Research Article

Patterns of central venous oxygen saturation, lactate and veno-arterial CO_2 difference in patients with septic shock

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Abstract

Background and Aims: Tissue hypoperfusion is reflected by metabolic parameters such as lactate, central venous oxygen saturation ($ScvO_2$) and the veno-arterial CO_2 ($vaCO_2$) difference. We studied the relation of these parameters over time and with outcome in patients with severe septic shock. **Materials and Methods:** In this single-center, prospective observational cohort study, adult patients (≥18 years) with circulatory shock were included. Echocardiography and simultaneous arterial and venous blood gases were done on enrolment (0 h) and at 24, 48 and 72 h. The partial pressure of CO_2, lactate and $ScvO_2$ were recorded from the central venous blood samples. The $vaCO_2$ was calculated as the difference in CO_2 between paired venous and arterial blood gas samples. **Results:** Of the 104 patients with circulatory shock, 79 patients (44 males) with septic shock aged 49.8 (standard deviation ± 14.6) years and with sequential organ failure assessment (SOFA) score of 11.0 ± 3.4 were included. 71 patients (89.9%) were ventilated (11.4 ± 12.3 ventilator-free days). The duration of hospitalization was 16.6 ± 12.8 days and hospital mortality 50.6%. Lactate significantly decreased over time with a greater decrement in survivors than nonsurvivors (−0.35 vs. −0.10, $P < 0.001$). For every l/min increase in cardiac output, $vaCO_2$ decreased by 0.34 mmHg ($P = 0.006$). There was no association between $ScvO_2$ and mortality ($P = 0.930$). 0 h SOFA and $vaCO_2$ ≤6 mmHg were strongly associated ($P = 0.005$, $P = 0.018$, respectively) with higher odds of mortality. However, this association was evident only in those with $ScvO_2$ >70% and not in $ScvO_2$ ≤70%. **Conclusion:** In septic shock, $vaCO_2$ ≤6 mmHg is independently associated with mortality, particularly in those with normalized $ScvO_2$ consistent with metabolic microcirculatory abnormalities in these patients.

Keywords: Metabolic, microcirculation, outcome, resuscitation, septic

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.167035

Quick Response Code:

Introduction

The cardiovascular system provides tissue perfusion essential for cellular metabolism. Inadequate tissue perfusion, due to reduced perfusion pressure or abnormal distribution of blood flow, as occurs in shock, results in impaired tissue oxygenation, anaerobic metabolism, and organ-system dysfunction.[1] Although macrocirculatory decreases in cardiac output (CO) often elicit increased sympathetic tone that sustains blood pressure and causes tachycardia,[2] the impact

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How to cite this article: Mahajan RK, Peter JV, John G, Graham PL, Rao SV, Pinsky MR. Patterns of central venous oxygen saturation, lactate and veno-arterial CO_2 difference in patients with septic shock. Indian J Crit Care Med 2015;19:580-6.

of these compensatory mechanisms and the primary pathologic process on tissue oxygen delivery is more difficult to assess, because regional oxygen delivery is regulated by the microcirculation.[2] Microcirculatory dysfunction in shock can lead to refractory circulatory failure. Moreover, deranged cellular energetics in sepsis is not only due to inadequate tissue perfusion but also impaired mitochondrial respiration; their combination can contribute to treatment failure.[3] Thus, hemodynamic assessment and support requires consideration of both global and regional perfusion as well as end-organ function.[2]

Presently, resuscitation endpoints may be considered upstream targets, including CO, mean arterial pressure and global oxygen delivery. It is unclear, however, how such global resuscitation targets are influenced by and alter metabolic downstream variables such as serum lactate, central venous oxygen saturation ($ScvO_2$), and the veno-arterial CO_2 ($vaCO_2$) difference. These measures are markers of global tissue perfusion and resuscitation effectiveness.[4] Elevated serum lactate in circulatory shock usually reflects inadequate tissue perfusion relative to metabolic demand and an associated tissue hypoxia.[5] Lactate levels correlate with morbidity and mortality in patients in shock. However, lactate levels, particularly in the critically ill, may be influenced by factors other than global hypoperfusion.[5] $ScvO_2$, as a surrogate for mixed venous O_2 saturation, is another marker of the adequacy of the circulation.[6,7] Early optimization of $ScvO_2$ within the first 6-h of resuscitation may improve outcome in septic shock.[8] However, given the perfusion heterogeneity in septic shock,[9] $ScvO_2$ might be normal despite overt or occult hypoperfusion.[1] $vaCO_2$ difference, another metabolic parameter that has been explored in shock, is dependent on CO_2 and CO. A $vaCO_2$ >6 mmHg, as a result of increased oxygen utilization and CO_2 production, reflects a low output state with hypoperfusion.[10] A low $vaCO_2$ of <6 mmHg, on the other hand, has been postulated to reflect impaired utilization of oxygen and low CO_2 production due to mitochondrial dysfunction.[3,10] Although recent interest has focused on the evaluation of these parameters as endpoints of resuscitation,[11,12] it is unclear as to the relative value of using these measures as early sepsis resuscitation goals.[13]

A few studies have examined these metabolic parameters over time in patients resuscitated from circulatory shock. As suggested in a recent editorial, several patterns of microcirculatory abnormalities may exist in shock.[12] We hypothesized that different patterns of metabolic dysfunction occurred in patients in shock that may define pathophysiologic prognostic categories useful in tailoring resuscitation strategies amongst a diverse critically ill population.

Materials and Methods

Setting and subjects

We performed a prospective observational cohort study over 8-month (November 2012 until June 2013) in the Medical and Surgical Intensive Care Unit (ICU) and high Dependency Units of a Tertiary Care Hospital in India. The study was approved by the Institutional Review Board. Adult patients (≥18 years) were considered for inclusion if they fulfilled two or more criteria for systemic inflammatory response syndrome[14] and had refractory hypotension, defined as a systolic blood pressure that either was < 90 mmHg or required vasopressor therapy to maintain 90 mmHg even after an intravenous fluid challenge (20–30 ml/kg over 30-min). Exclusion criteria were pregnancy, do not resuscitate status, readmission to ICU within a single hospital stay, absence of an internal jugular or subclavian central venous access, patients who denied consent or who survived <24 h. Patients with other etiologies of shock as discovered during their ICU stay (cardiogenic, hypovolemic, and obstructive shock) were also excluded. Patients were followed up until death or hospital discharge.

Study protocol

All included patients had arterial (radial or femoral) and central catheters (internal jugular or subclavian, inserted according to standard protocol, with the tip of the catheter at the upper part of the right atrium). Echocardiography and simultaneous arterial and venous blood gas analyses were carried out, and sequential organ failure assessment (SOFA) score[15] and vasoactive inotrope score (VIS)[16] were calculated on enrolment (0 h, T0) and at 24 (T24), 48 (T48), and 72 h (T72) postenrolment. All assessments were done within 2 h of the specified time. The partial pressure of carbon dioxide, lactate and $ScvO_2$ were recorded from the central venous blood samples. The $vaCO_2$ was calculated as the difference in CO_2 between paired venous and arterial blood gas samples. Central venous PCO_2 has been used as a surrogate for mixed venous PCO_2 to identify inadequately resuscitated patients in septic shock.[12,17] The cut-off values of 6 mmHg for $vaCO_2$ and 70% for $ScvO_2$ were chosen according to previous studies.[8,17] CO was measured by transthoracic echocardiography using the left ventricular outflow method[18] with the Sonosite® Turbo portable ultrasound machine, as recently validated for the assessment of cardiac hemodynamics in ICU.[19] All

measurements were taken by a single physician trained in ICU ultrasonography, and an average of three values was taken to reduce intra-observer variability. We also assessed inferior vena cava (IVC) diameter variability in mechanically ventilated patients with no spontaneous breathing (heavily sedated or paralyzed)[20] and IVC collapsibility in spontaneously breathing patients.[21] IVC variability of >12%[20] and collapsibility of >50%[21] were considered as markers of volume responsiveness and an under-filled intravascular state, respectively. All blood gas samples were analyzed by a point-of-care blood gas analyzer (GEM® Premier 4000, GEM® Premier 3000, Radiometer ABL800 flex®, Copenhagen Denmark). Additional tests for the evaluation of shocks such as complete blood counts, electrolytes, liver and renal function tests, electrocardiogram, and appropriate cultures were done as the clinical situation warranted.

Patients were categorized as a septic, cardiogenic, hypovolemic or obstructive shock. Patients in septic shock were analyzed for the stated outcomes. The diagnosis of septic shock was based on an identifiable focus of infection with shock.[22]

Outcomes

The primary outcome assessed was in-hospital mortality. Other outcomes included need and duration of ventilation, ventilator-free days,[23] and length of hospital stay. Mortality in the hospital included patients who took discharge against medical advice in a moribund condition.

Statistical analysis

Each of the metabolic parameters (lactate, $ScvO_2$ and $vaCO_2$) was assessed for their relationship with hospital outcome, CO and trends over time. Analysis of categorical outcome data was done by Fisher's exact test. Linear mixed effects models were used for assessment of change in outcome over time. Logistic regression analysis was undertaken to see the independent association of the baseline parameters with mortality. Data were expressed as mean ± standard deviation (SD). $P \leq 0.05$ was considered statistically significant. Statistical analysis was performed using R version 3.0.1. Graphics were created using the ggplot2 package within R.[24]

Results

During the study period, 175 patients were admitted to the ICUs with hypotension, refractory to fluid therapy. Of these, 71 patients were excluded [Figure 1]. Of the remaining 104 patients who were enrolled, 79 patients (44 males, 35 females) with septic shock of diverse etiology [Table 1] and aged 49.8 (SD ± 14.6) years formed the study cohort.

The T0 SOFA score of 11.0 ± 3.4 suggested a cohort of very sick patients with septic shock. T0 $ScvO_2$, $vaCO_2$ and lactate were 71.6% ± 15.2%, 7.1 ± 4 mmHg and 5.8 ± 4.9 mmol/dl, respectively. At the time of recruitment, more than half the patients (59.5%) were under-filled as assessed by IVC variability and

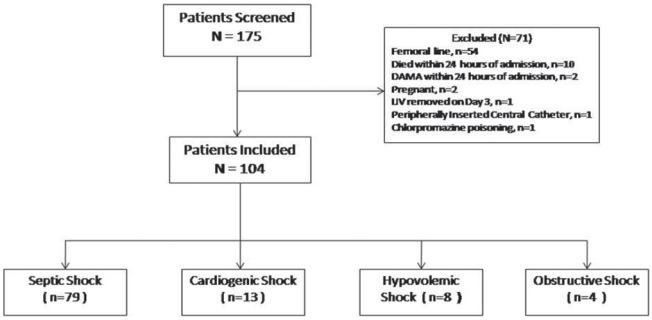

Figure 1: Flow chart depicting patients screened, and reasons for exclusion - of the 175 patients screened, 104 patients were included. 79 patients were categorized as septic shock, 13 as cardiogenic shock, 8 as hypovolemic shock and 4 as an obstructive shock. One patient with chlorpromazine poisoning who presented with distributive shock was excluded as the patient did not fit into any specific etiologic category. DAMA: Discharged against medical advice

Table 1: Etiology of shock

Cause of shock	Number of patients
Septic shock	79*
Intra-abdominal sepsis	27
Lower respiratory tract infection	18
Community-acquired pneumonia	8
Hospital-acquired pneumonia	8
Aspiration pneumonia	2
Skin/soft tissue/bone infection	12
Complicated urinary tract infection	10
Undifferentiated fever (scrub typhus)	5
Obstetric complications	3
HELLP** syndrome	2
Puerperal sepsis	1
Acute central nervous system infection	2
Febrile neutropenia	1
Catheter-related blood stream infection	1
Cardiogenic shock	13
Acute coronary syndrome	6
Toxin induced†	3
Scorpion sting induced myocarditis	1
Congestive heart failure	1
Primary amyloidosis	1
Mitral stenosis	1
Hypovolemic shock	8
Trauma	6
Postoperative hemorrhage	1
Massive hemoptysis	1
Obstructive shock	4
Pulmonary embolism	2
Tension pneumothorax	2

*12 patients with septic shock has significant myocardial dysfunction related to sepsis and 5 patients had significant hypovolemia, **Hemolysis, elevated liver enzymes, low platelet count, †Toxin induced included one patient each with beta-blocker overdose, yellow oleander poisoning, Oduvanthalai poisoning

Table 2: Outcome data overall and categorized by type of shock

Outcome parameter	All patients (*n*=104)	Septic shock (*n*=79)	Cardiogenic shock (*n*=13)	Hypovolemic shock (*n*=8)	Obstructive shock (*n*=4)
Mortality incl. DAMA, *n* (%)	49 (47.1)	40 (50.6)	6 (46.2)	2 (25.0)	1 (25.0)
Hospital LOS	16.0 (12.0)	16.6 (12.8)	12.2 (7.0)	18.8 (11.2)	11.0 (8.0)
Ventilation, *n* (%)	90 (86.5)	71 (89.9)	9 (69.2)	8 (100)	2 (50.0)
Ventilation duration, mean (SD) days†	5.3 (5.6)	5.9 (6.0)	2.4 (1.9)	5.1 (4.4)	2.3 (2.9)
Ventilator-free days, mean (SD) days†	12.5 (12.4)	11.4 (12.3)	14.3 (13.8)	16.6 (11.1)	19.5 (13.3)

†Available only in 103 patients overall and in 78 patients with septic shock. DAMA: Discharged against medical advice; LOS: Length of stay; SD: Standard deviation

collapsibility. 71 (89.9%) patients were ventilated; ventilator-free days being 11.4 ± 12.3. The duration of hospitalisation was 16.6 ± 12.8 days, and in-hospital mortality was 50.6% [Table 2].

Enrolment SOFA was significantly (P = 0.005) associated with increased odds of death in patients with septic shock (odds ratio [OR]: 1.23, 95% confidence interval [CI]: 1.07–1.45. SOFA score declined significantly over time (P < 0.001) in septic [Table 3] as well as all types of shock (P < 0.001, not presented).

Veno-arterial CO_2

In septic patients, enrolment $vaCO_2$ ≤6 mmHg was significantly associated (P = 0.018) with increased mortality (OR: 3.06, 95% CI: 1.23–7.94). However, this association was restricted to those with $ScvO_2$ >70% (P = 0.039) and not in patients with $ScvO_2$ ≤ 70 (P = 0.450). There was no evidence of a change in $vaCO_2$ (P = 0.747) values over time [Table 3]. For every 1/min increase in CO, $vaCO_2$ significantly decreased by 0.338 mmHg after adjusting for repeated measures over time [P = 0.006, Figure 2].

Central venous oxygen saturation

In patients with septic shock, enrolment $ScvO_2$ >70 was not associated (P = 0.930) with higher odds of mortality (OR: 1.00, 95% CI: 0.42–2.60). There was no evidence of a change in $ScvO_2$ (P = 0.063) values over time [Table 3]. For every 1/min increase in CO, $ScvO_2$ increased by 1.11% after adjusting for repeated measures over time [P = 0.027, Figure 3].

Lactate

Initial lactate was not associated (P = 0.109) with higher odds of mortality (OR: 1.09, 95% CI: 0.99–1.22). Lactate significantly decreased over time [P < 0.001, Table 3] with the rate of decrease more pronounced in survivors than nonsurvivors (0.35 vs. 0.10, P < 0.001).

Other parameters

Patients in septic shock also showed a significant decrease in hemoglobin level (0.39 g/dl every 24 h, P < 0.001) and VIS (4.42 units every 24 h, P < 0.001), [Table 3]. For every 24 h time interval, the odds of having IVC variability were significantly lower (OR: 0.69 every 24 h, P = 0.006). A significant increase in serial mean arterial pressure (3.56 mmHg every 24 h, P < 0.001) was also seen.

Table 3: Mixed-effects models of change in each outcome over time in patients with septic shock

Outcome	Number of observations	Change in outcome per 24 h	95% CI	*P*
SOFA score	79	−1.09	−1.35-−0.84	<0.001
Log lactate	79	−0.24	−0.30-−0.17	<0.001
$ScvO_2$	79	−1.26	−2.58-0.07	0.063
$vaCO_2$	77	−0.06	−0.44-0.31	0.747
Cardiac index	68	−0.08	−0.18-0.01	0.081
Hemoglobin	79	−0.39	−0.54-−0.24	<0.001
Mean art. pressure	79	3.56	2.12-5.01	<0.001
VIS	79	−4.42	−6.78-−2.05	<0.001
IVC variability†	74	0.69	0.51-0.92	0.006

†Odds of IVC variability. VIS: Vasoactive inotrope score; SOFA: Sequential organ failure assessment; $vaCO_2$: Veno-arterial CO_2 difference; $ScvO_2$: Central venous oxygen saturation; IVC: Inferior vena cava

Discussion

Several metabolic patterns may exist in patients with shock. In our study, in septic patients, baseline $vaCO_2$ of ≤ 6 mmHg was associated with a higher mortality, but only in those patients with $ScvO_2$ >70%. Enrolment SOFA scores were associated with mortality. There was no significant association between initial $ScvO_2$ and lactate levels with mortality. The lactate levels however significantly decreased over time, and the rate of decrease was more pronounced in survivors than nonsurvivors. For every 1/min increase in CO, $vaCO_2$ decreased by 0.34 mmHg (P = 0.006) and $ScvO_2$ increased (P = 0.027) by 1.11% after adjusting for repeated measures over time. These observations are consistent with the hypothesis that primary metabolic failure in septic shock may be an important contributor for increased mortality.

Hypovolemia, hypotension, and low CO, along with ineffective oxygen utilization may be seen in shock patients. Downstream tissue parameters such as $vaCO_2$, $ScvO_2$, and lactate are used as markers of tissue

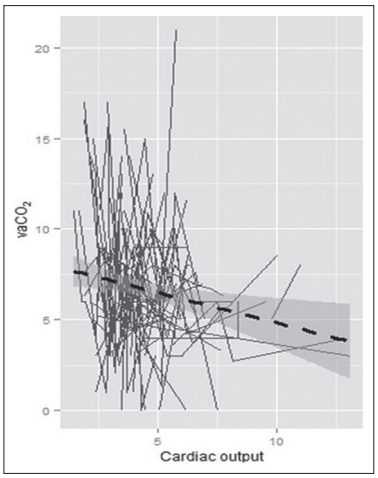

Figure 2: Relationship between veno-arterial CO_2 difference and cardiac output over time in septic patients - when veno-arterial CO_2 was examined against time and cardiac output, there was no significant interaction between cardiac output and time ($P = 0.664$), that is, the slope was constant over time. Removing the interaction, there was no significant effect of time ($P = 0.849$) but for every l/min increase in cardiac output, the veno-arterial CO_2 decreased significantly by 0.338 mmHg ($P = 0.006$). The dotted lines indicate mean values and the shaded area the 95% confidence interval

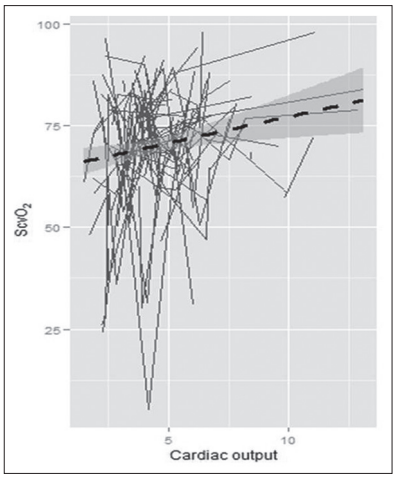

Figure 3: Relationship between central venous oxygen saturation and cardiac output over time in septic patients - central venous oxygen saturation versus cardiac output plus time showed no significant interaction ($P = 0.990$), implying the same effect of cardiac output on central venous oxygen saturation at each time point. Removing the interaction, there was a non-significant effect of time ($P = 0.054$) and significant effect of cardiac output ($P = 0.027$) implying that for every l/min increase in cardiac output, the central venous oxygen saturation increased by 1.11%. The dotted lines indicate mean values and the shaded area the 95% confidence interval

perfusion.[4] A decrease in $ScvO_2$ may be explained by a decrease in oxygen delivery or increase in tissue oxygen consumption or both.[25] Thus, increasing oxygen delivery to reverse a low $ScvO_2$ has been used in resuscitation protocols, particularly the early goal-directed therapy in septic shock.[8] $ScvO_2$ after the first 48 h of admission rather than initial $ScvO_2$ may predict better mortality.[26] Overzealous correction of $ScvO_2$ to supranormal levels can also lead to increased mortality in patients with preexistent hypoperfusion-induced organ injury.[25,27] In our study, enrolment $ScvO_2$ was not associated with mortality.

Some patients after resuscitation "normalize" $ScvO_2$ (>70%) but continue to manifest features of tissue hypoperfusion as evidenced by an increased $vaCO_2$.[17] These patients with a $vaCO_2$ "gap" of >6 mmHg may indicate a subset who continue to remain inadequately resuscitated.[17] On the other hand, impaired mitochondrial respiration in sepsis with nonutilization of oxygen by the cell may decrease CO_2 production and result in a "narrow" $vaCO_2$ gap, since anaerobic metabolism is less efficient in producing CO_2.[3,10] These patients may reflect those with cytopathic dysoxia or regional microcirculatory abnormalities in sepsis.[12] In such patients (those with normalized CO [$ScVO_2$ >70%] and narrow $vaCO_2$ gap), clinical recovery may be more reliant on reversal of the underlying process causing microcirculatory dysfunction rather than further aggressive attempts at optimization of CO and oxygen delivery. Indeed in our cohort, septic patients with a narrow $vaCO_2$ gap and normalized $ScvO_2$ had a higher mortality compared with those with a high $vaCO_2$ gap.

Lactate has traditionally been used as a marker of anaerobic metabolism and tissue hypoperfusion. Hyperlactatemia represents the imbalance between lactate production and clearance. Lactate levels, particularly in critically ill patients, can be influenced by factors other than global perfusion such as hepatic dysfunction, drugs (e.g., catecholamine, metformin, and anti-HIV drugs), and regional (e.g., bowel) ischemia.[5] Serial lactate measurements and lactate clearance over time have been shown to be better prognostic markers of mortality than single lactate concentration, which are themselves not sensitive or specific for tissue hypoperfusion.[28] Our results are consistent with these previous observations. Initial lactate levels were not associated with mortality. However, the reduction in lactate level over time was more pronounced in survivors than in nonsurvivors ($P < 0.001$). These observations suggest that the rapidity of reversal of the septic process (either because therapy is instituted promptly or because the pathophysiology is reversible) is more important than the absolute enrolment (extent of derangement) lactate value.

While lactate, $ScvO_2$ and $vaCO_2$ reflect downstream tissue markers, CO reflects an upstream endpoint of resuscitation more easily manipulated[4] and determines the global delivery of oxygen to tissues. In support of this assumption, we noted that higher CO was associated

with a significant reduction in $vaCO_2$ [Figure 2] and a significant increase in $ScvO_2$ [Figure 3]. This observation is consistent with earlier studies.[6,29]

SOFA score has been used as a prognostic indicator during the first few days of ICU admission.[30] Consistent with other studies, the enrolment SOFA score in our study was associated with mortality.

Our study has some limitations. First, four discrete time points were chosen at 24-h intervals for the evaluation of the various parameters. Continuous monitoring of these parameters and measuring changes with specific interventions would have been more relevant for defining the impact of specific interventions. However, this was not feasible due to cost constraints. Second, we did not use a defined treatment protocol common to all patients, but rather titrated care individually as the intensivists deemed appropriate. However, our treatment approach is common across the institution, and the same intensivists cared for all patient groups independent of shock etiology. Third, although we show a clear separation of sepsis mortality in those patients with $ScvO_2$ >70% and $vaCO_2$ <6 mmHg we did not assess mitochondrial function or see any correlation between these differences and macrocirculatory parameters. Fourth, we did not account for other factors affecting CO_2 production and elimination like diet and alveolar ventilation. Thus, our conclusion that impaired mitochondrial function in sepsis caused the increased mortality remains hypothesis generating and warranting further study.

Conclusion

In septic shock, low $vaCO_2$ is a predictor of mortality in patients with normalized $ScvO_2$. These findings are consistent with cytopathic dysoxia and microcirculatory dysfunction in septic shock.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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