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To evaluate PCO2 –gap as earlier marker of tissue hypo perfusion and mortality predictor, compared to SCVO2 and lactate, in patients admitted with septic shock in medical ICU.

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ABSTRACT

Objectives: The prime objective of present investigation was to assess arterial and venous PCO2 –gap, in comparison to SCVO2 and lactate as valuable, earlier and reliable marker of tissue hypoxia and therefore mortality in septic shock patients

Methodology: It was a retrospective observational study on patients admitted with SIRS, severe sepsis or septic shock, in medical ICU of Agha Khan University hospital in year 2014-2015. All the patients aged 16 or above, admitted in year 2014 -2015 at medical ICU of Agha Khan University Hospital with septic shock defined as per surviving sepsis guidelines The patient's data were organized under categories of age, sex, source of infectious etiology, mechanical ventilation need, renal replacement therapy, co morbidities, and total length of hospital stay, ICU stay, outcome, and 28 days mortality. SPSS version 19.0 (statistical package for social sciences) was used to conduct statistical analyses. An independent sample t-test was applied for comparison of quantitative variables, whereas a chi square test was performed to examine categorical variables across the categories of survival and PCO_2 gap.

Results: A total of 98 patients were identified from the hospital records with mean age (SD) of 54.9(18.8) years. A higher number of patients had hypertension (n=40, 40.8%) followed by

diabetes (n=30, 30.6%), IHD (n=15, 15.0%), CKD (n=8, 8.2%) and Hep-C, COPD, CLD (n=6, 6.1%). 18 patients had no comorbid conditions whereas most of the patients had one comorbid condition (n=34, 34.7%). A higher number of participants had pneumonia (n=34, 34.7%) as compared to urinary tract infection, brain, blood, others and multiple sources. Mean survival time in minutes were compared across categories of PCO2, SCVO2 and lactate. Patients with lactate levels of less than 2 survived for longer time as compared to those with lactate levels of 2 or more (lactate less than 2: 41.4, 95% CI 29.1 to 53.7 vs. lactate levels of 2 or more: 18.5, 95% CI 12.4 to 24.5, log rank test p=0.002). In addition, higher lactate levels were significantly associated with PCO2 gap being high (p=0.05). On multivariate level, one unit increase in lactate levels was associated with 11% increase in mortality while adjusting for age, PCO2 gap, length of ICU stay and albumin globulin ratio. A unit increase in PCO2 gap was associated with only 1% increase in mortality.

Conclusion: We have reaffirmed the significance of age, comorbid conditions, lactate levels, and pH as predictors of mortality, consistent with previous research. Additionally, our study suggests that the PCO2 gap may be a valuable parameter to consider in the assessment and management of these patients, potentially providing new avenues for enhancing patient care.

Key words: Tissue hypoperfusion, Mortiality predictor

INTRODUCTION:

Shock is described as an extensive low perfusion of tissues induced by an incongruity between systemic oxygen distribution (DO2) and oxygen requirement (VO2). Global tissue hypoxia caused by a generalized inflammatory reaction or circulatory failure, is a warning indication of severe ailment before multiple organ failure.

The consequences of organ failure can be predicted at the commencement of organ failure [1]. The global tissue hypoxia if not diagnosed and treated well increases the morbidity as well as mortality, moreover declining levels of mixed venous oxygen saturation (SvO2) or central venous oxygen saturation (ScvO2) indicate an adverse outcome in septic shock [2, 3].

A great number of patients who directly admits at the intensive care unit (ICU) presenting either with sepsis or septic shock have ScvO2 levels greater than 70% [4,5]. Consequently, normal ScvO2 interpretations do not confirm satisfactory tissue oxygenation, and supplementary circulatory procedures are obligatory to evaluate resuscitation efforts. The central venous-arterial carbon dioxide differential (pCO2gap) is one variable discussed in this context [6].

Under standard circumstances, the venous-arterial carbon dioxide differential often does not surpass 0.8 kPa (6 mmHg) [7], representing sufficient venous flow, or cardiac output (CO) [8, 9]. An inverse association between pCO2gap and cardiac index (CI) has been recognized in seriously ill patients [10, 11].

In fact, those individuals who fulfilled resuscitation targets in accordance with international standards [1], a pCO2 gap threshold value of 0.8 kPa can be used to discriminate between high and poor lactate clearance and CI [6]. Thus, by utilizing ScvO2 scores as a substitution for global tissue hypoxia and the pCO2gap as a substitute for CI during revival of critically ill patients could be beneficial. Though, in individuals with severe sepsis, it is dependent of CO [12, 13]. This infers that, in sepsis, carbon dioxide (CO2) accumulation might happen despite of appropriate CO levels. Determining whether there is an agreement between the mixed and central venous-arterial carbon dioxide variance in septic patients seems to be useful, in keeping with studies that are on agreement between SvO2 and ScvO2 [5,11].

The current study aims to investigate the potential extra usefulness of central venous-arterial carbon dioxide variances in predicting the course of treatment for patients suffering from septic shock. Sepsis remains to be a foremost reason of morbidity and mortality in ICU. An additional marker is needed, apart from usual SCVo2 and lactate measurement, to classify patients earlier with severe sepsis and later at an increased risk of suffering from multi organ failure and mortality with the disease.

As both arterial and venous blood samples are routinely sent in all medical ICU patients with SIRS, severe sepsis and septic shock, PCO2- gap can be evaluated by just analyzing already available data from our hospital records.

OBJECTIVES:

The prime objective of present investigation was to assess arterial and venous PCO2 –gap, in comparison to SCVO2 and lactate as valuable, earlier and reliable marker of tissue hypoxia and therefore mortality in septic shock patients.

The secondary intent of the current study was to identify the duration of inpatient stay, ITU stay, 28-day mortality, and outcome of patients admitted with SIRS, severe sepsis and septic shock by using PCO_2-GAP.

METHDOLOGY

It was a retrospective observational study on patients admitted with SIRS, severe sepsis or septic shock, in medical ICU of Agha Khan University hospital in year 2014-2015. This study was conducted by using hospital electronic data base records on patients admitted with septic shock in medical ICU for the year 2014-2015, based on septic shock definition as per surviving sepsis guidelines.All the patients aged 16 or above, admitted in year 2014 -2015 at medical ICU of Agha Khan University Hospital with septic shock defined as per surviving sepsis guidelines. All the patients with any other admitting diagnosis apart from septic shock were excluded from the study

The data was collected from medical ICU's records of patients admitted in year 2014-2015 with diagnosis of septic shock based on survive sepsis guidelines.The patient's data were organized under categories of age, sex, source of infectious etiology, mechanical ventilation need, renal replacement therapy, co morbidities, and total length of hospital stay, ICU stay, outcome, and 28 days mortality. We will also identify cases based on source of admissions (emergency department or wards). As our study is administrative data based on hospital's electronic records , no consent is being sought.

Statistical Analyses:

SPSS version 19.0 (statistical package for social sciences) was used to conduct statistical analyses. All quantitative data, such as age, number of comorbid conditions, Arterial PCO2, PCO2gap, initial SVO2, Ph on admission, lactate on admission, AG ratio, and duration of ICU and hospital stay were provided with their mean and standard deviation. Frequencies with percentages were reported for all categorical variables such as age categories, comorbidities, categories of clinical variables such as initial arterial PCO2, Initial venous PCO2, initial SVO2, pH on admission, lactate on admission, AG ratio and source of infection.

An independent sample t-test was applied for comparison of quantitative variables, whereas a chi square test was performed to examine categorical variables across the categories of survival and PCO_2 gap. Mean survival times with 95% confidence intervals were measured by using Kaplan Meier survival method and were compared across the categories of PCO2 gap, initial SVO2 and lactate using log rank test. A p-value of equals to or less than 0.05 was considered as significant. Cox proportional hazards model was utilized to determine predictors of mortality. Crude hazards ratio with 95% confidence intervals were reported. All variables having a p-value of <0.25 were considered for multivariate analysis. Multicolinearity, Interaction and confounding variables were also measured and the final results were reported as adjusted hazards ratio with 95% confidence intervals.

RESULTS

During the research phase, a total of 98 patients were identified from the hospital records with mean age (SD) of 54.9(18.8) years. A higher number of patients had hypertension (n=40, 40.8%) followed by diabetes (n=30, 30.6%), IHD (n=15, 15.0%), CKD (n=8, 8.2%) and Hep-C, COPD, CLD (n=6, 6.1%). 18 patients had no comorbid conditions whereas most of the patients had one comorbid condition (n=34, 34.7%). A higher number of participants had pneumonia (n=34, 34.7%) as compared to urinary tract infection, brain, blood, others and multiple sources. A number of patients had multiple sources of infection. Amongst others, most common ones were blood infections other than bacteremia i.e malaria, sepsis, congo (n=5), blood infection and pneumonia (n=3), pneumonia and brain (n=3), brain, pneumonia and UTI (n=3) and pneumonia and UTI (n=4), Clinical and demographic features of the study participants are mentioned in table 1

On the basis of survival status of patients, various different characteristics were also analyzed. Age, comorbid conditions such as liver disease and renal disease, PCO2 gap, pH on admission, lactate on admission and albumin-globulin ratio were found to be significantly associated with the rate of survival. Comparison of participants characteristics based on survival status is provided in table 1.

Mean survival time in minutes were compared across categories of PCO2, SCVO2 and lactate. Patients with lactate levels of less than 2 survived for longer time as compared to those with

lactate levels of 2 or more (lactate less than 2: 41.4, 95% CI 29.1 to 53.7 vs. lactate levels of 2 or more: 18.5, 95% CI 12.4 to 24.5, log rank test p=0.002). In addition, higher lactate levels were significantly associated with PCO2 gap being high (p=0.05). However, survival times were not found to be significantly different across the categories of PCO2 and SCVO2. Figure 1 compares Kaplan Meier survival curves across lactate groups.

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On univariate level, higher age, having a renal or liver disease, higher venous PCO2, higher PCO2 gap, on admission PH, higher lactate and length of ICU stay were established to be significantly linked with mortality. Table 2 shows univariate cox proportional hazards model with factors related with mortality. On multivariate level, one unit increase in lactate levels was associated with 11% increase in mortality while adjusting for age, PCO2 gap, length of ICU stay and albumin globulin ratio. A unit increase in PCO2 gap was associated with only 1% increase in mortality. Multiple interaction terms were developed and model was checked for confounding and interactions and no interactions were found. Final multivariate model showing factors associated with mortality is shown in table 3.

Table 1. Clinical and demographic Characteristics of 98 study Participants based on survival status

Characteristics	Overall n=98	Survived n=38	Expired n=60	P-values
Age, mean(SD)	54.9(18.8)	50.8(22.0)	57.5(16.2)	0.08
18-35	19(19.4)	13(34.2)	6(10.0)	0.02
36-55	26(26.5)	7(18.4)	19(31.7)	
56-65	20(20.4)	7(18.4)	13(21.7)	
66-75	21(21.4)	5(13.2)	16(26.7)	
76-90	12(12.2)	6(15.8)	6(10.0)	
Comorbid conditions				
Liver diseases	9(9.2)	1(2.6)	8(13.3)	0.07

Cardiovascular diseases	26(26.5)	12(31.6)	14(23.3)	0.36
Renal diseases	12(12.2)	1(2.6)	11(18.3)	0.02
Resp diseases	20(20.4)	8(21.1)	12(20.0)	0.90
Others	22(22.4)	11(28.9)	11(18.3)	0.22
Malignancy	7(7.1)	1(2.6)	6(10.0)	0.16
DM	30(30.6)	11(28.9)	19(31.7)	0.77
HTN	40(40.8)	15(39.5)	25(41.7)	0.83
No comorbid	18(18.4)	6(15.8)	12(20.0)	0.6
Number of comorbid	1.7(1.4)	1.6(1.4)	1.8(1.4)	0.49
None	18(18.4)	6(15.8)	12(20.0)	0.22
One	34(34.7)	16(42.1)	18(30.0)	
Two	18(18.4)	9(23.7)	9(15.0)	
3 or more	28(28.6)	7(18.4)	21(35.0)	
Initial Arterial PCO2	33.5(13.1)	33.6(10.6)	33.5(14.5)	0.95
Low	68(69.4)	24(63.2)	44(73.3)	0.52
Normal(35-45)	16(16.3)	8(21.1)	8(13.3)	
High	14(14.3)	6(15.8)	8(13.3)	
Initial Venous PCO2	41.7(18.9)	38.5(12.3)	43.7(21.9)	0.18
Low	59(60.2)	27(71.1)	32(53.3)	0.19
41-51	22(22.4)	7(18.4)	15(25.0)	
52 and above(high)	17(17.3)	4(10.5)	13(21.7)	
PCO2 Gap, mean(SD)	14.5(15.9)	9.8(11.1)	17.5(17.8)	0.02
Normal	25(25.5)	13(34.2)	12(20.0)	0.11
High(6 and above)	73(74.5)	25(65.8)	48(80.0)	
Initial SVO2	69.7(11.5)	70.3(10.8)	69.4(12.0)	0.71
Less than 65	29(29.6)	10(26.3)	19(31.7)	0.57
65 and above normal	69(70.4)	28(73.7)	41(68.3)	
pH on admission	7.38(0.09)	7.4(0.06)	7.3(0.11)	0.18
Acidosis	26(26.5)	8(21.1)	18(30.0)	0.08
Normal	51(52.0)	25(65.8)	26(43.3)	

Alkalosis	21(21.4)	5(13.2)	16(26.7)	
Lactate on admission Less than 2 2 and more	3.9(4.0) 2.3(1.3, 5.4) 39(39.8) 59(60.2)	2.4(2.1) 22(57.9) 16(42.1)	4.9(4.5) 17(28.3) 43(71.7)	0.003 0.004
AG ratio Less than 12 12 and above (normal)	15.3(5.9) 27(27.6) 71(72.4)	13.8(5.1) 13(34.2) 25(65.8)	16.2(6.2) 14(23.3) 46(76.7)	0.03 0.24
Ventilator Yes No	 95(96.9) 3(3.1)	 36(94.7) 2(5.3)	 59(98.3) 1(1.7)	0.31
Length of ICU stay in days, mean(SD)	6.4(5.1)	6.53(4.9)	6.4(5.30)	0.94
Length of hospital stay in days, mean(SD)	15.8(15.0)	18.8(14.9)	13.9(14.9)	0.11
Source of Infection UTI Pneumonia Brain Blood Others Multiple	 12(12.2) 34(34.7) 6(6.1) 10(10.2) 15(15.3) 21(21.4)	 5(13.2) 16(42.1) 2(5.3) 3(7.9) 4(10.5) 8(21.1)	 7(11.7) 18(30.0) 4(6.7) 7(11.7) 11(18.3) 13(21.7)	0.79

Table 2: Univariate cox proportional hazard model showing factors associated with mortality

Characteristics	Unadjusted HR	95% CI	P-values
Age, mean(SD)	1.02	1.00 to 1.03	0.006
Liver diseases			

No	1		0.002
Yes	3.29	1.52-7.12	
Renal diseases			0.007
No	1		
Yes	2.60	1.30 to 5.19	
Number of comorbid	1.08	0.91 to 1.29	0.34
None	1		
One	0.72	0.34 to 1.52	
Two	0.87	0.36 to 2.09	
3 or more	1.31	0.64 to 2.69	
Initial Arterial PCO2			
Low	1		
Normal(35-45)	0.70	0.33 to 1.50	0.33
High	0.60	0.28 to 1.29	
Initial Venous PCO2			
Low	1		0.02
41-51	1.44	0.77 to 2.69	
52 and above(high)	2.43	1.26 to 4.70	
PCO2 Gap, mean(SD)	1.01	1.005 to 1.03	0.008
Initial SVO2			
Less than 65	1.32	0.76 to 2.30	0.32
65 and above normal	1		
Ph on admission	0.07	0.04	0.04
Lactate on admission	1.14	1.08 to 1.20	<0.001
AG ratio	1.08	1.03 to 1.14	<0.001
Ventilator			0.55
Yes	1.81	0.25 to 13.1	
No	1		
Length of ICU stay hrs.	0.91	0.86 to 0.96	0.002

Source of Infection			0.12
UTI	1		
Pneumonia	0.72	0.30 to 1.76	
Brain	0.83	0.24 to 2.84	
Blood	0.52	0.17 to 1.57	
Others	1.27	0.49 to 3.29	
Multiple	0.38	0.14 to 1.01	

Table 3: Multivariate cox proportional hazard model showing factors associated with mortality

Variables	**Adjusted HR(95% CI)**	**P-values**
Lactate on admission	1.11(1.04 to 1.18)	<0.001
Age	1.01(1.001 to 1.03)	0.04
PCO2 gap	1.01(1.004 to 1.03)	0.01
ICU stay in days	0.91(0.86 to 0.97)	0.003
Albumin-Globulin ratio	1.05(0.99 to 1.10)	0.05

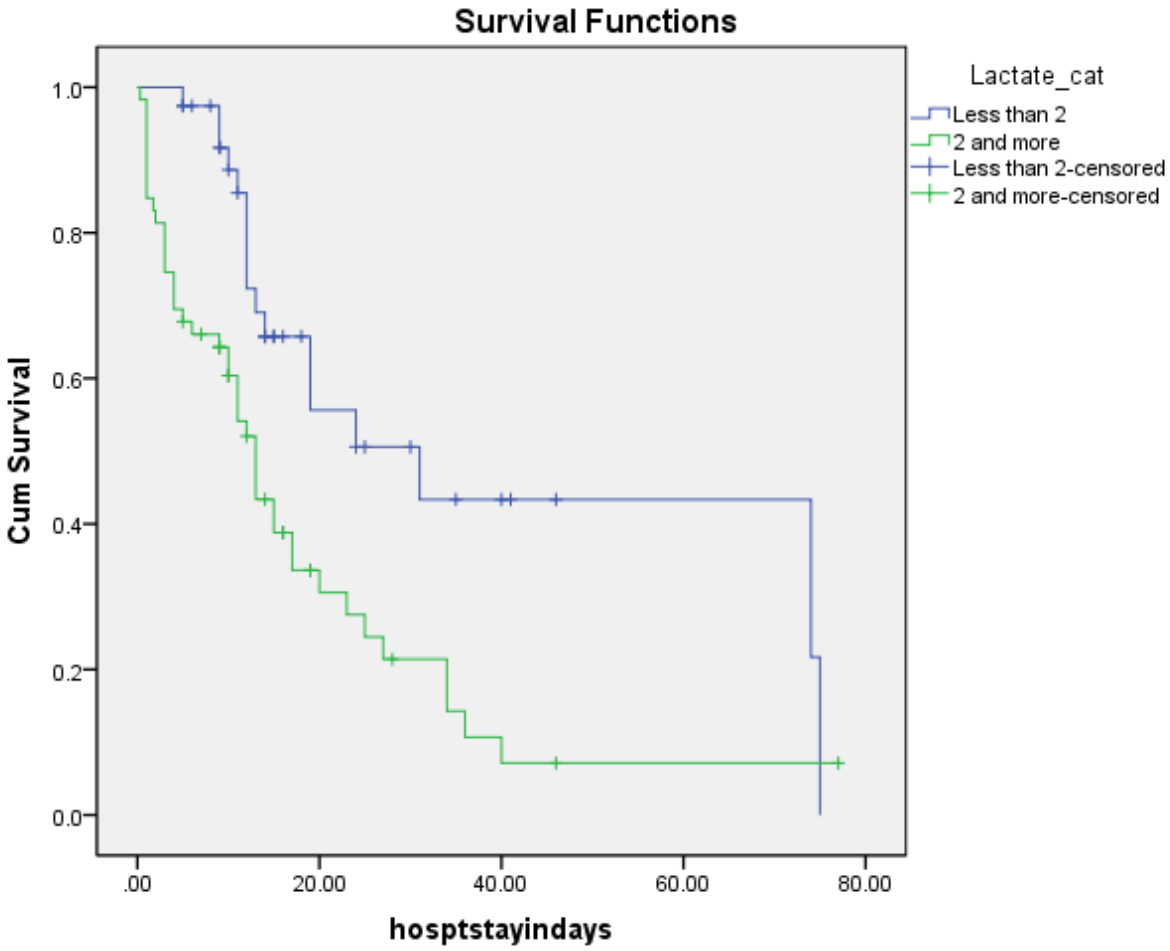

Figure 1: Kaplan Meier survival curves showing time to death by lactate categories.

DISCUSSION:

Our findings unequivocally emphasize the pivotal role of lactate levels as a robust forecaster of mortality in septic shock patients, which is consistent with the existing body of literature. The association between elevated lactate levels on admission and shorter survival times, as observed in our study, underscores the value of early lactate measurement as a vital tool for gauging the severity of septic shock [14]. Elevated lactate levels reflect impaired tissue perfusion and oxygen utilization, serving as a sentinel marker of the gravity of the underlying condition.

Another noteworthy aspect of our findings pertains to age and comorbid conditions. Age was found to be remarkably linked with increased mortality risk. This aligns with prior research, highlighting that older patients may exhibit diminished physiological reserve, rendering them more susceptible to severe infections [15]. Furthermore, the presence of comorbidities, particularly liver and renal diseases, significantly contributed to higher mortality rates. This underscores the imperative nature of factoring in these comorbidities when assessing and managing patients with septic shock.

While the PCO2 gap emerged as a potential predictor of mortality, it exhibited a relatively smaller effect size compared to lactate levels. This implies that while the PCO2 gap may provide valuable insights into tissue perfusion and circulation, it might not possess the same sensitivity as lactate levels in forecasting patient outcomes. Moreover, various factors such as initial arterial and venous PCO2, initial SVO2, pH on admission, and the albumin-globulin ratio were associated with survival status but did not establish themselves as strong independent predictors of mortality [16].

Comparing these findings with the existing body of literature, our study reaffirms the consensus that lactate levels are a potent prognostic marker in septic shock. Multiple studies have corroborated that elevated lactate levels are intricately linked with heightened mortality and organ dysfunction in septic shock patients [17]. The current conclusions add to the expanding body of research demonstrating the therapeutic value of lactate measurement as an early indication of tissue hypoxia and septic shock severity.

However, our study has several boundaries. First, it's a single-center investigation with a comparatively small number of samples. Potentially restricting the generalizability of our findings to broader patient populations. Secondly, the retrospective nature of our study could introduce bias and may not encompass all relevant variables. Additionally, our study did not delve into interventions or treatments based on the identified predictors, presenting an avenue for future research to explore targeted interventions to enhance outcomes in this high-risk patient cohort.

Our study underscores the pivotal role of lactate levels as a potent analyst of mortality in septic shock patients. It emphasizes the critical need for early lactate measurement in assessing and

managing these patients. Moving forward, there is an opportunity for further research to refine risk stratification and explore interventions tailored to patients with elevated lactate levels to optimize outcomes. Larger, multicenter studies may be instrumental in validating our findings and delineating precise lactate thresholds associated with varying mortality risks.

CONCLUSION:

We have reaffirmed the significance of age, comorbid conditions, lactate levels, and pH as predictors of mortality, consistent with previous research. Additionally, our study suggests that the PCO2 gap may be a valuable parameter to consider in the assessment and management of these patients, potentially providing new avenues for enhancing patient care.

The comprehensive evaluation of these factors in critical care settings is indispensable for risk categorization, treatment decisions, and ultimately refining patient outcomes. Additional exploration and prospective studies are warranted to authenticate these findings and determine their clinical implications, contributing to the ongoing enhancement of critical care practices.

REFERENCES:

1. Dellinger RP, Carlet JM, Masur H,Gerlach H, Calandra T, Cohen J, Gea-Banacloche J, Keh D, Marshall J,Parker MM, Ramsay G, ZimmermanJL, Vincent JL, Levy MM (2004)Surviving Sepsis Campaign guidelinesfor management of severe sepsis andseptic shock. Crit Care Med32:858–8732.

2. Krafft P, Steltzer H, Hiesmayr M,Klimscha W, Hammerle AF (1993)Mixed venous oxygen saturation incritically ill septic shock patients. Therole of defined events. Chest103:900–9063.

3. Rivers E, Nguyen B, Havstad S, ResslerJ, Muzzin A, Knoblich B, TomlanovichM; for the Early Goal-Directed Therapy Collaborative Group (2001) Early Goal-Directed Therapy in the treatment of severe sepsis and septic shock . N Engl JMed 345:1368–13774. van Beest PA, Hofstra JJ, Schultz MJ,Boerma EC, Spronk PE, Kuiper MA(2008) The incidence of low venousoxygen saturation on admission in theICU: a multicenter observational studyin the Netherlands. Crit Care 12:R335.

4. van Beest PA, Hofstra JJ, Schultz MJ,Boerma EC, Spronk PE, Kuiper MA(2008) The incidence of low venousoxygen saturation on admission in

the ICU: a multicenter observational studyin the Netherlands. Crit Care 12:R33.

5. van Beest PA, van Ingen J, Boerma EC,Holman ND, Groen H, Koopmans M,Spronk PE, Kuiper MA (2010) Noagreement of mixed venous and centralvenous saturation in sepsis, independent of sepsis origin Crit Care 14:R219.

6. Valle´e F, Vallet B, Mathe O,Parraguette J, Mari A, Silva S, Samii K,Fourcade O, Genestal M (2008) Centralvenous-to-arterial carbon dioxidedifference: an additional target for goal-directed therapy in septic shock?Intensive Care Med 34:2218–2225.

7. Guyton AC, Hall JE (2000) Transportof oxygen and carbon dioxide in theblood and body fluids. In: Guyton AC(ed) Textbook of medical physiology, 10th edn. WB Saunders Co,Philidelphia, pp 463–472.

8. Johnson BA, Weil MH (1991)Redefining ischemia due to circulatoryfailure as dual defects of oxygen deficitsand of carbon dioxide excesses. CritCare Med 19:1432–1438

9. Weil MH, Rackow EC, Trevino R,Grundler W, Falk JL, Griffel MI (1986)Difference in acid-based state betweenvenous and arterial blood duringcardiopulmonary resuscitation. N Engl JMed 315:153–156

10. Durkin R, Gergits MA, Reed JF,Fitzgibbons J (1993) The relationshipbetween arteriovenous carbon dioxidegradient and cardiac index. J Crit Care8:217–221

11. Cuschieri J, Rivers EP, Donnino MW,Katilius M, Jacobson G, Nguyen HB,Pamukov N, Horst HM (2005) Centralvenous-arterial carbon dioxidedifference as an indicator of cardiacindex. Intensive Care Med 31:818–822

12. Creteur J, De Backer D, Sakr Y, KochM, Vincent JL (2006) Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care

Med 32:516–523

13. Fries M, Weil MH, Sun S, Huang L,Fang X, Cammarata G, Castillo C, TangW (2006) Increases in tissue pCO2during circulatory shock reflect selective decreases in capillary bloodflow. Crit Care Med 34:446–452

14. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, Bennett ED. Base excess and lactate as prognostic indicators for patients admitted to intensive care. Intensive Care Med. 2001 Jan;27(1):74-83. doi: 10.1007/s001340051352. PMID: 11280677.

15. Martin, G. S., Mannino, D. M., Eaton, S., & Moss, M. (2003). The Epidemiology of Sepsis in the United States from 1979 through 2000. New England Journal of Medicine, 348(16), 1546–1554. doi:10.1056/nejmoa022139

16. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy: A Randomized Clinical Trial. JAMA. 2010;303(8):739–746. doi:10.1001/jama.2010.158

17. Puskarich MA, Trzeciak S, Shapiro NI, Arnold RC, Horton JM, Studnek JR, Kline JA, Jones AE; Emergency Medicine Shock Research Network (EMSHOCKNET). Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med. 2011 Sep;39(9):2066-71. doi: 10.1097/CCM.0b013e31821e87ab. PMID: 21572327; PMCID: PMC3158284.