Prognostic value of central venous-to-arterial carbon dioxide difference in patients with bloodstream infection

Zhonghua Wang, Xuebiao Wei, Tiehe Qin, Shenglong Chen, Xiaolong Liao, Weixin Guo, Peihang Hu, Yan Wu, Jie Li, Youwan Liao, Shouhong Wang

1. Department of Critical Care Medicine, Guangdong Geriatrics Institute, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China.
2. Department of Critical Care Medicine, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China.

Zhonghua Wang and Xuebiao Wei are contributed equally to this work as Co-first authors.

Corresponding authors: Zhonghua Wang, Department of Critical Care Medicine, Guangdong Geriatrics Institute, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou 510080, Guangdong, China. E-mail address: wangzhonghua@gdph.org.cn

© The author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/). See http://ivyspring.com/terms for full terms and conditions.

Received: 2020.08.03; Accepted: 2020.12.17; Published: 2021.01.01

Abstract

**Background:** Bloodstream infection (BSI) are prone to circulation disorders, which portend poor outcome. The central venous-to-arterial carbon dioxide difference (Pcv-aCO2) is a biomarker for circulation disorders, but the prognostic value of Pcv-aCO2 in BSI patients remains unclear. This study was to investigate the association of Pcv-aCO2 with adverse events in BSI patients.

**Methods:** The patients with BSI between August 2014 and August 2017 were prospectively enrolled. Clinical characteristic and laboratory results were collected. We analyzed the association of the level of Pcv-aCO2 with clinical variables and 28-day mortality.

**Results:** A total of 152 patients were enrolled. The Pcv-aCO2 was positively correlated with white blood cell count (r=0.241, p=0.003), procalcitonin (r=0.471, p<0.001), C-reactive protein (r=0.192, p=0.018), lactate (r=0.179, p=0.027), Sequential Organ Failure Assessment (r=0.318, p<0.001) and Acute Physiology And Chronic Health Evaluation II score (r=0.377, p<0.001), while that was negatively correlated with central venous oxygen saturation (r=-0.242, p<0.001) and platelet (r=-0.205, p=0.011). Kaplan-Meier curves demonstrated that patients with Pcv-aCO2>6mmHg had a worse prognosis than those without (log rank=32.10, p<0.001). Multivariate analysis showed Level of Pcv-aCO2 was an independent risk factor for 28-day mortality (HR: 3.10, 95% CI: 1.43-6.74, p=0.004). The area under the receiver operating characteristic curve of Pcv-aCO2 for prediction of 28-day mortality in patients with BSI was 0.794. Pcv-aCO2>6 mmHg had 81.1% sensitivity and 78.8% specificity for predicting 28-day mortality.

**Conclusion:** Pcv-aCO2 may be a simple and valuable biomarker to assessment of 28-day mortality in patients with BSI.

Key words: central venous-to-arterial carbon dioxide difference; biomarker; prognostic factor; bloodstream infection

Introduction

Bloodstream infection (BSI) is common systemic infection in intensive care unit (ICU), affecting 189/100000 patients [1]. It is associated with increased risk of organ failure and mortality, and one-year mortality from BSI is between 8% and 48% [2]. BSI bring a huge financial burden to families and society [3]. Therefore, early accurate identification of patients at high risk of poor outcomes may have an essential role in improving prognosis.

The common pathological change of BSI is
microcirculation disorder [4]. Previously, lactate and central venous oxygen saturation \( (S_{\text{cVO}_2}) \) are accepted clinical indicators of organ perfusion and oxygen metabolism \([5, 6]\). At present, central venous-to-arterial carbon dioxide difference (Pcv-aCO\(_2\)) as a biomarker of perfusion is gradually recognized. Pcv-aCO\(_2\) has reported to be associated with poor prognosis in critical patients suffering from shock, and Pcv-aCO\(_2\) is recommended as a biomarker for further resuscitation interventions \([7]\). In addition, persistently high Pcv-aCO\(_2\) during the early phases of resuscitation was a predictor for poor outcomes in patients with septic shock \([8, 9]\). However, the prognostic role of Pcv-aCO\(_2\) in patients with BSI remains to be seen. In this study, we attempted to explore the association between Pcv-aCO\(_2\) and 28-day mortality in patients with BSI.

Patients and methods

Study objects

We prospectively enrolled patients with BSI between August 2014 and August 2017 in Geriatric ICU, Guangdong Provincial People’s Hospital, Guangzhou, China. Inclusion criterion were as follows: (1) age>18 years; (2) clinical symptoms meet systemic inflammatory response syndrome or hypotension; (3) at least one positive blood culture; (4) only a single bloodstream infection pathogen. Exclusion criteria included: (1) patients refused cardiopulmonary resuscitation or aggressive measures; (2) mismatch of the time of arterial and venous blood gas test. The eligible patients were divided into two groups based on a cut-off value of Pcv-aCO\(_2\) of >6 mmHg from previous study on septic shock \([8]\). The present study was approved by the Ethics Committee of Guangdong Provincial People’s Hospital (No. GDREC2014006H), and written informed consent was obtained from all included patients or their relatives.

Data collection

The demographic including sex, age were recorded and Acute Physiology And Chronic Health Evaluation II (APACHE II) score, and Sequential Organ Failure Assessment (SOFA) were calculated when the patients were diagnosed with BSI. The biochemical data, such as Pcv-aCO\(_2\), ScvO\(_2\), white blood cell (WBC) count, platelet (PLT), procalcitonin (PCT), C-reactive protein (CRP), and lactate were tested when the patients were diagnosed with BSI. We routinely performed arterial and central venous blood gas analysis while taking blood culture specimens. Pcv-aCO\(_2\) and ScvO\(_2\) were obtained by simultaneous analysis of arterial and central venous blood gases with a blood gas analyzer (ABL 800; Radiometer Medical, Denmark); other demographic and clinical characteristics of enrolled participants were collected by a researcher with the use of an electronic case report form, and then were confirmed by another researcher.

Follow-up and endpoints

All the patients were followed-up for 28 days by telephone interviews after BSI diagnosis. The primary endpoint was 28-day all-cause mortality.

Statistical analysis

Statistical analyses were performed by using SPSS 24.0 software (IBM, Armonk, NY, USA). The continuous variables were presented as mean ± standard deviation (SD), and compared using independent sample t-test when they were normally distributed; for non-normally distribution, the Wilcoxon rank-sum test was conducted, and the data presented as median and interquartile range. Categorical variables were presented as a percentage and compared using \( \chi^2 \) or Fisher’s exact test. Bivariate correlations were calculated by Pearson’s or Spearman’s correlation coefficients. Survival curves were depicted by using Kaplan-Meier analysis. Cox proportional hazards regression model was used to analyze the association between the variables and the risk of death. Multivariate Cox regression analysis was performed with the variables whose p-value was less than 0.05 in univariate logistic regression analysis for 28-day mortality. Receiver operating characteristic (ROC) curves were plotted to evaluate the predictive power of Pcv-aCO\(_2\) for 28-day mortality. A p-value < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics of patients with BSI

Finally, 152 patients were enrolled and 53 (34.9%) patients died within 28 days. All the patients were divided into two groups: Pcv-aCO\(_2\) ≤ 6 mmHg (n=88) and Pcv-aCO\(_2\) > 6 mmHg (n=64). The baseline characteristics were presented in Table 1. There were no significant differences between the two groups in terms of age, gender, concurrent foci of infection, the main history, non-infection comorbidity and CRP. The SOFA (11.89 ± 4.08 vs 9.69 ± 3.18, p<0.001), APACHE II score (28.63 ± 6.11 vs 24.78 ± 5.38, p<0.001), PCT (34.17 ± 39.52 vs 9.73 ± 21.24, p=0.001), WBC (16.90 ± 7.12 vs 14.20 ± 6.02, p=0.013), lactate (3.48 ± 3.44 vs 2.34 ± 2.67, p=0.023) were higher and platelet (114.78 ± 80.42 vs 146.23 ± 90.05, p<0.028) , ScvO\(_2\) (53.15 ± 12.05 vs 70.53 ± 10.73, p<0.001) were lower in Pcv-aCO\(_2\) > 6 mmHg group. The demand for mechanical ventilation, vasopressor and continuous
renal replacement therapy (CRRT) in Pcv-aCO₂ > 6 mmHg group is significantly greater than in Pcv-aCO₂ ≤ 6 mmHg group. Gram-positive (GP) bacteria were the predominant pathogens in Pcv-aCO₂ ≤ 6 mmHg group, while Gram-negative (GN) bacteria are the predominant pathogens in Pcv-aCO₂ > 6 mmHg group. The 28-day mortality (60.9% vs 15.9%, p<0.001) was higher in Pcv-aCO₂ > 6 mmHg group.

**Table 1. Patients’ baseline clinical characteristics at different levels of Pcv-aCO₂**

| Clinical variables | Pcv-aCO₂≤6mmHg | Pcv-aCO₂>6mmHg | p     |
|--------------------|----------------|----------------|-------|
| Age (years)        | 80.5±7.62      | 82.8±8.24      | 0.119 |
| Women, %           | 31(35)         | 19(30)         | 0.200 |
| SOFA               | 9.69±3.18      | 11.89±4.08     | <0.001|
| APACHE II          | 24.78±5.38     | 28.63±6.11     | <0.001|
| Concurrent foci of infection (%) |               |                |       |
| Pneumonia          | 64(72.7)       | 38(59.3)       | 0.084 |
| Urinary tract infection | 15(17.0)    | 10(15.6)       | 0.600 |
| Abdominal infection | 3(3.4)         | 7(10.9)        | 0.129 |
| Skin and soft tissues infection | 4(4.5)       | 7(10.9)        | 0.236 |
| Others             | 1(1.1)         | 2(3.1)         | 0.780 |
| History, %         |                |                |       |
| Diabetes           | 30(34.1)       | 20(31.3)       | 0.713 |
| Hypertension       | 51(57.9)       | 33(51.6)       | 0.434 |
| Cerebral infarction| 30(34.1)       | 15(23.4)       | 0.155 |
| COPD               | 28(31.8)       | 12(18.8)       | 0.071 |
| CAD                | 16(18.2)       | 7(10.9)        | 0.192 |
| Previous cardiovascular surgery | 9(10.2)     | 6(9.4)         | 0.862 |
| Chronic renal insufficiency | 10(11.4)   | 5(7.8)         | 0.469 |
| Non-infection comorbidity, n (%) |             |                |       |
| NYHA III-IV        | 21(23.9)       | 11(17.2)       | 0.319 |
| Surgical treatment | 9(10.2)        | 6(9.4)         | 0.862 |
| Massive haemorrhage| 6(6.8)         | 2(3.1)         | 0.523 |
| Traumatic brain injury | 7(8.0)      | 2(3.1)         | 0.369 |
| PCT (ng/ml)        | 9.73±21.24     | 34.17±39.52    | <0.001|
| WBC(x10^9/mm³)     | 14.20±6.02     | 16.90±7.12     | 0.013 |
| Platelets (x10^9/mm³) | 146.23±90.05  | 114.78±80.42   | 0.028 |
| CRP (mg/L)         | 122.60±61.37   | 130.35±52.86   | 0.417 |
| Lactate (mmol/L)   | 2.34±2.67      | 3.48±5.44      | 0.023 |
| SOVO₂ (%)          | 70.53±10.73    | 53.15±12.05    | <0.001|

**Correlation of Pcv-aCO₂ with other parameters**

We found that Pcv-aCO₂ was positively correlated with WBC (r=0.241, p=0.003), PCT (r=0.471, p<0.001), CRP (r=0.192, p=0.018), lactate (r=0.179, p=0.027), SOFA (r=0.318, P<0.001), and APACHE II score (r=0.377, p<0.001), while that was negatively correlated with ScVO₂ (r=-0.242, p<0.001) and PLT (r=-0.205, p=0.011) (Table 2).

**Table 2. Spearman’s correlation analysis between Pcv-aCO₂ and other clinical variables among all patients included in the study (n=152)**

|        | r      | p    |
|--------|--------|------|
| WBC    | 0.241  | 0.003|
| Platele| -0.205 | 0.011|
| PCT    | 0.471  | <0.001|
| CRP    | 0.192  | 0.018|
| ScVO₂  | -0.242 | 0.003|
| Lactate| 0.179  | 0.027|
| SOFA   | 0.318  | P<0.001|
| APACHE II | 0.377 | <0.001|

WBC, white blood cell; PCT, procalcitonin; CRP, C-reaction protein; ScVO₂, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology And Chronic Health Evaluation II.

**Pcv-aCO₂ and 28-day mortality**

The survival curves were shown in Figure 1. Kaplan-Meier survival curves show that patients with Pcv-aCO₂ > 6 mmHg had a worse prognosis than those with Pcv-aCO₂ ≤ 6 mmHg (log-rank=32.10, p<0.001).

The risk of death was significantly correlated with the levels of Pcv-aCO₂ (hazard ratio (HR): 4.90, 95% confidence interval (CI): 2.66-9.05, p<0.001), PLT (HR: 3.90, 95% CI: 2.16-7.03, p<0.001), PCT (HR: 2.87, 95% CI: 1.62-5.07, p=0.001), lactate (HR: 2.53, 95% CI: 1.46-4.45, p=0.001), ScVO₂ (HR: 2.04, 95% CI: 1.17-3.53, p=0.011), SOFA (HR: 3.25, 95% CI: 1.81-5.84, p=0.001) and APACHE II score (HR: 2.61, 95% CI: 1.44-4.75, p=0.002). Multivariate Cox regression analysis was used to analyze the associations of the risk of death and adjustment of Pcv-aCO₂, PLT, PCT, lactate, ScVO₂, SOFA and APACHE II score. The levels of Pcv-aCO₂ (HR: 3.10, 95% CI: 1.43-6.74, p=0.004) and PLT (HR: 2.08, 95% CI: 1.08-3.98, p=0.028) were independent risk factors for 28-day mortality in patients with BSI (Table 3).

**Table 3. Univariate and multivariate Cox regression analyses of the 28-day mortality**

| Variables  | Univariate Cox regression | Multivariate Cox regression |
|------------|----------------------------|-----------------------------|
|            | HR  | 95% CI | p   | HR  | 95% CI | p   |
| Pcv-aCO₂   | 4.90 | 2.66-9.05 | <0.001 | 3.10 | 1.43-6.74 | 0.004 |
| WBC        | 3.18 | 0.77-13.07 | 0.108 | 3.16 | 0.77-13.07 | 0.108 |
| Platelet   | 3.90 | 2.16-7.03 | <0.001 | 2.08 | 1.08-3.98 | 0.028 |
| PCT        | 2.87 | 1.62-5.07 | <0.001 | 1.39 | 0.72-2.69 | 0.327 |
| CRP        | 1.40 | 0.81-2.43 | 0.229 | 1.40 | 0.81-2.43 | 0.229 |
| ScVO₂      | 2.04 | 1.17-3.53 | 0.011 | 0.72 | 0.38-1.36 | 0.311 |
| Lactate    | 2.53 | 1.46-4.45 | 0.001 | 1.97 | 0.85-2.88 | 0.147 |
| SOFA       | 3.25 | 1.81-5.86 | <0.001 | 1.86 | 0.91-3.82 | 0.09 |
| APACHE II  | 2.61 | 1.44-4.75 | 0.002 | 1.28 | 0.62-2.64 | 0.507 |

Pcv-aCO₂, central venous-to-arterial carbon dioxide difference; WBC, white blood cell; PCT, procalcitonin; CRP, C-reaction protein; ScVO₂, central venous oxygen saturation; SOFA, Sequential Organ Failure Assessment; APACHE II, Acute Physiology And Chronic Health Evaluation II.
The predictive accuracy for 28-day mortality

The ROC curve of Pcv-aCO₂ predicting 28-day mortality in patients with BSI, as shown in Figure 2, revealed that the area under the ROC curve was 0.794. Furthermore, Pcv-aCO₂ greater than 6 mmHg was the best threshold for predicting 28-day mortality, with a sensitivity of 81.1% and specificity of 78.8%.

Discussion

The present study demonstrated that increased Pcv-aCO₂ at the time of blood culture was independently associated with 28-day mortality in patients with BSI. In addition, Pcv-aCO₂>6 mmHg was a valuable predictor of the increased risk of 28-day mortality. In this study, the 28-day mortality was 34.9%, which were higher than previous studies [10]. It might be due to the advanced age of the patients in our study, because age is one of the risk factors for poor prognosis [11]. The other reasons should be considered was more serious patients enrolled in our study. Patients included in this study had higher SOFA and APACHE II score than previous studies [10].
It is well-known that BSI often cause circulatory disorder, which associated with poor outcomes [12]. In recent years, Pcv-aCO₂ is considered one of indicator for monitoring of tissue perfusion [13]. A previous study reported that a significant increase in Pcv-aCO₂ during cardiac arrest results from cardiovascular stagnation [14]. Similarly, another research showed that Pcv-aCO₂ is inversely proportional to cardiac output in animal models of hemorrhage, hypovolemia, and obstructive shock [15-17]. When cardiac output reduce, the blood flow is slow and the elution ability of CO₂ is impaired; therefore, more CO₂ is accumulated in the tissue, and the Pcv-aCO₂ increases as the CO₂ diffuses easily and quickly [18]. In the early fluid resuscitation of septic shock, a persistent increase in Pcv-aCO₂ suggests a poor prognosis, and monitoring Pcv-aCO₂ during early fluid resuscitation is a helpful indicator for assessing the adequacy of tissue perfusion [8, 19]. As an indicator of tissue perfusion, Lactate is the goal of early fluid resuscitation in septic shock [20]. There was a correlation between Pcv-aCO₂ and lactate in our study. In Pcv-aCO₂ > 6 mmHg group, the lactate level, circulatory disorders and vasopressor used were more, which suggest that Pcv-aCO₂ can be an good indicator of tissue perfusion and prognosis.

In severe infections, oxygen supply-demand imbalance often leads to increased mortality [21]. In fact, Pcv-aCO₂ monitoring not only can reflect cardiac output and tissue microcirculation perfusion, but also show a balance between tissue oxygen supply and demand, thereby objectively reflecting tissue oxygen metabolism [22]. A study showed that the changes of cardiac output were not consistent with those of Pcv-aCO₂ during septic shock, suggesting that hemodynamic changes cannot be used to explain an increase in Pcv-aCO₂ in this case, which may be associated with poor tissue oxygen supply and increased oxygen consumption [23]. Kocsi et al [24] found that Pcv-aCO₂ is an important indicator to monitor an imbalance between tissue oxygen supply and demand caused by low blood volume. The oxygen supply and demand of tissue can be timely detected by monitoring dynamic changes of Pcv-aCO₂ in case of insufficient blood volume. The ratio of Pcv-aCO₂ to arteriovenous oxygen content is a better marker of global anaerobic metabolism than lactate in septic shock patients [25]. Furthermore, we found that Pcv-aCO₂ was negatively correlated with S_{CV}O₂ which is an indicator of the balance of oxygen metabolism, suggesting that Pcv-aCO₂ is an appropriate indicator for tissue perfusion and oxygen metabolism.

The mortality of bloodstream infections caused by different pathogen is different [26]. Furthermore, different pathogen infections may cause different circulation disorders [27], which indicated by Pcv-aCO₂. Since Pcv-aCO₂ can reflect tissue perfusion, it may be used for the identification of BSI pathogens. As we know, PCT plays an important role in the diagnosis of BSI [28]. It helps identify pathogens and guides the choice of antibiotics [29]. In this study, Pcv-aCO₂ and PCT were found to be significantly correlated, suggesting that Pcv-aCO₂ may contribute to the identification of pathogens. Moreover, we found the pathogen distribution was different in different groups presented based on the level of Pcv-aCO₂ and there was more GN bacteria infection in the higher level of Pcv-aCO₂ group. This shows that Pcv-aCO₂ can provide a clue to identify pathogens and predict outcomes.

Additionally, we found that Pcv-aCO₂ has a significant correlation with S_{CV}O₂, lactate, PCT, CRP, SOFA and APACHE II score in patients with BSI. PCT and CRP plays an important role in the early diagnosis and prognosis of BSI patients [30, 31]. S_{CV}O₂ and lactate guides early fluid resuscitation can effectively predict the prognosis of patients with sepsis [32, 33]. Pcv-aCO₂, S_{CV}O₂ and lactate are taken as important indicators for treatment and prognosis of sepsis [34]. In our study, the patients with different levels of Pcv-aCO₂ showed significant differences in S_{CV}O₂, lactate, PCT, PLT, SOFA, APACHE II score, and prognosis. The use of mechanical ventilation, vasopressor, and CRRT were significantly more in Pcv-aCO₂ >6mmHg group than those in Pcv-aCO₂ ≤6mmHg group. Therefore, Pcv-aCO₂ can properly reflect the illness severity of the patient. We also further analyzed the association between Pcv-aCO₂ and the risk of death by using Cox regression analysis, which indicated that Pcv-aCO₂ was an independent risk factors for 28-day mortality. After that, ROC curves were plotted to evaluate the predictive power of Pcv-aCO₂ for the occurrence of 28-day mortality. We found that the Pcv-aCO₂ is an important predictive factor for 28-day mortality in patients with BSI.

**Limitation**

This was a retrospective analysis based on prospectively collected data. There are several limitations in this study. One limitation is that there was no dynamic monitoring of Pcv-aCO₂ that may ignore the impact of different treatments on clinical outcomes. In addition, the use of basic drugs, especially sodium bicarbonate, in patients during the study was not fully clarified, which may affect the accuracy of the results of Pcv-aCO₂ monitoring. Moreover, this is a single-center study, that included limited research samples, therefore further
multi-center large-scale studies need to be conducted.

**Conclusion**

Our results demonstrated that increased Pcv-aCO₂ while blood culture was an independent predictor of 28-day mortality in patients with BSI even after adjusting a previous risk model. Furthermore, patients with Pcv-aCO₂ greater than 6mmHg were more likely to have poor outcomes. The use of Pcv-aCO₂ as a prognostic marker provides valuable information for risk stratification.

**Acknowledgments**

The work was supported by Medical Science and Technology Foundation of Guangdong Province (Grant No. A2017602), the National Natural Science Foundation of China (Grant No. 81701875), and the National Clinical Key Specialty Subject Construction Project (Grant Nos. 2012-649, 2013-544).

**Author Contribution**

Zhonghua Wang and Xuebiao Wei contributed equally to this article. Zhonghua Wang and Xuebiao Wei conceived and designed the study, and drafted the article. Xiaolong Liao, Weixin Guo, Peihang Hu, Yan Wu, Jie Li, Youwan Liao collected the clinical data. Shenglong Chen analyzed statistically the data. Tiehe Qin and Shou-hong Wang conceived and designed the study, reviewed the article, and all authors approved the final version of the article. All authors meet the ICMJE authorship criteria.

**Competing Interests**

The authors have declared that no competing interest exists.

**References**

1. Laupland KB: Incidence of bloodstream infection: a review of population-based studies. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2013, 19(6):492-500.
2. McNamara JF, Righi E, Wright H, Hartel GF, Harris PNA, Paterson DL: Long-term morbidity and mortality following bloodstream infection: A systematic literature review. The Journal of infection 2018, 77(1):1-8.
3. Nuckols TK, Keeler E, Morton SC, Anderson L, Doyle B, Booth M, Shanman R, Goon J, Shekelle P: Economic Evaluation of Quality Improvement Interventions for Bloodstream Infections Related to Central Catheters: A Systematic Review. JAMA Intern Med 2016, 176(12):1843-1854.
4. Artero A, Zaragoza R, Camarena JI, Sancho S, Gonzalez R, Nogueira JM: Prognostic factors of mortality in patients with community-acquired bloodstream infection with severe sepsis and septic shock. Journal of critical care 2010, 25(2):276-281.
5. Chertoff J, Chisum M, Garcia B, Lascano J: Lactate kinetics in sepsis and septic shock: a review of the literature and rationale for further research. Journal of intensive care 2015, 3:39.
6. Vincent JL, De Backer D: From Early Goal-Directed Therapy to Late(r) ScvO2 Checks. Chest 2018, 154(6):1267-1269.
7. Van Beest PA, Loest MC, Holman ND, Loet B, Kuiper MA, Boerma EC: Central venous-to-arterial PCO₂ difference as a tool in resuscitation of septic patients. Intensive care medicine 2013, 39(6):1034-1039.
8. Osipina-Tascon GA, Bautista-Rincon DF, Umana M, Tafur JD, Gutierrez A, Garcia AF, Fernandez V, Granados M, Arango-Davila C, Hernandez G: Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Critical care 2013, 17(6):R294.
9. Muller G, Mercier E, Vignon P, Henry-Lagarrigue M, Kemel T, Desachy A, Botoc V, Plantefève G, Frat JP, Bellec F et al: Prognostic significance of central venous-to-arterial carbon dioxide difference during the first 24 hours of septic shock in patients with and without impaired cardiac function. British journal of anaesthesia 2017, 119(2):239-248.
10. Hattori H, Maeda M, Nagatomo Y, Takuma T, Niki Y, Naito Y, Sasaki T, Ishino K: Epidemiology and risk factors for mortality in bloodstream infections: A single-center retrospective study in Japan. American journal of infection control 2018, 46(12):e75-79.
11. Kaye KS, Marchaim D, Chen TY, Baures T, Anderson DJ, Choi Y, Sloane R, Schmdier KE: Effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults. Journal of the American Geriatrics Society 2014, 62(2):306-311.
12. Laupland KB, Zygun DA, Doig CJ, Bagshaw SM, Svensson LW, Fick GH: One-year mortality of bloodstream infection-associated sepsis and septic shock among patients presenting to a regional critical care system. Intensive care medicine 2005, 31(2):213-219.
13. Osipina-Tascon GA, Umana M, Bermudez WF, Bautista-Rincon DF, Valencia JD, Madrinar HJ, Hernandez G, Bruhn A, Arango-Davila C, De Backer D: Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? Intensive care medicine 2016, 42(2):211-221.
14. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Grifell M: Difference in acid-base state between sepsis and arterial blood during cardiopulmonary resuscitation. The New England journal of medicine 1986, 315(3):153-156.
15. Zhang H, Vincent JL: Arteriosavenous differences in PCO₂ and pH are good indicators of critical hyperperfusion. The American review of respiratory disease 1993, 148(4 Pt 1):867-871.
16. Van der Linden P, Rausin J, Deleff B, Bekrar Y, Gillaert E, Bakker JJ, Vincent JL: Detection of tissue hypoxia by arteriovenous gradient for PCO₂ and pH in anesthetized dogs during progressive hemorrhage. Anesthesia and analgesia 1995, 80(2):269-275.
17. Groeneveld AB, Vermeij CG, Thijis LG: Arterial and mixed venous blood acid-base balance during hyperperfusion with incremental positive end-expiratory pressure in the pig. Anesthesia and analgesia 1991, 73(5):576-582.
18. Vallet T, Bteoul JL, Cain S, Curtis S: Venous-to-arterial CO₂ difference during regional ischemic or hypoxic hypoxia. J Appl Physiol (1985) 2000, 89(4):1317-1321.
19. Mallat J, Pepy F, Lemyze M, Gasan G, Vangrunderbeek N, Tronchon L, Vallet B, Thiévenin D: Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. European journal of anaesthesiology 2014, 31(7):371-380.
20. Ryoo SM, Lee J, Lee YS, Lee JH, Lim KS, Huh JW, Hong SB, Lim CM, Koh Y, Kim WY, Lactate Level Versus Lactate Clearance for Predicting Mortality in Patients With Septic Shock. Defined by Sepsis-3. Critical care medicine 2018, 46(6):e899-e945.
21. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI, Emergency Medicine Shock Research Network: Multicenter study of central venous oxygen saturation (ScvO2) as a predictor of mortality in patients with sepsis. Ann Emerg Med 2010, 55(4):40-46 e41.
22. Teboul JL, Mercat A, Lenique F, Berton C, Richard C: Value of the venous-to-arterial PCO₂ gradient to resuscitate patients with failing oxygen transport in human septic shock. Chest 1992, 101(2):509-515.
23. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Vangrunderbeek N, Tronchon L, Thiévenin D: Value of the venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. European journal of anaesthesiology 2015, 32(1):371-380.
24. vaccination and antibody levels in healthy volunteers are better markers of global anaerobic metabolism than lactate in septic shock patients. Annals of intensive care 2016, 6(1):10.
25. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrallier S, Durville E, Temime J, Vangrunderbeek N, Tronchon L et al: Ratios of central venous-to-arterial carbon dioxide content or tension to arterial oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Annals of intensive care 2016, 6(1):10.
26. Moll A, Hartugh S, Lydersen S, Paulsen J, Avsol JD, Solligard E, Damas JK, Edna TH: Prior statin use and 90-day mortality in Gram-negative and Gram-positive bloodstream infection: a prospective observational study. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 2015, 34(7):609-617.
27. Munford RS: Severe sepsis and septic shock: the role of gram-negative bacteremia. Annual review of pathology 2006, 1:467-489.
28. Arora R, Campbell JP, Simon G, Sahni N: Does serum procalcitonin aid in the diagnosis of bloodstream infection regardless of whether patients exhibit the systemic inflammatory response syndrome? Infection 2017, 45(3):291-298.
29. Thomas-Ruddell DO, Poidinger B, Kott M, Weiss M, Reinhart K, Bloos F, group Js: Influence of p-thawon and focus of infection on procalcitonin values in sepsis patients with bacteremia or candidemia. Critical care 2018, 22(1):128.
30. Hattori T, Nishiyama H, Kato H, Ikekami S, Nagayama M, Asani S, Usami M, Suzuki M, Murokami I, Minoshima M et al: Clinical value of procalcitonin for patients with suspected bloodstream infection. American journal of clinical pathology 2014, 141(1):43-51.
31. Povoa P, Coelho L, Almeida E, Fernandes A, Mehal L, Moreira S, Sabino H: Pilot study evaluating C-reactive protein levels in the assessment of response
to treatment of severe bloodstream infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005, 40(12):1855-1857.

32. Lee YK, Hwang SY, Shin TG, Jo IJ, Suh GY, Jeon K: Prognostic Value of Lactate and Central Venous Oxygen Saturation after Early Resuscitation in Sepsis Patients. PloS one 2016, 11(4):e0153305.

33. Mahmoodpoor A, Shadvar K, Sanaie S, Golzari SEJ, Parthvi R, Hamishehkar H, Nader ND: Arterial vs venous lactate: Correlation and predictive value of mortality of patients with sepsis during early resuscitation phase. Journal of critical care 2020, 58:118-124.

34. Wittayachamnankul B, Chentanakij B, Sruamsiri K, Chattipakorn N: The role of central venous oxygen saturation, blood lactate, and central venous-to-arterial carbon dioxide partial pressure difference as a goal and prognosis of sepsis treatment. Journal of critical care 2016, 36:223-229.