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ORIGINAL ARTICLE

Diagnostic Validity of Ratio between Differences of Central Venous to Arterial CO2 and Arterial to Central Venous O2 Content in Diagnosis of Anaerobic Metabolism among Septic Patients

Subroto Kumar Sarker[1], Umme Kulsum Choudhury[2], Mohammad Mohsin[3], Subrata Kumar Mondal[4], Muslema Begum[5]

[1]Assistant Professor, Department of Critical Care Medicine, Dhaka Medical College, Dhaka, Bangladesh; [2]MD Critical Care Medicine, Department of Critical Care Medicine, Dhaka Medical College, Dhaka, Bangladesh; [3]Assistant Professor, Department of Critical care Medicine, Dhaka Medical College, Dhaka, Bangladesh; [4]Associate Professor, Department of Anaesthesiology, Dhaka Medical College, Dhaka, Bangladesh; [5]Assistant Professor, Department of Anaesthesiology, Dhaka Medical College, Dhaka, Bangladesh

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Abstract

Background: Detection of anaerobic metabolism is very crucial for the management of the septic patients. **Objective:** The purpose of the present study was to validate the ratio between differences of central venous to arterial CO_2 and arterial to central venous O_2 content in diagnosis of anaerobic metabolism among septic patients. **Methodology:** This prospective observational study was conducted in the Intensive Care Unit of the department of Anaesthesia Analgesia, Palliative and Intensive Care Medicine at Dhaka Medical College Hospital, Dhaka, Bangladesh from January 2016 to December 2016. All patients admitted to ICU with the features of severe sepsis and septic shock according to SSC guidelines with the age of more than or equal to 18 years in both sexes were included in this study. The arterial and central venous blood gases were measure simultaneously. At the same time serum lactate was measured. **Result:** Among the 69 patients, 31(44.9%) were of severe sepsis and 38(55%) were of septic shock patients. In the severe sepsis and septic shock patients the mean $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ is 1.39±0.41 and 1.11±0.40 respectively. Serum lactate in case of severe sepsis and septic shock patients is 2.85±1.40 and 3.85±1.04 respectively. The ROC analysis showed an area under curve 0.89 and $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio cutoff value of 1.21 showed sensitivity 0.84 and specificity 0.94. **Conclusion:** The $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio is also a another marker of global anaerobic metabolism. [*Journal of Current and Advance Medical Research, January 2021;8(1):34-38*]

Keywords: Diagnostic validity; ratio; central venous to arterial CO_2; arterial to central venous O_2 content; anaerobic metabolism; septic patients

Correspondence: Dr. Subroto Kumar Sarker, Assistant Professor, Department of Critical Care Medicine, Dhaka Medical College, Dhaka, Bangladesh; Email: subrotormc@gmail.com
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Introduction

The cornerstone of severe sepsis is the early diagnosis, administration of appropriate antibiotic and early hemodynamic resuscitation[1]. Despite successful initial resuscitation septic shock frequently evolves into multiple system organ failure (MSOF) and death[2]. There is a need to test the prognostic value of factors that could be used for guiding therapy after the initial resuscitation. Only a few laboratory tests for markers of sepsis are currently available.

Serum lactate is a component of diagnostic and prognostic models in severe sepsis and septic shock and concentration increased in these patients[3]. The sensitivity and specificity of single lactate concentrations as a marker of tissue hypo-perfusion have been established. Though lactate is produced in body in different situations, but elevated serum lactate is widely used as a marker of anaerobic metabolism[4]. However, for doing serum lactate, needs special ABG machine, special cartridges or laboratory facilities. It is also expensive. However, central venous to arterial CO_2 difference / arterial to venous O_2 difference ratio can be easily done by any simple ABG machine within very short time in the ICU. The $P(v-a)CO_2/C(a-v)O_2$ ratio can be measured as a "snapshot," and less expensive. Therefore central venous to arterial CO_2 difference/arterial to venous O_2 content difference ratio can be used as a diagnostic tool in the persistence of tissue hypo-perfusion or anaerobic metabolism in septic patient[5].

Ratios of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ are better markers of global anaerobic metabolism than lactate in septic shock patient[6]. The Delta $PCO_2/C(a\text{-}v)O_2$ ratio seems a reliable marker of global anaerobic metabolism[7].The lactate or central venous to arterial CO_2 difference/arterial to venous O_2 content difference ratio is considered as an indicator of anaerobic metabolism instead of central venous O_2 saturation for starting hemodynamic resuscitation[8]. High $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ is associated with poor lactate clearance in septic patient after resuscitation (He et al.2016).

In a population of septic shock patients with normalized MAP and $ScvO_2$, the presence of elevated $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio values significantly reduced the odds of adequate lactate clearance during the following hours[9]. This study was conducted to identify the cutoff value of the ratio of $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ and to see the sensitivity and specificity by ROC curve between the ratio and serum lactate for diagnosis of anaerobic metabolism in septic patients of adult Bangladeshi population admitted to ICU, Dhaka Medical College Hospital.

Methodology

This was a prospective observational study. This study was conducted in the Intensive Care Unit of the department of Anaesthesia Analgesia, Palliative and Intensive Care Medicine, Dhaka Medical College Hospital, Dhaka, Bangladesh. This study was carried out over a period of 12 months starting from January 2016 to December 2016. All adult patients admitted in the Intensive Care Unit, with the features of severe sepsis and septic shock who fulfilled the selection criteria. Purposive sampling technique was applied for collection of the sample. All patients admitted to ICU with the features of severe sepsis and septic shock according to SSC guidelines with the age of more than or equal to 18 years in both sexes were included in this study. Appropriate data were collected by using a preformed data sheet. Other necessary data were collected from history sheet and investigation papers. Prior to this study, written permission was obtained from institutional ethical review committee. This study was performed in a 20-bed mixed ICU in Department of Anaesthesiology, Pain, Palliative Care and Intensive Care, Dhaka Medical College Hospital, Dhaka, Bangladesh. All patients who were admitted to the ICU and fulfill the SIRS criteria during a 12-month period were examined and data was recorded in the preformed structured data sheet. After meeting inclusion criteria and who fulfill the diagnostic criteria for sepsis was evaluated. If it found that clinically the patient was amenable to be included in the study, the objective, procedure, any risk involved and benefit of the study was explained to the patients and/or his or her responsible guardians. Following the detailed information, informed written consent of the patient and/or guardian was obtained. Then detailed history and physical examination were performed. After that arterial and central lines were inserted. Then arterial and central venous blood was collected for analysis. Then blood sample for serum lactate from arterial line was collected and specimen for culture was collected from primary source of infection. Then arterial blood gas analysis (ABG) and venous blood gas analysis (VBG) were done by the ABG machine (ABL 80 FLEX Basic, Brand Radiometer,USA) in the ICU. Serum lactate level was done by Biosen C Line lactate analyzer. Culture was by done using FAN method. Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection i.e. SIRS. Data from each patient was

collected in structured data sheets individually. Finally all data was compiled together and data were presented as mean with SD. All statistical analysis was performed by using the Statistical Package for Social Sciences version 16 for Windows (SPSS Inc., Chicago, Illinois, USA). Prior to the commencement of this study, the research protocol was approved by the Ethical Review Committee of the Dhaka Medical College.

Result

A total number of patients was 69 cases. The mean with SD was 38.72 ±13.43 with the age range of patient 18 to 65 year. Majority of the patients were in the age group of 21 to 40 years which was 39(56.5%) followed by 41 to 60 years, ≤20 years and >60 years which were 21(30.4%) cases, 5(7.3%) cases and 4(5.8%) cases respectively (Table 1).

Table 1: Distribution of patients according to Age Group (n=69)

Age Groups	Frequency	Percent
≤20 Years	5	7.3
21 to 40 Years	39	56.5
41 to 60 Years	21	30.4
>60 Years	4	5.8
Total	**69**	**100.0**
Mean ± SD	38.72 ±13.43	
Range (min-max)	18.00 – 65.00	

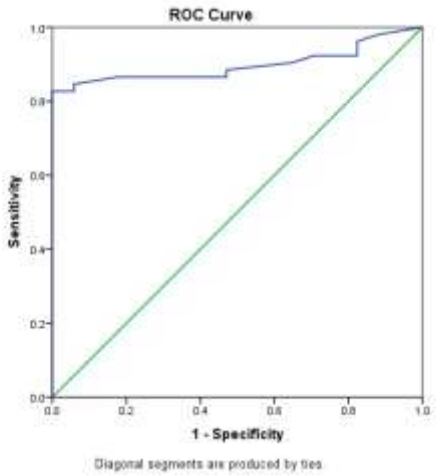

Figure I: Shows ROC curve

ROC curve for the assessment of P(v-a)CO_2/C(a-v)O_2 in diagnosis of anaerobic metabolism in septic patients. Here area under curve was 0.898 (Figure I). Best cut off value of P(v-a)CO_2/C(a-v)O_2 ratio was 1.21 in which sensitivity is 0.84 and specificity was 0.94 (Table 2).

Table 2: Sensitivity and specificity of P(v-a)CO_2/C(a-v)O_2 at different cut off value in diagnosis of anaerobic metabolism in septic patients

P(v-a)CO_2/C(a-v)O_2	Sensitivity	Specificity
0.92	88.5	52.9
0.97	86.5	52.9
1.05	86.5	70.6
1.15	86.5	82.4
1.21	84.6	94.1
1.30	82.7	94.1
1.38	82.7	100.0
1.40	61.5	100.0

The ratio between differences of central venous to arterial CO_2 and arterial to central venous O_2 content [P(v-a)CO_2/C(a-v)O_2] was in 44(84.6%) cases considering ≥1.21 with serum lactate ≥2.0 level. Low level of serum lactate (<2.0) was found in 16(94.1%) cases in <1.21 in P(v-a)CO_2/C(a-v)O_2 (Table 3).

Table 3: P(v-a)CO_2/C(a-v)O_2 in Low and High Level Serum Lactate in Septic Patients (n=69)

P(v-a)CO_2/C(a-v)O_2	Serum Lactate	
	≥2.0	**<2.0**
≥1.21	44(84.6%)	1(5.9%)
<1.21	8(15.4%)	16(94.1%)
Total	**52(100.0%)**	**17(100.0%)**

In this study the test validity of P(v-a)CO_2/C(a-v)O_2 in diagnosis of anaerobic metabolism in septic patients had shown a high sensitivity and specificity which were 84.6% and 94.1% respectively. The Positive predictive value (PPV) and Negative predictive value (NPV) were 97.8% and 66.7% respectively. However, the accuracy was 87.0% (Table 4).

Discussion

The incidence of sepsis and the number of sepsis related death is increasing. Early identification of tissue hypo-perfusion and adequate resuscitation are

key factors in the management of patient with shock. Serum lactate is a marker of tissue hypo-perfusion. Central venous-to arterial CO_2 difference / arterial-to venous O_2 content difference P(v-a)CO_2/C(a-v)O_2 ratio is an another indicator of anaerobic metabolism in septic patients.

Table 4: Validity test of P(v-a)CO_2/C(a-v)O_2 in diagnosis of anaerobic metabolism in septic patients (n=69)

Variable	Value
Sensitivity	84.6%
Specificity	94.1%
Positive predictive value (PPV)	97.8%
Negative predictive value (NPV)	66.7%
Accuracy	87.0%

The sensitivity and specificity of single lactate concentrations as a marker of tissue hypo-perfusion have been established. Though lactate is produced in body in different situations, but elevated serum lactate is widely used as a marker of anaerobic metabolism. But for doing serum lactate, needs special ABG machine, special cartridges or laboratory facilities. It is also expensive. But central venous-arterial CO_2 difference / arterial-venous O_2 difference ratio can be easily done by any simple ABG machine within very short time in the ICU.

Predicting patient outcome is an important component of patient care in the critical care units. It has an importance to the intensivists. Because it allows the planning of early aggressive therapeutic interventions, optimum resource allocation and appropriate counseling of the family as well as the patient is required. The identifications of tissue hypoxia and hypo-perfusion play important roles in the management of critically ill septic patients. Global metabolism measurements that are derived from blood gas analysis are the frequently practical methods for assessing global anaerobic metabolism. The P(v-a)CO_2/C(a-v)O_2 ratio had been shown to reflect anaerobic metabolism (defined by a lactate level $\geq$ 2 mmol/L). The ratio between veno-arterial carbon dioxide difference and arterial to venous oxygen content difference P(v−a)CO_2/C(a−v)O_2 is a hallmark of oxygen deficit caused by septic shock. According to Surviving Sepsis Campaign (SSC), serum lactate is a marker of tissue perfusion variable and serum lactate level is elevated in severe sepsis and septic shock. Though elevated serum lactate is an indicator of anaerobic metabolism but it is not very easy to do always. Several studies[10-13] in severe sepsis and septic shock patient were done abroad regarding P(v-a)CO_2/C(a-v)O_2 ratio for diagnosis and resuscitation of septic patients. For serum lactate test, special ABG machine, special cartridge and laboratory facilities are required. It is also expensive. In a low socio-economic country like Bangladesh, it is very tough to do serum lactate repeatedly. But P(v-a)CO_2/C(a-v)O_2 ratio can be easily done by simple ABG machine in ICU within very short time and also less expensive. The ratio obtained from this study may guide the intensivists in diagnosis and early therapeutic intervention in the management of septic patients admitted in ICU in Bangladesh.

There have been a number of studies to identify the cut off value of ($PvCO_2$-$PaCO_2$)/(CaO_2-CvO_2) ratio for anaerobic metabolism in severe sepsis and septic shock in different journals. This study showed that the combination of veno-arterial PCO_2 difference with arterio-venous oxygen content difference to detect anaerobic metabolism in patient. It was a retrospective study over a 17 month period in medical ICU. Total 89 patients were included and 148 sets of measurements obtained. They tested the value of delta PCO_2 /C(a-v)O_2 ratio in detecting the presence of global anaerobic metabolism as defined by arterial lactate above 2 mmol/L. The delta PCO_2/C(a-v)O_2 ratio was higher in those with increased (n=73) than in the normo lactetemic group. Among all the oxygen and carbon dioxide derived parameter the delta PCO_2/C(a-v)O_2 ratio had highest correlation with the arterial lactate level. The threshold value of 1.4 the delta PCO_2 /C(a-v)O_2 ratio predicted significantly better than other parameters. The overall survival was greater when the delta PCO_2/C(a-v)O_2 ratio was less than 1.4 on the first set of measurement[11].

In another study it has been showed 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. It showed significantly increased Pc(v-a)CO_2/C(a-v)O_2 ratio values (1.9 ± 0.9 in non survivors vs. 1.4 ± 0.45 in survivors (P=0.03). Although the present study is not powered to explore the prognostic value of the Pc(v-a)CO_2 gap and the Pc(v-a)CO_2/ Ca-v)O_2 ratio in terms of organ failure evolution or survival, data suggested a significant association between mortality and the presence of an elevated Pc(v-a)CO_2/C(a-v)O_2 ratio at the end of early goal-directed therapy. Patient who died similar lactate and $ScvO_2$ and Pc(v-a)CO_2 gap at inclusion but showed significantly increased Pc(v-a)CO_2/ C(a-v)O_2 ratio values[13].

In another study combination of arterial lactate levels and venous-arterial CO_2 to arterial-venous O_2 content difference ratio is calculated as markers of resuscitation in patients with septic shock. Persistent hyperlactatemia combined with a high $C(v\text{-}a)CO_2/D(a\text{-}v)O_2$ was associated with the most severe organ dysfunction and worst clinical outcomes, while simultaneous normalization of lactate and $C(v\text{-}a)CO_2/D(a\text{-}v)O_2$ ratio was associated with the best outcomes. $C(v\text{-}a)CO_2/D(a\text{-}v)O_2$ >1.0 reflects anaerobic metabolism and could be associated with more unfavorable clinical outcomes[14].

Conclusion

This study has showed that anaerobic metabolism in septic patients can effectively be diagnosed by the ratio between central venous to arterial CO_2 difference and arterial to central venous O_2 content difference. The $P(v\text{-}a)CO_2/C(a\text{-}v)O_2$ ratio 1.21 can be used for diagnosis anaerobic metabolism in septic patient and is equally effective with serum lactate. A further study can be undertaken using the newer definition of sepsis.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Critical care medicine. 2001;29(7):1303-10

2. Bakker J, Gris P, Coffernils M, Kahn RJ, Vincent JL. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. The American Journal of Surgery. 1996;171(2):221-6

3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. Intensive care medicine. 2013;39(2):165-228

4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive care medicine. 2017;43(3):304-77

5. Campaign SS, Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. International guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med. 2013;41(2):580-637

6. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive care medicine. 2008;34(1):17-60

7. Angus DC, Van der Poll T. Severe sepsis and septic shock. New England Journal of Medicine. 2013;369(9):840-51

8. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Intensive care medicine. 2018;44(6):925-8

9. Nichol AD, Egi M, Pettila V, Bellomo R, French C, Hart G, et al. Relative hyperlactatemia and hospital mortality in critically ill patients: a retrospective multi-centre study. Critical care. 2010;14(1):R25

10. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrailler S, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Annals of intensive care. 2016;6(1):10

11. Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, et al. Combination of venoarterial PCO 2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive care medicine. 2002 Mar 1;28(3):272-7

12. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, et al. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Critical care medicine. 2013 Jun 1;41(6):1412-20

13. Mesquida J, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, Artigas A. 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. Critical care. 2015 Dec;19(1):126

14. Ospina-Tascón GA, Umaña M, Bermúdez W, Bautista-Rincón DF, Hernandez G, Bruhn A, et al. Combination of arterial lactate levels and venous-arterial CO 2 to arterial-venous O 2 content difference ratio as markers of resuscitation in patients with septic shock. Intensive care medicine. 2015;41(5):796-805