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Normal Lactate/Pyruvate Ratio during Overwhelming Polymicrobial Bacteremia and Multiple Organ Failure

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OCCULT tissue hypoxia, when unrelieved, is thought to be a cause of multiple organ failure and of the consequent high mortality reported for patients with sepsis.[1,2] Because clinical endpoints are not always accurate markers of perfusion in sepsis, other parameters of subclinical tissue ischemia include lactic acidosis and pathologic supply-dependent oxygen consumption (V_{O_2}).[3–5] Mild hyperlactatemia (blood lactate 2–5 mM/l) not accompanied by acidosis can occur as a result of sepsis-related hypermetabolism. Clinically significant lactic acidosis (blood lactate ≥4–5 mM/l) is presumed to reflect anaerobic metabolism and the magnitude of the tissue oxygen debt.[5,‡] Reversal of lactic acidosis is recommended as a guide by which to titrate hemodynamic resuscitation[5–8,‡] and is associated with improved survival from sepsis and in high-risk surgical patients.[8]

Interventions that increase systemic oxygen delivery (D_{O_2}) for microcirculatory resuscitation are deemed adequate when flow-independent V_{O_2} and the clearance of lactic acid are achieved.[5,6,8] Moreover, the failure of increased blood lactate levels to decrease in response to measures that increase D_{O_2} may serve as evidence against the presence of tissue hypoxia, refuting the need for further hyperresuscitation efforts.[5,7,8] This procedure has been called the "oxygen flux test."[5] While physiologically sound, this principle has not been fully validated in the patient with sepsis. We could find no studies of human sepsis in which increments in D_{O_2} or reductions in lactic acidosis were compared with more sophisticated measures of cellular oxygenation, *i.e.*, bioenergetics spectroscopy,[9] the lactate/pyruvate (L/P) ratio,[10] or adenosine triphosphate degradation products.[11]

We present a case of postoperative polymicrobial bacteremia accompanied by lactic acidosis and multiple organ failure in an immunosuppressed host. Despite the attainment of supranormal D_{O_2} to very high levels, marked hyperlactatemia persisted. We hypothesize that this "negative" oxygen flux test demonstrates lactic acidosis was not a product of inadequate tissue D_{O_2} and anaerobic metabolism. Documentation of a normal L/P ratio confirmed this finding.

Case Report

A 36-yr-old man with Laennec's cirrhosis and a history of variceal bleeding underwent elective orthotopic liver transplantation. The procedure was complicated by massive variceal hemorrhage, with an estimated blood loss of 110 l. Intraoperative transfusion requirements included 125 U packed erythrocytes, 170 U platelets, 150 U fresh frozen plasma, 120 U cryoprecipitate, and 26 l of cell saver blood. At one point during the operation, before control of variceal hemorrhage, the supply of banked blood products was exhausted and intragastric blood was transfused directly into the patient to prevent exsanguination. Control of hemorrhage ultimately was obtained, the donor liver implanted, and the patient transferred to the surgical intensive care unit.

The patient was febrile and agitated during the early postoperative period. Blood cultures drawn on the 2nd postoperative day grew *Staphylococcus aureus* and *Pseudomonas aeruginosa*. On the 3rd postoperative day, sputum, T-tube drainage, and drainage from all three abdominal Jackson-Pratt sites were culture-positive for *S. aureus* and *P. aeruginosa*. Antibiotic sensitivities for these organisms were identical among all cultures; treatment consisted of vancomycin, ceftazidime, and piperacillin. The patient's trachea was intubated and lungs mechanically ventilated. An arterial blood gas obtained on the 1st postoperative day ("baseline") showed *p*H 7.38, P_{CO_2} 38 mmHg, P_{O_2} 100 mmHg, and HCO_3 23 mM/l on a FI_{O_2} of 1.00 and 12.5 cmH_2O PEEP; the calculated intrapulmonary shunt was 31% (normal 3–7%).

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‡ Vary TC, Siegel JH, Rivkind A: Clinical and therapeutic significance of metabolic patterns of lactic acidosis. Perspectives in Critical Care 1:85–129, 1988.

The patient exhibited a hyperdynamic circulation (tachycardia, high cardiac index, low systemic vascular resistance index) on the 1st postoperative day; clinical signs of hypoperfusion, including oliguria, hypotension, altered mental status, and cool extremities, were not present. At approximately 8 h from the end of surgery, the first measured blood lactate was 4.5 mM/l (normal 0.1–2 mM/l; table 1). As there was concern that this might reflect a tissue oxygen deficit, the patient was hyperresuscitated with 3 l of normal saline, 1 l 5% albumin, 6 U packed erythrocytes, and digoxin (10 μg/kg intravenously over 3 min) with the aim of progressively increasing D_{O_2} until the blood lactate concentration began to decrease. In response to these measures, the pulmonary artery wedge pressure increased from 14 to 18 mmHg, the hematocrit increased from 26% to 41%, and the cardiac index increased from 5.00 to 7.25 $l \cdot min^{-1} \cdot m^{-2}$. On clinical examination, the patient appeared to be well perfused (no evidence of hypotension or oliguria; extremities warm to touch), and no further therapeutic maneuvers were made. Blood lactate never decreased to less than 4.5 mM/l despite increments in D_{O_2}. The peak D_{O_2} of 1,029 $ml \cdot min^{-1} \cdot m^{-2}$ was achieved approximately 24 h following the start of resuscitation, yet was associated with an increase in blood lactate concentration to 6.3 mM/l (table 1). Lactate/pyruvate levels were obtained from the patient; simultaneous L/P levels were obtained from another subject who had recovered from critical illness to serve as a set of control values (table 2).

Multiple organ failure developed rapidly. Hyperbilirubinemia (total serum bilirubin = 188 μM/l (11 mg/dl)) and elevated hepatic enzymes on the 2nd postoperative day signalled acute hepatic dysfunction. Nonoliguric renal failure, with the serum creatinine doubling on the 1st postoperative day and increasing from 90 to 470 μM/l (1.0 to 5.3 mg/dl), was thought to be secondary to a combination of intraoperative hypotension, postoperative sepsis, and cyclosporine. Initially awake and following commands, the patient became stuporous by the 5th postoperative day. Physical examination showed no focal neurologic findings and intact brainstem reflexes. On postoperative day 7, the neurologic examination results changed: the pupils were fixed and dilated, the patient was apneic, and there was an abnormal oculocephalic response. A head computed tomography scan revealed cerebral edema with acute hydrocephalus. A ventriculostomy was performed, with return of bloody cerebrospinal fluid under pressure; this fluid was culture-positive for *S. aureus*. However, there was no improvement in mental status or return of brainstem reflexes.

The patient was declared brain dead, and all care was withdrawn. Autopsy results demonstrated cerebral edema, peritonitis, and pneumonia with cavitary abscess formation.

Table 1. Hemodynamic and Oxygen Transport Data before and after Resuscitation

	Baseline	Peak Oxygen Delivery
Temperature (° C)	38.1	37.9
Heart rate ($beats \cdot min^{-1}$)	109	103
Mean arterial pressure (mmHg)	77	85
Pulmonary arterial wedge pressure (mmHg)	14	18
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	5.00	7.25
Systemic vascular resistance ($dyn \cdot s \cdot cm^{-5}$)	649	503
Mixed venous oxygen saturation (%)	71	83
Oxygen delivery ($ml \cdot min^{-1} \cdot m^{-2}$)	795	1029
Oxygen consumption ($ml \cdot min^{-1} \cdot m^{-2}$)	225	167
Oxygen extraction ratio	0.28	0.16
Lactate (mM)	4.5	6.3
Arterial *p*H	7.38	7.40
HCO_3	23	23

Baseline = first postoperative day, at steady state (after the residual effects of intraoperative medications have subsided); peak oxygen delivery = approximately 24 h after the baseline data, and as a consequence of the hyperresuscitative efforts described in the case report.

Table 2. Lactate and Pyruvate Data

	Patient	Control
Lactate (mM)	5.2	2.0
Pyruvate (mM)	0.45	0.21
Lactate/pyruvate ratio	11.9	10.1

Discussion

Interpretation of an increased blood lactate level in the patient with severe sepsis, a hyperdynamic circulation, and an increased metabolic rate can be complicated. Mild hyperlactatemia, in the absence of anaerobic metabolism and metabolic acidosis, occurs as a consequence of factors that increase the glycolytic flux of glucose to pyruvate and lactate. The usual range in which this occurs is approximately 2–5 mM/l.[5] Clinically relevant lactic acidosis, that associated with shock and mortality, is more likely at blood concentrations in excess of 4–5 mM/l.[12] Because of the concern that underresuscitation could increase mortality from septic shock, the hyperlactatemia observed in our patient was presumed to be clinically relevant, and efforts were made to increase D_{O_2}.

Elevated blood lactate concentration in the critically ill patient is commonly the result of overproduction and reduced clearance. Only a small fraction (1–2%) of the circulating lactate is excreted, even during states of circulatory shock; renal, hepatic, and cardiac uptake to support gluconeogenesis (Cori cycle) account for the majority of lactate clearance. Hepatic failure will prolong lactate clearance, which will proceed three times more slowly when the host is stressed.[13] Hepatic failure, however, will not cause hyperlactatemia until complicated by circulatory shock.[14]

We wondered whether the large citrate load (approximately 1,750 mM in our patient) associated with massive blood transfusion could serve as a metabolic

substrate to produce hyperlactatemia. Massive transfusion for liver transplantation commonly is accompanied by metabolic alkalosis, not lactic acidosis.[15] The half-life of citrate is measured in minutes[16] and would not account for the blood lactate levels between 4 and 7 mM/l measured for 7 consecutive postoperative days. Moreover, an increased blood citrate concentration exerts negative feedback on phosphofructokinase, thus inhibiting glycolysis and the rate of lactate formation.[16] For these reasons, large quantities of citrate in association with massive blood transfusion would not be responsible for the prolonged hyperlactatemia seen in our patient.

This case points out some of the limitations in relying solely on blood lactate as a determinant of tissue hypoxia. Use of the oxygen flux test in our patient called for increments in D_{O_2}; yet the blood lactate concentration did not decrease in response. Routine augmentation of D_{O_2} may be insufficient to lower blood lactate in the adequately resuscitated patient with sepsis. Therein lies the dilemma. How much should D_{O_2} be increased before it can be certain the oxygen flux test is negative? Interventions that augment cardiac index and D_{O_2} are not without risk to the patient, given the possible detrimental effects of fluid overload, blood transfusions, and increased myocardial work.[17] Authorities may advocate the use of an oxygen flux test without specifying what constitutes an adequate level of supranormal D_{O_2} for an individual patient.[5-7] Our patient was adequately resuscitated and had an D_{O_2} in excess of 20 $ml \cdot min^{-1} \cdot kg^{-1}$, exceeding the critical D_{O_2} level of 15 $ml \cdot min^{-1} \cdot kg^{-1}$ identified by Tuchschmidt *et al.* in their retrospective study of patients surviving septic shock.[6]

What is the relationship between the oxygen flux test and increased blood lactate in the patient with sepsis? Based on a study of 49 patients with sepsis by Vincent *et al.*[18] in which D_{O_2} was augmented by a standard protocol with fluids and dobutamine, only patients with increased blood lactate demonstrated increases in V_{O_2}. Patients with normal blood lactate levels did not sustain increases in V_{O_2}. From these results, the authors concluded that increases in V_{O_2} in critically ill patients with increased blood lactate occur with the coexistence of tissue hypoxia. In our patient, D_{O_2} was increased approximately 30%, yet there was no increase in V_{O_2} (negative oxygen flux) and elevated blood lactate did not resolve. The peak D_{O_2} of 1,029 $ml \cdot min^{-1} \cdot m^{-2}$ achieved in our patient is approximately double the mean D_{O_2} (541 ± 147 $ml \cdot min^{-1} \cdot m^{-2}$) sustained by patients with sepsis in the report by Vincent *et al.*[18] Overall, the demonstration of supply-independent V_{O_2} in our patient who had been hyperresuscitated is further evidence that severe hyperlactatemia was not due to tissue hypoxia.

This notion additionally is supported by a study of oxygen transport in 32 high-risk surgical patients with hyperlactatemia and sepsis.[8] Patients received volume expansion and inotropic support (dobutamine, 5–200 μg/kg/min) with the goal of achieving D_{O_2} >600 $ml \cdot min^{-1} \cdot m^{-2}$ and assessing outcome. Two groups were identified based on the subsequent change in V_{O_2}. One group (n = 15), responding to increases in D_{O_2} by increasing V_{O_2} and normalizing blood lactate (positive oxygen flux), sustained a 94% survival rate. By contrast, the second group (n = 17) of patients sustained a negative oxygen flux and remained hyperlactatemic, and only 6% survived. The findings in the second group may be explained by an inability of tissues to properly utilize oxygen. Alternatively, a tissue oxygen deficit may not be present and thus may not be the underlying mechanism at work that results in organ failure and death. This latter explanation would be more plausible in our reported patient, who experienced a negative oxygen flux, persistent hyperlactatemia, and a normal L/P ratio.

The L/P ratio is considered an excellent index of the adequacy of cellular oxygenation and can be used to differentiate hyperlactatemia arising from hypermetabolism compared to that produced by organ or regional ischemia.[7,9] Lactate/pyruvate values exceeding 15–20 are indicative of tissue hypoxia; the higher the value, the greater is the magnitude of the oxygen debt and the worse is the prognosis.[19] Our patient experienced a marked and persistent hyperlactatemia in the face of hyperresuscitation. Although not available before hemodynamic intervention, an L/P ratio was obtained immediately afterward. The blood lactate was significantly increased at 5.2 mM/l, yet the L/P ratio of 11.9 identified a normal redox state, thus strongly arguing against the possibility of significant regional or systemic hypoperfusion as a cause of hyperlactatemia. The normal L/P ratio validated the negative response to the oxygen flux test and nullified the need for further increments in D_{O_2}.

This case demonstrates that clinically significant hyperlactatemia, by itself and as noted in our patient with severe sepsis, may not be a consistent marker of tissue ischemia. It also documents the validity of a "negative" oxygen flux test by showing it can accurately predict

a normal redox state and the potential futility of overly exuberant attempts at hyperresuscitation.

References

1. Barton R, Cerra FB: The hypermetabolism multiple organ failure syndrome. Chest 96:1153–1160, 1989

2. Bihari D, Smithies M, Gimson A, Tinker J: The effects of vasodilation with prostacyclin on oxygen delivery and uptake in critically ill patients. N Engl J Med 397–403, 1987

3. Gutierrez G, Pohil RJ: Oxygen consumption is linearly related to O_2 supply in critically ill patients. J Crit Care 1:45–53, 1986

4. Astiz ME, Rackow EC, Falk JL, Kaufman BS, Weil MH: Oxygen delivery and consumption in patients with hyperdynamic septic shock. Crit Care Med 15:26–28, 1987

5. Mizock BA, Falk JL: Lactic acidosis in critical illness. Crit Care Med 20:80–92, 1992

6. Tuchschmidt J, Oblitas D, Fried JC: Oxygen consumption in sepsis and septic shock. Crit Care Med 19:664–671, 1991

7. Bone RC: Abnormal cellular metabolism in sepsis: A new interpretation. JAMA 267:1518–1519, 1992

8. Hayes MA, Yau EHS, Timmins AC, Hinds CJ, Earnest HS, Watson D: Response of critically ill patients to treatment aimed at achieving supranormal oxygen delivery and consumption: Relationship to outcome. Chest 103:886–895, 1993

9. Hotchkiss RS, Karl IE: Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA 263:1503–1510, 1992

10. Cerra FB, Caprioli J, Siegel JH, McMenamy RR, Border JR: Proline metabolism in sepsis, cirrhosis and general surgery. Ann Surg 190:577–586, 1979

11. Grum CM, Simon RH, Dantzker DR, Fox IH: Evidence for adenosinetriphosphate degradation in critically ill patients. Chest 88: 763–767, 1985

12. Luft D, Deichsel G, Schmulling R-M, Stein W, Eggstein M: Definition of clinically relevant lactic acidosis in patients with internal diseases. J Clin Pathol 80:484–489, 1983

13. Almenoff PL, Leavy J, Weil MH, Goldberg NB, Vega D, Rackow EC: Prolongation of the half-life of lactate after maximal exercise in patients with hepatic dysfunction. Crit Care Med 17:870–873, 1989

14. Kruse JA, Zaidi SAJ, Carlson RW: Significance of blood lactate levels in critically ill patients with liver disease. Am J Med 83:77–82, 1987

15. Driscoll DF, Bistrian BR, Jenkins RL, Randall S, Dzik WH, Gerson B, Blackburn GL: Development of metabolic alkalosis after massive transfusion during orthotopic liver transplantation. Crit Care Med 15:905–908, 1987

16. Collins JA, Knudson MM: Metabolic effects of massive transfusion, Principles of Transfusion Medicine. Edited by Rossi EC, Simon TL, Moss GS. Baltimore, Williams & Wilkins, 1991, pp 419–422

17. Vincent J-L, Roman A, DeBacker D, Kahn RJ: Oxygen uptake/supply dependency: Effects of short-term dobutamine infusion. Am Rev Respir Dis 142:2–7, 1990

18. Terradellas JB, Bellot JF, Saris AB, Gil CL, Torrallardona AT, Garriga JR: Acute and transient ST segment elevation during bacterial shock in seven patients without apparent heart disease. Chest 81: 444–448, 1982

19. Weil MH, Afifi AA: Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation 41:989–1001, 1970

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Postanesthetic Apnea in Full-term Infants after Pyloromyotomy

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POSTANESTHETIC apnea in the former premature infant less than 60 weeks postconceptional age is a well described phenomenon, with specific strategies recommended for its prevention, monitoring, and treatment.[1–6] Apnea has been described in four full-term infants after anesthesia for a variety of surgical procedures.[7–10] We report four cases of apnea after anesthesia for pyloromyotomy for full-term infants without perinatal problems.

Patient characteristics, preoperative laboratory values, and details of the anesthetic techniques are presented in table 1.

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Case Reports

Case 1

This infant appeared mildly dehydrated, and after 2 h of rehydration consisting of normal saline 20 ml/kg, he was taken to the operating