Lactate

Dead End Waste Product or Physiological Treasure Trove?

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Objectives

- Describe the pathophysiology of lactate in:
  - Septic shock
  - Hemorrhagic shock
- List clinical conditions associated with elevated lactate concentrations
- Review the utility of lactate as both a prognostic biomarker and indicator of severity of critical illness (with orthopedic considerations)

Questions … Answers ?

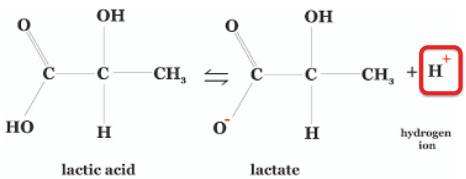
- Does lactate really indicate tissue hypoxia?
- What is the difference between Type A and B lactatemia? Is this a misnomer?
- What is meant by lactate "clearance?"
- How can lactate be used as an early warning marker / endpoint for resuscitation?
- Is lactate a good biomarker for mesenteric ischemia?
- How can lactate be used to assess/stratify orthopedic patients?
- Does Ringers lactate increase serum lactate?

"I have yet to see any problem, however complicated, which, when you looked at it in the right way, did not become still more complicated"

-Poul William Anderson

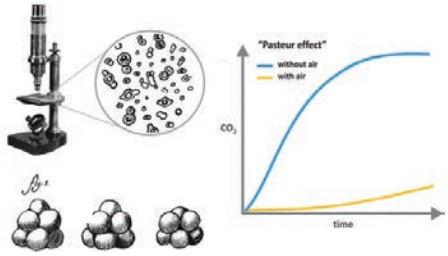
LACTATE PHYSIOLOGY

Lactate vs. Lactic Acid

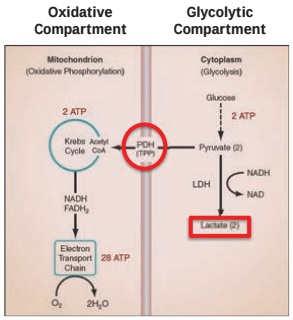


Hyperlactatemia > 2.0 mmol/L

Pasteur / Meakins



Meakins J. J Clin Invest 1927.
Pasteur L. C R Hebd Seances Acad Sci Paris 1861.

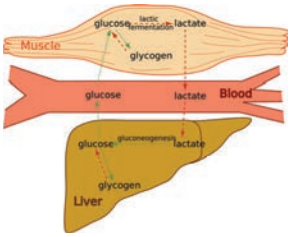


- Glycolysis: 2 ATP / glucose
- Mitochondrial pathway: 30 ATP / glucose
- TPP: thiamine dependent
- Lactate: end product of glycolysis

Marino PL. *Oxygen: Creating a New Paradigm*. 2022.

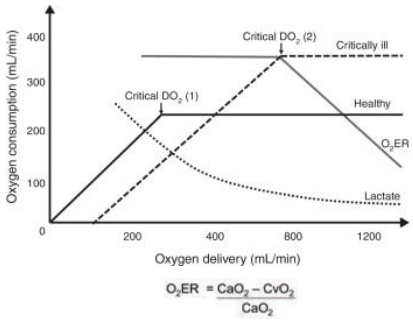
Lactate Metabolism

- Cori cycle
  - Lactate: most important gluconeogenic precursor
- Hepatocytes
  - Major site of oxidative lactate uptake
- Kidneys
  - 30% of lactate metabolism



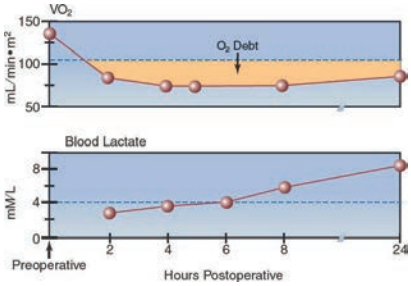
Mazzeo RS. J Appl Physiol 1986.

Oxygen Extraction



Rocha LL. Rev Bras Anestesiol 2015.

Oxygen Debt



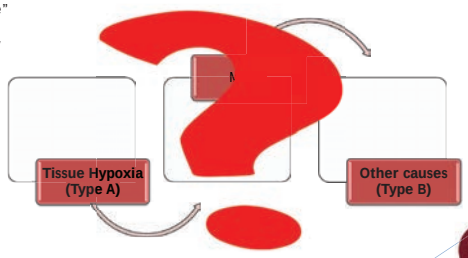
Hyperlactatemia May represent a cellular energy deficit, not necessarily tissue hypoxia

Lactate as Oxidative Fuel

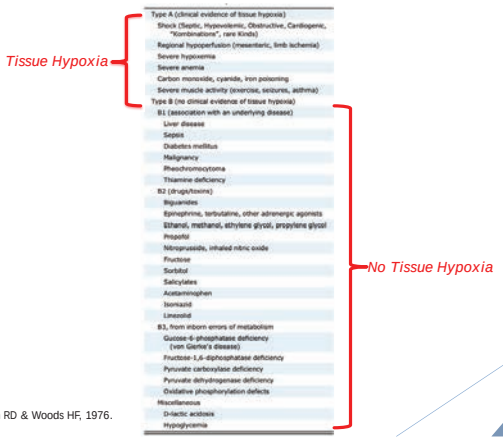
- Heart takes up and oxidizes lactate at rest
- Increases during exercise, stress, shock
- During shock, heart oxidizes lactate for majority of energy needs (**60%**)
- **7%** of cerebral energy at rest→**25%** during exercise

Classic Teaching

- "Clearance"
- Drugs
- Malignancy



Barbee RW. Shock 2010.
Cohen RD & Woods HF, 1976.



Cohen RD & Woods HF, 1976.

So, where does the acid come from?

- Glycolysis **generates** H^+
  - Conversion of pyruvate to lactate **consumes** H^+
- ATP hydrolysis is major generator of H^+
- For acidosis to occur, must have *decrease* in oxidative metabolism in mitochondria
- Increased lactate production or decreased consumption do not necessarily indicate tissue hypoxia

Suetrong B. Chest 2016.

Lactate in sepsis

Lactate is an unreliable indicator of tissue hypoxia in sepsis

Lactate ≠ anaerobic metabolism

Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021

Evans L, et al.

Crit Care Med 2021

- *For adults suspected of having sepsis, we suggest measuring blood lactate*
  - Quality of evidence: **Low**
- *For adults with sepsis or septic shock, we suggest guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate*
  - Quality of evidence: **Low**

Septic Shock

Vasopressor to keep MAP > 65 mmHg

AND

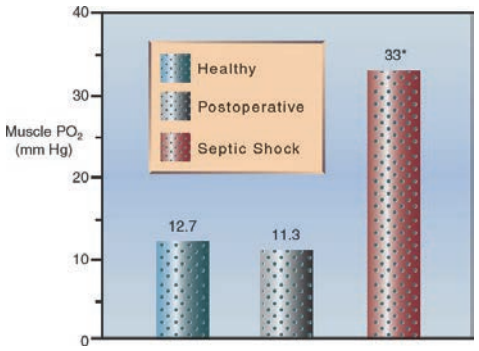
Lactate > 2 mmol/L
(after fluid resuscitation)

Sepsis and Tissue Oxygenation

- Severity of hyperlactemia related to mortality

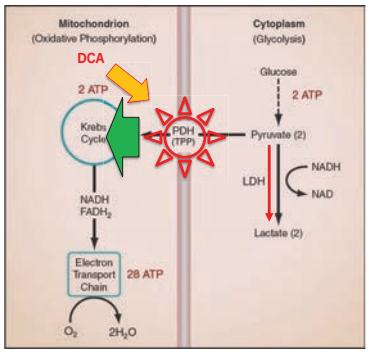
But…

- PaO_2 is *increased* in sepsis and septic shock
  - *Increased* glycolysis
  - Inhibition of pyruvate dehydrogenase (PDH)
  - Thiamine deficiency (20% in sepsis)
  - *Increased* NO production



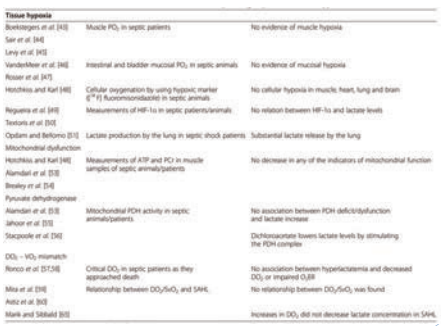
INEFFECTIVE MITOCHONDRIAL UTILIZATION

Marino PL. *Oxygen: Creating a New Paradigm* 2022.
Fink MP. Crit Care clin 2001.
Boekstegers P. Crit Care Med 1994.



Marino PL. *Oxygen: Creating a New Paradigm* 2022.
Thomas GW. J Trauma 2009.
Curtis SE. Am Rev Respir Dis 1992.

Lack of Evidence for "Traditional" Mechanisms Explaining Sepsis-Associated Hyperlactatemia



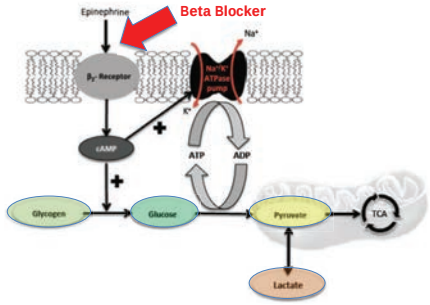
Garcia-Alvarez M. Critical Care 2014.

So where is it coming from???

- Lungs
- Adrenergic-driven aerobic glycolysis
- Skeletal muscle
- Splanchnic region: uncommon source
  - Splanchnics *consume* rather than produce lactate

Opdam H. Crit Care 2000.
Bellomo R. Chest 1996.
James JH. Lancet 1999.

Epinephrine-Increased Glycogenolysis and Glycolysis



James JH. Lancet 1999.
Levy B. Intensive Care Med 2007.

Plasma Epinephrine Concentrations
Rest: 150-300 pg/mL
Olympians: 1500-2000 pg/mL
Septic shock: > 500 pg/mL
Trauma: > 2000 pg/mL

Effect of Ultrashort-Acting ß-Blockers on Mortality in Patients With Sepsis With Persistent Tachycardia Despite Initial Resuscitation: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Hasegawa D, et al. Chest 2021

- Seven RCTs, N=613
- Esmolol or landiolol use in patients with sepsis and septic shock
  - **Lower 28-day mortality**
  - RR, 0.68; 95% CI, 0.54-0.85; P < .001
  - ARR 18.2%
  - NNT=5.5
- Use of ultrashort-acting ß-blockers in patients with sepsis with **persistent tachycardia despite initial resuscitation** may improve mortality

Airplane! 1980
Paramount Pictures

Lactate "Clearance"

- Percentage decrease in lactate
- "Clearance" scientifically and pharmacokinetically incorrect
  - **Clearance = removal of a substance from a unit of volume over a unit of time (i.e., mL/min)**
- Improvement in sepsis associated hyperlactatemia is likely due to *increased removal, dilution, or decreased production*

Suetrong B. Chest 2016.

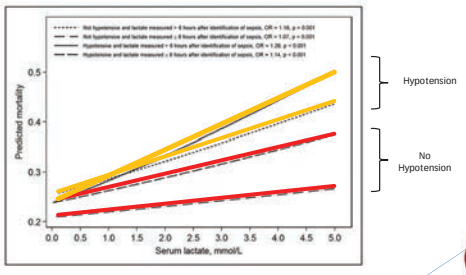
Lactate Measurements In Sepsis-Induced Tissue Hypoperfusion: Results from the Surviving Sepsis Campaign Database

Casserly B, et al. Crit Care Med 2015

- N=28,150 patients at 218 sites
- Elevated lactate highly associated with in-hospital mortality
- **>4 mmol/L** (with or without hypotension)
  - OR 2.10 (95% CI, 1.93-2.27)
  - >3 mmol/L also significant if associated with hypotension

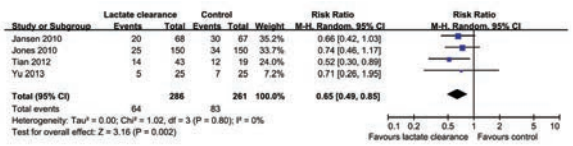
Lactate Measurements In Sepsis-Induced Tissue Hypoperfusion: Results from the Surviving Sepsis Campaign Database

Casserly B, et al. Crit Care Med 2015



Early Lactate Clearance-Guided Therapy in Patients with Sepsis: A Meta-Analysis with Trial Sequential Analysis of Randomized Controlled Trials

Gu WJ, et al. Intensive Care Med 2015



Problems

- *Assumption*: increased lactate is the result of tissue hypoperfusion
  - *Assumption*: Quantitative resuscitation will improve outcomes
- Increased lactate is not the only indicator of tissue hypoperfusion
- Septic patients with increased lactate should receive treatment focused on the **cause** of the increased lactate
  - Metabolic effects should not be neglected

Bakker J. Crit Care Med 2015.

Sepsis-induced hyperlactatemia represents a change in metabolic state, not simply a response to tissue hypoxia

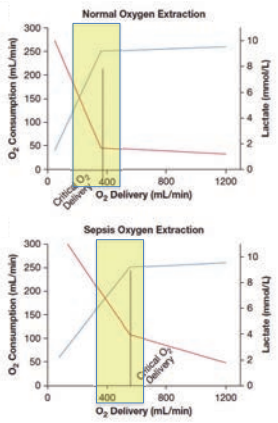
Lactate: Oxidative Fuel

- Alternative fuel during periods of metabolic stress
- Similar energy yield to glucose!

Substrate	Molecular Weight	Energy Yield	Caloric Density
Glucose	180 g/mol	673 kcal/mol	3.74 kcal/g
Lactate	90 g/mol	326 kcal/mol	3.62 kcal/g
Lactate × 2	180 g/mol	652 kcal/mol	

Marino PL. *Oxygen: Creating a New Paradigm*. 2022.

"Energy Shuttle"



Suetrong B. Chest 2016.

Inadequate Do_2 occurs in septic shock as well as all causes of shock

Other causes of hyperlactatemia must be considered

Sepsis: Conclusions

- Hyperlactatemia is common in septic shock
- Lactate is not just a waste product—it is an oxidative fuel
- Tissue hypoxia is not the sole cause
- Hyperlactatemia represents a change in metabolic state

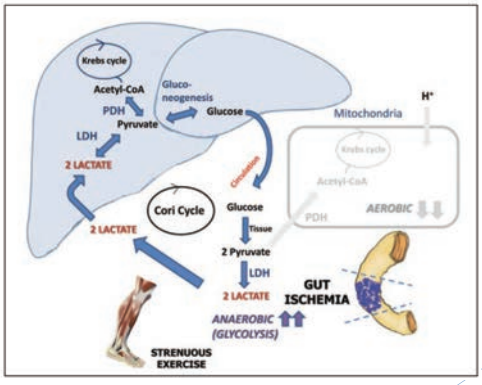
Lactate is a powerful metabolic marker

Lactate in MESENTERIC ischemia

Acute Mesenteric Ischemia

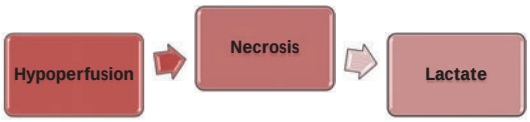
- GI/vascular emergency
  - Risk increases with age
- Reduction of mesenteric blood flow
- "Intestinal stroke center"

Canfora A. Open Med 2019.



Demir IE. Dig Surg 2012.

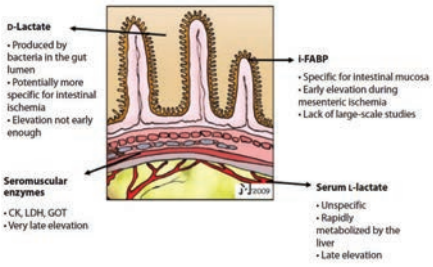
Rationale



- **Doesn't take into account other causes of hyperlactatemia**
  - Glycolysis
  - Decreased lactate utilization in the liver
- **Multiple small studies subjected to significant selection bias**

Jakob SM. Shock 2000.
Nutz V. Arch Chir 1987.

D- vs L-Lactate



Demir IE. Dig Surg 2012.
Montagnana M. Ann Transl Med 2018.

Investigators	Study design	Lactate in mesenteric ischemia	Limitations	Evaluation
Lange and Jackel 1994 [4]	prospective study patients with acute abdomen n = 85 blood sampling before operation/final diagnosis	elevated lactate in all cases of mesenteric ischemia (n = 20)	elevated lactate in: all cases of bacterial peritonitis some cases of intestinal obstruction (10 out of 20)	very low specificity (42%) no remark on the elevation time course of lactate
Meyer et al. 1998 [17]	retrospective study patients with clinically suspected mesenteric ischemia	elevated lactate in over 90% of mesenteric ischemia	16 out of a total of 22 patients with mesenteric ischemia were diagnosed [illegible]	elevated serum lactate does not prove mesenteric ischemia
[illegible] [36]	[illegible] patients with abdominal complaints	[illegible] 23 out of 25 patients with mesenteric ischemia	[illegible] 20 out of 20 general bacterial peritonitis patients	[illegible] no remark on the elevation time course of lactate
[illegible] 2003 [36]	[illegible] patients with clinically suspected mesenteric ischemia	[illegible] 24 out of 31 patients with intestinal necrosis	[illegible] present when subanalysis performed with small bowel necrosis	[illegible] 53% specificity accuracy of more 87–49%
O'rourk et al. 2006 [65]	validation cohort of patients admitted for mechanical small bowel obstruction n = 21	L-lactate with i-FABP levels	patients with gut necrosis false negative elevation in 5 out of 18 patients without gut necrosis	72% specificity small cohort for evaluating serum lactate in bowel necrosis
Acosta et al. 2011 [26]	retrospective study patients with acute mesenteric artery occlusion n = 55	elevated lactate and troponin I in mesenteric ischemia	elevated lactate in 12 out of 27 patients	normal lactate may not be infrequent after mesenteric artery occlusion
Akutsu et al. 2007 [25]	case report type B aortic dissection	near-normal serum lactate upon admission	single case in contradiction to another case report in which increased serum lactate was detected during type A aortic dissection	aortic dissection may not be associated with serum lactate elevation despite intraoperatively observed overt mesenteric ischemia

VERY LOW SPECIFICITY / LATE INCREASE IN PATIENTS WITH MESENTERIC ISCHEMIA

Demir IE. Dig Surg 2012.

Nomogram for Predicting Transmural Bowel Infarction in Patients with Acute Superior Mesenteric Venous Thrombosis

Jiang M, et al.

World Journal of Gastroenterology

World J Gastroenterol 2020

- Rare condition (1:1000), but 5-10% of all mesenteric ischemia
  - >30% mortality
- Nomogram developed with regression, calibration, bootstrapping validation
- Lactate > 2 mmol/L, history of DVT, rebound tenderness, bowel wall enhancement (CT)
- AUC: 0.86 (0.77-0.93); NPV 92%

Mesenteric Ischemia: Conclusions

- Diagnostic challenge
- Lactate is a nonspecific marker of acute mesenteric ischemia
  - D-lactate slightly better
  - Se: 82%, Sp: 48%
- No single marker is reliable enough for diagnosis
- Search remains for a rapid, stable, highly specific/sensitive, inexpensive biomarker

Lactate in Hemorrhagic SHOCK

Mesenteric and Renal Oxygen Transport During Hemorrhage and Reperfusion: Evaluation of Optional Goals for Resuscitation

Chiara O, et al. and Scalea TM (Senior Author)

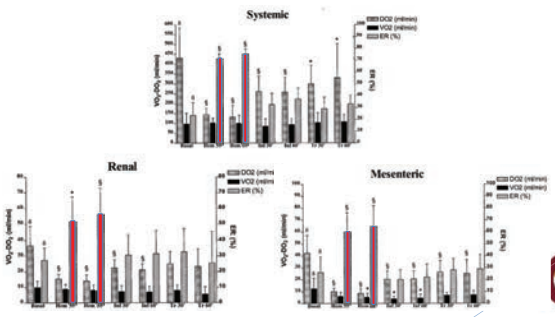
J Trauma 2001

- Porcine model of controlled hemorrhage
- Evaluation of systemic and splanchnic perfusion change and O_2 transport
- DO_2, VO_2, O_2ER, lactate, BE, intramucosal pH
- Flows to mesenteric and renal vascular beds measured

Mesenteric and Renal Oxygen Transport During Hemorrhage and Reperfusion: Evaluation of Optional Goals for Resuscitation

Chiara O, et al. and Scalea TM (Senior Author)

J Trauma 2001



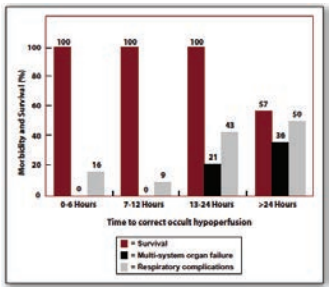
Mesenteric and Renal Oxygen Transport During Hemorrhage and Reperfusion: Evaluation of Optional Goals for Resuscitation

Chiara O, et al. and Scalea TM (Senior Author)

J Trauma 2001

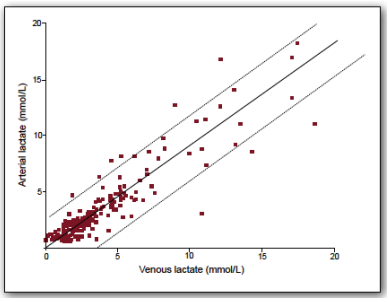
- Oxygen dependency demonstrated
- Compensatory mechanisms vary by organ system / region
- Shock persists after resuscitation
- Lactate: sensitive indicator of regional hypoperfusion

The "Silver Day"



Blow. *J Trauma Acute Care Surg* 1999.
Odom SR. J Trauma Acute Care Surg 2013.
Regnier MA. *Anesthesiology* 2012.
Belaunzaran M. *Am Surg* 2022.

Arterial vs. Venous



Klein E. Acta Med Austriaca 1976.

Lactate

> **2** associated with increased mortality

> 4 worse

- AUROC 0.78-0.82 for LSIs, mortality
  - Better than systolic blood pressure

Galvagno SM. Shock 2019.
Guyette FX. J Trauma Acute Care Surg 2015.
Mullen M. Prehosp Disaster Med 2014.
Strnad M. BioMed Research International 2015.
Gonzalez-Robledo J. Med Intensiva 2015.
Tobias AZ. Prehosp Emerg Care 2014.

Prehospital Point of Care Testing for the Early Detection of Shock and Prediction of Lifesaving Interventions

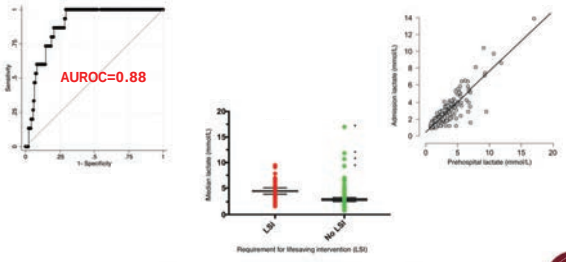
Galvagno SM, et al.

Shock 2020

- N=300
- 16 laboratory tests, StO_2, continuous vital signs
- Multiple logistical regression + Bayesian analysis
- **Hypothesis**: Prehospital lab results can predict the need for lifesaving interventions in trauma patients

Prehospital Point of Care Testing for the Early Detection of Shock and Prediction of Lifesaving Interventions

Galvagno SM, et al.



Lactate ≥ 4 mmol/L: best AUROC compared with SI or mSI

The Bitter and the Sweet: Relationship of Lactate, Glucose, and Mortality After Severe Blunt Trauma

Richards JE, et al.

Aneth Analg 2021

- Retrospective cohort, N=1,439
- Association of glucose / lactate and mortality
- Adjustments for age, ISS, SI
- Only lactate remained significantly associated with mortality

Lactate is a marker of ongoing metabolic stress

Does Lactate Affect the Association of Early Hyperglycemia and Multiple Organ Failure in Severely Injured Blunt Trauma Patients?

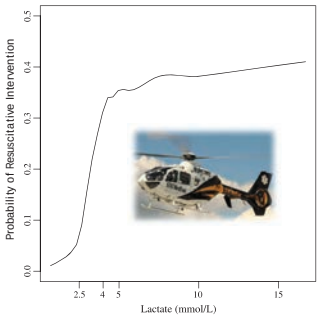
Richards JE, et al.

Anesth Analg 2018

- Retrospective cohort, N=507
- Effect modification: are levels of lactate and glucose associated with organ failure?
- Cox proportional hazards
  - Only lactate significantly associated with organ failure

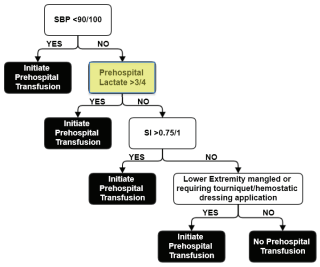
Glucose exhaustion → transition to glycolysis?

"Guyette Curve"



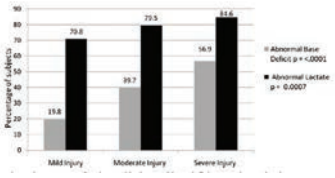
Guyette FX. J Trauma Acute Care Surg 2015.
Zadorozny EV. Prehosp Emerg Care 2021.

Fast Frugal Trees



Guyette FX. Under review (unpublished) 2024.

Limitations: Alcohol

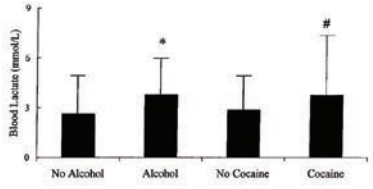


- Herbert, 2011
  - N=1,083
  - Minor vs. major injuries
  - Poor mortality indicator

Herbert HK. Am Surg 2011.

Dunne / Zehtabchi

- N=3,536 / 520
- Higher lactate in alcohol groups
- Significant independent predictor of mortality



Zehtabchi S. Acad Emerg Med 2004.
Dunne JR. J Trauma 2005.

Lactate in Orthopedics

Chapter 14
Compartment Syndrome in Polytrauma Patients

Christopher Lee and Robert V. O'Toole

- Kosir, 2017
  - PA-catheter directed shock resuscitation
  - Tibial shaft fractures ± lower vascular injury ± pelvic ± lower extremity crush injury
- Screening every 4 h x 48 h
  - Exam, compartment pressure
- *Higher lactate (13 ± 5.2 mmol/L) and base deficits (12.9 ± 5.9 mEq/L) in those with compartment syndrome*

Resuscitation Before Stabilization of Femoral Fractures Limits Acute Respiratory Distress Syndrome in Patients With Multiple Traumatic Injuries Despite Low Use of Damage Control Orthopedics

O'Toole R, et al. J Trauma 2009

- Retrospective, N=582 (n=287 with ISS > 17)
- Increased risk of ARDS? Lungs "primed" for secondary insult?
- No nailing until lactate < 2.5 mmol/L
- **12%** DCO / **88%** primary reamed nailing / **3%** plated

Resuscitation Before Stabilization of Femoral Fractures Limits Acute Respiratory Distress Syndrome in Patients With Multiple Traumatic Injuries Despite Low Use of Damage Control Orthopedics

O'Toole R, et al. J Trauma 2009

TABLE 1. Patient Descriptive Parameters for Two Treatment Groups With Femoral Fractures and Injury Severity Scores >17

	Primary Nailing (n = 199)	DCO (n = 28)
Age (yr)	30.5	26.9
ISS	27.4	36.2*
Presenting SBP (mm Hg)	130.6	109.2*
Percentage of patients with SBP <90 mm Hg	10.6%	32.1%*
Presenting HR (beats/min)	101.6	120.1*
Presenting RR (breaths/min)	18.6	16.6
Presenting lactate value (mmol/L)	3.8	6.5*
Brain AIS score >2 (percentage of patients)	28.1%	39.3%
Abdomen AIS score >2 (percentage of patients)	21.6%	32.1%
Thoracic AIS score >2 (percentage of patients)	75.9%	85.7%
Exploratory laparotomy during first 24 h	11.6%	35.7%*
Pelvic fracture	23.6%	25.0%
Unstable pelvic fracture (Young-Burgess APC-II, APC-III, LC-II, LC-III, or VS)	14.0%	14.3%

Resuscitation Before Stabilization of Femoral Fractures Limits Acute Respiratory Distress Syndrome in Patients With Multiple Traumatic Injuries Despite Low Use of Damage Control Orthopedics

O'Toole R, et al. J Trauma 2009

- Dobutamine (!)
- Limited crystalloids
- Invasive monitoring
- DCO if lactate > 2.5 mmol/L

What about Ringers?

- Content is sodium lactate, not lactic acid
- Only a modest rise in healthy volunteers
- Can be safely used in CPB, renal transplants
- Liver transplant: *does* increase lactate

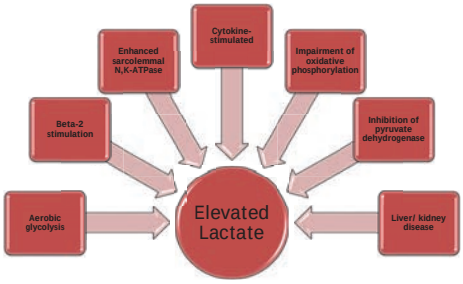
Probably safe to use, even in sepsis!

Caution in liver transplants

O'Malley CMN. Anesth Analg 2005. Shin WJ. Acta Anaesthesiol Scand 2011. Zitek T. J Emerg Med 2018.
Modi MP. Saudi J Kidney Dis Transpl 2012. Hadimioglu N. Anesth Analg 2008. Weinberg L. Perfusion 2018.

Summary

Causes of Increased Lactate



SUMMARY

Lactate…

- May represent a cellular energy deficit, not necessarily tissue hypoxia
  - Oxidative fuel
- Consider other causes when elevated in septic shock
  - Tissue oxygenation is often adequate
- **> 4 mmol/L** (and not improving); highly concerning in sepsis, burns and hemorrhage
- Not a "stand alone" diagnostic marker for mesenteric ischemia
- Marker of ongoing metabolic stress
- Not increased with Ringers (in most patients)