SHOCK, Vol. 44, Supplement 1, pp. 90–95, 2014

OPEN

COMPARISON OF NONINVASIVE PH AND BLOOD LACTATE AS PREDICTORS OF MORTALITY IN A SWINE HEMORRHAGIC SHOCK WITH RESTRICTED VOLUME RESUSCITATION MODEL

Babs Soller,* Fengmei Zou,* M. Dale Prince,† Michael A. Dubick,† and Jill L. Sondeen†

**Reflectance Medical Inc, Westborough, Massachusetts; and †US Army Institute of Surgical Research, San Antonio, Texas*

Received 24 Sep 2014; first review completed 16 Oct 2014; accepted in final form 18 Nov 2014

ABSTRACT—Recent clinical studies have demonstrated that high blood lactate in the prehospital setting and poor lactate clearance in the emergency department are predictive of in-hospital mortality. This analysis of data collected from a swine model of hemorrhage and restricted volume resuscitation investigated the hypotheses that noninvasive muscle pH (pHm) and H^+ clearance would predict mortality, and the responses would be similar between pHm and lactate. Data from a set of 57 swine were analyzed over the first 2 h after controlled hemorrhage and uncontrolled splenic bleeding. Surviving animals were ones that lived for the full 5-h experimental period. Venous lactate was determined at baseline, shock, and at 30, 60, and 120 min after injury. Spectra were collected continuously from the posterior thigh using a prototype CareGuide 1100 Oximeter and pHm calculated from the spectra; H^+ concentration was determined from pHm. Lactate clearance rate was calculated from the difference in lactate concentration at 120 min and shock, and H^+ clearance was calculated in a similar manner. Comparison of the area under the receiver operator characteristic curves was used to assess prediction of survival at 5 h after injury. At 120 min after injury, lactate, lactate clearance, noninvasive pHm, and noninvasive H^+ clearance were equivalent predictors of mortality each with a receiver operator characteristic area under the curve of 0.87. Thresholds for single lactate (<3.8 mmol/L) or pHm (>7.30) determinations were found to be consistent with a resuscitation goal targeted to reverse acidosis. Continuous, noninvasive pHm monitoring may provide a substitute for lactate measurement in trauma patients, particularly in the prehospital and emergency department settings.

KEYWORDS—Lactate, pH, hemorrhage, NIRS, mortality, prehospital, noninvasive monitoring

INTRODUCTION

Hemorrhage is the leading cause of death on the battlefield and accounts for nearly 90% of those deaths deemed from potentially survivable injuries in combat casualties (1). Logistic limitations on the battlefield provide few options and limited resources for treating bleeding casualties in far-forward areas of operation, although many advances have been seen in the past decade (2). Thus, in military prehospital settings, it is important to identify hemorrhagic shock early, to ensure that the injured patient receives appropriate treatment and is rapidly transported to the appropriate setting if specialized trauma care is required. Circumstances such as mass casualty events or rural locations may result in similar scenarios for prehospital treatment of civilian trauma victims. Historically, a systolic blood pressure (SBP) of less than 90 mmHg triggered transport to a civilian trauma center where advanced resuscitation can be provided. Recent studies have illustrated that prehospital SBP assessment is a late indicator of shock (3–5). Young people, in particular, can compensate for bleeding through an increase in peripheral vascular resistance to divert blood from the skeletal muscle and splanchnic circulation to preserve blood pressure, resulting in normal SBP, but hypoperfusion of vital organs. Uncorrected hypoperfusion has been shown to result in infection, multiple organ dysfunction, and mortality (6, 7)

Hypoperfusion is marked by an increase in serum lactate concentration. Guiding treatment of septic patients to reduce lactate levels is well known and an established method for reducing sepsis mortality (8, 9). There has been growing interest in lactate assessment as a tool to evaluate and monitor trauma patients to help determine adequacy of fluid resuscitation of hemorrhagic shock. Abramson et al. (10) provided early evidence that trauma patients whose lactate levels were normalized within the first 24 h in the intensive care unit were more likely to survive, consistent with reports that improved lactate clearance was associated with survival in patients in the intensive care unit (8, 9). Large retrospective studies looking at lactate levels and lactate clearance for trauma patients in the emergency department (ED) found that both high initial levels of lactate as well as poor lactate clearance were strong predictors of mortality (11, 12) even in the presence of normal blood pressure (13). It is presumed that rapid reduction of serum lactate concentration indicates that tissue hypoxia and acidosis are minimized, increasing chances for survival. Availability of portable lactate monitors has made prehospital monitoring of lactate possible. High lactate levels in the prehospital setting have also been associated with high hospital mortality

Address reprint requests to Babs Soller, PhD, Reflectance Medical Inc, 116 Flanders Rd, Suite 1000, Westborough, MA 01581. E-mail: babs.soller@reflectancemedical.com.

This work was supported by the US Army Medical Research and Materiel Command (USAMRMC) under contract W81XWH-11-C-0001, USAMRMC Core Funds, and the Defense Medical Research and Development Program.

B.S., and F.Z. are all employees of Reflectance Medical Inc and hold stock or stock options in the company. B.S. is an officer of Reflectance Medical. M.D.P., M.A.D., and J.L.S. have no conflicts to declare.

DOI: 10.1097/SHK.0000000000000307

(5, 7), although its predictive value may only be modest for nontrauma patients (13).

It has been suggested that it may be the metabolic acidosis, not the high serum lactate itself that is an indicator of mortality for critically ill patients, particularly those with tissue hypoperfusion and hypoxia (14, 15). Hydrogen ions (H^+) are directly produced as a result of anaerobic metabolism. Whenever ATP is hydrolyzed to ADP, an H^+ ion is released into the cytoplasm. During aerobic metabolism (oxidative phosphorylation), these H^+ ions are consumed in the mitochondrial respiratory chain for production of new ATP (16, 17). If there is not enough oxygen for oxidative phosphorylation (anaerobic metabolism), H^+ ions accumulate, and they are transported out of the cell into the tissue interstitial fluid via the Na^+/H^+ exchanger, resulting in tissue acidosis.

Muscle (interstitial fluid) pH, determined with small microelectrodes, was shown to have the same sensitivity to liver injury as blood lactate measured during swine hemorrhagic shock and resuscitation (18). New technology has become available that enables the continuous, noninvasive measurement of muscle pH (pHm) using near-infrared spectroscopy (NIRS) (19, 20). This technology was recently characterized in a swine model of uncontrolled hemorrhage and restricted volume resuscitation (21) and investigated the relationship between pHm and SmO_2 to standard invasive measures of arterial and venous pH and SO_2. The present study is a retrospective review from those animals plus an additional 31 swine under the same experimental protocol (21, 22) to investigate, in detail, the relationship between noninvasive pHm and serum lactate. With this larger data set, we tested the hypotheses that (*a*) pHm and H^+ clearance will predict mortality, and (*b*) the responses will be similar between pHm and lactate.

MATERIALS AND METHODS

The animal study related to this current evaluation was conducted in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International, and was performed under a protocol approved by the Institutional Animal Care and Use Committee of the US Army Institute of Surgical Research (Fort Sam Houston, Tex). The study was conducted in compliance with the Animal Welfare Act, the implementing Animal Welfare Regulations, and the principles of the Guide for the Care and Use of Laboratory Animals. The experimental procedures have been described in detail in previous publications (22) but are described briefly below.

Experimental protocol

Yorkshire-cross female pigs weighing 39.4 ± 0.4 kg (Midwest Swine Research, Gibbon, Minn) were used for this study. After an overnight fast, pigs were sedated with tiletamine-zolazepam (Telazol, 8 mL/kg; Wyeth, Fort Dodge, Iowa) and anesthetized with isofluorane in 30% oxygen using a ventilator and monitor (Apollo; Draeger Medical, Telford, Pa). Core temperature was maintained at 38°C ± 1°C with a water-filled blanket and patient-warming system. The animal was instrumented with catheters in the arteries (carotid, femoral) and veins (jugular, femoral) for blood pressure monitoring, Swan-Ganz cardiac output, arterial and venous samples, resuscitation fluid administration, and hemorrhaging. A midline laparotomy was performed to expose the spleen.

All signals (analog and RS232) were collected continuously on a data-acquisition system (DREW; US Army Institute of Surgical Research). After a baseline period, a controlled hemorrhage of 24 mL/kg was performed over approximately 15 min using a custom servo-controlled computerized pump program as previously described (22). The uncontrolled hemorrhage was then induced by transecting the spleen along the long axis, offset 1 cm from the midline to avoid the large vessels. The spleen was allowed to bleed for 15 min to mimic the time for a medic to arrive. Hypotensive resuscitation was then begun with amounts that resulted in equivalent volume expansion capability. The pump was turned on and off to maintain the mean arterial pressure (MAP) at 65 ± 2 mmHg. Animals were monitored for 5 h after the splenic injury or until death, with no additional fluids administered to mimic limited resources as found on the battlefield. The experimental protocol is illustrated in Figure 1.

Arterial and venous blood samples for lactate and Hgb analysis were collected at baseline, 15 min (posthemorrhage, preresuscitation), 30 min, and then hourly or at death. All resuscitation fluid was administered within 30 min, so the 60-min (after spleen injury) time point was considered end of resuscitation. The end point of death was considered to be when the pig's MAP fell to 20 mmHg or less and its expiratory P_{CO_2} level measured less than 15 mmHg, or a flatline electrocardiogram was observed. At the end of 5 h, the surviving animals were killed with pentobarbital Na 90 mg/kg intravenously (Fatal Plus, Fort Dodge, Iowa).

The data used for this article were collected from two different experiments that used this same model. No other treatments were given except hypotensive resuscitation as described. In the first study (n = 26) (21), the animals received 15 mL/kg administered at a rate of 1 mL/kg per minute of either fresh frozen plasma (FFP), FFP and platelets, FFP and cryoprecipitate (50 mg fibrinogen/kg), or Hextend. In the second study (n = 31), the animals received either 15 mL/kg of colloid (Hextend, FFP with cryoprecipitate [150 mg/kg] and platelets) or 45 mL/kg of 0.9% saline, 5 mL/kg of lyophilized human fibrinogen (50 mg/kg, RiaSTAP; CSL Behring USA, King of Prussia, Pa) followed by saline (10 mL/kg), or 3% hypertonic saline at 10 mL/kg.

Near-infrared spectroscopy to determine pH

Near-infrared spectral data were collected continuously from the biceps femoris muscle with a prototype version of the CareGuide Oximeter 1100 (Reflectance Medical Inc, Westborough, Mass). The CareGuide uses more than 200 wavelengths of NIR light to create an absorbance spectrum from the small blood vessels in the muscle. pH changes the shape of the hemoglobin (Hgb) absorbance spectrum, and a mathematical relationship can be developed to relate these spectral variations to pH (19, 20). Such an algorithm is contained in the Mobile CareGuide 3100 product, a Food and Drug Administration–cleared device. The same algorithm was used to determine pHm for the spectra collected from the pigs in this study.

Data analysis and statistics

This current investigation is a retrospective analysis of prospectively collected data (22) plus data from 31 additional pigs subjected to the same experimental protocol, and the animals were divided into survivors and nonsurvivors. Survivors were the animals that were alive for 5 h after splenic

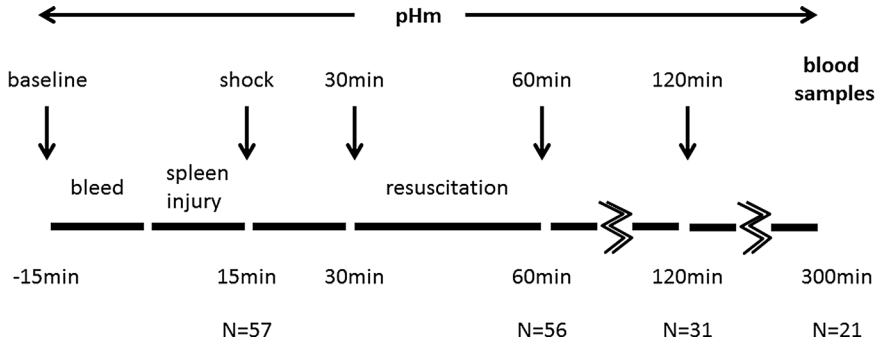

Fig. 1. **Experimental timeline**. Muscle pH is measured continuously; blood sample times for this analysis are indicated with arrows. The number of surviving animals at the end of shock (15 min), end of resuscitation (60 min), 2 h (120 min), and end of study (300 min) are indicated at the bottom.

injury. Because there was no significant difference in survival as a function of type of resuscitation fluid, most likely because of lack of power with the subgroups, the fluid type was not considered as a factor for this analysis.

Noninvasive pHm was collected continuously and updated approximately every 30 s. The value of pHm at the time of each blood draw was determined as the average of the 2 min of data prior to the blood draw time. Hydrogen ion concentration ($[H^+]$) in nmol/L was determined from the pHm values using Equation 1. $[H^+]$ was used for ease of visual comparison with lactate, because they both trend up with increasing acidosis.

$$[H^+] = 10^{-pHm} \times 10^9 \quad [1]$$

Lactate clearance at 2 h, as a percent change per hour, was calculated from the blood values determined at the end of shock (15 min) and 2 h after splenic injury (120 min) using Equation 2, similar to that described by Régnier et al. (11), although with the opposite sign. We subtracted the initial lactate (15 min) from the final lactate (120 min), so a reduction in lactate concentration as a result of resuscitation would presumably yield a negative rate.

$$Lactate\ Clearance\ (\%hr^{-1}) = \frac{lactate_{120\text{min}} - lactate_{15\text{min}}}{lactate_{15\text{min}}} \times 100/2hr \quad [2]$$

The same calculation was repeated for $[H^+]$ to determine H^+ clearance at 2 h in the same units (% h^{-1}). The 2-h period was chosen in part because of the high mortality rate and also to allow direct comparison to Régnier and colleagues' work (11).

A two-way repeated-measures analysis of variance with a Tukey post hoc test for pairwise multiple comparisons was performed to assess the differences between survivors and nonsurvivors for all parameters and between time points for pHm, $[H^+]$, and lactate. Data were analyzed with SigmaPlot version 12.5 (Systat Software, Chicago, Ill). Significance was determined at $P < 0.05$. Values are reported and plotted as mean ± SE.

Receiver operator characteristic (ROC) curves were constructed to determine the sensitivity and specificity for identifying mortality. Lactate and H^+ clearance, lactate concentration, and pHm were evaluated using the method of Hanley and McNeil (23) to compare the area under the ROC curve (AUC) using MedCalc Statistical Software version 13.2.2 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

A total of 57 swine completed the surgical procedure. Five hours after splenic injury, there were 21 survivors. The number of survivors at each stage of the study is shown in Figure 1. The characteristics of survivors and nonsurvivors are shown in Table 1. Both survivors and nonsurvivors experienced the same decrease in MAP and cardiac output at the end of shock (15 min), but nonsurvivors had significantly lower MAP at 60 and 120 min. Heart rate responses to hemorrhage and resuscitation for the two groups were similar. Changes in Hgb were also similar between survivors and nonsurvivors, but nonsurvivors had lower Hgb at 60 min. Blood loss was significantly higher for nonsurvivors, and these animals had slightly higher resuscitation volumes, possibly related to greater crystalloid volumes. Figure 2A shows the noninvasive pHm measurement at the five time points where lactate was determined. Both survivors and nonsurvivors have a similar drop in pH as a result of shock and the first 30 min of resuscitation. Muscle pH was significantly lower for nonsurvivors at 60 and 120 min. $[H^+]$ (Fig. 2B) trends up with shock as does lactate (Fig. 2C), to indicate similar degrees of metabolic acidosis for survivors and nonsurvivors. Both $[H^+]$ and lactate were significantly higher for nonsurvivors at 60 and 120 min. As for pHm, no difference in outcome was detected with either $[H^+]$ or lactate at 30 min. At 120 min, both pHm and $[H^+]$ returned to baseline levels for survivors, but lactate was still elevated relative to baseline ($P = 0.006$).

Table 2 compares the sensitivity, specificity, and ROC curve prediction of mortality at 60 and 120 min. At 60 min, the end of resuscitation, both lactate and pHm distinguished survivors and nonsurvivors with good sensitivity and specificity represented with an AUC of 0.78 for lactate and 0.76 for pHm. Sensitivity and specificity were improved at 120 min, with lactate, pHm lactate clearance, and H^+ clearance, all with an AUC of 0.87. For lactate at 120 min, a value of 3.8 mmol/L or less indicated survival; for pHm at 120 min, a value greater than 7.24 indicated survival. The H^+ clearance rate was $-7.4\%\ h^{-1}$, indicating a net decrease in acidosis after 2 h, whereas the lactate clearance rate was $+14.7\%\ h^{-1}$, suggesting continued acidosis, rather than a reduction, 2 h after injury.

DISCUSSION

This study compared two measures of acidosis and their clearance rates for the prediction of mortality during resuscitation from hemorrhagic shock. The main finding was that at 2 h after injury, lactate, lactate clearance, noninvasive pHm, and noninvasive H^+ clearance were equivalent predictors of mortality with an AUC of 0.87.

TABLE 1. **Characteristics of survivors and nonsurvivors**

	Survivors				Nonsurvivors			
	0 min	**15 min**	**60 min**	**120 min**	**0 min**	**15 min**	**60 min**	**120 min**
MAP, mmHg	67 ± 2	37 ± 3	55 ± 2	56 ± 2	68 ± 1	37 ± 1	38 ± 1*	35 ± 3*
HR, beats/min	102 ± 3	190 ± 8	198 ± 7	208 ± 7	114 ± 6	207 ± 6	212 ± 5	215 ± 16
CO, L/min	4.3 ± 0.2	1.5 ± 0.2	3.5 ± 0.2	3.3 ± 0.1	4.4 ± 0.2	1.5 ± 0.1	2.2 ± 0.2*	1.6 ± 0.4*
Hgb, g/dL	9.8 ± 0.3	9.9 ± 0.3	7.5 ± 0.2	7.7 ± 0.2	9.7 ± 0.2	9.8 ± 0.2	6.1 ± 0.2*	7.1 ± 0.4
BL, mL/kg	N/A	30 ± 1	34 ± 1	35 ± 1	N/A	32 ± 1†	47 ± 1*	46 ± 1*
Fluid In, mL/kg	N/A	N/A	16 ± 1	18 ± 1	N/A	N/A	21 ± 1†	26 ± 1†
Lac, mmol/L	2.2 ± 0.2	4.5 ± 0.5	4.9 ± 0.5	3.9 ± 0.5	2.1 ± 0.1	4.0 ± 0.3	7.3 ± 0.5*	8.6 ± 1.5*
pHm, pH units	7.32 ± 0.02	7.19 ± 0.02	7.31 ± 0.02	7.33 ± 0.02	7.30 ± 0.02	7.16 ± 0.02	7.20 ± 0.02*	7.15 ± 0.05*
$[H^+]$, nmol/L	49 ± 2	67 ± 4	50 ± 3	48 ± 3	51 ± 2	72 ± 3	66 ± 3*	77 ± 8*

Values are presented as mean ± SE.
*$P < 0.001$ compared with survivors.
†$P < 0.05$ compared to survivors.
MAP indicates mean blood pressure; HR, heart rate; CO, cardiac output; BL, blood loss; Fluid In, resuscitation volume; Lac, lactate concentration; pHm; $[H^+]$, hydrogen ion concentration; N/A, not applicable.

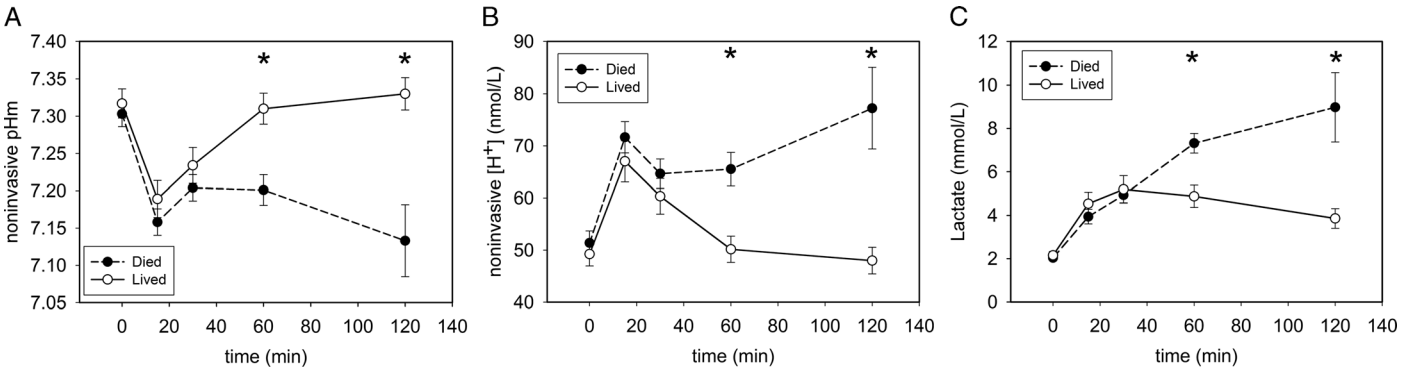

FIG. 2. **Muscle pH, [H+], and lactate for survivors (○) and nonsurvivors (•) at 0 (baseline), 15 (end of shock), 30, 60 (end of resuscitation), and 120 min**. Mean ± SE; *$P < 0.05$ survivors versus nonsurvivors.

Target values

Lactate is considered a marker for tissue hypoxia resulting from insufficient oxygen delivery to meet metabolic demand (14, 16), but when the critical level of oxygen delivery is reached, that is, it can no longer keep up with oxygen consumption, anaerobic metabolism results in a large reduction in ATP production and a sharp increase in serum lactate (15). For this reason, high levels of lactate have been associated with mortality in several groups of patients. The goal of resuscitation is to improve perfusion and deliver oxygen to tissues. If successful, a secondary benefit would be reduction or elimination of metabolic acidosis. Thus, target lactate and pH values should be consistent with the definition of acidosis. Lactic acidosis that results from hemorrhage-induced tissue hypoxia has been defined as lactate concentration exceeding 4 mmol/L with metabolic acidosis (24). Stacpoole (17) defined lactate acidosis as metabolic acidosis with serum lactate of greater than 5 mmol/L and arterial pH of less than 7.35. Régnier et al. (11) found that patients in their study who had initial values of lactate greater than 5 mmol/L were more likely to die. The Netherlands prehospital study (5) found that a lactate cutoff of 3.5 mmol/L on arrival at the scene and also on arrival at the ED predicted mortality, despite any treatment that occurred during transport. The group from Beth Israel (12, 25) considered lactate to be low when it was less than 2.5 mmol/L, moderately elevated between 2.5 and 4 mmol/L, and severely elevated at greater than 4 mmol/L. The determination of 3.8 mmol/L threshold from our present analysis is consistent with the findings of other authors.

This article is the first to report on target values of noninvasively measured pHm to guide resuscitation with the aim of reducing mortality. At 60 min, the cutoff or target value of pHm that indicated survival was greater than 7.30. At 120 min, that cutoff was greater than 7.24. During swine shock and resuscitation, pHm has been shown to be equivalent to venous pH (21). An arterial pH of 7.35, as suggested by Stacpoole (17) to indicate acidosis, would be equivalent to a venous pH of approximately 7.32 (26). Previous work with invasive sensors indicated that hepatic dysoxia in swine hemorrhagic shock occurred at a pH between 7.19 and 7.29 (27). Thus, a target goal of 7.30, as observed at 60 min in the present analysis, would be conservative but in alignment with previous publications.

Clearance rates (change in concentration per hour)

Long periods of elevated lactate are assumed to also be lengthy periods of tissue hypoxia and acidosis. Further work has focused on using serial lactate measurements to assess lactate clearance as an indicator of mortality (10–12, 28) and guide successful fluid resuscitation (29). A number of investigators have looked at the lactate clearance rate (change in lactate concentration over a specified time period) as a predictor of mortality and therefore an indicator of successful resuscitation from traumatic injury (10–12, 28, 29). A reduction in serum

TABLE 2. **ROC curve analysis for prediction of survival at 5 h**

	Sensitivity	Specificity	Cutoff value	AUC	95% Confidence interval
Determined at 60 min					
Lactate, mmol/L	81.0	79.4	≤5.5	0.78	0.64–0.91
pHm, pH units	61.9	82.9	>7.30	0.76	0.64–0.89
$[H^+]$, nmol/L	80.0	66.7	>51	0.77	0.64–0.89
Determined at 120 min					
Lactate, mmol/L	71.4	88.9	≤3.8	0.87	0.74–1.0
pHm, pH units	85.7	88.9	>7.24	0.87	0.72–1.0
$[H^+]$, nmol/L	80.0	85.7	>55	0.86	0.71–1.0
Lactate clearance, % h^{-1}	85.7	88.9	<14.7	0.87	0.69–1.0
H^+ clearance, % h^{-1}	85.7	88.9	≤−7.4	0.87	0.69–1.0

Comparisons of AUC for acidosis parameters determined at 60 and 120 min. No significant differences within each time period.

lactate concentration over 2, 4, 6, and 24 h has been considered. Only 2 and 4 h would be relevant to our study, which ended 5 h after injury, and may be relevant to trauma patients, where the majority of early deaths occur in the first 6 h after injury (30). Régnier and colleagues (11) demonstrated in their study of patients admitted to a trauma center that 2-h lactate clearance was a superior predictor of mortality compared with a single lactate level or 4-h clearance (11). In particular, a 20% h^{-1} reduction in lactate concentration was an indicator of survival. In our current analysis, a lactate clearance rate of 15% h^{-1} and an H^+ clearance rate of 7% h^{-1} distinguished survivors from nonsurvivors. Both lactate clearance rate and a 2-h lactate measurement were equivalent in predicting mortality. However, this could be because in our laboratory study we controlled the time of lactate sampling relative to the time of injury. For trauma patients, the time of injury may not be known, so the rate of clearance likely provides more consistent results because it removes the unknown time factor.

Our analysis allowed the comparison of lactate and H^+ clearance rates. Figure 2 illustrates the changes in lactate and pHm and therefore H^+ concentrations over time. Figure 2B shows that H^+ is cleared very quickly, back to baseline levels within 60 min (as is pHm). Figure 2C shows lactate changes very little 60 min after shock and on average decreases slightly during the subsequent 60 min, remaining higher than baseline levels 120 min after injury. Resuscitation-induced reduction in lactate and H^+ concentration is expected to occur when there is return of capillary perfusion both to deliver oxygen to restore aerobic metabolism and to remove the excess lactate and H^+. Generally, lactate cannot be detected until its concentration in the blood exceeds the detection limit of the analytical instrument used to determine its concentration and is not measured continuously. Consequently, there may be a lag in development of metabolic acidosis and the detected rise in lactate concentrations. In contrast, the NIRS-based technique to determine pHm measures H^+ in the capillaries and venules (20, 31, 32), which are in equilibrium with the interstitial fluid, so may be capable of detecting the adequacy of resuscitation earlier.

Limitations

A limitation of our analysis is that the animal model does not have a major soft tissue component with the hemorrhage, which would be commonly seen in trauma patients, particularly in military scenarios. The 15-min post–spleen injury time to start resuscitation may be somewhat too short for military situations, where available resuscitation fluids would be limited to target return of peripheral pulse or mentation according to Tactical Combat Care guidelines, rather than a targeted blood pressure. Despite these possible limitations, the cutoff values of lactate and lactate clearance, which distinguish survivors from nonsurvivors, were similar to values reported in clinical studies and represent target levels to eliminate acidosis.

One of the limitations of the NIRS-based pHm and H^+ measurements is that they are regional measurements, that is, represent the level of acidosis in the muscle under the sensor. Application in a clinical setting assumes that monitoring reduction in skeletal muscle acidosis would be predictive of the patient as a whole, or at least the most critical organs. In general, this assumption is also true for NIRS-based measurements of tissue oxygen saturation, which have shown good correlation with global oxygen delivery in experimental hemorrhage models (33) and both civilian and military trauma patients (34, 35). We have previously shown in swine hemorrhage and resuscitation that pHm is highly correlated with liver pH (18).

Clinical implications

Obtaining a single lactate measurement is now possible in the prehospital setting and has been demonstrated to be predictive of in-hospital mortality (5, 7). It would be challenging to obtain multiple lactate measurements during ambulance transport for the calculation of lactate clearance and possibly not meaningful in many civilian settings where transport times are short. However, the noninvasive pHm/H^+ can be rapidly deployed at the point of injury and provides pHm readings updated every 30 s, making possible a real-time assessment of adequacy of resuscitation to reduce tissue acidosis. This would be valuable for the military and remote civilian settings where air and ground ambulance transport times can be long. In urban areas, initial monitoring at the scene, continued through treatment in the ED, would help determine whether treatment targets should be a single pHm level or a H^+ clearance rate. This analysis in hemorrhaged/resuscitated swine demonstrated that pHm and H^+ clearance rate were equivalent to lactate and lactate clearance rate in predicting mortality. These data suggest that a prehospital clinical study of the noninvasive pHm sensor is warranted.

ACKNOWLEDGMENTS

The authors thank the following for their excellent technical support: I. Amy Polykratis, Rodolfo de Guzman, SSG Orlando Hernandez, SGT Anntoniette M. Pierce, SPC Tylor J. Johnson, SSG Jaime Torres-Mendoza, and the staff of the Research Support Divisions.

REFERENCES

1. Eastridge BJ, Mabry RL, Seguin P, Cantrell J, Tops T, Uribe P, Mallett O, Zubko T, Oetjen-Gerdes L, Rasmussen TE, et al.: Death on the battlefield (2001–2011): implications for the future of combat casualty care. *J Trauma Acute Care Surg* 73(6 Suppl 5):S431–S437, 2012.
2. Butler FK Jr, Blackbourne LH: Battlefield trauma care then and now: a decade of Tactical Combat Casualty Care. *J Trauma Acute Care Surg* 73(6 Suppl 5): S395–S402, 2012.
3. Parks JK, Elliott AC, Gentilello LM, Shafi S: Systemic hypotension is a late marker of shock after trauma: a validation study of Advanced Trauma Life Support principles in a large national sample. *Am J Surg* 192:727–731, 2006.
4. Vandromme MJ, Griffin RL, Weinberg JA, Rue LW III, Kerby JD: Lactate is a better predictor than systolic blood pressure for determining blood requirement and mortality: could prehospital measures improve trauma triage? *J Am Coll Surg* 210:861–867, 2010.
5. Jansen TC, van Bommel J, Mulder PG, Rommes JH, Schieveld SJM, Bakker J: The prognostic value of blood lactate levels relative to that of vital signs in the pre-hospital setting: a pilot study. *Crit Care* 12:R160–R167, 2008.
6. Claridge JAM, Crabtree TDM, Pelletier SJM, Butler KR, Sawyer RGM, Young JSM: Persistent occult hypoperfusion is associated with a significant increase in infection rate and mortality in major trauma patients. *J Trauma* 48:8, 2000.
7. Guyette F, Suffoletto B, Castillo JL, Quintero J, Callaway C, Puyana JC: Prehospital serum lactate as a predictor of outcomes in trauma patients: a retrospective observational study. *J Trauma* 70:782–786, 2011.
8. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich BP, Peterson E, Tomlanovich M: Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 345:1368–1377, 2001.
9. Nguyen HBM, Rivers EPM, Knoblich BPM, Jacobsen GM, Muzzin AB, Ressler JAB, Tomlanovich MCM: Early lactate clearance is associated with

improved outcome in severe sepsis and septic shock. *Crit Care Med* 32: 1637–1642, 2004.
10. Abramson D, Scalea TM, Hitchcock R, Trooskin SZ, Henry SM, Greenspan J: Lactate clearance and survival following injury. *J Trauma* 35:584–588, 1993.
11. Régnier MA, Raux M, Le Manach Y, Asencio Y, Gaillard J, Devilliers C, Langeron O, Riou B: Prognostic significance of blood lactate and lactate clearance in trauma patients. *Anesthesiology* 117:1276–1288, 2012.
12. Odom SR, Howell MD, Silva GS, Nielsen VM, Gupta A, Shapiro NI, Talmor D: Lactate clearance as a predictor of mortality in trauma patients. *J Trauma Acute Care Surg* 74:999–1004, 2013.
13. Tobias AZ, Guyette FX, Seymour CW, Suffoletto BP, Martin-Gill C, Quintero J, Kristan J, Callaway CW, Yealy DM: Pre-resuscitation lactate and hospital mortality in prehospital patients. *Prehosp Emerg Care* 18:321–327, 2014.
14. Fuller BM, Dellinger RP: Lactate as a hemodynamic marker in the critically ill. *Curr Opin Crit Care* 18:267–272, 2012.
15. Lee SW, Hong YS, Park DW, Choi SH, Moon SW, Park JS, Kim JY, Baek KJ: Lactic acidosis not hyperlactatemia as a predictor of inhospital mortality in septic emergency patients. *Emerg Med J* 25:659–665, 2008.
16. Bakker J, Nijsten MWN, Jansen TC: Clinical use of lactate monitoring in critically ill patients. *Ann Intensive Care* 3:12, 2013.
17. Stacpoole PW: Lactic acidosis. *Endorinol Metab Clin North Am* 22:221–245, 1993.
18. Soller BR, Khan T, Favreau J, Hsi C, Puyana JC, Heard SO: Investigation of muscle pH as an indicator of liver pH and injury from hemorrhagic shock. *J Surg Res* 114:195–201, 2003.
19. Soller BR, Sliwa J, Yang Y, Zou F, Ryan KL, Rickards CA, Convertino VA: Simultaneous spectroscopic determination of forearm muscle pH and SO_2 during simulated hemorrhage. *JNIRS* 20:141–150, 2012.
20. Ellerby G, Smith CP, Zou F, Scott P, Soller BR: Validation of a spectroscopic sensor for the continuous, noninvasive measurement of muscle oxygen saturation and pH. *Physiol Meas* 34:859–871, 2013.
21. Soller B, Smith C, Zou F, Ellerby GEC, Prince MD, Sondeen JL: Investigation of noninvasive muscle pH and oxygen saturation during uncontrolled hemorrhage and resuscitation in swine. *Shock* 42:44–51, 2014.
22. Sondeen JL, Prince MD, Kheirabadi BS, Wade CE, Polykratis IA, de Guzman R, Dubick MA: Initial resuscitation with plasma and other blood components reduced bleeding compared to hetastarch in anesthetized swine with uncontrolled splenic hemorrhage. *Transfusion* 51:779–792, 2011.
23. Hanley JA, McNeil BJ: A method of comparing the areas under receiver operating characteristic curves derived from the same cases: *Radiology* 148:839–843, 1983.
24. Chan ED, Terada LS, Kortbeek J, Winston BW: *Bedside Critical Care Manual*. Hanley & Belfus, Inc: Philadelphia, PA, 2002.
25. Callaway DW, Shapiro NI, Donnino MW, Baker C, Rosen CL: Serum lactate and base deficit as predictors of mortality in normotensive elderly blunt trauma patients. *J Trauma* 66:1040–1044, 2009.
26. Middleton P, Kelly AM, Brown J, Robertson M: Agreement between arterial and central venous values for pH, bicarbonate, base excess, and lactate. *Emerg Med J* 23:622–624, 2006.
27. Soller BR, Heard SO, Cingo N, Hsi C, Favreau J, Khan T, Ross RR, Puyana JC: Application of fiberoptic sensors for the study of hepatic dysoxia in swine hemorrhagic shock. *Crit Care Med* 29:1438–1444, 2001.
28. Zhang Z, Xu X: Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis [published online ahead of print]. *Crit Care Med* 42:2118–2125, 2014.
29. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, Willemsen SP, Bakker J, for the LACTATE study group: early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. *Am J Respir Crit Care Med* 182:752–761, 2010.
30. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, et al.: The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surgery* 148:127–136, 2013.
31. Fadel PJ, Keller DM, Watanabe H, Raven PB, Thomas GD: Noninvasive assessment of sympathetic vasoconstriction in human and rodent skeletal muscle using near-infrared spectroscopy and Doppler ultrasound. *J Applied Physiol* 96:1323–1330, 2004.
32. Liu H, Chance B, Hielscher AH, Jacques SL, Tittel FK: Influence of blood vessels on the measurement of hemoglobin oxygenation as determined by time-resolved reflectance spectroscopy. *Med Phys* 22:1209–1217, 1995.
33. Beilman GJ, Groehler KE, Lazaron V, Ortner JP: Near-infrared spectroscopy measurement of regional tissue oxyhemoglobin saturation during hemorrhagic shock. *Shock* 12:196–200, 1999.
34. Smith J, Bricker S, Putnam B: Tissue Oxygen Saturation Predicts the Need for Early Blood Transfusion in Trauma Patients. *Am Surg* 74:1006–1011, 2008.
35. Beekley ACM, Martin MJM, Nelson TM, Grathwohl KWM, Griffith MM, Beilman GM, Holcomb JBM: Continuous noninvasive tissue oximetry in the early evaluation of the combat casualty: a prospective study. *J Trauma* 69:S14–S25, 2010.