Basic Arterial Blood Gas Biomarkers as a Predictor of Mortality in Tetralogy of Fallot Patients

Abstract

Background: Serum lactate and base deficit have been shown to be a predictor of morbidity and mortality in critically ill patients. Poor preoperative oxygenation appears to be one of the significant factors that affects early mortality in tetralogy of Fallot (TOF). There is little published literature evaluating the utility of serum lactate, base excess (BE), and oxygen partial pressure (PO_2) as simple, widely available, prognostic markers in patients undergoing surgical repair of TOF. **Materials and Methods:** This prospective, observational study was conducted in 150 TOF patients, undergoing elective intracardiac repair. PO_2, BE, and lactate levels at three different time intervals were recorded. Arterial blood samples were collected after induction (T1), after cardiopulmonary bypass (T2), and 48 h (T3) after surgery in the Intensive Care Unit (ICU). To observe the changes in PO_2, BE, and lactate levels over a period of time, repeated measures analysis was performed with Bonferroni method. The receiver operating characteristics (ROC) analysis was used to find area under curve (AUC) and cutoff values of various biomarkers for predicting mortality in ICU. **Results:** The patients who could not survive showed significant elevated lactate levels at baseline (T1) and postoperatively (T2) as compared to patients who survived after surgery ($P < 0.001$). However, in nonsurvivors, the BE value decreased significantly in the postoperative period in comparison to survivors (-2.8 ± 4.27 vs. 5.04 ± 2.06) ($P < 0.001$). In nonsurvivors, there was a significant fall of PO_2 to a mean value of 59.86 ± 15.09 in ICU (T3), whereas those who survived had a PO_2 of 125.86 ± 95.09 ($P < 0.001$). The ROC curve analysis showed that lactate levels (T3) have highest mortality predictive value (AUC: 96.9%) as compared to BE (AUC: 94.5%) and PO_2 (AUC: 81.1%). **Conclusion:** Serum lactate and BE may be used as prognostic markers to predict mortality in patients undergoing TOF repair. The routine analysis of these simple, fast, widely available, and cost-effective biomarkers should be encouraged to predict prognosis of TOF patients.

Keywords: *Base excess, oxygen partial pressure, serum lactate, standard base deficit, tetralogy of Fallot*

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Introduction

Lactate, a by-product of anaerobic metabolism, is often considered a marker of tissue hypoxia.[1,2] Conventional clinical end points of resuscitation remained an insensitive marker of underlying physiological disturbance.[3,4] Serum lactate as a surrogate of hypoperfusion has been successfully used in predicting the need for resuscitation in trauma patients.[5] The serum lactate levels are a well-validated predictor of mortality in trauma,[6-10] sepsis,[11-13] and congenital cardiac surgeries.[14-16]

Base deficit (BD) represents the additional base that must be added to a liter of blood to normalize the pH. Significant BD has been shown to be a predictor of morbidity and mortality in critically ill and trauma patients.[17-21]

Tetralogy of Fallot (TOF), the most common form of cyanotic congenital heart disease, is characterized by a large ventricular septal defect, an overriding aorta, right ventricular (RV) outflow obstruction, and RV hypertrophy.[22] Poor preoperative oxygenation appears to be one of the significant factors that affect early mortality in the surgical treatment of TOF.[23]

The resurgence in interest to identify simple, widely available, clinical biomarkers for predicting impending major adverse events after surgical repair of TOF has spurred from the need to further decrease the mortality in these patients. The serum lactate, base excess (BE), and oxygen partial pressure (PO_2) that are easily available as blood gas analyzers

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are widely used in perioperative setup. These biomarkers can be utilized together to assess the ratio of oxygen delivery (DO_2) and oxygen consumption and thereby can help in estimating the likelihood of major adverse events following repair of TOF.

There is little published literature evaluating the utility of serum lactate, BE, and PO_2 as easily available cost-effective, prognostic markers in patients undergoing surgical repair of TOF. This study was, therefore, designed to evaluate serum lactate, BE, and PO_2 as prognostic biomarkers to predict mortality in TOF patients undergoing surgical repair.

Materials and Methods

After obtaining approval from the hospital Ethical Committee and written informed consent, this prospective, observational study was conducted in 150 TOF patients undergoing elective intracardiac repair on cardiopulmonary bypass (CPB). Patients with preexisting congestive cardiac failure, coagulopathy, renal failure (serum creatinine >2 mg/dl, anuria, or oliguria requiring dialysis), hepatic dysfunction (aspartate aminotransferase >40 U/L, alanine aminotransferase >40 U/L), immune or central nervous system dysfunction, local or systemic infection or inflammation (fever, leukocytosis, tachycardia, or tachypnea) were not included in the study.

Anesthetic and surgical management was standardized in all patients. Anesthesia was induced with ketamine (1–2 mg/kg), fentanyl (2–3 µg/kg), and rocuronium-bromide (0.8–1 mg/kg). Anesthesia was maintained with sevoflurane (0.5%–1%) in oxygen–air mixture with intermittent doses of fentanyl, midazolam, and vecuronium. Blood gas analysis and activated clotting time were performed intraoperatively, at half hourly intervals. At the end of the surgery, the sternum was closed, and patients were shifted to Intensive Care Unit (ICU) for elective ventilation. The intravenous infusion of injection dopamine was started in all patients, and if required, dobutamine was added to maintain hemodynamics.

The lactate, BE, and PO_2 levels were recorded through Roche cobas b-221 blood gas analyzer at three time points:
- T1 - After induction (baseline value)
- T2-20 min after protamine administration
- T3-48 h after surgery in the ICU.

Intraoperative CPB duration was noted. Once the patients were shifted to the ICU, the duration of postoperative ventilation, inotropic use, and stay in ICU was recorded.

Statistical analysis

The data were analyzed in SPSS software version 20 (IBM corporation, USA). The qualitative data were compared applying Chi-square test. The quantitative data were analyzed using Student's *t*-test and Wilcoxon-Rank sum, wherever applicable. To observe the change over a period of time in various biomarkers, repeated measures analysis was applied by Bonferroni method. The receiver operating characteristic (ROC) analysis was used to find area under curve (AUC) and cut-off values of various biomarkers for predicting mortality.

Results

A total of 150 patients were included in the study. Of them, 11 patients expired (nonsurvivors) and 139 patients (survivors) had a successful outcome. Their characteristics and perioperative parameters are shown in Table 1.

The patients who survived after surgical repair (survivors) demonstrated significant changes with time in lactate trends as compared to nonsurvivors. In survivors, lactate levels were increased from a mean value of 1.62 ± 0.45 at baseline (T1) to 3.20 ± 0.63 after CPB (T2) and then it decreased to 2.11 ± 0.63 in ICU (T3). However, in nonsurvivors, lactate instead of being cleared away from circulation continued to show a significant increasing trend measuring 2.29 ± 0.92, 3.26 ± 0.7, and 4.01 ± 0.73 at T1, T2, and T3, respectively. The patients who could not survive demonstrated significant elevated lactate levels at baseline (T1) and postoperatively (T2) as compared to patients who survived after surgery ($P < 0.01$).

The BE values were similar initially (T1) (5.86 ± 1.21 vs. 5.79 ± 1.20) ($P = 0.086$) and also after CPB (T2) (5.03 ± 2.01 and 4.90 ± 1.34) in survivors and nonsurvivors ($P = 0.774$). However, in nonsurvivors, the BE value decreased significantly in the postoperative period in comparison to survivors (−2.8 ± 4.27 vs. 5.04 ± 2.06) ($P < 0.001$). The mean initial PO_2 levels (T1) were similar in survivors and nonsurvivors ($P = 0.086$). In survivors,

Table 1: Baseline characteristics and perioperative parameters in survivors and nonsurvivors

Variable	All patients (*n*=150)	Survivors (*n*=139)	Nonsurvivors (*n*=11)	*P*
Age (years)	18.07±14.9	18.34±14.6	14.61±18.5	NS
Weight (kg)	33.78±21.8	34.29±21.3	27.36±27.5	NS
CPB duration (min)	93.03±50.9	93.34±52.8	89.1±6.6	NS
ICU duration (days)	2.83±1.4	2.85±1.3	2.6±1.6	NS
Hospital duration (days)	6.74±1.9	6.67±1.8	7.63±2.1	NS

Data presented as mean±SD. NS: Nonsignificant (*P*>0.05, survivors vs. nonsurvivors, Wilcoxon rank-sum test), SD: Standard deviation, ICU: Intensive Care Unit, CPB: Cardiopulmonary bypass

there was a significant increase in PO_2 after CPB (T2) in comparison to nonsurvivors (121.31 ± 69.95 vs. 79.40 ± 16.26) ($P < 0.001$). In patients who could not survive, there was a further significant fall of PO_2 to a mean value of 59.86 ± 15.09 in ICU (T3), whereas those who survived had a PO_2 of 125.86 ± 95.09 ($P < 0.001$) as shown in Table 2.

The ROC curve analysis [Figure 1] showed that lactate (T3) has the highest mortality predictive value with an AUC of 96.9% (sensitivity: 90.9%, specificity: 89.9%, cutoff value ≥3.0 mmol/l), while PO_2 (T3) has the lowest mortality predictive value out of these three biomarkers with an AUC of 81.1% (sensitivity: 72.7%, specificity: 72.7%, cutoff value ≤66.1). The mortality predictive value of BE (T3) was slightly lesser than lactate with an AUC of 94.5% (sensitivity: 89.9%, specificity: 90.9%, cutoff value ≤3.25) [Table 3].

Discussion

The quest for accurate identification of patients who have the potential to further deteriorate after cardiac surgery like TOF repair is still inadequate. Traditional end points of resuscitation such as heart rate, blood pressure, urine output, temperature gradient, and peripheral perfusion remained insensitive indicators of underlying physiological disturbance.[2-4]

The serum lactate is a well-validated marker of hypoperfusion, resuscitation, and mortality.[5-16] BD has also been utilized as a prognostic marker in various studies.[17-21] Recently, poor preoperative oxygenation has been found to be one of the significant factors to affect mortality in TOF patients.[22,23]

The easy availability of rapid blood gas and serum analyzers makes serum lactate, BE, and PO_2 measurements simple and cost-effective. However, there is little data

evaluating these three biomarkers together in predicting the outcome of TOF patients undergoing surgical repair. This study is a prospective observation of arterial blood lactate, BE, and PO_2 as prognostic markers in patients undergoing TOF repair.
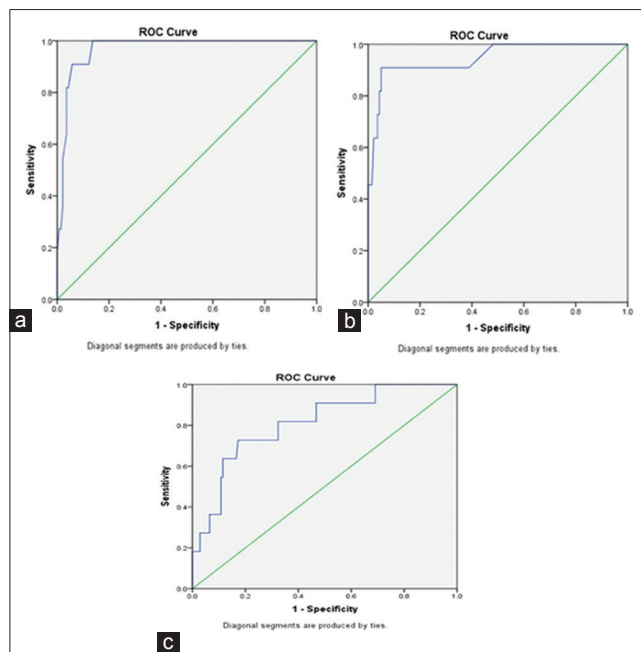
Elevated blood lactate level associated with metabolic acidosis is common among critically ill patients with systemic hypoperfusion and tissue hypoxia.[1,2] Several studies have suggested that blood lactate concentration has prognostic value in patients with trauma,[5-10] septic shock,[11,12] acute respiratory distress syndrome,[13] and cardiac surgeries.[14-16]

It has also been speculated that blood lactate concentration monitoring during CPB might be a sensitive tool to detect an imbalance between oxygen supply and demand.[24,25] The associated decreased organ perfusion and impaired DO_2 result in regional hypoxia and anaerobic metabolism. The end product of anaerobic metabolism is pyruvate, which is converted into lactic acid. In 1993, Abramson *et al.* demonstrated that the ability to clear lactate within 24 h to normal levels was the most accurate predictor of mortality in critically ill patients. They found a step-wise increase in the mortality rate as the time to lactate clearance increased.[26] In our study, the lactate levels increased from

Figure 1: (a) Receiver operating characteristic curve for lactate (T3), (b) receiver operating characteristic curve for base excess (T3) (c) Receiver operating characteristic curve for oxygen partial pressure. (a-c) Receiver operating characteristic curves at T3 time point for lactate, base excess, and oxygen partial pressure. The lactate levels (T3) showed highest mortality predictive value with an area under curve of 96.9% (sensitivity: 90.9%, specificity: 89.9%, and cutoff value ≥3.0 mmol/l). The mortality predictive value of base excess (T3) was close to lactate with an area under curve of 94.5% (sensitivity: 89.9%, specificity: 90.9%, and cutoff value ≤3.25), while oxygen partial pressure (T3) showed lowest mortality predictive value out of the three biomarkers with an area under curve of 81.1% (sensitivity: 72.7%, specificity: 72.7%, and cutoff value ≤ 66.1 mmHg)

Table 2: Trends of lactate (mmol/l), base excess, and oxygen partial pressure (mmHg) in survivors and nonsurvivors

Variable	Mean±SD		*P*
	Survivor (*n*=139)	Nonsurvivor (*n*=11)	
Lactate			
T1	1.62±0.45	2.29±0.92	<0.001
T2	3.20±0.63	3.26±0.7	0.753
T3	2.11±0.63	4.01±0.73	<0.001
Base excess			
T1	5.86±1.21	5.79±1.20	0.854
T2	5.03±2.01	4.90±1.34	0.774
T3	5.04±2.06	−2.8±4.27	<0.001
PO_2			
T1	83.68±24.56	70.69±14.81	0.086
T2	121.31±69.95	79.40±16.26	<0.001
T3	125.86±95.09	59.86±15.45	<0.001

SD: Standard deviation, PO_2: Oxygen partial pressure

Table 3: Prognostic value of lactate, base excess, and oxygen partial pressure at T3 time point

	Cutoff value	AUC (%)	Sensitivity (%)	Specificity (%)	PPV	NPV	OR (95% CI)	Correctly classified
Lactate	≥3.0	96.9	90.9	89.9	41.7	99.2	89.2 (10.6-750.2)	87.3
Base excess	≤3.25	94.5	89.9	90.9	41.7	99.2	25.2 (5.1-125.3)	84.6
PO$_2$	≤66.1	81.1	72.7	72.7	17.4	97.1	7.08 (1.78-28.1)	72.6

AUC: Area under curve, PPV: Positive predictive value, NPV: Negative predictive value, OR: Odds ratio, PO$_2$: Oxygen partial pressure, CI: Confidence interval

its baseline value (T1) to that after CPB (T2). However, the serum lactate started getting cleared from the circulation as shown by decreasing levels at T3 in survivors as compared to nonsurvivors. Although the rise in lactate levels can occur due to hepatic dysfunction, baseline and postoperative liver function tests were within normal limit. We observed that the baseline lactate levels (T1) as well as postoperative lactate levels were significantly higher ($P < 0.001$) in nonsurvivors as compared to the patients who survived after TOF repair. Hence, even a point analysis of baseline (AUC: 71.2%) and postoperative lactate levels (AUC 96.9%) was able to predict mortality in TOF patients.

The BE is defined as the amount of hydrogen ions that would be required to return the pH of the blood to 7.35 if the PCO$_2$ was adjusted to normal. The BE is thought to represent the presence of unmeasured anions and is usually taken as a surrogate marker of lactic acidosis.[27]

Martin *et al*. observed discordance between the serum lactate and BD levels. They found that increased lactate levels predict mortality and a prolonged course regardless of the associated BD level, whereas an increased BD level has no predictive value if the lactate level is normal.[28] In our study, we observed that postoperative BE level was significantly less ($P < 0.001$) in nonsurvivors as compared to survivors. The postoperative BE levels (AUC: 94.5%) were found to be almost a good prognostic marker as serum lactate (AUC: 96.9%).

When considering the adequacy of DO$_2$ to the tissues, factors such as hemoglobin, cardiac output, and oxygenation need to be considered. If DO$_2$ falls below oxygen consumption, the tissue extracts more oxygen from the blood. The decreased DO$_2$ cannot be compensated after a certain point, resulting in anaerobic metabolism and lactic acidosis.[29,30] In our study, we observed that the initial low PO$_2$ levels got raised after oxygenation during CPB and continued to be elevated in postoperative period in survivors. However, in nonsurvivors, the PO$_2$ rise was not sustained and declined in postoperative period. The PO$_2$ levels were significantly higher after CPB (T2) and in the postoperative period (T3) in survivors as compared to nonsurvivors ($P < 0.001$). The postoperative PO$_2$ levels (T3) were found to be a good prognostic marker with an ROC curve showing AUC of 81.1%. However, postoperative lactate (AUC: 96.9%) and BE (AUC: 94.5%)

levels were found to be a better predictor of mortality than PO$_2$ (AUC: 81.1%).

Our study has some limitations. The limitation of lactate as a prognostic marker is reflected by the fact that hyperlactemia early after CPB may represent intraoperative factors, early postoperative tissue oxygen debt, impaired lactate clearance, or a combination of these conditions. The BE level may be less accurate or misleading in patients with acute alcohol intoxication, significant renal dysfunction, after large-volume crystalloid resuscitation, or in the presence of hypoalbuminemia. The PO$_2$ levels may not always reflect tissue DO$_2$ and utilization. There may be various clinical factors affecting arterial PO$_2$.

Another limitation is that we have not done serial measurements of these markers for every 4–6 hours.

Although we have observed that baseline and postoperative lactate levels are a good prognostic marker, serial lactate levels and lactate clearance from the body could be a better predictor of mortality in TOF patients.

The serum lactate, lactate clearance and base excess have emerged as important biomarker with significant prognostic value in various clinical settings. The routine use of these simple, easy accessible biomarkers should be encouraged before any other advanced biomarker. The deranged levels of these biomarkers may indicate significant morbidity, mortality and requirement of prompt systematic approach to treatment.[31-34]

Conclusion

Serum lactate and BE may be used as prognostic markers to predict mortality in patients undergoing TOF repair. The routine analysis of these simple, fast, widely available, and cost-effective biomarkers should be encouraged to predict prognosis of TOF patients.

Conflicts of interest

There are no conflicts of interest.

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