



Serum lactate and base deficit as predictors of mortality and morbidity

Farah A. Husain, M.D.*, Matthew J. Martin, M.D., Philip S. Mullenix, M.D.,
Scott R. Steele, M.D., David C. Elliott, M.D.

Department of Surgery, Madigan Army Medical Center, Fort Lewis, WA 98431, USA

Manuscript received January 13, 2003; revised manuscript January 23, 2003

Presented at the 89th Annual Meeting of the North Pacific Surgical Association, Seattle, Washington, November 8–9, 2002

Abstract

Objectives: To determine whether lactate levels and base deficits in critically ill surgical intensive care unit (SICU) patients correlate and whether either measure is a significant indicator of mortality and morbidity.

Methods: A review was made of 137 SICU patients who had serial lactate and blood gas measurements. Patients were stratified by absolute lactate and base deficit values as well as time to lactate clearance.

Results: Initial and 24-hour lactate level was significantly elevated in nonsurvivors versus survivors ($P = 0.002$). Initial base deficit was not significantly different; 24-hour base deficit did achieve statistical significance ($P = 0.02$). Subgroup analysis among trauma patients ($n = 36$) and major abdominal surgery ($n = 101$) confirmed the significant correlation between lactate levels and survival. There was poor correlation between initial and 24-hour lactate and base deficit among all patients ($r = -0.3$ and -0.5). Mortality if lactate normalized within 24 hours was 10%, compared with 24% for >48 hours and 67% if lactate failed to normalize. Physical status at discharge was related to initial lactate ($P = 0.05$), as well as to lactate clearance time ($P = 0.01$).

Conclusions: Elevated initial and 24-hour lactate levels are significantly correlated with mortality and appear to be superior to corresponding base deficit levels. Lactate clearance time may be used to predict mortality and is associated with outcome at discharge. Initial base deficit is a poor predictor of mortality and did not correlate with lactate levels except in trauma nonsurvivors. In addition to being used as an endpoint for resuscitation, lactate may be predictive of certain morbidities and patient outcome at discharge. © 2003 Excerpta Medica, Inc. All rights reserved.

Keywords: Serum lactate; Base deficit; Surgical intensive care unit; Mortality; Morbidity

Historically, resuscitation of trauma and surgical critical care patients has been guided by a combination of basic laboratory values, invasive monitoring and clinical findings. However, the optimal guide to the endpoint of resuscitation remains controversial. The ideal marker of adequate resuscitation should be able to accurately and reliably assess resolution of tissue hypoxia and should be predictive of patient mortality and outcome. In addition, it is critical that this information is provided in a timely fashion (within the first several hours) to avoid the adverse consequences of longer periods of tissue hypoxia and under-resuscitation.

Traditionally, normalization of vital signs, such as blood pressure, urine output, and heart rate have been used as endpoints of resuscitation. However, critical analysis of

these endpoints has revealed the inadequacy of relying solely upon vital signs in resuscitation of critically ill patients. Scalea et al [1] found that up to 80% of critically ill patients who are normotensive and have adequate urine output may remain in a state of compensated shock. Measures of oxygen extraction variables and gastric intramucosal pH have been explored as viable alternatives [2]. However, Joynt et al [3] demonstrated gastric intramucosal pH did not distinguish survivors from nonsurvivors over time. The two most commonly used markers in assessing resuscitation remain base deficit and lactate.

Both tests are easily obtained during resuscitative efforts and results are provided quickly. Base deficit is calculated directly from the blood gas analyzer from the PCO_2 , pH, and HCO_3^- values as applied to a standard nomogram. Base deficit represents the number of mEq/L of additional base that must be added to a liter of blood to normalize the pH.

* Corresponding author. Tel.: +1-253-474-5435.

E-mail address: farahh@gwu.edu

Additional calculation of an elevated anion gap can further serve as evidence of an organic cause to the elevated base deficit. A significant base deficit has been a marker of mortality in many studies [4–6]. Normal values vary among institutions, but tend to be greater than -2 mmol/L. In one study of trauma patients without head injury, a base deficit of ≥ 8 mmol/L predicted a 25% mortality rate in patients younger than 55 years old [7]. Furthermore, changes in the base deficit will often precede changes in other hemodynamic parameters in hemorrhagic shock [8]. Whereas physiological response mechanisms can maintain blood pressure, urine output, and pH, hemorrhage will cause early changes in both arterial and venous base deficit. This can then be used to follow trends in the patient's overall resuscitation. Base deficit is frequently used as an indirect measure of lactic acidosis. However, base deficit can be elevated in many other situations such as diabetic ketoacidosis, salicylate overdose, and renal dysfunction [5].

Lactate is a byproduct of anaerobic metabolism after glycolysis. The conversion of pyruvate to lactate is catalyzed by lactate dehydrogenase. Lactate is often considered a measure of tissue hypoxia. However, it can be elevated in nonhypoxic situations such as pyruvate dehydrogenase deficiency, and stress leading to increased glycolysis [9]. Although lactate can be elevated in other situations, the utility of guiding resuscitation by lactate clearance has been validated in many series [10–14]. Although elevated lactate levels are predictive of mortality, the time to clear or normalize the lactate level appears to also be strongly predictive. McNelis et al [10] reported that mortality directly correlated with the time to normalization (or failure to normalize) of lactate levels, with 100% mortality in patients who failed to achieve normal lactate levels.

While there have been numerous studies assessing both base deficit and lactate as endpoints of resuscitation and predictors of mortality, few have adequately compared the two in terms of correlation, reliability, and accuracy. The question remains whether initial lactate or base deficit values provide any insight in patient morbidity or mortality as well as discharge status. While the importance of lactate clearance has been studied, it remains uncertain whether the absolute lactate level on admission or clearance time of lactate is a better predictor of patient outcome. Additionally, lactate and base deficit are often thought of as related, but a true correlation between the values during resuscitation has not been established.

Methods

The charts of 137 consecutive surgical admissions to the Madigan Army Medical Center intensive care unit (ICU) from September 1996 to December 2001 were reviewed retrospectively. All patients were admitted to the ICU by the general surgery service for the identified purpose of resuscitation from shock due to trauma, pancreatitis, or as a

consequence of a major abdominal surgery. Vascular and cardiothoracic patients were excluded. All patients had both serial lactate and base deficit measurements determined simultaneously. Clinical management decisions were by senior surgical residents in concert with a general surgery attending staff member and ICU attending staff in a collaborative ICU. All patients had an initial arterial lactate and blood gas (with calculated base deficit) measured at the time of admission to the ICU. Our routine protocol is to check lactate levels and base deficit every 4 to 6 hours during the initial resuscitation, but the timing of repeat measurements was at the discretion of the managing surgical team. A normal lactate level was defined as ≤ 2 mMol/L. The time of the first normal lactate was recorded as "clearance time." Normal base excess/deficit was defined as that between 2 and -2 mMol/L. APACHE II (Acute Physiology and Chronic Health Evaluation) scores and predicted mortality at 24 hours after ICU admission were calculated [15]. Injury Severity Scores (ISS) were calculated for all trauma patients [16]. Same admission mortality and incidence of pulmonary, cardiac, renal, and infectious events was recorded. Pulmonary events included adult respiratory distress syndrome or acute lung injury with a $\text{PaO}_2/\text{FiO}_2$ ratio less than 200 or 300, respectively, consistent chest radiograph findings of bilateral interstitial process, and a pulmonary capillary wedge pressure less than 18 mm Hg. Cardiac events included myocardial infarction, congestive heart failure, or life-threatening dysrhythmias. Renal events included acute renal failure (creatinine increase to at least double the baseline value) or new dialysis requirement. Infectious events included wound infection, pneumonia, urinary tract infection and sepsis with positive blood cultures. Among survivors, physical status at time of discharge or transfer was assessed. It was recorded as good (minimal to no assistance for daily living required), moderate (some nursing needs or assistance with activities of daily living), or poor (need for full time medical or rehabilitation care). Demographic, hemodynamic, laboratory and outcome data were recorded.

Initial and 24-hour lactate and base deficit levels, as well as time to lactate clearance were compared among survivors and nonsurvivors for the entire group. Subgroup analysis was then performed for the trauma patients and for those with nontrauma diagnoses, all of whom had either acute pancreatitis or had undergone major abdominal surgery. Patients were also stratified into four groups based on lactate clearance time. Group 1 never achieved normal lactate levels. Group 2 normalized lactate within 24 hours. Group 3 achieved a normal lactate level between 25 and 48 hours, and group 4 took longer than 48 hours to normalize. These groups were then compared with respect to mortality, morbidity, and functional status at time of discharge.

Data are presented as mean \pm standard deviation. Parametric data were analyzed by two-tailed Student *t* test or analysis of variance (ANOVA). Nonparametric data were analyzed utilizing a chi-square test. Selected variables identified during univariate analysis were then subjected to mul-

tivariate logistic regression to determine independent predictors of mortality. The strength of the relationship between lactate and base deficit was analyzed with Pearson's correlation coefficient (r) and coefficient of determination (R^2). A clinically relevant association was defined as $R^2 > 0.5$, as has been previously described [9]. Statistical significance was set at a P value less than 0.05.

Multivariate logistic regression analysis was utilized to examine the independent relationships between initial (L1) lactate, 24-hour lactate (L2), lactate clearance time (LCLR), initial base deficit (B1), and 24-hour base deficit (B2), and the outcome measure total mortality, adjusting for the covariates of age, gender, and APACHE II score. Two separate models were constructed, the first model evaluating all patients ($n = 137$), and the second analyzing the major abdominal surgery (MAS) subgroup only ($n = 101$). The dependent variable of total mortality was evaluated in dichotomous categorical fashion, and the independent variables L1, L2, LCR, B1, and B2, as well as the covariates age and APACHE score, were analyzed as continuous data. The covariate sex was evaluated in dichotomous categorical fashion. The probabilities for entry into or removal from the model were set at 0.05 and 0.20, respectively. Regression analysis was performed in a hierarchical stepwise conditional manner and equations took the following form: *outcome variable* = $b_0 = b_1$ (APACHE) + b_2 (LCLR) + b_3 (L2) + b_4 (age) + b_5 (L1) + b_6 (B1) + b_7 (sex) + b_8 (B2).

Statistical analyses were performed using Microsoft Excel (Microsoft, Redmond, Washington), Windows KWIK-STAT (Texasoft, Cedar Hill, Texas), and SPSS (SPSS, Chicago, Illinois).

Results

In all, 137 patients were included in the analysis: 36 were trauma patients, 90 had major abdominal surgery, and 11 had biliary tract infection (acute pancreatitis or cholangitis or both); 45% of the patients ($n = 62$) were women, and 55% ($n = 75$) were men. The mean APACHE II score for all patients was 22.7 ± 5.1 . The mean ISS for trauma patients was 22.8 ± 11.0 (Table 1).

Table 2 shows outcome data in relation to initial and 24-hour lactate and base deficit values. Among the entire study group, initial lactate significantly separated nonsurvivors from survivors (4.2 versus 2.8, $P = 0.002$). At 24 hours, there was even a more disparate and significant difference in lactate levels between nonsurvivors and survivors (5.1 versus 2.2, $P < 0.001$). Base deficit was not significant in initially (6.9 versus 6.0, $P = 0.33$). However, at 24 hours base deficit became significant in distinguishing nonsurvivors from survivors (6.6 versus 3.8, $P = 0.02$).

Among subgroups analyzed, initial lactate was significantly more elevated among those who died than among those who survived in the MAS subgroup (3.7 versus 2.7, $P = 0.04$), and continued to be significant at the 24-hour

Table 1
Study and subgroup characteristics

	All	Trauma	MAS/other
Number	137	36	101
Age	59 ± 17	54 ± 20	63 ± 14
Male	75 (55%)	22 (61%)	53 (52%)
Female	62	14	48
APACHE II	22.7 ± 5.1	20.7 ± 11.0	23.4
Deaths	31 (23%)	7 (19%)	24 (24%)
Initial pH	7.33 ± 0.12	7.28 ± 0.04	7.35 ± 0.06
Initial MAP	70.3 ± 20.8	66 ± 17.0	71.5 ± 16.7

MAS = major abdominal surgery; MAP = mean arterial pressure.

lactate level (4.1 versus 2.1, $P < 0.001$). Initial base deficit was not significant in the MAS group (6.6 versus 6.0, $P = 0.58$). In addition, base deficit approached but did not reach significance at 24 hours in this subgroup (6.0 versus 3.9, $P = 0.054$).

The trauma subgroup followed a similar pattern with significantly higher lactate levels among nonsurvivors at admission (5.9 versus 3.0, $P = 0.006$) and 24 hours (8.8 versus 2.4, $P < 0.001$). Initial base deficit did not distinguish trauma nonsurvivors from survivors (8.1 versus 5.9, $P = 0.34$). Twenty-four hour base deficit was found to be significantly elevated in the trauma subgroup (8.7 versus 3.6, $P = 0.006$).

Correlation between initial lactate and base deficit revealed a weak relationship ($r = -0.32$, $R^2 = 0.11$; see Fig. 1). Twenty-four hour lactate and base deficit showed a moderate statistical correlation ($r = -0.55$) that did not achieve clinical significance ($R^2 = 0.31$). Subgroup analysis revealed a similar pattern in MAS and trauma patients. The only group to achieve statistical and clinically significant correlation between lactate and base deficit was trauma nonsurvivors. Both initial lactate and base deficit ($r = -0.78$, $R^2 = 0.61$), and 24-hour measures ($r = -0.96$, $R^2 = 0.92$) correlated well.

Lactate clearance time was also predictive of mortality and morbidity. We divided clearance time into four groups based on the time to achieve a normal lactate level. Group 1 cleared lactate levels in less than 24 hours and had a 10% mortality rate. Group 2 cleared lactate levels in 25 to 48 hours with a corresponding 20% mortality rate. Group 3 cleared lactate in greater than 48 hours with 23% mortality. Group 4 failed to achieve a normal lactate level and demonstrated a mortality rate of 67%. Included in group 4 were several patients who had initially elevated lactate levels and clinically responded well to resuscitation but did not have lactate levels observed until normalization (in violation of our protocol).

Prolonged lactate clearance time had an association with patient discharge status and morbidity. Patients whose discharge condition was classified as good ($n = 39$) cleared lactate at an average of 22 hours and had an average initial lactate of 2.8. Patients in moderate discharge condition ($n = 51$) had an average lactate clearance time of 27 hours, and

Table 2
Mortality versus lactate and base deficit

	All patients			Trauma patients			MAS patients		
	Lived	Died	P	Lived	Died	P	Lived	Died	P
Lactate (mMol/L)									
Initial	2.8	4.2	0.002	3.0	5.9	0.006	2.7	3.7	0.04
24 hour	2.2	5.1	<0.001	2.4	8.8	<0.001	2.1	4.1	<0.001
Base deficit (mMol/L)									
Initial	6.0	6.9	0.33	5.9	8.1	0.34	6.0	6.6	0.58
24 hour	3.8	6.6	0.02	3.6	8.7	0.006	3.9	6.0	0.054

average initial lactate level of 2.7. The group classified as poor condition at transfer or discharge (n = 10) had an average initial lactate of 3.9 and clearance time of 50 hours. Both initial lactate (P = 0.05) and clearance times (P <0.001) were found to be significant in predicting patient outcome at discharge.

The incidence of defined morbidity was calculated as a function of clearance time and compared by chi-square analysis. Prolonged lactate clearance was significantly associated with the incidence of acute renal failure (P <0.001), increasing from 12% if lactate was cleared within 24 hours to 70% in the greater than 48 hours group. Overall, the incidence of infection approached but did not reach significance in its correlation with lactate clearance time (P = 0.06). Significance was reached when the subgroup which never cleared lactate was excluded (P <0.007). A significant relationship was not demonstrated between adult respiratory distress syndrome (P = 0.28) or cardiac events (P = 0.23) and prolonged lactate clearance.

The multivariate analysis supports the univariate findings. Among all patients (Table 3), time to lactate clearance (P = 0.007) was an excellent independent predictor of mortality, as was the 24-hour lactate value (P = 0.021). Neither initial or 24-hour base deficit was a useful index of survivability. As one would expect, the strongest predictor of mortality was the APACHE II score (P = 0.000), an instrument that has been well validated externally and serves primarily as a covariate in this analysis. The expected predictive power of older age may have been diminished by

the contribution to total variance made by the trauma patient component. The trauma patients in this series were in general younger (mean 54 versus 63 years), and had a lower overall mortality (19% versus 24%). Interestingly, initial lactate was not an independent predictor of mortality. This is likely because this analysis also considers the contribution to variance made by the significant number of patients with an initially elevated lactate who subsequently responded to resuscitation with an improved 24-hour lactate value and a good clinical outcome (something univariate analysis does not do as effectively). Hence, the predictive power of lactate lies primarily in whether or not subsequent values drawn remain elevated and, most importantly, it is the time to clearance that ultimately helps discriminate survivors from nonsurvivors.

Among the MAS subgroup lactate clearance time (P = 0.002) and APACHE II score (P = 0.007) remained significant predictors of mortality (Table 4). As expected, with the younger and relatively less morbid trauma subgroup excluded, older age achieved significance in terms of contributing to total mortality (P = 0.047). Although the 24-hour lactate value was not found to be a predictor among MAS patients, there was a strong trend toward significance with a p of 0.079.

Comments

The search for the optimal marker of shock and adequate resuscitation from shock continues. Astute clinicians now

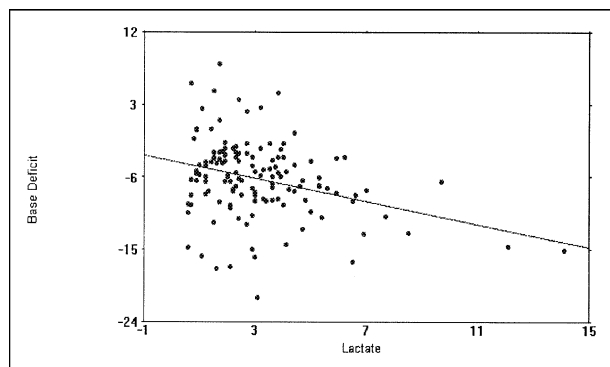


Fig. 1. Initial lactate level versus base deficit.

Table 3
Independent predictors of total mortality among all patients (n = 137)

Independent variable	Significance (P)
Significant independent predictor	
APACHE II score	0.000
Lactate clearance time	0.007
24-Hour lactate	0.021
Not significantly predictive	
Initial base deficit	0.179
Age	0.436
Sex	0.573
Initial lactate	0.872
24-Hour base deficit	0.957

Table 4
Independent predictors of total mortality among the major abdominal surgery subgroup (n = 101)

Independent variable	Significance (P)
Significant independence predictor	
Lactate clearance time	0.002
APACHE II score	0.007
Age	0.047
Not significantly predictive	
24-Hour lactate	0.079
Initial lactate	0.314
Initial base deficit	0.437
Sex	0.690
24-Hour base deficit	0.796

uniformly acknowledge that traditional markers, such as blood pressure and urine output, are necessary but not sufficient indicators of adequate global perfusion and resolution from shock. The importance of discovering such a reliable indicator of perfusion is obvious: in today's ICU, most deaths are secondary to multiple organ failure, an end-product of systemic inflammatory response (traditionally known as "sepsis"), which in itself is most often an immune system result of repeated or continuing hypoperfusion [17].

The optimal marker, or end point, of adequate resuscitation would possess a number of desirable qualities: superior accuracy (positive and negative predictive value), ease and rapidity of acquisition, reproducibility in a broad variety of clinical shock states, consistent results among different providers, and rapidity of change in response to change in clinical condition or to resuscitation. This study is a retrospective examination of two of the more widely used and respected markers of shock and resuscitation: blood lactate level and base deficit. Both markers share the qualities of ease and rapidity of acquisition as well as consistency of results among providers at different times and at different facilities. This study examines diagnostic accuracy in predicting outcome as well as reproducibility in two common clinical scenarios causing shock: severe trauma and non-trauma high-risk surgical disease.

Lactate is a byproduct of anaerobic cellular metabolism, elevated in hypoperfusion states when pyruvate cannot enter the Krebs cycle and subsequent mitochondrial oxidative phosphorylation due to insufficient cellular oxygen supply. As a result, the pyruvate is shunted to lactate through the enzyme lactate dehydrogenase, productive of only two molecules of the energy-rich adenosine triphosphate for every two molecules of pyruvate (from one molecule of glucose), compared with 38 molecules of adenosine triphosphate for each glucose molecule through the aerobic mitochondrial process when sufficient oxygen is present. In states of global hypoperfusion, or shock, when ubiquitous anaerobic metabolism predominates, lactate production exceeds its rate of metabolism in the liver and kidneys, resulting in an eleva-

tion in the blood level. Elevated blood lactate has been correlated strongly with mortality in many types of shock [11,18]. The rapidity at which lactate is cleared from the blood through vigorous resuscitation strongly correlates with ultimate outcome, including mortality, organ failure, and infection. The best chance of survival occurs when resuscitation efforts result in lactate clearance to normal values within 12 to 24 hours [12,19,20].

Base deficit is defined as the amount of alkali buffer required to titrate one liter of blood to a pH of 7.40 at normal body temperature and a normal arterial partial pressure of carbon dioxide. It is a calculated value from the Astrid and Siggard-Anderson nomogram, available widely on every obtained arterial blood gas, and a validated measure of metabolic acidosis [21]. Its use as a marker of shock and resuscitation evolved as an indirect measurement of lactic acidosis. In states of pure hemorrhagic and septic shock, and resuscitation therefrom, base deficit has been shown to have a direct correlation to lactate level [4,22]. Large retrospective human studies have shown that severity of base deficit on admission and response of base deficit to resuscitation serve as valuable markers of survivability after trauma [7,23].

Proponents of using base deficit as an end point of resuscitation point to superior ease of obtaining this value, [4] although newer laboratory equipment make this point moot [24]. Certain studies also suggest that an elevated base deficit persisting after achievement of a normal lactate level suggests an ongoing hypoperfusion state and an increased risk of mortality [25]. Proponents of use of lactate as an endpoint of resuscitation point to the substantial body of literature, including multiple prospective human studies, validating its use as an end point of adequate resuscitation [12,20,26]. There exists other evidence that significant hyperlactemia and dangerous hypoperfusion states can exist despite normal base deficit and lack of acidosis [20,27]. Jeng et al [14] recently published a comparison of lactate and base deficit levels in a series of burn patients. Similar to our results, lactate level was found to be a significant predictor of mortality while base deficit failed to achieve significance. Ultimately, it is unclear whether these two values are equivalent in the same populations of patients in shock [25,28]. It is also unclear whether base deficit is only a valuable marker for shock resuscitation in trauma patients, or whether it can be utilized in a mixed group of similarly hypoperfused patients in a surgical ICU.

The results of this study indicate that lactate level is superior to base deficit as a marker for shock and resuscitation. Lactate levels on admission and after 24 hours in hospital separated survivors from nonsurvivors. This relationship held true for trauma patients, nontrauma surgical ICU patients, and all patients combined, making it a useful marker for potential mortality in all types of shock encountered.

In contradistinction, base deficit was not as useful: values were no different between survivors and nonsurvivors in

most patient populations. Only in trauma patients at the 24-hour point was base deficit different between survivors from nonsurvivors. There was no significant difference in base deficit value between those who lived and those who died, among nontrauma patients having undergone major abdominal surgery. This was true on admission and at 24 hours after admission and attempted resuscitation.

More significant than absolute lactate level as a marker of shock and resuscitation was the time to lactate clearance—the time it took for blood lactate level to return to a normal level. Survival was 90% if lactate could be normalized within 24 hours, compared with 33% if lactate could not be normalized. It should also be mentioned that this is a conservative analysis of the power of lactate clearance time as several patients were included in group 4 who clearly responded well to resuscitation but did not have lactate values observed to normalization (in violation of protocol). If these patients were excluded, survival in the “never cleared” group, the mortality would approach 100%. This is consistent with other studies reporting that time to clearance of hyperlactemia is important to survival [12,19,20]. In multivariate analysis, lactate clearance time was shown to be a powerful independent predictor of mortality in all patients and in the major abdominal surgery subgroup.

Beyond looking at survival as an outcome, this study also reports end points of infection, organ dysfunction, and return to functional status in relationship to admission lactate values. Of note, physical status at discharge was improved and chance of acute renal failure minimized if hyperlactemia was cleared within 24 hours. As opposed to other studies, [13,20,29] we could show no correlation of lactate or clearance time to development of infection or multiple organ dysfunction.

This retrospective study supports that base deficit should be used with caution as a marker of shock and resuscitation from shock. It is unreliable in predicting presence, depth, or lethality of shock, as well as response to resuscitation, especially in the early phase. In our series initial base deficit was not useful in identifying those in need of aggressive resuscitation and did not become useful as a marker until 24 hours after presentation, at which point irreversible consequences of underresuscitation may have begun. At all time points it remained inferior to simultaneously measured lactate levels. As opposed to blood lactate level, the value of base deficit is affected by a plethora of factors causing metabolic acidosis above and beyond anaerobic metabolism, factors such as renal dysfunction, saline fluid resuscitation, gastrointestinal bicarbonate losses, and diabetic ketoacidosis. The argument that base deficit is more easily and quickly obtainable is offset by the ubiquitous presence of rapid lactate analyzers.

This study is one of a large series validating that lactate level, as well as time to lactate clearance, accurately predict life-threatening shock and response to resuscitation. Nonetheless, a prospective and controlled study comparing base deficit to lactate in various populations of patients in shock

would more definitively settle the question of whether the two markers of perfusion were equivalent.

References

- [1] Scalea TM, Maltz S, Yelon J, et al. Resuscitation of multiple trauma and head injury: role of crystalloid fluids and inotropes. *Crit Care Med* 1994;22:1610–15.
- [2] Shoemaker WC, Appel PL, Kram HG, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. *Chest* 1988;94:1176–86.
- [3] Joynt GM, Lipman J, et al. Gastric intramucosal pH and blood lactate in severe sepsis. *Anaesthesia* 1997;52:726–32.
- [4] Davis JW. The relationship of base deficit to lactate in porcine hemorrhagic shock and resuscitation. *J Trauma* 1994;36:168–72.
- [5] Bannon MP, O'Neill CM, Martin M, et al. Central venous oxygen saturation, arterial base deficit, and lactate concentration in trauma patients. *Am Surg* 1995;61:738–45.
- [6] Sauaia A, Moore FA, Moore EE, et al. Early predictors of postinjury multiple organ failure. *Arch Surg* 1994;129:39–45.
- [7] Rutherford EJ, Morris JA, Reed GW, et al. Base deficit stratifies mortality and determines therapy. *J Trauma* 1992;33:417–23.
- [8] Davis JW, Kaups KL, Parks SN. Base deficit is superior to pH in evaluating clearance of acidosis after traumatic shock. *J Trauma* 1998;44:114–18.
- [9] Aduen J, Bernstein WK, Miller J, et al. Relationship between blood lactate concentrations and ionized calcium, glucose, and acid-base status in critically ill and noncritically ill patients. *Crit Care Med* 1995;23:246–52.
- [10] McNelis J, Marini CP, Jurkiewicz A, et al. Prolonged lactate clearance is associated with increased mortality in the surgical intensive care unit. *Am J Surg* 2001;182:481–5.
- [11] Weil MH, Afifi AA, et al. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation* 1970; 41:989–1001.
- [12] Abramson D, Scalea TM, Hitchcock R, et al. Lactate clearance and survival following injury. *J Trauma* 1993;35:584–8.
- [13] Manikis P, Jankowski S, Zhang H, et al. Correlation of serial blood lactate levels to organ failure and mortality after trauma. *Am J Emerg Med* 1995;13:619–22.
- [14] Jeng JC, Jablonski K, Bridgeman A, Jordan MH. Serum lactate, not base deficit, rapidly predicts survival after major burns. *Burns* 2002; 28:161–6.
- [15] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13: 818–29.
- [16] Baker SP, et al. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974;14:187–96.
- [17] Shoemaker WC, Appel PL, Kram HB. Role of oxygen debt in the development of organ failure sepsis, and death in high-risk surgical patients. *Chest* 1992;102:208–15.
- [18] Groeneveld ABJ, Kester ADM, Nauta JJP, et al. Relation of arterial blood lactate to oxygen delivery and hemodynamic variables in human shock states. *Circ Shock* 1987;22:35–53.
- [19] Vincent JL, Dufaye P, Berre J, et al. Serial lactate determinations during circulatory shock. *Crit Care Med* 1983;11:449–51.
- [20] Claridge JA, Crabtree TD, Pelletier SJ, et al. Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma* 2000;48:8–14.
- [21] Mizoock BA. Utility of standard base excess in acid-base analysis. *Crit Care Med* 1998;26:1146–7.
- [22] Rudinsky BJ, Meadow WL. Relationship between oxygen delivery and metabolic acidosis during sepsis in piglets. *Crit Care Med* 1992; 20:831–9.

- [23] Davis JW, Parks SN, Kaups KL, et al. Admission base deficit predicts transfusion requirements and risk of complications. *J Trauma* 1996;41:769–74.
- [24] Slomovitz BM, Lavery RF, Tortella BJ, et al. Validation of a hand-held lactate device in determination of blood lactate in critically injured patients. *Crit Care Med* 1998;26:1523–8.
- [25] Kincaid EH, Miller PR, Meredith JW, et al. Elevated arterial base deficit in trauma patients: a marker of impaired oxygen utilization. *J Am Coll Surg* 1998;187:384–92.
- [26] Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA* 1993;270:2699–707.
- [27] Mikulashek A, Henry SM, Donovan R, et al. Serum lactate is not predicted by anion gap or base excess after trauma resuscitation. *J Trauma* 1996;40:218–22.
- [28] Moomey CB, Melton SM, Croce MA, et al. Prognostic value of blood lactate, base deficit, and oxygen-derived variables in an LD50 model of penetrating trauma. *Crit Care Med* 1999;27:154–61.
- [29] Bakker J, Gris P, Coffernils M, et al. Serial blood lactate levels can predict the development of multiple organ failure following septic shock. *Am J Surg* 1996;171:221–6.