

RESEARCH

Open Access



Effects of respiratory rate on venous-to-arterial CO₂ tension difference in septic shock patients undergoing volume mechanical ventilation

Zhixiang Guo^{1†}, Yapeng Wang^{2†}, Chao Xie³, Guofang Hua³, Shenglin Ge^{1*} and Yuedong Li^{3*}

Abstract

Background: To explore the effects of the respiratory rate (RR) on the venous-to-arterial CO₂ tension difference (gapCO₂) in septic shock patients undergoing volume mechanical ventilation.

Methods: Adult patients with septic shock underwent volume mechanical ventilation between October 2015 and October 2016. RR was started at 10 breaths/min, and 2 breaths/min were added every 60 min until 16 breaths/min was reached. At every point, central venous and arterial blood gas measurements were obtained simultaneously.

Results: In this study, gapCO₂ induced by hyperventilation significantly increased, while the central venous carbon dioxide pressure (PvCO₂) and the partial pressure of CO₂ (PaCO₂) in arteries decreased. The decreasing trend of the PaCO₂ was more obvious than that of the PvCO₂. HCO₃⁻ and ctCO₂ were markedly decreased, when the RR was increased ($P < 0.05$). Central venous oxygen saturation (S_{cv}O₂) had a decreasing trend between 14 (77.1 ± 8.3%) and 16 (75.2 ± 8.7%) breaths/min; however, the difference was not significant.

Conclusions: In septic patients undergoing ventilation, respiratory alkalosis induced by hyperventilation caused an increase in the gapCO₂. Clinicians should cautiously interpret the gapCO₂ in hemodynamically stable ventilated septic shock patients and its relationship with low cardiac output and inadequate perfusion.

Keywords: Sepsis, Septic shock, Venous-to-arterial carbon dioxide tension difference, Volume-controlled ventilation, Respiratory rate

Background

The current consensus and guidelines for the hemodynamic management of severe sepsis and septic shock advocate clinicians to regard the use of lactate clearance

and central venous oxygen saturation (S_{cv}O₂) normalization as tissue perfusion endpoints [1–3]. Abnormally high S_{cv}O₂ values have been related to higher mortality in septic shock patients [4], while lactate clearance has proved to be as beneficial as the S_{cv}O₂ in the hemodynamic management of sepsis. However, when clinicians face the uncertainty of a high lactate value, they have to identify whether it indicates persistent hypoperfusion or whether it will eventually normalize. Therefore, normalized S_{cv}O₂ values and lactate values do not rule out persistent hypoxia and hypoperfusion during initial resuscitation.

*Correspondence: shenglin_ge@sohu.com; yuedongli@yeah.net

[†]Zhixiang Guo and Yapeng Wang contributed equally to this work and should be considered co-first authors

¹ Department of Cardiovascular Surgery, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230022, Anhui, China

³ Department of Critical Care Medicine, The 901st Hospital of the Joint Logistics Support Force of PLA, No. 424 Changjiang West Road, Hefei 230000, Anhui, China

Full list of author information is available at the end of the article



A few authors have reported that the central venous-to-arterial CO₂ difference (gapCO₂) demonstrated prognostic value in different conditions [5–8] and have recommended that the gapCO₂ combined with the S_{cv}O₂ and lactate values should be used to rule out patients with persistent global hypoperfusion [3]. Under steady states of both CO₂ production and oxygen consumption, the gapCO₂ was observed to be increased in parallel with the reduction in cardiac output [9]. However, spontaneous breathing and hyperventilation may reduce the partial pressure of CO₂ in arteries (PaCO₂) and prevent the CO₂ stagnation-induced rise in central venous carbon dioxide pressure (PvCO₂). Mallat et al. demonstrated that acute hyperventilation provoked a significant increase in gapCO₂ and oxygen consumption (VO₂) [10]. To date, little is known about the gapCO₂ and respiratory rate (RR) in septic shock patients undergoing volume mechanical ventilation. Therefore, in this study, we investigated the underlying effect of the RR on the gapCO₂ in septic shock patients undergoing volume mechanical ventilation.

Materials and methods

Patients

This observational and prospective study was performed at a single, mixed medical and surgical adult intensive care unit (ICU) with 14 beds at 105 Hospital of Chinese People's Liberation Army from October 2015 to October 2016. The study was approved by the ethics committee of the 105 Hospital of Chinese People's Liberation Army. Informed consent was obtained from each subject.

The study included 17 patients within 24 h of septic shock onset. The diagnosis of septic shock was determined according to the Second International Consensus of Definitions for Sepsis and Septic Shock [11]. As part of the routine management of septic shock in our ICU, all patients underwent volume mechanical ventilation with a fractional inspired oxygen level (FiO₂) no greater than 65%, using an 840 Ventilator System.

Sedation with propofol and analgesia with remifentanyl were provided so that patients without spontaneous breathing could be included in the study. The inclusion criteria were oliguria, mottled skin [12], central venous oxygen saturation (S_{cv}O₂) > 65% and lactate level < 4 mmol/L after achieving adequate intravascular volume and adequate mean arterial pressure (MAP) > 65 mmHg, as recommended by the Surviving Sepsis Campaign [1]. The exclusion criteria were pregnancy, COPD, age less than 18 years, unstable hemodynamic condition (change of vasoactive drug dosage or fluid administration within 60 min before the protocol), high blood lactate levels (> 4 mmol/L) after adequate resuscitation, and uncontrolled tachyarrhythmia (heart rate > 140 beats/min).

Measurements

Demographic data, septic shock etiology, and acute physiology and chronic Health evaluation (APACHE) II [13] and sequential organ failure assessment (SOFA) scores were obtained on the day of enrollment. Blood gas analysis was performed using a blood gas analyzer (ABL 900 Radiometer, Copenhagen, Denmark). S_{cv}O₂ was determined in a sample taken from the central venous catheter with the tip (confirmed by X-ray) in the superior vena cava near or at the right atrium. The gapCO₂ was calculated as the difference between the central PvCO₂ tension and PaCO₂ tension.

Study protocols

Ventilation parameters and vasopressor drugs were kept constant during the 60-min period prior to the measurements being taken. After the baseline measurements were taken, an RR of 10 breaths/min was started, and 2 breaths/min were added every 60 min until 16 breaths/min was attained. For each procedure, all parameters were measured. The study ended when arterial hypotension (MAP < 60 mmHg), tachycardia (heart rate > 150 beats/min), acute atrial fibrillation, or changes in the ST segment of the electrocardiogram occurred.

Statistical analysis

Statistical analysis was performed using SPSS 10.0 software. A *p* value (2-tailed) of 0.05 or less was considered significant. Continuous variables were presented as mean ± standard deviation (SD) if normally distributed, or as median if otherwise, and compared using Wilcoxon–Mann–Whitney test. Comparisons of hemodynamic indexes and blood gas in accordance with the RR from 10 to 16 breaths/min were performed by the Bonferroni method.

Results

Basic characteristics of the 17 patients are presented in Table 1. All hemodynamic effects following the change in RR are listed in Table 2. Blood pressure, heart rate, lactate level, and BE changes were not statistically significant from 10 to 16 breaths/min. Hyperventilation induced a significant RR-dependent increase in the gapCO₂, which was related to the combined trend of decreases in PaCO₂ and PvCO₂ (Figs. 1 and 2). Changes in HCO₃⁻ were paralleled by a significant decrease in ctCO₂ (Fig. 3). S_{cv}O₂ significantly increased with increasing RR from 10 to 14 breaths/min, but had a decreasing trend from 14 to 16 breaths/min. Hypocapnia provoked by hyperventilation

Table 1 Patients characteristics

Demographics	All patients (n = 17)
Age (years)	69 ± 11
APACHE II	20 ± 5
SOFA score at admission	7 ± 2
ICU mortality, n (%)	6
Lactate levels (mmol/L)	4.03 ± 0.2
CVP (cmH ₂ O)	12.5 ± 3.6
Mottled skin, n (%)	6
Source of infection, n (%)	17
Pneumonia	8
Abdominal infection	5
Urinary tract infection	3
Mediastinal infection	1

Data are presented as mean ± SD or absolute values (%)

APACHE II, acute physiology and chronic health evaluation; SOFA, sepsis-related organ failure assessment; ICU, intensive care unit; CVP, central venous pressure

significantly decreased from 10 to 16 breaths/min, while the gapCO₂ exhibited an opposite trend (Fig. 4).

Discussion

Septic patients with respiratory failure suffer myocardial systolic and diastolic dysfunction [14]. Mechanical ventilation plays a critical role in these patients. At present, the gapCO₂ has been considered an evaluation of tissue hypoperfusion and has been recommended as a guide

for resuscitation in septic patients [5, 6]. However, it is unknown whether the clinical significance of the gapCO₂ also applies to septic patients with mechanical ventilation. Therefore, we explored the effects of the respiratory rate on the gapCO₂ in septic shock patients undergoing volume mechanical ventilation and found a significant difference in the gapCO₂ induced by hyperventilation.

When the respiratory rates increased with the tidal volume unchanged, the total minute ventilation and alveolar ventilation, as well as the PaO₂, improved. The PaCO₂ decreased because excessive ventilation enabled the increased expiration of CO₂. Our results showed that the PcvCO₂ and PaCO₂ decreased with an increasing respiratory rate, and this difference was statistically significant. However, the decreasing trend of the PaCO₂ was more obvious than that of the PcvCO₂. Consequently, the difference in the gapCO₂ values when the RR varied from 10 to 16 breaths/min was significant. We consider that the following physiological factors can explain this phenomenon.

The combination of oxygen and hemoglobin can promote the release of CO₂. Furthermore, CO₂ more easily combines with hemoglobin at lower oxygen saturation, which is a phenomenon called the Haldane effect [15]. Clearly an increase in alveolar ventilation increases CO₂ excretion and alveolar PaO₂. Increased alveolar ventilation causes respiratory alkalosis with immediate changes in hydrogen ion concentrations and bicarbonate concentrations. There are transcellular shifts

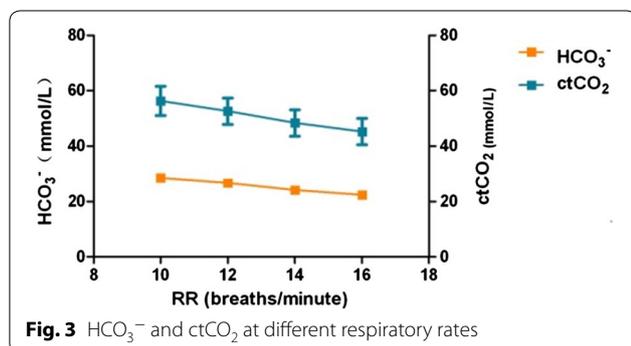
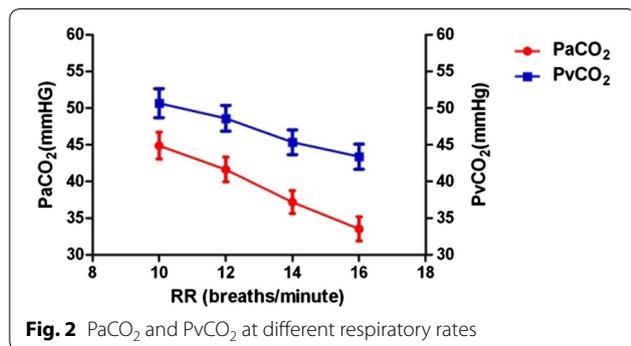
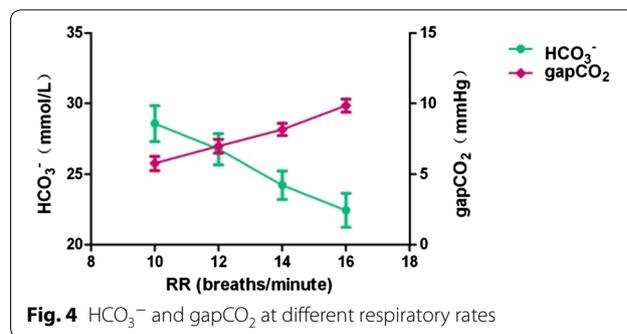
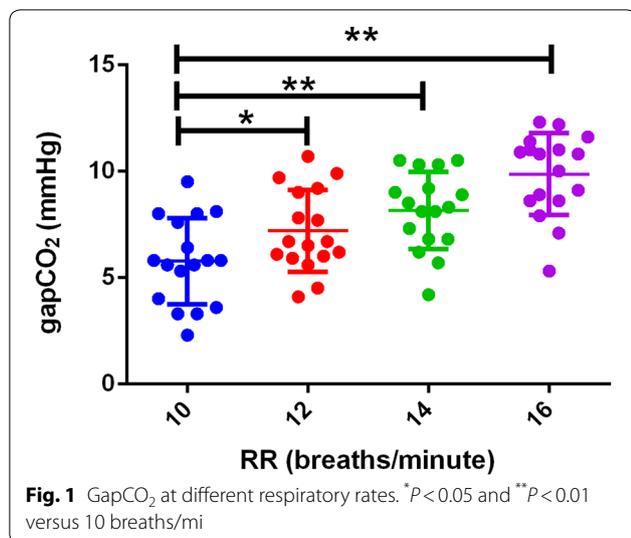
Table 2 Hemodynamic, blood gas, and metabolic parameters during different RRs after achieving adequate intravascular volume

Parameters	Level 1 (RR = 10)	Level 2 (RR = 12)	Level 3 (RR = 14)	Level 4 (RR = 16)
HR, beats/minute	95 ± 19	98 ± 17	97 ± 17	97 ± 15
MAP, mmHg	84 ± 9.5	84 ± 10.9	83 ± 9.8	86.9 ± 11.7
pH	7.35 ± 0.078	7.38 ± 0.092*	7.42 ± 0.059**	7.43 ± 0.078**
PaCO ₂ , mmHg	44.9 ± 7.60	41.6 ± 6.92**	37.2 ± 6.42**	33.5 ± 6.80**
PaO ₂ , mmHg	114.1 ± 24.96	125.0 ± 24.67*	137.6 ± 26.86**	144.3 ± 27.57**
SaO ₂ , %	98.9 ± 1.15	99.1 ± 0.91	99.2 ± 0.74	99.1 ± 0.90
Lactate, mmol/L	1.78 ± 0.95	1.89 ± 1.29	1.98 ± 0.72	2.15 ± 2.06
BE	0.59 ± 9.48	0.42 ± 6.51	0.70 ± 4.59	0.84 ± 4.40
K ⁺ , mmol/L	4.3 ± 0.9	4.3 ± 0.7	4.2 ± 0.7	4.4 ± 0.6
HCO ₃ ⁻ , mmol/L	28.58 ± 5.22	26.76 ± 4.56*	24.23 ± 4.20*	22.44 ± 4.99*
ctCO ₂ , mmol/L	56.32 ± 21.9	52.62 ± 19.7*	48.33 ± 19.5**	45.21 ± 19.6**
PcvCO ₂ , mmHg	50.66 ± 8.09	48.61 ± 7.21**	45.35 ± 6.99**	41.43 ± 12.50**
S _{cv} O ₂ , %	73.1 ± 7.7	75.3 ± 7.0	77.1 ± 8.3**	75.2 ± 8.7*
gapCO ₂ , mmHg	5.76 ± 2.02	7.19 ± 1.93*	8.16 ± 1.81**	9.85 ± 1.92**

Data are presented as mean ± SD or absolute values (%)

MAP, mean arterial pressure; PaCO₂, partial pressure of carbon dioxide in artery; PcvCO₂, central venous carbon dioxide pressure; gapCO₂, central venous-to-arterial carbon dioxide difference; S_{cv}O₂, central venous oxygen saturation

* P < 0.05 compared with RR of 10 breaths/min, **P < 0.01 compared with RR of 10 breaths/min. Multiple comparisons were used to adjust for the Bonferroni method



of venous blood should increase, leading to a higher gapCO₂. If patients with sepsis have disordered cellular metabolism, then the production CO₂ may decrease, which in turn results in a lower gapCO₂. Furthermore, the depression of oxidative adenosine triphosphate (ATP) production also led to pulmonary vasoconstriction [16]. Nitric oxide synthesis defect has shown to be another cause [17]. As a consequence, the reducing trend of the CO₂ partial pressure of venous blood is less marked than that of arterial blood. This has been demonstrated by other scholars as well [18]. The increase in alveolar ventilation increases CO₂ excretion and should increase the alveolar PaO₂ provided other factors stay the same. Increased alveolar ventilation causes respiratory alkalosis with immediate changes in hydrogen ion concentrations and bicarbonate concentrations. There should be transcellular shifts with hydrogen ion coming out cells into the plasma and shifts of potassium from the plasma into cells. Respiratory alkalosis can cause peripheral vasoconstriction and decreased flow through various vascular beds. This is probably not a uniform effect in all vessels and may or may not occur in patients with sepsis. However, if blood flow decreases but metabolism is unchanged, then the CO₂ content of venous blood should increase, resulting in a gapCO₂. If patients with sepsis have dysfunctional cellular metabolism, then the production CO₂ may decrease, which would result in a lower gapCO₂. This likely varies in the vascular bed from tissue to tissue. CO₂ binding hemoglobin may not have an important effect in these experiments.

with H ions coming out cells into the plasma and shifts of potassium from the plasma into cells. Renal compensation with bicarbonate excretion takes hours. Nevertheless, respiratory alkalosis can cause peripheral vasoconstriction and decreased flow through the various vascular beds. This is probably not a uniform effect in all vessels and may or may not occur in patients with sepsis. However, if blood flow decreases but metabolism is unchanged, then the CO₂ content

When vasoconstriction is caused by hypocapnia, poor oxygen delivery may add tissue oxygen extraction [19]. Hence, when patients are in hypocapnia provoked by hyperventilation, the CO₂ partial pressure of the venous blood does not obviously decrease compared with the CO₂ partial pressure of the arterial blood. For instance, Khambatta et al. reported that mechanically ventilated dogs undergoing 2 h of hyperventilation had 20% CO₂ production and 25% O₂ consumption [20]. In

this study, the $S_{cv}O_2$ significantly increased with the RR increase from 10 to 14 breaths/min, but there was no significant decreasing trend in $S_{cv}O_2$ between 14 and 16 breaths/min, which was consistent with a previous report [21]. Moreover, it is widely accepted that the $gapCO_2$ depends on measurements from the superior vena cava (SVC) but does not reflect measurements from the inferior vena cava (IVC) and tissues draining into the IVC [22].

Patients with septic shock lack an effective circulating blood volume, which leads to systemic anoxia and metabolic acidosis. Acidosis and excess CO_2 can cause mitochondrial dysfunction [23, 24]. Metabolic acidosis and respiratory alkalosis due to excessive hyperventilation further reduce the function of mitochondria oxidative phosphorylation, which may impact CO_2 production. In summary, our data suggested that in septic patients with mechanical ventilation, respiratory alkalosis induced by hyperventilation enabled the increase of $gapCO_2$. Clinicians should be cautious when interpreting the $gapCO_2$ as low cardiac output and inadequate perfusion in hemodynamically stable ventilated septic shock patients.

Conclusions

However, there were some limitations in our paper. In this study, we used a central venous sample to measure the $gapCO_2$ instead of using a mixed venous sample, despite the latter having a better correlation. We cannot state the relationship between the $gapCO_2$ and cardiac output, as we did not include the indexes of cardiac function in this study. We included fewer patients than other studies, and the included patients suffered from different etiological factors, so the results from this study should be further confirmed in the future.

Acknowledgements

Not applicable.

Authors' contributions

ZG, YW designed the study; ZG, YW, CX, GH, SG, YL performed the study; ZG, YW, YL analyzed the data; YL drafted the paper. All authors read and approved the final manuscript.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the ethics committee of the 105 Hospital of Chinese People's Liberation Army.

Consent for publication

Informed consent was obtained from each subject.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Department of Cardiovascular Surgery, The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230022, Anhui, China. ² Department of Cardiac Intensive Care Unit (CICU), The First Affiliated Hospital of Anhui Medical University, No. 218 Jixi Road, Hefei 230022, Anhui, China. ³ Department of Critical Care Medicine, The 901st Hospital of the Joint Logistics Support Force of PLA, No. 424 Changjiang West Road, Hefei 230000, Anhui, China.

Received: 27 August 2019 Accepted: 5 February 2020

Published online: 17 March 2020

References

- Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580–637.
- Mesquida J, Borrat X, Lorente JA, Masip J, Baigorri F. Objectives of hemodynamic resuscitation. *Med Intens*. 2011;35(8):499–508.
- Vallet B, Pinsky MR, Cecconi M. Resuscitation of patients with septic shock: "please mind the gap!". *Intensive Care Med*. 2013;39(9):1653.
- van Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA. The incidence of low venous oxygen saturation on admission to the intensive care unit: a multi-center observational study in The Netherlands. *Crit Care*. 2008;12(2):R33.
- Vallée F, Vallet B, Mathe O, Parraguet J, Mari A, Silva S, Samii K, Fourcade O, Genestal M. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Med*. 2008;34(12):2218.
- Futier E, Robin E, Jabaudon M, Guerin R, Petit A, Bazin JE, Constantin JM, Vallet B. Central venous O_2 saturation and venous-to-arterial CO_2 difference as complementary tools for goal-directed therapy during high-risk surgery. *Crit Care*. 2010;14(5):R193.
- Ospinatascón GA, Bautistarincón DF, Umaña M, Tafur JD, Gutiérrez A, García AF, Bermúdez W, Granados M, Arangodávila C, Hernández G. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. *Crit Care*. 2013;17(6):R294.
- Beest PAV, Lont MC, Holman ND, Loeff B, Kuiper MA, Boerma EC. Central venous-arterial pCO_2 difference as a tool in resuscitation of septic patients. *Intensive Care Med*. 2013;39(6):1034–9.
- Rocha M, Costa F, Barreto JEF. Central venous-to-arterial carbon dioxide difference (CO_2 GAP) in patients with arterial pulmonary hypertension: a pilot study. *Eur Respir J*. 2014;40:P3920.
- Mallat J, Mohammad U, Lemmyze M, Meddour M, Jonard M, Pepy F, Gasan G, Barrailler S, Temime J, Vangrunnderbeeck N. Acute hyperventilation increases the central venous-to-arterial PCO_2 difference in stable septic shock patients. *Ann Intensive Care*. 2017;7(1):31.
- Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brunbuisson C, Beale R. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med*. 2008;34:17–60.
- Ait-Oufella H, Lemoine S, Boelle PY, Galbois A, Baudel JL, Lemant J, Joffre J, Margetis D, Guidet B, Maury E. Mottling score predicts survival in septic shock. *Intensive Care Med*. 2011;37(5):801.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med*. 1986;13(10):818–29.
- Flynn A, Mani BC, Mather PJ. Sepsis-induced cardiomyopathy: a review of pathophysiological mechanisms. *Heart Fail Rev*. 2010;15(6):605.
- Teboul JL, Scheeren T. Understanding the Haldane effect. *Intensive Care Med*. 2017;43(1):91–3.
- Rounds S, Mcmurry IF. Inhibitors of oxidative ATP production cause transient vasoconstriction and block subsequent pressor responses in rat lungs. *Circ Res*. 1981;48(3):393.
- Gardiner SM, Kemp PA, Bennett T, Palmer RM, Moncada S. Nitric oxide synthase inhibitors cause sustained, but reversible, hypertension and hindquarters vasoconstriction in Brattleboro rats. *Eur J Pharmacol*. 1992;213(3):449–51.

18. Morel J, Gergel  L, Domin  A, Molliex S, Perrot JL, Labeille B, Costes F. The venous-arterial difference in CO₂ should be interpreted with caution in case of respiratory alkalosis in healthy volunteers. *J Clin Monit Comput*. 2017;31(4):701–7.
19. Mas A, Saura P, Joseph D, Blanch L, Baigorri F, Artigas A, Fern ndez R. Effect of acute moderate changes in PaCO₂ on global hemodynamics and gastric perfusion. *Crit Care Med*. 2000;28(2):360–5.
20. Khambatta HJ, Sullivan SF. Effects of respiratory alkalosis on oxygen consumption and oxygenation. *Anesthesiology*. 1973;38(1):53–8.
21. Morel J, Gergele L, Verveche D, Costes F, Auboyer C, Molliex S. Do fluctuations of PaCO₂ impact on the venous-arterial carbon dioxide gradient? *Crit Care*. 2011;15(6):456.
22. Riva JA, Bouchacourt JP, Kohn WE, Hurtado FJ. The changes in the oxygen saturations in the superior vena cava and the pulmonary artery are not the same during cardiac surgery. *Rev Esp Anesthesiol Reanim*. 2015;62(3):140–4.
23. Jubrias SA, Crowther GJ, Shankland EG, Gronka RK, Conley KE. Acidosis inhibits oxidative phosphorylation in contracting human skeletal muscle in vivo. *J Physiol*. 2003;553(2):589–99.
24. Vohwinkel CU, Lecuona E, Sun H, Sommer N, Vad sz I, Chandel NS, Szneider JI. Elevated CO₂ levels cause mitochondrial dysfunction and impair cell proliferation. *J Biol Chem*. 2011;286(43):37067–76.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

