks of patient misclassification while evaluating their acid-base status. In addition, the PhD project has shown that the performance of v-tac is as good as other models in its ability to transform central venous values. As central venous blood is evaluated most amongst the critically ill, further research needs to be done to evaluate the use of v-tac amongst the critically ill.

Dansk Resume

Arteriel blodgasanalyse (a-gasser) er guldstandarden for vurdering af syre-base status. En arteriel punktur er imidlertid smertefuld og har mange komplikationer. Venøst blod foreslås som et surrogat for arterielt blod, hvor det adskiller sig ved prøvetagning, men resultatet er mindre pålideligt uden for det normalt fysiologiske område. En alternativ metode kaldet v-tac™, der benytter venøse blodprøver og involverer matematiske fysiologiske modeller, har vist sig at kunne omdanne perifere venøse værdier til arterialiserede ækvivalenter. Metoden er blevet testet hos patienter på akut- og lungeafdelinger, og har vist sig at fungere godt inden for klinisk acceptable grænser.

A-gasser påvirkes hurtigt af ændringer i respirationsmønstre og sådanne ændringer kan være til stede på tidspunktet for blodprøvetagning, hvilket kan ændre resultaterne af blodgasanalyserne. Lignende påvirkninger fra ændringer i respiration på venøst blod eller v-tac udregninger er endnu ikke undersøgt. Det samme gør sig gældende for forskellen mellem graden af påvirkning for perifert og centralt venøst blod. Dette PhD-projekt har netop til formål at evaluere reaktionerne på arterielt, perifert og centralt venøst blod fra akutte ændringer i respiration, hvilket simulerer de ændringer der kan opstå ved blodprøvetagning. Derudover blev brugen af v-tac efter akutte respirationsændringer evalueret samt metodens evne til at omdanne værdier af centralt venøst blod til arterialiserede ækvivalenter.

Resultaterne viser, at arterielt blod reagerer hurtigt på akutte ændringer i respiration, hvorimod venøst blod viser en mere forsinket og dæmpet reaktion. Ved at benytte det stabile veneblod var v-tac i stand til nøjagtigt at beregne arterialiserede værdier og derved bedre repræsentere de steady-state/baseline arterielle værdier, sammenlignet med de hurtigt ændrende syre-baseparametre målt i arterielt blod. Det betyder, at hvis der er mistanke om en ændring i respirationsmønsteret ved udtagning af en arteriel blodprøve, kan det være fordelagtigt at udtage en venøs blodprøve og bruge de v-tac konverterede værdier i stedet for den traditionelle ABG for derved at undgå risiko for fejlklassificering af patienten baseret på evaluering af deres syre-base status. Derudover har ph.d.-projektet vist, at v-tac er i stand til at transformere centralt venøst blod til arterialiserede værdier på højde med andre tilgængelige modeller. Da centralt venøst blod oftest benyttes blandt de kritisk syge patienter, er der behov for yderligere forskning for at evaluere brugen af v-tac hos netop denne type af patienter.

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List of Papers

Paper I (1)

Is venous blood a more reliable description of acid-base state following simulated hypo- and hyperventilation?
Scand J Trauma Resusc Emerg Med. 2021;29:35

Paper II (2)

Changes in central venous to arterial carbon dioxide gap (PCO_2 gap) in response to acute changes in ventilation.
BMJ Open Respir Res. 2021;8(1):e000886

Paper III (3)

Mathematically arterialised venous blood better represents acid-base status of the blood following acute changes in ventilation.
Under review in the Journal of Clinical Monitoring and Computing

Paper IV (4)

Comparison of two methods for converting central venous values of acid-base status to arterial values in critically ill patients.
Comput Methods Programs Biomed. 2021;203:106022

CHAPTER 1.

Introduction

Blood gas analysis is regularly used in the emergency, pulmonary, anaesthesiology, and intensive care departments to evaluate the extent of potential acid-base disturbance, oxygen saturation, effect of treatment and to adjust/confirm the effects of a change in ventilator settings (5,6). Blood gas values can be determined for both arterial and venous blood, where arterial blood gas (ABG) is considered the 'gold standard' for assessment of blood acid-base and oxygenation status.

Over 100,000 ABGs are ordered annually in a single tertiary hospital (7), where most commonly, they are ordered as a routine, or otherwise called 'daily ABGs' (7,8) without a specific indication. However, an arterial puncture is painful (9,10), and comes with a host of complications including haematoma, bruising, damage to the blood vessel, loss of pulse, and thrombo-emboli (11); Over 60% of patients experience complications following an arterial puncture (11). With these challenges, are we sure that ABGs are robust and the only sure way to evaluate acid-base status? Could there be other methods of assessing a patient's acid-base status that could be as good as a traditional ABG?

1.1. Robustness of and challenges associated with blood gas analysis

ABGs are used to diagnose respiratory conditions and titrate treatment options such as non-invasive ventilation (NIV) for patients with chronic obstructive pulmonary disease (COPD) and other chronic lung diseases (12–15). Particularly in the pulmonary department and outpatient clinics, these measurements are typically done daily to monitor the patient's response while on active treatment and involve daytime arterial punctures especially for those on home management. Alternatives like transcutaneous CO_2 (15,16) and end tidal CO_2 ($EtCO_2$) (17) have been proposed to

replace ABGs for monitoring COPD progression, as they are continuous measurements and are able to capture nocturnal variability. However, they are unreliable outside steady state conditions (18). Thus, ABGs still remain the primary choice for assessing acid-base disturbances in the guidelines for management of respiratory conditions (6,12,13,15).

ABGs, however, are rapidly influenced by ventilatory changes, which are common around the time of blood sampling. Prevalent in the emergency department (ED) are patients who are anxious and perhaps fearful – of the doctors, unknown sequence of events or even of the needle (19,20) – giving rise to hyperventilation or perhaps breath-holding in response to this fear, or in response to the pain of the puncture; An arterial puncture is shown to be three times more painful than a venous puncture, even with the injection of local anaesthesia prior to the puncture (9,10,21). Hyperventilation and breath-holding rapidly change the arterial acid-base status (22,23). In 1 min the $PaCO_2$ was shown to decrease by an average of 2.3 kPa (22) or increase by 1.4 kPa (23), respectively. Likewise, patients on NIV and other forms of ventilatory support, tend to experience irregular and unstable patterns of breathing (24–26) including extra breaths or skipped breaths/periods of apnoea, i.e., patient-ventilator asynchrony, which albeit transient, can rapidly influence ABG results (22,23). Adding to this is the arterial blood's inherent variability, which represents the spontaneously oscillating nature of the blood gases resulting from breath-by-breath variations, fluctuations in the cardiac cycle, metabolic changes and other physiological disturbances (27). This inherent variability can range from 0.02 to 0.05 for pHa and 0.3 to 0.6 kPa for $PaCO_2$ (28,29), illustrated in **Figure 1.1** where the 'steady state' value is depicted as the solid line and the variability as dotted lines. The changes in ventilation add more uncertainty and variability to the ABG results; so then, how much can we trust arterial blood values?

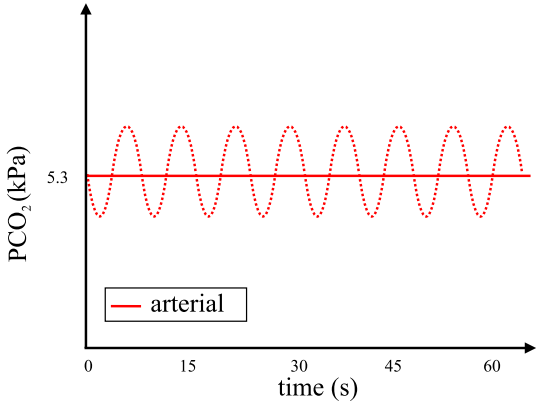

Figure 1.1 Inherent arterial variability

Figure illustrating the perceived 'steady state' values (solid line) overlaid with the breath-by-breath variability (dotted lines) for arterial PCO_2 values.

1.1.1. Alternative methods to assess arterial acid-base status

The use of venous blood has been proposed as a surrogate for arterial acid-base status, however, there is debate on the range of its clinical use (30–33). Meta analyses (31,32) using data from several different medical centres conclude that the agreement between arterial and peripheral venous blood pH is largely acceptable, but the agreement of PCO_2 was less so. Given the evidence for transient arterial variability, it could be possible that the agreement between arterial and venous blood could have been influenced by errors in the ABG results and not the venous blood alone. However, we do not know if venous blood is also susceptible to acute changes in ventilation, or to what degree. Venous PCO_2 was shown to decrease by 1.39 kPa after 2 min of hyperventilation (34), which was a smaller change with a longer time delay. This reduced and delayed effect could be a consequence of the larger venous pool in combination with the time it takes for the blood to reach the veins themselves (35). In conjunction with the buffering capacity at the capillary level (36), these factors could allow venous blood to filter out the changes due to ventilation and present a more stable representative of the patient's acid-base status (illustrated in **Figure 1.2**). The two studies evaluating the effect of hyperventilation on blood acid-base status (22,34) were different in terms of their experimental protocol and were therefore not directly comparable, whereas the venous response to breath-holding/hypoventilation has not been previously evaluated. So how much is the extra pain of arterial puncture worth when compared to venous blood if values are not substantially more accurate and precise?

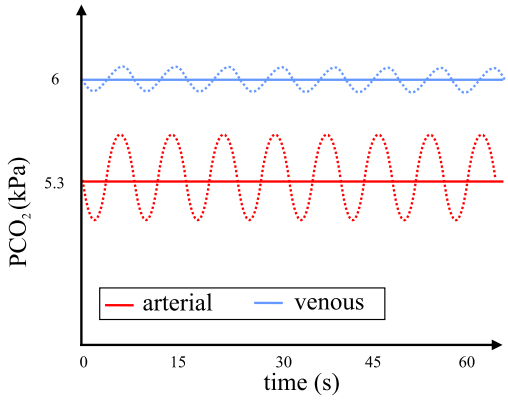

Figure 1.2 Inherent venous variability
Figure illustrating the perceived 'steady state' values (solid line) overlaid with the variability (dotted lines) for arterial and venous PCO_2 values. The venous blood postulated to have smaller oscillations as a result of dampening of the breath-by-breath oscillations after passage through the tissues.

Rang and colleagues (37) attempted to determine what clinicians thought are the appropriate 'clinically acceptable differences' between arterial and venous values by way of a survey, where the study team presented a statement to a group of ED physicians to complete:

> "*I would feel uncomfortable using only the venous value for clinical decisions if it was more than ____ units away from the arterial value*."

On average, physicians thought that the acceptable arterio-venous difference in pH should not exceed 0.05 and PCO_2 not be more than 0.88 kPa. These results, albeit limited by being from a single country/center, likely reflect patterns from their daily practice rather than a standard that is followed. Even so, there was a variation amongst those who responded, meaning that there is a lack of consensus on what is 'clinically acceptable' in the medical society. More so, venous blood values themselves differ depending on location of the sample, i.e., whether it is from a peripheral or centrally located vein. Further, treatment guidelines have only been formulated with arterial values, making it a challenge – and perhaps a risk – to use venous values alone for clinical decisions.

Table 1.1 Summary of different predictive models used to predict arterial blood acid-base equivalents from venous blood values.

Study	pHa	$PaCO_2$ (mmHg)
Walkey 2010 (38)	$pH_v + 0.05$	$P_vCO_2 - 5$
Ak 2006 (39)	$1.004 \cdot pH_v$	$0.873 \cdot P_vCO_2$
Bohloli 2018 (40)	$4.68 + (0.366 \cdot pH_v)$	$6.087 + (0.784 \cdot P_vCO_2)$
Chu 2003 (41)	$0.45 + (0.94 \cdot pH_v)$	$3.06 + (0.76 \cdot P_vCO_2)$
Boulain 2016 (42)	1.0649 + ('chronic heart failure' · 0.0052) + ('liver cirrhosis' · -0.0089) + ('vasopressor dosage' · -0.0061) + ($pH_{cv} \cdot 0.8693$) + ($Lact_{cv} \cdot -0.0019$) + ($P_{cv}CO_2 \cdot -0.0008$) + ($S_{cv}O_2 \cdot -0.0008$) + ($SpO_2 \cdot 0.0003$)	96.3474 + ($pH_{cv} \cdot -12.3695$) + ($P_{cv}CO_2 \cdot 0.6877$) – ($P_{cv}O_2 \cdot 0.0209$) + ($S_{cv}O_2 \cdot 0.1987$) - ($Lact_{cv} \cdot 0.4768$) - ($SpO_2 \cdot 0.1060$
Rees 2006 (43)	Physiology based mathematical models (v-tac method): simultaneously solving over 25 mass balance and mass action equations using physiological principles of acid-base chemistry	

In lieu of these challenges, several alternative methods have been developed as a means to calculate/predict arterial equivalents of acid-base from venous blood, rather than using venous values alone (**Table 1.1**). Each of these methods use different types of models, ranging from addition of a constant (38), to simple linear predictive models (39–41), multiple linear regression models (42) and finally physiology-based mathematical models (43). The method evaluated further in this PhD project is the one by Rees *et al.* (commercially called Roche v-TAC™, referred to as 'v-tac' in the dissertation) (43) which calculates arterial equivalents from peripheral venous blood and has been suggested for use in the ED (44,45) and pulmonary departments (46). This method employs physiology-based mathematical models, where it assumes good perfusion at the tissues, with little or no anaerobic metabolism across the tissue bed (details of the method are described in papers III and IV (3,4)). v-tac has been evaluated on acute patients (45,47), patients with COPD (44,48,49), respiratory failure (50) and those undergoing NIV treatment (47), and has been shown to function well within 2 standard deviations (SD) of ± 0.026 and ± 0.5 kPa for pH and PCO_2 (48) when compared to measured arterial values; well within the limits of what Rang *et al.* (37) reported as clinically acceptable. However, v-tac has been evaluated with the assumption that the arterial acid-base status is always true and undisturbed by underlying variation. While we know that acute ventilatory changes can influence arterial blood in under a minute, similar changes in venous blood or with use of v-tac has not been evaluated.

Can venous blood act as a filter to the ventilatory changes by virtue of the larger venous pool and longer time delay before the blood from the lungs reaches the veins? As a consequence of using the more stable venous blood, can v-tac better represent arterial blood values prior to the onset of the ventilatory changes, while simultaneously providing 'arterial' values to be interpreted with reference to treatment guidelines? **Figure 1.3** helps illustrate these postulates in a graphical form, where the 'steady-state' values of arterial, venous and v-tac calculated PCO_2 values are overlaid by the biological oscillations observed (Figure 1.3 A). In addition, a hypothesised response to a transient ventilatory change is also depicted (Figure 1.3 B).

The precision displayed by the various methods described above are well within the clinically significant range of values previously evaluated by Rang *et al.* (37). While the model by Boulain and colleagues employed additional clinical data from the patients, it was still in fact a statistics-based model, derived from a fixed population, and perhaps has a limited applicability until further tests are conducted. The v-tac method by Rees *et al.* individualises the transformations using the patient's own blood gas values as a reference and applies concepts of human physiology and acid-base chemistry rather than having a universally applicable factor to add/subtract from the venous blood. The main limitation of the v-tac method is that it has not been tested using central venous blood amongst the critically ill, where ABGs are most frequently used (7).

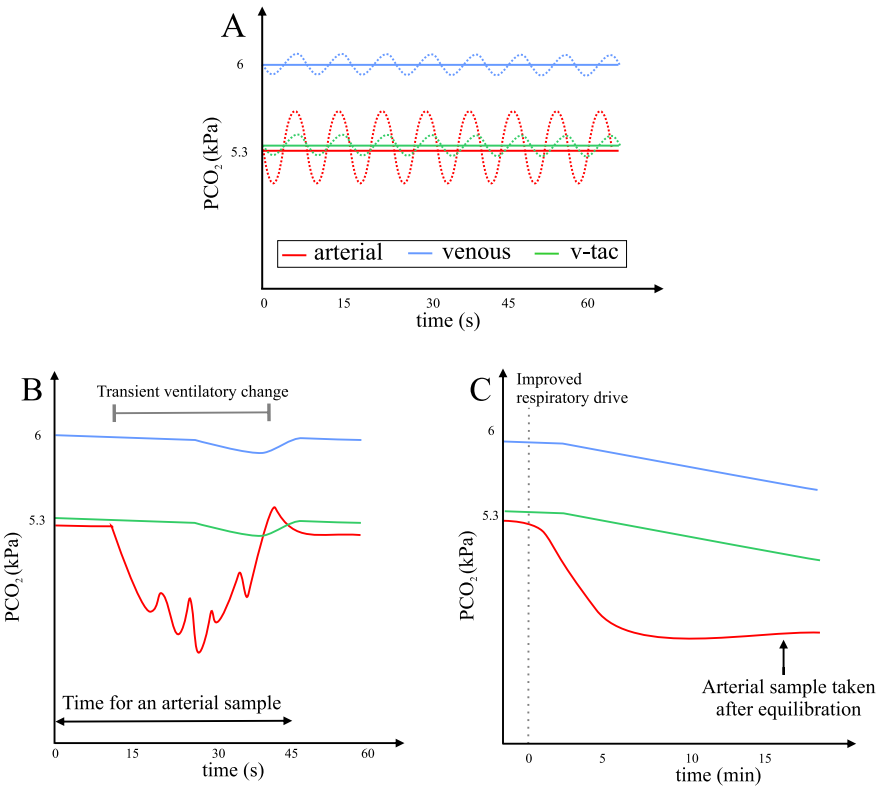

Figure 1.3 Graphical representation of the postulates of this PhD project.
Figure A represents the inherent variability in arterial (red) and venous blood (blue), wherein the v-tac converted values (green) are postulated to filter out the arterial breath-by-breath variability, while still providing reliable arterial acid-base values. Average 'steady-state' values depicted as solid lines, while the variability is represented by dotted lines around it.
Figure B illustrates the hypothesis of what would happen to the blood gases following a transient ventilatory change. The ventilatory disturbance would primarily affect the arterial blood, especially within the duration of the blood draw. We hypothesise that venous blood, and hence v-tac would show a smaller and more delayed response. Therefore, using arterialised acid-base values in such a scenario would better represent the arterial steady state values. While the lines on this plot represent the average values, they are still overlaid by the blood's inherent variability.
Figure C illustrates the response of blood gases following an improved respiratory drive. Following NIV titration in a clinical setting, one can expect the arterial blood gases to change rapidly, and guidelines recommend waiting at least 10 min for equilibration before taking an ABG. Venous blood gases and hence v-tac would take longer to respond and eventually equilibrate with the arterial blood values.

1.1.2. Challenges with ABGs in intensive care

Over 87% of ABGs ordered in a hospital are from the intensive care units (ICU) (7). Critically ill patients, especially those suffering from sepsis or septic shock, require serial blood gases, essentially monitoring acid-base trends in response to treatment. These patients commonly have indwelling arterial and central venous catheters, where both arterial and central venous blood gases are measured, allowing for the calculation of parameters such as the CO_2 gap. This gap is the difference between central venous and arterial PCO_2 providing an early indication of decreased perfusion and inadequate fluid resuscitation (51), and predicting ICU mortality (52). Other derived ratios like the CO_2 gap/ΔtO_2 (difference between arterial and central venous oxygen content) are also used to determine insufficient perfusion and as a guide for resuscitation goals (53).

The issues in using venous blood to determine acid-base status are multi-factorial. In pulmonary or emergency medicine where patients are lightly sedated or fully awake, peripheral venous blood is readily avaliable and an ABG requires an arterial puncture. Issues here are related to whether peripheral venous values are a good surrogate and whether ventilatory changes significantly affect blood acid-base status. However, in intensive care, where patients are more sedated and relaxed and where arterial and central venous catheters are present, the issues relate to whether *central* venous blood is an acceptable surrogate for arterial acid-base status. Even with use of v-tac to transform values of central venous blood, a reliable alternative for arterial acid-base status in the intensive care could lead to more rapid removal of arterial lines in patients who are otherwise heamodynamically stable, thereby precluding the onset of catheter related infections and side-effects like pseudoaneurysms and iatrogenic anemia (54,55). In addition, if similar transient ventilatory changes are present, perhaps in lightly ventilated patients on support mode ventilation, then how long would it take for the change to appear in the central venous blood? Could it also affect the values of the CO_2 gap and other arterial - central venous gradients? Can v-tac essentially be used to effectively transform values of central venous blood to arterialised equivalents?

1.2. Aims

Although ABGs are considered gold standard for assessment of acid-base status, they have a few caveats; arterial samples are difficult to obtain, punctures are painful, and the values are susceptible to acute changes in ventilation. Several alternatives – such as venous blood and methods like v-tac – have been proposed to assess a patient's acid-base status. Indeed, these alternatives show promise in steady state conditions, but their response to acute changes in ventilation has not been evaluated. In addition, the use v-tac to transform values of central venous blood has not been evaluated. To bridge these gaps in our understanding of blood gases and challenge the routine use of ABGs, the following aims were outlined.

Aim 1. To determine the variability of acid-base parameters in arterial, peripheral, and central venous blood following acute changes in ventilation.

Aim 2. To examine the use of v-tac following acute changes in ventilation in a normal physiological setting using peripheral venous blood.

Aim 3. To evaluate use of v-tac in a critically ill population using central venous blood.

CHAPTER 2.

Summary of the studies

This section of the dissertation summarises the studies conducted during the PhD project and is detailed further in the 4 papers associated with the dissertation. Study I was a prospective observational study involving 30 patients and resulting in papers I and III. Study II was also a prospective observational study but involved 8 pigs and resulted in paper II. Study III was a retrospective study involving 1109 blood sample pairs from 541 patients and is summarised in paper IV.

2.1. Study I

Aim: The aim of Study I was to determine the variability of acid-base parameters in arterial and *peripheral* venous blood following acute hyper- and hypoventilation (aim 1). It also aimed to examine the use of v-tac following the same changes in ventilation in a normal physiological setting using peripheral venous blood (aim 2).

Methods: This study included 30 patients without cardiovascular or respiratory disease, who were anaesthetised and ventilatory changes simulated using a combination of changes in tidal volume and respiratory rate to achieve 100% increase and 60% decrease in alveolar ventilation. Multiple blood samples were simultaneously taken from indwelling arterial and peripheral venous catheters at baseline, and at 15, 30, 45, 60, 90 and 120 s following the ventilatory change. This was done to map out the precise response to acute hyper- and hypoventilation, within the time it takes to draw an arterial sample in practice (19). A pair of baseline samples was used to examine the inherent arterial-arterial and venous-venous variability in pH and PCO_2, which served as a boundary, beyond which any changes to the acid-base status were considered to be due to the simulated ventilatory change. Consideration of this boundary to define a true change in acid-base status was a novel approach in

the PhD. Responses of arterial and peripheral venous pH and PCO_2 following hyper- or hypoventilation were analysed as changes from baseline.

Further, peripheral venous values measured here were transformed into arterialised values using v-tac. v-tac transformations at baseline were evaluated using a Bland-Altman plot. To determine the use of v-tac values, the difference between the transformed values at each time point and the corresponding baseline value were compared to the previously published precision of the method with pH: ± 0.03 and PCO_2: ± 0.5 kPa. Results where the differences from baseline at each timepoint were within these limits were considered as 'not different from baseline'. The percentage of samples that were not different from baseline were calculated at each sampling timepoint for both measured arterial and v-tac transformed values.

Results: Study I demonstrated that the inherent variability of arterial and peripheral venous blood were similar. The largest limits of agreement (LoA) for pH (± 0.007) and PCO_2 (± 0.25 kPa) were used to determine the boundary beyond which any changes to the acid-base status were considered to be due to the simulated ventilatory changes. Following hyper- and hypoventilation, arterial blood values were altered within 30s while venous blood values remained stable and displayed a smaller and delayed response, observed after 60-90s.

At baseline, v-tac performed with similar precision as in previous publications with bias and LoA for pH = -0.001 (-0.022 to 0.020) and PCO_2 = -0.02 (-0.37 to 0.33) kPa. Following acute hyper- and hypoventilation, v-tac was able to accurately transform 100% of the samples for the first 60s. In comparison, over half of the measured arterial values had changed and were outside the limits of pH: ± 0.03 and PCO_2: ± 0.5 kPa when compared to baseline.

Conclusions: These results show that peripheral venous blood, and thereby v-tac converted values can better represent arterial values at baseline, prior to a change in ventilation. This means that in the event of acute, transient changes in ventilation occurring around the time of sampling, there is an increased likelihood of the arterial acid-base status being altered whereas peripheral venous values remained stable and were less likely to change for the duration of a blood sample draw. As a consequence of this, v-tac could prove to be a better representative of steady-state arterial blood values, free from the changes due to an acute, transient change in ventilation.

2.2. Study II

Aim: The aim of Study II was to determine the variability of acid-base parameters in arterial and *central* venous blood following acute hyper- and hypoventilation (aim 1).

Methods: This study included 8 pigs without cardiovascular or respiratory disease, who were anaesthetised, and ventilatory changes simulated by doubling or halving the respiratory rate from a common baseline. Similar to Study I, multiple blood samples were simultaneously taken from indwelling arterial and central venous catheters, at baseline and 30, 60, 90, 120, 180 and 240s after a change in ventilation. In addition to pH and PCO_2, the response of the CO_2 gap (difference between the central venous and arterial PCO_2) to hyper- and hypoventilation was also evaluated. As the aim of the study was to explore physiological responses in central venous blood without the added influences of metabolic and perfusion disturbances, an animal model was chosen instead of human. The risk of inserting a central venous catheter in healthy volunteers would be too high and unnecessary for a study of this nature, while studying patients with indwelling central venous catheters (usually in critical care) would bring in the additional and unwanted effects of critical illness, thereby influencing (and perhaps contaminating) the results. Responses of arterial and peripheral venous pH and PCO_2 and the CO_2 gap following hyper- or hypoventilation were analysed as changes from baseline.

Results: Following hyper- and hypoventilation, arterial blood values changed within 30s while central venous blood values remained stable for nearly two minutes and displayed a smaller and delayed response. Interestingly, the CO_2 gap showed statistically significant changes 30s following both hyper- and hypoventilation.

Conclusions: These results show that similar to peripheral venous values, central venous acid-base status observes a slower and more dampened response when compared to arterial blood, following an acute change in ventilation. The longer delay in comparison to the peripheral venous values likely reflects the time it takes for the blood to reach the central veins, combined with the additional buffering capacity of the tissue bed. The change in CO_2 gap, while previously thought to be due to the CO_2 stagnation phenomenon in the under-perfused tissues, could instead be due to the rapid arterial changes following acute hyper or hypoventilation. The stability of central venous blood, and the ease of sampling in a critically ill patient with an indwelling catheter could provide an opportunity for the use of v-tac to obtain arterialised values, instead of measured arterial values that could rapidly change. v-tac has however, not been tested on central venous blood, and this will be explored in study III of the PhD project.

2.3. Study III

Aim: The aim of Study III was to evaluate use of v-tac in a critically ill population using *central* venous blood (aim 3).

Methods: This was a retrospective study in collaboration with Thierry Boulain, whose research group previously derived a statistical-based mixed effect multiple linear regression model to predict arterialised values from central venous blood (42). Data from the study by Boulain *et al*. – where blood gases were collected every 6 hours, for 24 hours, from patients diagnosed with acute circulatory failure – were used for analysis in Study III.

Boulain *et al.* measured paired arterial and central venous blood gases from 590 critically ill patients, with a total of 2385 sample pairs. Two-thirds of these data were used to derive a statistical based model to predict arterialised equivalents from central venous values, and one-third of these were used to validate the model. In paper IV, performance of the statistical model and v-tac were compared, wherein only data used for validation of the statistical model were used for the analysis, thereby avoiding any bias towards the statistical model. However, for evaluation of v-tac alone, data used for the derivation of Boulain's model would not result in any bias towards v-tac and was therefore included in a subsequent analysis, highlighted in this dissertation.

Of the 2385 sample pairs, 1226 did not have the additional data required to implement v-tac and were excluded, resulting in 1159 sample pairs. To these, rules were applied to identify clearly erroneous samples (**Figure 2.1**), leading to the further exclusion of 50 sample pairs. These data were omitted, as it is not physiologically plausible for arterial blood to have dramatically higher values of PCO_2 and lower values of pH than venous blood, or to have oxygen production at the tissues.

The 1109 sample pairs that remained after exclusion were analysed by comparing the v-tac converted pH and PCO_2 with the corresponding measured arterial values using a Bland-Altman comparison, reporting biases and LoAs. Further, a subset of the data was identified where v-tac could not calculate arterialised values with the precision of the method previously reported, i.e., an arterialised pH within 0.03 of measured arterial values and an arterialised PCO_2 within 0.5 kPa of measured arterial values (48). This precision was previously found in patients who had peripheral venous blood sampled from warm well-perfused extremities, and therefore, represents a suitable cut-off for identification of samples where anaerobic metabolism might have occurred, as one would expect in a critically ill population.

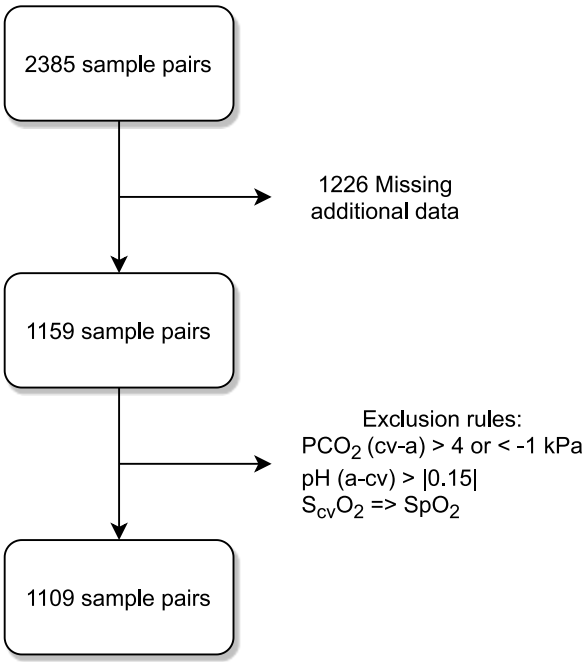

Figure 2.1 Summary of the retrospective data handling using paired arterial and central venous samples from the study by Boulain *et al.* (42).
a: arterial; cv: central venous; PCO_2: CO_2 tension; kPa: kilo Pascal; $S_{cv}O_2$: venous blood oxygen saturation; SpO_2: peripheral oxygen saturation via pulse oximetry.

To account for the discrepancies of when v-tac was unable to calculate arterialised values within the previously reported precision, two modifications were made to the method. The first modification evaluated whether an addition or removal of an excess of total CO_2 content (xCO_2), beyond that accounted for by aerobic metabolism, could result in v-tac values calculated with the same precision as previously reported. For the subset of cases that could not be explained by the addition or removal of xCO_2 alone, a second analysis with modifications in both xCO_2 and addition or removal of strong acid/base (xBE) at the tissues were required. Measured arterial and v-tac values of pH and PCO_2 prior to and following modifications with xCO_2 were compared using Bland-Altman analysis and calculation of bias and LoA for all 1109 samples (4). For cases requiring both xCO_2 and xBE, the correlation between xBE and xCO_2 was investigated, in a similar fashion to Loeppky *et al.* 1993 (56), where the analysis was done to understand the relationship between CO_2 transport and acid-base balance in the context of buffering contributions from the different fluid compartments in the body.

Results: Results from this study show that v-tac was able to transform central venous values with the same precision as the statistical model by Boulain *et al*. Neither of these models, however, have LoAs within the limits where they could be recommended for use amongst the critically ill on their own. Upon modification of v-tac with xCO_2, 95% of the samples could be transformed within v-tac's previously reported precision. The remaining 5% required a combination of both xCO_2 and xBE to achieve the same precision.

Conclusions: While neither of these models have the precision required for recommendation to be used amongst the critically ill on their own, v-tac manages to transform central venous values of acid-base to arterialised equivalents with the same precision as the statistical model, without the need for additional clinical data, for example liver cirrhosis or vasopressor dosage as is needed for the statistical model. In addition, modifications made to v-tac were able to account for some of the nuances of critical illness, not explained by aerobic metabolism alone.

CHAPTER 3.

Discussion

In this dissertation the traditional assessment of acid-base status using ABGs in clinical practice has been challenged in several ways. Could arterial blood gas values just be a simple mathematical function of its corresponding venous equivalent? Is it better to use v-tac in situations where there could be transient changes in ventilation? Would using an ABG in such situations be detrimental? To explore if venous blood or v-tac could better assess acid-base status in various clinical scenarios and patient groups, three aims were outlined, and these will be discussed below in the context of the dissertation.

3.1. v-tac better represents steady state arterial blood values prior to a transient change in ventilation

Studies I & II demonstrate that arterial blood responds rapidly to acute hyper- and hypoventilation, where significant changes are observed in 30s, while venous blood was slower to respond and showed a dampened effect. Peripheral venous blood responded after 1 min while central venous blood took longer, and showed a response after 2-3 min. We hypothesised that this was due to the sluggish flow of blood once it leaves the arterial system, until it reaches the venous pool. In addition, blood buffer systems help to dampen the effect of the ventilatory changes, thereby accounting for the smaller effect in venous blood at the end of the study protocol, more so in central venous blood as it takes a longer time to reach the central veins. These results, although not directly comparable to previous studies showing a rapid arterial response to maximal voluntary hyperventilation (22) or breath holding (23), still demonstrated a similar response time for arterial blood, i.e., within 1 min, corresponding to the duration of the procedure of an arterial puncture. The corresponding peripheral and

central venous blood's delayed response to hyper- and hypoventilation, to the author's knowledge, is a novel result in this PhD project.

Results from Study I also demonstrate that at steady-state ventilation, v-tac can calculate arterialised acid-base parameters with the same precision as previously reported (45,46). Following acute hyper- and hypoventilation, we found that v-tac could still predict the arterial values at baseline – within clinically acceptable limits – with 100% accuracy up to 1 min and >50% after 2 min. In comparison, >50% of the measured arterial samples were outside these clinically acceptable limits as early as 45s, and all the samples were outside these limits at the end of 2 min. This means, that as a result of more stable peripheral venous values, v-tac can better represent steady state arterial values for up to a minute following a change in ventilation (1,3).

The clinical implications of these changes can be illustrated with a patient example **(Figure 3.1)**. In this example (also discussed in (3)), the patient's arterial pH and PCO_2 were measured to be 7.35 and 6.7 kPa. In the presence of acute transient changes in ventilation (illustrated earlier in Figure 1.3 B) it could be possible for the patient's real steady state arterial pH and PCO_2 values to be anywhere between 7.32 - 7.38 and 6.07 – 7.33 kPa. While these values reflect those taken from the results in study I above, in reality, changes in ventilation could range from hyperventilating at frequencies of over 30 breaths per minute, to varying durations of apnoea: disturbances much greater than those studied here. The degree of these responses initiated by transient ventilatory disturbances, could affect the decisions and treatments in the sequence of patient management. In the example, the patient's original value could have placed them in the chronic hypercapnia, normal, acute hypercapnia bands, or veering towards chronic base excess. Indications for treatment of acute hypercapnic respiratory failure with NIV are if pH < 7.35 and PCO_2 > 6.5 kPa (12,24). In this instance, the patient could potentially miss out on treatment if they hyperventilated while the sample was being drawn. To put things in perspective, a trained individual takes between 30 - 60s to perform an arterial puncture (19), and it is therefore likely that changes in ventilation could affect the arterial blood being sampled within this period. This however is not applicable to cases where there is acute respiratory failure for example, where the declining arterial oxygenation levels are of concern, and there is an obvious ongoing deterioration and threat of hypoxia. In such cases, an ABG is most certainly the preferred test of choice.

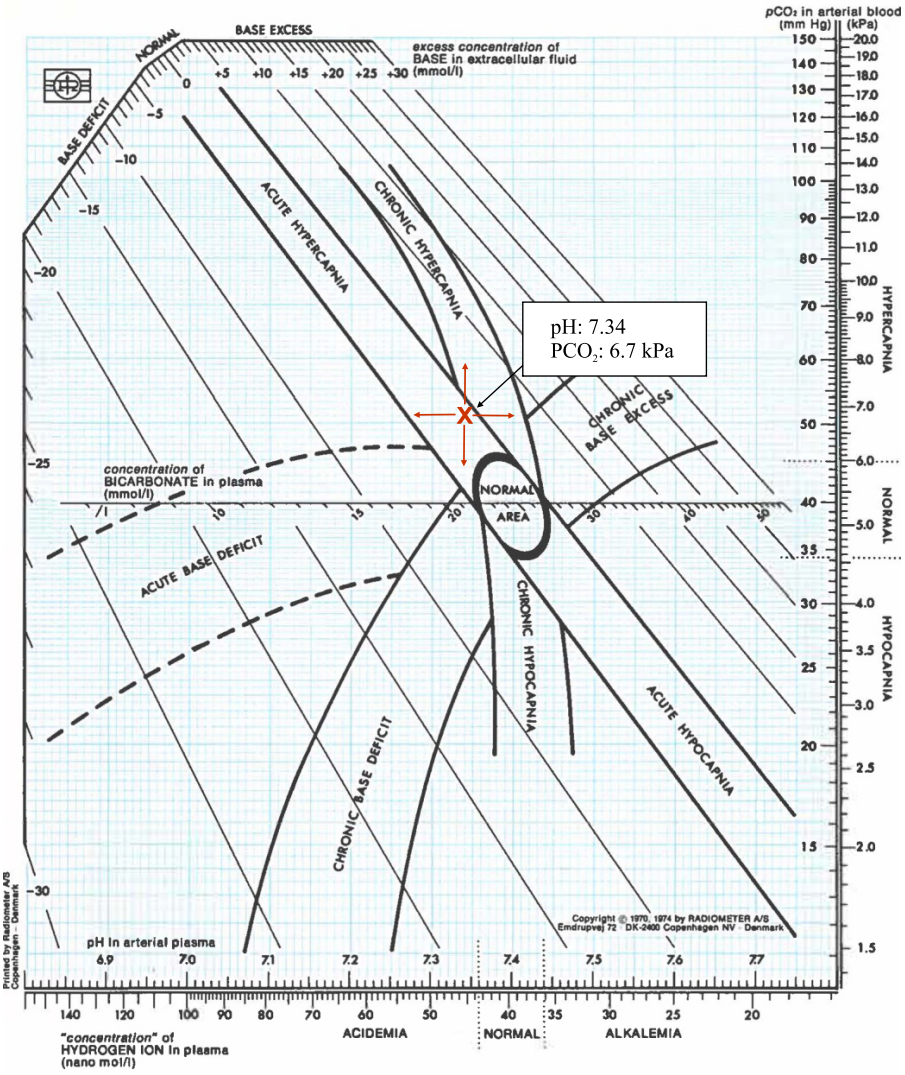

Figure 3.1 Patient example plotted on the Siggaard-Andersen acid-base chart.

Figure illustrating the possible effects of hyper- and hypoventilation on a patient with an arterial pH of 7.34 and PCO_2 of 6.7 kPa, marked in the figure with an 'x', with arrows representing the possible results due to acute ventilatory changes.

Although venous blood remained stable and was less likely to be influenced by acute transient changes in ventilation, if the ventilatory change was sustained for a longer duration, the arterial and venous blood values would likely reach a new equilibrium. Due to several reasons, outlined in the methodological considerations, the sampling protocols in studies I & II were limited and the response to a longer duration of ventilatory change, as well as the dynamics of a return to baseline were not investigated. However, these could be the basis for further investigation into the kinetics/dynamics of blood acid-base responses to acute changes in ventilation.

In addition to the dynamics of acid-base parameters, study II demonstrated the response of the CO_2 gap to acute changes in ventilation, which was similar to those observed by Morel *et al*. (57). Albeit traditionally calculated using mixed venous blood, from a sample taken from a pulmonary arterial catheter, the CO_2 gap in study II was calculated using central venous blood; Values of both are well correlated and can be used interchangeably in daily clinical practice (58,59). CO_2 gap of above 0.8 kPa (6 mmHg) is considered a marker of inadequate tissue perfusion (60,61), therefore, clinically significant changes of ± 0.6 kPa (2) from the true value could lead to patient misclassification. Physiologically, the CO_2 gap lies between 0.5 – 0.8 kPa (4-6 mmHg) (61) and in less than 2 min this could exceed the critical value of 0.8 kPa, in response to acute changes in ventilation (2). These variations extend to the CO_2 gap derived indices like the CO_2 gap /ΔtO_2 ratio that are used as a marker for the early onset of anaerobic metabolism and to predict prognosis at early stages of resuscitation (53,58,59,62). Such indicators could be crucial for critically ill patients with sepsis and septic shock, especially in the early hours of resuscitation, where early detection of tissue hypoxia could mean timely intervention and lower mortality rates (52,58,63). These ratios can be complementary tools to S_vO_2 which serves as a common fluid resuscitation target ($S_{cv}O_2 > 70\%$), where a high CO_2 gap can suggest the presence of insufficient blood flow even if the S_vO_2 is over the target (60).

3.1.1. Inherent variability in venous blood is not different from arterial blood

Study I confirmed that the inherent steady-state variability in arterial and venous blood were similar. Arterial and venous variability observed by Mallat *et al.* (29) most closely reflected the values in study I as they also drew two blood samples immediately after each other, and took active precautions in trying to minimise pre-analytical and analytical errors. The variability in arterial blood reported here was less than half the magnitude compared to those in previous studies with SDs ranging from 0.01 to 0.02 and similarly for PCO_2 with SDs of 0.14 to 0.29 kPa (28,29,64,65). These studies (28,64,65) focussed only on ABGs, kept the samples on ice before analysis, and sampled blood over a longer time period which could suggest that they could have been influenced by variations in ventilation. We know now that these factors contribute to pre-analytical and analytical errors, thereby resulting in the observation of larger variabilities in blood gases (6,66,67).

Although evaluating 'stable' patients, studies investigating arterial variability could not have ensured that the patient was in a steady state for the long duration of the protocols (28,64,65). In addition, they examined a mix of patients who were mechanically ventilated (assist or controlled modes) or spontaneously breathing. Patients on mechanical ventilation are prone to patient-ventilator interactions, leading to asynchronous breathing (15,24). These are unpredictable and the hour-long protocols increase the chances of these ventilatory perturbations affecting the results of the blood gas analysis. This brings about the concept of a 'physiological steady state', and its ever-changing, oscillating nature (68). In the event that an ABG must be taken, ensuring the patient is in a calm state, using local anaesthesia (10) to alleviate pain and having an expert to perform the procedure (to avoid multiple puncture attempts) helps with minimising pre-analytical errors; while making sure the blood gas analyser is close by, free, and calibrated before the blood sampling, helps to minimise delays with analysis and any further analytical errors (6). Albeit considered the gold standard, these characteristics of arterial blood itself and its sampling procedure make it particularly vulnerable to transient changes in ventilation – even if in a physiological steady state – and should be considered whenever ABGs are interpreted. The inherent variability in arterial and venous blood must be taken into account especially whenever blood gas 'trends' are measured, i.e., it should only be considered a change in patient state if the magnitude of change is over and above the blood's inherent variability.

3.2. The use of v-tac in a critically ill population using central venous blood

Thus far, the main critique of v-tac has been its possible limitations in relation to its assumptions. The method assumes no strong acid addition or removal at the tissue level, which was previously thought to limit its use on central venous blood or amongst the critically ill; Study III challenged this assumption. v-tac transformed over 65% of the samples within the previously defined clinically acceptable limits (pH ± 0.03 and PCO_2 ± 0.5 kPa), while calculating arterialised values with the same precision as the statistical model of Boulain *et al.* (42), which claimed to incorporate the necessary complexities to eliminate the assumptions of the v-tac method (4,69). It is interesting that a physiological model, derived from first principles without training to data, can in this context behave as well as a statistical model trained to two-thirds of these data, and which uses individual clinical variables over and above acid-base and oxygenation status (4). v-tac was previously tested on ICU patients, but using peripheral venous blood (50) where it worked with the same precision as with peripheral venous blood from non-critically ill patients. The reason results were not as expected when tested on central venous blood measured in study III could have been due to various reasons, primarily related to the presence of circulatory disturbances. Unlike in peripheral venous blood where one can ensure sampling from

a warm, well perfused extremity (with visual inspection), central venous sampling is more complex. The central venous blood itself is a representation of the venous drainage from all the body organs, any of which could be affected by perfusion insufficiencies. This could suggest the presence of varying degrees of anaerobic metabolism in one or more organ systems, such that there are different levels of acid addition to the blood, buffering responses and overall attempts at normalising the pH to maintain homeostasis.

For the 35% that could not be transformed within acceptable limits, attempts were made at finding a suitable parameter that could effectively represent the changes seen amongst the critically ill. Looking at the CO_2 gap/ΔtO_2 ratio (derived using Fick's principle and illustrated in **Figure 3.2**), we know that this increases in the event of anaerobic metabolism. However, there is no oxygen utilisation in anaerobic metabolism, therefore only an increase in the CO_2 gap (or ΔtCO_2) would result in an increase of that ratio. Since v-tac can account for the aerobic CO_2 production, we modelled the anaerobic production of CO_2 (xCO_2). Following this transformation, the precision of v-tac was nearly equivalent to that previously calculated using peripheral venous blood (48). Although this was just a modelling parameter, it was nevertheless able to account for a majority of the cases where v-tac alone could not transform venous to arterialised values within the previously defined clinically acceptable limits. For the remaining few, an additional exchange of strong acid – measured in the form of base excess (xBE) – was required to transform central venous values to within the previously defined precision of v-tac. Amongst those that required xBE, we found that they required xBE and xCO_2 in an equimolar fashion, possibly representing the movement of bicarbonate into the blood: one of the first responses to a decrease in pH, seen commonly with inadequate circulation and the onset of anaerobic metabolism (70). Lactic acidosis and ketoacidosis are some of the common outcomes of anaerobic metabolism, adding strong acid to the blood and reducing the pH. Even so, we did not find any correlation with the concentration of lactate with xCO_2. Finding a single parameter that could act as a surrogate for anaerobic metabolism without having to conduct multiple additional tests, could perhaps improve v-tac's performance and expand its usability to central venous blood and potentially patients with critical illness and perfusion disturbances. Investigating this concept in addition to examining the relationship between peripheral venous and central venous blood amongst the critically ill could prove beneficial to understand the different roles they may play in interpreting the various facets of critical illness.

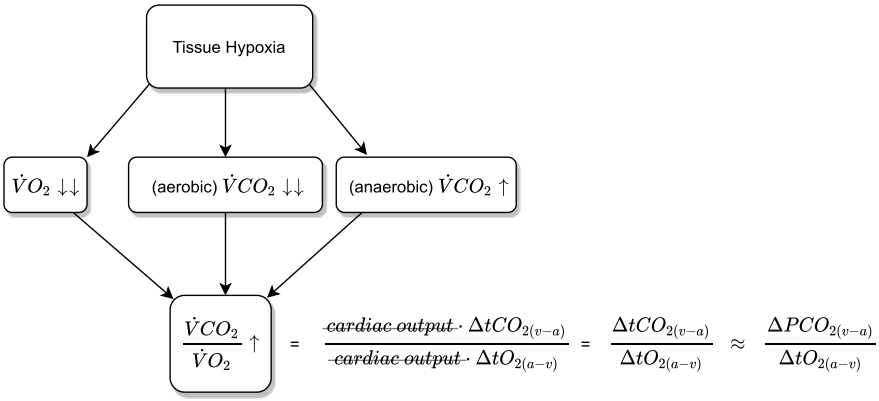

Figure 3.2 Derivation of the $\Delta PCO_2/\Delta tO_2$ ratio using Fick's principle.

In states of inadequate microcirculatory perfusion or tissue hypoxia, the change in oxygen consumption and CO_2 production alters the respiratory quotient (RQ), represented here by the ratio of $\dot{V}CO_2/\ \dot{V}O_2$. The RQ can also be calculated based on the cardiac output using Fick's principle and is outlined in the figure above, leading to the surrogate ratio of $\Delta PCO_2/\Delta tO_2$, where ΔPCO_2 is the CO_2 gap. In addition, the derivation of xCO_2, a parameter used in the analysis of study III is also illustrated as the anaerobic part of the CO_2 gap, over and above the contributions from aerobic metabolism (71,72).

3.3. Methodological Considerations

3.3.1. Study I & II

Analytical errors from the blood gas analyser were reported as bias for pH = -0.002 and PCO_2 = -0.03 kPa in the physiological range. In addition, repeatability for PCO_2 was reported as 0.05 kPa, representing the SD obtained from repeated measurements within a short interval of time using the same instrument and sample (73). These values underline the precision of using the same instrument, where analytical errors are minimal. In contrast, variability for PCO_2 calculated while using multiple blood gas analysers varied between 0.09 – 0.45 kPa (73), which would be an addition of over 6 times the inherent variability seen in the arterial blood itself, thereby adding a

great deal of error to the analysis; thus reinforcing our decision to use a single blood gas analyser for this study.

Care was taken to ensure minimisation of errors while sampling blood. A team of doctors was familiarised with the sampling protocol to ensure precise sampling at 15s or 30s intervals. Although it would have been ideal to have monitored the response to changes in ventilation for a longer duration, the number of blood samples were limited such that they could all be analysed within 30 min on the same analyser without storing them on ice, keeping in line with the IFCC guidelines (74). With the advent of newer blood gas analysers, which allow for faster measurements, it would be possible to monitor the response of blood gases for more than two minutes in the future.

The sampling protocols in the two studies were different as it is known that the time it takes for the arterial blood to reach the peripheral veins in the arm compared to the great veins is shorter, and the protocols were adjusted to reflect this difference. This was later reflected in the results where response in central venous blood was seen later than peripheral venous blood. We also focussed on evaluating the acid-base status and not on the oxygenation status, as oxygenation would not be influenced by changes in volume while the fraction of inspired oxygen was kept constant. This was monitored by the SpO_2 for the duration of the study, which was constant throughout. Further, as the colour of pig Hb was of a different wavelength, the co-oximeter results from the blood gas analyser were unreliable. Without the venous oxygen saturation and Hb values, it was not possible to calculate the v-tac values from central venous blood collected in study II.

Responses to hyper- and hypoventilation were previously tested using maximal voluntary hyperventilation (22,34) and breath-holding (23), where minute volume was changed to ~ +300% or to ~ –100%, respectively. We, however, chose to mimic conditions as close as possible to what one might encounter in reality, while also keeping in mind patient safety as they were under anaesthesia. In addition, voluntary manoeuvres previously employed (22,23,34) facilitate variability; although the respiratory rate was controlled using a metronome, the tidal volume was dependant on the participant. Simulating these conditions with mechanical ventilation and standardising the changes allowed for a more controlled study, where the results could be easily replicated and be comparable to others.

Novel to this project was the use of the blood's inherent variability, where a magnitude outside the bands of variability were considered a real change, or a response to the simulated ventilatory conditions. This enabled us to filter the changes due to the natural variation of the blood and analyse only the changes initiated by the study protocol, that were well above that of any possible analytical error.

3.3.2. Study III

Data for study III were collected on the premise of another study (42) and therefore did not have all the data needed to implement v-tac, leading to the exclusion of a large number of blood samples. In the publication itself (4), when comparing the statistical and physiological model, we could only use data that were not used to derive the statistical model, thereby reducing any bias towards the results. However, for the purpose of this dissertation, and evaluation of only v-tac in paper IV, we could include all data that fulfilled the criteria for analysis. These data were however, collected from multiple centers, and therefore have an additional degree of variability, especially when compared to the highly regulated study I. Evaluating the performance of the statistical model and v-tac using new data that would not be biased towards either of the models could help us better understand the performance of both methods and provide clarity on the ease of use of either model in a critically ill population.

CHAPTER 4.

Conclusions

This PhD project has shown that arterial blood responds rapidly to acute changes in ventilation, while venous blood displays a more delayed and dampened response. As a consequence of using the stable venous blood, v-tac was able to accurately calculate arterialised values, thereby better representing the steady-state/baseline arterial values, when compared to the rapidly changed acid-base parameters measured in the arterial blood. In essence, the oscillations seen in arterial blood values, i.e., the baseline variability, is augmented by the changes in ventilation, which essentially shift what we assume to be the average steady-state arterial value. This means that if there is any suspicion of a change in ventilatory pattern when collecting an arterial blood sample, it might be prudent to draw a venous blood sample and use the v-tac converted values instead of the traditional ABG, to avoid risks of patient misclassification while evaluating their acid-base status.

In addition, the PhD project has also shown that v-tac shows promise for use with central venous blood amongst the critically ill. Modifications with xCO_2 or xBE were able to account for some of the limitations of v-tac, however, this requires more clinical testing to find more accessible parameters that can provide an indication as to the degree of circulatory disturbance/perfusion insufficiencies/other measures of critical illness, that can be used to enable the use of v-tac in critical care.

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Abbreviations

ΔtO_2: Arterial – Venous difference in tO_2

ABG: Arterial Blood Gas

CO_2 gap: Central Venous – Arterial PCO_2 difference

CO_2: Carbon dioxide

COPD: Chronic Obstructive Pulmonary Disease

ED: Emergency Department

$EtCO_2$: End-tidal CO_2

ICU: Intensive Care Unit

IFCC: International Federation of Clinical Chemistry and Laboratory Medicine

LoA: Limits of Agreement

NIV: Non-Invasive Ventilation

PCO_2: Partial pressure of CO_2

PO_2: Partial pressure of O_2

RQ: Respiratory Quotient

SO_2: Saturation of O_2

SpO_2: Peripheral oxygen saturation

tCO_2: total content of CO_2

tO_2: total content of O_2

$\dot{V}CO_2$: Volume of CO_2 released in a minute

$\dot{V}O_2$: Volume of O_2 absorbed in a minute

xBE: Additional Base Excess above the aerobic metabolism

xCO_2: Excess of total CO_2 content above the aerobic metabolism

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Publications

Paper I (1)

Is venous blood a more reliable description of acid-base state following simulated hypo- and hyperventilation?
Scand J Trauma Resusc Emerg Med. 2021;29:35

Paper II (2)

Changes in central venous to arterial carbon dioxide gap (PCO_2 gap) in response to acute changes in ventilation.
BMJ Open Respir Res. 2021;8(1):e000886

Paper III (3)

Mathematically arterialised venous blood better represents acid-base status of the blood following acute changes in ventilation.
Under review in the Journal of Clinical Monitoring and Computing

Paper IV (4)

Comparison of two methods for converting central venous values of acid-base status to arterial values in critically ill patients.
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