doi • 10.5578/tt.20229701
Tuberk Toraks 2022;70(3):221-230
Received: 07.05.2022 • Accepted: 21.06.2022

RESEARCH ARTICLE

Venous-arterial CO_2 to arterial-venous O_2 content ratio in different shock types and correlation with hypoxia indicators

Göksel GÜVEN[1] (ID)
Anke Van STEEKELENBURG[2] (ID)
Şakir AKIN[2] (ID)

[1] Department of Intensive Care, Hacettepe University Faculty of Medicine, Ankara, Türkiye
[2] Department of Intensive Care, Haga Hospital, The Hague, The Netherlands

ABSTRACT

Venous-arterial CO_2 to arterial-venous O_2 content ratio in different shock types and correlation with hypoxia indicators

Introduction: *Shock is a generalized form of acute circulatory failure characterized by low tissue perfusion. If not recognized early, it highly increases patient morbidity and mortality. Central venous-arterial CO_2 (Carbon dioxide) to arterial-central venous O_2 (Oxygen) content ratio (Pcv-aCO_2/Ca-cvO_2) has been used for the early prediction of anaerobic metabolism in septic shock patients. However, knowledge about the usability of this ratio in cardiogenic shock is scarce.*

Materials and Methods: *We retrospectively collected the data of patients admitted to our 18-bed intensive care unit (Haga Hospital, Department of Intensive Care, The Hague, The Netherlands) with a diagnosis of septic shock or cardiogenic shock in 2018. All patients who had undergone Swan-Ganz or Pulse index Continuous Cardiac Output device insertion were included in the study. The hemodynamic variables were recorded both at ICU admission and during catheterization.*

Results: *Forty-six (n= 46) patients with a mean age of 62 ± 13 years and 52% female gender were enrolled in the study. The Acute Physiology and Chronic Health Evaluation IV (APACHE IV) score was 96 ± 39. Twenty-four patients had septic shock, and twenty-two were diagnosed with cardiogenic shock. Although Pcv-aCO_2 (Central venous-arterial CO_2) and ScvO_2 (Central venous oxygen) were not found different between the cardiogenic and septic shock groups, the Pcv-aCO_2/Ca-cvO_2 ratio was significantly lower in patients with cardiogenic shock (p= 0.035). The Pcv-aCO_2/Ca-cvO_2 ratio had a weak correlation with ScvO_2 (r= 0.21, p= 0.040). Pcv-aCO_2 and ScvO_2 showed negative lower moderate correlation (r= -0.40, p= 0.030). Twenty patients [nine (19%) with cardiogenic shock, and eleven (23%) with septic shock] died during their ICU or hospital stay. Although Ca-cvO_2, Pcv-aCO_2, and ScvO_2 were not associated with mortality, a higher Pcv-aCO_2/Ca-cvO_2 ratio was associated with increased mortality (p= 0.035).*

Cite this article as: *Güven G, Steekelenburg AK, Akın Ş. Venous-arterial CO_2 to arterial-venous O_2 content ratio in different shock types and correlation with hypoxia indicators. Tuberk Toraks 2022;70(3):221-230.*

Address for Correspondence

Dr. Göksel GÜVEN
Intensive Care Unit, Hacettepe University Faculty of Medicine
ANKARA-TÜRKİYE
e-mail: drgoksel@hotmail.com

Conclusion: *The Pcv-aCO_2/Ca-cvO_2 ratio is a valuable hypoxia indicator in states of shock. However, cutoff levels should be identified for different shock types.*

Key words: *Septic shock; cardiogenic shock; Pcv-aCO_2/Ca-cvO_2; Pcv-aCO_2; ScvO_2*

ÖZ

Farklı şok tiplerinde Venoz–arteriyel CO_2 farkının arteriyel-venöz O_2 farkına oranı ve diğer hipoksi belirteçleri ile korelasyonu

Giriş: *Şok, doku perfüzyon bozukluğu ile karakterize akut ve sistemik dolaşım yetmezliği tablosudur. Erken fark edilmemesi durumunda hasta morbidite ve mortalitesini belirgin artırır. Septik şok hastaları ile yapılan araştırmalarda, anaerobik metabolizmanın erken öngörülmesi için Pcv-aCO_2/Ca-cvO_2 oranı kullanılmıştır. Ancak bu oranın kardiyojenik şokta kullanılabilirliği ile ilgili bilgiler oldukça azdır.*

Materyal ve Metod: *2018 yılında 18 yataklı yoğun bakım ünitemize (Haga Hastanesi, Yoğun Bakım Ünitesi, The Hague, Hollanda) septik şok veya kardiyojenik şok tanısı ile başvuran hastaların verilerini geriye dönük olarak kaydettik. Swan-Ganz veya Pulse index Contour Cardiac Output (PiCCO) kateteri takılan tüm hastalar çalışmaya dahil edildi. Hemodinamik değişkenler hem yoğun bakıma yatışta hem de kataterizasyon sırasında kaydedildi.*

Bulgular: *Çalışmaya kırk altı (n= 46) hasta dahil edildi ve yaş ortalamaları 62 ± 13 yıl olarak saptandı. %52'si kadın olan hastaların Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi IV (APACHE IV) skoru 96 ± 39 idi. Yirmi dört hastaya septik şok, yirmi iki hastaya kardiyojenik şok teşhisi kondu. Kardiyojenik ve septik şok hastaları arasında Pcv-aCO_2 ve ScvO_2 farklı bulunmamakla birlikte (sırasıyla p= 0,633 ve p= 0,124), kardiyojenik şoklu hastalarda Pcv-aCO_2/Ca-vO_2 oranı anlamlı olarak daha düşüktü (p= 0,035). Tüm popülasyonda Pcv-aCO_2/Ca-cvO_2 oranı, Pcv-aCO_2 ile orta düzeyde (r= 0,60, p< 0,001) ve ScvO_2 ile zayıf (r= 0,21, p= 0,04) korelasyona sahipti. Pcv-aCO_2 ve ScvO_2 negatif ve düşük orta korelasyon gösterdi (r= -0,40, p= 0,03). Yirmi hasta [dokuz (%19) kardiyojenik şok, 11 (%23) septik şok] yoğun bakım veya hastane yatışı sırasında kaybedildi. Pcv-aCO_2 ve ScvO_2 mortalite ile ilişkili saptanmadı; ancak, Pcv-aCO_2/Ca-cvO_2 oranı artışı mortalite ile ilişkili saptandı (p= 0,02).*

Sonuç: *Pcv-aCO_2/Ca-cvO_2 oranı, şok durumlarında değerli bir hipoksi göstergesidir. Ancak, farklı şok tiplerinde farklı referans seviyeleri tanımlanmalıdır.*

Anahtar kelimeler: *Septik şok; kardiyojenik şok; Pcv-aCO_2/Ca-cvO_2; Pcv-aCO_2; ScvO_2*

INTRODUCTION

Shock is a generalized form of acute circulatory failure characterized by low tissue perfusion. As a result, the circulatory system cannot provide sufficient oxygen (O_2) to match the tissue demand, or O_2 cannot be utilized at the mitochondrial level (1). If tissue perfusion is not adequately supplied; consequently, cellular dysfunction arises and progresses to organ failure (2). Delayed recognition and ineffectual resuscitation of shock results in multiorgan failure and increased mortality (3).

Several clinical and laboratory indicators have been used for the early prediction of shock. Normalization of these indicators over time is also used for patient follow-up and guiding the hemodynamic resuscitation (4). In routine practice, alterations in serum lactic acid, central venous-arterial carbon dioxide (Pcv-aCO_2) difference, and central venous oxygen saturation (ScvO_2) indicate tissue hypoxia. Lactic acid is produced as an end product during anaerobic metabolism and indicates tissue hypoperfusion/hypoxia; however, it rises hours after the shock begins (5). ScvO_2 represents the O_2 saturation of the hemoglobin of the central venous blood and is an integrative indicator that reflects the mismatch between global O_2 delivery (DO_2) and consumption (VO_2) according to the Fick equation (6). However, clinical studies reported controversial results on the role of ScvO_2 in shock detection (7). Its essence has been investigated over conventional tissue hypoxia indicators in severely ill with an impaired O_2 diffusion barrier and tissue microcirculation, such as in tissue edema. However, using it as an indicator of tissue oxygenation is controversial (8). Recently, the central venous-arterial carbon dioxide to arterial-central venous O_2 content ratio (Pcv-aCO_2/Ca-cvO_2) was suggested as an early indicator of global tissue hypoxia (9). Furthermore, this ratio was shown to be superior in the early prediction of anaerobic metabolism compared to the indicators above (10-12).

The physiological rationale behind this is that the increase in Pcv-aCO_2/Ca-cvO_2 ratio reflects the higher carbon dioxide (CO_2) production than VO_2. If VO_2 does not meet DO_2 up to a critical point, tissue hypoxia and anaerobic metabolism develop (13). Compared to aerobic metabolism, global carbon dioxide production (VCO_2) increases higher than VO_2 in anaerobic metabolism due to hydrogen ions generated in a hypoxic environment being buffered by bicarbonate (9). Therefore, Pcv-aCO_2/Ca-cvO_2

increases much higher. However, no specific indicator value defines the critical point at which VO_2/DO_2 mismatch occurs and tissue hypoxia begins.

The Pcv-aCO_2/Ca-cvO_2 ratio was found to be a valuable early predictor of anaerobic states in patients with sepsis and septic shock (4,9,11,14). Additionally, this ratio was defined as a predictor of restoring adequate tissue perfusion recovery. Although a limited study assessed the role of the Pcv-aCO_2/Ca-cvO_2 ratio in other shock types, this ratio has never been compared in patients with cardiogenic shock and septic shock (15). The current study aimed to investigate the difference in the Pcv-aCO_2/Ca-cvO_2 ratio between cardiogenic shock and septic shock. We also sought to analyze the correlation of the indicators in different shock types.

MATERIALS and METHODS

We retrospectively collected the data of patients admitted to our 18-bed intensive care unit (XXX) with a diagnosis of septic shock or cardiogenic shock in 2018. The septic shock was defined as a critical state characterized by organ dysfunction secondary to a dysregulated systemic response to infection showing increases in lactate as evidence of end-organ hypoperfusion (16). Cardiogenic shock was defined as a syndrome characterized by an inadequate cardiac output due to primary cardiac dysfunction, which results in life-threatening tissue hypoperfusion and multiorgan failure (17). Patients under the age of 18, those who were moribund, pregnant, or only monitored with a femoral catheter, and those with severe valvular insufficiency were excluded from the study. The Institutional Ethics Committee XXX approved the study with number T18-150 and waived the need to obtain informed consent since the study was retrospective in nature and only clinical data were collected. All patients were followed from ICU admission to exitus or discharge from the hospital.

The demographic data was first recorded once the patient was admitted to the ICU. The laboratory and clinical data, including vital signs [heart rate (HR), mean arterial blood pressure (MAP), central venous pressure (CVP), urine output], blood gas analysis [pH, arterial or central venous CO_2 ($PaCO_2$ or $PcvCO_2$), arterial O_2 saturation (SaO_2), central venous O_2 saturation ($ScvO_2$), arterial O_2 pressure (PaO_2), central venous O_2 pressure ($PcvO_2$), lactate], serum electrolytes and enzymes [sodium, potassium, urea, creatinine, glucose, leukocyte, procalcitonin, C-reactive protein (CRP), troponin, albumin, lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST)], hemoglobin, arterial O_2 content (CaO_2), central venous O_2 content ($CcvO_2$) were recorded in the first 24 hours of ICU stay. The cardiac index (CI) was estimated when one of the invasive hemodynamic monitorization techniques [Pulse index Continuous Cardiac Output device (PiCCO) or Swan-Ganz catheterizations] was inserted. The attending intensivists determined the kind of hemodynamic monitoring technique. Our department has been using the Pcv-aCO_2/Ca-cvO_2 ratio as a marker of systemic anaerobic metabolism, and this ratio has been routinely calculated in addition to Pcv-aCO_2 and $ScvO_2$.

All patients in the study had a central venous catheter inserted via a subclavian or internal jugular vein. Additionally, all patients had an invasive arterial catheter (radial or femoral artery) for continuous arterial pressure monitoring. Pairs of central venous and arterial blood samples were obtained to determine the study parameters, which are PaO_2, SaO_2, $PaCO_2$, $PcvO_2$, $PcvCO_2$, $ScvO_2$, lactate, hemoglobin, and serum electrolytes. Each parameter was used for the calculation of the equations defined below.

$CaO_2 = 0.003*PaO_2 + 1.34*SaO_2*Hb$

$CcvO_2 = 0.003*PcvO_2 + 1.34*ScvO_2*Hb$

Ca-$cvO_2 = CaO_2 - CcvO2$

Pcv-a$CO_2 = PcvCO_2 - PaCO_2$

Pcv-aCO_2/Ca-cv$O_2 = (PcvCO_2 - PaCO_2)/(CaO_2 - CcvO_2)$

$EO_2 = (SaO_2 - ScvO_2)/SaO_2$

Statistical Analysis

The continuous variables were displayed as mean ± standard deviation or median (interquartile range) when the distribution of the variables was normal or skewed, respectively. The Student's t-test and the Mann-Whitney U test were used to compare the groups with continuous variables. In addition, the categorical variables were compared using the Chi-squared test and Fisher's exact test. To test the correlation of the parameters, we used Pearson's or Spearman's correlation analysis depending on the distribution of data. The statistical analysis was performed using R statistical computing, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). A two-sided p-val-

ue <0.05 was considered as a criterion for significance.

RESULTS

Forty-six (n= 46) patients were enrolled in the study. Their mean age was 62 ± 13 years, and 52% were (n= 24) female. On the first day, Acute Physiology and Chronic Health Evaluation IV (APACHE IV) was 96 ± 39 (Table 1). ICU admission of 52% (n= 24) was for medical reasons. On the other hand, 15% (n= 7) required urgent surgery (four for aortic dissection type A, two for perforated bowel, and one for post-pneumonic empyema), and 33% (n= 15) were admitted for elective surgery (open heart operations). The diagram shown in Figure 1 summarizes the flow chart of the study.

Twenty-four patients had septic shock, and twenty-two were diagnosed with cardiogenic shock. APACHE IV score within 24 hours of hospital admission and first-day SOFA score did not show a significant difference between septic and cardiogenic shock patients (p= 0.140 and p= 0.068, respectively). The hemodynamic variables of all patients were recorded within the first hour of ICU admission. MAP, CVP, urine output, and end-tidal CO_2 did not show significant differences between groups. However, heart rate was found significantly higher in patients with septic shock (p< 0.001). Arterial and venous blood gas parameters obtained at ICU admission were not different between groups (pH, PaO_2, $PaCO_2$, $PcvCO_2$, SaO_2, $ScvO_2$, $PcvO_2$). CaO_2 and $CcvO_2$ also did not show a difference between the

Table 1. Disease severity scores, the worst macrohemodynamic variables, and blood gas values within the first 24 hours of ICU admission

Parameter	All population (n= 46)	Cardiogenic shock (n= 22)	Septic shock (n= 24)	p
ICU Scores				
APACHE IV	91.5 (63.7; 131.2)	70.50 (56.75; 114.25)	103.5 (69.3; 136.2)	0.14
SOFA	10 ± 4	9 ± 4	11 ± 3	0.068
Vital Signs				
HR (beat/min)	99 ± 26	83 ± 18	113 ± 24	<0.001
MAP (mmHg)	75 ± 20	74 ± 16	75 ± 23	0.959
CVP (mmHg)	11.5 (8.2; 13)	10 (8;15)	12 (11; 13)	0.658
Urine output (mL/day)	760 (340; 1286)	912 (568; 1234)	578 (193; 1526)	0.575
Arterial and venous blood gas analysis				
pH	7.3 (7.24; 7.36)	7.32 (7.25; 7.35)	7.29 (7.24; 7.36)	0.700
PaO_2 (mmHg)	89.6 (68.6; 124.9)	110 (79; 120)	74.25 (64.88; 128.4)	0.118
$PcvO_2$ (mmHg)	40.9 (35.4; 44.25)	42.4 (39.4; 44.8)	37.5 (34.9; 43.1)	0.399
$PaCO_2$ (mmHg)	42.4 (37.5; 48)	42.8 (39.8; 48.8)	40.9 (31.9; 47.4)	0.333
$PcvCO_2$ (mmHg)	49.9 (43.5; 58.5)	50.3 (44.3; 58.5)	46.9 (39.9; 55.3)	0.459
$ScvO_2$ (%)	68.3 ± 12.6	69 ± 8.4	70.7 ± 10.1	0.568
SaO_2 (%)	96.0 (92.25; 98.0)	98.0 (94.25; 98.75)	94 (90.5; 98)	0.138
Lactate (mmol/L)	2.05 (1.12; 5.2)	1.65 (1.1; 4.8)	3.6 (1.6; 5.8)	0.194
Arterial and venous oxygen content				
CaO_2 (mL/L)	14.3 (12.6; 16.6)	14.6 (13.6; 16.2)	14.0 (11.4; 17.4)	0.534
$CcvO_2$ (mL/L)	10.4 (8.9; 11.9)	10.5 (9.2; 11.8)	10.6 (8.3; 13.9)	0.919

Continuous variables are presented as mean ± standard deviation or median (IQRs). The statistical differences between the septic and cardiogenic shock were calculated using the non-parametric Mann-Whitney U test and the Student's t-test (for continuous variables). Values in bold are statistically significant at the 5% significance level (p< 0.05). The significant p values are shown in bold.
ICU: Intensive care unit, APACHE: Acute physiology and chronic health evaluation, SOFA: Sequential organ failure assessment, SAPS II: Simplified acute physiology score II, HR: Heart rate, MAP: Mean arterial blood pressure, CVP: Central venous pressure, PaO_2: Partial arterial oxygen pressure, $PcvO_2$: Partial central venous oxygen pressure, $PaCO_2$: Partial arterial carbon dioxide pressure, $PcvCO_2$: Partial central venous carbon dioxide pressure, $ScvO_2$: Arterial oxygen saturation, SaO_2: Arterial oxygen saturation, CaO_2: Arterial oxygen content, $CcvO_2$: Central venous oxygen content.

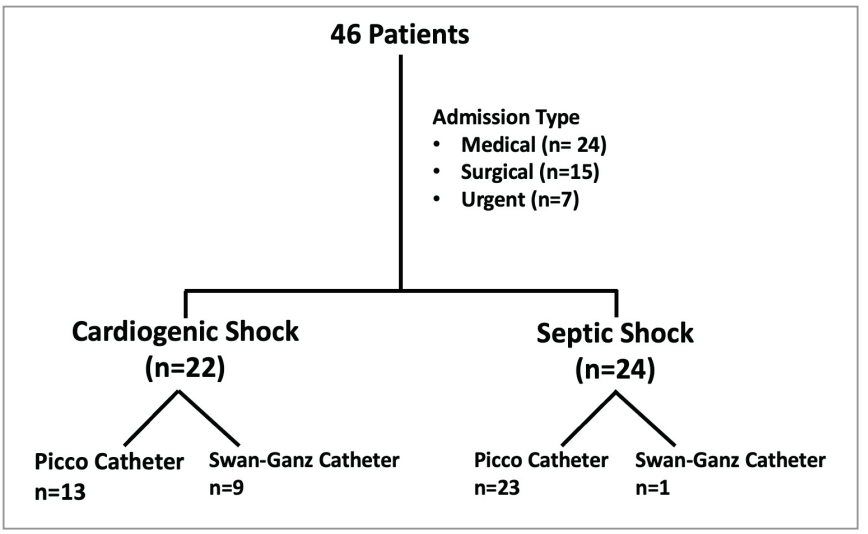

Figure 1. Flow diagram of the study.

two groups. Since the patients did not have PiCCO or Swan-Ganz catheterizations at ICU admission, DO_2 and VO_2 could not be calculated.

The laboratory parameters were recorded for all patients at admission (Table 2). Hb, sodium, potassium, urea, creatinine, LDH, and AST were not different between the groups. Procalcitonin showed a trend toward significance but was not found significantly different between groups (p= 0.078). Serum glucose (p= 0.008), leukocyte (p= 0.001) and troponin (p= 0.003) levels were higher in patients with cardiogenic shock. On the other hand, CRP (p= 0.047) and ALT (p= 0.017) were higher in patients with septic shock.

Table 2. Laboratory parameters on ICU admission

Parameter	All population (n= 46)	Cardiogenic shock (n= 22)	Septic shock (n= 24)	p
Hemoglobin (mg/dL)	11.3 ± 2.9	11.3 ± 1.7	11.3 ± 3.8	0.999
Sodium (mEq/L)	137 (133; 140)	138 (136; 140)	136 (131; 139)	0.067
Potassium (mEq/L)	4.5 ± 0.8	4.7 ± 0.6	4.4 ± 1.1	0.345
Urea (mmol/L)	8.8 (6.3; 13.8)	8.2 (6.4; 12.2)	10.2 (6.1; 17.7)	0.367
Creatinine (micromoles/L)	106 (76; 148)	92 (76; 120)	130 (77; 192)	0.099
Glucose (mmol/L)	151 (114; 204)	169 (144; 225)	123 (97; 160)	**0.008**
Leukocyte (10^9/L)	13.2 (9.5; 16.9)	15.3 (13.5; 21.8)	11.5 (5.4; 13.1)	**0.001**
Procalcitonin (ng/mL)	0.9 (0.14; 4.6)	0.4 (0.16; 1.0)	3.1 (0.08; 13.8)	0.078
CRP (mg/L)	55 (27.5; 176.2)	43 (24.3; 116.5)	111.5 (27.5; 216)	**0.047**
Troponin (ng/mL)	0.56 (0.12; 1.46)	0.73 (0.24; 1.68)	0.12 (0.04; 0.19)	**0.003**
Albumin (g/dL)	2.7 ± 0.7	2.6 ± 0.6	2.7 ± 0.8	0.801
LDH (U/L)	296 (200; 556)	334 (210; 616)	288 (191; 509)	0.693
AST (U/L)	67.5 (42; 174)	84 (43; 193)	56 (40; 164)	0.696
ALT (U/L)	32 (21; 55)	26 (17; 44)	40 (30; 57)	**0.017**

Continuous variables are presented as mean ± standard deviation or median (IQR). The statistical differences between the septic and cardiogenic shock were calculated using the non-parametric Mann-Whitney U test and the Student's T-test (for continuous variables). Values in bold are statistically significant at the 5% significance level (p< 0.05). The significant p values are shown in bold.
CRP: C-Reactive protein, LDH: Lactate dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

Table 3. Hemodynamic variables of patients during catheterization

Parameter	All Population (n= 46)	Cardiogenic Shock (n= 22)	Septic Shock (n= 24)	p
CI (L/min/m^2)	3.0 (2.3; 3.4)	2.9 (2.1; 3.2)	3.1 (2.4; 4.3)	0.285
DO_2 (mL/min)	38.8 (30.9; 48.7)	37.5 (30.9; 47.0)	42.7 (31.6; 52.6)	0.465
VO_2 (mL/min)	10.8 (7.4; 14.6)	12.0 (10; 15.3)	9.5 (7.3; 13)	0.164
O_2ER (%)	28.4 (19.3; 35.1)	31.3 (28.2; 36.1)	23.0 (17.8; 30.2)	**0.026**
HR (beat/min)	91 (80; 109)	85 (78; 94)	104 (85; 118)	**0.013**
MAP (mmHg)	67 (62; 77)	70 (62; 78)	65 (62; 73)	0.420
CVP (mmHg)	12 (10;15)	11 (8; 17)	12.5 (11; 14)	0.821
PaO_2 (mmHg)	78 (69; 94)	79 (74; 100)	77.2 (65.8; 87.9)	0.312
$ScvO_2$ (%)	67 (62; 76)	66 (61; 70.5)	72 (64; 78)	0.124
$CcvO_2$ (mL/L)	9.1 (7.4; 11.8)	8.8 (7.3; 11.0)	9.4 (7.7; 12.9)	0.492
$PaCO_2$ (mmHg)	39.8 (35.3; 53.3)	38.3 (35.3; 44.3)	43.5 (36; 56.3)	0.306
Pcv-aCO_2 (mmHg)	6.0 (4.5; 7.5)	6.4 (4.5; 7.5)	5.6 (4.5; 7.7)	0.633
$PcvO_2$ (mmHg)	38.2 (34.5; 45)	36.4 (33.8; 40.3)	41.6 (36.4; 48.9)	**0.035**
Ca-cvO_2 (mL/L)	3.7 (2.9; 4.6)	4.0 (3.6; 5.1)	3.1 (2.7; 4.0)	**0.010**
Pcv-aCO_2/Ca-cvO_2	1.56 (1.28; 1.93)	1.32 (1.21; 1.75)	1.72 (1.45; 2.2)	**0.022**

Continuous variables are presented as mean ± standard deviation or median (IQR). The statistical differences between the septic and cardiogenic shock were calculated using the non-parametric Mann-Whitney U test and the Student's t-test (for continuous variables). Values in bold are statistically significant at the 5% significance level (p< 0.05). The significant p values are shown in bold.
CI: Cardiac index, DO_2: Oxygen delivery, VO_2: Oxygen consumption, O_2ER, Oxygen extraction rate, HR: Heart rate, MAP: Mean arterial pressure, CVP: Central venous pressure, SaO_2: Arterial oxygen saturation, PaO_2: Arterial partial oxygen pressure, $ScvO_2$: Central venous oxygen saturation, $CcvO_2$: Central venous oxygen content, $PaCO_2$: Arterial partial carbon dioxide pressure, Pcv-aCO_2: Central venous and arterial carbon dioxide difference, $PcvO_2$: Partial central venous oxygen pressure, Ca-cvO_2: Arterial and central venous oxygen content difference.

During their stay in ICU, 36 patients had PiCCO catheterization, and the other 13 had Swan-Ganz catheterization. These catheters enabled continuous measurement of CI, DO_2, and VO_2. The groups were not found significantly different for CI (0.285), DO_2 (0.465), and VO_2 (0.164). However, the oxygen extraction ratio (EO_2) was significantly higher in cardiogenic shock patients (p= 0.026). Moreover, other invasive macrohemodynamic parameters including MAP, CVP, SaO_2, PaO_2, $ScvO_2$ $CcvO_2$, $PaCO_2$, and Pcv-aCO_2 were not significantly different between the groups. Conversely, $PcvO_2$ was significantly higher in patients with septic shock (p= 0.035), and Ca-cvO_2 was higher in patients with cardiogenic shock (p= 0.01). The Pcv-aCO_2/Ca-cvO_2 ratio was significantly higher in patients with septic shock (p= 0.02) (Table 3).

The correlation of the Pcv-aCO_2/Ca-cvO_2 ratio, Pcv-aCO_2, and $ScvO_2$ was shown in Figure 2. In the entire population, Pcv-aCO_2/Ca-cvO_2 ratio had a moderate correlation with Pcv-aCO_2 (r= 0.60, p< 0.001) and a weak correlation with $ScvO_2$ (r= 0.21, p= 0.040). Pcv-aCO_2 and $ScvO_2$ showed negative lower moderate correlation (r= -0.40, p= 0.030). The correlation between Pcv-aCO_2/Ca-cvO_2 ratio and Pcv-aCO_2 was high in patients with cardiogenic shock (r= 0.80, p< 0.001). However, there was no correlation between Pcv-aCO_2/Ca-cvO_2 ratio and $ScvO_2$ in the same group (r= 0.08, p= 0.600). Pcv-aCO_2 and $ScvO_2$ also did not show a correlation (r= -0.37, p= 0.490). In septic patients, Pcv-aCO_2/Ca-cvO_2 ratio was found to have moderate correlation with Pcv-aCO_2 (r= 0.44, p= 0.040) and showed moderate but not significant correlation with $ScvO_2$ (r= 0.27, p= 0.100). Pcv-aCO_2 and $ScvO_2$ showed moderate but negative correlation (r= -0.46, p= 0.030).

Twenty patients [nine (19%) with cardiogenic shock, and eleven (23%) with septic shock] died during their ICU or hospital stay. The mortality was significantly increased with high Pcv-aCO_2/Ca-cvO_2 ratio (CI= 0.04-1.15, p= 0.035). Although there was a trend toward significant difference at Pcv-aCO_2, it was not found significantly different between survival

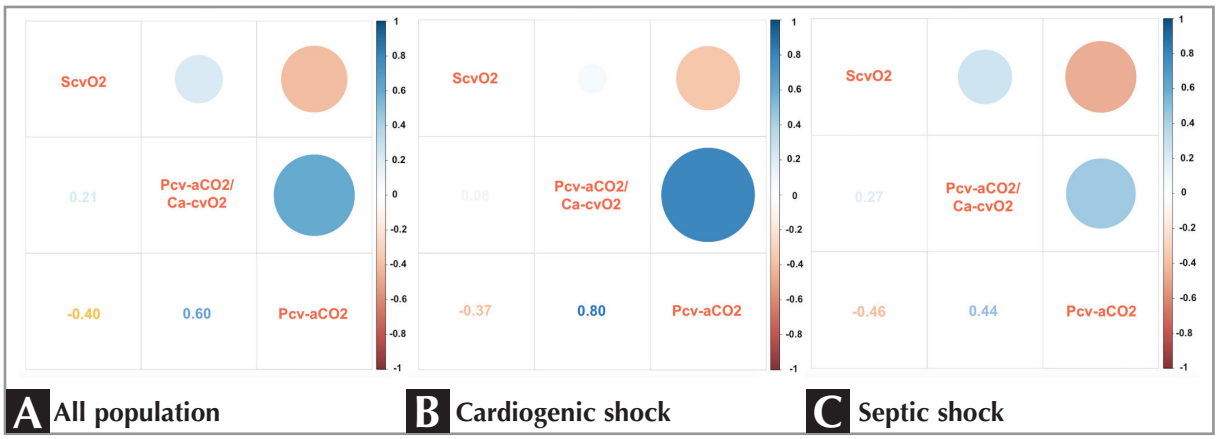

Figure 2. Correlation of hypoxia indicators.
The correlation of $ScvO_2$, Pcv-aCO_2/Ca-cvO_2, and Pcv-aCO_2 is shown in the figure. The size of each circle is linked with the correlation coefficient between two parameters. Blue and red colors show positive and negative correlations, respectively. The other colors correspond to the coefficients at the scale bar shown on the right side of each figure. The numbers on the left side of each figure correspond to the correlation coefficient between the two parameters.
$ScvO_2$: Central venous oxygen saturation, Pcv-aCO_2: Central venous and arterial carbon dioxide difference, Ca-cvO_2: Arterial and central venous oxygen content difference.

and nonsurvival [CI= (-8.4)-(0.1), p= 0.055]. Ca-cvO_2 [CI= (-0.94)-(0.95), p= 0.989] and $ScvO_2$ [CI= (-5)-(8.7), p= 0.582] were not significantly different between survival and nonsurvival. The mortality was significantly higher in older, but there was no statistical difference in gender in our population. These patients also had higher SOFA and APACHE IV scores. Lower pH values were seen with higher lactate (p< 0.001), Pcv-aCO_2 (p= 0.09), Pcv-aCO_2/Ca-cvO_2 (p= 0.02).

DISCUSSION

To the best of our knowledge, the current study is the first to assess the difference in Pcv-aCO_2/Ca-cvO_2 ratio between cardiogenic shock and septic shock patients. We found that patients with septic shock have a higher Pcv-aCO_2/Ca-cvO_2 ratio despite having similar Pcv-aCO_2 and $ScvO_2$ levels. These hypoxia indicators are routinely used during ICU follow-up, and not all are correlated with each other.

The predictive value of the Pcv-aCO_2/Ca-cvO_2 ratio on septic shock and comparison with other hypoxia indicators have been widely searched in the last decade (7,18,19). Either alone or in combination, the Pcv-aCO_2/Ca-cvO_2 ratio reflects anaerobic metabolism in septic shock. Consequently, it has become a suggested marker for patient follow-up and estimating the success of the resuscitation (7,20,21). However, it should be noted that this ratio consists of two parts: Numerator and denominator. The denominator part is the difference between arterial and central venous oxygen content, which is expected to be low in septic states due to the presence of cytopathic hypoxia in tissue cells and shunting in the microvascular field (22). Therefore, the Pcv-aCO_2/Ca-cvO_2 ratio would increase in septic conditions. The current study's finding is compatible with the previous studies, and the Pcv-aCO_2/Ca-cvO_2 was found higher than cardiogenic shock.

The numerator of the Pcv-aCO_2/Ca-cvO_2 ratio is correlated with cardiac contractility. The diffusion capacity of CO_2 is prominently higher than oxygen, and the Pcv-aCO_2 increases due to the stagnation of the circulatory system (23). In theory, in cardiogenic shock, the Pcv-aCO_2/Ca-cvO_2 ratio is expected to be higher than in septic shock depending on the higher Pcv-aCO_2 level. However, the Ca-cvO_2 ratio is also higher in cardiogenic shock than in septic shock due to sustaining low systemic oxygen. Taken together, the balance between the increase in the percentage of both Pcv-aCO_2 and Ca-cvO_2 designates the ratio in cardiogenic shock. In the current study, Pcv-aCO_2 was higher in cardiogenic shock than in septic shock; however, it did not reach a statistically significant level. Conversely, Ca-cvO_2 was significantly higher in patients with cardiogenic shock and even had a higher impact on discrimination of different shocks. Therefore, the Pcv-aCO_2/Ca-cvO_2 ratio was found lower in these patients. Unfortunately, we did not have the SOFA score during the catheterization peri-

od; however, similar APACHE IV and SOFA scores at ICU admission, as well as a similar in-hospital mortality rate, can help predict similar disease severity between the two shock groups. Even if all shock types are characterized by tissue hypoxia, the Pcv-aCO_2/Ca-cvO_2 ratio may have a different cutoff level to best reflect anaerobic metabolism.

A decreased myocardial contractility characterizes the cardiogenic shock by definition (24). As a result, decreased tissue blood flow plays a major role in widening Pcv-aCO_2 (25,26). A cut-off value for Pcv-aCO_2 has already been defined, and >6 mmHg is associated with low cardiac contractility (7,26). In the current study, Pcv-aCO_2 was found a bit higher than the cut-off value. However, it was not significantly different between cardiogenic shock and septic shock. The CI was also similar in patients with septic and cardiogenic shock, which contradicts basic pathophysiological principles. The current study's inconsistent results are not surprising, given that the measurements were taken after shock resuscitation rather than at the time of shock diagnosis. In parallel with this perspective, several studies reported controversial results for using Pcv-aCO_2 as a predictive or follow-up marker in shock patients (14,27-29). This is because of the lack of power as a single marker for detecting tissue hypoxia, as reported in previous research. If combined with other hypoxia indicators, Pcv-aCO_2 can be used in some instances. The time interval for Pcv-aCO_2 measurements, such as resuscitation, optimization, stabilization, and de-escalation phases, gains importance. For example, Ospina-Tascon et al. showed that persistently high Pcv-aCO_2 is associated with low survival rates measured during shock resuscitation (30). Similarly, Guo et al. reported that CI and Pcv-aCO_2 are negatively correlated, and Pcv-aCO_2 is beneficial for estimating cardiac output during shock resuscitation (31).

$ScvO_2$ was also not found significantly different between cardiogenic and septic shock patients in the current study. This finding is not consistent with general knowledge. Higher $ScvO_2$ values frequently accompany septic shock due to the capillary shunting and inability of the mitochondria to utilize oxygen (22,32). Conversely, cardiogenic shock is characterized by lower $ScvO_2$ values (9). However, in the current study, $ScvO_2$ was measured following the resuscitation stage. The value of the use of $ScvO_2$ varies depending on the period of the evaluation. Indeed, increased $ScvO_2$ values during resuscitation have been correlated with high mortality in septic shock patients (33,34). Moreover, not all levels of $ScvO_2$ display the same power for detecting hypoxia in septic shock. Mallat et al. showed that $ScvO_2$ is not a good marker for predicting global tissue hypoxia under $ScvO_2$ 80% in septic shock patients. Besides, they reported that Pcv-aCO_2/Ca-cvO_2 ratio is a more reliable marker of global anaerobic metabolism than serum lactate (12). Mesquida et al. searched the impact of hypoxia indicators in septic shock patients with normalized MAP and $ScvO_2$. They found that Pcv-aCO_2/Ca-cvO_2 ratio predicts the lactate clearance in the following hours of shock resuscitation (14).

The correlation of the Pcv-aCO_2/Ca-cvO_2 ratio, Pcv-aCO_2, and $ScvO_2$ was consistent with previous studies (28,35,36). The Pcv-aCO_2/Ca-cvO_2 ratio was highly correlated with Pcv-aCO_2 in the whole shock population, which is much higher in the cardiogenic shock subgroup. Conversely, there was a weak correlation with $ScvO_2$. This finding might suggest that $ScvO_2$ could be used if the Pcv-aCO_2/Ca-cvO_2 ratio could not be calculated. Likewise, the Pcv-aCO_2/Ca-cvO_2 ratio was correlated with hospital mortality. Hence, this can conclude that the Pcv-aCO_2/Ca-cvO_2 ratio is of added value.

Limitations

The current study has several limitations. First and foremost, this is a single-center study and conducted with a low population. In addition, the patients' blood samples were not obtained intermittently so we cannot show the trend in changes. Furthermore, some patients had PiCCO catheterization while others had Swan-Ganz catheterization. In other words, central venous blood samples were obtained as mixed venous blood inside the right atrium in some and as the sample from the junction of the right heart and superior vena cava in others.

The quantitative CI measurement was recorded just after PiCCO and PAC insertion in the current study. However, considering that these patients were already resuscitated with fluid and vasoactive treatment, CI was not found to be different between septic and cardiogenic shocks, although it was expected to be different if measured at hospital admission. Finally, central venous oxygen saturation was reported as $ScvO_2$ even if the blood sample was obtained directly from the right atrium via PAC. This assumption might have an impact on the results because $ScvO_2$ and SvO_2 are not equal in a patient.

The Pcv-aCO_2/Ca-cvO_2 ratio has distinct cut-off levels between septic and cardiogenic shocks. To determine the anaerobic metabolism in different pathophysiologic states, further randomized controlled trials with a large population are warranted to define the cutoff values for each shock type.

Acknowledgments

The current research was performed using the dataset of Anke Van STEEkELENBURG's thesis.

Ethical Committee Approval: The manuscript was approved by Southwest Holland Medical Ethics Review Committee (Decision no: 18-118, Date: 21.11.2018).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GG, AVS, SA

Analysis/Interpretation: GG, AVS, SA

Data acqusition: GG, AVS, SA

Writing: GG, AVS, SA

Clinical Revision: GG, AVS, SA

Final Approval: GG, AVS, SA

REFERENCES

1. *Cecconi M, De Backer D, Antonelli M, Beale R, Bakker J, Hofer C, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. Intensive Care Med 2014; 40(12): 1795-815. https://doi.org/10.1007/s00134-014-3525-z*
2. *Vincent JL, De Backer D. Circulatory shock. N Engl J Med 2013; 369(18): 1726-34. https://doi.org/10.1056/NEJMra1208943*
3. *Rivers EP, Kruse JA, Jacobsen G, Shah K, Loomba M, Otero R, et al. The influence of early hemodynamic optimization on biomarker patterns of severe sepsis and septic shock. Crit Care Med 2007; 35(9): 2016-24. https://doi.org/10.1097/01.CCM.0000281637.08984.6E*
4. *Pavez N, Kattan E, Vera M, Ferri G, Valenzuela ED, Alegría L, et al. Hypoxia-related parameters during septic shock resuscitation: Pathophysiological determinants and potential clinical implications. Ann Transl Med 2020; 8(12): 784. https://doi.org/10.21037/atm-20-2048*
5. *Revelly JP, Tappy L, Martinez A, Bollmann M, Cayeux MC, Berger MM, et al. Lactate and glucose metabolism in severe sepsis and cardiogenic shock. Crit Care Med 2005; 33(10): 2235-40. https://doi.org/10.1097/01.CCM.0000181525.99295.8F*
6. *van Beest P, Wietasch G, Scheeren T, Spronk P, Kuiper M. Clinical review: Use of venous oxygen saturations as a goal - a yet unfinished puzzle. Crit Care 2011; 15(5): 232. https://doi.org/10.1186/cc10351*
7. *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. Crit Care Med 2013; 41(6): 1412-20. https://doi.org/10.1097/CCM.0b013e318275cece*
8. *Scheeren TWL, Wicke JN, Teboul JL. Understanding the carbon dioxide gaps: Curr Opin Crit Care 2018; 24(3): 181-9. https://doi.org/10.1097/MCC.0000000000000493*
9. *Mekontso-Dessap A, Castelain V, Anguel N, Bahloul M, Schauvliege F, Richard C, et al. Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 2002; 28(3): 272-7. https://doi.org/10.1007/s00134-002-1215-8*
10. *Shaban M, Salahuddin N, Kolko MR, Sharshir M, AbuRageila M, AlHussain A. The predictive ability of PV-ACO2 gap and PV-ACO2/CA-VO2 ratio in shock: A prospective, cohort study. Shock 2017; 47(4): 395-401. https://doi.org/10.1097/SHK.0000000000000765*
11. *Wang M, Liu T, Niu Z, Zuo J, Qi D. Utility of venous-to-arterial carbon dioxide changes to arteriovenous oxygen content ratios in the prognosis of severe sepsis and septic shock: A systematic review and meta-analysis. Hong Kong J Emerg Med 2021; 28(4): 241-53. https://doi.org/10.1177/1024907921994970*
12. *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. Ann Intensive Care 2016; 6(1): 10. https://doi.org/10.1186/s13613-016-0110-3*
13. *Jakob SM, Groeneveld ABJ, Teboul JL. Venous-arterial CO2 to arterial-venous O2 difference ratio as a resuscitation target in shock states? Intensive Care Med 2015; 41(5): 936-8. https://doi.org/10.1007/s00134-015-3778-1*
14. *Mesquida J, Saludes P, Gruartmoner G, Espinal C, Torrents E, Baigorri F, 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. https://doi.org/10.1186/s13054-015-0858-0*
15. *Dubin A, Pozo MO, Hurtado J. Central venous minus arterial carbon dioxide pressure to arterial minus central venous oxygen content ratio as an indicator of tissue oxygenation: A narrative review. Rev Bras Ter Intensiva. 2020; 32(1): 115-22. https://doi.org/10.5935/0103-507X.20200017*
16. *Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016; 315(8): 801. https://doi.org/10.1001/jama.2016.0287*

17. *van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, et al. Contemporary management of cardiogenic shock: A scientific statement from the American Heart Association. Circulation 2017; 136(16): e232-e268. https://doi.org/10.1161/CIR.0000000000000525*

18. *Abou-Arab O, Braik R, Huette P, Bouhemad B, Lorne E, Guinot PG. The ratios of central venous to arterial carbon dioxide content and tension to arteriovenous oxygen content are not associated with overall anaerobic metabolism in postoperative cardiac surgery patients. Bachschmid MM, editor. PLoS One 2018; 13(10): e0205950. https://doi.org/10.1371/journal.pone.0205950*

19. *Mukai A, Suehiro K, Kimura A, Funai Y, Matsuura T, Tanaka K, et al. Comparison of the venous-arterial CO2 to arterial-venous O2 content difference ratio with the venous-arterial CO2 gradient for the predictability of adverse outcomes after cardiac surgery. J Clin Monit Comput 2020; 34(1): 41-53. https://doi.org/10.1007/s10877-019-00286-z*

20. *Ospina-Tascón GA, Madriñán HJ. Combination of O2 and CO2-derived variables to detect tissue hypoxia in the critically ill patient. J Thorac Dis 2019; 11(S11): S1544-50. https://doi.org/10.21037/jtd.2019.03.52*

21. *Zang H, Shen X, Wang S, He Z, Cheng H. Evaluation and prognostic value of CvaCO2/DavO2 in patients with septic shock receiving fluid resuscitation CvaCO2/CavO2. Exp Ther Med 2019; 18(5): 3631-5. https://doi.org/10.3892/etm.2019.7956*

22. *Ince C. The microcirculation is the motor of sepsis. Crit Care 2005; 9(Suppl 4): S13. https://doi.org/10.1186/cc3753*

23. *Mallat J. 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. https://doi.org/10.5492/wjccm.v5.i1.47*

24. *McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021; 42(36): 3599-726. https://doi.org/10.1093/eurheartj/ehab368*

25. *Vallet B, Teboul JL, Cain S, Curtis S. Venoarterial CO 2 difference during regional ischemic or hypoxic hypoxia. J Appl Physiol 2000; 89(4):1317-21. https://doi.org/10.1152/jappl.2000.89.4.1317*

26. *Gutierrez G. A mathematical model of tissue-blood carbon dioxide exchange during hypoxia. Am J Respir Crit Care Med 2004; 169(4): 525-33. https://doi.org/10.1164/rccm.200305-702OC*

27. *Mallat J, Pepy F, Lemyze M, Gasan G, Vangrunderbeeck N, Tronchon L, 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): 371-80. https://doi.org/10.1097/EJA.0000000000000064*

28. *Bouchacourt JP, Hurtado FJ, Kohn E, Illescas L, Dubin A, Riva JA. Role of Pv-aCO2 gradient and Pv-aCO2/Ca-vO2 ratio during cardiac surgery: A retrospective observational study. Braz J Anesthesiol Engl Ed 2021; S0104001421003146. https://doi.org/10.1016/j.bjane.2021.07.025*

29. *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: 223-9. https://doi.org/10.1016/j.jcrc.2016.08.002*

30. *Ospina-Tascón GA, Bautista-Rincón DF, Umaña M, Tafur JD, Gutiérrez A, García AF, 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. https://doi.org/10.1186/cc13160*

31. *Guo Z, Yin M, Kong J, Wang B, Dai K, Zuo T, et al. Relationship analysis of central venous-to-arterial carbon dioxide difference and cardiac index for septic shock. Sci Rep 2019; 9(1): 8822. https://doi.org/10.1038/s41598-019-45252-6*

32. *Ince C, Mik EG. Microcirculatory and mitochondrial hypoxia in sepsis, shock, and resuscitation. J Appl Physiol 2016; 120(2): 226-35. https://doi.org/10.1152/japplphysiol.00298.2015*

33. *Textoris J, Fouché L, Wiramus S, Antonini F, Tho S, Martin C, et al. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care 2011; 15(4): R176. https://doi.org/10.1186/cc10325*

34. *Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO2) as a predictor of mortality in patients with sepsis. Ann Emerg Med 2010; 55(1): 40-46.e1. https://doi.org/10.1016/j.annemergmed.2009.08.014*

35. *He H, Long Y, Liu D, Tang B, Ince C. Relationship of relevant factors to P(v-a)CO 2 /C(a-v)O 2 ratio in critically ill patients. J Int Med Res 2020; 48(1): 030006051985463. https://doi.org/10.1177/0300060519854633*

36. *Dubin A, Pozo MO, Kanoore Edul VS, Risso Vazquez A, Enrico C. Poor agreement in the calculation of venoarterial PCO2 to arteriovenous O2 content difference ratio using central and mixed venous blood samples in septic patients. J Crit Care 2018; 48: 445-50. https://doi.org/10.1016/j.jcrc.2018.07.010*