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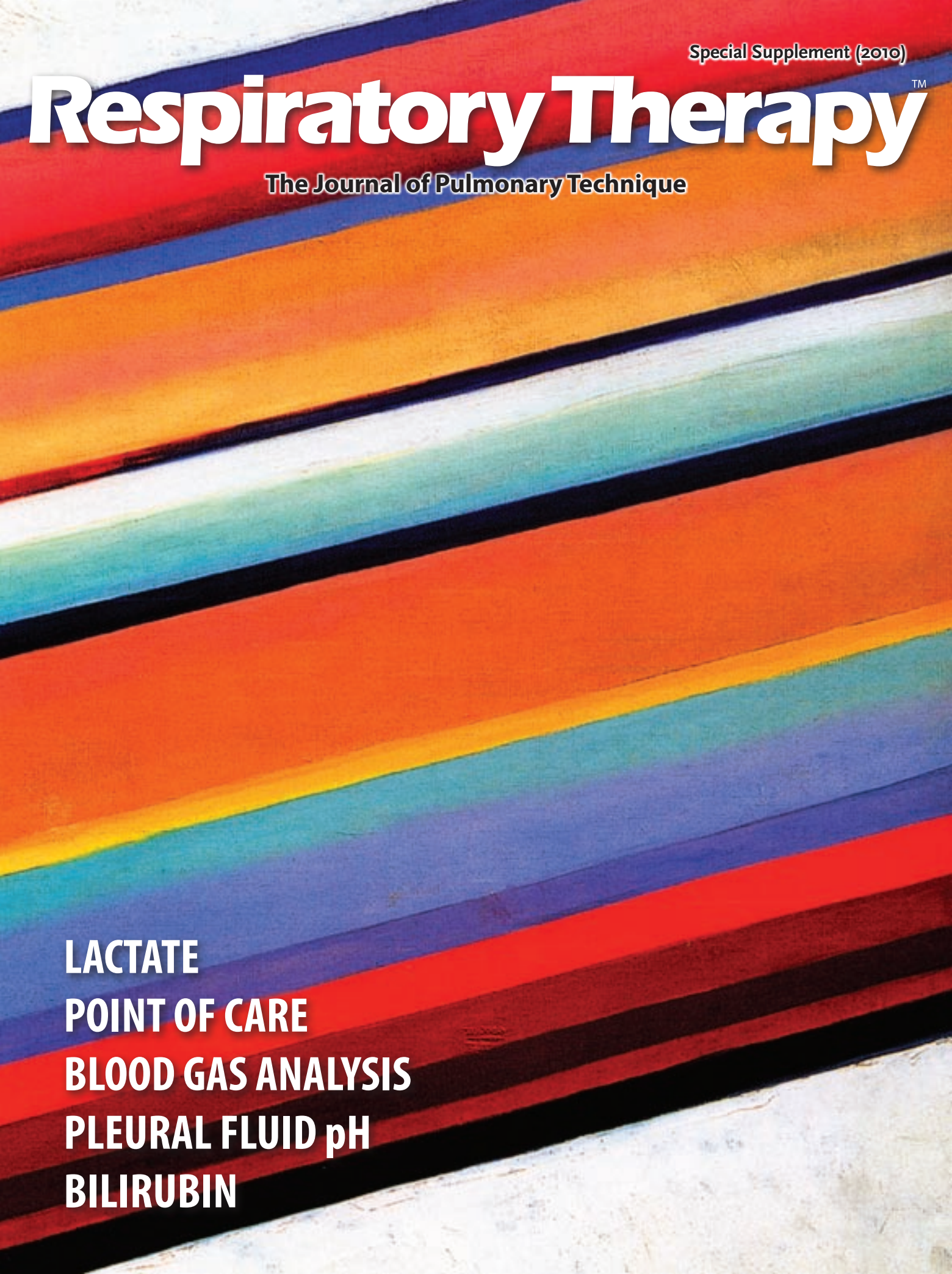

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Lactate in Critical Illness: Implications for Monitoring

Karen Robinson RCP (NBRC), POCS; Gail L. Kongable, RN, MSN, FNP

Introduction

Under normal physiologic conditions, serum lactate levels are between 0.5 and 1 mEq/L, representing balanced lactate metabolism. Hyperlactatemia in critical illness is considered an adaptive response to anaerobic glycolysis[1] and levels are common during conditions of sepsis or trauma,[2,3,4] as accumulation exceeds the rate of clearance until hemodynamic stabilization.[5,6] While lactate levels at concentrations outside the reference range (<2 mEq/L-4 mEq/L) are tolerated in patients, higher levels have been found to be independently related to increased mortality[7] and call for intervention in the form of early goal-directed therapy.[8] In modern intensive care units (ICU) the frequent measurement of lactate using blood glucose analyzers is useful in identifying patients at increased risk of death and serve as an early marker of a potentially reversible state.[9] Outcomes may be improved by adapting resuscitation to serial lactate measurements. This review presents a brief discussion of the available evidence.

Lactate as an indicator of severity of illness

Early studies found that elevated venous lactate (≥4 mEq/L) was often present in shock patients on admission to the medical ICU and was associated with increased incidence of organ failure and mortality rates of greater than 30%.[2,3,7] More recently, not only the presence of hyperlactatemia on admission, but also subsequent development and duration of elevated lactate are reported to increase the risk of mortality in surgical and trauma ICU patients.[9]

Cerovic et al[10] postulated that blood lactate concentrations in injured patients on hospital admission might be an objective indicator of the patient's true condition and serve as an independent predictor of injury severity, morbidity and mortality. These researchers examined the correlation of the admission Injury Severity Score (ISS)[11] and Trauma Injury Severity Score (TRISS)[12] with lactate levels drawn at admission, twice daily for the first 2 days, and daily for a following 3 days. Lactate levels in non-survivors were significantly higher than those in survivors on admission (6.3±5.9 vs 4.2±3.3 mEq/L) and at 12 hours (6.1±7.0 vs 3.2±1.9 mEq/L). Regression analysis demonstrated that injury severity, as measured by the ISS can also be predicted from lactate concentration on admission, while actual or predicted survival, as measured by the TISS can be predicted from lactate concentration after 12 hours. In surviving patients, lactate showed a progressive decline over time, while levels remained high in non-survivors, from the 12 hour sampling until death.

Karen Robinson is with Lewis Gale Medical Center, Salem VA; Gail Kongable is with The Epsilon Group, Charlottesville, VA. The authors acknowledge Roche Diagnostics Corporation, Professional Diagnostics for the Hospital, maker of cobas b 221 blood gas analyzer for supporting the development of this manuscript.

More recently, in a retrospective observational study, Jansen et al[13] examined whether the level and duration of increased blood lactate (>2 mEq/L) was associated with daily Sequential Organ Failure Assessment (SOFA)[14] scores and organ subscores during the early and late phases of ICU stay. At 28 days, they found a 57% increased risk of death for every day lactate was elevated and every 1 mEq/L above 2 mEq/L. This clear association between lactate and SOFA score was strongest in the early phase of ICU care compared with later. This confirmed the relationship between blood lactate levels and injury severity and of the prognostic value of lactate clearance for survival of severely injured patients.

Mikkelsen et al,[15] determined that initial lactate levels were associated with mortality, independent of organ failure and shock. In this study of 830 patients admitted to the ED with severe sepsis, initial lactate was categorized as low (<2 mEq/L) intermediate (2-3.9 mEq/L) and high (≥4 mEq/L). Mortality at 28 days was 8.7%, CI of 4.9-14.2; 16.4%, CI 12.5-20.9; and 31.8%, CI 24.6-39.7 for the low, intermediate and high lactate levels in non-shock patients and 15.4%, CI 5.9-30.5; 37.3%,CI 25.0-50.8; and 46.9%, CI 36.8-57.3 in the low, intermediate and high lactate levels in patients with shock. A second important finding was related to the conventional lactate threshold of >4 mEq/L and that some risk of death is associated with lactate levels that are deemed "normal."[15]

A recently published clinical study examining this association of "relative" hyperlactatemia, (<2 mEq/L), also found increased risk of hospital death to confirm these findings.[9] This retrospective observational study of prospectively collected data on 7155 consecutive critically ill patients admitted to the ICU examined the relationship of on admission, maximum, and time-weighted relative hyperlactatemia with hospital outcome. Findings concluded that even lactate concentrations >0.75 mEq/L can be used by clinicians to identify patients at higher risk of death. These findings suggest that the current reference range for lactate levels that trigger early goal-directed therapy in the critically ill may need to be reassessed.[9]

Lactate as a clinical marker for hypoxia

Jansen et al[16] studied lactate levels in septic patients versus other patients with hemorrhage or conditions generally associated with low-oxygen transport (LT) and in patients who were hemodynamically stable compared to those who were not. They found that a reduction in lactate concentration during the first 24 hours after ICU admission was associated with improved outcome in septic patients, but not in patients presenting with hemorrhage or LT, and that lactate on admission, not the reduction over time, predicted mortality in the hemorrhage and LT group. They hypothesized that the patients who experienced hemorrhage and LT and significantly higher lactate levels sustained a more severe

insult and irreversible organ damage that would not respond to interventions designed to reduce lactate levels.[16]

Lactate as a predictor of mortality

Significantly higher lactate levels in non-survivors have been reported in several studies[16,17] demonstrating that hyperlactatemia adds mortality risk to all critically ill patient populations, regardless of admission diagnosis. In a study of 11,581 adult patients[16] admitted to 4 ICUs with serious medical, cardiac surgical, surgical and neuro/trauma conditions, the incidence of one episode of high lactate (>2 mEq/L) was present in 40% of patients and the average prevalence was 20 per 100 days of hyperlactatemia during the average ICU stay. The occurrence of hyperlactatemia varied significantly by admitting diagnostic category (p<0.001) with the highest cumulative incidence observed among the neuro/trauma patients, followed by the medical, then surgical, then cardiac surgical patient groups. Higher lactate levels were found in patients with higher Acute Physiology and Chronic Health Evaluation v.II (APACHE II) scores,[18] and increased with patient age. Among patients who did not have elevated lactate on admission, subsequent hyperlactatemia occurred in 6%. Mortality was highest among all patient groups with hyperlactatemia on admission, (20% vs 5%, p<0.001). This affected medical patients most (47%) followed by neuro/trauma (25%), surgical (15%) and cardiac surgical (13%) patients (p<0.001). After controlling for confounding variables, increasing levels of hyperlactatemia at presentation were independently associated with stepwise increased risk for subsequent ICU-related mortality. Lactate concentrations of 2-5 mEq/L conferred increased risk of death (Odds Ratio [OR], 95% CI; 1.94,1.62-2.32, while concentrations of 5-10 mEq/L (OR 3.38, 95% CI 2.64 to 4.33); 10-15 mEq/L (OR 4.41, 95% CI 2.99 to 6.50); 15-20 mEq/L (OR 7.58, 95% CI 3.93 to 14.60) and >20 mEq/L (OR 10.89, 95% CI 4.89 to 24.48) respectively.[16] Howell et al[17] reported that patients with a lacate level ≥4 mEq/L in the presence of normal blood pressure had a mortality rate of 15.0%, 6.0-24 (95% CI) while patients who had either septic shock or lactate ≥4 mEq/L had a mortality rate of 28.3% (21.3-35.3%), which was significantly higher than for those who had neither (2.5%, 1.6-3.4%). Additionally, patients with a lacate level of 2.5-4.0 mEq/L had adjusted odds ratio of death of 2.2 (1.1-4.2) and those with lactate ≥4 mEq/L had 7.1 (3.6-13.9) times the odds of experiencing death.[17] Jansen et al[19] also found that mortality was significantly higher in ED patients with lactate levels of ≥3.5 mEq/L compared to those with lactate levels below 3.5 mEq/L at first measure (T1) and on ED arrival (T2); T1: 41% vs 12% and T2: 47% vs 15%).[19] These findings suggest that a clinical intervention for lactate concentration >4 mEq/L may miss opportunities for preventing ICU death.

Early lactate clearance may decrease mortality

Early studies of lactate clearance demonstrated that lactate metabolism and the time needed to normalize lactate levels is also an important prognostic factor for survival in severely injured patients.[20] Serum lactate levels and oxygen transport were measured from admission up to 48 hours in 76 consecutive patients with multiple trauma. Patients were analyzed with respect to survival and lactate clearance to normal (≤2 mEq/L) by 24 and 48 hours. While there were no differences in interventions and severity scores, all patients whose lactate levels normalized in 24 hours survived. When lactate cleared to normal between 24 and 48 hours, the survival rate was 75%, and only 3 of the 22 patients who did not clear their lactate level at 48 hours survived, demonstrating that optimization of treatment of hypoxia and perfusion alone does not predict survival.[20]

Nguyen et al,[21] further examined the clinical implications of clearance of high lactate levels on presentation to the emergency department (ED). As the ED is frequently the initial point of care for patients with sepsis and shock, the hypothesis was that initiating early goal directed therapy to reduce lactate levels early in the course of therapy (prior of ICU admission) may improve outcomes from severe sepsis and septic shock. In this prospective observational study, therapy was initiated on recognition of sepsis in the ED and continued in the ICU. Survivors had a lactate clearance of 38.1±34.6 mEq/L compared to 12.0±51.6 mEq/L (p=0.005) in nonsurvivors. Multivariate logistic regression demonstrated lactate clearance had a significant inverse relationship with mortality (p=0.04). The investigators found an approximately 11% decrease in likelihood of mortality for each 10% higher lactate clearance. Finally patients with a lactate clearance ≥10% had a lower 30 day and 60 day mortality rate when compared to patients with a <10% lactate clearance (37.5% vs67.7% and 42.5% vs 71.0%) respectively, (p=0.004, p=0.007).[21] This is consistent with efforts emphasizing the importance of recognizing high lactate as a sign of tissue hypoperfusion and initiating treatment in the earliest hours of severe sepsis presentation.[8,22,23,24]

Lactate and early goal directed therapy

Early goal-directed therapy (EGDT)[8,23] and implementation of sepsis bundles[24] for the early management of severe sepsis and septic shock has become the standard of care in the ED and ICU. Rivers et al[8] demonstrated that interventions that adjusted cardiac perfusion to balance oxygen delivery with oxygen demand provided significant benefits with respect to outcome in patients with severe sepsis and septic shock. This study compared in-hospital mortality rates in patients randomized to EGDT or standard therapy in the first 6 hours of care. Parameters of central venous oxygen saturation, lactate concentration, base deficit and pH were monitored during the first 6 hours of resuscitation and the following interval (7-72 hours) to determine the efficacy of the two therapies and in-hospital mortality. The two patient groups were similar in risk factors at baseline (lactate levels, APACHE II scores, and perfusion parameters). During the interval from 7-72 hours, the patients assigned to early goal-directed therapy had a significantly improved central venous oxygen saturation (mean ± SD) 70.4±10.7% compared to 65.3±11.4% in the group assigned to standard care (p=0.009). EGDT was associated with a lowering of lactate concentration (3.0±4.4 vs 3.9±4.4 mEq/L; a lowering of base deficit (2.0±6.6 vs 5.1±6.7 mEq/L; and a higher pH (7.40±0.12 vs 7.36±0.12 than patients receiving standard care. Additionally, during the same period, APACHE II scores were significantly improved, indicating less severe organ dysfunction in the patients assigned to EGDT than in those assigned to standard therapy; (13.0±6.3 vs 15.9±6.4, p<0.001).[8] Subsequently, guidelines for protocolized management of severe sepsis and septic shock have incorporated measurement of lactate as soon as possible on arrival, as a primary indicator of tissue hypoperfusion, and initiation of treatment when lactate is ≥4 mEq/L, even in patients who are not hypotensive. However, these authors state, "although lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation.[22,24]

Is lactate reliable?

While hyperlactatemia is thought to be an indication of the

metabolic stress response, energy failure, and impaired organ perfusion, it can be present under stable oxygenation and hemodynamic conditions.[25,26] Additionally, elevated lactate concentrations can be found irrespective of the presence of lactic acidosis, and may precede clinical signs which appear at a critical stage.[25] In fact, elevated lactate may be the only indication of tissue hypoxia and anaerobic glycolysis when blood pressure, cardiac output, and urine output are within clinically acceptable ranges. Levraut et al[26] demonstrated that a combination of low lactate production and low clearance could mask abnormal lactate metabolism in septic patients with normal or near normal lactate levels. In this prospective observational study, the investigators found that when lactate levels were the same in survivors and non-survivors, production and clearance were higher in sepsis survivors at 28 days.[26] Under these circumstances, lactate production and low lactate clearance could be the expression of very different metabolic situations with opposing effects on prognosis.

This was evident in the study by Revelly et al,[6] evaluating the mechanisms leading to hyperlactatemia in patients with severe sepsis or cardiogenic shock. In these patients, elevated lactate levels were related to increased production from increased glucose turnover from concomitant hyperglycemia and not impaired lactate clearance. Therefore, treatment aimed at correction of hyperglycemia and tissue perfusion could result in decreased lactate levels and improved patient outcomes.[6,27]

Summary

Hyperlactatemia occurs in nearly half of all patients admitted to the ICU, and presentation with or development of hyperlactatemia is associated with significantly increased mortality. While there are multiple factors that may contribute to high lactate production or low lactate clearance, lactate levels have been found to increase the risk of death directly and proportionately. Currently, elevated lactate levels of ≥4 mEq/L, if recognized at any time, stimulates EGDT, but evidence suggests a lower lactate threshold should be established for resuscitation to be most effective. In modern intensive care units (ICU) the frequent measurement of lactate using blood glucose analyzers is useful in identifying patients at increased risk of death and serve as an early marker of a potentially reversible state. While lactate measurement as an optimal guide to the endpoint of resuscitation remains controversial, it is superior to other markers of resolution of tissue hypoxia and hypoperfusion. This evidence holds true for all patients with severe sepsis or shock regardless of the underlying pathology. Consideration for future research should be given to:

- whether the serum lactate threshold used to prompt EGDT be adjusted downward
- whether serum lactate should be measured prior to arrival to the ED to take advantage of the golden hours and optimize resuscitation
- whether serum lactate should be used to risk stratify patients in the ED and ICU to determine which patients would potentially benefit most from aggressive resuscitation strategies.

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College Station Finds Solution for High-Volume BGE Testing at POC

Networked control, minimal maintenance facilitate remote testing

Laszlo Sandor

Facility	College Station Medical Center, College Station, Texas
Profile	Full-service facility; official provider for Texas A&M athletics
Number of beds	150
BGE testing sites	ICU, NICU, ED, OR
Challenge	Expand POC blood gas testing; retain centralized control
Solution	cobas b 221, DataCare POC and cobas bge link software

Decentralized blood gas testing—running tests at multiple point-of-care sites vs the lab—became standard procedure several years ago at College Station Medical Center, located about 100 miles north of Houston. But as testing volumes grew, the respiratory care director wanted to add analyzers at various remote sites and yet be able to manage them all from a single location.

In conjunction with Roche Diagnostics, College Station implemented a comprehensive solution that provided centralized control and helped simplify regulatory compliance in the process.

Laszlo Sandor is Associate Editor of Respiratory Therapy. COBAS, COBAS B, DATACARE POC, BGE LINK and LIFE NEEDS ANSWERS are trademarks of Roche. For more information on the cobas b 221 system, contact your Roche Diagnostics representative, call 1-800-428-5076 or visit www.poc.roche.com.

Looking for remote control

Known locally as The Med, College Station Medical Center recently received the Texas Health Care Quality Award of Excellence, which recognizes hospitals that have improved initial baseline performance on specific national quality measures aimed at improving outcomes. Respiratory care is one of the areas in which it excels.

Michael Nibert, RRT, BSRT, who serves as the Respiratory Care Director, says he has always taken a decentralized approach to blood gas testing because it supports the often critical, time-sensitive nature of respiratory care. "Our decentralized structure for blood gas testing enables us to provide fast, reliable and accurate results that impact physicians' treatment decisions in critical situations where a second saved may mean a life saved," he says.

A few years ago, College Station had two point-of-care (POC) blood gas analyzers, one in pulmonary and one in the OR. When the facility expanded recently, Nibert wanted to add analyzers to the neonatal ICU and the emergency department. But he was already having problems with instrument downtime, and the data management system required a lot of manual tasks and did not meet all his regulatory compliance needs. What he needed was a solution that could handle high-volume testing at the point of care, have less system downtime, and simplify data management. What he found was a solution that did all that and helped make compliance easier at the same time.

Delivering critical information with minimal downtime

College Station built its POC solution around the cobas b 221 blood gas system from Roche, a compact benchtop analyzer that provides full blood gas panel results in about two minutes and has a throughput range of 27-31 samples/hour. With "load-and-go" smart reagents, onboard QC and zero-maintenance electrodes, the system only requires brief instrument downtime about once every 42 days.

In addition, a recently updated firmware package (v7.02) offers Nibert's team a continuous self-monitoring feature that helps simplify regular maintenance in several ways: it tracks the status of electrodes, sensors, and consumables; provides real-time onboard maintenance logs; lists all scheduled maintenance activities to be performed; and provides advance notice of needed maintenance.

The cobas b 221 system offered Nibert and his 28-member respiratory care team benefits on the clinical side as well. It is the first blood gas system with FDA 510(k) clearance for testing pleural fluid pH, giving clinicians an excellent alternative to pH meters and pH litmus paper.[1] "Having this clearance as a moderate-complexity CLIA standard in particular has provided an additional diagnostic tool for our surgeons and critical care and pulmonary intensivists," Nibert says. His team is also reporting bilirubin in the neonatal areas (using the system's COOX module), as well as lactate, BUN, glucose, and electrolytes to complement basic panels of blood gas testing and co-oximetry in all age groups.

cobas b 221 blood gas system

Managing instruments, data and compliance

One of Nibert's concerns about expanding the number of remote analyzers was keeping control and maintenance simple. Part of the solution was Roche's DataCare POC, a configurable software program for managing and reporting patient information. The program offers Nibert's team the ability to capture temperature and respiratory settings with blood gas results and to flag patients with critical values, and they can customize it to help meet regulatory needs, spot areas needing attention and simplify workflow.

The other part of the College Station solution was cobas bge link software, a network-level program that allows centralized control over multiple cobas b 221 systems from any PC on the hospital network. The program offers users the capability for remote diagnostics (through Axeda protected remote access software) and virtual 24/7 on-site technical support from Roche. It also provides a screen-sharing capability, enabling real-time data sharing between multiple users.

Stacy Howard, RRT, Lead Diagnostic Therapist, College Station Medical Center

Nibert is now in the process of upgrading the system with a bidirectional data interface to further augment its capabilities. "With these programs, [lead diagnostic therapist] Stacey Howard can manage instruments, review QC information, do maintenance and training, and make sure all the instruments are up and running through her PC," explains Nibert. "It not only enhances the services we provide to physicians and clinicians, it also greatly simplifies our regulatory compliance process. The analyzer upgrades, along with interfaces into our health information management system, have allowed us to take our blood gas service line to another level."

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Serial Measurement of Biochemical Parameters

Serial measurements of biochemical parameters in the **cobas b221** aren't affected by brief time intervals between first and subsequent analyses, according to a clinical poster abstract presented at IFCC World Lab.*

The study by Pozeti, et al demonstrated that blood gas analyzers are safe to use in clinical pathology labs not situated in proximity to emergency care units. Results of various biochemical parameters demonstrated the same precision and accuracy as in baseline tests. In the study, 128 blood samples were collected at ICUs, the emergency room, and surgery at the University of Campinas University Hospital. Collected samples were analyzed no more than two minutes after collection using the cobas b221 from Roche Diagnostics. Measured were pH, PO_2, PCO_2, oxygen saturation, sodium, potassium, choride, ionized calcium, glucose, lactate, and total hemoglobin. The blood samples were transported to the clinical pathology laboratory and re-analyzed with the same cobas device at ten, 20, and 30 minutes after the blood gas lab analysis.

Blood gas analyzers, ubiquitously used in various hospital venues, may be influenced by patient vent status, PO_2 level, and the method of specimen storage, as well as the container and by the preparation of the sample. Other factors that may affect sample specimens are storage, transport, and temperature. The study was aimed at evaluating pre-analytical time on blood parameter measurements by the cobas b 221 analyzer, to see if the above factors caused a variance in p values.

Similar results were reported in the four time periods of analysis, 0, 10, 20 and 30 minutes, suing the cobas b 221, with the following biochemical parameters (as mmHg)and p values (KW test, n=128):

chloride	0.3764
glucose	0.1505
ionized calcium	0.7594
lactate	0.3819
oxygen saturation %	0.9093
PCO2	0.6372
PO2	0.9771
potassium	0.8018
sodium	0.9167
total hemoglobin	0.9861

*The above is based on the poster presentation "Serial Measurements of Biochemical Parameters in the Blood Gas Analyzer cobas b221 Are Not Affected By Time Intervals Up To 30 Mintues After the First Analysis," Pozei RCS, Facin AC, Noronha JFA, Stein MCCP, Honorio HMS, Silva MJ, Castilho LN, Faria EC. Clin Chem Lab Med 2008; 46, Special Suppl, pp S1-S859, August 2008, Copyright by Walter de Gruyter, Berlin New York. Information was provided by Roche.

Point of Care Testing Using the OMNI-S Blood Gas Analyzer in an NICU

The authors' goal was to assess the OMNI-S analyzer (Roche Diagnostics), compared to other point of care equipment, and to assess the impact of its use and its potential cost-savings in a neonatal intensive care unit. Over three years, one year before and two years subsequent to the introduction of the OMNI-S, the study's authors reviewed hospital clinical information systems and pathology databases, patient admission rates, and workloads at the Neonatal Intensive Care Unit of Addenbrooke's Hospital, Cambridge.

During the three years of the study, NICU admissions increased by 15.7%, while there was a decrease of 38% in lab assays, and of 8.6% in transfusions. In all, over the time of the study, a 46.4% reduction in lab testing and a 21% reduction in transfusions per admission were recorded. Laboratory costs dropped by 24.5% (39,000 pounds) per year.

The authors concluded that the introduction of the OMNI-S point of care analyzer yielded cost savings, changed the methods of clinical practice, and reduced neonatal transfusion requirements.

Fourteen types of blood gas analyzers are used in the UK for intensive care purposes. The most commonly used near-patient tests are for blood gases and glucose, hematocrit, bilirubin, electrolytes, and lactate levels. Advantages of point of care testing are its accuracy, reliability, and quick accessibility of results. POC testing allows for multiple assays on smaller blood volulmes than with conventional testing, which means less handling of the baby. Because samples don't have to be transported to the lab, the possibility of error is mitigated. The chance of needlestick injury may also be reduced. In addition, using a single system for POC testing allows for consolidation of equipment, simplifies staff training, and potentially reduces costs. Using a smaller volume of blood for analysis reduces blood loss and decreases the number of transfusions.

The authors hypothesized that the introduction of an accurate point of care system would reduce the volume of blood samples to be sent for lab analysis and consequently reduce transfusion requirements. The authors reviewed their methodologies before and after introduction of the Roche OMNI-S gas analyzer to their NICU. The authors collected NICU activity demographics including admissions, days for relevant categories of care, days on ventilation, use of CPAP, and amount of total parenteral nutrition. The pathology department's databases were culled to identify the use of transfusion products. Lab tests were categorized and delineated in terms of their blood sample requirements. The OMNI-S gas analyzer provided measurements of ph, PCO_2, PO_2, bicarbonate level, base excess, Hb level, hematocrit, and levels of total serum bilirubin, lactate, sodium, and potassium, as well as ionized calcium concentrations. The analyzer was calibrated and maintained daily for quality control. The Omni-Sanalyzer used in this study required 200 [mu]L to allow full parameter analysis. Standard costs for lab departments totaled about 358 pounds. The cost of an OMNI-S (in 2003) was 14,000 pounds, at an annual consumable cost of about 5,000 pounds per year.

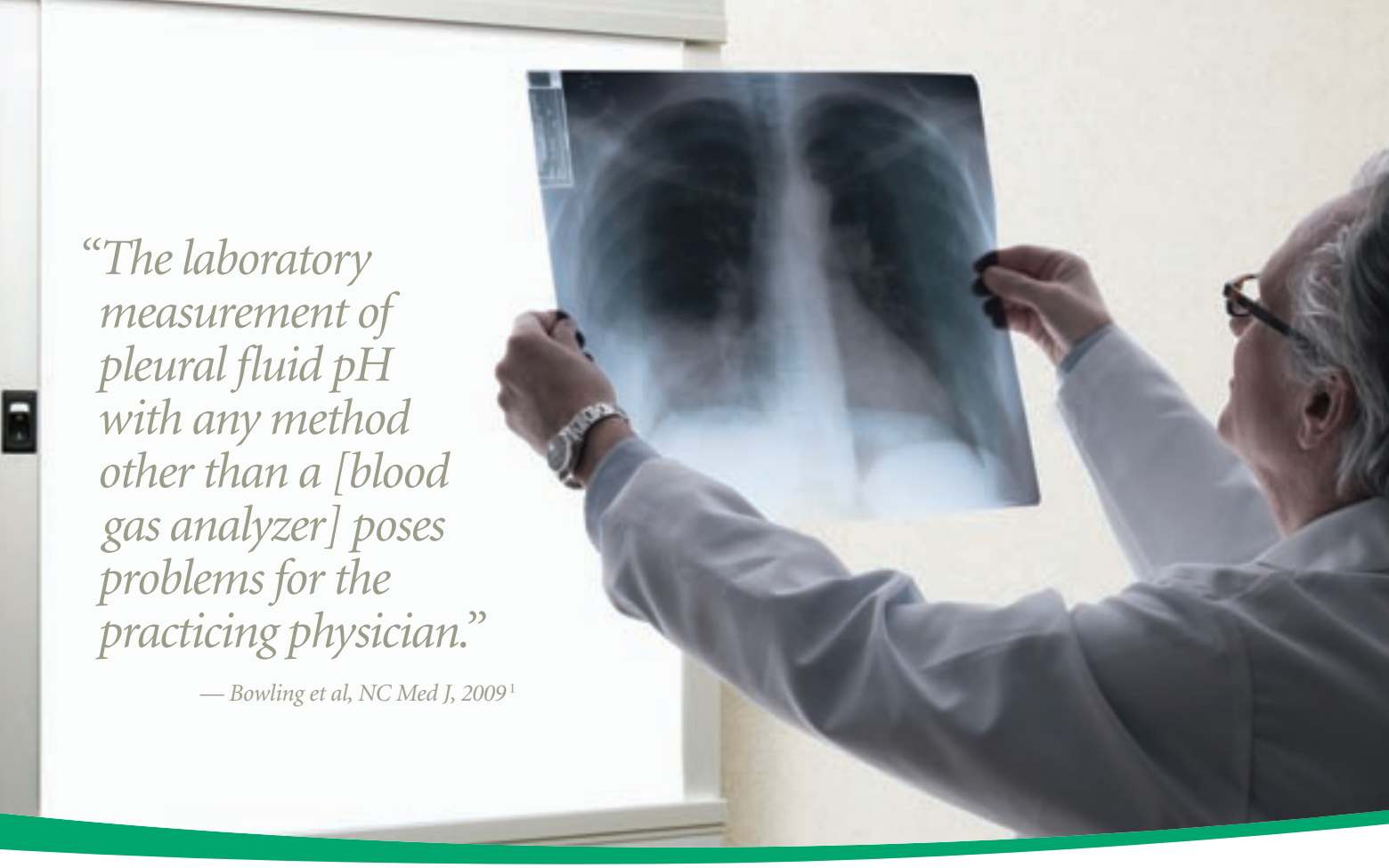
During the time of the study, NICU activity showed an increase in the number of admissions from 592 to 684 (15.7%). Delivered care days increased from 5,196 to 6,330 (21.8%); ICU and SCBU days increased 11.7% and 63.5%. The mean increase in neonatal care days per infant increased by 5.3%.

Meanwhile, the authors recorded a decrease in all laboratory activity indices. Between 2003 and 2005, the number of blood samples sent to the lab dropped from 7,020 to 4,350 (38%). This represented a mean reduction of 11.8 samples per infant to 6.4 (46.4%.) Biochemistry lab tests requests dropped by 49.2%, hematology tests by 32.2%, blood culture tests dropped by 12.3%. The need for transfusions was also reduced, with a decrease in Octapack subunits transfused from 338 to 275 (18.7%), which translated as a mean reduction per baby of 29.7%.

The yearly cost of lab tests and transfusions was reduced by 39,000 pounds, from 159,000 pounds in 2003 to 120,000 pounds in 2005 (24.5%). Taking increased patient activity into account, the equivalent mean cost reduction was 34.7%, from 287 pounds to 175 pounds.

The authors concluded, "Despite increased patient admissions and activity levels in the neonatal service, we have demonstrated a significant reduction in laboratory activity and blood transfusion requirement after the formal introduction of the Roche OMNI-S gas analyzer." Despite increases in levels of care, there was a sizeable reduction of 46% in the number of laboratory tests performed per admission. Total admission rates increased by 20% while blood sampling rates decreased by 38%. The authors noted, "We feel that the results of this study show that the introduction of the OMNI-S analyzer has had a significant impact on patient care in our neonatal unit… Our study has demonstrated the overall reduction in laboratory tests, resulting in a reduction in the number of transfusions needed per admission after introduction of the Omni-S analyzer. Our cost savings came from both a reduced number of laboratory tests and also a decreased number of transfusions in the unit after introduction of the Omni-S gas analyzer. It also made the training of junior physicians much simpler because rather than training on several different separate bedside analyzers… they now only require training on a single machine… The introduction of the Omni-S gas analyzer supported by a dedicated POC team has been very successful. There has been a significant change in clinical practice with substantial cost saving for the service and also reduction of blood transfusions."

The information in this article is from the paper, Clinical Impact of Point-of-Care Testing Using the OMNI-S Blood Gas Analyzer in a Neonatal Intensive Care Setting, Owen Arthurs, et al, in Point of Care: The Journal of Near-Patient Testing & Technology, Volume 9(1), March 2010, pp 21-24, copyright 2010 Lippincott Williams & Wilkins, Inc. The article was provided by Roche.



"The laboratory measurement of pleural fluid pH with any method other than a [blood gas analyzer] poses problems for the practicing physician."

— Bowling et al, NC Med J, 2009[1]

The cobas b 221 blood gas system: the only blood gas analyzer FDA-cleared for pleural fluid pH testing

Measuring pleural fluid pH is a clinically useful tool for diagnosing and managing patients with pleural effusions and can be especially important in critical care situations, when dependable performance is essential.

- About 1 million pleural effusions are diagnosed in the United States each year.[2] Pleural effusions can be caused by[3]
  - Congestive heart failure
  - Pneumonia
  - Cancer
  - Pulmonary embolus
  - Coronary-artery bypass surgery
  - Cirrhosis with ascites
- Measurement of pleural fluid pH improves diagnosis, expedites therapy, and determines prognosis in many cases of pleural effusion of unknown cause[4]
- Blood gas analyzers are the most accurate method for pleural fluid pH testing[1,5,6]

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Pleural Fluid pH Measurement

Laszlo Sandor

Researchers at Wake Forest University School of Medicine and Baptist Medical Center and the University of Mississippi School of Medicine recently investigated the measurement of pleural fluid pH at North Carolina hospitals to discover if physicians were aware of the measurement method used by their hospital laboratories.*

Pleural fluid pH is useful in the management of complex pleural effusions; however, its value is diminished when it is measured by methods other than a blood gas analysis, which may lead to erroneous management decisions especially if the clinician is unaware of the inaccuracy of the test when a BGA is not utilized. According to the study, "This represents a lost opportunity to improve the care of patients with pleural effusions."

The researchers noted that many hospital laboratories do not use a blood gas analyzer, and doctors who send fluid for analysis are mostly wrong about the testing done on their samples. They noted that, "Almost two-thirds of the chest physicians that order pleural fluid pH to help manage pleural effusions were using information that is not substantiated by the literature and, despite previous reports, hospitals still use suboptimal methods to measure pleural fluid pH."

The researchers found that 75% of pulmonologists in their study either did not know how pleural fluid pH was measured by their hospital laboratory or had inaccurate perceptions concerning the measurement of pleural fluid pH.

Background

Each year, there are about four million reported cases of community-acquired pneumonia in the US, a quarter of which require hospitalization. Fifty-seven percent of patients have a complicated course due to parapneumonic effusions. As such, the measurement of pleural fluid pH is an important factor in the management of infections and malignant effusions. Pleural drainage may decrease hospitalization, systemic toxicity, ventilatory impairment, and the spread of the inflammatory reaction. Research has shown that pleural fluid pH measurement has the highest accuracy for identifying complicated effusions. The American College of Chest Physicians has recommended that pleural fluid should be measured by blood gas analysis.

Current modes of pleural fluid pH measurement are by blood gas analyzer, pH meter, and pH indicator stick, at 32%, 35% and 31%, respectively. The researchers note that sample methods other than BGA are not validated in the literature. The use of a pH meter or stick can overestimate pH, which can result in misdiagnosis of the effusion and undertreatment.

The Study

The goal of the study was to find out how much pulmonologists know about the method by which pleural fluid is measured at their hospital, and to compare their belief against the actual type of measurement used by the hospital laboratory.

The researchers asked 90 pulmonary physicians to complete a survey about how pleural fluid pH was measured by their laboratory, whether by pH stick, pH meter, or blood gas analyzer. The researchers matched the respondents to the lab and asked what methods the lab used.

Results and Conclusions

Of the 28 physicians who responded, 20 said they ordered pleural fluid pH. Seventy-five percent said they believed the hospital lab measured the fluid by BGA, 3.5% said it was by pH indicator stick, and 17.9% said they didn't know how it was measured by the lab. In comparing physician response with the laboratory's actual method of measurement, researchers found that 57% of the physicians had inaccurate perceptions of how the pH was measured by the lab. Twenty-five percent were correct, and the rest didn't know how the fluid was measured.

Of the physicians who ordered pleural fluid pH analysis, 30% answered correctly about how it was actually measured, and 70% got it wrong. Ninety percent of the pulmonologists who ordered pleural fluid pH believed the laboratory was using a blood gas analyzer, but 72% were mistaken. In these instances, 24% of labs actually measured BGA, 37.5% used a pH meter, and 37.5% used a pH indicator stick. Of the eight physicians who said they don't order pleural fluid pH, just one knew the lab's method, which was by pH meter.

Obviously, there is a great deal of discrepancy between the type of measurement believed to be used and the actual method of measurement, insofar as just 30% of the physicians were correct about the measurement method employed by their hospital laboratory. Seventy-five percent thought pH was measured by blood gas analysis, but most of them, (72%), were wrong. Of course this means that clinical decisions are being made by recourse to measurement methods that aren't the most accurate, in that neither the pH meter or stick have the precision to provide accurate clinical accuracy.

For those physicians who did not rely on pH measurement, the researchers in this study speculated that they may be relying on other measures such as LDH or glucose, and noted that more studies were necessary to discover why the physicians weren't using pleural fluid pH measurement. The researchers also

*All information in this article is from the study: Perception vs. Reality: Measuring of Pleural Fluid pH in North Carolina, by Mark R. Rowling, MD; Arjun Chatterjee, MD, MS; John Conforti, DO; Norman Adair, MD; Edward Haponik, MD; and Robert Chin Jr, MD. In: NC Med J January/February 2009, Volume 70, Number 1, pages 9-13, © North Carolina Medical Journal. The source was provided to Respiratory Therapy by Roche Diagnostics, Inc.

noted that only 2 of 11 hospitals in their survey used a blood gas analyzer to measure pleural fluid pH, buttressing other studies showing that just 32% of labs in the southeastern US were using BGA. Reasons for not using BGA were reported as a belief that exuded pleural fluid could obstruct or damage the analyzer, and that manufacturers had informed them that BGA is validated only for whole blood and pleural fluid pH testing wasn't FDA-approved. However, it should be noted, it is approved for such use in the OMNI BGA, by Roche.) In fact, the measurement of pleural fluid pH by a non-FDA approved BGA is considered a complex test, defined by adherence to specific guidelines for precision and accuracy testing by the Clinical Laboratory Improvement Amendments (CLIA), and thus the decision to forego it may involve cost factors.

There were, of course, limitations to the above study: the number of respondents was small, and geographically localized (ie, North Carolina hospitals.) Nonetheless, the researchers pointed to similar results elsewhere. The researchers also didn't inquire about why the test wasn't ordered, nor about how samples were collected. Nor were the labs queried about the reasons for their choice of measurement modality.

The authors concluded that "only pleural fluid pH measured by BGA has been validated by clinical investigations… The majority of pulmonologists either did not know how pleural fluid pH was measured by their hospital laboratory or had an inaccurate perception of how it was measured… The clinical value of a test is in its validation… Pleural fluid pH is useful in the management of complex pleural effusions; however, its value is diminished when it is measured by methods other than BGA."

Understanding CO-Oximetry

This article is adapted from "Patient Primer: Understanding CO-Oximetry" by Frank Visco, editorial assistant of Advance, information adapted by Frank Visco from Foundations of Respiratory Care by K.A. Wyka and associates.

Hemoglobin picks up oxygen and carries it around the bloodstream. Problems occur when dyshemoglobins (oxygen-deprived hemoglobins) limit hemoglobin's ability to bind and release oxygen. Carboxyhemoglobin is hemoglobin saturated with carbon monoxide; methemoglobin can't carry oxygen because of iron oxidation. Untreated dyshemoglobins can result in symptoms from dizziness and tiredness to carbon monoxide poisoning and oxygen starvation (hypoxia).

The CO-oximeter measures carboxyhemoglobin and methemoglobin noninasively. The co-oximeter uses a probe placed over a patient's finger or earlobe. Light-emitting diodes shine eight wavelengths of light through skin. The CO-oximeter analyzes the absorption differential of these wavelengths. Pulse CO-oximetry measures the pulse rate along with oxygen levels in the blood.

CO-oximetry is used in hospital EDs for diagnosis of CO poisoning. Twenty-thousand patients visit the average emergency room each year, and four thousand have CO poisoning. Often, the early symptoms of such poisoning, ie, nausea, shortness of breath, headaches, are confused with the flu.

CO-oximetry is also used to diagnose and lead to treatment of anemia and blood loss from surgical treatments, and can reduce the need for arterial blood tests, and also has the advantage of determining fluid volume quickly and noninvasively.

Fluid volume determination is a challenge in the OR, especially since it is invasive and time-consuming. The CO-oximeter determines this volume through PVI, the pleth variability index, a measurement of pulse strength that reduces postoperative risks. Extremes of hydration can negatively affect cardiac function, circulation, and wound healing. CO-oximetry offers real-time assessment of fluid volume that warn caretakers of such attendant problems and offers physicians the ability to noninvasively assess an array of measurements, from total hemoglobin to fluid volume.

Bilirubin Measurement for Neonates

The authors stated, "Determinations of serum TB levels is one of the most frequently performed laboratory tests for neonates. However, this procedure is painful… and is time and cost consuming. In addition it leads to stress for both the infant and the parent. Therefore, it is important to reduce the number of blood samples taken, as much as possible."

The skin test is the initial recommended test for bilirubin, up to 200 mol/L. Devices used for bilirubin determination are noninvasive hand-held POC devices to measure TcB levels, nonchemical photometric devices to measure blood samples, and lab analyzers for measurement of TB levels. The authors compared nine methods for bilirubin determination. The Twin Beam, the ABL 735, and the Roche OMNI S measure TB levels using minimal blood volumes, at the point of care. The Twin Beam measures bilirubin levels in plasma, necessitating a centrifugation of the sample. The ABL 735 is a blood gas analyzer that uses co-oximetry. The Roche OMNI S analyzer is a blood gas analyzer with co-oximetry that measures bilirubin levels at 512 reading points between 478 nm and 672 nm. The OMNI S and the ABL 735 hemolyze the sample ultrasonically with co-oximetry before measurement. The researchers used premarketing software on the Roche OMNI S analyzer.

One hundred twenty-four (124) samples were collected from 122 infants with a mean gestational age of 39 weeks and a mean birth weight of 3,433 g. The mean age at blood sampling was three days, with a range up to 8 days. The infants didn't have sepsis, RDS, or cardiac or circulary disease. Bilirubin concentrations were between 9 and 388 mol/L. Seven percent of the neonates (9) had concentrations above 257 mol/L.

The three lab methods met expectations for imprecision (5%) and accuracy (5%). The measurement of samples with the three standard lab analyzers were co-correlative. Researchers found "good agreement" with comparison values for the photometric instruments. All the skin test devices, however, underestimated bilirubin levels at higher concentrations.

As the researchers stated, obviously, the paramount objective is not to miss high bilirubin concentrations that result in intervention. As such, the highest cutoff value that resulted in perfect sensitivity for detecting hyperbilirubinemia was determined for two concentrations, 222 mol/L and 257 umo/L. The Roche OMNI S analyzer had the highest bilirubin value at both concentrations.

The authors stated, "For physicians caring for neonates, it is essential to know the TcB values up to which they can trust the skin test device and avoid TB measurements without missing an infant in need of therapeutic intervention. Therefore, for clinical purposes, it is important to define a cutoff value describing the highest measurement result at which each device identifies correctly all infants with levels above a defined bilirubin concentration… For 257 mol/L TB, these cutoff values were between 209 and 224 mol/L for the different devices. Results up to these values need not be confirmed with a laboratory test… If no blood tests were performed below this cutoff value, then 93% of blood sampling could have been avoided for our study population."

The authors noted that POC devices are "popular because multiple other clinically important analytes, such as pH, sodium levels, and calcium levels, can be determined from the same blood sample. Results are provided quickly, and the amount of blood needed is small. Transport to the laboratory is no longer necessary."

Summary

The researchers used two blood gas analyzers, the BL 735 and the Roche OMNI S, which measure bilirubin levels through multiple-wavelength photometry. Results from the three nonchemical photometric devices correlated well with TB values. The researchers determined cutoff values above which blood samples should be sent to the lab. The Roche OMNI S analyzer had the highest cutoff value up to which all neonates were correctly identified. Ninety-five percent of blood sample transports to the lab could have been avoided using these analyzers. (The ABL 735 and Twin Beam correctly identified infants at lower cutoff values, with the avoidance of 92% of blood transports to labs.) Since all three lab methods employed in the study were strongly correlative, the authors stated, "their mean was considered to be close to the 'true' bilirubin concentration and served as a comparison value." The authors noted that the three skin test devices, the BiliCheck, JM-102 and JM-13, can be used in the hospital and in outpatient settings, and can reduce the number of blood samples. However, these skin test devices don't replace TB measurements because of the degree of their estimation of bilirubin levels at high concentrations. The authors concluded, "Nonchemical photometric devices give more accurate information on bilirubin concentrations than do skin test devices, but a blood sample is necessary. Readings above 250 uml/:L should be interpreted with care, because of the observed underestimation at high concentrations."

Early Lactate Clearance is Associated with Biomarkers of Inflammation, Coagulation, Apoptosis, Organ Dysfunction and Mortality in Severe Sepsis and Septic Shock

H. Bryant Nguyen Manisha Loomba, James J. Yang, Gordon Jacobsen, Kant Shah, Ronny M. Otero, Arturo Suarez, Hemal Parekh, Anja Jaehne, Emanuel P. Rivers

Abstract

Background: Lactate clearance, a surrogate for the magnitude and duration of global tissue hypoxia, is used diagnostically, therapeutically and prognostically. This study examined the association of early lactate clearance with selected inflammatory, coagulation, apoptosis response biomarkers and organ dysfunction scores in severe sepsis and septic shock.

Methods: Measurements of serum arterial lactate, biomarkers (interleukin-1 receptor antagonist, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor-alpha, intercellular adhesion molecule-1, high mobility group box-1, D-Dimer and caspase-3), and organ dysfunction scores (Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology Score II, Multiple Organ Dysfunction Score, and Sequential Organ Failure Assessment) were obtained in conjunction with a prospective, randomized study examining early goal-directed therapy in severe sepsis and septic shock patients presenting to the emergency department (ED). Lactate clearance was defined as the percent change in lactate levels after six hours from a baseline measurement in the ED.

Results: Two-hundred and twenty patients, age 65.0±17.1 years, were examined, with an overall lactate clearance of 35.5±43.1% and in-hospital mortality rate of 35.0%. Patients were divided into four quartiles of lactate clearance, -24.3±42.3, 30.1±7.5, 53.4±6.6, and 75.1±7.1%, respectively ($p<0.01$). The mean levels of all biomarkers and organ dysfunction scores over 72 hours were significantly lower with higher lactate clearance quartiles ($p<0.01$). There was a significant decreased in-hospital, 28-day, and 60-day mortality in the higher lactate clearance quartiles ($p<0.01$).

Conclusions: Early lactate clearance as a surrogate for the resolution of global tissue hypoxia is significantly associated with decreased levels of biomarkers, improvement in organ dysfunction and outcome in severe sepsis and septic shock.

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Introduction

The transition from sepsis to severe sepsis and septic shock is associated with a number of hemodynamic perturbations leading to global tissue hypoxia. Global tissue hypoxia accompanies a myriad of pathogenic mechanisms which contribute to the development of the multi-system organ dysfunction syndrome and increased mortality. Although there is significant interaction between inflammation, coagulation and organ dysfunction; a clear cause and effect between global tissue hypoxia and these molecular processes leading to multi-organ failure in severe sepsis and septic shock remains unclear.

There is an increasing body of literature establishing the clinical utility of biomarkers as diagnostic, therapeutic and prognostic indicators in the management of patients presenting with severe sepsis and septic shock. These studies, largely derived from the intensive care unit (ICU) patient population comprise a mixed picture of pro-inflammatory, anti-inflammatory, coagulation and apoptosis biomarker responses. However, the duration of stay for these patients prior to ICU admission whether on the general hospital ward or emergency department (ED) can be up to 24 hours. Despite the abundance of knowledge in the ICU phase of severe sepsis and septic shock, little is known regarding the natural history of the biomarkers during the most proximal stage of disease presentation.

Studies targeting the early detection and eradication of global tissue hypoxia even after normalization of traditional vital signs (heart rate, blood pressure and urine output) have realized significant mortality benefit in severe sepsis and septic shock, As a measure of tissue hypoxia and risk stratification, lactate

measurements have now been incorporated into treatment protocols and care bundles. We have previously reported that unresolved global tissue hypoxia reflected by inadequate lactate clearance during the early phase of resuscitation implicates organ dysfunction and increased mortality in severe sepsis and septic shock. The mechanistic explanation for these observations remains un-elucidated. The purpose of this study is to examine the association of early lactate clearance with the biomarker activity of inflammation, coagulation, and apoptosis and the subsequent relationship to organ failure and outcome in early severe sepsis and septic shock.

Materials and Methods

This study is an analysis of biological samples prospectively collected during and after a randomized, controlled study examining early goal-directed therapy for severe sepsis and septic shock. Patients presenting to the ED of an urban academic tertiary care hospital from March 1997 to March 2001 were consented if they met enrollment criteria. Patients were included if they had 1) a source of infection suspected by the treating physician; 2) at least two of four systemic inflammatory response syndrome (SIRS) criteria; and 3) either systolic blood pressure less than 90 mm Hg after a 20-30 ml/kg crystalloid fluid bolus or lactate greater than or equal to 4 mmol/L. Patients were excluded if they had age less than 18 years, pregnancy, acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, dysrhythmia as a primary diagnosis, contraindication to central venous catheterization, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, requirement for immediate surgery, uncured cancer, immunocompromised state, or do-not-resuscitate status. After meeting enrollment criteria, patients were invited to participate in the randomized protocol comparing early goal-directed therapy versus standard care and/or provide blood samples for serial biomarker measurements.

Patient demographics, hemodynamic variables, laboratories, sources of infection, comorbidities, and outcome were collected at baseline. Simultaneous measurements of serum arterial lactate, biomarkers and organ dysfunction scores were obtained at time 0, 6, 12, 24, 36, 48, 60 and 72 hours after enrollment. Therapeutic interventions, such as antibiotics, fluids, packed red cells transfusion, vasoactive agents, and mechanical ventilation, given in the ED and up to 72 hours were recorded. Information required for the Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, Multiple Organ Dysfunction Score (MODS), and Sequential Organ Failure Assessment (SOFA) score calculations were obtained at each time point. Patients were followed until in-hospital death or up to 60 days after enrollment.

Biomarkers were chosen to represent pro-inflammatory, anti-inflammatory, coagulation, and apoptosis pathways involved in the pathogenesis of severe sepsis and septic shock. The pro-inflammatory biomarkers included interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor- α(TNF- ϑ), intercellular adhesion molecule-1 (ICAM-1), and high mobility group box-1 (HMGB-1). Anti-inflammatory biomarkers included interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10). Coagulation and apoptosis biomarkers included D-Dimer and caspase-8, respectively. Assays were performed using immunometric (sandwich) assays with NeutrAvidin-coated 384-well block microtiter plates and a Genesis RSP 200/8 Workstation. Each sample was tested in duplicate. Before the

Table 1 Patient characteristics.

No. Patients	**220**
Age (years)	**65.0 ± 17.1**
Male:Female (%)	**54.1:45.9**
Time from ED arrival to enrollment (hours)	**1.6 ± 2.1**
Length of hospital stay (days)	**13.9 ± 16.6**
Vital signs and hemodynamic variables	
Temperature (°C)	**36.3 ± 2.8**
Heart rate (beats per min)	**117.1 ± 30.1**
Systolic blood pressure (mm Hg)	**107.5 ± 36.2**
Mean arterial pressure (mm Hg)	**74.8 ± 25.7**
Shock index (heart rate/systolic blood pressure)	**1.2 ± 0.5**
Respiratory rate (breaths per min)	**31.5 ± 11.1**
CVP (mm Hg)	**5.1 ± 8.5**
$ScvO_2$ (%)	**49.2 ± 12.6**
Laboratories	
White blood cells ($\times 10^3$ per mm^3)	14.0 ± 9.0
Hemoglobin (g/dL)	11.4 ± 2.7
Platelets ($\times 10^3$ per μL)	211.5 ± 122.0
Creatinine (mg/dL)	2.9 ± 2.0
Glucose (mg/dL)	259.4 ± 327.8
Anion gap (mEq/L)	21.5 ± 8.0
Total bilirubin (mg/dL)	1.5 ± 2.1
Albumin (g/dL)	2.8 ± 0.7
Lactate (mmol/L)	7.4 ± 4.6
Lactate clearance (%)	35.5 ± 43.1
Septic shock (%)	55.0
Culture positive (%)	65.6
Blood culture positive (%)	37.1
Organ dysfunction scores	
APACHE II	21.5 ± 7.0
SAPS II	49.8 ± 11.0
MODS	7.6 ± 3.1
SOFA	6.5 ± 2.9
Source of infection (%)	
Pneumonia	39.5
Urinary tract infection	13.2
Intra-abdominal	4.1
Other	43.2
Comorbidities (%)	
Chronic obstructive pulmonary disease	16.4
Chronic renal insufficiency	20.9
Congestive heart failure	30.9
Coronary artery disease	22.7
Diabetes mellitus	30.5
Hypertension	67.3
Liver disease	21.4
Outcome (%)	
In-hospital mortality	35.0
28-day mortality	36.4
60-day mortality	42.7

Vital signs, hemodynamic variables, laboratories and organ dysfunction scores represent baseline values at patient enrollment. ED - emergency department; CVP - central venous pressure; $ScvO_2$ - central venous oxygen saturation; Acute Physiology and Chronic Health Evaluation (APACHE) II; Simplified Acute Physiology Score (SAPS) II; Multiple Organ Dysfunction Score (MODS); Sequential Organ Failure Assessment (SOFA).

Table 2 Patient characteristics, basline vital signs, hemodynamics and laboratories by lactate clearance quartile.

	Quartile 1 N = 55	Quartile 2 N = 55	Quartile 3 N = 55	Quartile 4 N = 55	P-value
Lactate clearance (%)	- 24.3 ± 42.3	30.1 ± 7.5	53.4 ± 6.6	75.1 ± 7.1	<0.01
Age (years)	63.2 ± 16.5	68.2 ± 17.5	65.7 ± 15.7	66.7 ± 18.4	0.29
Septic shock (%)	70.9	58.2	54.6	36.4	<0.01
Culture positive (%)	45.5	33.3	42.6	32.7	0.41
Blood culture positive (%)	43.4	34.0	42.3	28.9	0.36
Vital signs and hemodynamics					
Temperature (°C)	36.3 ± 3.0	36.5 ± 3.2	36.1 ± 2.7	36.4 ± 2.5	0.67
Heart rate (beats per min)	113.8 ± 25.4	117.0 ± 27.6	120.0 ± 30.9	117.8 ± 36.0	0.70
Systolic blood pressure (mm Hg)	108.0 ± 39.7	103.3 ± 30.2	108.1 ± 35.0	110.4 ± 40.0	0.88
Mean arterial pressure (mm Hg)	76.1 ± 26.6	71.2 ± 21.8	75.8 ± 26.9	76.1 ± 27.4	0.81
Shock index (HR/SBP)	1.2 ± 0.5	1.2 ± 0.4	1.2 ± 0.5	1.2 ± 0.6	0.76
Respiratory rate (breaths per min)	29.5 ± 10.3	30.4 ± 10.9	34.2 ± 11.8	32.2 ± 10.9	0.16
CVP (mm Hg)	6.0 ± 8.7	4.5 ± 8.7	3.9 ± 8.9	5.7 ± 8.2	0.16
$ScvO_2$ (%)	49.3 ± 12.9	51.4 ± 12.0	44.1 ± 12.6	51.2 ± 12.3	0.28
Laboratories					
White blood cells ($\times 10^3$ per mm^3)	11.8 ± 7.1	13.5 ± 8.9	15.0 ± 10.5	15.6 ± 9.1	0.13
Hemoglobin (g/dL)	11.6 ± 2.6	11.0 ± 2.9	11.5 ± 2.5	11.3 ± 2.7	0.68
Platelets ($\times 10^3$ per μL)	163.7 ± 82.2	184.0 ± 116.7	254.1 ± 135.6	244.4 ± 124.8	<0.01
Creatinine (mg/dL)	2.5 ± 2.2	2.5 ± 1.7	2.6 ± 1.9	2.7 ± 2.4	0.94
Glucose (mg/dL)	303.5 ± 421.4	172.1 ± 150.6	240.9 ± 275.0	321.1 ± 382.0	0.07
Anion gap (mEq/L)	22.2 ± 9.6	20.0 ± 7.3	21.5 ± 7.9	22.2 ± 6.9	0.52
Total bilirubin (mg/dL)	1.9 ± 2.3	1.9 ± 3.1	1.2 ± 1.4	0.9 ± 0.7	0.03
Albumin (g/dL)	2.7 ± 0.7	2.8 ± 0.7	2.8 ± 0.7	3.1 ± 0.6	<0.01
Lactate (mmol/L)	7.5 ± 5.8	7.3 ± 4.9	7.3 ± 3.8	7.3 ± 3.5	0.47

Lactate clearance - defined as the percent change in lactate level after six hours from baseline measurement = $[(Lactate^{ED\ Presentation} - Lactate^{Hour\ 6})/Lactate^{ED\ Presentation}] \times 100$. A positive value denotes a decrease or clearance of lactate, whereas a negative value denotes an increase in lactate after 6 hours of intervention. Lactate clearance quartile - derived from sorting the study population by increasing lactate clearance and separating into four groups with equivalent number of patients. HR - heart rate; SBP - systolic blood pressure; CVP - central venous pressure; $ScvO_2$ - central venous oxygen saturation.

Table 3 Therapies during the first 6 hours in the ED and from 7 to 72 hours in the ICU by lactate clearance quartile.

	Quartile 1 N = 55	Quartile 2 N = 55	Quartile 3 N = 55	Quartile 4 N = 55	P-value
Therapies in first 6 hours					
Antibiotics (%)	72.2	77.5	72.1	75.0	0.95
Appropriate Antibiotics (%)	86.3	77.5	90.7	88.9	0.59
Fluids (mL)	4531.2 ± 2745.3	4263.5 ± 2872.9	4266.8 ± 3449.5	3741.7 ± 3136.4	0.27
Transfusion (%)	54.6	41.8	26.4	43.6	0.27
Vasopressor (%)	50.9	36.4	27.3	14.6	<0.01
Inotrope/dobutamine (%)	5.5	3.6	9.1	12.7	0.29
Mechanical ventilation (%)	74.6	50.9	58.2	38.2	<0.01
Therapies from 7 to 72 hours					
Antibiotics (%)	95.0	93.9	100	97.0	0.50
Fluids (mL)	8817.2 ± 5818.1	9666.7 ± 6555.2	10329.8 ± 6866.6	7141.9 ± 4097.8	0.06
Transfusion (%)	23.6	20.0	20.0	27.3	0.77
Vasopressor (%)	47.3	47.3	30.9	18.2	<0.01
Inotrope/dobutamine (%)	10.9	14.6	9.1	12.7	0.83
Mechanical ventilation (%)	12.7	14.6	7.3	7.3	0.48

Lactate clearance quartile - derived from sorting the study population by increasing lactate clearance and separating into four groups with equivalent number of patients.

assays, biotinylated primary antibody was diluted in assay buffer containing 10 mmol/L trishydroxymethylaminomethane HCl (pH 8.0), 150 mmol/L sodium chloride, 1 mmol/L magnesium chloride, 0.1 mmol/L zinc chloride, and 10 mL/L polyvinyl alcohol (9-10 kDa). The concentration of biotinylated antibody was predetermined by titration. The primary antibody (10 αL per well) was added to the plates and incubated. After washing, 10 g/L bovine serum albumin and 1 g/L sodium azide were added to

Table 4 Biomarker levels and organ dysfunction scores averaged over 72 hours by lactate clearance quartile.

	Quartile 1 N = 55	Quartile 2 N = 55	Quartile 3 N = 55	Quartile 4 N = 55	P-value
Biomarkers over 72 hours					
IL-1ra (ng/mL)	8455.9 ± 8838.4	7565.4 ± 8289.1	6421.3 ± 7957.5	2792.6 ± 3635.7	<0.01
IL-6 (pg/mL)	2839.5 ± 3487.0	2680.1 ± 3174.0	2426.7 ± 3269.4	663.2 ± 1583.5	<0.01
IL-8 (pg/mL)	480.3 ± 802.4	355.3 ± 559.1	356.3 ± 735.1	76.4 ± 218.0	<0.01
IL-10 (pg/mL)	303.6 ± 298.7	227.4 ± 218.5	180.2 ± 243.4	85.4 ± 121.9	<0.01
TNF-α (pg/mL)	65.2 ± 105.9	50.9 ± 69.2	47.4 ± 72.8	19.6 ± 19.8	<0.01
ICAM-1 (ng/mL)	409.1 ± 208.1	413.3 ± 204.5	379.7 ± 213.8	299.2 ± 156.1	<0.01
HMGB-1 (ng/mL)	4.6 ± 8.3	5.0 ± 10.4	2.5 ± 3.3	1.6 ± 2.4	<0.01
D-Dimer (μ/mL)	20.8 ± 9.5	18.9 ± 9.5	18.1 ± 8.9	15.7 ± 9.7	0.04
Caspase-3 (ng/mL)	3.8 ± 7.5	2.4 ± 3.8	1.9 ± 2.6	1.1 ± 0.8	<0.01
Organ dysfunction over 72 hours					
APACHE II	16.8 ± 6.3	16.6 ± 6.4	14.8 ± 6.9	11.6 ± 6.0	<0.01
SAPS II	43.9 ± 12.4	44.6 ± 43.5	39.5 ± 12.0	34.2 ± 11.9	<0.01
MODS	8.0 ± 3.5	7.0 ± 4.0	5.7 ± 4.2	3.4 ± 2.5	<0.01
SOFA	8.8 ± 3.3	8.0 ± 3.4	6.8 ± 4.3	4.4 ± 2.7	<0.01
Outcome (%)					
In-hospital mortality	52.7	41.8	29.1	16.4	<0.01
28-day mortality	54.9	49.0	33.5	21.6	<0.01
60-day mortality	63.1	52.9	38.0	33.6	0.01

Lactate clearance quartile - derived from sorting the study population by increasing lactate clearance and separating into four groups with equivalent number of patients. IL-1ra - interleukin-1 receptor antagonist; IL-6 - interleukin-6; IL-8 - interleukin-8; IL-10 - interleukin-10; TNF-α - tumor necrosis factor-α; ICAM-1 - intercellular adhesion molecule-1; HMGB-1 - high mobility group box-1; Acute Physiology and Chronic Health Evaluation (APACHE) II; Simplified Acute Physiology Score (SAPS) II; Multiple Organ Dysfunction Score (MODS); Sequential Organ Failure Assessment (SOFA).

the plate wells, which were then incubated at room temperature. Next, the plates were washed three times with borate-buffered saline containing 0.02% polyoxyethylene (20) sorbitan monolaurate (BBS-Tween).

For each sample, 10 αL aliquots were added to each plate well and the plates were incubated. Following this incubation, the plates were washed three times and alkaline phosphatase-conjugated antibody (10 αL per well) was added to each plate well and further incubated. The concentration of the alkaline phosphatase-conjugated antibody was predetermined to ensure a linear profile in the dynamic range of interest. After additional incubation, the plates were washed nine times with BBS-Tween. AttoPhos substrate, a fluorescence-enhancing substrate previously diluted in AttoPhos buffer (S1021, Promega), was then added to aid in the measurement of the activity of antibody-conjugated alkaline phosphatase bound in each well. The plates were then scanned in a fluorometer using an excitation wavelength of 430 nm and an emission wavelength of 570 nm. Each well was scanned 6 times at 114-sec intervals, and the rate of fluorescence generation was calculated. Calibration curves were derived from eight points tested at multiple locations on the assay plate using a 4-parameter logistic fit, from which sample concentrations were subsequently calculated. Each plate included calibration wells consisting of multiple analyte concentrations and control samples. Calibration curves for each biomarker assay were generated for IL-1ra, IL-6, IL-8, IL-10, TNF-α, ICAM-1, HMGB-1, D-Dimer, and caspase-3.

Lactate clearance was defined as the percent change in lactate level after six hours from a baseline measurement. It is calculated by using the following formula: lactate at ED presentation (hour 0) minus lactate at hour 6, divided by lactate at ED presentation, then multiplied by 100. A positive value denotes a decrease or clearance of lactate, whereas a negative value denotes an increase in lactate after 6 hours of intervention. The study population was sorted by increasing lactate clearance and divided into four groups with equivalent number of patients for comparisons among lactate clearance quartiles.

For the purpose of this study, lactate clearance, biomarkers and organ dysfunction scores were analyzed in all patients enrolled in the study, irrespective of the treatment group assigned to the patients. We a priori accepted that lactate clearance is a reflection of the therapies received by the patients, such as fluids, red cells transfusion, vasopressors, and inotrope; rather than a function of the randomization assignment to early goal-directed therapy or standard care.

Results

Two hundred and twenty-two patients, age 65.0±17.1 years, were enrolled within 1.6±2.1 hours of ED presentation. The initial hemodynamic parameters included central venous pressure of 5.1±8.5 mm Hg, mean arterial pressure 74.8±25.7 mm Hg, central venous oxygen saturation 49.2±12.6 percent, and lactate 7.4±4.6 mmol/L. Fifty-five percent of patients had septic shock, 37.1% had blood culture positive, and the most common source of infection was pneumonia. Lactate clearance was 35.5±43.1 percent and in-hospital mortality rate 35.0%. The lactate clearance quartiles were -24.3±42.3, 30.1±7.5, 53.4±6.6, and 75.1±7.1%, respectively. There was no significant difference among the lactate clearance quartiles with respect to age, demographics, co-morbidities, blood culture positive, hemodynamic variables, baseline lactate, and other laboratories (except platelets, total bilirubin and albumin). There was significant difference in the number of septic shock patients among the lactate clearance quartiles, with the highest percent of septic shock patients in the lowest clearance quartile (p<0.01).

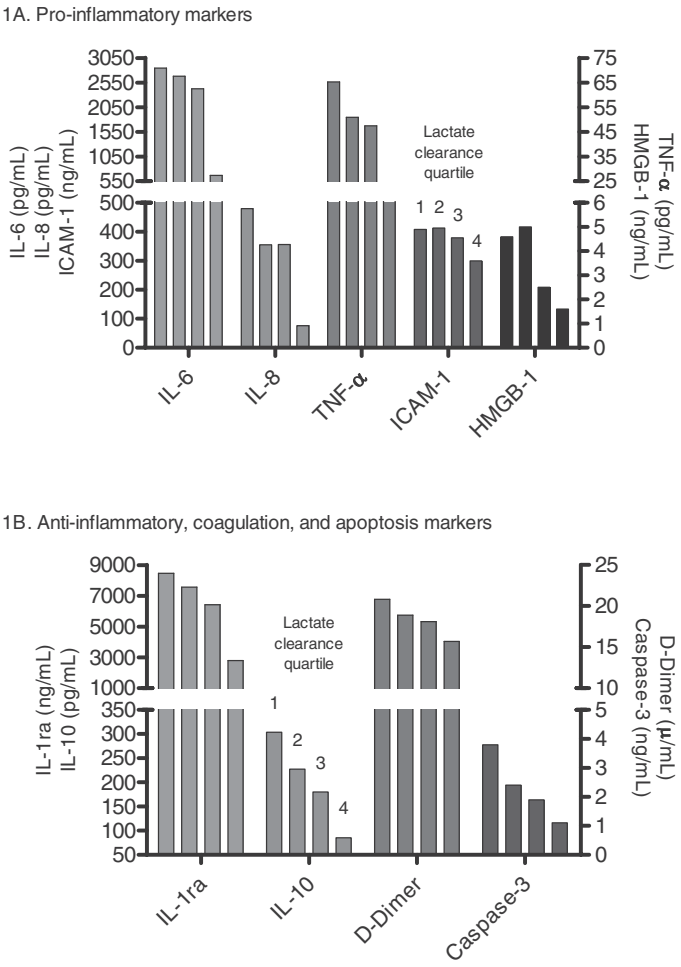

Figure 1. Mean biomarker levels averaged over 72 hours based on lactate clearance quartile. The mean levels of pro-inflammatory markers interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-a (TNF-a), intercellular adhesion molecule-1 (ICAM-1), and high mobility group box-1 (HMGB-1); anti-inflammatory markers interleukin-1 receptor antagonist (IL-1ra) and interleukin-10 (IL-10); coagulation marker D-Dimer; and apoptosis marker Caspase-3 are significantly lower over 72 hours with higher lactate clearance quartiles.

Quartiles with lower lactate clearance required significantly more vasopressor and mechanical ventilation during the first 6 hours. After 6 hours, only vasopressor remained significantly higher in lower lactate clearance quartiles. The mean levels of all biomarkers averaged over 72 hours were significantly lower with higher lactate clearance quartiles. Similarly, the mean organ dysfunction scores averaged over 72 hours were significantly lower with higher lactate clearance quartiles. There was significant decreased in-hospital, 28-day and 60-day mortality for higher lactate clearance quartiles. Kaplan-Meier survival analysis showed a survival benefit over 12 months for patients in the higher lactat quartiles.

Discussion

The current pathogenesis of severe sepsis and septic shock is described as a complex interaction of pro- and anti-inflammation, coagulation, and apoptosis triggered by the infecting microorganism. The bacteria outer membrane lipopolysaccharide molecule (LPS, endotoxin) activates a toll-like receptor 4 (TLR-4) signaling pathway that results in translocation of nuclear factor-αB (NF-αB) and production of inflammatory cytokines. The result is a production of pro-inflammatory cytokines that are balanced by an array of anti-inflammatory cytokines. The coagulation pathway is also activated by LPS-mediated signaling and further regulated by the cytokines, inducing the production of tissue factor, prothrombin conversion to thrombin, and fibrin production. Fibrinolysis is impaired due to increased production of plasminogen-activator inhibitor type-1 (PAI-1), decreased generation of plasmin and reduced removal of fibrin. The procoagulant state further down regulates the anticoagulant proteins, antithrombin, protein C, and tissue factor pathway inhibitor. The net result is deposition of fibrin clots throughout the endothelium, resulting in inadequate blood flow, organ hypoperfusion, global tissue hypoxia and cell death.

Clinically, lactate has been studied as a measure of illness severity in circulatory shock for several decades dating back to the 1800s. Although there are various explanations regarding the mechanisms responsible for lactate accumulation in severe sepsis and septic shock, it remains a robust surrogate marker for the development of multi-organ failure and poor outcome. Similar observations have been noted in other conditions of critical illness, including pediatric and adult cardiac surgery, the post-resuscitation period of cardiac arrest, trauma, general surgical, and liver surgery patients. A recurring theme in these studies is the inflammatory response plays a crucial mechanistic intermediate between lactate clearance and the development of multi-organ failure.

Evidence-based guidelines have recommended that an elevated lactate is sufficient to diagnosis shock, irrespective of hypotension. Sepsis with lactate level greater than or equal to 4 mmol/L is associated with high mortality and is an indication to initiate treatment protocols and care bundles. We previously reported a significant inverse relationship between lactate clearance (or resolution of global tissue hypoxia) during the first 6 hours and mortality in severe sepsis and septic shock. We have also shown that early goal-directed therapy targeting global tissue hypoxia to be more effective than standard care in decreasing lactate during the first six hours of intervention. In this study, we found a significant association between improving lactate clearance in the first 6 hours and a corresponding decrease in mean biomarker levels over 72 hours. This potential mechanistic link was also positively associated with improved organ dysfunction scores and decreased mortality.

The association between poor lactate clearance and the need for vasopressor therapy is consistent with observations that pathogenic but reversible correlates of outcome may be established in the first few hours of disease presentation. A limited course of vasopressor therapy indicates reversible tissue hypoxia; however, prolonged vasopressor usage for hemodynamic support is associated with worse lactate clearance and thus outcome. Additionally, lactate clearance has been shown to be significantly associated with improved microcirculatory flow. This provides supportive evidence for the mechanistic connection between prolonged vasopressor use, tissue ischemia, persistent lactate elevation, morbidity and mortality. Our results further support the notion that tissue hypoxia plays a crucial role in the early complex mechanisms leading to the endothelial response in severe sepsis and septic shock, rather than a terminal or irreversible event following inflammation and coagulopathy. Thus a goal-directed hemodynamic optimization strategy targeting the resolution of global tissue hypoxia, reflected by clearance of lactate, will likely reverse the diffuse endothelial and microcirculatory dysfunction in patients who most likely will benefit.

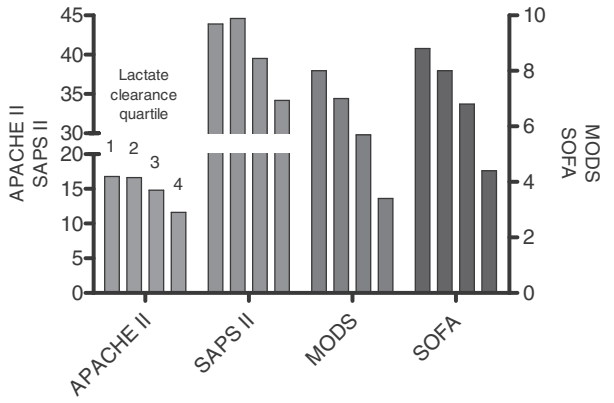

Figure 2. Mean organ dysfunction scores averaged over 72 hours based on lactate clearance quartile. The Acute Physiology and Chronic Health Evaluation (APACHE) II, Simplified Acute Physiology Score (SAPS) II, Multiple Organ Dysfunction Score (MODS), and Sequential Organ Failure Assessment (SOFA) score are significantly lower over 72 hours with higher lactate clearance quartiles.

In-vitro models have shown that hypoxia induces the pro-inflammatory cytokines, IL-1, IL-6, IL-8, and TNF-α. These cytokines then increase the expression of intercellular adhesion molecules (ICAM-1) and further activation and migration of neutrophils. In humans, IL-6 and IL-8 elevations correlated significantly to lactate levels (as a measure of tissue hypoxia) in sepsis. Recently, combined serial lactate and cytokine levels (IL-1, IL-6, IL-10, and HMGB-1) in septic shock patients were shown to be useful indicators of clinical outcome. In our study, IL-1ra, IL-6, IL-8, IL-10, and TNF-α were measured due to their close association with the early pro- and anti-inflammatory response. HMGB-1 was chosen as a pro-inflammatory mediator that appears much later than the other cytokines after LPS stimulation. We have shown that the higher lactate clearance in the first 6 hours, the greater the decrease in all pro-inflammatory and anti-inflammatory cytokines measured over 72 hours.

Hematologic abnormalities (leukocytotosis, anemia and thrombocytopenia) are common in severe sepsis and septic shock. Alterations in the levels of various mediators of coagulation and fibrinolysis have been reported to be associated

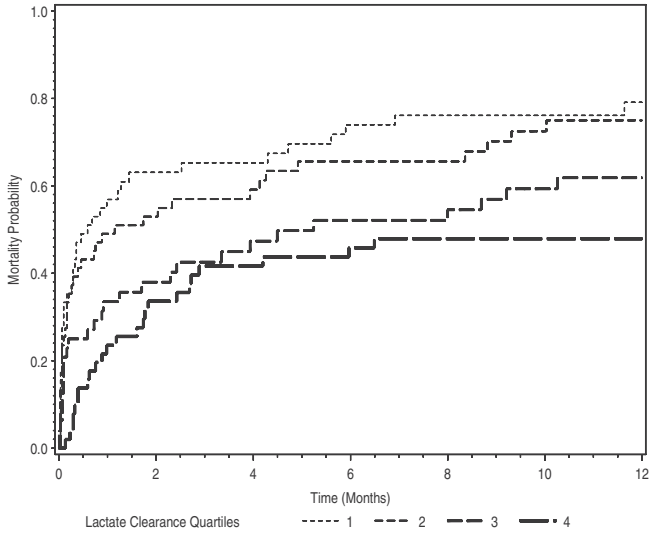

Figure 3. Kaplan-Meier 12-month survival analysis based on lactate clearance quartile. Lactate clearance quartile 1, 2, 3, and 4 have lactate clearance of -24.3±42.3, 30.1±7.5, 53.4±6.6, and 75.1±7.1%, respectively, during the first 6 hours in the emergency department ($p<0.01$).

with disseminated intravascular coagulation (DIC) and mortality.[45] Patients with SIRS and sepsis having DIC were shown to have higher serial lactate levels over 4 days compared to those patients without DIC, suggesting a pathogenic link between tissue hypoxia and intravascular coagulation. While no single marker measured at hospital admission is sufficiently sensitive or specific in diagnosing DIC, we chose to measure D-Dimer as a marker of coagulation in this study as it is widely available, a correlate to the pro-inflammatory cytokine levels, and a valuable screening marker for organ failure and mortality. It also has been used previously as an indicator of response to therapies such as recombinant human activated protein C in severe sepsis. In our study, we showed that improvements in coagulation (reflected by a decrease in D-Dimer levels over 72 hours) corresponded with lactate clearance during the first 6 hours. Our results provide further evidence that tissue hypoxia may be a preceding or parallel event to the pro-coagulant state in severe sepsis and septic shock, and therapies targeting tissue hypoxia may play a crucial role in reversing this coagulopathy.

Cell death through apoptosis is a highly regulated process in the presence or absence of inflammation.[51] Apoptosis is initiated by two pathways: 1) a receptor activated, caspase-8 mediated (extrinsic) pathway; and 2) a mitochondrial initiated caspase-9 mediated (intrinsic) pathway. Either of these caspases can activate caspase-3 in the common pathway resulting in final cell death. Caspases are pro-apoptotic proenzymes that inactivate protective proteins and contribute to cell death by direct cellular disassembly via cell shrinkage (pyknosis) and nuclear fragmentation (karyorrhexis). The regulation of apoptosis in sepsis is complex, as the infecting pathogen may inhibit or induce apoptosis, involving both the extrinsic and intrinsic pathways, to enhance its damaging effects to the host. Caspase activation in apoptosis is an energy-dependent process. Hypoxia can induce apoptosis as long as cells have an adequate amount of adenosine triphosphate. Previously, apoptosis was believed to occur via the intrinsic pathway with cytochrome c release and caspase-9 activation in oxygen-deprived cells.[54] However, the extrinsic pathway may also play an important role in oxidative stress induced apoptosis.[53] In this study, caspase-3 as a marker of the final common pathway in apoptosis was shown to be elevated over 72 hours in patients with decreased lactate clearance, compared to lower caspase-3 in patients with higher lactate clearance. This finding supports the premise that tissue hypoxia in severe sepsis and septic shock is associated with increased apoptosis, suggesting that the ill effects resulting in cell death may be mitigated by resolution of global tissue hypoxia.

Our results provide evidence that the design and interpretation of future clinical trials should consider the early stages of severe sepsis and septic shock. Previously, two studies failed to show significant outcome benefit with inhibition of TNF-α and IL-1ra in severe sepsis and septic shock patients enrolled in the ICU. The association of lactate clearance with these targeted biomarkers shown in our study suggests that the severity of tissue hypoxia should be part of patient selection criteria in studies examining novel therapies that may alter its down stream effects. The failure to consider the magnitude, duration of tissue hypoxia and the timing of patient enrollment in clinical trials will likely result in some degree of hemodynamic heterogeneity confounding any treatment effect.

The results of our study do not confirm a causal relationship,

but an association between lactate clearance in the first 6 hours and biomarker response over 72 hours. High lactate clearance quartiles had fewer patients in septic shock obviously requiring less vasopressor usage, but no difference in antibiotic and fluid administration. Lactate clearance over 6 hours may also depend on the patient's underlying comorbidities, such as liver disease, and the disease process rather than solely on the therapies themselves. However, baseline demographics, comorbidities, lactate and hemodynamic variables were similar in all quartiles. Thus the ability to clear lactate irrespective of the mechanism and its association with improved biomarkers suggests that further studies are needed to examine global tissue hypoxia as an inciting factor in the pathogenic pathways of severe sepsis and septic shock. Which of the three pathogenic pathways predominate as an association to tissue hypoxia cannot be discerned by this exploratory study. Nonetheless, our observation of a significant correlation of lactate clearance and decrease mortality is consistent with previous studies.

We have previously shown that early goal-directed therapy is significantly more effective than standard therapy in decreasing lactate (by 44% compared to 29%, $p<0.01$) during the first 6 hours, resulting in improved organ dysfunction and mortality. We further showed that global tissue hypoxia and early goal-directed therapy were associated with distinct biomarker patterns that were evident as early as 3 hours after intervention. The purpose of this study was to show that lactate clearance is associated with improved biomarkers and organ dysfunction scores. We a priori chose not to distinguish lactate clearance, biomarker responses, and organ dysfunction scores by resuscitation groups. While we have shown that lactate clearance is a mechanistic link in the early pathogenesis of sepsis, these findings do not support the substitution of lactate clearance as an independent alternative to an organized hemodynamic optimization strategy such as early goal-directed therapy.

Conclusions

This study showed a significant association between lactate clearance and biomarkers of pro- and anti-inflammation, coagulation, apoptosis; and further with multi-organ dysfunction and mortality in severe sepsis and septic shock. These findings support a growing body of evidence suggesting that global tissue hypoxia plays a crucial role in the complex mechanisms leading to the endothelial response in severe sepsis and septic shock rather than a terminal event. Future studies examining the pathogenic mechanisms or novel therapies for severe sepsis and septic shock should include lactate clearance as a measure of prognosis and therapeutic responses.

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