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Carbon Dioxide gap: a review of prognostic value and therapeutic effectiveness

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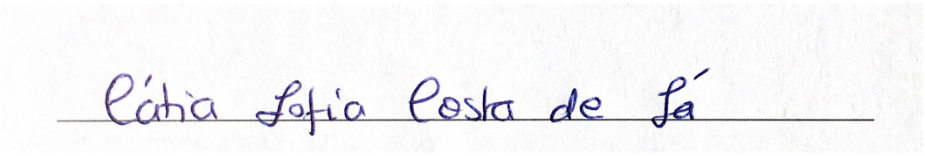

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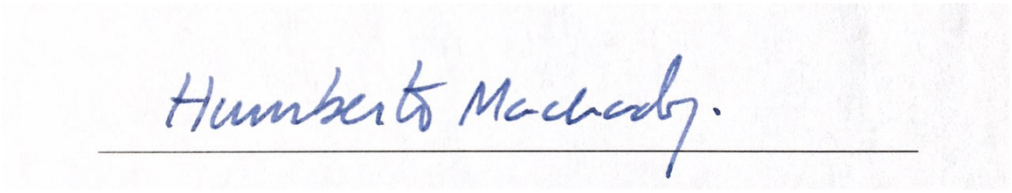

(Orientador Professor Doutor Humberto José da Silva Machado)

Dedicatória

À minha mãe, por todos os valores e ensinamentos transmitidos, esforço, empenho, dedicação, carinho e amizade. Por ter estado ao meu lado todos os dias, ter acreditado sempre em mim e nas minhas capacidades, tendo sido a maior impulsionadora deste trabalho. Por me motivar sempre a ser e a fazer melhor. E, acima de tudo, por me ter ensinado que todo o esforço traz sempre recompensa.

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Resumo

Introdução: Atualmente, the central venous-to-arterial carbon dioxide difference, ou PCO_2 gap, tem sido visto como um biomarcador de relevo para usar em doentes críticos, ajudando na monitorização e terapêutica destes. Vários marcadores têm sido utilizados com a mesma finalidade, mas as suas limitações levam à necessidade de estudar novos recursos para uma melhor gestão do doente. Deste modo, a sua relevância tem vindo a crescer nos últimos anos e vários estudos têm sido feitos no sentido de descobrir mais sobre a sua utilidade para a medicina.

Objetivos: A presente revisão bibliográfica visa avaliar a evolução do PCO_2 gap como um biomarcador e a sua sensibilidade e eficácia na monitorização da terapêutica e de prognóstico.

Métodos: Foi realizada uma pesquisa no Pubmed e Google Schoolar, tendo sido selecionados 47 artigos para esta revisão.

Resultados: O PCO_2 gap mostrou refletir a eficácia da circulação microvascular. Elevados valores de PCO_2 gap estão associados a menores percentagens de pequenos vasos perfundidos, menor densidade capilar funcional, alta heterogeneidade do fluxo sanguíneo microvascular, menor concentração e clearance de lactato. Além disso, um índice cardíaco mais baixo, maior administração de fluidos e vasopressores e falência múltipla de órgãos foram observados em doentes com valores de marcador aumentados. Em relação à mortalidade, valores elevados de PCO_2 gap revelaram alta mortalidade em 28 dias e foi associado com outros marcadores preditivos de mortalidade como a pressão arterial média. Além disso, o PCO_2 gap revelou-se útil noutros tópicos como extubação, demonstrando um aumento do valor aquando falha desta. Em doentes cardíacos, o PCO_2 gap teve um bom desempenho como preditor de MPC, tendo melhor performance do que outros marcadores usados no dia a dia. Em doentes com infeção da corrente sanguínea, o valor de PCO_2 gap ajuda na identificação dos agentes patogénicos e no prognóstico.

Conclusão: O PCO_2 gap tem efetivamente um papel como ferramenta adjuvante na eficácia terapêutica e prognóstica. A maioria dos estudos recomenda seu uso na gestão dos doentes, mostrando resultados muito positivos em diferentes patologias quer isoladamente quer em conjunto com outros marcadores. No entanto, por ser um tema recente, com poucos estudos realizados, ainda é necessária mais investigação nesta área.

Palavras-chave: PCO_2 gap; carbon dioxide gap; shock; CO_2; venous-to-arterial carbon dioxide difference.

Abstract

Introduction: Nowadays, the central venous-to-arterial carbon dioxide difference, or PCO_2 gap, has been reported as a relevant biomarker to use in critical ill patients, helping in their monitorization and therapeutic. Several markers have been used for the same purpose, but their limitations lead to the need to study news resources to guide the patient management. Thus, its relevance has been growing in the last years and several studies have been made in order to find more about its value for medicine.

Objectives: This literature revision aims to assess the evolution of the PCO_2 gap as a biomarker and its sensibility and effectiveness as a monitor of the therapeutic and a provider of prognostic.

Methods: A research was conducted on Pubmed and Google Scholar and 47 articles were selected for this revision.

Results: PCO_2 gap showed to reflect the adequacy of microvascular circulation. High PCO_2 gap is associated with lower percentages of small perfused vessels, lower functional capillary density, high heterogeneity of microvascular blood flow, lower lactate concentration and clearance. Also, a lower cardiac index, increased administration of fluids and vasopressors and multiple organ failure were seen in patients with elevated values of this marker. Regarding mortality, high PCO_2 gap values revealed high 28 day-mortality and was correlated with other predictive markers as MAP. Furthermore, PCO_2 gap revealed useful in other topics as extubation, increasing its value in extubation failure. In cardiac patients PCO_2 gap performed well as MPC predictor, being better than other markers used routinely. In patients with bloodstream infection PCO_2 gap helps with the identification of pathogens and predict outcomes.

Conclusion: PCO_2 gap has effectively a role as an adjuvant tool in therapeutic and prognostic effectiveness. The majority of studies recommends its use in the management of the patients, showing very positive outcomes in different pathologies not only alone but with other markers. However, for being a recent topic, with few studies carried out, more investigation is still needed.

Keywords: PCO_2 gap; carbon dioxide gap; shock; CO_2; venous-to-arterial carbon dioxide difference.

Abbreviations

APACHE II – Acute Physiology And Chronic Health Evaluation II
C_aCO_2 – Arterial blood dioxide carbon content
CCO_2 – Dioxide carbon content
CO_2 – Dioxide carbon
C_vCO_2 – Mixed venous dioxide carbon content
ICU – Intensive care unit
MAP – Mean arterial pressure
MPC – Major postoperative complications
O_2 – Oxygen
PAC – Pulmonary artery catheter
PCO_2 gap – Carbon dioxide gap
$PaCO_2$ – Partial pressure of carbon dioxide in arterial blood
$PvCO_2$ – Partial pressure of carbon dioxide in central venous blood
$ScvO_2$ – Central venous oxygen saturation
SvO_2 – Mixed venous oxygen saturation
SOFA – Sequential Organ Failure Assessment
VCO_2 – Dioxide carbon production
VO_2 – Oxygen consumption

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Introduction

In recent years, the central venous-to-arterial carbon dioxide difference, or only carbon dioxide gap (PCO_2 gap) has gained relevance as a measure of assessment of several parameters.[1] The balance of dioxide carbon (CO_2) production by the tissues and its elimination through the lungs can be reflected by the difference between the mixed venous content (C_vCO_2) and the arterial content (C_aCO_2). This venous-arterial difference in CO_2 content (CCO_2) can be estimated by the following equation: $\Delta PCO_2 = P_vCO_2 - P_aCO_2$, denominated PCO_2 gap and in physiological conditions it ranges from 2 to 5 mmHg.[1-3] In a few words, it indicates the difference between partial pressure of carbon dioxide in central venous blood ($PvCO_2$) and arterial blood (P_aCO_2).[4]

In critically ill patients, it is extremely important the assessment and monitoring of the tissue perfusion to avoid organ disfunction or death. To avoid this situation, it is made a preventive strategy as hemodynamic optimization based on blood pressure, cardiac output and perfusion parameters, such as the lactate and the central venous oxygen saturation ($ScvO_2$). However, these markers have limitations as the hemodynamic parameters and $ScvO_2$ does not ensure adequate tissue perfusion and the mortality and organ failure are still high. Moreover, the blood lactate concentration is not also a good marker of tissue hypoperfusion, since an elevated value may be associated with adrenergic stimulation and surgical stress. Due to this situation, with the aim to achieve better prognostic and therapeutic the question of additional markers of tissue hypoperfusion as the PCO_2 gap has been gaining relevance.[5-7]

The recognition and use of PCO_2 gap as a marker of the correlation between cardiac output and the global metabolic demand have been growing. Considering that the final product of the aerobic metabolism is CO_2, the venous CO_2 content, and consequently the PCO_2 gap, will reflect the global tissue blood flow relative to metabolic demand. This happens because it indicates whether blood flow is enough to transport CO_2 from the peripheral tissue to the lungs to clear it. Thus, the PCO_2 gap is being considered as a marker of the adequacy of the venous blood flow to remove the CO_2 produced by the peripheral tissues.[1-3,8]

This biomarker has become more popular in recent years as a resuscitation end point mainly because CO_2 is more soluble than oxygen (O_2) in the blood. This means than probably it is more capable to detect microcirculation dysfunction, even in a heterogeneous or poor microcirculatory flow.[9]

There are several factors that, in stable conditions, determine the PCO_2, for instance the difference in venous-arterial CO_2 content, the CO_2 dissociation curve, alveolar ventilation and cardiac output. The latter is considered as the highest influence on the CO_2 gap. [1-3] The partial pressure of CO_2 provides information about the ventilation status and is affected by hypoventilation, hyperventilation and acid-base status. In this manner, it is a more sensitive marker of hypoperfusion compared to O_2. Some authors have supported that the PCO_2 gap could be a complementary tool to identify patients with persistent global hypoperfusion and the cutoff value of 6 mmHg can be a guide to reflect if global flow is adequate or insufficient. [4,10,11]

The PCO_2 gap can be easily and expediently measured with a simultaneous sampling of arterial blood and a sample of mixed venous blood from the distal of a pulmonary artery catheter (PAC), but its usage is decreasing over the years and it carry many risks for patients. However, it is also possible to measure with a central venous catheter, being the best option for some patients.[12,13]

The purpose of the present review is to understand the evolution of the PCO_2 concept and its ability to provide a prognosis or to monitor the therapeutic effectiveness of O2 deficit in the periphery.

Materials and methods

An online search was carried out in Pubmed and Google Scholar using the following keywords combinations: "PCO_2 gap", "carbon dioxide gap", "shock", "CO_2" and "venous-to-arterial carbon dioxide difference".

For the inclusion criteria of this study were considered literature reviews, randomized studies, case reviews, clinical trials, books, documents and guidelines in the period between 2011 and 2021.

In addition, bibliographic sources cited in the selected articles were also seen and the some of them added to the study considering their relevance for the present review.

Furthermore, it was only selected articles written in English, Portuguese and Spanish.

From a total of 2791 studies found using the mentioned keywords, 24 were selected to this revision. The first articles were selected after reading the title and abstract. Subsequently, after this first selection, the remaining articles chosen were read in full and selected to integrate the study according to inclusion criteria and their relevance to the topic.

Figure 1 shows inclusion/exclusion methodology of manuscripts.

Results

Janotka et al made a review, where the authors summarize the application of some of these biochemical markers: mixed venous oxygen saturation (SvO_2), lactate, central venous-arterial carbon dioxide difference (PCO_2 gap) and PCO_2 gap/arterial-to-venous oxygen difference ($Ca\text{-}vO_2$) for hemodynamic assessment of tissue perfusion. However, the interpretation of measured values requires an understanding of complex physiological principles in the context of other hemodynamic findings. It was demonstrated that venous content of CO_2 and PCO_2 gap depends only on microvascular venous return and PCO_2 gap replicates venous return from the capillary bed and the capability of the microcirculation. When there is normal cardiac output and homogenous healthy capillary bed, all CO_2 production is quickly washed out and venous-arterial PCO_2 gap is minimal. [5,14]

A global tissue hypoxia secondary to an imbalance between systemic oxygen delivery and demand is the definition of shock. The presence of a global tissue hypoxia due to systemic inflammatory response or circulatory failure is a significant indicator of serious illness leading to multiple organ failure. It is the development of organ failure that indicates the outcome of the septic patient. In a post hoc study with 53 patients with severe sepsis, Van Beest et al demonstrated that patients with persistently high PCO_2 gap were associated with an increased in-hospital mortality at 24 hours after the start of treatment despite the normalization of lactate levels. In addition, it was also demonstrated a weak relationship between PCO_2 gap and cardiac index. [15]

In 2013, a prospective and observational study was conducted with 85 patients with a new septic shock episode. They were classified in four groups based on a predefined PCO_2 gap (higher or lower than 6mmHg) before the start of resuscitation and after 6 hours. It was seen that patients who were in the persistently high CO_2 gap group (> 6 mmHg before start of resuscitation and after 6 h) had an appreciably higher 28-day mortality and a considerably multiple organ failure score at day 3 when compared with the patients with normal PCO_2 gap.[16]

In a prospective observational study in 2014, Mallat et al investigated the behavior of PCO_2 gap and its relationship to cardiac index, blood lactate concentration and 28-day mortality during resuscitation in the early phase of septic shock. The results demonstrated a strong relationship between PCO_2 gap and cardiac index at the very early phase of resuscitation in septic shock: PCO_2 gap correlated negatively with cardiac index. The monitorization of the PCO_2 gap from the beginning of the resuscitation can be a valuable tool to assess the adequacy of

cardiac output in tissue perfusion. Normal values for both PCO_2 gap and $ScvO_2$ during the early resuscitation period of septic shock seemed to be better than only targeting a normal $ScvO_2$. The two variables together resulted in a greater decrease in lactate concentration. This one is independently associated with reduced 28-day mortality.[17]

Hernandez et al designed a prospective, observational clinical study with septic shock patients with hyperlactatemia. The patients were followed until hospital discharge. From the 84 patients, all of them had high lactate levels, 32 patients presented an elevated PCO_2 gap and 30 presented a capillary refill time abnormal as baseline value. Lactate, PCO_2 gap and capillary refill time showed a faster diminution from 0 to 6 h followed by a slower decay after that.[18]

Kriswidyatomo et al in their study saw the difference of lactate concentration in seven studies with 362 participants between the low and high gap groups. The analysis demonstrated a significantly lower lactate in the low gap group related to the high gap group.[4]

Vallé et al tested if in resuscitated septic shock patients PCO_2 gap can be a valuable tool as index of tissue perfusion when the patients already have a $ScvO_2$ goal value (>70%) reached. 50 patients with $ScvO_2$ >70% were divided in low PCO_2 gap group (< 6mmHg) with 26 patients and high PCO_2 gap group (> 6mmHg) with 24 patients at time 0h. Measurements were registered every 6 hours over 12 hours (T0, T6, T12). The low gap group patients had a significantly lower PCO_2 gap comparing with patients of the high gap group (3.2 ± 1.3 versus 8.9 ± 2.6 mmHg, $P < 0.0001$) at T0. PCO_2 gap was inversely correlated with cardiac index at T0, T6 and T12. The lactate clearance was larger for the low gap group than for the high gap group.[19]

Septic shock remains associated with high mortality and has been associated with microvascular alterations and these lead to the development of organ dysfunction. In 2016, Ospina-Tascón et al demonstrated that during the early phases of septic shock, PCO_2 gap can reflect the adequacy of microvascular circulation with results of lower percentages of small perfused vessels, lower functional capillary density and high heterogeneity of microvascular blood flow being observed at higher PCO_2 gap.[20]

Kriswidyatomo et al developed a literature review to assess the prognostic value of central venous-arterial carbon dioxide difference in septic shock. According to the authors, PCO_2 gap could potentially be used as a marker associated with mortality from septic shock. In addition, PCO_2 gap is significantly

associated with other predictive markers of mortality, such as Mean Arterial Pressure (MAP) and lactate clearance. No association was found between PCO_2 gap and intensive care unit (ICU) length of stay in this study. [4]

Ltaief et al performed a literature review on the physiological and pathophysiological determinants of the venous-arterial difference in carbon dioxide partial pressure (PCO_2 gap) and its implications for clinical assessment in circulatory shock. The authors considered that the PCO_2 gap is a reliable indicator of inadequate tissue perfusion, either as a result of an overall reduction in cardiac output or microcirculatory abnormalities. However, this parameter does not track dysoxia (also called hyperlactacidemia or cytopathic hypoxia) unless it is related to stagnation of the mechanism. The assessment of the PCO_2 gap is easy, available, and should be included in the assessment of circulatory shock.[21]

The PCO_2 gap may be a marker of cardiac output adequacy and the relation between PCO_2 gap and cardiac output has been demonstrated by several experimental and clinical setting. It has been demonstrated an inverse relationship between both. In severe sepsis, the PCO_2 gap may be a marker of the adequacy of cardiac output status. [17,22-24]

PCO2 gap has been suggested as a marker of interest in shock resuscitation, due to its ability to predict adverse clinical outcomes and simplicity of performance. According to Bitar et al PCO_2 gap has an important prognostic value in severe sepsis and a high PCO_2 gap can identify situations in which increased cardiac output is affected by fluid resuscitation. In a prospective observational study, these authors investigated the relationship between PCO_2 gap, cardiac index, serum lactate and the prognostic value on admission in relation to fluid administration in the initial phases of resuscitation in sepsis. High PCO_2 gap was associated with lower cardiac index, increased administration of fluids and vasopressors on admission. Lower mean arterial pressure was also observed in patients with high PCO_2 gap as higher lactate levels, indicating hypoperfusion. The in-hospital mortality was higher in patients with high PCO_2 gap. This biomarker may be a marker of the adequacy of cardiac output in severe sepsis and is an important hemodynamic variable in the treatment of circulatory failure. In a shock situation, a high PCO_2 gap value may suggest that an increase in cardiac output can be attempted with volume replacement. Thus, an elevated PCO_2 gap value is capable of identify situations in which increasing cardiac output can be attempted with fluid resuscitation in severe sepsis.[24]

Dobutamine is one of the first choices for septic shock patients with low cardiac index or ongoing signs of tissue hypoperfusion in the presence of adequate fluid resuscitation. Dobutamine's purpose is the restoration of an appropriate cardiac index to provide adequate oxygen supply in these patients. So, in 2013, Mallat et al made a study to assess the time course of the PCO_2 gap as an index of the carbon dioxide production / cardiac index ratio in stable septic shock patients receiving incremental doses of dobutamine. PCO_2 gap decreased expressively between 0 and 10 μg/kg/min of dobutamine, but remained unchanged from 10 to 15 μg/kg/min. Time course of PCO_2 gap was linked therefore to the biphasic changes of oxygen consumption (VO_2) and CO_2 production (VCO_2), seeing this biomarker as a good of the change of VCO_2 induced by dobutamine.[25]

In a multicentric, prospective and observational study, Mallat et al evaluated the ability of central venous-to-arterial carbon dioxide difference (PCO_2 gap), central venous oxygen saturation, and the combination of these two parameters to identify extubation failure in critically ill patients. They were measured in two times: immediately before spontaneous breathing trials and at 1 hour after spontaneous breathing trials initiation. The patients were divided in two groups: the successful group with extubation after successful spontaneous breathing trials and the failure group where the extubation failure was defined as the need for mechanical ventilation within 48 hours. Seventy-five patients were registered, and extubation failure was noticed in 18 (24%) patients. PCO_2 gap value increased in the extubation failure group and decreased in the success group.[26]

Al Duhailib et al performed a systematic review and meta-analysis with 21 studies to assess the association between a high CO2 gap and mortality in critically ill patients from medical, surgical and cardiovascular ICUs with circulatory shock. Al Dubailib et al showed that a high PCO_2 gap can be a strong predictor of mortality in cardiogenic shock. High PCO_2 gap was related to increased 28-day or in-hospital mortality in surgical and medical population. In cardiovascular population that correlation was not found. High lactate levels and lower cardiac index were also associated with higher PCO_2 gap values in this study. Beyond this, an increased PCO_2 gap was not associated with ICU length of stay, hospital length of stay, requirement for a replacement therapy and longer mechanical ventilation duration in the ICU. There were also no differences in vasopressor or inotropic support requirements between the high and low CO_2 gap groups.[6]

In a cardiac surgery with cardiopulmonary bypass, rapid identification and treatment of tissue hypoxia may reduce organ failure. In 2019, the ability of PCO_2

gap, blood lactate concentration and central venous oxygen saturation measured 2 hours after admission to the ICU was evaluated as a predictor of major postoperative complications (MPC). MPC are a composite of major cardiac and noncardiac complications occurring in the 48 hours after the intervention day such as acute respiratory failure, hemodynamic failure, cardiogenic and hemorrhagic shock, acute kidney injury, neurological failure, mesenteric infarction, revision surgery and death. 56.5% of 308 patients analyzed had MPC after cardiac surgery with cardiopulmonary bypass and the PCO_2 gap was the only dysoxia biomarker associated with higher occurrence of MPC with limited performance. Additionally, PCO_2 gap also performed better as MPC predictor than lactate and $ScvO_2$ which are used routinely in the clinical setting.[27]

However, in another study, Guinot et al search an association between increased PCO_2 gap following cardiac surgery with cardiopulmonary bypass and postoperative morbidity and mortality. In a population of 393 patients, 238 (61%) developed one or more complications. It was observed a higher arterial blood lactate levels and the $ScvO_2$ was lower in this group of patients with complications. PCO_2 gap was weakly associated with these tissue perfusion markers. Furthermore, PCO_2 gap did not demonstrate a noteworthy difference between the patients with and without complications.[28] In another study, a high PCO_2 gap did not predict post-operative complications after cardiac surgery. Due to the sudden variation of the parameters that interferes with tissue perfusion, PCO_2 gap is difficult to interpret in a cardiac surgery.[29]

A bloodstream infection is common systemic infection in ICU. They are a bridge to circulation disorders, associated with poor outcomes. In 2020, Wang et al, considering PCO_2 gap as a biomarker for circulation disorders, made a study to investigate the association of this biomarker with adverse events in bloodstream infection patients. The PCO_2 gap was positively correlated with white blood cell count, procalcitonin, C-reactive protein, lactate, Sequential Organ Failure Assessment and Acute Physiology And Chronic Health Evaluation II score. It was negatively correlated with central venous oxygen saturation and platelet. Patients with PCO_2 gap > 6mmHg had a worse prognosis than those without. PCO_2 gap was also an independent predictor of 28-day mortality in this group of patients. In addition, patients with PCO_2 gap >6mmHg were more likely to have poor outcomes. The use of this biomarker as a prognostic marker provides valuable information for risk stratification.[30]

Discussion

The target of the current review is to understand the evolution of the PCO_2 concept and its ability to provide a prognosis or to monitor the therapeutic effectiveness of O2 deficit in the periphery.

PCO_2 gap is defined as the difference between partial pressure of carbon dioxide in arterial and venous blood. It is proportional to CO_2 production in tissues and inversely related to cardiac output. It reflects the venous blood flow and the efficiency of the microcirculation. The venous PCO_2 gap depends on circulatory flow and arterial PCO_2 gap depends on pulmonary gas exchange. Hence, a decreased flow will increase the difference between these two variables. In the presence of normal condition, with normal cardiac output and homogeneous healthy capillary bed, the PCO_2 gap is minimal because all CO_2 produced was quickly washed out. The cut-off PCO_2 gap value that implies an inadequate cardiac output is > 6 mmHg and in that case, increase the cardiac output can be the therapeutic option to normalize PCO_2 gap.[5,15,24]

The hallmarks of shock are ischemia and tissue hypoxia due to microcirculatory and microcirculatory failure. The biochemical markers for microcirculatory most used are lactate and central venous oxygen saturation. However, the monitoring of microcirculation is still elusive because the mortality from shock is still high, despite the interventions aiming to normalize these variables. In consequence PCO_2 gap is gaining relevance as a new marker of microcirculatory.[6]

The distributive changes on microcirculatory level in patients with severe sepsis may be independent of cardiac output because on a regional level can happen in sepsis despite adequate cardiac output. In a population with sepsis (N = 53), van Beest observed a weak inverse logarithmic relation between PCO_2 gap and global blood flow (cardiac index). In another study (N = 83) was found a strong inverse correlation between PCO_2 gap and cardiac index. In this study the patients studied were a group with various diagnosis.[23] Various studies had also described an inverse relationship between PCO_2 gap and cardiac index in patients with sepsis.[13,17,19,20,24,31] These studies are in agreement with physiological theories as the modified Flick equation that affirms PCO_2 gap should be inversely correlated with cardiac output and the relationship between these two variables depends on the level of CO_2 production (VCO_2). The CO_2 stagnation leads to an increase of PCO_2 gap following cardiac output reduction because of the transit time is slower than

normal. Thus, there is an inadequate washout of CO_2 provoking a low flow state with failure in oxygen delivery to tissues and CO_2 increased in venous blood.[13,15,23]

In distributive shock the correlation between PCO_2 and cardiac output is weak due to the decreased functional capillary density, presenting different areas with good and bad perfusion. This situation can provoke an elevation of venous CO_2 content and, consequently, PCO_2 gap despite normal or high cardiac output.[5]

In patients with septic shock, a continuous elevated PCO_2 gap has been shown to be associated with worse prognosis.[5,6] In Ospina-Táscon et al study, septic shock patients with persistent high PCO_2 gap developed more multiorgan disfunction at day 3 than patients with a normal value of PCO_2 gap during the first 6 hours of resuscitation or even those who changed from high to normal PCO_2 gap value. Moreover, a persistent high PCO_2 gap value was allied with a lesser survival at day 28. Additionally, central venous oxygen saturation ($ScvO_2$) was also measured in these patients and observed that patients in septic shock achieving ScvO2 $\geq$ 70% or mixed venous oxygen saturation (SvO_2) $\geq$ 65% had worse outcomes when a simultaneous high PCO_2 gap is present.[16] Other observations have suggested that PCO_2 gap could recognize septic patients who still are ineffectively resuscitated despite achieving $ScvO_2$ goals being consistent with the study.[32] In patients with low $ScvO_2$, an increased PCO_2 gap indicates the contribution of low cardiac output, and measuring PCO_2 gap could help in accelerating therapies aimed at improving cardiac output, as opposed to the SaO_2 or hemoglobin concentration. When $ScvO_2$ is high (70%), the continuous increase in PCO_2 gap is responsible for the remaining impaired perfusion. Thus, the data corroborates the idea that PCO_2 gap can provide additional information to oxygen and hemodynamic parameters that are usually used during resuscitation of septic shock, offering additional help to make decisions about fluids and inotropes. However, the underlying mechanisms that explicate increases in PCO_2 gap during septic shock are incompletely understood and further studies are needed to confirm this hypothesis. [16,17]

The interpretation of high lactate levels in sepsis is very difficult, being even more in septic shock as anaerobic metabolism, non-anaerobic and slow clearance leads to lactate accumulation.[18] Increased levels of lactate are correlated with circulatory disfunction. The lactate clearance is the decrease of lactate after the treatment compared to initial lactate level occurring after successful resuscitation indicating sufficient tissue perfusion.[4,33] Several studies demonstrated a persistently high PCO_2 gap associated with high lactate levels and slower lactate

clearance during the first 6 hours of resuscitation. A high PCO_2 gap can indicate a decrease in global or microvascular blood flow leading to slow clearance lactate. Low PCO_2 gap values were expressively correlated with lower lactate levels when evaluated 6 hours after resuscitation. This suggests that low PCO_2 gap is a potential marker for survival that could be used together with lactate. It is also important the fact that perfusion-related variables have clearly distinctive normalization rates in septic shock patients. Lactate and PCO_2 gap exhibited a response characterized by two phases: the first with a faster improvement followed by the second phase with a slower tendency. This normalization ratio can help to decide the most adequate criteria to stop resuscitation in the right time and prevent over-resuscitation. [4,16-18,20] Nonetheless, the persistence of anaerobic metabolism could also present a high PCO_2 gap as proposed by Mekontso-Dessap et al. [34] But, Ospina-Táscon et al affirm that even in the presence of anaerobic metabolism it is possible to have a high efferent venous blood flow that can wash out the CO_2 generation from the hypoperfused peripheral tissues. So, in this situation, PCO_2 gap would not increase. Indeed, they observed hypoperfusion in some patients of their study with normal oxygen parameters, global hemodynamics and PCO_2 gap. So, it was concluded that PCO_2 gap is not a marker of tissue hypoxia that can be given by parameters as lactates. PCO_2 gap is a marker of the adequacy of blood flow to eliminate tissue CO_2. [4,16]

During the early phases of resuscitation of septic shock PCO_2 gap is closely related to microcirculatory blood flow. In septic shock, microcirculatory dysfunction is a generalized phenomenon that consists in the decreasing of functional capillary density associated with the increased heterogeneity of blood flow presenting zones with well-perfused vessels close to non-perfused capillaries. This seems to trigger the development of organ disfunction as the capillary blood flow lead cellular stress and hypoxia-inducible gene expression. Actually, according to De Backer et all, comparing with global hemodynamics parameters, microcirculatory alterations are stronger determinants of outcomes, with progressive increase in the risk of death. In a population of 75 patients, Ospina-Tascón showed an independent correlation between PCO_2 gap and the percentage of small cell perfused and, consequently with functional capillary density. In sepsis, the increase in the heterogeneity of microcirculatory blood flow with a consequent reduction in the functional capillary density can be liable for altered oxygen extraction abilities. Indeed, this heterogeneous flow ablation of individual capillaries can be an important factor determining the oxygen supply dependence

phenomenon during sepsis and with PCO_2 gap variations it is possible to track this heterogeneity of microvascular blood flow as observed in the study.[20,35]

The reestablishment of the mean arterial pressure (MAP) is a very important initial step for resuscitation and is a goal to restore end-organ perfusion. To guarantee an adequate perfusion, it is essential a sufficient oxygen delivery to the demands of O_2 consumptions and PCO_2 gap can provide information about the adequacy of tissue O_2 perfusion. In septic shock, increase MAP above 65 mmHg improves microcirculatory function and the PCO_2 gap value. The maintenance of a sufficient MAP is crucial to not develop hypoperfusion and is the secret in the management of distributive shock. Instead, due the lack of correlation between the PCO_2 gap and MAP after 6 hours of resuscitation, PCO_2 gap can possibly be used as a trustworthy prediction for adequacy of tissue O_2 supply and requirements in shock patients if measured after early resuscitation.[4]

According to Mallat et all, dobutamine infusion up to 15 μg/kg/min did not result in a dose-dependent diminution in PCO_2 gap despite a dose-related increase in cardia index and oxygen delivery. Dobutamine is the first-choice therapy recommended in order to increase cardiac index when there are signs of hypoperfusion next hypovolemia has been excluded and mean arterial pressure has been achieved. In a population of 22 patients with stable septic shock with no signs of anaerobic metabolism, the change in PCO_2 gap (as an index of CO_2 production/ cardiac index ratio) was interpreted with the change in the cardiac index and CO_2 production. When dobutamine ratio was increased from 0 to 10 lg/kg/min, it was observed a linear cardiac index increasement that resulted in a low PCO_2 gap, even with a slight increase of CO_2 production that is explained by the higher increase of cardiac index that permitted the elimination of both stagnated and newly created CO_2. In another study, Teboul et al investigate the effects of incremental doses of dobutamine on time course of PCO_2 gap in ten stable patients with chronic heart failure. From the same doses of dobutamine (0 to 10 lg/kg/min), it also was observed a decrease in PCO_2 gap correlated linearly with the increase of cardiac index. On the other side, the CO_2 production remained constant.[36] When dobutamine ratio was increased from 10 to 15 lg/kg/min, PCO_2 gap remained practically constant despite the continued increase of the cardiac index. The CO_2 production was not constant in this study, increasing appreciably when dobutamine was increased from 10 to 15 lg/kg/min in the same scale as cardiac index. This can probably explain why PCO_2 gap remained unchanged or slightly increased. Also, the increase of oxygen consumption with these doses of

dobutamine balances the increase of cardiac index, explaining the absence of any improvement in $ScvO_2$ and oxygen extraction. Also, Teboul et al found similar results in their study.[25,36]

The PCO_2 gap demonstrated a good performance to predict extubation failure. The combination analysis of PCO_2 gap and $Scvo_2$ together is better to detect the failure, and these two markers are independent predictors of extubation failure. In the transition from mechanical ventilation to spontaneous ventilation there is an increase in oxygen consumption of the respiratory muscles caused by the breathing. As stated in Fick equation applied to CO_2, PCO_2 gap is determined by the cardiac output and tissues CO_2 production. The adequacy of venous blood flow in the process of washing out the CO_2 created in the peripheric tissue has been indicated by PCO_2 gap. Despite the good results, this multicenter, prospective and observational study, with a population of 75 critical ill, is the first study that explored this topic and showed PCO_2 gap as a good marker for predicting extubation failure. So, future studies are needed to discuss these results. [2,19,20,26]

Al Duhailib et al in their systematic review and meta-analysis showed that in critical ill patients with circulatory shock high PCO_2 gap was related to increased mortality only in medical and surgical ICUs. That relation was not observed in the cardiovascular patients. Another systematic review studied this topic in patients with severe sepsis and septic shock and also demonstrated an association between high PCO_2 gap and 28-day or in-hospital mortality.[37] So, Al Duhailib et al added to the preview evidence demonstrating that is this marker is associated with increased mortality odds only in medical and surgical populations, but not in cardiovascular patients. This evidence can be related with overall lower mortality in in this population. The development in surgical techniques and meticulous patient selection processes resulted in a very low mortality in cardiac surgery rate (3.4-6.5%).[38] On the other hand, high mortality rates (> 46%) were seen in septic shock patients in the surgical and medical ICUs associated with critical microvascular dysfunction. [20,39]

According to Moussa et al, after a cardiac surgery with cardiopulmonary PCO_2 gap was independently associated with MPC. This was showed in a population of 308 cardiac patient. In another study, PCO_2 gap was measured 30 minutes after ICU admission in 30 patients and it was found an appreciably increased PCO_2 gap in 52% of patients who suffered postoperative complications. In addition, an abnormally high PCO_2 gap value was related to a higher rate of postoperative complications as cardiac arrhythmias, prolonged mechanical ventilation,

inadequate cardiac performance, increased creatinine and jaundice.[40] Also in pediatric population, high PCO_2 gap predicted poor outcomes and mortality after cardiac surgery in this age group.[41] In contrast, others studies as Guinot et al and Morel et al have showed different opposite results with a weakly association between PCO_2 gap, tissue perfusion markers and without association with postoperative complications after cardiac surgery. But it is important to refer that these authors studied their populations based on the theoretical PCO_2 gap value of 6 mmHg, dividing their patients according to this value and then compared both subgroups using only one variable analysis without any adjustment for confounders. The predefined PCO_2 gap value of 6 mmHg was formerly reported in experimental studies and revealed to be related with outcome in high-risk noncardiac surgery and shock patients but, it may be not the most adequate in cardiac surgery patients. Also, the difference in MPC definitions, the time of sampling, and patient management, mainly targeted temperatures during cardiopulmonary bypass, are valuable points that can justify these differences.[28,29,34,42,43]

In patients with bloodstream infection, at the time of blood culture, increased PCO_2 gap (> 6 mmHg) was found to be independently related with 28-day mortality. The study of Wang et al presented a 28-day mortality of 34.9%, being a higher value comparing with other study with 15.2%. However, the first study also had an older population, what is a risk factor for poor prognosis, and more severe patients with higher Sequential Organ Failure Assessment (SOFA) and Acute Physiology And Chronic Health Evaluation II (APACHE II) which can probably influence the results. Bloodstream infections are caused by different pathogen and that influences the mortality rate. Procalcitonin has an important diagnostic value in bloodstream infection and it helps with the identification of the pathogen and the therapeutic choices. PCO_2 gap revealed a considerably association, proposing that PCO_2 gap may help in the identification of pathogens and, consequently, predict outcomes. The fact that there was found more Gram-negative bacteria infection in patients with high levels of PCO_2 gap corroborates the previous sentence. Wang et al also showed a good correlation between PCO_2 gap and C-reactive protein which has an important role in the diagnosis and prognosis of bloodstream infection. The good relation evidenced between PCO_2 gap and $Scvo_2$ and lactate is also important as these last two markers are helpful guides in early fluid resuscitation and can predict the prognosis of sepsis and, as cited by other authors, the three markers are important indicators for treatment and prognosis

of that critical condition. At least, when PCO_2 gap > 6mmHg, the use of vasopressor, mechanical ventilation and continuous renal replacement therapy were expressively more comparing with lower values, suggesting that this marker can indicate the disease gravity of the patient [30,33,44-47]

Key Learning Point:

- PCO_2 gap reflects the adequacy of microvascular circulation and high values are associated with lower percentages of small perfused vessels, lower functional capillary density and high heterogeneity of microvascular blood flow.[20]
- PCO_2 gap is a marker of the adequacy of blood flow to eliminate tissue CO_2. [4,16]
- PCO_2 gap is inversely correlated with cardiac output and the relationship between these two variables depends on the level of CO_2 production.[13,15,23]
- In shock patients, PCO_2 gap is a great predictor of the microvascular blood flow maldistribution and can possibly be used as a trustworthy prediction for adequacy of tissue O_2 supply and requirements if measured after early resuscitation.[4,20,35]
- In patients with septic shock, PCO_2 gap is a potential marker for forming a prognosis and is associated with microcirculation disfunctions and a continuous elevated PCO_2 gap has been shown to be associated with worse prognosis and more multiorgan disfunction. Thus, in these patients, PCO_2 gap might identify a high risk of death [4,16,20]
- In septic shock patients PCO_2 gap provides additional information to oxygen and hemodynamic parameters that are usually used during resuscitation of septic shock, offering additional help to make decisions about fluids and inotropes. [16,17]
- PCO_2 gap is a potential marker for establishing prognosis for septic shock patients and a continuous elevated PCO_2 gap has been shown to be associated with worse prognosis.[5,6,15,19]
- Higher mortality rate is associated with a PCO_2 gap higher than 6 mmHg.[4]
- High PCO_2 gap is associated with slower lactate clearance. [4,16-19]

- Monitoring PCO_2 gap can be a useful tool to assess the adequacy of oxygen supply versus oxygen demand and, therefore, may help to guide therapy with dobutamine in stable septic shock patients.[25]
- High PCO_2 gap value (> 6 mmHg) can be a valuable biomarker to identify patients who still remain inefficiently resuscitated despite a ScvO2 > 70%.[19]
- PCO_2 gap is a helpful marker for prediction of extubation outcomes. The predictability of both PCO_2 gap and $Scvo_2$ is excellent and better than using the markers individually.[26]
- High PCO_2 gap is related with increased odds of 28-day and hospital mortality in medical and surgical ICU patients with shock.[6]
- High PCO_2 gap was related with postoperative complications in cardiac surgery with cardiopulmonary bypass.[27,40,41]
- In patients with bloodstream infection, PCO_2 gap can be a precious biomarker to assessment of 28-day mortality.[30]

Conclusion

Effectively, nowadays PCO_2 gap has been reaching an important role as a biomarker to guide the therapeutic and to predict the prognosis of the patients. Several studies that have been made showed very good results, considering it a useful tool in many pathologies.

Furthermore, the current trend shows an increase in the use of PCO_2 gap in critical ill patients as it is associated with microcirculation disfunctions and a continuous elevated PCO_2 gap has been demonstrated to be associated with worse prognosis and more multiorgan disfunction. Also, an elevated PCO2 gap value is being associated with higher risk of death and higher lactate levels with slower lactate clearance.

However, due to the fact that it is a recent marker, future studies are still necessary in order to have a larger sample of results that would allow to demonstrate its therapeutic and prognostic efficacy with robustness.

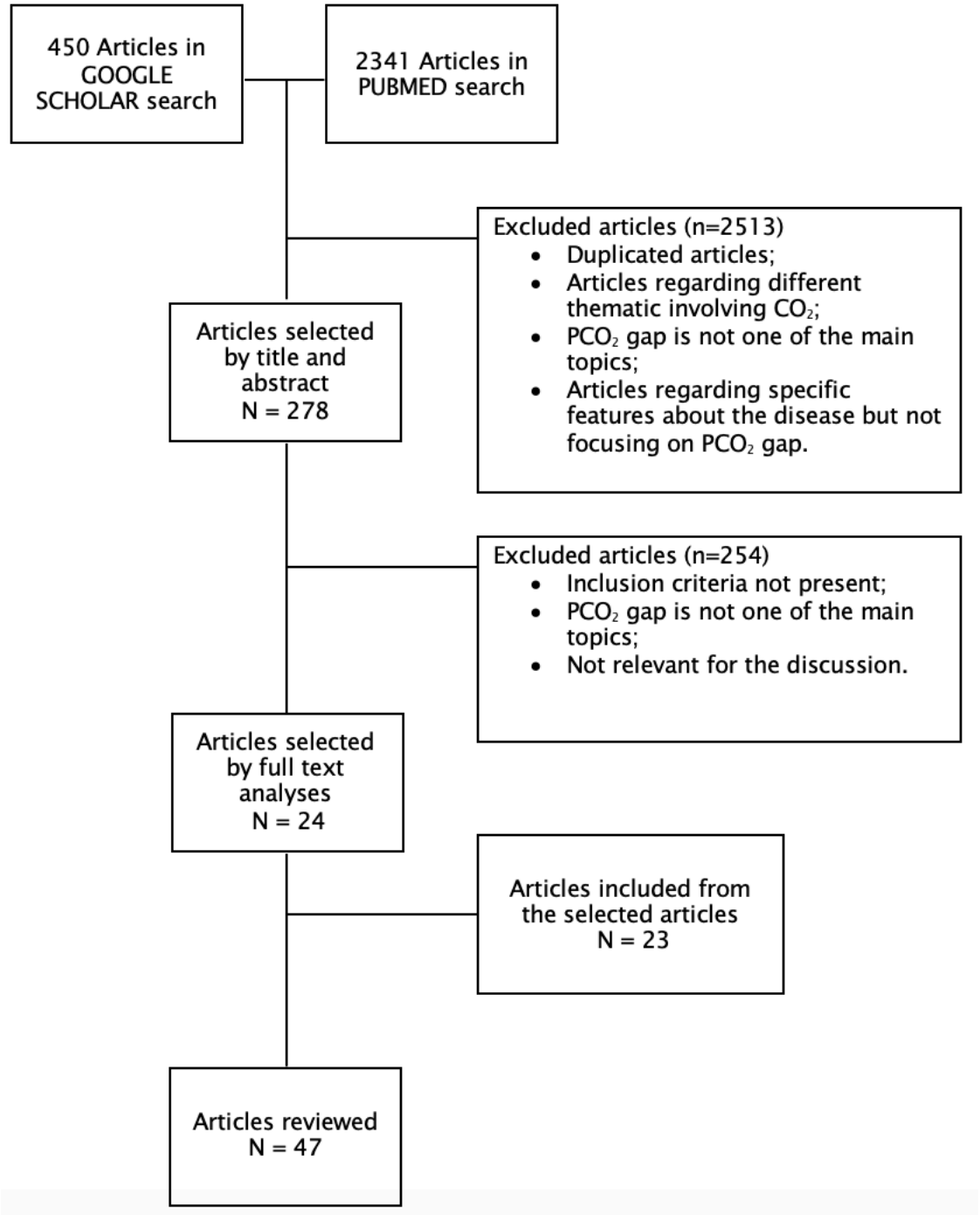

Figure 1 – Inclusion / exclusion methodology of manuscripts.

Bibliography

1. Mallat J, Lazkani A, Lemyze M, et al. Repeatability of blood gas parameters, PCO2 gap, and PCO2 gap to arterial-to-venous oxygen content difference in critically ill adult patients. *Medicine (Baltimore).* 2015;94(3):e415.
2. Gavelli F, Teboul JL, Monnet X. How can CO(2)-derived indices guide resuscitation in critically ill patients? *J Thorac Dis.* 2019;11(Suppl 11):S1528-s1537.
3. Patil VP. Mystery of PCO2 Gap in Sepsis. *Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine.* 2019;23(10):443.
4. Kriswidyatomo P, Kloping YP, Jaya MG, et al. Prognostic Value of PCO2 Gap in Adult Septic Shock Patients: A Systematic Review and Meta-Analysis.
5. Janotka M, Ostadal P. Biochemical markers for clinical monitoring of tissue perfusion. *Mol Cell Biochem.* 2021;476(3):1313-1326.
6. Al Duhailib Z, Hegazy AF, Lalli R, et al. The Use of Central Venous to Arterial Carbon Dioxide Tension Gap for Outcome Prediction in Critically Ill Patients: A Systematic Review and Meta-Analysis. *Crit Care Med.* 2020;48(12):1855-1861.
7. Huette P, Ellouze O, Abou-Arab O, Guinot PG. Venous-to-arterial pCO(2) difference in high-risk surgical patients. *J Thorac Dis.* 2019;11(Suppl 11):S1551-s1557.
8. Danin PE, Siegenthaler N, Levraut J, Bernardin G, Dellamonica J, Bendjelid K. Monitoring CO2 in shock states. *J Clin Monit Comput.* 2015;29(5):591-600.
9. Greenwood JC, Orloski CJ. End Points of Sepsis Resuscitation. *Emerg Med Clin North Am.* 2017;35(1):93-107.
10. Castro D, Patil SM, Keenaghan M. Arterial Blood Gas. *StatPearls*. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.
11. Mesquida J, Saludes P, Gruartmoner G, et al. Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference is associated with lactate evolution in the hemodynamic resuscitation process in early septic shock. *Crit Care.* 2015;19(1):126.
12. Scheeren TWL, Wicke JN, Teboul JL. Understanding the carbon dioxide gaps. *Curr Opin Crit Care.* 2018;24(3):181-189.
13. Lamia B, Monnet X, Teboul J. Meaning of arterio-venous PCO2 difference in circulatory shock. *Minerva anestesiologica.* 2006;72(6):597-604.
14. Pinsky MR, Teboul J-L, Vincent J-L, Medicine ESoIC. *Hemodynamic monitoring.* Springer; 2019.
15. van Beest PA, Lont MC, Holman ND, Loef 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):1034-1039.
16. Ospina-Tascón GA, Bautista-Rincón DF, Umaña M, et al. 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.
17. Mallat J, Pepy F, Lemyze M, et al. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. *Eur J Anaesthesiol.* 2014;31(7):371-380.
18. Hernandez G, Luengo C, Bruhn A, et al. When to stop septic shock resuscitation: clues from a dynamic perfusion monitoring. *Ann Intensive Care.* 2014;4:30.

19. Vallée F, Vallet B, Mathe O, et al. Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? *Intensive Care Medicine.* 2008;34(12):2218.
20. Ospina-Tascón GA, Umaña M, Bermúdez WF, et al. Can venous-to-arterial carbon dioxide differences reflect microcirculatory alterations in patients with septic shock? *Intensive Care Medicine.* 2016;42(2):211-221.
21. Ltaief Z, Schneider AG, Liaudet L. Pathophysiology and clinical implications of the veno-arterial PCO2 gap. *Critical Care.* 2021;25(1):1-9.
22. Yuan S, He H, Long Y. Interpretation of venous-to-arterial carbon dioxide difference in the resuscitation of septic shock patients. *J Thorac Dis.* 2019;11(Suppl 11):S1538-s1543.
23. Cuschieri J, Rivers EP, Donnino MW, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med.* 2005;31(6):818-822.
24. Bitar ZI, Maadarani OS, El-Shably AM, Elshabasy RD, Zaalouk TM. The forgotten hemodynamic (PCO2 Gap) in severe sepsis. *Critical care research and practice.* 2020;2020.
25. Mallat J, Benzidi Y, Salleron J, et al. Time course of central venous-to-arterial carbon dioxide tension difference in septic shock patients receiving incremental doses of dobutamine. *Intensive Care Med.* 2014;40(3):404-411.
26. Mallat J, Baghdadi FA, Mohammad U, et al. Central Venous-to-Arterial PCO2 Difference and Central Venous Oxygen Saturation in the Detection of Extubation Failure in Critically Ill Patients. *Crit Care Med.* 2020;48(10):1454-1461.
27. Moussa MD, Durand A, Leroy G, et al. Central venous-to-arterial PCO2 difference, arteriovenous oxygen content and outcome after adult cardiac surgery with cardiopulmonary bypass: A prospective observational study. *Eur J Anaesthesiol.* 2019;36(4):279-289.
28. Guinot PG, Badoux L, Bernard E, Abou-Arab O, Lorne E, Dupont H. Central Venous-to-Arterial Carbon Dioxide Partial Pressure Difference in Patients Undergoing Cardiac Surgery is Not Related to Postoperative Outcomes. *J Cardiothorac Vasc Anesth.* 2017;31(4):1190-1196.
29. Morel J, Grand N, Axiotis G, et al. High veno-arterial carbon dioxide gradient is not predictive of worst outcome after an elective cardiac surgery: a retrospective cohort study. *J Clin Monit Comput.* 2016;30(6):783-789.
30. Wang Z, Wei X, Qin T, et al. Prognostic value of central venous-to-arterial carbon dioxide difference in patients with bloodstream infection. *Int J Med Sci.* 2021;18(4):929-935.
31. Dres M, Monnet X, Teboul J-L. Hemodynamic management of cardiovascular failure by using PCO2 venous-arterial difference. *Journal of Clinical Monitoring and Computing.* 2012;26(5):367-374.
32. Vallet B, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol (1985).* 2000;89(4):1317-1321.
33. 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. *J Crit Care.* 2016;36:223-229.

34. Mekontso-Dessap A, Castelain V, Anguel N, et al. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. *Intensive Care Med.* 2002;28(3):272-277.
35. De Backer D, Donadello K, Sakr Y, et al. Microcirculatory alterations in patients with severe sepsis: impact of time of assessment and relationship with outcome. *Crit Care Med.* 2013;41(3):791-799.
36. Teboul JL, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. *Crit Care Med.* 1998;26(6):1007-1010.
37. Diaztagle Fernández JJ, Rodríguez Murcia JC, Sprockel Díaz JJ. Venous-to-arterial carbon dioxide difference in the resuscitation of patients with severe sepsis and septic shock: A systematic review. *Med Intensiva.* 2017;41(7):401-410.
38. Mazzeffi M, Zivot J, Buchman T, Halkos M. In-hospital mortality after cardiac surgery: patient characteristics, timing, and association with postoperative length of intensive care unit and hospital stay. *Ann Thorac Surg.* 2014;97(4):1220-1225.
39. Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama.* 2016;315(8):775-787.
40. Cavaliere F, Martinelli L, Guarneri S, Varano C, Rossi M, Schiavello R. Arterial-venous PCO2 gradient in early postoperative hours following myocardial revascularization. *J Cardiovasc Surg (Torino).* 1996;37(5):499-503.
41. Rhodes LA, Erwin WC, Borasino S, Cleveland DC, Alten JA. Central Venous to Arterial CO2 Difference After Cardiac Surgery in Infants and Neonates. *Pediatr Crit Care Med.* 2017;18(3):228-233.
42. Robin E, Futier E, Pires O, et al. Central venous-to-arterial carbon dioxide difference as a prognostic tool in high-risk surgical patients. *Crit Care.* 2015;19(1):227.
43. Mallat J, Lemyze M, Tronchon L, Vallet B, Thevenin D. Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. *World J Crit Care Med.* 2016;5(1):47-56.
44. Hattori H, Maeda M, Nagatomo Y, et al. Epidemiology and risk factors for mortality in bloodstream infections: A single-center retrospective study in Japan. *Am J Infect Control.* 2018;46(12):e75-e79.
45. 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.
46. Hattori T, Nishiyama H, Kato H, et al. Clinical value of procalcitonin for patients with suspected bloodstream infection. *Am J Clin Pathol.* 2014;141(1):43-51.
47. Mahmoodpoor A, Shadvar K, Sanaie S, et al. Arterial vs venous lactate: Correlation and predictive value of mortality of patients with sepsis during early resuscitation phase. *J Crit Care.* 2020;58:118-124.

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