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Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock

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Abstract

Introduction: Venous-to-arterial carbon dioxide difference (Pv-aCO₂) may reflect the adequacy of blood flow during shock states. We sought to test whether the development of Pv-aCO₂ during the very early phases of resuscitation is related to multi-organ dysfunction and outcomes in a population of septic shock patients resuscitated targeting the usual oxygen-derived and hemodynamic parameters.

Methods: We conducted a prospective observational study in a 60-bed mixed ICU in a University affiliated Hospital. 85 patients with a new septic shock episode were included. A Pv-aCO₂ value ≥ 6 mmHg was considered to be high. Patients were classified in four predefined groups according to the Pv-aCO₂ evolution during the first 6 hours of resuscitation: (1) persistently high Pv-aCO₂ (high at T0 and T6); (2) increasing Pv-aCO₂ (normal at T0, high at T6); (3) decreasing Pv-aCO₂ (high at T0, normal at T6); and (4) persistently normal Pv-aCO₂ (normal at T0 and T6). Multiorgan dysfunction at day-3 was compared for predefined groups and a Kaplan Meier curve was constructed to show the survival probabilities at day-28 using a log-rank test to evaluate differences between groups. A Spearman-Rho was used to test the agreement between cardiac output and Pv-aCO₂. Finally, we calculated the mortality risk ratios at day-28 among patients attaining normal oxygen parameters but with a concomitantly increased Pv-aCO₂.

Results: Patients with persistently high and increasing Pv-aCO₂ at T6 had significant higher SOFA scores at day-3 ($p < 0.001$) and higher mortality rates at day-28 (log rank test: 19.21, $p < 0.001$) compared with patients who evolved with normal Pv-aCO₂ at T6. Interestingly, a poor agreement between cardiac output and Pv-aCO₂ was observed ($r^2 = 0.025$, $p < 0.01$) at different points of resuscitation. Patients who reached a central venous saturation (ScvO₂) $\geq 70\%$ or mixed venous oxygen saturation (SvO₂) $\geq 65\%$ but with concomitantly high Pv-aCO₂ at different developmental points (i.e., T0, T6 and T12) had a significant mortality risk ratio at day-28.

Conclusion: The persistence of high Pv-aCO₂ during the early resuscitation of septic shock was associated with more severe multi-organ dysfunction and worse outcomes at day-28. Although mechanisms conducting to increase Pv-aCO₂ during septic shock are insufficiently understood, Pv-aCO₂ could identify a high risk of death in apparently resuscitated patients.

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Introduction

Inadequate tissue perfusion is a pivotal factor in the pathogenesis and clinical course of multiorgan failure in the critically ill [1]. Current techniques for monitoring tissue perfusion have largely focused on systemic blood flow and the balance between oxygen demand and supply [2,3]. An early hemodynamic optimization that targets central venous oxygen saturation (ScvO₂) and systemic hemodynamic parameters improves outcomes in severe sepsis and septic shock [4], reinforcing the idea that tissue perfusion abnormalities are flow dependent at least during the very early stages. However, normalizing systemic hemodynamic parameters does not guarantee adequate tissue perfusion [5-7], and in fact a substantial number of patients still progress to multiorgan dysfunction and death despite meeting ScvO₂ targets [4].

In the past, authors described the coexistence of venous acidemia and increased venous carbon dioxide (CO₂) during cardiac arrest in both animals [8] and critically ill humans [9]. Thereafter, increases in the venous-to-arterial carbon dioxide difference (Pv-aCO₂) were reported during hypovolemic, cardiogenic, obstructive, and septic shock [10-12]. Interestingly, an inverse curvilinear relationship between Pv-aCO₂ and cardiac output was described, highlighting the importance of blood flow on venous CO₂ accumulation [13,14]. Pv-aCO₂ thus aroused clinical interest as a marker of global perfusion during shock states, although some studies questioned its prognostic value [14]. In fact, some *in vivo* models evaluating the mechanisms conducting to venous CO₂ accumulation during non-inflammatory conditions [15-17] challenged the ability of Pv-aCO₂ to identify tissue dysoxia because it only rises during ischemic hypoxia, but not during hypoxic or anemic hypoxia for comparable declines in oxygen delivery and oxygen consumption. However, more recent data suggest that high Pv-aCO₂ could identify septic patients who remain inadequately resuscitated despite achieving oxygen metabolism targets, reinforcing the notion of Pv-aCO₂ as a marker of global perfusion due to its ability to track blood flow alterations [18] or even detect anaerobic CO₂ generation [19]. Furthermore, patterns of recovery or derangement of Pv-aCO₂ during very early stages of resuscitation of septic shock have not been widely described and recent studies trying to demonstrate the reliability of Pv-aCO₂ as a tool in resuscitation of septic patients could have been influenced by selection bias because not all potential patients were elected to catheter insertion and goal-directed therapy [20,21].

Recent publications in critical care demonstrate that oxygen-derived parameters such as ScvO₂ or mixed venous oxygen saturation (SvO₂) are commonly normalized at ICU admission [22] and maneuvers such as emergent intubation can quickly improve ScvO₂ despite regional and tissue perfusion derangements [23]. Because global

and regional hypoperfusion have been incriminated in the development of multiple organ failure, investigation on surrogate markers of such phenomenon remains important in critical care. Given that Pv-aCO₂ can track the adequacy of systemic perfusion during shock states, we sought to test whether the time course of Pv-aCO₂ during the early phases of resuscitation is related to the development of more severe multiorgan dysfunction and worse outcomes in a population of septic shock patients resuscitated by targeting the usual oxygen-derived and hemodynamic parameters.

Materials and methods

This prospective observational study was performed in a 60-bed mixed ICU in a university-affiliated hospital. We examined all patients with a new septic shock episode admitted to the emergency room or proceeding from clinical wards during a 24-month period. Septic shock was defined using the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference [24]. Patients were excluded if they were younger than 18 years old, pregnant, had severe chronic obstructive pulmonary disease (GOLD 3 and 4 categories according to the current classification at the time of our study) or advanced liver cirrhosis (Child-Pugh C).

General management

All patients admitted to the emergency room or proceeding from clinical wards who fulfilled the diagnosis criteria for septic shock were evaluated by the ICU rapid response team according to our local procedures. Each patient was equipped with an arterial cannula and a pulmonary artery catheter (CCO Swan-Ganz catheter; Edwards Life sciences, Irvine, CA, USA). Our early goal-directed therapy included a bundle of interventions that sought to obtain: mean arterial pressure ≥ 65 mmHg; urine output ≥ 0.5 ml/kg/minute; normalization of serum lactate; and ScvO₂ $\geq 70\%$ or SvO₂ $\geq 65\%$. The use of vasopressors (dopamine or norepinephrine) was standardized to maintain a mean arterial pressure ≥ 65 mmHg, and repeated fluid challenges with crystalloids or colloids were used to optimize the stroke volume as well as to allow the lowest dose of vasopressors and pulse-pressure variability $< 12\%$. Dobutamine was added for persistent ScvO₂ $\leq 70\%$ or SvO₂ $\leq 65\%$ after fluid resuscitation. A low dose of hydrocortisone was given within 6 hours of resuscitation when use of vasopressors persisted after an adequate fluid restitution. Mechanical ventilation was provided when needed under light sedation (midazolam) and analgesia (fentanyl); the tidal volume was limited to 6 to 8 ml/kg. Glycemic control was adjusted to maintain glucose levels < 150 mg/dl. Finally, stress ulcer and venous thrombosis prophylaxis were provided according to international recommendations [25].

Study protocol

The Fundación Valle del Lili's Ethical and Biomedical research committee approved the current study. A written informed consent was waived because no new therapeutic interventions were performed and all measurements and procedures routinely followed the local protocols for the management of severe sepsis and septic shock.

Time 0 (T0) was declared when the pulmonary artery catheter was inserted using common monitoring tracings to place the distal port in the pulmonary artery and the proximal port in the right atrium, approximately 3 cm above the tricuspid valve. In order to standardize T0, we recorded the total volume of fluids administered and the time elapsed between the start of resuscitation (first hypotension episode) and the pulmonary artery catheter insertion (T0).

We collected arterial venous blood samples and central and mixed venous blood samples for arterial-venous gases (ABL 300; Radiometer Copenhagen, Denmark) and arterial lactate measurements at T0, and 6 hours (T6), 12 hours (T12) and 24 hours (T24) later. We simultaneously registered hemodynamic and respiratory variables at each measurement. We defined Pv-aCO₂ as the difference between the mixed venous CO₂ partial pressure and the arterial CO₂ partial pressure. Previous studies considered Pv-aCO₂ ≥6 mmHg abnormal [14]. Hence, we classified the patients according to the Pva-CO₂ development during the first 6 hours of resuscitation: persistently high Pv-aCO₂ (high at T0 and T6); increasing Pv-aCO₂ (normal at T0, high at T6); decreasing Pv-aCO₂ (high at T0, normal at T6); and persistently normal Pv-aCO₂ (normal at T0 and T6). The Sequential Organ Failure Assessment score [26] was used to describe multiorgan dysfunction at day 3 and we also described mortality at day 28 for the pre-defined groups.

Data analysis

After exclusion of a normal distribution of the data by the Kolmogorov-Smirnov test, we used a Kruskal-Wallis test to compare continuous variables (followed by Bonferroni correction for multiple comparisons) and a *chi-squared test* (or Fisher's exact test, when appropriate) for discrete variables. Survival probabilities at day 28 were described using a Kaplan-Meier curve and differences between groups were calculated using a log-rank test before and after adjusting for SvO₂ at T6. The development of SvO₂, ScvO₂, lactate, cardiac output, mean arterial pressure and Pv-aCO₂ during the first 24 hours were analyzed using a repeated-measures analysis of variance. Spearman's rho was used to test the agreement between cardiac output and Pv-aCO₂. We also calculated the mortality risk ratios at day 28 in patients who attained ScvO₂ ≥70% or SvO₂ ≥65% but maintained persistently high Pv-aCO₂ at different points during

resuscitation (T0, T6, and T12). Data were expressed as medians and 25 to 75% interquartile ranges. $P \leq 0.05$ (two-tailed) was considered significant.

Results

During the 24-month period, 108 patients older than 18 years with a new episode of septic shock were screened. Patients with advanced cirrhosis ($n = 4$), patients with severe chronic obstructive pulmonary disease ($n = 8$) and pregnant women ($n = 4$) were not included for analysis; additionally, a central catheter could not be placed in four patients, and three refused the procedure. The final sample was therefore 85 patients. The median length of ICU stay for all patients was 6 days (25 to 75% interquartile range, 3 to 11 days), and the 28-day mortality rate was 37.6%. The median time elapsed from sepsis-induced hypotension to catheter insertion was 3.0 hours (25 to 75% interquartile range, 1.0 to 4.0 hours) and the median volume of fluids received before catheter insertion was 2,079 ml (25 to 75% interquartile range, 1,184 to 3,135 ml) for all patients.

Thirty-six patients had Pv-aCO₂ <6.0 mmHg at T0 and T6, and 17 patients had a high Pv-aCO₂ at T0 but it fell below 6 mmHg at T6 (a total of 53 patients had Pv-aCO₂ <6 mmHg at T6); on the other hand, 24 patients had a persistently high Pv-aCO₂ during the first 6 hours and the remaining eight evolved from normal at T0 to high Pv-aCO₂ at T6 (32 patients had Pv-aCO₂ ≥6 mmHg at T6).

We did not find any significant difference with regard to Acute Physiology and Chronic Health Evaluation II score, comorbidities, demographics, or respiratory and hemodynamic variables between groups (Tables 1 and 2), and neither for the volume of fluids received before inclusion (T0). Doses of vasopressors or inotropic received were similar for the groups both at T0 and T6 (Table 2). Multiorgan dysfunction at day 3 was significantly higher among patients with persistently high Pv-aCO₂ compared with those with persistently normal or decreasing Pv-aCO₂ during the first 6 hours of resuscitation (Kruskal-Wallis test, $P < 0.001$) (Figure 1). Likewise, patients with persistently high Pv-aCO₂ during the first 6 hours of resuscitation had a significant lower survival at day 28 compared with those who normalized Pv-aCO₂ during this period (log-rank, Mantel-Cox: 19.21, $P < 0.001$; Figure 2). These results were maintained after adjusting for the SvO₂ achieved at T6 (log-rank test, $P < 0.001$). The time course of SvO₂, ScvO₂ and cardiac output did not significantly differ between Pv-aCO₂ groups (Table 2) nor between survivors and nonsurvivors at day 28 (Figures S1a,b and S2 in Additional file 1). Interestingly, a poor agreement between cardiac output and Pv-aCO₂ was observed both at each time of resuscitation and when all data were pooled ($r^2 = 0.025$, $P < 0.01$) (Figure 3; Figure S3 in Additional file 1).

Table 1 Patient characteristics

Variable	Group 1, H-H (n = 24)	Group 2, L-H (n = 8)	Group 3, H-L (n = 17)	Group 4, L-L (n = 36)	P value
Age (years)	63.0 (54.7 to 75.0)	63.5 (50.5 to 76.5)	55.0 (53.0 to 76.0)	62.0 (49.3 to 71.8)	0.83
Gender, male (%)	17 (70.8)	4 (50.0)	10 (58.8)	22 (61.1)	0.72
APACHE II	24.4 (21.2 to 26.0)	25.2 (21.0 to 27.0)	23.4 (21.2 to 25.6)	24.8 (22.2 to 25.8)	0.11
Time between diagnosis and catheter insertion (T0)	2.0 (2.0 to 4.0)	1.0 (1.0 to 3.3)	3.0 (1.0 to 4.0)	3.0 (2.0 to 4.0)	0.44
Fluids received before catheter insertion	2,039 (1,343 to 2,834)	1,934 (849 to 4,575)	2,500 (1,430 to 3,628)	2,000 (1,025 to 3,153)	0.76
Temperature (°C)	37.5 (37.2 to 37.9)	37.4 (37.1 to 37.9)	37.6 (37.0 to 38.0)	37.4 (37.4 to 37.8)	0.74
Hemoglobin (g/dl)	9.4 (8.7 to 11.6)	8.8 (7.4 to 11.4)	9.8 (9.1 to 11.4)	9.9 (9.1 to 11.4)	0.47
Source of infection, n (%)					
Pneumonia	9	3	4	10	
Abdominal	8	4	6	14	
Urinary	2	1	3	4	
Soft tissue	2	0	1	2	
No specific site	3	0	2	4	
Other	0	0	1	2	
Culture positive, n (%)	20 (83.3)	5 (62.5)	12 (70.6)	19 (52.8)	0.11
Antibiotics given at T0, n (%)	24 (100)	7 (87.5)	16 (94.1)	32 (88.9)	0.38
Antibiotics adequate, n (%)	23 (95.8)	7 (87.5)	16 (94.1)	27 (75.0)	0.10
Hydrocortisone, n (%)	22 (91.7)	8 (100)	15 (88.2)	31 (86.1)	0.68
Transfusion RBC, n (%)	4 (16.7)	3 (37.5)	3 (17.6)	4 (11.1)	0.35
Fluids and vasoactive agents					
Fluids (ml), IQ 25 to 75					
T0	2,039 (1,343 to 2,834)	1,934 (849 to 4,575)	2,500 (1,430 to 3,628)	2,000 (1,025 to 3,153)	0.76
T6	4,733 (3,196 to 6,360)	4,082 (1,576 to 7,584)	4,845 (2,550 to 6,560)	4,673 (3,380 to 7,348)	0.83
Norepinephrine (µg/kg/minute), IQ 25 to 75, n					
T0	0.25 (0.19 to 0.36), 24	0.29 (0.14 to 1.20), 6	0.19 (0.10 to 0.37), 16	0.23 (0.10 to 0.38), 30	0.81
T6	0.20 (0.11 to 0.40), 24	0.36 (0.09 to 0.49), 6	0.12 (0.11 to 0.18), 15	0.19 (0.08 to 0.39), 31	0.45
Dopamine (µg/kg/minute), IQ 25 to 75, n					
T0	–	7.1 (7.1 to 7.3), 2	10.7 (10.7 to 10.7), 1	5.1 (2.8 to 6.6), 5	0.14
T6	–	–	8.0 (8.0 to 8.0), 1	5.3 (2.5 to 6.4), 4	0.16
Dobutamine (µg/kg/minute), IQ 25 to 75, n					
T0	3.1 (2.7 to 4.5), 5	–	5.9 (5.1 to 6.7), 2	3.3 (3.0 to 4.2), 3	0.15
T6	3.1 (2.7 to 5.6), 3	–	5.1 (4.7 to 6.3), 4	3.8 (3.3 to 4.8), 3	0.21

H-H, venous-to-arterial carbon dioxide difference (Pv-aCO₂) high at T0 and T6; L-H, Pv-aCO₂ normal at T0 and high at T6; H-L, Pv-aCO₂ high at T0 and normal at T6; and L-L, Pv-aCO₂ normal at T0 and T6. APACHE, Acute Physiology and Chronic Health Evaluation; IQ 25 to 75, 25 to 75% interquartile range; RBC, red blood cells; T0, time 0; T6, 6 hours after Time 0.

Patients with elevated Pv-aCO₂ at T6 had slower lactate clearances at T6 and T12 than patients attaining a normal Pv-aCO₂ during the first 6 hours of resuscitation (Figure 4). We also observed a significant linear correlation between mixed-venous to arterial pCO₂ and central-venous to arterial pCO₂ (Pearson correlation: 0.71, 95% confidence interval: 0.47 to 0.86; $P < 0.001$) but with moderate agreement between them ($R^2 = 0.556$, $P < 0.001$) (Figure 5). Additionally, significant differences

were observed for the time course of Pv-aCO₂ and central venous-to-arterial carbon dioxide difference (Pvc-aCO₂) during the first 24 hours for survivor and nonsurvivors at day 28 (repeated-measures analysis of variance, $P = 0.003$ and $P = 0.03$, respectively; Figure S4a,b in Additional file 1).

Finally, patients who achieved ScvO₂ \geq 70% or SvO₂ \geq 65% but maintained high Pv-aCO₂ at T0, T6 and T12 had a higher mortality risk at Day 28 (Table 3).

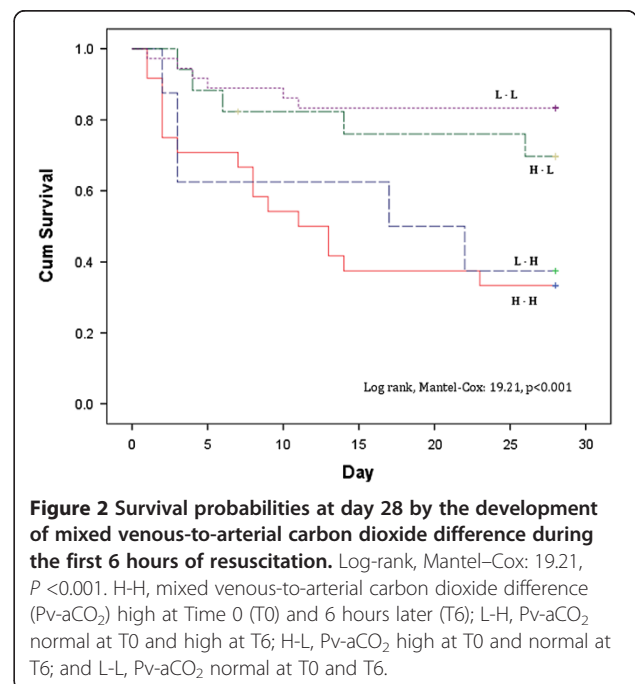
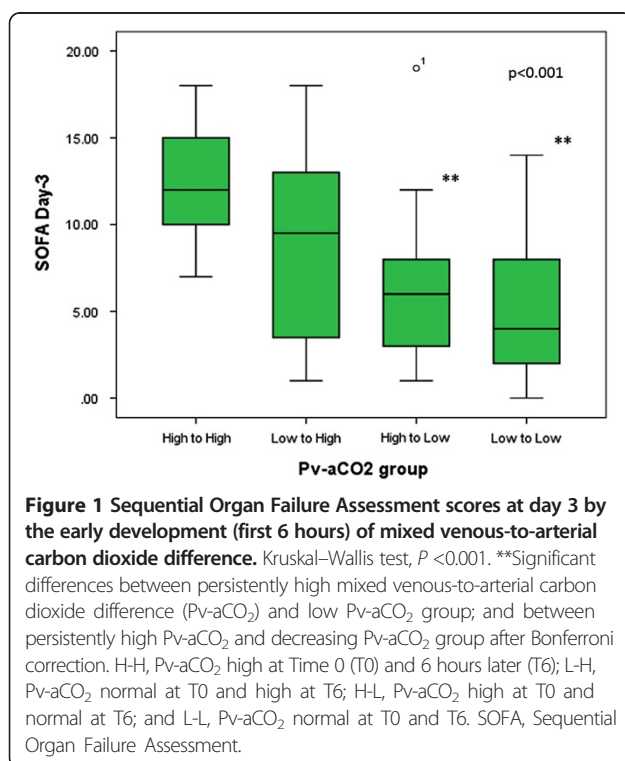
Table 2 Hemodynamic, oxygen and ventilatory parameters

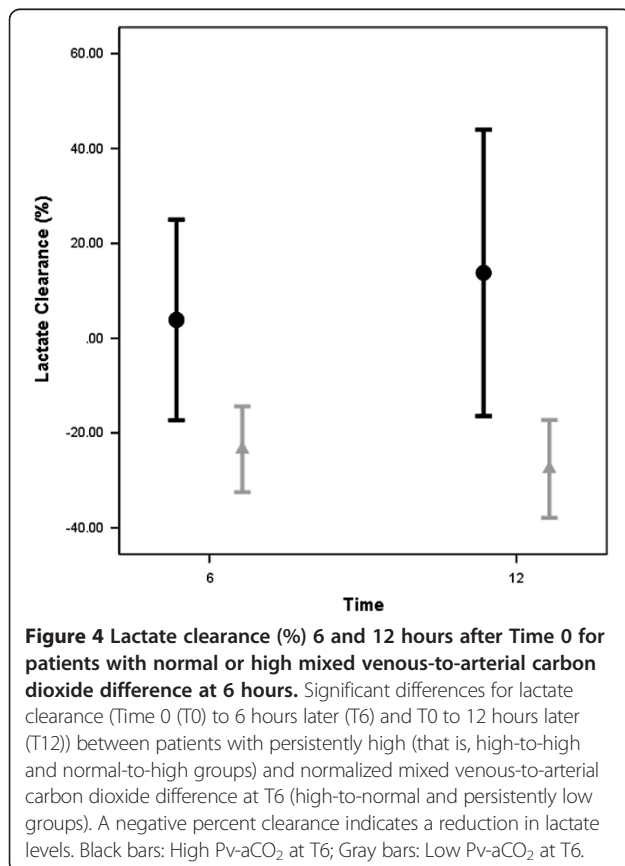
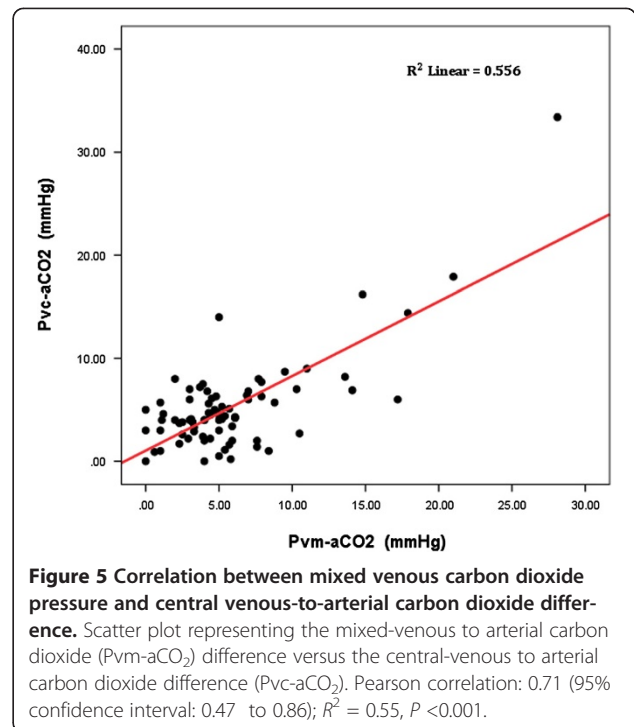
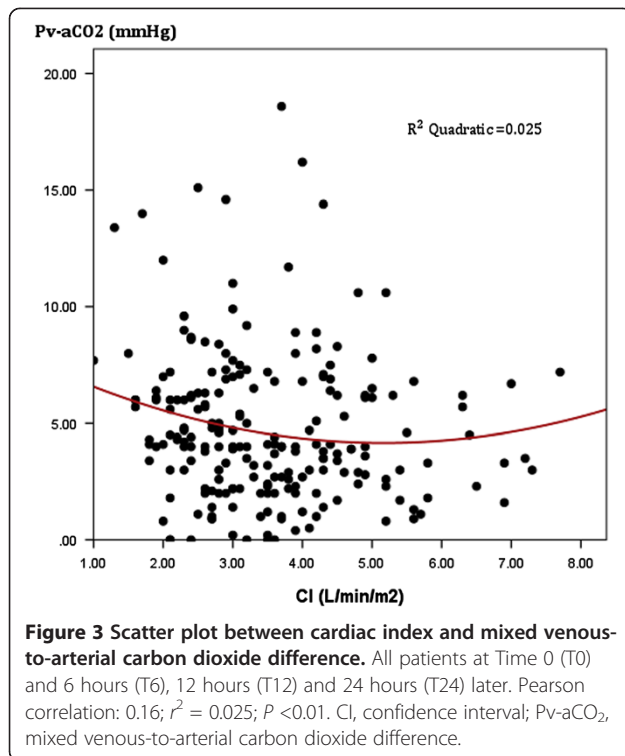
Variable	Group 1, H-H (n = 24)	Group 2, L-H (n = 8)	Group 3, H-L (n = 17)	Group 4, L-L (n = 36)	P value
Hemodynamic variables					
Heart rate (beats/minute)					
T0	112 (103 to 129)	111 (77 to 138)	104 (86 to 126)	109 (93 to 118)	0.31
T6	114 (101 to 125)	103 (73 to 127)	98 (85 to 114)	103 (88 to 118)	0.14
Cardiac index (l/minute/m ²)					
T0	3.0 (2.3 to 4.2)	3.6 (2.7 to 4.6)	3.0 (2.5 to 5.0)	3.5 (2.7 to 4.5)	0.63
T6	3.2 (2.2 to 4.3)	3.3 (2.4 to 3.8)	3.7 (2.2 to 5.5)	3.6 (2.8 to 4.3)	0.75
MAP (mmHg)					
T0	65.0 (61.0 to 72.8)**	67.0 (65.3 to 69.5)	73.0 (68.0 to 82.5)**	72.0 (64.5 to 77.0)	0.02
T6	69.0 (65.3 to 75.8)	77.5 (70.5 to 96.0)	68.0 (63.5 to 72.0)	71.5 (65.0 to 78.8)	0.06
CVP (mmHg)					
T0	14.5 (10.3 to 17.0)	10.0 (9.0 to 12.8)	12.0 (8.5 to 15.0)	10.0 (7.0 to 14.0)	0.10
T6	13.5 (10.0 to 15.8)**	15.0 (10.0 to 17.0)	10.0 (5.0 to 12.5)**	10.0 (7.3 to 13.0)	0.03
PAOP (mmHg)					
T0	17.0 (14.0 to 20.0)	12.5 (10.0 to 15.0)	17.0 (12.0 to 22.0)	15.0 (11.0 to 20.0)	0.52
T6	19.0 (15.0 to 24.0)**	14.5 (10.0 to 19.0)	13.0 (10.0 to 15.0)**	16.0 (12.0 to 20.0)	0.03
Blood gases and oxygen variables					
pH					
T0	7.30 (7.18 to 7.37)	7.31 (7.22 to 7.40)	7.34 (7.22 to 7.41)	7.32 (7.24 to 7.40)	0.85
T6	7.32 (7.20 to 7.36)	7.35 (7.30 to 7.42)	7.35 (7.26 to 7.39)	7.34 (7.30 to 7.39)	0.33
PaCO ₂ (mmHg)					
T0	30.5 (24.1 to 36.6)	34.2 (24.7 to 36.9)	31.0 (23.6 to 33.6)	27.5 (23.7 to 36.5)	0.81
T6	26.1 (22.4 to 32.7)	31.0 (21.6 to 34.0)	31.3 (26.8 to 33.6)	27.5 (21.7 to 32.1)	0.25
PvmCO ₂ (mmHg)					
T0	40.6 (33.9 to 46.5) [¶]	29.5 (25.0 to 35.3)	39.7 (35.5 to 47.1) 34.3	32.8 (27.3 to 40.9) [¶]	0.03
T6	38.0 (29.9 to 39.7) [¶]	38.3 (28.0 to 46.2)	(30.4 to 36.8)	30.0 (25.5 to 35.5) [¶]	0.02
PvcCO ₂ (mmHg)					
T0	38.2 (29.1 to 50.5)	40.1 (34.2 to 43.4)	36.7 (35.5 to 47.1) 33.9	32.5 (28.1 to 38.4)	0.12
T6	33.7 (28.3 to 36.9)	33.8 (31.4 to 41.4)	(30.4 to 36.8)	29.0 (25.1 to 35.8)	0.20
PaO ₂ (mmHg)					
T0	112.2 (79.3 to 167.3)	117.1 (77.5 to 139.5)	115.7 (81.4 to 140.8)	100 (86.0 to 123.9)	0.70
T6	113.6 (83.0 to 147.3)	132.5 (109.8 to 197.8)	105.0 (83.5 to 127.4)	111.5 (86.2 to 135.7)	0.34
PaO ₂ /FiO ₂ (mmHg)					
T0	188.9 (117.1 to 265.0)	166.9 (143.8 to 244.1)	233.7 (184.6 to 314.0)	214.3 (141.6 to 368.0)	0.28
T6	177.9 (136.4 to 298.4)	265.0 (185.5 to 383.5)	239.3 (185.1 to 306.3)	253.5 (181.6 to 368.0)	0.17
Lactate (mmol/l)					
T0	4.3 (2.0 to 7.9)	2.9 (2.0 to 9.7)	2.7 (1.5 to 3.9)	2.9 (1.7 to 4.7)	0.16
T6	3.3 (2.1 to 6.8)** [¶]	2.9 (1.1 to 7.1)	1.3 (0.9 to 2.3)**	2.0 (1.0 to 3.5) [¶]	0.002
ScvO ₂ (%)					
T0	64.0 (54.7 to 75.1)	66.8 (59.7 to 74.5)	73.0 (70.8 to 76.7)	67.1 (62.1 to 75.9)	0.36
T6	70.8 (66.4 to 73.5)	73.4 (69.3 to 78.0)	72.3 (67.2 to 75.9)	76.0 (60.0 to 77.9)	0.53
SvO ₂ (%)					
T0	66.0 (56.8 to 71.4)	68.0 (54.9 to 81.0)	68.1 (57.0 to 71.0)	69.7 (62.1 to 75.9)	0.39

Table 2 Hemodynamic, oxygen and ventilatory parameters (Continued)

T6	69.0 (63.3 to 72.9)	70.6 (63.4 to 73.8)	71.2 (64.4 to 75.1)	68.0 (58.7 to 74.3)	0.77
Oxygen extraction ratio					
T0	34.7 (28.3 to 44.3)	30.8 (22.7 to 38.4)	29.4 (25.0 to 36.8)	30.7 (24.9 to 37.5)	0.36
T6	29.8 (26.4 to 36.6)	30.2 (24.9 to 31.3)	29.3 (24.1 to 33.3)	30.7 (23.4 to 39.3)	0.68
Pv-aCO ₂ (mmHg)					
T0	8.2 (7.0 to 10.6) ^{*¶}	1.4 (1.1 to 5.3) ^{*φ}	6.3 (6.1 to 7.2) ^{φξ}	2.7 (2.0 to 4.0) ^{¶ξ}	<0.001
T6	7.6 (6.4 to 9.4) ^{**¶}	8.6 (6.5 to 11.7) ^{φψ}	3.5 (0.9 to 4.3) ^{**φ}	3.3 (2.2 to 4.1) ^{¶ψ}	<0.001
Pvc-aCO ₂ (mmHg)					
T0	9.7 (7.0 to 12.1) [¶]	4.6 (3.3 to 6.1)	7.3 (4.6 to 9.1)	4.4 (2.7 to 5.4) [¶]	<0.001
T6	7.0 (5.8 to 9.7)	8.5 (5.6 to 9.6) ^ψ	4.4 (2.1 to 5.5)	4.0 (1.7 to 5.4) ^ψ	0.003
Ventilatory parameters					
Mechanical ventilation					
T0	24	5	11	23	0.01
T6	24	5	11	23	0.01
PEEP (mmHg), n					
T0	6.0 (5.0 to 8.0), 24	5.0 (5.0 to 6.0), 5	5.0 (5.0 to 8.0), 11	8.0 (5.0 to 10.0), 23	0.48
T6	6.5 (5.0 to 8.0), 24	5.0 (5.0 to 7.5), 5			
Tidal volume (ml/kg)					
T0	7.1 (6.3 to 7.7)	7.3 (6.3 to 7.6), 5	7.0 (6.5 to 8.0), 11	7.5 (6.6 to 8.0), 23	0.65
T6	7.2 (6.3 to 7.9)	7.2 (6.6 to 7.6), 5	7.5 (6.8 to 8.0), 11	7.5 (6.9 to 8.0), 23	0.65

Data presented as mean (25 to 75% interquartile range). CVP, central venous pressure; FiO₂, oxygen inspired fraction; MAP, mean arterial pressure; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure; PAOP, pulmonary artery occlusion pressure; PEEP, positive end-expiratory pressure; Pv-aCO₂, mixed venous-to-arterial carbon dioxide difference; Pvc-aCO₂, central venous-to-arterial carbon dioxide difference; PvcCO₂, central venous carbon dioxide pressure; PvmCO₂, mixed venous carbon dioxide pressure; ScvO₂, central venous oxygen saturation; SvO₂, mixed venous oxygen saturation; T0, time 0; T6, 6 hours after Time 0. **P* <0.05 for Groups 1 vs. 2; ***P* <0.05 for Groups 1 vs. 3; ¶*P* <0.05 for Groups 1 vs. 4; φ*P* <0.05 for Groups 2 vs. 3; ψ*P* <0.05 for Groups 2 vs. 4; and ξ*P* <0.05 for Groups 3 vs. 4.





Discussion

We studied a cohort of patients during the very early phases of septic shock who were subjected to a comprehensive resuscitation aimed to target the usual hemodynamic and oxygen metabolism parameters. A recent study demonstrated how Pv-aCO₂ could be a tool to detect persistent inadequate resuscitation during septic shock [18] although it was not conducted during very early stages of resuscitation. Even a faster enrollment, our study showed that a number of patients had approximately normal SvO₂ and ScvO₂ at catheter insertion as it has been reported at ICU admission [22], and most of them reached normal oxygen-derived parameters at 6 hours. However, despite attaining the SvO₂ and ScvO₂ targets (and after adjusting for SvO₂) and an apparent global hemodynamic normalization in most patients, those with persistently high Pv-aCO₂ developed more severe multiorgan dysfunction at day 3 than patients evolving with normal Pv-aCO₂ during the first 6 hours of

Table 3 Mortality risk ratio for patients with mixed oxygen saturation $\geq 65\%$ but with mixed venous-to-arterial carbon dioxide difference ≥ 6 mmHg at day 28

Time	Relative risk ^a	Confidence interval	P value
0 hours	1.77	0.97–3.22	0.06
6 hours	2.23	1.20–4.13	0.01
12 hours	2.41	1.42–4.10	0.001

^aRelative mortality risk at day 28.

resuscitation or those who evolved from high to normal Pv-aCO₂. Additionally, we observed that persistently high Pv-aCO₂ was associated with a lower survival at day 28.

Venous hypercarbia is a marker of limited blood flow during cardiac arrest and shock states [8-19]. Recent observations have suggested that Pv-aCO₂ might identify septic patients who remain inadequately resuscitated despite achieving ScvO₂ goals [15]. Consistent with these findings, we found that patients in septic shock achieving ScvO₂ ≥70% or SvO₂ ≥65% had worse outcomes when a concomitant high Pv-aCO₂ was observed. These data reinforce the idea that Pv-aCO₂ provides additional information to hemodynamic and oxygen parameters habitually used during resuscitation of septic shock. Nevertheless, the underlying mechanisms that explain increases in Pv-aCO₂ during septic shock are incompletely understood; however, to current knowledge, an increased Pv-aCO₂ results from the interactions between blood flow to the tissues, aerobic and anaerobic CO₂ generation, and the CO₂ dissociation curve.

According to the Fick equation, during steady state the CO₂ excretion equals the product of cardiac output by the difference between mixed venous blood CO₂ content and arterial blood CO₂ content. Some studies have emphasized on the key role of cardiac output on venous to arterial CO₂ content differences and indeed a curvilinear relationship between these two variables has been described [14]. However, in our study we found a poorer concordance between cardiac output and Pv-aCO₂ at each time point of resuscitation (Figure 3) and, in fact, the cardiac output remained normal or even high during the first 24 hours of resuscitation (Figure S2 in Additional file 1), suggesting some independence between Pv-aCO₂ and macrovascular blood flow changes. While in non-inflammatory low-flow states tissue and regional hypercarbia can be easily explained by the CO₂ stagnation phenomenon [15,16], the interpretation of an increased tissue and/or regional CO₂ during inflammatory conditions is more complex. Sepsis may thereby be associated with the coexistence of normal or even high cardiac output, inter-organ and intra-organ blood flow redistribution, and altered microvascular and oxygen extraction capabilities. All of these alterations can influence the tissue CO₂ production and elimination.

A study by Neviere and colleagues thus demonstrated the key role of microvascular blood flow on gastric CO₂ accumulation [27]. Similarly, using simultaneous gastric tonometry and laser Doppler flowmetry, Elizalde and colleagues demonstrated the association between gastric mucosal pH and mucosal blood flow, regardless of macrohemodynamic variations [28]. Likewise, Tugtekin and colleagues demonstrated in a porcine sepsis model that the increase of mucosal to arterial CO₂ gap was related to the

heterogeneity of gut mucosal blood flow, even though cardiac output and mesenteric blood flow were maintained [29]. Meanwhile, Creteur and colleagues found a significant correlation among sublingual CO₂, gastric mucosal CO₂ and microcirculatory heterogeneity in human septic shock during dobutamine infusion, and suggested that the primary determinant of tissue CO₂ accumulation was the microcirculatory blood flow [30]. Hence, there is an evident link between blood flow and tissue or local CO₂ accumulations conducting to increase tissue or venous-to-arterial CO₂ differences, but sometimes normal macrohemodynamics does not prevent elevation of Pv-aCO₂. The near normalization of the oxygen and hemodynamic parameters between the subgroups in our study suggests that venous CO₂ accumulation encloses more complex mechanisms than macrovascular stagnation, and we could hypothesize that microvascular blood flow distribution is one of several factors potentially influencing the behavior of Pv-aCO₂ during inflammatory conditions in which the heterogeneity of microvascular blood flow is increased. However, this hypothesis should be confirmed in future studies.

The interpretation of hyperlactatemia in sepsis is very complex, especially in septic shock [31] since anaerobic metabolism, non-anaerobic generation and slow clearance can conduct lactate accumulation. We observed higher lactate levels and slower lactate clearance at T6 and T12 in patients with persistently high Pv-aCO₂ during the first 6 hours of resuscitation. Interestingly, Pv-aCO₂ (and Pvc-aCO₂) kinetics seems to anticipate a slower lactate clearance (Figure S5 in Additional file 1). A high Pv-aCO₂ could indicate a decrease in global or microvascular blood flow conducting to slow lactate clearance. However, a high Pv-aCO₂ could also reflect the persistence of anaerobic metabolism as result of bicarbonate buffering of protons derived from fixed acids [32]. Thus, an increased Pv-aCO₂ to oxygen consumption ratio could reflect global anaerobic metabolism as was proposed by Mekontso-Dessap and colleagues [19]. However, even in the presence of anaerobic metabolism, a high efferent venous blood flow could be sufficient to wash out the global CO₂ generation from the hypoperfused peripheral tissues and, in this case, Pv-aCO₂ could not increase. In fact, hypoperfusion could persist in some of our patients and even oxygen parameters, global hemodynamics or Pv-aCO₂ remain normal.

Finally, we found a significant linear correlation but moderate agreement between venous-arterial CO₂ differences obtained from mixed venous and central venous samples that agree with recent observations published simultaneously to the review of our paper [21]. Even though Pvc-aCO₂ can be easily obtained and speedily usable in the emergency room, the point about whether Pvc-aCO₂ and mixed venous carbon dioxide pressure

(Pv-aCO₂ in our study) are really interchangeable should be addressed in future studies.

Our study has some limitations. First, our observations are restricted to macro-hemodynamic variables, and Pv-aCO₂ is another global variable that does not necessarily represent tissue or regional vascular perfusion at different beds. We did not describe regional perfusion variables as gastric tonometry or local tissue CO₂ accumulation; hence, normal Pv-aCO₂ might also occur when regional hypoperfusion is ongoing.

Second, we suggest that persistently high Pv-aCO₂ reflects tissue or regional hypoperfusion. We hypothesized that Pv-aCO₂ could reflect the venous CO₂ accumulation due to the heterogeneous microcirculatory blood flow when cardiac output and oxygen parameters remain normal or even high or, eventually, Pv-aCO₂ could reflect anaerobic CO₂ generation. However, mechanism conducting to venous CO₂ accumulation during inflammatory conditions should be explored in future studies.

Third, during conditions of tissue hypoxia but with preserved blood flow (even though during anaerobic metabolism carbon dioxide production - VCO₂ - decreases less than oxygen consumption -VO₂-), venous blood flow might be high enough to ensure adequate washout of the CO₂ produced by hypoxic cells, thereby preventing a Pv-aCO₂ increase.

Fourth, we assumed that a linear relationship exist between partial CO₂ pressure and CO₂ content at the venous and arterial levels [33,34]. Pv-aCO₂ could thus be used as a surrogate for the Cv-aCO₂. However, previous research has shown that the Haldane effect causes paradoxical increases in Pv-aCO₂ during blood flow increases [33,34]. Unfortunately, the calculation of CO₂ content is complex and subject to errors due to the number of variables included in the formulas. Simplified formulas are easy to use, but wide differences in venous and arterial acid-base status (for example, ischemic hypoxia) can preclude their use. Nevertheless, some authors consider that the Haldane effect exerts a minor influence, and in most cases Pv-aCO₂ and CO₂ content differences develop similarly [35].

Finally, our observations were restricted to a small sample of patients in septic shock. Although our findings seem logical and biologically plausible, they should be confirmed in future studies.

Conclusions

The persistence of high Pv-aCO₂ during the early resuscitation of patients in septic shock is associated with significant higher multiorgan dysfunction and poor outcomes. Although underlying mechanisms that increase Pv-aCO₂ among patients in septic shock must be clarified, Pv-aCO₂ might identify a high risk of death in apparently resuscitated patients. Future studies should test Pv-aCO₂ as a

perfusion goal during early phases of the resuscitation of patients in septic shock.

Key messages

- Persistent high Pv-aCO₂ is related to more severe multiorgan dysfunction and worse outcomes in apparently resuscitated septic shock patients.
- Mechanisms conducting to increase Pv-aCO₂ during inflammatory conditions are insufficiently understood. Variations in Pv-aCO₂ were independent of macro-flow variables (that is, cardiac output) or oxygen metabolism targets (that is, SvO₂, oxygen extraction rate), suggesting that venous stagnation is not the single explanation for venous CO₂ accumulation.
- Pv-aCO₂ might identify a high risk of death in apparently resuscitated septic shock patients, and could be explored as a tissue perfusion goal during resuscitation as Pv-aCO₂ tracks ischemic hypoxia.

Additional file

Additional file 1: Figure S1a presenting the time course of ScvO₂ (%) during the first 24 hours for survivors and nonsurvivors at day-28.

Figure S1b presenting the time course of SvO₂ (%) during the first 24 hours for survivors and nonsurvivors at day 28. **Figure S2** presenting the time course of cardiac output (l/minute) during the first 24 hours for survivors and nonsurvivors at day 28. **Figure S3** presenting the scatter plot between cardiac index and Pv-aCO₂ (according to Pv-aCO₂ at T6).

Figure S4a presenting the time course of Pv-aCO₂ (mmHg) during the first 24 hours for survivors and nonsurvivors at day 28. **Figure S4b** presenting the time course of Pvc-aCO₂ (mmHg) during the first 24 hours for survivors and nonsurvivors at day 28. **Figure S5** presenting the time course of lactate levels (mmol/l) during the first 24 hours for survivors and nonsurvivors at day 28.

Abbreviations

CO₂: Carbon dioxide; Pv-aCO₂: Mixed venous-to-arterial carbon dioxide difference; Pvc-aCO₂: Central venous-to-arterial carbon dioxide difference; ScvO₂: Central venous oxygen saturation; SvO₂: Mixed venous oxygen saturation.

Competing interests

The authors declare they have no competing interests.

Authors' contributions

GAO-T contributed to the study conception, design and manuscript preparation. DFB-R, MU, JDT, AG and WB were involved in data collection and revising the manuscript. AFG, MG, CA-D and GH revised the manuscript critically. All authors read and approved the final manuscript.

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