Utility of mathematically converted venous to arterial blood gas values for clinical monitoring

Utility of v-TAC in the clinical setting

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UTILITY OF MATHEMATICALLY CONVERTED VENOUS TO ARTERIAL BLOOD GAS VALUES FOR CLINICAL MONITORING

BY
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by

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SUMMARY

Arterial blood gas (ABG) analysis provides essential detailed information on the blood gas and acid-base content of the blood in acutely ill patients. However, sampling of arterial blood is not without drawbacks as sampling to some extent is a technically challenging procedure. Furthermore, arterial puncture is painful for the patients and up to 59% develop subcutaneous haematoma following the procedure. Sampling of venous blood is a less painful alternative. However, venous blood gas (VBG) values do not approximate the ABG values with a clinical acceptable level of accuracy.

The venous to arterial conversion (v-TAC) method is a software program that has been developed to transform VBG values to compatible ABG values. This transformation is based on a mathematical simulation that inverts the process of gas exchange which occurs in the capillaries when blood travels from arteries to veins. In 2015, this method was implemented into blood gas analysers in the emergency department (ED) at the North Denmark Regional Hospital as part of a pilot project. However, the utility of the method has not, so far, been evaluated in real-time conversion of blood gas values in a daily clinical practice setting, and moreover there is a gap is a gap of knowledge of the validity of the method in patients with extreme pathophysiological abnormalities. These areas were elucidated in three studies.

In Study A, the validity of the v-TAC method and different sampling procedures were examined in a random ED patient population. We concluded that sample obtainment in 4.5 mL heparinised venous blood sampling tubes was safe, and samples could be stored up to 15 minutes if not tilted before being analysed. The strength of agreement was acceptable for all parameters except PO_2. Extreme-to-extreme misclassification of PO_2 was unacceptably high.

In Study B, the utility of v-TAC and selected venous blood gas values was assessed in conjunction with the triage process among patients admitted consecutively to the ED. A large proportion of the patients were detected with abnormal blood gas values but only few with severe deviations from normal reference intervals (NRI). Interestingly, most of these patients were at high risk of being overlooked in a following physician panel audit regarding the need for blood gas analysis. No associations were observed when comparing the patients' blood gas values with the assigned level of triage urgency, which on the contrary only showed a weak correlation with level of venous lactate.

In Study C, the validity of the v-TAC method was assessed in critically ill patients admitted to the ICU. In this patient group, the method calculated blood gas values

with clinically acceptable or marginal levels of accuracy. The method might not estimate pH values with acceptable validity in critically ill patients with diabetic ketoacidosis.

In summary, the v-TAC method offers a less painful alternative to obtain blood gas analysis by venous sampling as opposed to arterial puncture. If assessment of oxygenation status is imperative or the patient is critically ill, an ABG sample should be recommended. The v-TAC method contributes obvious benefits in patients requiring repeated blood gas analysis as this method may reduce the need for painful arterial punctures.

RESUMÉ

Arteriel blodgas (ABG) analyse giver essentiel information on oxygenerings- og syre-baseindholdet i blodet hos akut syge patienter. Arteriepunktur, som er metoden hvormed ABG-prøver opsamles, er dog vanskelig at udføre for klinikeren idet arterier, i modsætningen til vener, ikke er synlige gennem huden. Derudover er proceduren smertefuld for patienterne of 59% udvikler subcutant hæmatom efterfølgende. Venepunktur, til opsamling af venøs blodgas (VBG), er mindre smertefuld for patienten, men VBG-værdier estimerer ikke ABG værdier med klinisk tilfredsstillende præcision.

Venøs til arteriel konvertering (v-TAC) er et software program, som er udviklet til at transformere VBG værdier til estimater af ABG-værdier. Denne transformation er baseret på matematisk simulation og inverterer gasudvekslingsprocesses under blodets transport fra arterier gennem kapillærer og til venerne. I 2015 blev denne software implementeret i blodgasanalyseapparater i akutmodtagelsen (ED) på Regionshospital Nordjylland i forbindelse med et pilotprojekt. Anvendeligheden af v-TAC-metoden til realtid konvertering af blodgasværdier i daglig klinisk praksis er dog ikke tidligere blevet undersøgt, og tilmed er metoden ikke undersøgt tilstrækkeligt hos kritisk syge patienter med ekstreme patofysiologiske anormaliteter. Disse problematikker belyses gennem tre forskellige studier.

I Studie A undersøges validiteten af v-TAC-metoden og forskelige prøvehåndterings-metoder med inklusion af en tilfældig ED-patient population. Vi konkluderede, at prøveopsamling i 4.5 ml heparinierede venøse blodprøveglas var sikkert, og blodprøverne kunne opbevares i 15 minutter inden analyse, hvis de ikke rystes.

I Studie B blev v-TAC og VBG-værdier screenet for abnorme værdier hos konsekutivt indlagte ED-patienter, for at undersøge anvendeligheden af v-TAC-metoden til detektering af respiratoriske eller metaboliske sygdom, og for at undersøge sammenhæng mellem blodgasværdier og nødvendighed for akut behandling målt ved triage. En stor andel af indlagte patienter blev detekteret med abnorme blodgasværdier, men kun få havde alvorligt devierende værdier. Af patienterne med alvorligt devierende værdier ville kun en lille andel havde fået undersøgt blodgasværdier vurderet ud fra en post-hoc analyse udført at et panel af klinikere. Ved sammenligning af patienternes blodgasværdier og niveauet af triage fandtes ingen åbenbar association. Venøs laktat viste som den eneste blodgasparameter en meget svag korrelation med niveauet af triage.

I Studie C blev validiteten af v-TAC-metoden undersøgt hos kritisk syge patienter indlagt på intensiv afdeling. Hos denne patientgruppe beregnede v-TAC-metoden blodgasværdierne PCO_2 og pH med acceptabel og marginal nøjagtighed. Metoden beregner måske ikke pH hos patienter med kritisk sygdom grundet diabetisk ketoacidose med tilfredsstillende præcision og nøjagtighed.

I opsummering tilbyder v-TAC-metoden et mindre smertefuldt alternativ til blodgasanalyse. Hvis vurdering af valid oxygeneringsstatus er imperativt, eller patienten er kritisk syg, bør en ABG-analyse foretrækkes. v-TAC-metoden har åbenlyse fordele hos patienter, hvor hyppig eller rutinemæssig blodgasanalyse er påkrævet, idet behovet for smerteful arteriepunktur kan reduceres.

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LIST OF OBJECTS

Permissions to reuse been obtained for all objects when required. References are reported in the captions.

EQUATIONS

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ABBREVIATIONS

ABG	Arterial blood gas.
BE	Base excess.
caBG	Calculated arterial blood gas.
$caBG_{CVC}$	Calculated arterial blood gas from central VBG samples.
$caBG_{PVC}$	Calculated arterial blood gas from peripheral VBG samples.
CAT	Clinically acceptable threshold
COHb	Carboxyhaemoglobin.
CVC	Central venous catheter.
DPG	2,3-diphosphoglycerate.
ED	Emergency department.
ICU	Intensive care unit.
MetHb	Methaemoglobin.
NRI	Normal reference interval.
VBG	Venous blood gas.
v-TAC	The venous to arterial conversion method.
PCO_2	Partial pressure of carbon dioxide.
PO_2	Partial pressure of oxygen.
PVC	Peripheral venous catheter.
SO_2	Saturation of oxygen.
SOP	Standard operating procedure.
tCO_2	Total content of carbon monoxide.
tO_2	Total content of oxygen.
tNBB	Total non-bicarbonate buffer base.
95% CI	95% confidence intervals.
95% LOA	95% limits of agreement.

THESIS DETAILS

This PhD thesis is based on the following scientific papers:

Paper A: Lumholdt M, Damgaard KA, Christensen EF, Leutscher PDC. Mathematical arterialisation of peripheral venous blood gas for obtainment of arterial blood gas values: a methodological validation study in the clinical setting. J Clin Monit Comput. 2018 Sep, [E-publication ahead of print].

Paper B: Lumholdt M, Leutscher PDC, Christensen EF, Damgaard KA. Use of calculated and venous blood gas screening as a tool to support the clinical quality of triage in the emergency department. *In preparation*.

Paper C: Lumholdt M, Leutscher PDC, Damgaard KA, Christensen EF. Evaluation of the venous to arterial conversion (v-TAC) method among critically ill patients admitted to intensive care unit. *In preparation*.

The studies on which the papers are based are referred to as such:

Paper A: Study A

Paper B: Study B

Paper C: Study C

ACKNOWLEDGEMENT

What was originally through to be a minor study of the v-TAC method in 2015 developed into something completely different when we realised that further research of the v-TAC method was needed. The progress of this project has been the most rewarding, challenging and exiting process of my life. I have had the profound pleasure of collaborating with many enthusiastic, wise and hard-working people in this process, and I would like to express my special appreciation to some of those in the following.

Firstly, I would like to thank my three supervisors, Peter Leutscher, Kjeld Damgaard and Erika F. Christensen. Thank you for your supervision and help, and for giving me the opportunity to conduct this research in the first place. Peter, I have valued your admirable commitment to this project very highly. Thank you for your never-ending willingness to help, and for the many late hours you spend correcting my mistakes in manuscripts and texts. I have numerous times benefitted from your sharp perspectives on different problems, and from your amazing ability to make complex matters simple by use of a whiteboard and a marker. Kjeld, I would never have conducted this research or handed in this thesis if it was not for you. You introduced me to this project and has always stood by my side as a supervisor and mentor. Thank you for believing in me. Erika, thank you for your ability to always bear the aim in mind. You helped me keep focus when I drowned myself in numbers and algorithms. And thank you for the comprehensive work of arranging the research stay in Stavanger.

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Finally, the most important appreciation goes to my family. Thank you for your encouragement and endless support, and for tolerating all the hours I spend on research and work.

1. BACKGROUND

1.1. HISTORY OF MEASURING BLOOD GAS VALUES

Examining gas content in blood began as early as 1670 when Magnus, Hooke, and Boyle obtained gas from blood by means of a vacuum pump (1). Boyle and Hooke further observed that providing a constant flow of air through the trachea would keep dogs with multiple pleural punctures alive even without movement of the lungs (2). In 1754, Black first described 'fixed air' which was generated by heating or acidifying chalk, and later he proved that the same gas was present in exhaled air (3). Until this point, no one realised that during respiration something was removed from air and something else added.

Priestley discovered 'dephlogisticated air' by heating mercuric oxide and observed a much brighter flame than in plain air, but it was Lavoisier who recognised Priestley's gas as oxygen (O_2) in 1777 after observing phosphorous and sulphur gain weight when heated (2,4). Lavoisier realised that oxygen combines with fuel when burning takes place and theorised that Black's 'fixed air' must consist of carbon and oxygen (carbon dioxide, CO_2). In collaboration with mathematician Laplace, Lavoisier concluded that the principle of heat generation when coal burned in a fire was the same process taking place in the body (2).

In the following one and a half centuries, haemoglobin, pH-electrodes, and acidic and alkaline salts were discovered in blood (2), but it was not until Henderson formulated the laws of mass action for weak acids and their salts in 1907 that the buffer solutions in blood were better understood (5). Hasselbalch adapted Henderson's laws to the logarithmic form in 1917 creating the Henderson-Hasselbalch equation, which is applied nowadays in clinical acid-base analysis (5,6):

$$pH = pK + \log \frac{[HCO_3^-]}{[CO_2]}$$

Equation 1. The Henderson-Hasselbalch equation.

The clinical use of blood gas analysis originated from the epidemic of poliomyelitis in the early 1950s, which showed unprecedented mortality rates in Denmark. Up to 90% in of the patients with bulbar paralysis died, and chief physician and epidemiologist Lassen from Blegdams Hospital in Copenhagen, Denmark, sought help from Ibsen, a free-lance anaesthetist at Copenhagen's University Hospital, Denmark (7). Ibsen proposed using hand-supplied positive pressure to assist respiration in patients with

CO_2 retention due to respiratory failure (8). The treatment was implemented, and mortality rates decreased to 25% (2). Throughout the epidemic, approximately 1,500 medical and dental students participated in 165,000 hours of life-preserving breathing assistance in polio patients by squeezing rubber bags (9).

Total CO_2 blood content was measured using Van Slyke's method as ventilation guidance, but shortly after the epidemic ended, Radiometer A/S, Denmark, began manufacturing analysers that measured pH and partial pressure of CO_2 (PCO_2). Furthermore, Astrup's equilibration method was implemented in these instruments so that bicarbonate (HCO_3^-) and base excess could be calculated (2,10), and soon after, blood gas and acid-base values were used in the assessment of patients with a variety of respiratory and metabolic conditions (2).

1.2. ARTERIAL BLOOD GAS ANALYSIS TODAY

Arterial blood gas (ABG) analysis provides essential detailed information on oxygenation, circulation, ventilation, and acid-base status in acutely ill patients (11–13). The parameters generally measured by modern blood gas analysers are pH, PCO_2, partial pressure of O_2 (PO_2), concentration of haemoglobin (Hb), dyshaemoglobin (carboxyhaemoglobin, COHb, and methaemoglobin, MetHb), lactate, glucose, and electrolytes (sodium, potassium, and chloride), while HCO3 and base excess are calculated from measured values (14–17).

In intensive care units (ICU) many patients have arterial catheters (AC) for direct blood pressure measuring, which simplifies arterial sample collection (18). However, in other hospital wards, arterial blood is collected by puncturing an artery, typically the radial, brachial or femoral artery, although arterial blood can be obtained from any artery carrying oxygenated blood (17).

1.2.1. DISADVANTAGES OF ABG

In general, serious adverse events occurring in conjunction with ABG sampling are rare. The rate of adverse events such as air or clotted-blood embolism, arterial occlusion, or introduction of contagion in relation to arterial puncture is not available in the literature (18–20), but the incidence rate of artery pseudoaneurysm following arterial puncture has been estimated to 0.05% (21–24). However, as ABG sampling is a commonly ordered test (25) less severe drawbacks should be considered.

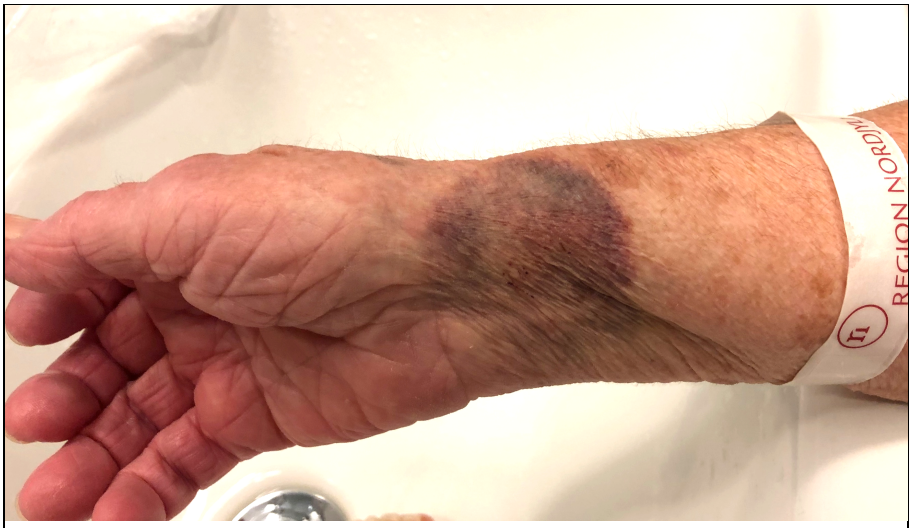

Figure 1. Subcutaneous haematoma. Developed after repeated arterial puncture in woman with COPD. Used with permission by patient.

Less severe adverse events such as haematoma (Figure 1) after radial artery puncture occur in up to 59% of the patients (26,27). Pain due to the procedure is also commonly present. In a study by Giner et al. (28) patients reported mean (±standard deviation, SD) pain ratings of 3.5 (1.89) on an 11-point analogue scale (zero indicating no pain and 10 indicating the worst possible pain). Matheson et al. (29) found a mean rating of 6.2 (0.4) by the patients using the same pain scale

In a questionnaire-based follow-up study, Turner et al. (30) evaluated recall of patients' collective experience of their ICU stay and found that ABG sampling was rated by 48% of the patients as the most unpleasant experience during admission followed by tracheal suction in 44% of the patients. Some pain is diminished if local anaesthesia is infiltrated before ABG sample collection (29,31). However, ABG sampling with anaesthesia is still as painful as venous blood gas (VBG) sampling without the use of local anaesthesia (28). Moreover, ABG sampling may well in some cases be a challenging procedure for the clinicians to perform compared to VBG sampling (25,32,33). McKeever et al. (34) demonstrated that clinicians conducted arterial puncture successfully in 69% of the patients on the first attempt, while venous puncture was successfully performed in 90% on the first attempt.

1.3. VENOUS BLOOD GAS

VBG has been suggested as an alternative to ABG to avoid the disadvantages associated with the arterial puncture described in Section 1.2.1. above. However, VBG pH has been found to agree reasonably well with ABG pH by systematic reviews, whereas the arteriovenous agreement of PO_2 and PCO_2 do not (35–38). Multiple studies have examined the arteriovenous agreement of pH, PCO_2 and lactate values since 2014. Thus, the meta-analysis calls for an update.

1.3.1. SEARCH STRATEGY

PubMed Medline was searched for eligible studies comparing ABG and VBG pH, PCO_2 and PO_2, and lactate. Lactate was included as the prognostic properties of this parameter has been found useful in multiple studies (13,39–41). The complete search strategy is shown in Appendix 1.

1.3.1.1. FLOW-CHART OF THE SEARCH

Studies published in the last 10 years examining the agreement between ABG and VBG values were included. This time frame was applied as systematic reviews have described earlier studies. The flowchart of the search is shown in Figure 2.

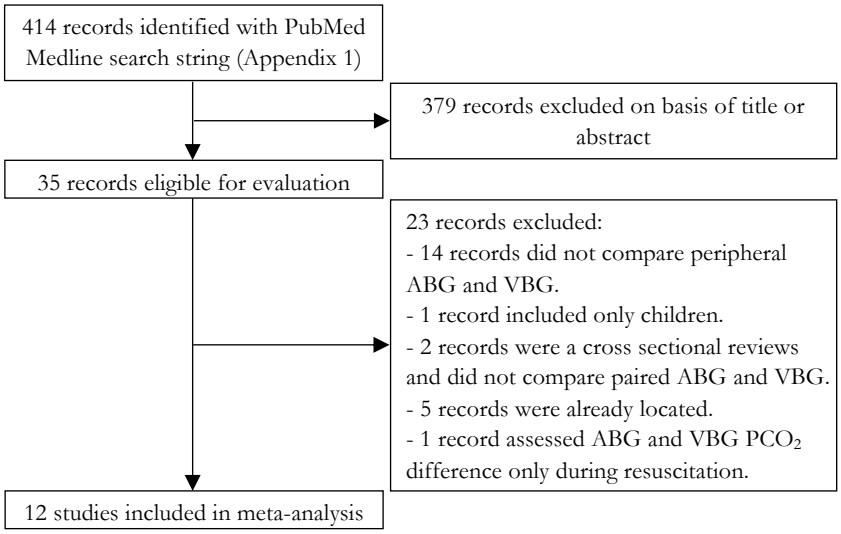

Figure 2. Flow-chart of the study inclusion process for meta-analysis.

1.3.2. META-ANALYSIS

Twelve more recent studies were identified reporting arteriovenous agreement of either pH, PCO_2 or lactate. None of those studies reported arteriovenous PO_2 agreement. Thus, PO_2 agreement is not included in the meta-analysis. Bland and Altman analysis (42) was used for assessing agreement in all included studies. The difference between ABG and VBG values were presented as mean bias and variation of the difference as the 95% limits of agreement (95% LOA) defined as mean bias ±1.96SD.

Most of the studies presented summary data; hence an overall Bland and Altman analysis was not possible. Therefore, for pooling data, the arteriovenous mean difference and 95% CI of the difference were processed in forest plots made in the software program Review Manager (version 5.3.5, The Nordic Cochrane Centre) (43).

The standard error (SE) used to compute 95% CI was calculated from the interval of 95% LOA divided by 2 and 1.96 and again divided by the square root of the number of participants. The meta-analysis is based on the systematic review by Bloom et al. (36) as the most recently published. In the following forest plots studies reporting arteriovenous agreement between the respective parameters is referred to in the paraphrased in each forest plot figure.

1.3.2.1. ARTERIOVENOUS PH DIFFERENCE

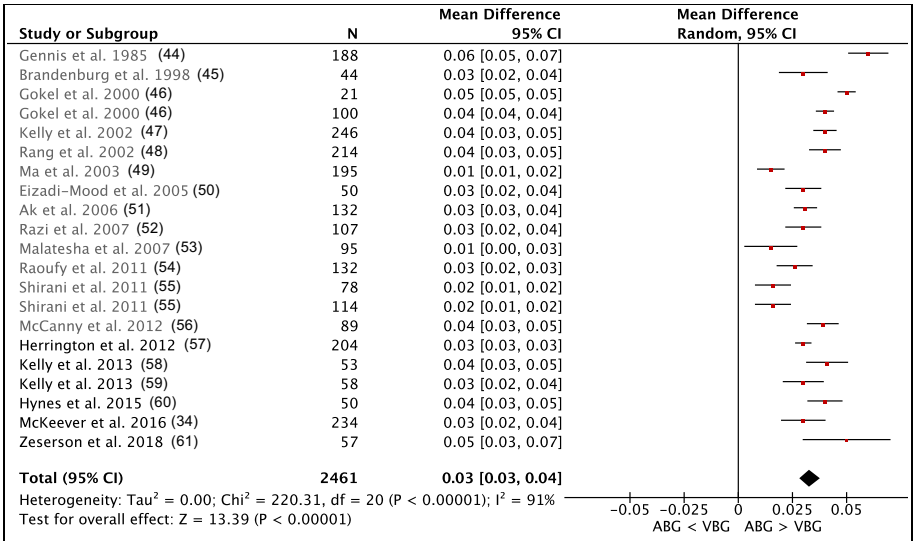

Figure 3. Pooled mean difference and 95% CI of ABG-VBG pH.
Studies presented by dimmed text are described by Bloom et al. (36).

Twenty studies reported an arteriovenous difference of pH, and 13 of those were described by Bloom et al. (36). Figure 3 shows forest plots of all 20 studies.

A random-effects model was applied as Higgins I^2-test showed high heterogeneity between studies (62). Of the 20 studies, 16 (80%) included patients from an emergency department (ED) setting, 3 (15%) included ICU patients and 1 (5%) included patients admitted both to the ED and to a pulmonary medicine department.

Pooled data available from 2461 patients in the included studies showed a mean difference [95% CI] between ABG and VBG pH of 0.03 [0.03 to 0.04].

1.3.2.2. ARTERIOVENOUS PCO_2 DIFFERENCE

Twelve of 17 studies reporting arteriovenous PCO2 difference were described by Bloom et al. (36). A forest plot of included studies is shown in Figure 4. PCO_2 values reported in millimetres of mercury (mmHg) in some of the studies were converted to kilopascals (kPa) to ensure consistency between all studies referred to in this thesis.

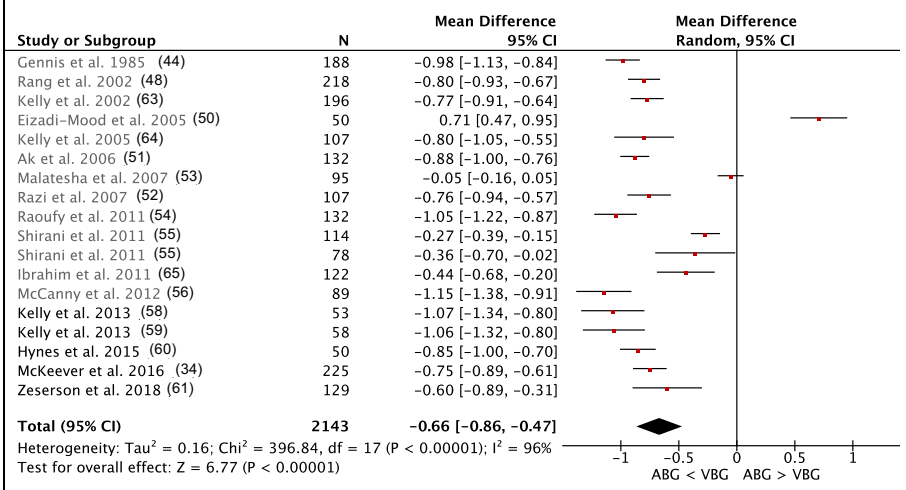

Figure 4. Pooled mean difference and 95% CI of ABG-VBG PCO_2. Studies presented by dimmed text are described by Bloom et al. (36). Units are kPa.

There was high heterogeneity between reported results in the 17 studies. Fifteen included ED patients and two included ICU patients. Data from a total of 2143 patients showed a mean difference [95% CI] of -0.66 [-0.89 to 0.31] kPa.

1.3.2.3. ARTERIOVENOUS LACTATE DIFFERENCE

Nine studies assessed arteriovenous lactate agreement. Bloom et al. (36) described three of the included studies. Forest plots are shown in Figure 5 with the difference in lactate reported in millimoles per litre (mmol/L).

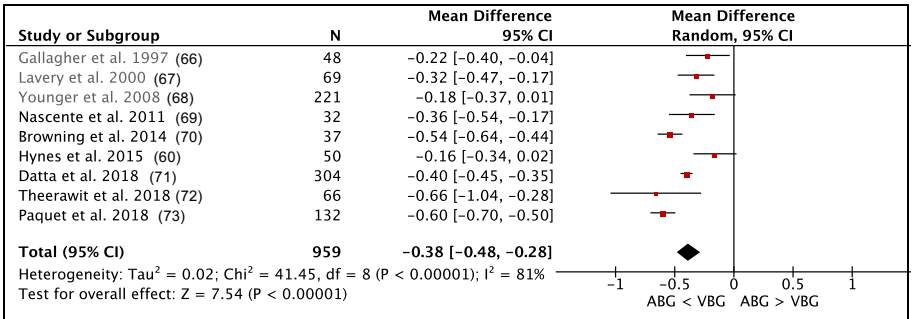

Figure 5. Pooled mean difference and 95% CI of ABG-VBG lactate. Studies presented by dimmed text are described by Bloom et al. (36). Units are mmol/L.

There was high heterogeneity between the studies and pooled mean difference [95% CI] between ABG and VBG lactate from 959 patients was -0.38 mmol/L [-0.48 to -0.28]. Of the nine studies, six included ED patients and three included ICU patients.

1.3.2.4. RECAPITULATION OF THE META-ANALYSIS

Gennis et al. (44) reported the highest mean difference [95% CI] between ABG and VBG pH of 0.060 [0.051 to 0.069], while Malatesha et al. (53) reported the lowest of 0.015 [0.003 to 0.027]. The widest 95% LOA from a Bland and Altman analysis of agreement was reported by Malatesha et al. (53) with a mean bias (95% LOA) of 0.015 (-0.1 to 0.13). This study was included in the meta-analysis by Bloom et al. (36). All recently-included studies have reported narrower 95% LOA between ABG and VBG pH. Thus, the additional knowledge did not support a change of Bloom et al.'s conclusion that ABG and VBG pH do agree within reasonable levels.

In the comparison of ABG and VBG PCO_2, the lowest mean difference [95% CI] was reported by Shirani et al. (55) of -0.27 [-0.39 to -0.15] kPa in normotensive patients, and the highest by McCanny et al. (56) of -1.15 [-1.38 to -0.91] kPa. The widest 95% LOA was reported by Shirani et al. (55) with a mean bias (95% LOA) on -0.36 (-3.45 to 2.73) kPa in hypotensive patients. The intervals of the 95% LOA varied greatly between studies from 1.76 kPa as reported by Ak et al. (51) to the 6.18 kPa as reported by Shirani et al. (55). Bloom et al. (36) concluded that VBG PCO_2 compared to ABG PCO_2 varied too substantially to be relied upon in clinical practice. This conclusion should be maintained.

In the comparison of ABG and VBG lactate, the lowest mean difference [95% CI] was reported by Hynes et al. (60) of -0.16 [-0.34 to 0.02] mmol/L. The highest mean difference [95% CI] between ABG and VBG lactate was reported by Theerawit et al. (72) of -0.66 [-1.04 to -0.28] mmol/L. This study included patients admitted to the ICU with sepsis or septic shock. The widest 95% LOA was reported by Theerawit et al. (72) with a mean bias (95% LOA) of -0.66 (-3.66 to 2.33) mmol/L. The intervals of the 95% LOA varied greatly between studies with Datta et al. (71) reporting the lowest of 1.6 mmol/L. Bloom et al. (36) stated that VBG lactate could be used as a proxy for ABG lactate. While this seems to be true in normotensive non-ICU patients, the recent study results indicate that clinicians should use caution when applying VBG lactate in hypotensive patients with sepsis or septic shock (71–73).

1.4. PROBLEM STATEMENT

The literature suggests that blood gas values are useful in the process of identifying critically ill patients who could benefit from early targeted medical intervention. Hucker et al. (74) showed that a combination of blood gas values (pH, PCO2, etc.) and measurements of vital signs could help to identify patients admitted to the ED at risk of severe disease deterioration and also to predict mortality with an area under the receiver operating curve (AUC) of 0.84. Furthermore, in a systematic review, Vincent et al. (75) concluded that kinetics of lactate constituted a robust prognostic clinical parameter in the evaluation of the critically ill patients in general, and not only septic patients. In another systematic review, Zhou et al. (76) showed that arterial lactate and the number of organ failures predicted mortality in ICU patients with acute-on-chronic liver failure. Similarly, Barfod et al. (77) concluded that venous lactate was independently associated with in-hospital mortality of critically ill patients admitted to the ED.

The systematic review by Bloom et al. (36) and the updated meta-analysis have shown that VBG values obtained from the less painful venous puncture deliver reliable pH values which could replace ABG pH in most situations if slightly different normal reference intervals (NRI) are applied (78). In contrast, VBG PCO_2 may vary considerably and to an extent that this parameter is difficult to rely upon as a replacement for ABG PCO_2.

While blood gas values may be useful as a screening tool in the ED setting, arterial puncture is unfit as a widespread routine practice due to pain for the patients and its challenging sampling procedure as discussed in Section 1.2.1.

It is not only in the ED setting that pain related to arterial puncture poses a problem. Hospitalised patients with the need of blood gas assessment on a close routine monitoring basis (e.g., patients with acute exacerbation in chronic obstructive pulmonary disease) may also benefit from a less painful venous blood gas sampling procedure. Local anaesthetics have been shown to reduce the discomfort for the patients (28,31), but unfortunately, local infiltration analgesia is seldom applied before arterial puncture in the daily clinical practice (79).

Different procedures have been proposed to correct the inaccuracy of VBG values for better estimation of ABG values. Several models based on linear regression has been proposed to form equations for estimation of ABG values from VBG values (80–82). Boulain et al. (83) calculated ABG values from central venous blood gas values and clinical measurements using a logistic regression model. Both studies showed that calculating ABG from VBG was a feasible analytical step.

In 2006, Rees et al. (84) introduced venous to arterial conversion (v-TAC, Obimedical, Denmark), which is a method for calculating blood gas (caBG) values by converting VBG values in combination with peripheral saturation measured by pulse oximetry measurements to ABG values. This method is based on a mathematical simulation that inverts the process of gas exchange that occurs in the capillaries when blood travels from arteries to veins.

In 2015, the v-TAC software was incorporated into blood gas analysers in the ED at the North Denmark Regional Hospital as a pilot project. The validity of the method, however, had never been evaluated in real-time conversion of blood gas values in a daily clinical practice setting before.

Only limited knowledge was available regarding the robustness of the method under different VBG sample handling conditions in daily clinical practice, and it was unknown which patient groups would benefit from implementation of this blood gas analysis method.

The v-TAC method is based on the principle that the peripheral limb is well perfused, and the amount of acid added from the tissue to the blood is small. However, this may not be true in the critically ill patients, and there is a grave gap in the literature on the validity of the method in critically ill patients with severe respiratory and metabolic acidosis or alkalosis.

1.4.1. OBJECTIVES

Toftegaard (85) previously published a PhD thesis on the mathematical and technical aspects of the v-TAC method and functions using laboratory-acceptable performance criteria.

As the next step, this PhD thesis has elaborated on the clinical perspectives of the v-TAC method. One of the main objectives has been to assess the validity and utility of the v-TAC calculated values in the ED setting with a particular interest in blood gas values as a supportive screening tool in the triage process. Another main objective has been to evaluate the validity of the v-TAC method in the critically ill patient group with various respiratory or metabolic disturbances in order to fill the gap of knowledge on the robustness of the method under extreme pathophysiological circumstances. These objectives have been addressed in three separate studies.

1.4.1.1. AIMS OF THE STUDIES

1. In Study A, the aim was to test the validity of the v-TAC method and different sample handling procedures in a random haemodynamically stable ED patient population.
2. In Study B, the aim was to assess the utility of v-TAC calculated and selected venous blood gas values as a screening and triage aid tool to determine the usefulness of routine blood gas analysis in a consecutively admitted ED patient population.
3. In Study C, the aim was to test the validity of the v-TAC method in a critically ill ICU patient population.

Valid results from blood gas analysis are essential for correct assessment and treatment of patients; hence this thesis will remain critical towards the v-TAC method as a trusted tool in the clinical practice.

In studies A and C, the alternative hypothesis that a clinically significant difference between ABG and caBG values was expected was tested. The null hypothesis, that no difference was expected, is a secondary point of navigation.

Study B is an observational explorative study; thus, formulating a hypothesis is futile. However, it was anticipated that caBG and selected venous blood gas values are not useful as a screening and triage aid tool.

2. METHODS

2.1. THE VENOUS TO ARTERIAL CONVERSION METHOD

The v-TAC method was applied in the conversion of venous blood gas values to arterial blood gas values in all three studies; thus, a general description of the principles of the method will be given in this section. The method calculates arterial values of pH, PCO_2 PO_2 and oxygen saturation in the blood (SO_2) from VBG values obtained from a peripheral vein and the peripheral oxygen saturation measured by pulse oximetry (SpO_2). Figure 6 shows the five steps of conversion of blood gas values referred to as arterialisation.

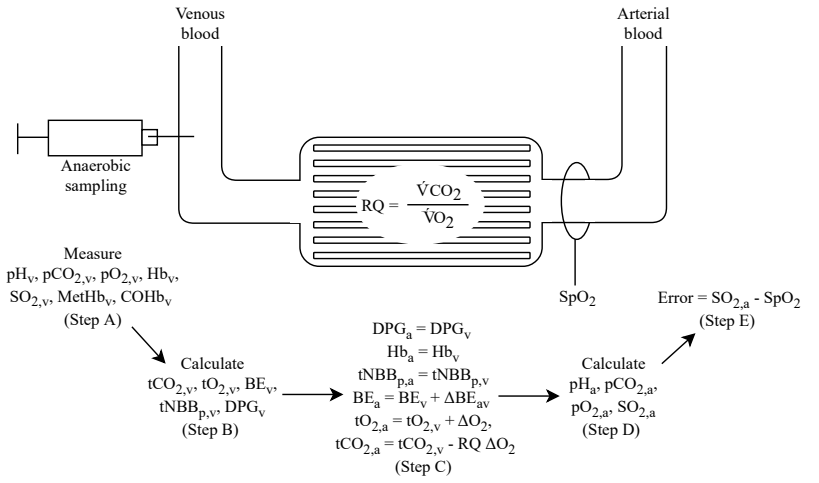

Figure 6. The principles of the v-TAC method. Reproduced with permission from the publisher (84).

Each step will be summarised in the following based on descriptions by Rees et al. (84).

1. Step A, the venous values of pH, PCO_2, PO_2, Hb, COHb, MetHb, and SO_2 are measured in a VBG sample by a blood gas analyser, and peripheral blood oxygen saturation is measured by pulse oximetry. Parameters with subscripts $_a$, $_v$, and $_p$ symbolise arterial, venous, and plasma values, respectively.
2. Step B, from the measured values the total venous CO_2 content ($tCO_{2,v}$), the total venous O_2 content ($tO_{2,v}$), the concentration of venous base excess

(BE_v) (NB in this context BE is defined as the concentration of strong acid necessary to titrate blood plasma to pH 7.4), the concentration of 2,3-diphosphoglycerate (DPG), and the concentration of total venous plasma non-bicarbonate buffer base ($tNBB_{p,v}$) is calculated. DPG is formed in red blood cells from glycolytic metabolism and binds to haemoglobin, which increases the energy required for oxygen to bind to haemoglobin. Thus, DPG moderates the affinity of haemoglobin for oxygen (86). The $tNBB_p$ is calculated if measurements of strong ions, Na^+, K^+, and Cl^-, are available. Otherwise, a fixed value of $tNBB_p$ = 23.5 milliequivalent per litre (mEq/L) is applied.

3. Step C, the variables $tCO_{2,v}$, $tO_{2,v}$, Hb_v, BE_v, DPG_v, and $tNBB_{p,v}$ are used to calculate arterial values. However, four assumptions are necessary to perform the calculation. The assumptions are:

    - $DPG_v = DPG_a$.
    - $Hb_v = Hb_a$.
    - $tNBB_{p,v} = tNBB_{p,a}$.
    - The respiratory quotient (RQ) is 0.82 (87).

    Then, the $tO_{2,a}$ is calculated by adding a concentration of O_2 (ΔO_2) to $tO_{2,v}$ and $tCO_{2,a}$ is calculated by subtracting the RQ multiplied with ΔO_2.
4. Step D, then the arterialised values of $tCO_{2,a}$, $tO_{2,a}$, Hb_a, $tNBB_{p,a}$ and DPG_a are used to calculate arterialised values of pH_a, $PCO_{2,a}$, $PO_{2,a}$ and $SO_{2,a}$.
5. Step E, the difference between the arterialised oxygen saturation $SO_{2,a}$ and SpO_2 measured by peripheral pulse oximetry is used to calculate an error that used to vary the value of ΔO_2 and steps C to E are repeated which gives an error of zero. Using the adjusted value of ΔO_2 the concentration of $tCO_{2,a}$ is re-calculated. Consequently, the venous values of pH, PCO_2, PO_2, and SO_2 are converted to arterialised values.

2.2. STUDY A

2.2.1. DESIGN AND SETTING

In this study the validity of the v-TAC method and different sample handling processes were tested in clinical practice in an ED patient population. This study was divided into a methodological pre-study in which the sampling procedures and sample containers were evaluated, and a clinical validation study in which appropriate sample handling procedures and agreement between ABG and v-TAC caBG values were assessed.

The study was conducted in the ED at the North Denmark Regional Hospital. This hospital offers 24-hour acute care facilities with medical, surgical, and ICU services for 250,000 citizens in the North Denmark Region. All patients are handled in the ED facilities, except patients with major trauma, ST-segment elevation myocardial infarction, or certain subspecialised injuries such as eye or urological trauma. The ED has approximately 15,000 patient contacts annually and is staffed by physicians in postgraduate clinical training and senior medical professionals.

2.2.2. STUDY PARTICIPANTS

Hemodynamically stable ED adult patients requiring both ABG for respiratory or metabolic assessment and routine venous blood analysis for any purpose were included in the study. Thirty subjects were planned to be included, 10 patients in the methodological pre-study and 20 patients in the validation study.

2.2.3. SAMPLE COLLECTION AND HANDLING

In the methodological pre-study, paired VBG samples were collected in 4.5 mL heparinised venous blood sample tubes and 2.0 mL heparinised SafePICO blood gas syringes (Radiometer, Denmark). The samples were obtained as close to simultaneously as possible using a three-way stopcock attached to the standard venous blood sampling kit (Figure 7).

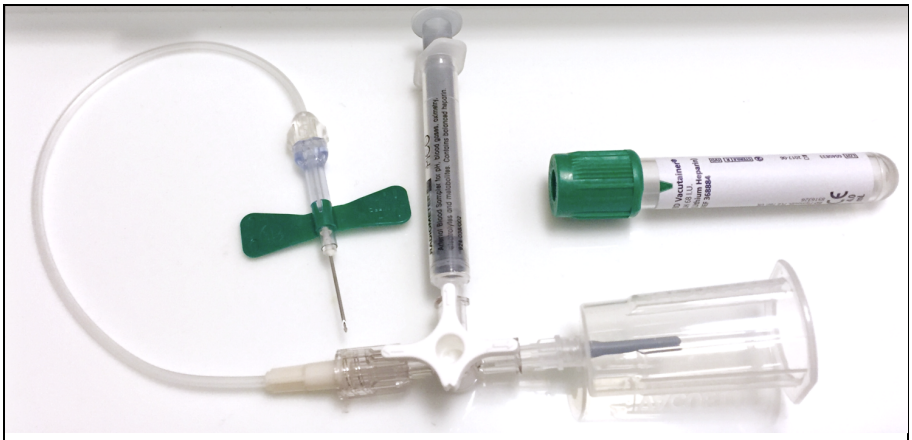

Figure 7. Blood gas sampling kit in the methodological pre-study in Study A. The three-way stopcock was attached to the standard sampling kit for uniform and rapid sampling.

VBG sampling in syringes was found to be inconvenient in our hospital setting due to the impracticality of requiring the three-way stopcock for sampling. If the stopcock was neglected and samples were to be collected in syringes directly from the standard venous blood sampling kit, an unacceptable risk of accidental needle injury arose. This problem is further discussed in Section 4.2. Therefore, VBG samples were obtained in the 4.5 mL tubes in the validation study (Figure 8).

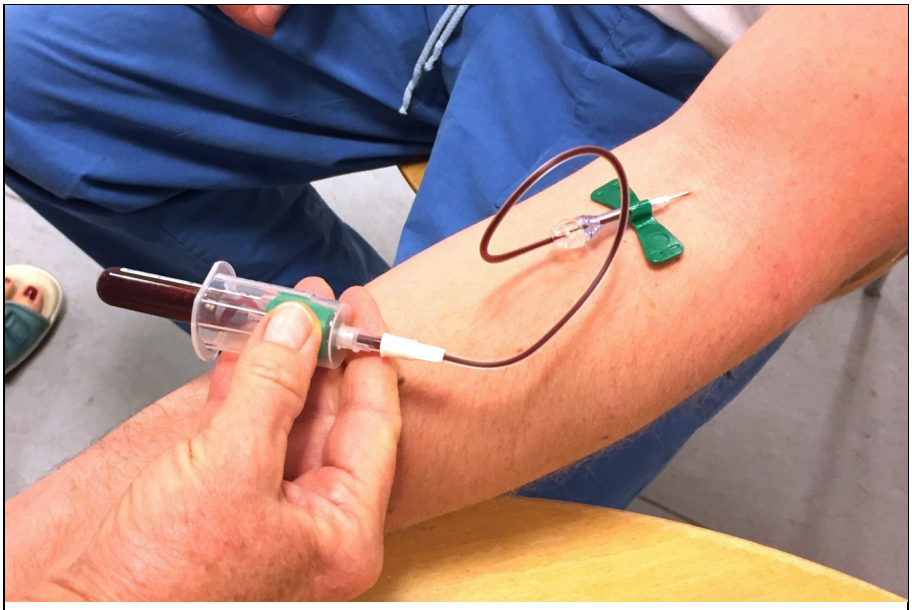

Figure 8. VBG sampling in the validation study.

Three VBG samples and one ABG sample were collected from each patient in the validation study. The attending physician performed the arterial puncture and VBG sample obtainment, while the attending phlebotomist collected the VBG samples. The three VBG samples were treated differently; the first was held steady and analysed within five minutes of sample collection, the second was tilted in five minutes and analysed after seven minutes, and the third was held steady and analysed 15 minutes after sample collection. ABG samples were treated as the first VBG sample. All blood gas samples were analysed using the same ABL800 FLEX blood gas analyser (Radiometer, Denmark). The VBG values were converted to caBG values using the v-TAC software incorporated into the ABL800 FLEX analyser. Information on patient age, cause of admission, and comorbidities were extracted from the patient admission files. In the following, the caBG values from the first VBG sample handling method is referred to as $caBG_1$, the second as $caBG_2$, and the third $caBG_3$.

2.2.4. DEFINING THE CLINICALLY ACCEPTABLE DIFFERENCE

Limited evidence is available regarding what difference between ABG and caBG values is acceptable in clinical practice. In a questionnaire-based survey, Rang et al. (48) asked 45 certified ED physicians to report how different ABG and VBG values of pH, PCO_2, and HCO_3^- could be before they would feel uncomfortable to rely solely on the VBG samples in clinical practice. The physicians would accept a mean difference [95% CI] of pH on ±0.05 [0.04 to 0.06] and PCO_2 on ±0.88 [0.74 to 1.01] kPa. Rang et al. did not examine which maximum difference was allowed for PO_2.

For studies A and B, the predetermined clinically acceptable thresholds (CATs), defined as the maximum clinically acceptable deviation of caBG values from ABG values, is fixed to ±0.05 for pH and ±0.88 for both PCO_2 and PO_2 (Table 1)

Parameters	Clinically acceptable ABG-caBG thresholds
pH	± 0.05
PCO_2	± 0.88 kPa
PO_2	± 0.88 kPa

Table 1. Clinically acceptable thresholds.

2.2.5. SAMPLE SIZE

The required sample size for the validation study in Study A was calculated based on ABG and caBG agreement results reported by Tygesen et al. (88). This study was selected because the patient admitted to the ED was included. The predetermined CATs were inserted in MedCalc (version 18.6, MedCalc Software bvba), and the calculated minimum required paired samples were 14 using alpha level 0.05 and 80% power.

2.2.6. STATISTICAL ANALYSIS

Agreement between ABG and caBG values was assessed using Bland and Altman statistics (42). The mean difference between ABG and caBG values were plotted against the average of the values in Bland and Altman plots (89). After calculating the mean bias and 95% LOA the LOAs were compared with the CATs as Bland and Altman states that two compared methods can be used interchangeably if the mean bias and 95% LOA are within the CATs (42).

Strength of the agreement between ABG and caBG values was assessed by calculating tolerability interval ratios. The tolerability interval ratios are calculated by dividing the interval of the CATs by the intervals of the actual 95% LOA observed in the study as

recommended by Columb (90). The interval of the CATs is 0.1 for pH and 1.76 kPa for both PCO_2 and PO_2.

The rate of misclassification of caBG values compared to paired ABG values was calculated as suggested by Boulain et al. (83). However, a misclassification was defined as a deviation of the caBG values from the ABG values that exceeded the CATs. Rate of one-way misclassification was defined as the proportion of caBG values that exceeded the CATs once, but now twice. If the caBG values deviated more than twice from the ABG values, this scenario was defined as extreme-to-extreme misclassification. Statistical analysis was conducted using Stata (version 13 SE, StataCorp, College Station) and R (version 1.1.383, RStudie, Inc., USA).

2.3. STUDY B

2.3.1. DESIGN, SETTING, AND STUDY PARTICIPANTS

In this observational study the utility and value of v-TAC calculated and selected venous blood gas values were evaluated as a screening tool for detecting patients with respiratory or metabolic disturbances and improving triage.

The study was conducted in the ED at the North Denmark Regional Hospital during three weeks in January and February 2016. The facilities of the hospital and ED are described in Section 2.2.1. All patients needing venous blood sampling were included in the study.

2.3.2. THE DANISH EMERGENCY PROCESS TRIAGE TOOL

The Danish Emergency Process Triage (DEPT) tool was used in the process of identifying a high-acuity patient with a high risk of mortality in the ED. The DEPT tool consists of differently coloured triage groups based on urgency: green (not urgent, re-evaluation within 180 minutes), yellow (less urgent, re-evaluation within 60 minutes), orange (urgent, re-evaluation within 15 minutes), and red (resuscitation, continuous re-evaluation) (Figure 9). The DEPT tool has a blue triage group for patients with minor injuries and complaints; however, a patient allocated to this triage group was not included in the study as venous blood sampling was rarely indicated.

The DEPT tool is based mainly on clinical measurements of SpO_2, respiratory- and heart rate, temperature, and Glasgow coma score (GCS), but also allows for a one-

level change of DEPT score based on specific symptoms of the patient (e.g., severe pain) (91).

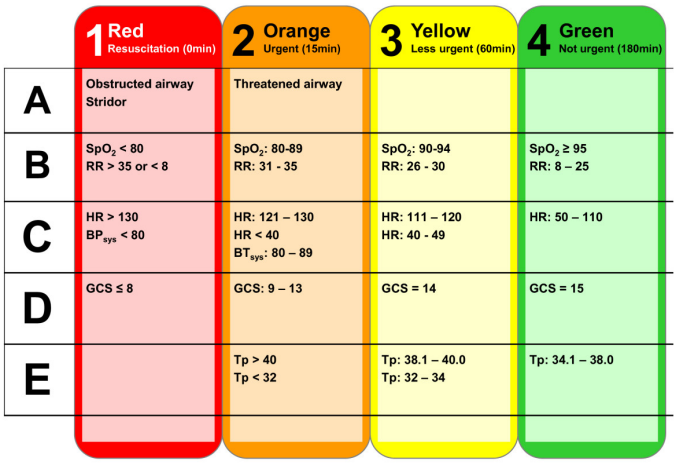

Figure 9. The Danish Emergency Process Triage. Figure lent from Barfod et al. (77).

The admission procedure in the ED at the North Denmark Regional Hospital is to allocate patients to a triage group immediately after admission using the DEPT tool. Specialised ED nurses conducted the obtainment of clinical measures of the patients and allocation to a DEPT group.

2.3.3. DATA COLLECTION AND BLOOD GAS SAMPLING

Clinical measurement, reasons for admission, and comorbidities of the patients were obtained from the medical file system, Clinical Suite (DXC Technology, Healthcare Denmark) and registered in patient records. Using the Quan-Deyo's algorithm (92,93) comorbidities, obtained as ICD-9 and ICD-10 codes, were classified into the 17 comorbidity categories.

VBG samples were obtained by a phlebotomist in 4.5 mL heparinised tubes in conjunction with routine venous blood sampling upon patient admission (Figure 8 in Section 2.2.3). The VBG samples were analysed using an ABL800 FLEX blood gas analyser and converted to caBG values using the v-TAC software incorporated in the blood gas analyser.

Only caBG values of pH and PCO_2 were extracted for analysis as PO_2 values in patients with SpO_2 above 96% are incorrectly calculated (88,94). As venous lactate and base excess are essential in the assessment of the acid-base status of the patients these values were also extracted for analysis (12,13,95,96). The caBG and VBG lactate and base excess values were extracted from Labka II (DXC Technology, Healthcare Denmark).

In a post hoc analysis, a panel consisting of four physicians reviewed the patient records and categorised reasons for admission into the following groups based mainly on the affected body system:

1. Central nervous system (CNS).
2. Respiratory.
3. Circulatory.
4. Gastrointestinal.
5. Urogenital.
6. Endocrine.
7. Poisoning (e.g., drugs, medicament, or biological substances).
8. Others (e.g., observational or causa socialis admissions).

Furthermore, the panel of physicians was asked to determine the need for blood gas assessment based on the patient records but not the caBG and VBG lactate and base excess values.

2.3.4. INDICATIONS FOR BLOOD GAS ANALYSIS

The panel of physicians was requested to follow national and international guidelines on indications for blood gas analysis. As no guidelines describe indications for obtainment of caBG values, the guidelines on ABG was the reference. According to the American Association for Respiratory Care, the guidelines on indications for ABG are as follows (14).

- The need for evaluation of patients' ventilatory (PCO_2), oxygenation (PO_2 and COHb) and acid-base status; the oxygen-carrying capacity (PO_2, Hb, COHb; and MetHb) and intrapulmonary shunt (97).
    - The need for monitoring severity and progression of documented respiratory, circulatory, or metabolic disease processes (14,19,98,99).
- The need to quantify response to therapeutic intervention (e.g., oxygen therapy or mechanical ventilation) (19,100).

- The need for evaluation of gold-directed therapy in patients with sepsis, septic shock, and after major surgery (19,101).

Additional high fraction of central venous/arterial PCO_2 can indicate inadequate perfusion in patients with severe haemorrhagic shock, poor cardiac output, or during cardiopulmonary resuscitation or major surgery (102,103).

No provisions were instituted to make sure the panel of physicians followed these guidelines in the post hoc assessment.

2.3.5. STATISTICAL ANALYSIS

The variance of caBG and VBG lactate and base excess between DEPT groups were assessed using an ANOVA (parametric) or Kruskal-Wallis (non-parametric) test. If a statistically significant difference between DEPT group was observed, the Spearman's rank-order correlation or Pearson product-moment correlation was used to test the correlation between caBG or VBG lactate and base excess values and the DEPT group. P-values below 0.05 were considered statistically significant.

Parameters	Reference intervals
pH, arterial	
Both genders	7.35 to 7.45
PCO_2, arterial	
Female	4.26 to 5.66 kPa
Male	4.66 to 6.38 kPa
Lactate, venous	
Both genders	< 2 mmol/L
Base excess, plasma	
Female	-2.3 to 2.7 mmol/L
Male	-3.2 to 1.8 mmol/L

Table 2. Normal reference intervals (78,104).

The sensitivity and specificity of the panel of physician's decision on the need for blood gas analysis were calculated by analysing patients with caBG and VBG lactate and base excess values outside of the normal reference interval (NRI).

The NRI applied in this study is based on Klæstrup et al.'s findings (104), and Radiometer's Acute Testing Handbook prepared by Seeger et al. (78). The NRIs are presented in Table 2. The patients detected with caBG and VBG lactate and base excess outside of NRI were analysed in a subgroup analysis to explore whether patients with certain characteristics or conditions were at risk of being overlooked regarding the need for blood gas analysis.

Unsupervised machine learning was used to simulate a clinical assessment of the patients' blood gas values in order to detect severe deviations of caBG pH and PCO_2 and VBG lactate and base excess values. The detection of these patients was attempted by using hierarchical clustering with single linkage and Euclidean distance. The height

of the dendrograms of combined caBG and VBG values of each patients was cut off using visual assessment to identify clusters of patients with the outermost presentation of combined caBG and VBG lactate and base excess values.

2.3.5.1. HIERACHICAL CLUSTERING

Hierarchical clustering is a type of unsupervised machine learning used to arrange data in trees of clusters (105). As opposed to the more well-known K-means algorithm, hierarchical clustering does not rely on a fixed number of clusters, and the user is, therefore, able to have some influence on the division of clusters (106). Single linkage is the simplest agglomerative hierarchical clustering approach in which each data point is allocated in its own cluster, and the clusters are merged iteratively until all clusters belong in one cluster based on the Euclidean distance from one cluster to the other (107,108). The arrangement of the clusters is plotted as dendrograms in which the height scale is an arbitrary measure of the distance between the clusters (106,109), and the actual distance between the clusters are presented as the edges in the dendrograms (109). The division of clusters relies on the observer to apply cut off lines in the dendrograms as shown in Figure 10.

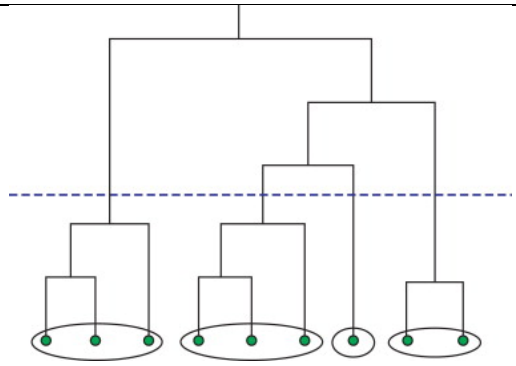

Figure 10. Hierarchical cluster dendrogram with cut-off line. The dots in the bottom represent data points and clusters whereas the edges in the dendrograms represent the distance between the clusters. The applied cut-off line arranges data points in clusters as visualised by the eclipses around the data points. The figure is shown with permission from the publisher (109).

The number of parameters included in the machine learning analysis determines the dimensions of each data point. In this study, each data point will have four dimensions as it consists of four blood gas parameters: the caBG pH and PCO_2 values, and the

VBG lactate and base excess values. All statistical and machine learning analysis was conducted using R (version 1.1.383, RStudie, Inc., USA).

2.4. STUDY C

2.4.1. DESIGN AND SETTING

The objective in this validation and case series study was to test the validity of the v-TAC method in a heterogenic, critically ill, ICU patient population. The study was conducted in the ICU at the North Denmark Regional Hospital from December 2017 to December 2018.

The seven-bed ICU receives and treats critically ill patients from the ED, medical and surgical wards, and patients from other ICUs in the North Denmark Region. A total of 17,800 surgical procedures are performed at the hospital annually (97). The facilities of the hospital are described further in Section 2.2.1.

2.4.2. STUDY PARTICIPANTS

Critically ill adult patients admitted to the ICU were included in this study if acidosis or alkalosis was present in the initial ABG analysis of the critically ill patients (ABG pH <7.35 or >7.45, respectively (78,104)). Furthermore, patients were included only if they had arterial catheters for ABG sampling or invasive continuous blood pressure measurement and peripheral venous catheters (PVC) and/or central venous catheters (CVC).

2.4.3. SAMPLING PROCEDURES AND DATA COLLECTION

The sample collection process followed standard operating procedures (SOPs) described before study commencement. The SOPs were approved by the chief medical officer of the intensive care unit. Multiple paired ABG and VBG samples were collected from critically ill ICU patients simultaneously from arterial catheters and PVC and/or CVC, respectively. Sampling from both PVC and CVC was chosen as CVC sampling may be desirable in certain clinical situations (e.g., problematic identification of blood vessels or when the peripheral circulation has shut down due to shock).

All blood gas samples were collected in 2.0 mL heparinised SafePICO blood gas syringes from catheters and analysed using an ABL800 FLEX blood gas analyser located at the ICU. All samples were analysed within five minutes after sample obtainment. The VBG values were converted to caBG values using the commercially available v-TAC method.

Clinical measures of heart- and respiratory rate, SpO_2, blood pressure, temperature, and information on respirator settings, simplified acute physiology (SAPS) 3 score, type and rate of inotropic therapy, cause of admission, and a clinical assessment of circulatory and oxygenation status of the patients were registered on patient charts (Appendix 2).

2.4.3.1. LIMITATIONS OF THE V-TAC METHOD

Three limitations of the v-TAC method were implemented after studies A and B were completed but before the commencement of Study C. The limitations were as follows:

- Arterialisation could not be performed if venous pH was below 6.8.
- Arterialisation could not be conducted if SpO_2 was below 75%.
- Arterialised PO_2 values above 10.0 kPa was reported with the label >10.0 kPa.

2.4.4. SAMPLE SIZE

The minimum required sample size for the comparison of ABG values and caBG values from peripheral venous blood was 21 pairs, and for the comparison of ABG values and caBG values calculated from central venous blood, the required sample size was 16 pairs. Sample size calculations were performed on the basis of results reported by Toftegaard et al. (110). The alpha level was 0.05, and the statistical power was 80%. Sample size calculations were conducted using predefined CATs in MedCalc as presented in Section 2.2.4.

2.4.5. STATISTICAL ANALYSIS

Similar to statistics conducted in Study A, the agreement between ABG and caBG values was assessed using Bland and Altman statistics (42). However, as ABG values were considered the gold standard and multiple samples per patient were obtained, the mean bias between ABG and caBG values was plotted against the ABG values in Bland and Altman plots as advised by Krouwer (111). The strength of agreement between

ABG and caBG values was evaluated by calculating tolerability interval ratios and rate of one-was and extreme-to-extreme misclassification was calculated as described in Section 2.2.6.

In accordance with recommendations provided by Bland and Altman (112), the variances of differences between ABG and caBG values were analysed in individual patients and between patients to determine whether 1) sample pairs should be treated as if they were from individual subjects or 2) averages of both ABG and caBG values should be calculated in each patient before comparison analysis. Bland and Altman recommend comparing the in-patient variance of the difference of ABG and caBG values with the variance of the difference of ABG and caBG values between patients using one-way ANOVA. If there was a statistically significant difference, the 95% LOA was calculated for both scenarios, and the method providing the widest 95% LOA was chosen.

2.5. ETHICAL CONSIDERATIONS AND DATA PROTECTION

All studies were conducted according to the Danish ethical regulations. The Danish Research Ethics Committee in the North Denmark Region was notified about the studies. The Danish Data Protection Agency was notified and approved all studies. Only approved database storage solutions were used.

3. RESULTS

3.1. STUDY A

3.1.1. METHODOLOGICAL PRE-STUDY

The 10 ED patients included in the methodological pre-study had a median (range) age of 76 (26-86) years, and the distribution of gender M/F was 6/4. The mean difference (±SD) between pH, PCO_2, and PO_2 values collected in 2.0 mL syringes and 4.5 mL tubes was 0.01 (0.01), -0.02 (0.27) kPa, and 0.57 (1.1) kPa, respectively (94). The difference between the 4.5 mL tube and 2.0 mL syringe was not considered clinically important at the time, and due to the risk of needle injury using other methods, the 4.5 mL tube was chosen over the syringe for VBG sampling in the validation study.

3.1.2. PATIENT CHARACTERISTICS

Twenty patients requiring ABG analysis were included in the study. Table 3 shows a summary of demographic features of the patients. The proportion of females was 40%. None of the patients were haemodynamically unstable or suffered from severe hypoxia.

Demographics			
n	20	Comorbidities	
Age, median (range)	66 (36 to 96)	COPD	8 (40)
		Heart failure	5 (25)
Gender, M/F	12/8	Essential hypertension	4 (20)
Cause of admission, n (%)		Ischemic heart disease	2 (10)
COPD exacerbation	6 (30)	Arterial fibrillation	2 (10)
Pneumonia	3 (15)	Diabetes mellitus	2 (10)
Suspected abdomen ischemia	3 (15)	Myxoedema	1 (5)
Dehydration	3 (15)	Small cell carcinoma	1 (5)
Cor pulmonale	2 (10)		
Diabetic ketoacidosis	1 (5)		
Dysregulated diabetes mellitus	1 (5)		
Bleeding haemorrhoid	1 (5)		

Table 3. Demographics of the patients in Study A. COPD, Chronic obstructive pulmonary disease. Reproduced from Paper A with permission from the publisher (94).

3.1.3. COMPARISON OF ABG AND CABG

Table 4 shows ABG and caBG values and agreement calculated using Bland and Altman statistics. Higher mean bias and broader 95% LOA were observed in all parameters in the comparison with $caBG_2$, which was calculated from tilted VBG samples. The tilting treatment produced an increase in PCO_2 of 0.5 kPa, which caused a decrease in pH. A minor increase in PO_2 was also observed.

Parameters	ABG	caBG		Bland and Altman analysis	
	Mean (±SD)	Type	Mean (±SD)	Mean bias	95% LOA
pH	7.42 (0.05)	$caBG_1$	7.42 (0.05)	0.00	-0.04 to 0.03
		$caBG_2$	7.39 (0.04)	0.03	-0.01 to 0.07
		$caBG_3$	7.42 (0.05)	0.00	-0.03 to 0.03
PCO_2, kPa	4.9 (0.6)	$caBG_1$	5.0 (0.6)	-0.01	-0.47 to 0.38
		$caBG_2$	5.5 (0.6)	-0.54	-1.09 to 0.02
		$caBG_3$	5.0 (0.6)	-0.01	-0.48 to 0.46
PO_2, kPa	10.3 (1.8)	$caBG_1$	11.2 (NA)	-0.96	NA
		$caBG_2$	11.5 (NA)	-1.25	NA
		$caBG_3$	11.3 (NA)	-1.00	NA

Table 4. ABG and caBG values in Study A. ABG, arterial blood gas; caBG, calculated arterial blood gas using v-TAC; 95% LOA, 95% limits of agreement; $caBG_1$, VBG analysed within five minutes; $caBG_2$, VBG tilted in five minutes and analysed after seven minutes; $caBG_3$, held steady and analysed after 15 minutes. Standard deviations of caBG PO2 values were erroneously presented in Paper A; however, the mean difference between ABG and caBG PO_2 did not follow a normal distribution and should not be presented. Reproduced from Paper A with permission from the publisher (94).

The strength of the agreement was acceptable between all comparisons of ABG and caBG pH and PCO_2 as the tolerability interval ratio was below 1 (see Section 2.4.5). The difference in PO_2 values did not follow a normal distribution; hence, tolerability interval ratios should not be calculated for this parameter although this was performed in Paper A.

There was no one-way or extreme-to-extreme misclassifications of $caBG_1$ and $caBG_3$ pH compared to ABG values, but the rate of one-way misclassification of $caBG_2$ pH was 10%. Similarly, there was no misclassification of $caBG_1$ and $caBG_3$ PCO_2 values, but rate of $caBG_2$ PCO_2 one-way misclassification was 15%. In contrast the rate of one-way misclassification of $caBG_1$, $caBG_2$, and $caBG_3$ PO_2 was 35%, 35%, and 30%,

respectively. The rate of extreme-to-extreme misclassification was 25%, 25% and 25%, respectively.

3.2. STUDY B

3.2.1. PATIENT CHARACTERISTICS

In the three week, 631 admissions were registered in the ED. In 520 of the admissions, caBG and VBG lactate and base excess values and DEPT score were obtainable.

Eight patients were re-admitted in the inclusion period, four of whom were allocated to the same DEPT group (green), and the four remaining patients were allocated to a different group upon the second admission. A summary of the demographics of the included patients is shown in Table 5.

		Danish Emergency Process Triage score				
Demographics	Total	Green	Yellow	Orange	Red	P-value
n admissions	520	204	168	131	17	
Age, median (range), year	66 (9-99)	64 (9-99)	66 (13-97)	69 (18-96)	80 (57-91)	**
Gender, M/F	239/281	101/103	71/97	61/70	6/11	NS
Reasons for admission, n (%)						
Gastrointestinal	164 (31)	75 (37)	70 (42)	19 (14)	0	***
Respiratory	101 (19)	17 (8)	30 (18)	46 (35)	8 (47)	***
Circulatory	76 (15)	32 (16)	8 (5)	30 (23)	6 (35)	***
Central nervous system	52 (10)	27 (13)	10 (6)	15 (11)	0	NS
Urogenital	29 (6)	13 (6)	13 (8)	3 (2)	0	NS
Poison	14 (3)	3 (2)	5 (3)	5 (4)	1 (6)	NS
Endocrine	10 (2)	10 (3)	4 (2)	0	0	NS
Other	74 (14)	31 (15)	28 (16)	13 (10)	2 (12)	NS
Panel assessment, n (%)						***
BG indicated	107 (21)	16 (8)	24 (15)	53 (41)	14 (82)	
BG not indicated	413 (79)	188 (92)	144 (85)	78 (59)	3 (18)	

Table 5. Summarised demographics of the patients in Study B. P-values: NS, not significant; * <0.05; ** <0.01; *** <0.001. Reproduces from Paper B.

A statistically significant increase in the age of the patients with triage urgency was observed. The proportion of patients with respiratory and circulatory reasons for admission were significantly larger in the orange and red DEPT groups compared to the green and yellow groups. In contrast, the proportion of patients with

gastrointestinal reasons for admission was small in the orange and red DEPT groups compared to the green and yellow groups.

The most frequent Quan-Deyo's comorbidities of the patients were chronic pulmonary disease (n = 164, 22%), diabetes mellitus (n = 101, 14%) and previous history of stroke (n=76, 14%). In all Quan-Deyo's comorbidity categories the proportion of patients with chronic pulmonary disease and congestive heart failure showed a statistically significant increase with triage urgency.

The proportion of patients with chronic pulmonary disease increased from 13% (n = 27) in the green DEPT group to 47% (n = 8) in the red group, and the proportion of patients with congestive heart failure increased from 5% (n = 11) to 18% (n = 3).

3.2.2. BLOOD GAS VALUES AND TRIAGE URGENCY

Median and range of caBG and VBG lactate and base excess values are shown by DEPT group in Table 6. Venous lactate was the only parameter which showed a minor but statistically significant increase with triage urgency.

Using Spearman's rank order, a very weak correlation between venous lactate and DEPT group were detected with (r_s = 0.18). The range of the blood gas values shows that patients with extreme values were observable in the lesser urgent green and yellow DEPT groups.

Blood gas values		Danish Emergency Process Triage score				
Median (range)	All	Green	Yellow	Orange	Red	P-value
pH, caBG	7.43 (7.20-7.67)	7.44 (7.25-7.65)	7.44 (7.27-7.67)	7.43 (7.20-7.60)	7.44 (7.28-7.51)	NS
PCO_2, kPa, caBG	4.8 (1.8-11.0)	4.8 (1.8-6.8)	4.7 (2.8-10.1)	4.8 (2.6-11.0)	4.6 (3.9-10.2)	NS
Lactate, mmol/L, Venous	1.4 (0.0-14.7)	1.4 (0.0-6.0)	1.4 (0.0-4.6)	1.6 (0.8-14.7)	2.0 (0.0-4.4)	***
Base excess, mmol/L, Venous	1.2 (-18.6-11.0)	1.2 (-16.3-8.8)	1.3 (-13.2-10.7)	0.9 (-18.6-11.0)	1.1 (-6.1-9.5)	NS

Table 6. Median (range) of blood gas values in the DEPT groups in Study B. P-values: NS, not significant; * <0.05; ** <0.01; *** <0.001. Reproduced from Study B.

Patients with one or more of the caBG or VBG values outside the NRI (see section 2.3.5.) were detected in 413 of the 520 admissions. The distribution of the 413 registered cases by DEPT group were as follows: 67% (n admissions = 137), 76% (n

admissions = 127), 76% (n admissions = 99), and 88% (n admissions = 15) in the green, yellow, orange, and red DEPT groups, respectively (Figure 11). Although the proportion increased with triage urgency, the difference did not reach statistical significance.

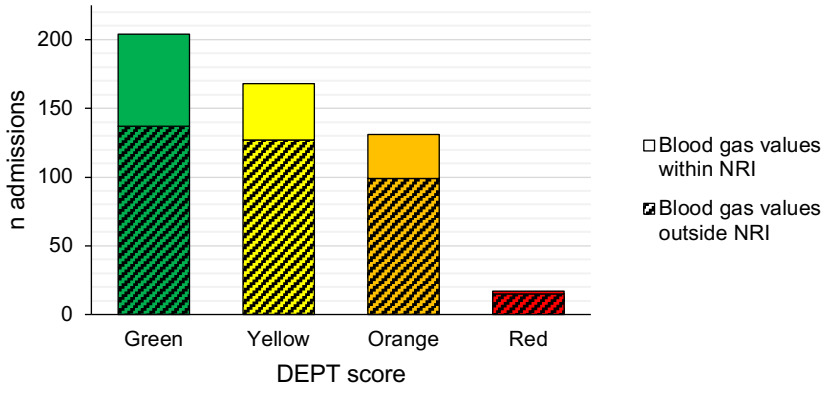

Figure 11. Admissions with blood gas values outside NRI by DEPT group. The hatched proportion represents the patients with caBG pH and PCO_2 and VBG lactate and base excess values outside normal reference intervals (NRI).

3.2.3. PREDICTION OF ABNORMAL BLOOD GAS VALUES

The panel of four physicians decided blood gas analysis was indicated in 21% (n admission = 107) of the patient admissions. Among this proportion, 75% (n admissions = 85) were detected with caBG and VBG values outside of NRI.

The sensitivity of the panel's decision was 23% and the specificity was 85% in detecting patients with caBG and VBG values outside NRI. The negative and positive predictive values for the decisions were 29% and 79%, respectively.

The panel decided that patients with respiratory reasons for admission required blood gas analysis most often (61%) and patients with gastrointestinal reasons for admission least often (4%).

Observing only the admissions in which the panel decided that blood gas analysis was not required, the risk of overlooking patients with caBG and VBG values outside NRI

were highest in patients with gastrointestinal reasons for admission (66%) and lowest in patients with respiratory reasons for admission (36%).

Using the patient group with respiratory reasons for admission as reference the odds ratio for overlooking caBG pH and PCO_2 and VBG lactate and base excess values outside NRI is shown in Table 7.

Reasons for ED admission	n admissions	Odds ratio [95% CI]]	P-value
Central nervous system	52	6.8 [2.6 to 20.4]	***
Circulatory	76	5.9 [2.5 to 15.8]	***
Gastrointestinal	164	29.4 [10.7 to 101.8]	***
Urogenital	29	7.3 [1.9 to 41.8]	***
Endocrine	10	2.8 [0.5 to 18.1]	NS
Poison	14	3.2 [0.7 to 20.5]	NS
Other	74	12.5 [4.4 to 44.5]	***

Table 7. Odds ratio for overlooking caBG and VBG values outside NRI. The risk is ordered by patients' reason for admission. P-values: NS, not significant; * <0.05; ** <0.01; *** <0.001. Reproduced from Study B.

The odds ratio for overlooking abnormal blood gas values in patients with gastrointestinal reasons for admission was statistically significantly the highest, and the odds ratio was more than twice the risk for a patient admitted with other reasons for admission.

3.2.4. MACHINE LEARNING AND ABNORMAL BLOOD GAS VALUES

The patients with the outmost combined caBG pH and PCO_2, and VBG lactate and base excess values were detected using cluster dendrograms with cut off limits on the height scale as shown in Figure 12.

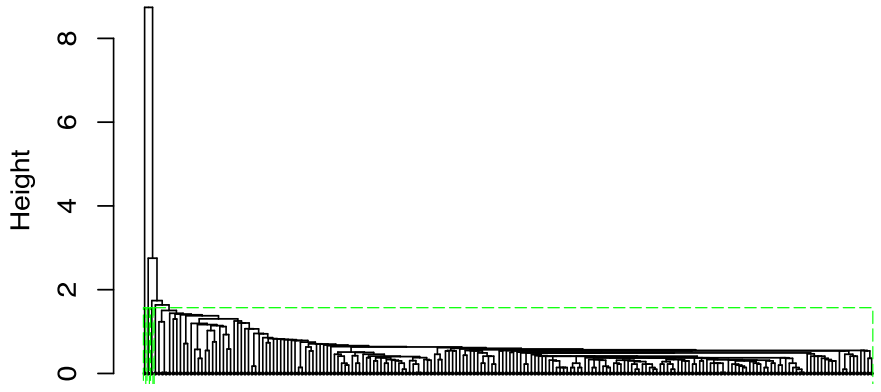

Figure 12. Dendrogram of combined blood gas values in the green DEPT group.

Cluster dendrograms from machine learning analysis in the remaining DEPT groups are presented in Appendix 3. Detection of patients with outmost combined blood gas values in the red DEPT group was not meaningful as only 17 patients were allocated to this group, and it already was the highest urgency level. Fourteen patients were detected with outmost combined caBG and VBG values in the green, yellow, and orange DEPT groups. Characteristics of the patients are presented in Table 8.

Patient no.	DEPT group	Reason for admission	caBG and VBG values			
			pH	PCO_2	Lactate	Base excess
1	Green	Gastrointestinal	7.65	2.0	6.0	-2.1
2	Green	Other	7.25	2.6	0.7	-16.3
3	Green	Other	7.32	6.8	2.9	2.0
4	Yellow	Respiratory	7.27	10.1	1.2	8.2
5	Yellow	Respiratory	7.40	3.8	1.4	-6.4
6	Yellow	Gastrointestinal	7.54	4.8	4.6	9.6
7	Yellow	Gastrointestinal	7.27	3.4	1.4	-13.2
8	Yellow	Poison	7.27	5.5	0.9	-6.7
9	Orange	CNS	7.20	2.6	1.4	-18.6
10	Orange	Respiratory	7.28	11.0	1.3	11.0
11	Orange	Respiratory	7.24	5.9	0.8	-7.0
12	Orange	Gastrointestinal	7.21	4.0	14.7	12.4
13	Orange	Other	7.47	6.2	4.8	9.6
14	Orange	Other	7.29	2.7	1.1	-11.6

Table 8. Characteristics of the patients with outmost combined blood gas values. Patients were detected using unsupervised machine learning. Reproduced from Paper B.

The median (range) of the caBG pH and PCO2 and VBG lactate and base excess were 7.28 (7.20 to 7.65), 4.4 (2.0 to 11.0) kPa, and 1.4 (0.7 to 14.7) mmol/L and -6.6 (-18.6 to 11.0) mmol/L, respectively. One or more severely diverging blood gas parameter was observed in the majority of the patients, but not in all; For example, patient no. 5 did not appear to have severely abnormal blood gas values apart from a negative base excess value.

In the subgroup consisting of 14 patients, the panel of physicians decided that blood gas analysis was required in four. Figure 13 shows the reasons for admission of the 14 patients and the panel decisions on blood gas need.

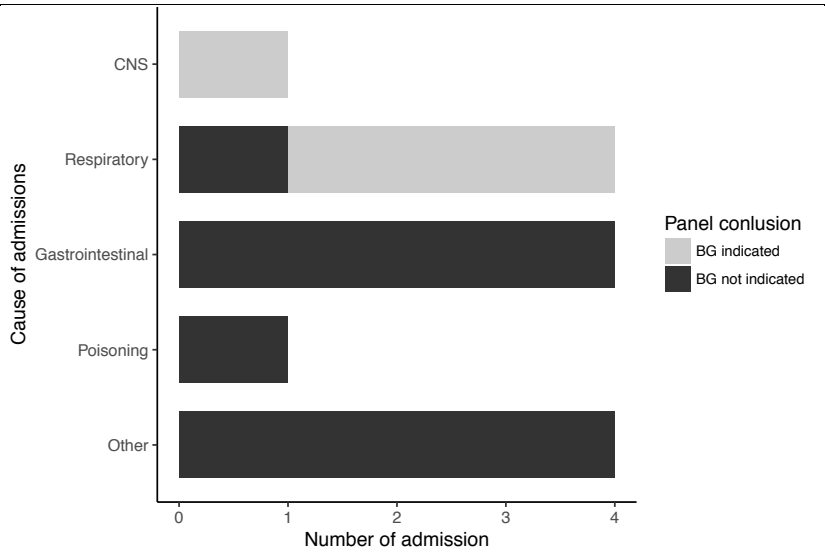

Figure 13. Decision on blood gas need in patient with outmost blood gas values.
The panel conclusion refers to the decisions on blood gas need made by the panel of physicians in the post hoc analysis of patient records. BG, blood gas analysis. Reproduced from Paper B

The panel decided that blood gas analysis was required mainly in the patients with respiratory reasons for admission and the one patient with symptoms from the central nervous system. The panel concluded that blood gas analysis was not required in all patients with gastrointestinal reasons for admission, poisoning or other reasons for admissions.

3.3. STUDY C

3.3.1. PATIENT CHARACTERISTICS

Fifty-eight paired samples were collected from 26 patients. Sample pairs from 28 patients were included; however, caBG could not be calculated in two patients due to the limitations of the v-TAC method (1 patient with pH < 6.8 and 1 with SpO_2 < 75%, see Section 2.4.3.1).

Demographics	ABG vs $caBG_{PVC}$	ABG vs $caBG_{CVC}$
n	14	16
n sample pairs	23	39
Age, median (range)	68 (38 to 82)	72 (18 to 83)
Gender, M/F	10/4	9/7
SAPS 3 score, median (range)	57 (34 to 99)	70 (49 to 99)
Inotrope therapy		
Norepinephrine, n (%)	5 (35)	8 (50)
μg/kg/min, median (range)	0.32 (0.03 to 1.00)	0.41 (0.05 to 1.00)
Dobutamine, n (%)	0	1 (6)
μg/kg/min		3.0
Reasons for admission, n (%)		
Sepsis	4 (29)	8 (50)
COPDe	2 (14)	1 (6)
Cardiac arrest	2 (14)	1 (6)
Diabetic ketoacidosis	1 (7)	1 (6)
Hypokalaemia	1 (7)	1 (6)
Status asthmaticus	1 (7)	0
Poisoning (medicaments)	1 (7)	0
ARDS	1 (7)	0
Congestive heart failure	1 (7)	0
Ileus	0	2 (13)
Pancreatitis	0	1 (6)
Pneumonia	0	1 (6)

Table 9. Demographics of the patients in Study C. SAPS 3, simplified acute physiology score 3; COPDe, chronic obstructive pulmonary disease exacerbation; ARDS, acute respiratory distress syndrome. The sum of the patients appears as 30 but is 26 as caBG values were calculated both from VBG samples from PVC and CVC in four patients. Reproduced from Paper C.

Table 9 shows a summary of demographic features of the patients in the studies. In four patients, VBG samples were collected both from CVC and PVC and compared

to the corresponding ABG sample; thus, the included number of patients appear as 30 in the table but is, in fact, 26.

3.3.2. COMPARISON OF ABG AND CABG

The ABG and caBG values and mean difference (±SD) between paired is presented in Table 10. The limitations of the v-TAC method of only reporting PO_2 values below 10.0 kPa caused an exclusion of 14 and 18 pairs in comparison of this parameter in the ABG and $caBG_{PVC}$ and ABG and $caBG_{CVC}$ comparison, respectively.

Parameters	n paired samples	ABG Median (range)	caBG Median (range)	Difference Mean (±SD)
ABG vs $caBG_{PVC}$				
pH				
PCO_2, kPa	23	7.29 (6.99 to 7.50)	7.31 (7.02 to 7.50)	-0.02 (0.09)
PO_2, kPa	23	5.2 (2.3 to 12.3)	5.4 (1.1 to 11.8)	0.1 (0.4)
	9	8.5 (6.2 to 11.5)	8.6 (6.6 to 10.0)	-0.1 (NA)
ABG vs $caBG_{CVC}$				
pH				
PCO_2, kPa	39	7.29 (6.95 to 7.66)	7.30 (6.95 to 7.67)	0.00 (0.02)
PO_2, kPa	39	5.2 (2.1 to 10.1)	5.1 (2.0 to 10.0)	0.0 (0.45)
	11	9.2 (7.5 to 14.5)	9.0 (7.8 to 9.9)	0.9 (NA)

Table 10. ABG and caBG values in Study C. Reproduced from Paper C.

3.3.2.1. BLAND AND ALTMAN ANALYSIS

The in-patient variance of the ABG and $caBG_{PVC}$ (caBG values calculated from peripheral VBG samples) value difference was not statistically significant compared to the variance between patients. Therefore, averages of multiple samples of ABG and $caBG_{PVC}$ paired values were calculated in each patient.

There was a statistically significant difference in-patient variance of the difference of ABG and $caBG_{CVC}$ (caBG values calculated from central VBG samples) pH and PO_2 values ($P = .013$ and $P < 0.001$, respectively). The calculations of mean bias and 95% LOA were wider when treating sample pairs as if they were from individual subjects. The variance of difference of ABG and $caBG_{CVC}$ PCO_2 values was not statistically significant; however, mean bias and 95% LOA were identical regardless of how

samples were treated. To improve consistency in data presentation of the study, the sample pairs were treated as if they were from individual patients.

Bland and Altman plots of agreement between ABG and $caBG_{PVC}$ paired values are shown in Figure 14 A1-3. The mean biases (95% LOA) of agreement of pH and PCO_2 was 0.01 (-0.10 to 0.09) and -0.03 (-0.73 to 0.77) kPa, respectively. The difference of ABG and $caBG_{PVC}$ PO_2 did not follow a normal distribution, hence 95% LOA could not be calculated. The mean bias was -0.12 kPa.

Figure 14 B1-3 shows the Bland and Altman plots of ABG and $caBG_{CVC}$ agreement. The mean biases (95% LOA) of pH and CO_2 were 0.00 (-0.04 to 0.05) and 0.0 (-0.9 to 0.9) kPa, respectively. The mean bias of PO_2 was 0.9 kPa.

An outlier was observed in the ABG and $caBG_{PVC}$ pH agreement. This data point consisted of four paired samples from one critically ill patient with diabetic ketoacidosis and considerable hyperventilation to compensate for the metabolic acidosis. In two of four pairs of this patients' caBG pH values were calculated as being within normal reference intervals (pH 7.42 and 7.42, respectively), although the patient had severe metabolic acidosis measured by ABG (pH 7.07 and 7.16, respectively). The VBG from which the caBG values were calculated also showed severe acidosis (pH 7.04 and 7.17, respectively. Median (range) ABG pH values were 7.24 (7.07 to 7.32) in this patient, while $caBG_{PVC}$ pH median (range) was 7.37 (7.31 to 7.42). Median (range) of ABG PCO_2 was 3.0 (2.3 to 3.6) kPa and of $caBG_{PVC}$ PCO_2 was 2.5 (1.1 to 3.6) kPa. All $caBG_{PVC}$ values of PO_2 were above the limit of 10.0 kPa, in this patient.

The difference between ABG and caBG PO_2 values increased with higher measured values. The limitations of the v-TAC method which was introduced before Study C (exact values of PO2 > 10.0 kPa was not calculated) caused an exclusion of 8/14 and 28/39 data points in the ABG and $caBG_{PVC}$, and ABG and $caBG_{CVC}$ PO_2 comparisons, respectively. Two data points were observed in the ABG and $caBG_{CVC}$ comparison of PO_2 as the ABG values were above 10.0 kPa but the caBG values were not.

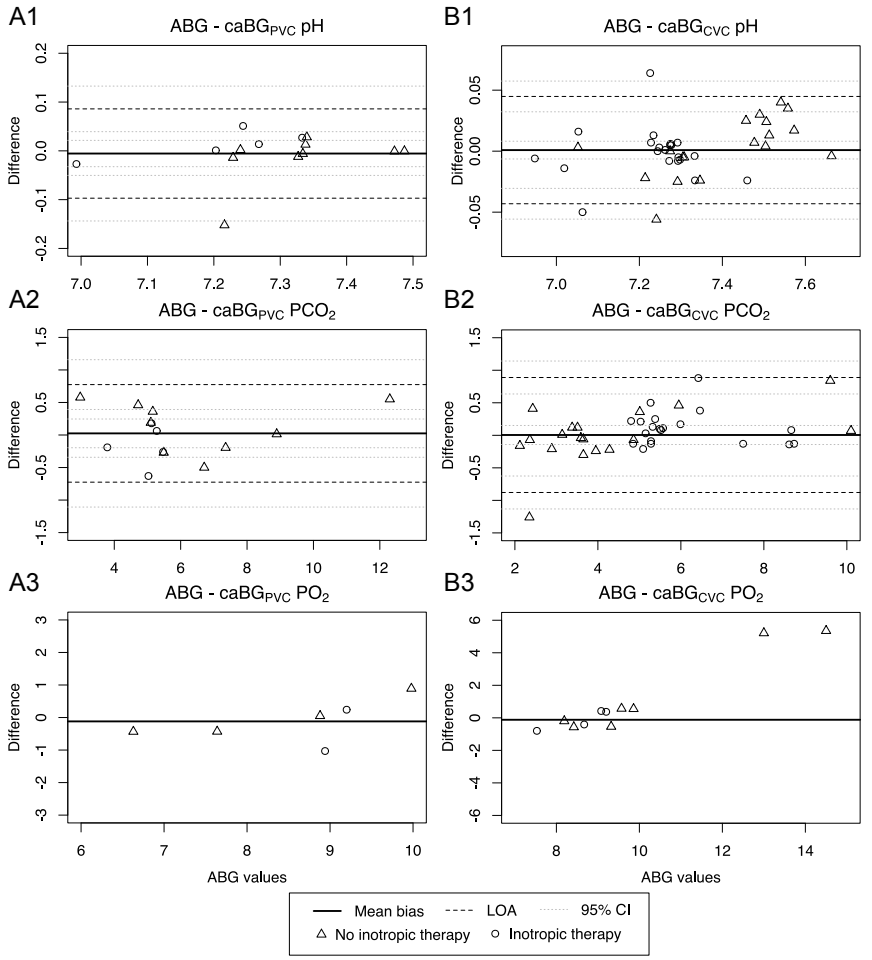

Figure 14. Bland and Altman plots on ABG and caBG agreement in Study C. A1-3 ABG and $caBG_{PVC}$ agreement and B1-3 ABG and $caBG_{CVC}$ agreement. $caBG_{PVC}$, the caBG values calculated from peripheral VBG samples; $caBG_{CVC}$, the caBG values calculated from central VBG samples. Reproduced from Paper C.

In the comparison of ABG and VBG from PVC the mean biases (95% LOA) of pH, PCO_2, and PO_2 were 0.03 (-0.04 to 0.10), -0.7 (-2.6 to 1.1) kPa and 6.2 kPa, respectively. In the comparison of ABG and VBG from CVC the findings were 0.03 (-0.02 to 0.08), -0.7 (-1.6 to 0.3) kPa and 6.0 kPa, respectively.

3.3.3. STRENGTH OF AGREEMENT

Strength of agreement	Tolerability interval ratio
Acceptable	< 1
Marginal	1-2
Unacceptable	> 2

Table 11. Interpretation of the tolerability interval ratio. Reproduced with permission from the publisher (90).

The strength of the agreement between ABG and $caBG_{PVC}$ values was assessed by calculating tolerability interval ratios (TIRs). For pH and PCO_2, the TIRs were 1.83 and 0.85, respectively, which is marginal, and an acceptable agreement (Table 11) according to Columb (90). The TIRs of the ABG and $caBG_{CVC}$ pH and PCO_2 values in were calculated to 0.88 and 1.00, which equivalents acceptable and marginal strength of agreement.

The strength of the agreement of ABG and VBG from PVC pH and PCO_2 were 1.39 and 2.13, respectively. Between ABG and VBG from CVC, the strength was 1.03 and 1.12, respectively.

3.3.4. RATE OF MISCLASSIFICATION

The rates of one-way misclassification and extreme-to-extreme misclassification between ABG and caBG pH, PCO_2, and PO_2 values are shown in Table 12.

Misclassification	ABG vs $caBG_{PVC}$	ABG vs $caBG_{CVC}$
n	14	16
n pairs	23	39
One-way		
pH	4.4%	7.7%
PCO2	8.7%	5.1%
PO2	11.1%*	0%*
Extreme-to-extreme		
pH	12.2%	0%
PCO2	0%	0%
PO2	11.1%*	18.2%*

Table 12. One-way and extreme-to-extreme misclassification in Study C. * Pairs with caBG PO_2 values above 10.0 kPa were excluded as the v-TAC method did not calculate exact values, leaving 9/23 sample pairs in the ABG and $caBG_{PVC}$ comparison and 11/39 in the ABG and $caBG_{CVC}$ comparison in Study B. Reproduced from Paper C

Rates of one-way misclassification of $caBG_{PVC}$ pH and PCO_2 to ABG values were low, but extreme-to-extreme misclassification of $caBG_{PVC}$ pH occurred in 8.7% of the

sample pairs. This misclassification was caused by deviating $caBG_{PVC}$ pH values in 2/4 comparisons to ABG pH values in the patient with hyperventilation and severe metabolic acidosis due to diabetic ketoacidosis mentioned above in Section 3.3.2.1.

The rate of extreme-to-extreme misclassification of caBG PO_2 was marginally smaller if caBG values were calculated from peripheral VBG values but still high even with the limitations of 10.0 kPa applied.

The rates of one-way misclassification between ABG and VBG from PVC in parameters pH, PCO_2 and PO_2 were 13.0%, 8.7% and 4.3%, respectively. Between ABG and VBG from CVC the rates were 20.5%, 20.5% and 0%, respectively.

Extreme-to-extreme misclassification between ABG and VBG from PVC pH, PCO_2 and PO_2 occurred in 4.3%, 13.0% and 78.3%, respectively. Between ABG and VBG from CVC the rates were 0%, 5.1% and 100%, respectively.

4. DISCUSSION

4.1. GENERAL ASPECTS

In this PhD thesis, the validity and utility of the v-TAC method was assessed in a clinical setting in three studies. The main findings in the studies are presented in the following.

In a random ED population, the v-TAC method converted pH and PCO_2 values to caBG values with high accuracy and precision compared to ABG values. VBG samples could safely be stored up to 15 minutes before analysing the samples and performing the v-TAC calculations. However, tilting samples is counter advised, at least not if the VBG samples are obtained in 4.5 mL tubes, as a minor increase of approximately 0.5 kPa was observed in samples treated that way. In normoxic hemodynamically stable ED patients, more than half of the caBG PO_2 values were misclassified (above CATs) when compared to ABG PO_2 values.

Systematic blood gas screening in patients admitted to the ED was performed with ease and without any practical or logistical obstacles. A substantial proportion of patients were detected with v-TAC caBG pH, PCO_2, venous lactate and base excess values outside normal reference intervals (NRI). However, when examining the association between blood gas values and the DEPT triage groups, only venous lactate showed an association with triage urgency, although the correlation was very weak. Decisions on indication for blood gas analysis performed by a panel of physicians showed low sensitivity for detection of patients with abnormal blood gas values, but the specificity for detecting patients who did not need blood gas analysis was moderate to high. In a machine learning analysis, the patients with extreme blood gas values were detected, but this subgroup consisted of only 14 (3%) patients. All of them were from the green, yellow, and orange DEPT groups, and while most of the patients presented with severely abnormal blood gas values, some did not. The question remains whether complete routine blood gas screening in patients admitted to the ED is clinically justified only to identify a small proportion of patients with severely abnormal blood gas values at risk of being overlooked in the initial clinical assessment. Patients admitted for a gastrointestinal reason or reasons that did not fit into the predefined reasons for admissions (other reasons for admission) may, in particular, benefit from routine blood gas screening.

In the critically ill patients with severe respiratory or metabolic acidosis, the v-TAC method validly calculated arterial PCO_2 values from VBG samples collected from peripheral and central venous catheter sampling sites. The caBG pH values were

calculated with high validity, although significant bias of caBG pH was observed in multiple pairs from one patient. The precision of caBG pH was not superior to that of VBG pH. Even though the recently implemented v-TAC limitations allowed for reporting of only calculated PO_2 values below 10.0 kPa, misclassification of approximately a quarter of the caBG PO_2 values was observed when compared to ABG values. From a clinical perspective, the agreement between ABG and caBG values were similar regardless of whether the caBG values were calculated from peripheral or central VBG values.

The methodology and findings in each study are discussed separately in the following.

4.2. STUDY A

In this combined methodological pre-study and validation study the aim was to test two samplings methods and test the effects of different VBG sample handling procedures on the validity of the caBG values compared to ABG values in a daily clinical ED practice setting.

4.2.1. HANDLING OF VBG SAMPLES

In the pre-study, the 4.5 mL tube was chosen over the 2.0 mL blood gas syringe as the preferred container for VBG samples, even though PO_2 was 0.57 kPa higher in the tube compared to the syringe. This decision was based mainly on practical reasons as a three-way stopcock did not need to be connected to the standard venous blood sampling kit. Furthermore, if the three-way stopcock was not applied to the kit, and the sampling was performed with a blood gas syringe pushed directedly against the rubber covered needle in the blood sampling kit, the risk of accidental needle injury was considered significant. However, the choice of sample container may have contributed to the poor agreement between ABG and caBG PO_2 values.

In the validation study, the v-TAC method delivered valid caBG values of pH and PCO_2 if samples were not tilted as the 95% LOA of the pH and PCO_2 did not exceed the CATs. The tilting process caused a slight increase in caBG PCO_2 values of approximately 0.5 kPa. Hence, the rate of one-way misclassification was 15%, which implies that VBG samples should be carefully handled and not routinely tilted for more than 5 minutes, at least not if collected in 4.5 mL venous blood tubes. A drop in PO_2 could have been expected as O_2 is utilised in the production of CO_2 (113); however, this was not observed. The underlying cause for this increase remains unknown. However, pre-analytical errors concerning air in the hose connecting the needle and

the tube being sucked into the 4.5 mL tube or, while there is a vacuum in the tube, there also might be leftover gas which may have caused the increase in PO_2 or PCO_2 (114,115).

4.2.2. ACCURACY OF PH, PCO_2, AND PO_2

In the introduction of this thesis, the issue of inaccurate values of VBG PCO_2 has been presented, and in the updated meta-analysis the 95% LOA varied greatly from 1.76 to 6.18 kPa (51,55). The precision of mean bias but most importantly the accuracy of the arterial estimations of PCO_2 were considerably improved by use of the v-TAC method. The high accuracy of caBG PO_2 values has also been found in a recently published study by Ekström et al. (116) in which the validity of v-TAC was assessed in 46 patients admitted to a Swedish pulmonary medicine department. The mean bias (95% LOA) between ABG and caBG PO_2 was -0.14 (-0.46 to 0.19) kPa. In the comparison of ABG and caBG pH, the mean bias (95% LOA) was 0.00 (-0.02 to 0.02). Hence, the v-TAC could contribute to the valid estimated of arterial PCO_2.

4.2.3. THE PROBLEM WITH CALCULATING PO_2

The validity of the v-TAC method has been assessed by Rees et al. (117) and Tygesen et al. (88) by including patients with COPD and patients for various reasons admitted to the ED, respectively. Both research teams found acceptable performance of the method in calculation of pH and PCO_2 using laboratory-acceptable thresholds. However, while the mean bias of caBG PO_2 was of a minor magnitude in the two studies, the bias increased exponentially in PO_2 values higher than 8-9 kPa.

The concern about the incorrect estimation of arterial PO_2 values has been recognised since the introduction of the method by Rees et al. (84). In his paper, it was stated that the incorrect PO_2 values were due to the flat shape of the oxygen dissociation curve at blood oxygen saturations above 96%, meaning even minor changes in oxygen saturation percentage would result in major changes of the calculated PO_2 value. However, this principle also applies to the analysis of ABG PO_2 (118). The selected sample collection tube in the study may also explain the wrongful estimation of PO2 values as mean venous PO2 was 0.57 kPa higher in the 4.5 ml tube.

4.2.4. LIMITATIONS OF THE STUDY

This study has some limitations. It was a single-centre study with a very small heterogenic patient population; hence, the generalisability of the results is low. Furthermore, no standard operating procedures were formulated to reduce risk of preanalytical errors and ensuring anaerobic VBG sampling in the 4.5 mL tubes. The validity of calculated PCO_2 and PO_2 may have improved if such guidelines had been formulated.

4.3. STUDY B

In this observational study the aim was to examine the utility of calculated and selected venous blood gas values as a screening tool to detect patients with abnormal blood gas values, and examine congruency with DEPT triage in patients admitted to the ED.

4.3.1. DETECTING THE ACUTELY ILL PATIENT

A large proportion of patients admitted to the ED were detected with blood gas values outside the NRI in one or more parameters (caBG pH, caBG PCO_2, VBG lactate and/or VBG base excess). However, venous lactate only showed only a very weak correlation with triage urgency. This association was not unexpected as Baron et al. (119) and Contenti et al. (120) have found arterial and venous values of lactate to correlate. Moreover, lactate is useful in the evaluation of the severity of sepsis, in addition to prediction of resuscitation requisite and patient mortality in the ED. These findings were supported by Barfor et al. (41), who found venous lactate levels to be independently associated with mortality, and patients with measures above 4 mmol/L were at highest risk of mortality with an odds ratio of 19.9 [95% CI 7.3 to 55.1].

In a cohort study by Kristensen et al. (121) including more than 12,000 patients VBG parameters were combined with measurements of vital signs to identify patients with the highest risk of mortality using a multiple logistic regression model. The AUROC was calculated to 0.88 [95% CI: 0.84 to 0.89], whereas the AUC was 0.63 [95% CI 59.1 to 67.5] when using the DEPT tool only to identify patients at mortality. In contrast to Kristensen et al.'s findings, Iversen et al. (122) showed that a simple visual assessment of the patients upon admission, a so-called eye-ball triage, was not inferior to the DEPT tool. The simple triage was conducted by phlebotomists and medical students who were responsible for routine venous blood sampling. While this simple eye-ball approach may seem alluring, it should be emphasised that a simple clinical

examination did also take place during venous blood sampling (e.g., patient alertness feeling skin temperature). Nevertheless, the findings in this study should be considered in the search for the ideal triage process or tool, as a combination of blood parameters and clinical measures may not provide adequate assessment outcome.

4.3.2. THE CHALLENGES OF EVALUATING INDICATIONS

The panel of physicians in Study B did not detect patients with abnormal caBG and VBG values with high accuracy as the sensitivity of their decisions was low, whereas the specificity of the panel's decision was high. The risk for overlooking abnormal caBG and VAG values was unambiguously highest in patients admitted with gastrointestinal reasons for admission, while it was lowest in patients with respiratory reasons for admission. Patients with the lowest risk of having blood gas values overlooked were patients with respiratory reasons for admission. In the patients detected with the most abnormal blood gas values, it was only those with respiratory reasons for admission and one patient with a central nervous system reason among whom the panel decided that blood gas analysis was required.

The results suggest that evaluating indications for blood gas analysis might be a more challenging task for physicians than anticipated. Moreover, the panel displayed a predilection for judging the need for blood gas analysis in patients with respiratory reasons for admission; however, while respiratory symptoms may be a reason for analysing blood gas values, other indications are also relevant (see Section 2.3.4). Therefore, it is imperative to know and follow the established indications for blood gas analysis.

4.3.3. LIMITATIONS OF THE STUDY

Several limitations of this study should be considered. It was a single-centre study with 17 patients allocated only to the red triage group and a few patients detected with severely abnormal blood gas values in the subgroup analysis. These circumstances made stratification troublesome, and the results should, therefore, be interpreted with caution. Electronic admission records were reviewed by the panel of physicians to determine the need for blood gas analysis; therefore, no proper physical examination was conducted. However, this procedure was necessary as physical examination of the patients and assessment of blood gas indication in conjunction with the triage process would make the triage process redundant. Furthermore, no provisions were established to make sure that the blood gas values were not reviewed by the physicians before deciding on the need for blood gas analysis. The study design and setting did not allow

for a follow-up on the mortality of the patients; hence, no conclusions can be drawn regarding the benefits of blood gas values in predicting mortality.

4.4. STUDY C

In this case series study, the aim was to evaluate the validity of the v-TAC method in a critically ill ICU patient population with various causes of admission to identify clinical situations in which the v-TAC method is inaccurate.

4.4.1. VENOUS BLOOD SAMPLING SITES

Toftegaard et al. (110) reported a clinically significant difference between the agreement of ABG and caBG calculated from peripheral VBG samples compared to agreement of ABG and caBG calculated from central VBG samples. The mean biases (2*SD) pH were 0.00 (0.03) in the ABG and $caBG_{PVC}$ comparison, and 0.01 (0.02) in the ABG and $caBG_{CVC}$ comparison. The difference in the agreement of PCO_2 was -0.04 (0.52) kPa and -0.18 (0.35) kPa in the comparison of ABG and $caBG_{PVC}$ and ABG and $caBG_{CVC}$, respectively. Toftegaard et al. recommended using peripheral venous blood for the v-TAC conversion as blood from a well-perfused extremity is unlikely to have major metabolic disturbances, which may not be true for central venous blood.

The results from Study C showed slightly broader 95% LOA in the ABG and caBG PCO_2 agreement if the VBG samples were obtained from CVC. In the agreement of pH, narrower 95% LOA were observed in the ABG and $caBG_{CVC}$ comparison, but this was mainly due to the poor agreement in the patient with diabetic ketoacidosis.

From a clinical perspective, the observed differences between caBG calculated from peripheral blood and central blood is small. Thus, central venous blood may be used for calculations of blood gas values in patients without major metabolic disturbances; however, the caBG results should be interpreted with caution.

4.4.2. THE PROBLEM WITH FIXED V-TAC LIMITS

Before the commencement of Study C, some limitations of the v-TAC method were formulated. A lower limit of peripheral oxygen saturation input was set to 75%, which is reasonable as the accuracy of many peripheral transcutaneous pulse oximetry sensors declines considerably in measurements below 75% (123,124). However, application of the fixed upper limit of PO_2 on 10.0 kPa may not be just be smart.

The v-TAC method does take the Bohr effect into account as the DPG values are calculated (84,87). The Bohr effect is the principle that an increase in H^+-ions (and a decrease in pH) lowers haemoglobin affinity for oxygen, which causes the oxygen dissociation curve to shift right (86,125). This principle is shown in Figure 15.

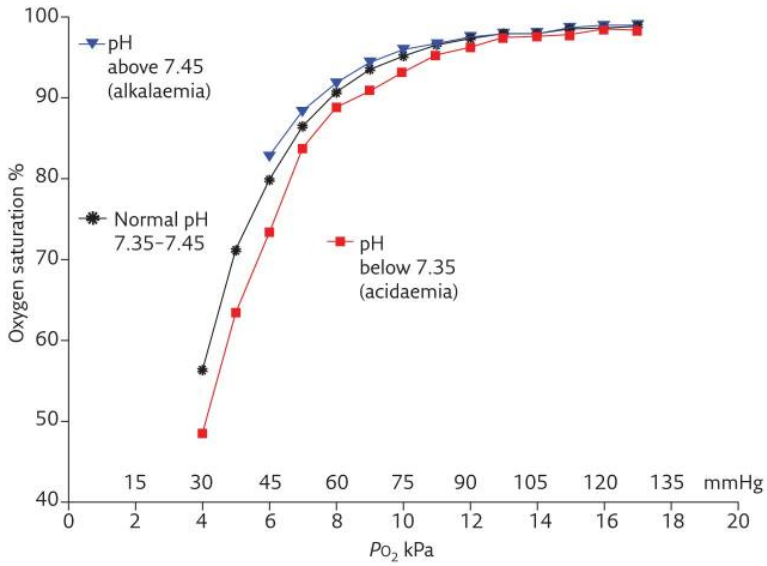

Figure 15. The oxygen dissociation curve.
Lent from Collins et al. (118)

Hamilton et al. (126) showed that p50 (the oxygen tension when haemoglobin is 50% saturated with oxygen) shifted to the right by 0.7 kPa in patients with acidosis and pH 7.24. In this present Study C pH as low as 7.0 was observed, which would result in an even larger right-shift. The v-TAC method may take this phenomenon into account, but the limits of 10.0 kPa in reported caBG PO_2 does not. Instead of limits of oxygen tension, providing upper limits of pulse oximetry oxygen saturation may have been more reasonable.

4.4.3. PITFALLS OF THE V-TAC METHOD

The v-TAC method relies on a set of assumptions presented in Section 2.1. One of these is that the respiratory quotient does not vary outside the interval of 0.7 to 1.0, and the calculations are performed with a fixed value of 0.82 (84,87). In the critically ill patients, the respiratory quotient may vary substantially depending on the underlying

pathophysiological mechanisms of the patients, and the method may not be valid in subgroups of patients with different tissue metabolism (127,128). The respiratory quotient was not measured in the included patients; hence, the extent of this concern could not be explored further.

In the comparison of ABG and caBG pH values, a serious misclassification was observed in a patient with diabetic ketoacidosis. Both the ABG and VBG values showed severe metabolic acidosis in this patient, but the VBG values were converted to caBG values with normal pH. BG values showing acidosis was wrongfully converted to normal pH values. The reason for this serious error is unknown, but may be caused by the presence of acidic ketone bodies (129).

Obimedical, the company commercialising the v-TAC method, postulates the following on their FAQ page regarding the use of v-TAC in patients with conditions with excess acids such as diabetic ketoacidosis, lactate acidosis, or salicylate poisoning.

> *An excess of acid will present itself as a negative base excess in the blood. Our mathematical models account for changes in base excess. The v-TAC™ method assumes that the value of base excess is the same in the arterial and venous blood samples. Systemic, whole-body changes in acid-base balance resulting in acid production will result in negative base excess in blood measured at any site. Systemic changes are therefore not a problem for the method.*(130)

The statement continues to explain why it should not be a problem for the method:

> *For peripheral venous samples it is unlikely that there are large differences between arterial and venous BE values due to local acid production. This is particularly true if the peripheral venous site is warm and well perfused, which is easily identifiable by clinical inspection or by the presence of a pulse oximetry signal. In a warm, well-perfused extremity, the likelihood of local tissue anaerobic metabolism is small, and BE values should be the same in both arterial and venous blood at this site.*(130)

This misclassification was observed in only two ABG and caBG pairs and may not form a basis of a v-TAC guideline. However, an event of misclassifying extremely abnormal blood gas values to normal values should not be accepted in a clinical setting, and an ABG analysis must be applied.

4.4.4. LIMITATIONS OF THE STUDY

This study has several limitations. The sample sizes were above the required sample sizes but small for both ABG-caBG$_{PVC}$ and ABG-caBG$_{CVC}$ comparisons. Furthermore, there was no statistically significant ABG and caBG$_{PVC}$ in-patient variance of the difference between methods; thus, averages of ABG and caBG values were calculated within each patient which lowered the total number of paired observations below the required sample size. In comparison of ABG and caBG PO_2 values, the majority of pairs were excluded as the caBG PO_2 was above limits of the v-TAC method on 10.0 kPa. Selection bias may have been introduced in the study as all paired samples were collected as convenience samples, and sometimes the acuity of the patients did not allow for paired sampling as life-saving treatment was prioritised. Moreover, a considerable number of samples were discarded as ABG pH had reached normality due to treatment.

5. CONCLUSIONS

In summary, we investigated the validity and utility of a method for conversion of venous blood gas values (v-TAC) to arterial blood gas values in different clinical settings.

In a random ED population, the v-TAC method delivered adequate validity for calculation of arterial pH and PCO_2 values. The VBG samples from which the values were calculated could safely be stored up to 15 minutes before sampling but should not be tilted routinely.

We managed blood gas screening in admitted acute patients with practical and logistical ease using VBG sampling and v-TAC arterialisation of blood gas values with inclusion of 520 patients. A large proportion of patients were detected with abnormal blood gas values, but only few showed severely deviating values. However, a majority of these patients were at high risk of being overlooked by the physician regarding an assessed need for blood gas analysis. In comparing the patients' blood gas values with their assigned level of triage urgency, no obvious associations were detected except for very weak correlation between the triage urgency and level of venous lactate.

In the critically ill patients, the v-TAC method calculated PCO_2 values with clinically acceptable accuracy. If the v-TAC method were to replace ABG analysis in the critically ill patients, higher clinically acceptable thresholds would have to be applied. The v-TAC method might not estimate pH values with acceptable validity in critically ill patients with diabetic ketoacidosis. This aspect should be assessed in future research.

6. PERSPECTIVES

In patients admitted to the ED and needing assessment of their respiratory or metabolic status, the v-TAC method may offer a less painful alternative by venous sampling as opposed to arterial puncture. However, if the assessment of oxygenation status is imperative, or the patient is critically ill, an ABG sample should always be recommended. Also, in clinical situations where only a pH value is necessary to determine the severity of acidaemia or alkalemia, a simple VBG sample with slightly different normal reference intervals should suffice.

In the ICU setting, the v-TAC method may not have an obvious role in patients with arterial catheters. However, in the assessment of the ventilatory status of patients without arterial catheters, the method has potential uses. Likewise, the method may also be useful if minor respiratory deterioration is observed in patients during a step-down discharge process from the ICU.

The obvious contribution the v-TAC method may deliver is in the patient where repeated blood gas is required (e.g., in patients with COPD). These patients in need of assessment of ventilatory status may benefit radically from the reduction of painful arterial punctures as sample obtainment can be achieved in conjunction with routine venous sampling. The v-TAC method seems to provide valid estimates of arterial PCO_2 values under most conditions and can be used safely.

We found one patient with severe metabolic acidosis and arterial pH of 7.01 in which the v-TAC method wrongfully calculated pH values within normal reference intervals. Based on finding in the studies, a further investigation of the validity of the v-TAC method in critically ill patients with diabetic ketoacidosis is recommended.

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8. APPENDICES

LIST OF APPENDICES

APPENDIX 1. SEARCH STRING

Database: PubMed Medline
Limits: Species, Humans; Language, English, Danish, Norwegian and Swedish; Ages, >12 years; published in the last 10 years.
Date: March 21, 2019.

Search no.	Terms	Results
#1	"arteries"[MeSH Terms] OR "arterial"[All Fields] OR "arterial/venous"[All Fields] OR "arterial/venous blood"[All Fields] OR "arterial/venous carbon dioxide tension"[All Fields] OR "artery"[All Fields] OR oxygenat*[All Fields] OR arteriovenous[All Fields]	160565
#2	venous[All Fields] OR "vein"[All Fields] OR "venous/arterial"[All Fields] OR "venous/arterial blood"[All Fields] OR "central venous catheterization"[MeSH Terms]	67909
#3	"analyses, blood gas"[MeSH Terms] OR "analysis, blood gas"[MeSH Terms] OR "blood gas analyses"[MeSH Terms] OR "blood gas analysis"[MeSH Terms] OR "blood gas/acid base"[All Fields] OR "blood gas/acid base status"[All Fields] OR "blood gas/oximetry"[All Fields] OR "blood gas acid base"[All Fields] OR "blood gas status"[All Fields] OR acidosis[All Fields] OR alkalosis[All Fields] OR "blood gas analyzer"[All Fields] OR "blood gas content"[All Fields] OR "blood gas data"[All Fields] OR ph[All Fields] OR co2[All Fields] OR o2[All Fields] OR oxygen[MeSH Terms] OR "carbon dioxide"[MeSH Terms] OR lactate[All Fields] OR bicarbonate[All Fields] OR HCO3*[All Fields]	1034144
#4	“comparison, paired”[MeSH Terms] OR “comparisons, paired”[MeSH Terms] OR “paired comparison”[MeSH Terms] OR “paired comparisons”[MeSH Terms] OR agreement[All Fields] OR “bland and altman”[All Fields] OR “correlation studies”[MeSH Terms] OR “correlation study”[MeSH Terms] OR correlate[Title] OR correlation [Title]	46815
#5	#1 AND #2 AND #3 AND #4	414

379 records were excluded on basis of title or abstract.
35 records were eligible for assessment.

APPENDIX 2. ICU DATA CHART

v-TAC på intensiv afdeling

ID nr._____

Ark til dataindsamling

BEMÆRK: Dette ark skal udfyldes til hvert enkelte prøvesæt
(et prøvesæt er: ét arterielt udskrift og venøst udskrift fra CVK og/eller PVK).

Patientlabel:

Dato for prøveindsamling: _____/_____ 2018

Tidspunkt for prøveindsamling: Kl _____:_____

Ny SAPS 3 score: _____

Indlæggelsesårsag(er):_____

Vitale parametre:

Saturation:_____ Respirationsfrekvens:_____

Puls: _____ Blodtryk:_____

Temperatur:_____

Respiratorindstillinger:

Modus:_____ FiO2:_____

Press/PEEP:_____/_____ TV:_____

Cirkulatorisk status:

Perifert varm ☐ Kold distalt for albue ☐ Kold proksimalt for albue ☐

Cyanose:

Ingen cyanose ☐ Cyanose lokaliseret til: Negle ☐ Læber ☐ Universel ☐

Inotropibehov:

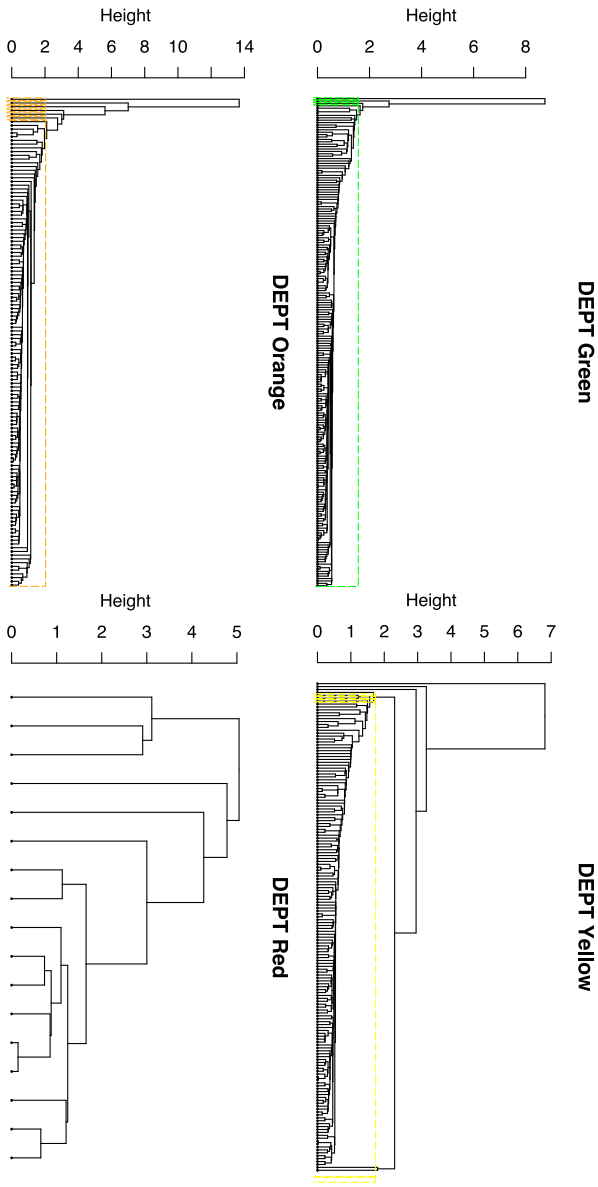
Type:_____ Infusionshastighed:_____

Adgange hvorfra blodgas er taget (sæt kryds):

Arteriekateter/-punktur ☐ CVK ☐ PVK ☐

APPENDIX 3. DENDROGRAMS

Dendrograms from unsupervised machine learning analysis of patients with combined caBG and VBG values in the DEPT groups in Study B.



PAPER A

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ORIGINAL RESEARCH

Mathematical arterialisation of peripheral venous blood gas for obtainment of arterial blood gas values: a methodological validation study in the clinical setting

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Abstract
Arterial blood gas (ABG) analysis is an essential tool in the clinical assessment of acutely ill patients. Venous to arterial conversion (v-TAC), a mathematical method, has been developed recently to convert peripheral venous blood gas (VBG) values to arterialized VBG (aVBG) values. The aim of this study was to test the validity of aVBG compared to ABG in an emergency department (ED) setting. Twenty ED patients were included in this study. ABG and three aVBG samples were collected from each patient. The aVBG samples were processed in three different ways to investigate appropriate sample handling. All VBG samples were arterialized using the v-TAC method. ABG and aVBG samples were compared using Lin's concordance correlation coefficient (CCC), Bland–Altman plots and misclassification analysis. Clinical acceptable threshold of aVBG value deviance from ABG values were ± 0.05 pH units, ± 0.88 kPa pCO_2 and ± 0.88 kPa pO_2. CCC revealed an agreement in pH and pCO_2 parameters for both aVBG in comparison to ABG. In all aVBG samples, an overestimation of pO_2 compared to ABG was observed. Bland–Altman plot revealed clinically acceptable mean difference and limits-of-agreement intervals between ABG and aVBG pH and pCO_2, but not between ABG and aVBG pO_2. Arterialization of VBG using v-TAC is a valid method for measuring pH and pCO_2, but not for pO_2. Larger clinical studies are required to evaluate the applicability of v-TAC in different patient subpopulations.

Keywords Arterial blood gas analysis · Emergency service, hospital · Venous to arterial conversion · Matched-pair analysis

1 Introduction

Arterial blood gas (ABG) analysis is essential in assessment of respiratory and metabolic status in acutely ill patients. In comparison to peripheral venous blood sampling, the ABG sampling procedure is more painful for the patient and technically more challenging for the clinician to perform [1, 2]. Other drawbacks of ABG sampling include adverse events such as subcutaneous hematoma, arterial thrombosis, and the serious, though rare, complication pseudoaneurysms [3, 4].

Peripheral venous blood gas (VBG) sampling has been suggested as an alternative to the ABG procedure. This procedure causes less patient discomfort and the sample can be analysed in combination with other venous blood tests [5]. A recent systematic review comparing ABG and VBG in the emergency department (ED) have revealed that pH and bicarbonate show reasonable agreement with mean difference − 0.033 pH units and 1.03 mmol/l bicarbonate, respectively. Limits-of-agreement was − 0.13 to 0.10 for pH and − 6.24 mmol/l to 10.00 mmol/l for bicarbonate. pCO_2 showed mean difference of 4.41 mmHg and wide limits-of-agreement of − 20.40 to 25.8 mmHg. Authors concluded that

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venous and arterial pH and bicarbonate agree acceptable, but arteriovenous agreement of pCO_2 was poor [6].

However, a new method has been developed to calculate ABG values mathematically from peripheral venous blood by use of venous to arterial conversion (v-TAC) software (Obimedical, Denmark), supplemented with oxygen saturation measurement by pulse oximetry [7]. The principle of the method is a mathematical transformation of VBG values to arterialized values (aVBG) by simulating the transport of blood back through the tissue. The authors made assumptions; Firstly, the peripheral limb must be well perfused with normal capillary response and temperature. Secondly, the respiratory quotient [RQ, i.e. rate of CO_2 production (VCO_2) and O_2 utilisation (VO_2)] must not vary beyond the range of 0.7–1.0.

Earlier testing of the v-TAC method in an ED setting has shown acceptable congruence levels between arterial and mathematically arterialized pH and pCO_2 with only minor differences ($\pm 2 \times SD$) $- 0.001$ (± 0.024) and 0.00 (± 0.46) kPa, respectively. However, inaccurate values of pO_2 were observed when oxygen saturation measured by pulse oximetry was above 96%, due to the flat shape of the oxygen dissociation curve (ODC) at higher oxygen saturation [8].

The aim of this study was to evaluate the validity of the v-TAC method in an acute medical emergency setting and test appropriate practical handling of VBG samples.

2 Methods

2.1 Patient inclusion

The study was conducted in the ED at the North Denmark Regional Hospital from September through October 2015. Circulatory stable patients needing ABG analysis for clinical respiratory and metabolic assessment were selected randomly for participation in the study. A total of 30 adult patients were included; 10 patients for a methodological pre-study and then 20 patients for the following validation study and test of different blood samples procedures. Allocation was performed by simple quasi-random algorithm in order of admission. The clinical decision for performance of ABG analysis was made on discretion by the attending physician in the ED upon patient admission and based on national guidelines [9].

2.2 Blood collection

All VBG samples were collected by a biomedical laboratory technician in conjunction with routine venous blood sampling in the methodological pre-study. VBG was collected in the 4.5 ml tube as opposed to the arterial blood 2.0 ml syringe as a three-way stopcock would have to be coupled with the venous blood sampling kits, but we found this inconvenient in our hospital setting. Furthermore, biomedical laboratory technicians were at risk of accidental needle injury if a syringe was coupled directly over the sampling kit needle. For that reason, we conducted this methodological pre-study to compare VBG samples in paired 2.0 ml and ABG syringes.

2.3 Blood sample handling

In the validation study paired ABG and VBG samples were collected simultaneously from each of the 20 patients. Blood for VBG analysis was collected by the laboratory technician in three 4.5 ml tubes and converted to arterialised VBG (referred to as aVBG). ABG samples were collected by the attending physician. Each aVBG tube was processed differently as follows: $aVBG_1$ was held steady and analysed within 5 min of sample collection, $aVBG_2$ was tilted in 5 min and analysed after 7 min and $aVBG_3$ was handled as $aVBG_1$ but analysed after 15 min. ABG samples were analysed within 5 min after sampling.

2.4 Blood analysis

All ABG and VBG samples were analysed with ABL800 blood gas analyser (Radiometer, Denmark) an VBG samples were converted mathematically to aVBG using v-TAC software integrated into the ABL800. Figure 1 show calculations of the v-TAC simulation in five steps (A–E) [7]. On the standard of care basis, only the ABG results were used as the usual standard reference in the medical evaluation of the patients. Normal reference ranges of study variables were as follows pH, 7.35–7.45, pCO_2, 4.26–6.38 kPa and pO_2, 10.6–13.3 kPa, respectively [10].

2.5 Threshold values

In this present study, clinically acceptable thresholds between ABG and aVBG values were determined as ± 0.05 for pH, and ± 0.88 kPa for both pCO_2 and pO_2. Consequently, clinically acceptable intervals of calculated arterial values were determined to be 0.1 pH units and 1.76 kPa for both pCO_2 and pO_2 compared to ABG values. Acceptable rate of misclassification was set to 5% as in a similar study [11]. Extreme-to-extreme misclassification was not allowed.

2.6 Sample size

A previous study on the v-TAC method reported mean difference ($\pm 2 \times SD$) of -0.001 ± 0.024 and -0.00 ± 0.46 kPa between calculated arterial and ABG pH and pCO_2, respectively [8]. With the predetermined clinical acceptable threshold of calculated arterial pH ± 0.05 and pCO_2 ± 0.88 kPa,

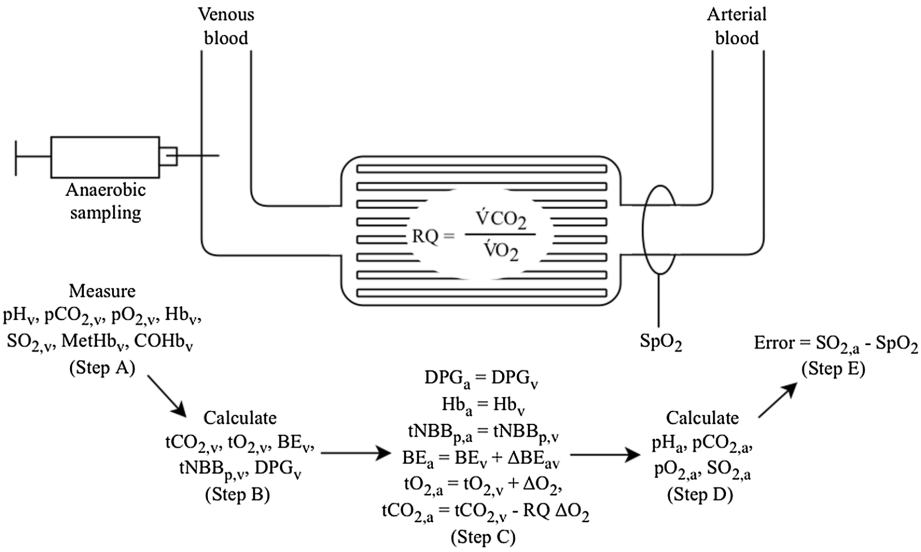

Fig. 1 Calculation of arterial acid–base and oxygen values from VBG using v-TAC. Step A an anaerobic venous blood sample is collected and pH_v, $pCO_{2,v}$, $SO_{2,v}$, $pO_{2,v}$, haemoglobin (Hb_v), methaemoglobin ($MetHb_v$), and carboxyhaemoglobin ($COHb_v$) are measured. Step B measured values are used to calculate total CO_2 concentration ($tCO_{2,v}$), total O_2 concentration ($tO_{2,v}$) and 2,3-diphosphoglycerate concentration (DPG_v) in venous blood. Base excess is estimated independently of O_2 levels by calculating the total concentration of plasma non-bicarbonate buffer ($tNBB_{p,v}$) and combining the concentration with pH_v. Step C variables $tCO_{2,v}$, $tO_{2,v}$, Hb_v, BE_v, DPG_v and $tNBB_{p,v}$ are used to estimate the respective variables in arterial blood. It is assumed that Hb, $tNBB_p$ and DPG concentrations are the same in arterial and venous blood. Calculations of arterial O_2 and CO_2 is then performed by simulating addition of a difference in O_2 concentration (ΔO_2), to the venous pO_2 measurement and removing a difference in concentration of CO_2 (ΔCO_2) from pCO_2 in the venous blood. Step D calculated values of arterialised blood $tCO_{2,a}$, $tO_{2,a}$, Hb_v, BE_a, $tNBB_{p,a}$ and DPG_a are used to estimate pH_a, $pCO_{2,a}$, $pO_{2,a}$ and $SO_{2,a}$. Step E calculated $SO_{2,a}$ is compared with measured pulse oximeter (SpO_2), the difference between the two gives an error = $SO_{2,a}$–SpO_2. By repeating steps C–E, a value of ΔO_2 is found for which the error is zero. Multiplying the respiratory quotient (RQ) with ΔO_2, the concentration of CO_2 removed is calculated. Thus calculated values of pH_a, $pCO_{2,a}$, $pO_{2,a}$ and $SO_{2,a}$ should be equal to measured arterial values. Reproduced with permission from publisher [7]

the requires study sample size (alpha level 0.005 and 80% power) was estimated to 11 paired samples with pH as reference and 14 paired samples with pCO_2 as reference using MedCalc v18.6 (MedCalc Software bvba) sample size calculator for agreement studies. If power was increased to 90%, 13 and 16 paired samples, respectively, were sufficient using pH and pCO_2 as reference. Because, SD of pO_2 was missing in the study [8], a sufficient sample size could, therefore, not be calculated with pO_2 as reference.

2.7 Statistics

Assessment of agreement between sample collection methods, and between ABG and aVBG values, were conducted using Bland–Altman's analysis, Pearson's correlation coefficient (PCC), and Lin's concordance correlation coefficient (CCC). Strength of agreement was assessed by calculating tolerability interval ratio, which is the actual limits-of-agreement interval in this study expressed as the proportion of the clinically acceptable interval [12]. Additionally, rate of misclassification and rate of extreme-to-extreme misclassification is calculated for individual sample pairs with ABG values as gold standard [12]. Statistical analysis was conducted using Stata 13 SE (StataCorp, College Station).

2.8 Ethics and data protection

This study was approved by the Danish Data Protection Agency. The Danish Research Ethics Committee in the North Denmark Region was notified about the study. Since the v-TAC method has previously been approved in clinical research and blood sampling was performed as routine practice based on clinical indication, ethical approval was not required.

3 Results

3.1 Methodological pre-study

Median age of the ten patients in the methodological pre-study was 56 years (range 26–86). Comparison of paired VBG samples collected in 2 ml syringes and 4.5 ml tubes displayed close correlation with mean difference (SD) of pH and pCO_2 was on 0.01 (0.01) pH units and − 0.02 (0.27) kPa, respectively, and CCC values was 0.925 and 0.943 (Table 1). However, pO_2 displayed poor agreement between the two sampling containers with a mean difference (SD) pO_2 value of − 0.57 (1.10) kPa and CCC value on 0.660 because mean pO_2 (SD) was higher in the tube, 4.74 (1.66) kPa, compared to the syringe, 4.18 (1.22) kPa.

3.2 The validation study

Median age of the 20 patients was 66 years (range 36–96 years). All patients were circulatory stable and none suffered from severe respiratory failure. Patient characteristics are presented in Table 2. Comparison analysis between ABG and aVBG samples are summarised in Table 3. The CCC displayed good agreement between pH and pCO_2 in all comparison of ABG and aVBG, except between ABG and $aVBG_2$ pCO_2, where a CCC value of 0.639 displayed weak agreement. Overestimation of pO_2 in aVBG samples resulted in a higher mean difference (SD) − 0.97 (1.32) kPa, − 1.25 (1.73) kPa and − 1.00 (1.34) kPa in the three aVBG samples compared to ABG. Therefore, CCC analysis displayed poor agreement values of 0.720, 0.652 and 0.716 between ABG and $aVBG_{1+2+3}$ pO_2.

Table 2 Characteristics of patients in the validation study

Patient parameters	*n* (%)
Age (year)	
≤ 64	5 (25)
65–74	6 (30)
≥ 75	9 (45)
Sex	
Female	8 (40)
Male	12 (60)
Cause of admission	
COPD exacerbation	6 (30)
Pneumonia	3 (15)
Suspected abdominal ischemia	3 (15)
Dehydration	3 (15)
Cor pulmonale	2 (10)
Diabetic ketoacidosis	1 (5)
Dysregulated diabetes mellitus	1 (5)
Bleeding haemorrhoid	1 (5)
Comorbidities	
COPD	8 (40)
Heart failure	5 (25)
Essential hypertension	4 (20)
IHD	2 (10)
Arterial fibrillation	2 (10)
Diabetes mellitus	2 (10)
Myxoedema	1 (5)
Small cell carcinoma	1 (5)

Patient characteristics and comorbidities in the validation study

COPD chronic obstructive pulmonary disease, *IHD* ischemic heart disease

3.3 Bland and Altman analysis

Bland and Altman plots are presented in Fig. 2. The Bland–Altman findings were in accordance with the CCC findings in the validation study. Mean pH difference between ABG and $aVBG_1$ and between ABG and $aVBG_3$ was within predefined threshold values. Mean difference between all $aVBG_2$ pH samples and ABG pH samples was within acceptable threshold range. Similar tendencies were observed when comparing pCO_2 results. Mean difference in pCO_2 was within predefined acceptable threshold range in overall comparison between all ABG and aVBG pCO_2 values (Table 2), but at an individual patient level, three $aVBG_2$ pCO_2 samples were above threshold values, hence rate of misclassification was 15%. Mean difference of pO_2 between ABG and all aVBG samples was unacceptably above predefined thresholds regardless of sample handling procedure. This was caused by overestimation of pO_2 in a

Table 1 Comparison of blood gas sampling in 2 ml ABG syringe and 4.5 ml tube in the pre-study patients ($n = 10$)

Parameters	ABG syringe Mean (SD)	Tube Mean (SD)	Mean difference (SD)	Concordance correlation analysis			
				CCC	95% CI	*r*	Cb
pH	7.39 (0.04)	7.39 (0.03)	0.01 (0.01)	0.925	0.838–1.013	0.949	0.975
pCO_2 (kPa)	5.90 (0.82)	5.91 (0.75)	− 0.02 (0.27)	0.943	0.869–1.017	0.947	0.996
pO_2 (kPa)	4.18 (1.22)	4.74 (1.66)	− 0.57 (1.10)	0.660	0.326–0.994	0.750	0.880

Comparison of sample containers in group A: *CCC* Lin's concordance correlation coefficient, *95% CI* 95% confidence interval of CCC, *r* Pearson's correlation coefficient, *Cb* bias-correction factor, *kPa* kilopascal

Table 3 Comparison of ABG and arterialized VBG values in the validation study patients ($n=20$)

Parameters	ABG Mean (SD)	aVBG Mean (SD)	Mean difference (SD)	Concordance correlation analysis			
				CCC	95% CI	*r*	Cb
pH	7.42 (0.05)	7.42 (0.05)[a]	0.00 (0.02)[a]	0.939[a]	0.885–0.994[a]	0.941[a]	0.998[a]
		7.39 (0.04)[b]	0.03 (0.02)[b]	0.744[b]	0.590–0.899[b]	0.918[b]	0.811[b]
		7.42 (0.05)[c]	0.00 (0.02)[c]	0.942[c]	0.891–0.994[c]	0.942[c]	1.000[c]
pCO_2 (kPa)	4.94 (0.62)	4.98 (0.61)[a]	− 0.05 (0.22)[a]	0.935[a]	0.878–0.993[a]	0.938[a]	0.997[a]
		5.48 (0.61)[b]	− 0.54 (0.28)[b]	0.639[b]	0.453–0.825[b]	0.895[b]	0.714[b]
		4.95 (0.60)[c]	− 0.01 (0.24)[c]	0.923[c]	0.856–0.991[c]	0.924[c]	0.999[c]
pO_2 (kPa)	10.28 (1.76)	11.24 (2.38)[a]	− 0.97 (1.32)[a]	0.720[a]	0.539–0.902[a]	0.837[a]	0.861[a]
		11.53 (2.92)[b]	− 1.25 (1.73)[b]	0.652[b]	0.467–0.838[b]	0.841[b]	0.775[b]
		11.27 (2.41)[c]	− 1.00 (1.34)[c]	0.716[c]	0.534–0.898[c]	0.839[c]	0.854[c]

Comparison analysis of ABG and aVBG in group B

ABG arterial blood gas, *aVBG* arterialised venous blood gas, *CCC* Lin's concordance correlation coefficient, *95% CI* 95% confidence interval of CCC, *r* Pearson's correlation coefficient, *Cb* bias-correction factor, *kPa* kilopascal

[a]aVBG analysed within 5 min after sampling

[b]aVBG tilted in 5 min and analysed after 7 min

[c]aVBG held steady and analysed after 15 min

majority of the $aVBG_1$ (n = 12), $aVBG_2$ (n = 12) and $aVBG_3$ (n = 11) samples.

3.4 Tolerability interval ratio

The strength of limits-of-agreement expressed as the tolerability interval ratio was 0.65, 0.77 and 0.64, respectively, in pH between ABG and all three $aVBG_{1+2+3}$ samples. Being less than one in each single comparison, it can be concluded that the limits-of-agreement interval is sufficiently narrow for pH as to assure correct assessment of patients' blood gas values when using v-TAC. Likewise, tolerability interval ratio in pCO_2 between ABG and all three $aVBG_{1+2+3}$ samples was 0.48, 0.63 and 0.53. However, tolerability interval ratios for pO_2 agreement was 2.94, 3.84 and 2.97 between ABG and $aVBG_1$, ABG and $aVBG_2$ and ABG and $aVBG_3$, respectively, which is above two and therefore unacceptable.

3.5 Misclassification

Rate of misclassification was zero comparing pH in the $aVBG_1$ and ABG, and $aVBG_3$ and ABG sample pairs. The $aVBG_2$ versus ABG pH rate of misclassification was 10% (2/20). Similar tendencies were observed comparing pCO_2, with $aVBG_1$ versus ABG, and $aVBG_3$ versus ABG rate of misclassification of zero, but 15% (3/20) in $aVBG_2$ versus ABG pCO_2. Rate of misclassification was 60% (12/20), 60% (12/20) and 55% (11/20) between ABG versus $aVBG_{1+2+3}$ pO_2, respectively.

No extreme-to-extreme misclassification occurred comparing aVBG versus ABG in pH and pCO_2. Extreme-to-extreme misclassification was 25% (5/20), 25% (5/20) and 25% (5/20) between ABG and $aVBG_{1+2+3}$ pO_2 values, respectively.

4 Discussion

This study has shown that the v-TAC method delivers clinically valid information on pH and pCO_2 in patients admitted to the ED. Bland and Altman differences were within predefined clinical acceptable threshold ranges for pH and pCO_2 between ABG and aVBG sample pairs. Analogously, tolerability interval ratios were below one between all ABG and aVBG comparison in the parameters pH and pCO_2, hence it can be concluded that the limits-of-agreement interval was sufficiently narrow for the two parameters in all aVBG and ABG sample pairs as to assure correct assessment and treatment of patients when using v-TAC in daily clinical practice. Difference between ABG and calculated aVBG pO_2, however, was outside predefined threshold ranges in all sampled pairs. Moreover, tolerability interval ratio showed unacceptable broad limits-of-agreement and a rate of extreme-to-extreme misclassifications as high as 25%. Reliable acid–base and blood gas values are important for correct patient treatment in the ED setting, thus extreme-to-extreme misclassification was not allowed. Extreme-to-extreme misclassification could result in undertreatment of patients with severely abnormal acid–base or blood gas values.

As also observed in this study, research team behind the v-TAC method found high levels of pO_2 in aVBG samples compared to ABG, but argued that the poor agreement is due to the flat shape of the ODC close to 100% blood oxygen saturation level [7]. Even minor changes in blood O_2

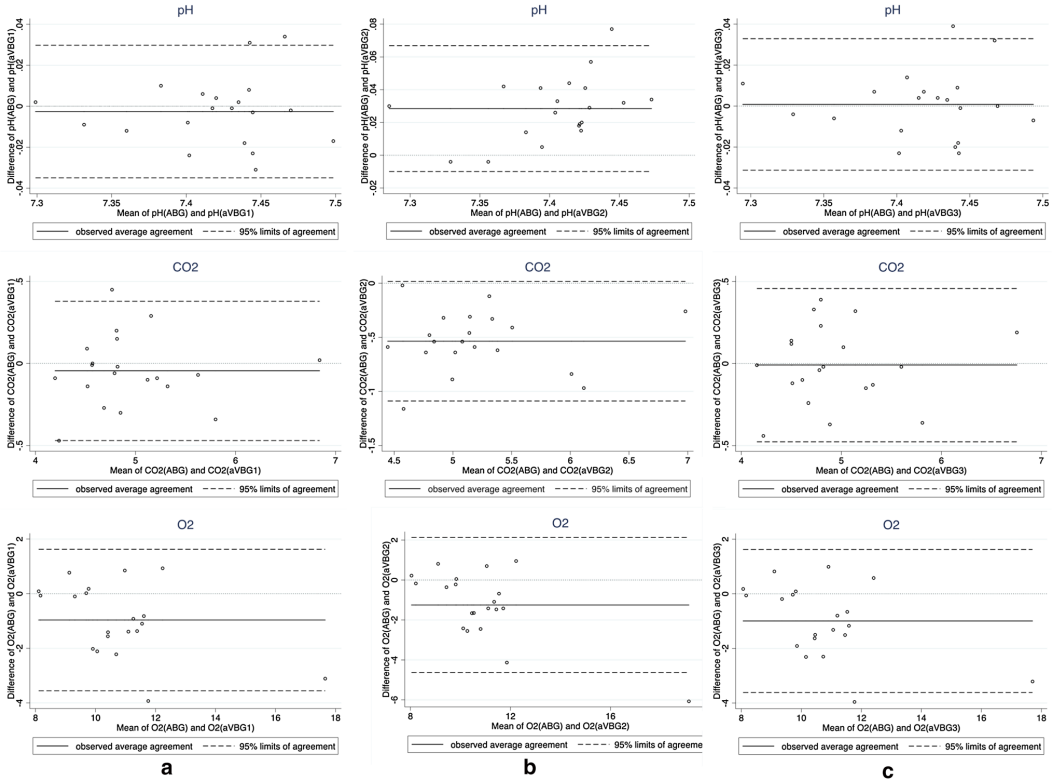

Fig. 2 Bland and Altman plots of ABG and aVBG value agreement in the validation study. **a** ABG and $aVBG_1$; **b** ABG and $aVBG_2$; **c** ABG and $aVBG_3$. *ABG* arterial blood gas, *aVBG* arterialized venous blood gas, *CCC* Lin's concordance correlation coefficient, *95% CI* 95% confidence interval of CCC, *r* Pearson's correlation coefficient, *Cb* bias-correction factor. aVBG1 analysed within 5 min after sampling. aVBG2 tilted in 5 min and analysed after 7 min. aVBG3 held steady and analysed after 15 min

saturation may affect calculated pO_2 pressure significantly when saturation is above 96%. At low O_2 saturation calculating pO_2 should be more accurate due to the steepness of the ODC at O_2 saturation. The same principle applies to the ABG analysis regarding the difference between ABG and aVBG pO_2 values [13]. The selected sample collection tube in the study may also explain the overestimated pO_2 values. In the methodological pre-study mean venous pO_2 was 0.57 kPa higher in the 4.5 ml tube compared with the syringe. Furthermore, the correlation between containers was poor. Higher oxygen values could have been caused by oxygen bubbles in the venous blood sampling kit, which have been sucked into the tube and then absorbed by the venous blood. Leftover oxygen in the vacuum of the tubes could also explain this difference. Hence, the observed overestimation of calculated aVBG pO_2 in the validation study could very well be related to an inappropriate choice of sample container, and the reliability of v-TAC pO_2 should be investigated further in different sample containers, before its use is ruled out in the ED setting.

It was surprising that the v-TAC method managed to calculate pCO_2 with both accuracy and precision, as established previously, the method relies on calculated arteriovenous difference in O_2 to calculate pCO_2 values (step E in Fig. 1). Since calculated pO_2 is generally overestimated and limits-of-agreement was observed at an unacceptable level in this study, the accuracy of the difference in O_2 may not be of major importance in the overall calculation.

Tilting of VBG_2 samples collected in 4.5 ml tubes caused an increase of pCO_2 and lowered pH, which resulted in misclassification rate of $aVBG_2$ pCO_2 just above the predefined 5% threshold. Although a larger sample size might lower the misclassification rate for calculated pCO_2, careful sample handling should be advised to obtain valid estimations of pCO_2.

McCanny et al. reject VBG as a reliable alternative to ABG due to variations in venous pCO_2 agreement with arterial pCO_2 [14]. Bland and Altman's plot demonstrated average difference in 8.6 mmHg (1.15 kPa) and limits of agreement from − 7.84 mmHg (− 1.02 kPa) to 25.05 mmHg (3.34 kPa) between venous and arterial pCO_2 [14]. Although only 20 patients were included in the present study clinically acceptable difference and narrow limits-of-agreement of pCO_2 between aVBG and ABG were observed. Therefore, the v-TAC could contribute to make for a more precise estimation of arterial pCO_2.

Clinically acceptable ranges of difference between ABG and aVBG is challenging to determining. Either, normal reference ranges are used as tolerable intervals [12], or alternatively acceptable laboratory intervals are calculated ($\pm 2 \times$ SD) [15]. In questionnaire-based survey certified ED physicians reported maximum figures they would feel comfortable about regarding differences between monitored arterial and calculated arterial values for pH and pCO_2 in clinical practice. The results were as follows: mean (95% CI) 0.05 (0.04–0.06) for pH and 0.88 (0.74–1.01) kPa for pCO_2 [16]. These acceptable thresholds were used in this present study. Values for pO_2 were not covered in the survey.

According to the research team behind the v-TAC method, the peripheral limp has to be well perfused and the respiratory quotient has to be within 0.7 and 1.0 for v-TAC to deliver accurate estimates of ABG [7]. In this present study all included patients were circulatory stable and no one suffered from severe respiratory failure. However, in the critically ill patient, both the respiratory quotient and peripheral blood perfusion may vary considerably, depending on the underlying pathophysiological mechanisms [17, 18]. The v-TAC method may not be appropriate to assess patients with extreme conditions, but it may be able to identify potential critically ill patients with extreme acid–base status or blood gas values in a mixed ED patient population.

Our study has a number of limitations. It was designed as a single-centre study with a small number of participants without specific clinical characteristics. Hence, in this heterogenous study group results could not be generalised. Moreover, randomisation was performed by a simple quasi-random allocation and the study results suggest that anaerobic sampling might not have been guaranteed in the 4.5 ml tube even if air bubbles in the venous blood sampling kit was avoided.

In medical departments where repeated blood gas is required (e.g. in patients with COPD), the v-TAC method may reduce the need for repeated painful arterial punctures, since sampling of blood gas is achieved in conjunction with routine venous blood sampling. The reliability and utility of method should be examined in large studies, preferably multicentre studies, which renders subdivision of patients into groups according to cause of admission, severity of symptoms or conditions (e.g. hypoxia, hypo- or hypercapnia, severe acidosis or severe anaemia) in order to clarify under which conditions this method is reliable.

5 Conclusion

Mathematical arterialisation of VBG was found to be a valid method for calculation of pH and pCO_2 ABG values in circulatory stable ED patients, whereas the arterialised values of pO_2 showed overestimation and clinically unacceptable broad limits-of-agreement. This observation could be due to the venous blood sampling procedure in which 4.5 ml tubes were used. The usability of v-TAC in critically ill patients with reduced peripheral blood perfusion or extreme acid–base or blood gas values remains to be explored in future studies.

Compliance with ethical standards

Conflict of interest None declared from all authors.

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