

# Resistance: Preload, Fluids, and Lactate

- Title
- Objectives
- Shock
- ▼ CV Physiology (Heart-Lung Interactions)
  - ▼ SVV and Concept of Dose Response
    - ?PPV
    - Undulating pattern of arterial line
  - ▼ Functional hemodynamic monitoring
    - Measuring a response to a defined stress
    - Measure response may be on venous-side or an arterial side
    - Defined stress is often a change intra-thoracic pressure (ITP)
  - Dose-response relationship
  - ▼ Passive-ventilated patient
    - ▼ ITP is related to the ventilator-applied tidal volume and compliance of chest wall
      - Obesity, ascites, chest wall edema, lung water
    - Unpredictable if pt generates inspiratory force or fights the ventilator
  - ▼ Cardiac output is at the cross-roads of venous return and cardiac function
    - Guyton Diagram
    - Defines the operating point of the cardiovascular system, the operating point determines the central venous pressure, and cardiac output
- Fluid Responsiveness
- ▼ Lactate
  - ▼ Lactate Production
    - It is not a “waste product” of anaerobic metabolism
    - It is an important energy shuttle
  - ▼ Normal Metabolism
    - Lactate production arises mainly from skeletal muscle (25%), skin (25%), brain (20%), intestine (10%), and erythrocytes (20%).
  - ▼ Glycolysis metabolizes glucose to pyruvate
    - Catalyzed by phosphofructokinase in the Embden-Meyerhof pathway.
  - ▼ Under aerobic conditions, pyruvate enters the mitochondria and is converted to Acetyl-CoA which enters the Krebs cycle to produce ATP
    - Oxygen provides a very low-energy electron sink at the end of the electron transport chain, allowing generation of 38 ATP molecules for each molecule of metabolized glucose.
  - ▼ Pyruvate is also in equilibrium with lactate in the cytosol

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- Bidirectionally catalyzed by LDH
- Normal lactate:pyruvate ratio of approximately 10:1.
- ▼ There is also a glycolytic compartment that complements the oxidative compartment.
  - Beta2-adrenergic stimulates cAMP inducing glycogenolysis and glycolysis for ATP production
  - Na/K-ATPase pump consumes the ATP
- ▼ Metabolism occurs in the liver (60%) and kidney (30%)
  - Urinary excretion threshold is 5-6 mmol/L
- ▼ In hypoxic tissue
  - Pyruvate cannot enter the Krebs cycle, so it is shunted to lactate
  - This requires NADH and H<sup>+</sup>
- ▼ Abnormal Production of Lactate
  - Leukocytes also generate lactate during phagocytosis or when activated in sepsis.
  - ▼ The lungs can create lactate during acute lung injury without tissue hypoxia
    - Accelerate glucose production in inflammatory lung tissue
  - ▼ Increased glycolytic flux
    - Severe exercise
    - High work of breathing
    - Catecholamine administration
    - Sepsis
  - ▼ Maintains normal lactate:pyruvate ratio if adequate oxygen
    - Hyperlactatemia occurs
  - ▼ If pyruvate is prevented from entering Krebs cycle
    - Already mentioned hypoxia
    - Exceeds capability of mitochondria
    - Mitochondrial dysfunction (sepsis induced cytokines)
    - Thiamine deficiency
    - Abnormal lactate/pyruvate ratio develops
- ▼ Lactate Clearance
  - ▼ Consumption by local or distant mitochondria for energy production
    - Via pyruvate and Krebs cycle
  - ▼ Utilized as substrate for gluconeogenesis
    - Cori cycle
  - ▼ Elevated reducing environment (high NADH)
    - Ketoacidosis

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- Ethanol ingestion
- ▼ Acid Production
  - ▼ Tissue Hypoxia Myth
    - ▼ Lactic acid in septic shock is not produced by anaerobic metabolism
      - Septic patients have hyperdynamic circulation
      - Oxygen delivery to tissues is adequate
      - However, lactate production independent of tissue hypoxia can also occur.
  - ▼ Mt Everest Climbers
    - PaO<sub>2</sub> 24
    - Lactate normal
    - PaO<sub>2</sub> 100, PvO<sub>2</sub> 40, P<sub>c</sub>ytosol = 5
    - Mitochondrial threshold 1
    - Critical oxygen delivery occurs at 4 mL/kg/min (CO<sub>2</sub> 2 L/min)
    - Studies trying to correct oxygen delivery fail to improve
- ▼ Controversially
  - ▼ Glycolysis metabolism to pyruvate produces H<sup>+</sup>, pyruvate to lactate consumes H<sup>+</sup>
    - Stoichiometrically does not generate any net protons
    - But lactic acid by p-chem must generate acidosis
    - Protons are consumed by Krebs cycle
    - Hyperlactatemia without acidosis can persist as long as there is not a decreased Krebs cycle flux
    - So acidosis generated by production of lactate occurs when lactate:pyruvate ratio is altered by failure of Krebs cycle
    - Pyruvate is converted to lactate in a proton-neutral process
    - Degrading glucose to pyruvate produces 2 protons and 2 pyruvate molecules and converting 2 molecules of pyruvate to lactate consumes 2 protons
- ▼ Other explanations
  - ▼ Impaired Tissue Extraction
    - Microcirculatory dysfunction
    - Inflammatory changes to endothelium
    - Regional and microregional oxygen delivery does not meet demand
    - Mitochondrial dysfunction
  - ▼ Diminished clearance
    - Hepatic dysfunction
    - These don't improve with increased cardiac output or tissue oxygen perfusion.

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- ▼ Lactate in septic shock produced by beta-2 adrenergic stimulation
  - Endogenous catecholamines stimulate beta-2 receptors
  - This upregulates glycolysis, generating pyruvate
  - Pyruvate is generated in excess of mitochondrial capability to use in the TCA cycle
  - Excess pyruvate is converted into lactate
  - This is entirely aerobic
- ▼ Elevated lactate might be compensatory response
  - Lactate is not a toxin
- ▼ Lactate serves as a metabolic fuel for heart and brain in stress
  - More bioefficient than glucose in the heart and brain
- Depletion of lactate caused cardiovascular collapse
- Cardiac myocytes use lactate as fuel in some circumstances, such as during exercise, beta-adrenergic stimulation, and shock.
- Giving lactate has been shown to improve outcomes in CAB and HF patients
- ▼ Measuring lactate
  - ▼ Arterial and venous samples are good
    - Avoid long tourniquet times
  - ▼ On ice is preferred if processing time exceeds 15 min
    - Leukocyte and Erythrocyte metabolism
- ▼ Prognostic value of lactate
  - ▼ Lactate is a marker for sepsis and badness
    - Like sinus tachycardia
    - Lactate as marker of critical illness and metabolic stress
  - ▼ Identification of occult shock
    - Autonomic nervous system and endogenous catecholamine response are mysterious and confounding
    - Lactate can be positive even with normal anion gap
    - Different patients have a weak response and immediately develop hypotension
  - ▼ Other patients have a robust response supporting their blood pressure and thereby preventing hypotension
    - ▼ These patients may have deceptively reassuring vital signs
      - But they are in a catecholamine dependent shock state
      - These patients have an increased risk of decompensation and death
- ▼ Lactate is ultimately a marker of catecholamine release
  - This makes it useful for detection of occult shock

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- ▼ Hyperlactatemia is correlated with increased mortality regardless of etiology
  - Sepsis-induced hypotension has a much better prognosis than septic shock with a lactic acidosis
- ▼ Lactate level of 4 mmol/L
  - The Surviving Sepsis Campaign recommends using a lactate level of 4 mmol/L as the threshold for identifying cryptic shock, but lactate has a continuous curvilinear association with mortality and a 4 mmol/L threshold seems like an arbitrary cutoff.
- ▼ There is no clear cut point that is evident
  - Intermediate concentrations (lactate 2-4) or even high-end normal range (1.4-2.3) still indicated a poorer prognosis than normal lactate concentrations
- ▼ What about other forms of shock?
  - ▼ Elevated lactate prognostics mortality in PE
    - This is generally unsurprising, because elevated lactate levels are associated with increased mortality, even in unselected ED patients.
    - Lactate levels >2 mmol/L were more associated with 30-day mortality than shock/hypotension, hypoxia, or right-ventricular dysfunction.
- ▼ Lactate Clearance as marker of adequate resuscitation
  - ▼ Rivers trial established EGDT in severe sepsis and septic shock
    - NEJM 2001
    - Used proprietary designs continuous ScvO<sub>2</sub> as a target to assess than oxygen delivery was adequate
    - Intermittent measurement of ScvO<sub>2</sub> correlated well
  - ▼ Jones studied RCT of lactate clearance vs ScvO<sub>2</sub>
    - No difference between the two
    - Jones used 10%
    - Jones's most compelling point is that either central or mixed venous O<sub>2</sub> sats can be normal or high in severe sepsis, even in the presence of severe organ hypoperfusion, because if oxygen extraction varies throughout the body (as it does during sepsis), the mixed blood can "average out" to a misleadingly normal/high value. Therefore, following ScvO<sub>2</sub> results in mismanagement.
  - ▼ Lactate clearance has repeatedly been shown to independently predict survival from sepsis
    - Crit Care Med. 2004 Aug;32(8):1637-42. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock.
  - ▼ This is not true of SvO<sub>2</sub> (as a single variable)
    - N Engl J Med. 1995 Oct 19;333(16):1025-32. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO<sub>2</sub> Collaborative Group.
  - Lactate is a test, and it holds the false promise of simplifying clinical decision making to a numerical value, one that you can order, even from afar.
- ▼ When looked at separately they do not alter outcomes
  - ARISE, ProCESS studies
  - We dont know if clearing lactate improves outcomes

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- Lactate as a marker for hypoxemia caused by hypoperfusion is false therefore trending it or using interventions ie fluid boluses to bring it down is devoid of evidence, which is important especially in an age where doctors live behind a screen and worship numbers on that screen.
- Lactate should generally be used together with ScvO<sub>2</sub>, echocardiography, VaCO<sub>2</sub> difference, mental status, urine output
- ▼ What to do
  - Reasonable amount fluids
  - Pressors
  - Source control
  - Antibiotics
- ▼ What if it is not improving
  - It is not telling us that we did not fix anaerobic metabolism
  - You need functioning liver and kidney
- ▼ Do nothing empirically
  - ▼ If left ventricular dysfunction — give inotrope
    - Low Cardiac Output
    - On Echocardiography
  - ▼ Assess volume — give volume
    - Tricky task
    - If Hgb low — give blood
  - ▼ Look for ischemic/infarction tissue (ie regional lactate production)
    - Bowel ischemia/infarction
    - Limb arterial occlusion
    - Compartment syndrome
  - ▼ Consider thiamine to maximize aerobic metabolism
    - Especially if malnourished
  - ▼ Limit beta-adrenergic stimulation
    - Vasopressor choice
    - Esmolol
  - ▼ Reduce skeletal muscle work
    - Mechanical ventilation for work of breathing
    - Paralytics
    - Avoid hepatotoxins
- References