Central venous–arterial CO_2 pressure difference in correlation to dynamic changes of serum lactate level in patients with polytrauma

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Background and aim of work
Early diagnosis, rapid intervention, and correction of tissue hypoperfusion are the major aims in the management of polytraumatized patients. The venous-to-arterial carbon dioxide tension difference is a marker of the adequacy of cardiac output to global metabolic demand, and so, its detection is a helpful method to determine patients who stay under resuscitation way. Regarding this, its monitoring could help the physicians to make the decision to give treatment targeting at improving cardiac output.

Patients and methods
This is a prospective single-center observational study done on 40 patients with polytrauma admitted to Assiut University Hospital resuscitation room and followed for the first 12 h of ICU stay. At the start of resuscitation, central venous and arterial blood samples were obtained to estimate the mixed venous-to-arterial carbon dioxide tension difference from the baseline values. All consecutive paired blood samples were collected for each studied patient within the following first hour, after the sixth hour, and after the 12th hour.

Other data collection
Hourly urine output during the early 12 h, kidney function, and hemodynamics of arterial carbon dioxide tension, arterial oxygen tension, central venous carbon dioxide tension, and central venous oxygen tension were assessed. Arterial oxygen saturation and mixed venous oxygen saturation, arterial and central venous lactate, hemoglobin concentration, and ICU stay were examined as well.

Results
The differences between arterial tenson and oxygen tension showed insignificant differences. There were changes in the mixed venous-to-arterial carbon dioxide tension difference over time period. Comparison between basal value and the follow-up results showed insignificant difference as well. There was significant difference between baseline lactate level and its corresponding measure at the 12th hour after resuscitation reflecting to somewhat optimal resuscitation. The hemodynamic changes (increases) over time included mean arterial blood pressure and central venous pressure. There were significant changes during the whole follow-up period in comparison with the baseline values. Urine output showed significant increases over time when compared with the second hour urine volume. There is significant correlation between blood lactate level and the difference between venous and arterial oxygen after 6 h of resuscitation; this was a strong positive correlation. The difference between blood lactate level and the difference between venous and arterial carbon dioxide is statistically significant at the baseline of resuscitation there is a moderate positive correlation.

Conclusion
Central venous–arterial carbon dioxide pressure difference in correlation to dynamic changes of serum lactate could be used as an indicator of tissue perfusion in patients with polytrauma.

Keywords:
hemodynamic monitoring, lactate, polytrauma

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Introduction

Patients with polytrauma status are at a high risk for complications, with high mortality rate as a primary or secondary sequence of organ dysfunction related to hypoperfusion. However, predictors of tissue hypoperfusion are still not studied very well in such group of patients. The arteriovenous difference in partial pressure of CO_2 [P (v – a) CO_2] has a reverse correlation to cardiac output in surgical patients [1].

Early diagnosis, rapid intervention, and correction of tissue hypoperfusion are the major aims in the management of polytraumatized patients. The venous-to-arterial carbon dioxide tension difference

is a marker of the adequacy of cardiac output to global metabolic demand, and so, its detection is a helpful method to determine patients who stay under resuscitation way. Regarding this, its monitoring could help the physicians to make the decision to give treatment targeting at improving cardiac output [2].

Many reports showed that PCO_2 difference is a blood flow marker to remove total CO_2 produced by the peripheral tissue [3]. Therefore, we assume that venoarterial PCO_2 gap and lactate dynamics may reflect the adequacy of blood flow during resuscitation and could be used as a predictor for tissue perfusion and expected complications in patients with polytrauma.

Primary outcome

The difference between carbon dioxide partial pressure in venous and arterial blood in correlation to changes in serum level of lactate within the early 12th hour after admission and resuscitation was the primary outcome.

Secondary outcome measures

The following were the secondary outcomes:

(1) Kidney function (time frame: 72 h), including serum creatinine in mg/dl and urine output/h.
(2) Hemodynamic stability, including pulse rate and mean arterial blood pressure (time frame: 72 h).
(3) Duration of stay in the critical care unit (time frame: 72 h).

Patients and methods

This is a prospective single-center observational study done on 40 patients with polytrauma admitted to Assiut University Hospital resuscitation room, who were followed for the first 12 h of ICU stay. Approval of Local Ethics Committee of Faculty of Medicine, Assiut University, was obtained, and then the study was registered on clinical trials NCT02727946.

The inclusion criteria were as follows:

(1) Patients aged 18–60 years.
(2) Polytraumatized patients with greater than three Abbreviated Injury Scale [4], which required resuscitation and insertion of a central venous catheter and admission at ICU.

Exclusion criteria

Severe cardiopulmonary conditions (cardiac ischemia, previous stroke, and chronic obstructive pulmonary disease), chronic kidney disease (blood urea nitrogen >100 mg/dl or creatinine >mg/dl), involvement of aorta, or advanced vascular disease were the exclusion criteria.

All patients were resuscitated according to the trauma protocol:

(1) Ensure patent airway.
(2) Establish adequate oxygenation and ventilation.
(3) Safe venous access – two large-bore cannula (16 G).
(4) Manage any external bleeding source.
(5) Rapid determination of patients needing operative hemostasis.
(6) Infusion of crystalloids or colloids to maintain central venous pressure (CVP) above 8–10 mmHg and maintain systolic blood pressure to be more than 80–90 mmHg.
(7) Infusion of blood products if hemoglobin less than 8 g/dl and Fresh Frozen Plasma if international normalized ratio greater than 1.2.
(8) Maintain adequate urine output more than 0.5 ml/kg//h.
(9) Pain control using paracetamol or low-dose opioids.

At the start of resuscitation, central venous and arterial blood samples were obtained to estimate 'P (v – a) CO_2' (baseline values). All consecutive paired blood samples were collected from each studied patient within the following first hour, after the sixth, and the 12th hours.

Other data collection

Hourly urine output during the early 12 h, kidney function, and hemodynamics of arterial carbon dioxide tension ($PaCO_2$), arterial oxygen tension (PaO_2), central venous carbon dioxide tension ($PcvCO_2$), and central venous oxygen tension ($PcvO_2$) were assessed. Arterial oxygen saturation (SaO_2) and SvO_2, arterial and central venous lactate, and hemoglobin concentration, and ICU stay were examined as well.

Ethical consideration

All participants' data obtained in this study were kept confidential. The patients were not identified by name in any way concerning this study.

Statistical analysis

Data were expressed as mean values ± SD or numbers (%). Student's *t*-test was used to analyze the parametric data, and discrete (categorical) variables were analyzed using the χ^2-test, with P less than 0.05 being considered statistically significant. Wicoxon rank sum test was used for analysis of nonparametric data. The sample size calculation was based on a previous study [5]. We have used G*Power 3 software (G* Power version 3.1.9.4 program witten by franz faul, univeristy of kiel, germany), with a power of 90% and

type I error of 5%, and the minimum required sample size is 35 patients, so we have enrolled 40 participants.

Results

Table 1 shows the demographic and clinical data of the participants. Overall, 5% of the patients did not survive in spite of proper resuscitation protocols.

Fig. 1 shows that the changes of Pa – vCO_2 over time period. Comparison between basal value and the follow-up results showed insignificant difference.

Regarding the differences between Pa – vO_2, they have been represented in Fig. 2. The comparison between each value at different time interval and basal value showed insignificant differences.

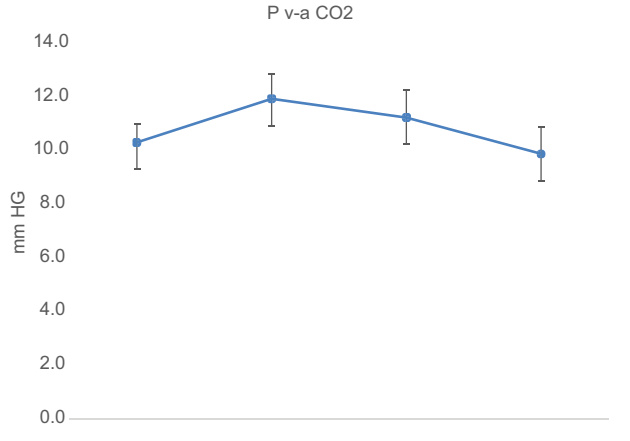
Serum lactate level dynamic changes over time are shown in Table 2. There was a significant difference between baseline lactate level and its corresponding measure at the 12th hour after resuscitation.

Fig. 3 shows the hemodynamic changes (increases) over time including mean arterial blood pressure and CVP. There were significant changes during the whole follow-up period values in comparison with the baseline values, which means good resuscitation.

Urine output showed significant increases over time when compared with the 2nd hour urine volume, and this is demonstrated in Fig. 4.

Table 3 shows the correlations between blood lactate level and the difference between venous and arterial oxygen, as well as carbon dioxide.

Figure 1



Changes in differences between venous and arterial CO_2 tension over time. *P* v – a CO_2 1 baseline, *P* v – a CO_2 2 after first hour, *P* v – a CO_2 3 after sixth hour, *P* v – a CO_2 4 after 12th hour.

The difference between blood lactate level and the difference between venous and arterial carbon dioxide is statistically significant at the baseline of resuscitation (a moderate positive correlation). There is also significant correlation between blood lactate level and the difference between arterial and venous oxygen after 6 h of resuscitation; this is a strong positive correlation.

Discussion

Experimental and clinical studies support the evidence that *P* (v – a) is dependent on the cardiac output, the global CO_2 production, and on the complex relationship

Table 1 Demographic and clinical data

Variables	Values
Age (years)	47±13.5
Sex: male/female	32/8
Height (cm)	170±5.7
Weight (kg)	80.6±13.8
Injury severity score	37±9.3
ICU stay (days)	1.95±0.28
Mechanical ventilation days	1.2±0.2
Mortality rate	12.5%

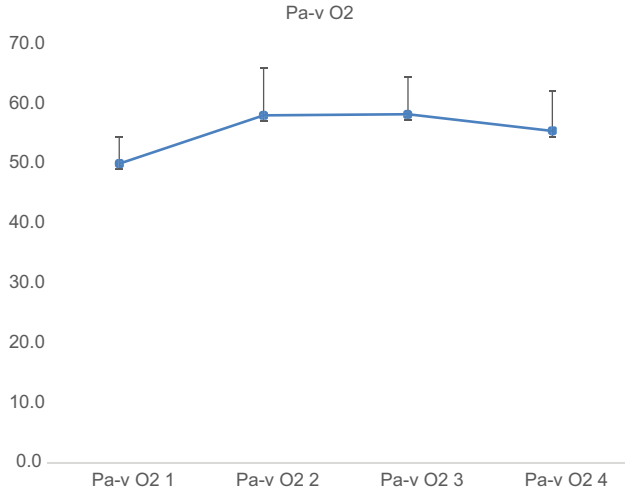
Data are expressed as mean±SD, number (percentage).

Table 2 Changes in serum lactate level

Variables	Serum locate level (mmol/l)	*P* value in comparison to baseline
Baseline	3.3±2.2	-
First hour	3.2±1.8	0.5
Sixth hour	2.9±1.2	0.09
12th h	2.6±0.8	0.02*

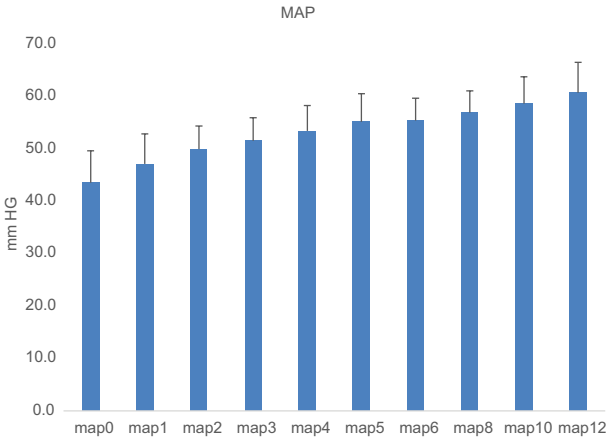
Data are expressed as mean±SD. If *P*<0.05 is considered statistically significant. *Significant difference in comparison to the base line value.

Figure 2



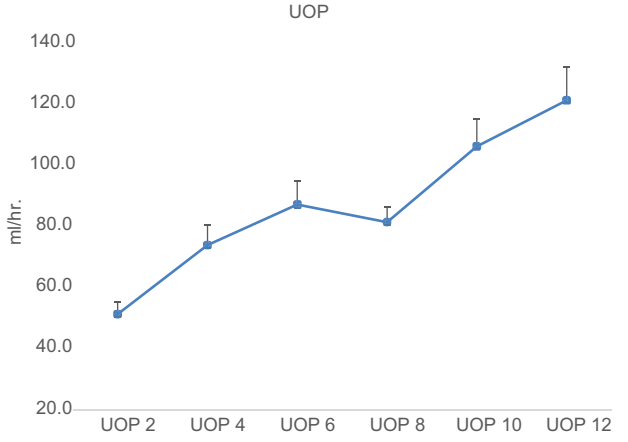
Changes in differences between arterial and venous O_2 tension over time. Pa – v $O_2$1 baseline, Pa – v $O_2$2 after first hour, Pa – v $O_2$3 after sixth hour, Pa – v $O_2$4 after 12th hour.

Figure 3



Changes in the mean arterial blood pressure over time.

Figure 4



Changes in the urine output over time.

Table 3 Pearson correlation between blood lactate level and corresponding Pa–v O_2 and P v–a CO_2

Time	Lactate/Pa–v O_2		Lactate/P v–a CO_2	
	P	Pearson *r*	*P*	Pearson *r*
Baseline	0.6	–0.06	0.002	0.48
First hour	0.2	0.17	0.09	0.27
Sixth hour	<0.001*	0.83	0.16	0.22
12th h	0.6	–0.07	0.2	0.22

*P<0.05 is considered statistically significant

between PCO_2 and CO_2 content. In addition, clinical studies support the evidence that P (v – a) CO_2 is an indicator of the adequacy of venous blood to wash out the total CO_2 produced by the peripheral tissues and can serve as an indicator of tissue hypoxia [6].

In our study, we revealed that the changes of Pv – aCO_2 over time period (i.e. comparison between basal value and the follow-up results) showed insignificant difference (P > 0.05). This is against Vallet *et al.* [3] who showed in their study that of monitoring central venous-to-arterial carbon dioxide partial pressure difference (ΔPCO_2) could be a helpful additional method to guide the resuscitation in the early phase of septic shock.

The results of laboratory investigations in patients with septic shock have determined that the decreased cardiac output is the major determinant factor in the increase of P (v – a) CO_2. Mecher and colleagues, in a previous study, have observed that shocked patients with P (v – a) CO_2 greater than 6 mmHg had a significantly lower mean cardiac output in comparison with patients with P (v – a) CO_2 less than or equal to 6 mmHg.

In our results, regarding the Pa – vO_2 differences, it showed insignificant differences, if we combine the Pa – vO_2 with CO_2 difference in venous and arterial. Furthermore, it can be combined with the O_2-derived parameters for estimating the combination of venoarterial PCO_2 difference with arteriovenous O_2 content difference (ΔPCO_2/C (a – cv) O_2), which could be used for recognition of the presence of global anaerobic metabolism [7].

Oxygen delivery is a compound parameter related to cardiac index and arterial oxygen content. Previous researches demonstrated that gradient of central venous-to-arterial CO_2 (CVA-CO_2) tension correlate inversely with the cardiac index [8].

Rapid detection and sufficient resuscitation of tissue hypoperfusion are particularly important in the management of shock to avoid the tissue hypoxia and development of multiple organ failure. Measurtment of mixed venous oxygen saturation (SvO_2) from a pulmonary artery catheter has been suggested as an indirect indicator of global tissue oxygenation [9]. SvO_2 is a reflection of the balance between oxygen demand and supply. A Low SvO_2 represents a high oxygen extraction (O_2ER) to maintain aerobic metabolism and oxygen consumption (VO_2) – which is the total amount of oxygen removed from the blood due to tissue oxidative metabolism per minute – being constant in response to an acute decrease in global oxygen delivery (DO_2), which is the total amount of oxygen delivered to the tissues per minute, irrespective of the distribution of blood flow. However, when DO_2 decreases under a critical level, O_2ER is no longer able to uphold VO_2, and global tissue hypoxia appears, as indicated by the lactic acidosis occurrence [10–12].

It has been found that the early hemodynamic optimization using a resuscitation bundle aiming to increase $ScvO_2$ greater than 70% was related to an important decrease in the shock mortality [13]. So that, monitoring of $ScvO_2$ has become widely recommended [14].

In our study, there was a significant difference between baseline lactate level and its corresponding measure at the 12th hour after resuscitation reflecting to somewhat optimal resuscitation.

In the literature, a direct relationship between blood lactate and mortality has been suggested by investigating shock of various causes. The closest relationship, however, was with 'terminal lactate' when estimation was of lowest clinical value. A more practically helpful suggestion was that a decrease in blood lactate in the first hour of resuscitation was a reliable marker of outcome from shock [15].

Hyperlactataemia is common to occur in severely ill patients. The presence of increased lactate levels has prognostic implications of major importance in these patients [15].

Lactate has also been shown as a resuscitation endpoint [16,17]. However, no advantage have been gained for lactate decrease-guided treatment over resuscitation guided by $ScvO_2$ in hypovolemic shocked patients [5].

The hemodynamic changes (increases) over time including mean arterial blood pressure and CVP. There were significant changes during the whole follow-up period values in comparison with the baseline values.

In this case, the management of this hemodynamic scenario usually includes fluid therapy to expand the intravascular compartment and increase venous return [18].

Alot of minimally invasive and non invasive diagnostic techniques are now available that allow physicians to assess volume responsiveness using dynamic tools that according to the Frank-Starling law, fluid challenge in polytrauma chocked patients. These technologies complement one another; each has helpful place in the continuity of the resuscitation process [18].

Urine output showed significant increases over time when compared with the second hour urine volume. Urine output is the single important clinical parameter that is not monitored electronically in most of medical centers.

Early detection of kidney dysfunction in polytraumatized patients is highly important in the prevention of further renal injury, a sequence which often adversely affects the clinical outcome [19].

There is significant correlation between blood lactate level and the difference between arterial and venous oxygen after 6 h of resuscitation; this is a strong positive correlation.

The difference between blood lactate level and the difference between venous and arterial carbon dioxide is statistically significant at the baseline of resuscitation, and there is a moderate positive correlation.

Moreover, these correlations make sense as because of that during proper resuscitation, the differences between arterial and venous CO_2, and O_2 are correlated to lactate levels.

Another study showed a negative and statistically significant correlation coefficient between central venous-arterial carbon dioxide tension gradient ($\Delta CVA\text{-}CO_2$ tension gradient) and global oxygen delivery (DO_2) following fluid therapy [8].

Moreover, an another study supports the concept that the central venoarterial carbon dioxide difference/ arterial-central venous oxygen difference (P (v – a) CO_2/C (a – v) O_2) ratio can identify adverse outcome in a manner similar to lactate clearance in the high $ScvO_{2\,case}$. The monitoring of the *P* (v – a) CO_2/C (a – v) O_2 ratio could give more information on global anaerobic metabolism in high ($SvcO_2$) mixed venous saturation condition [20].

Conclusion and recommendation

Early detection and management of tissue hypoperfusion are cornerstones in the management of shock patients. The venous-to-arterial carbon dioxide tension difference, which is an indicator of the adequacy of cardiac output to global metabolic demand, is a useful additional tool to recognize patients who stay under resuscitated after correction of O_2-derived parameters. Regarding this, its monitoring should help the physicians for the decision of giving therapy targeting at increasing cardiac output.

Our study denotes that optimal resuscitation of the polytrauma patients correlates with decrease in the terminal lactate level, with a measurable positive correlation between lactate level and arteiovenous blood gas difference.

We assume that Pv–a CO_2 and Pa–v O_2 and dynamic changes in lactate plasma level could be used as indicators of tissue perfusion in patients with polytrauma.

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Conflicts of interest

There are no conflicts of interest.

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