Resistance: Preload, Fluids, & Lactate

Charles Bruen, MD

resusreview.com/resistanceJun17

Objectives

- Right side rules cardiac output
- Dynamic indices to guide fluids
- Catecholamines produce lactate

Preload

Dario Maestrini
1886-1975

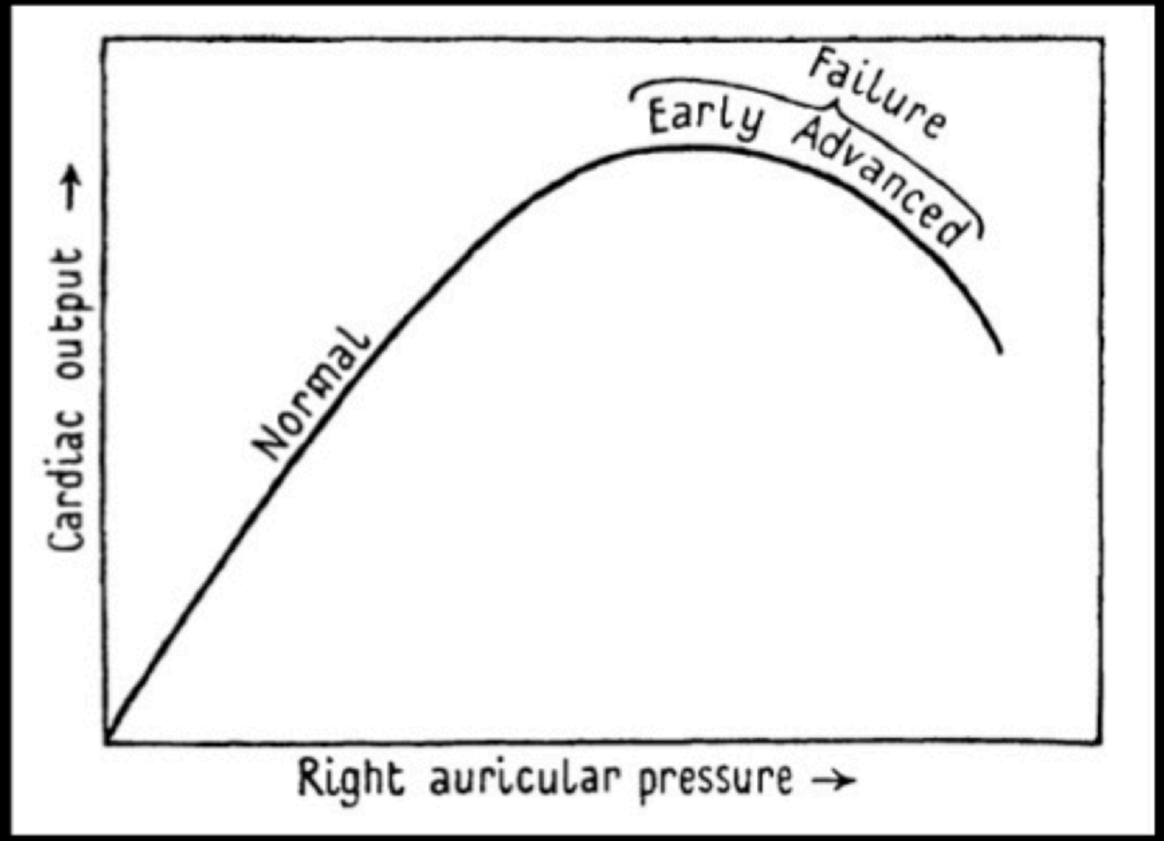
The mechanical energy set free in the passage from the resting to the active state is a function of the length of the fibre.

Legge dei cuore: 1914

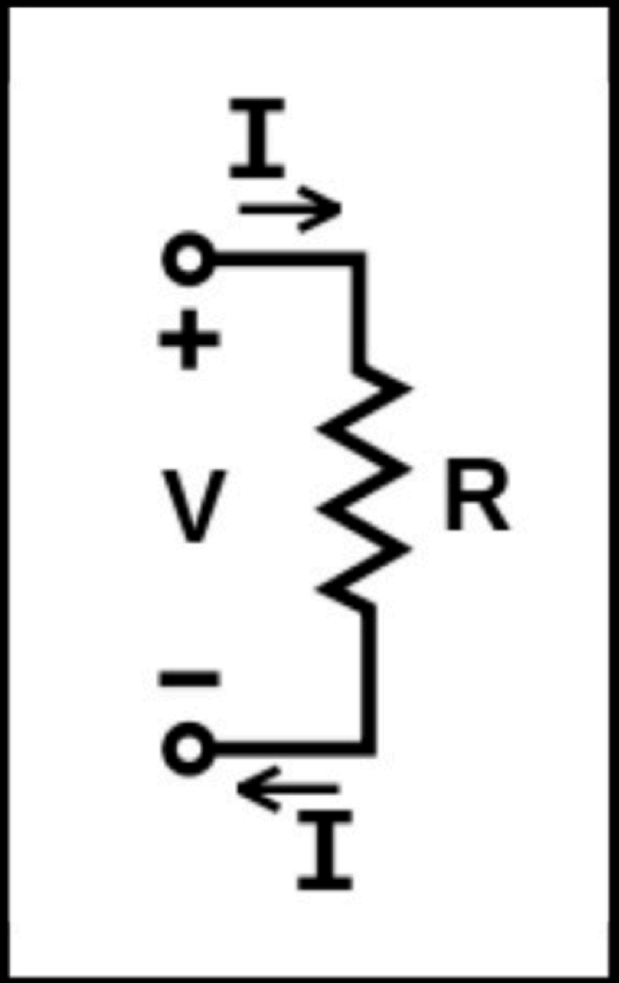
Frank-Starling

Ernest Starling
1866-1927

Otto Frank
1865-1944

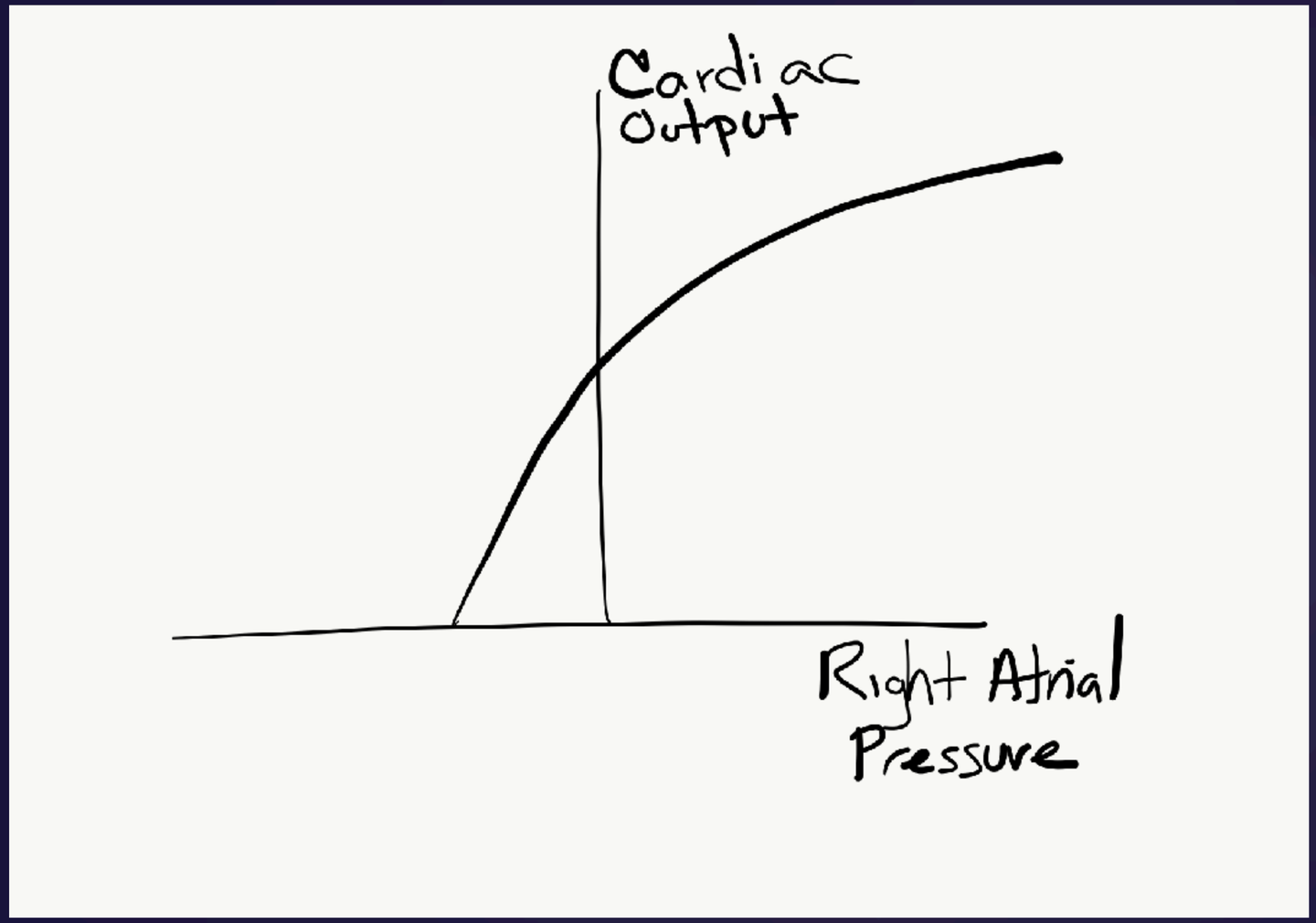


Georg Ohm
1789-1854



Die galvanische Kette, mathematisch bearbeitet: 1927

Frank-Starling

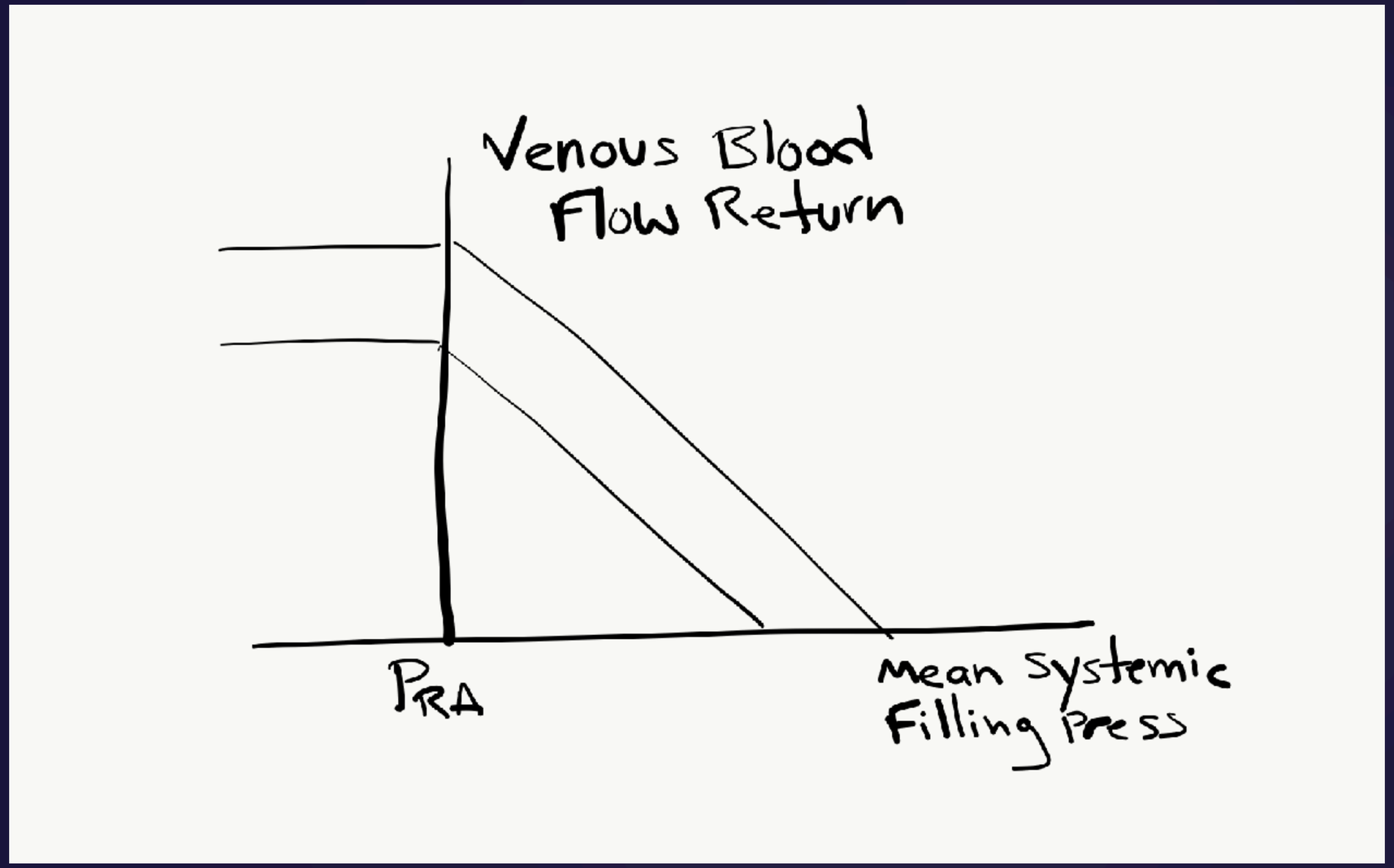


Frank-Starling

- Focus of LV Physiology
- Adequate when thinking about ischemia and heart failure
- Especially given complexity of RV physiology and assessment

- When assessing a broader range of physiology though, need a system that incorporates cardiac and vascular elements

Venous Blood Return



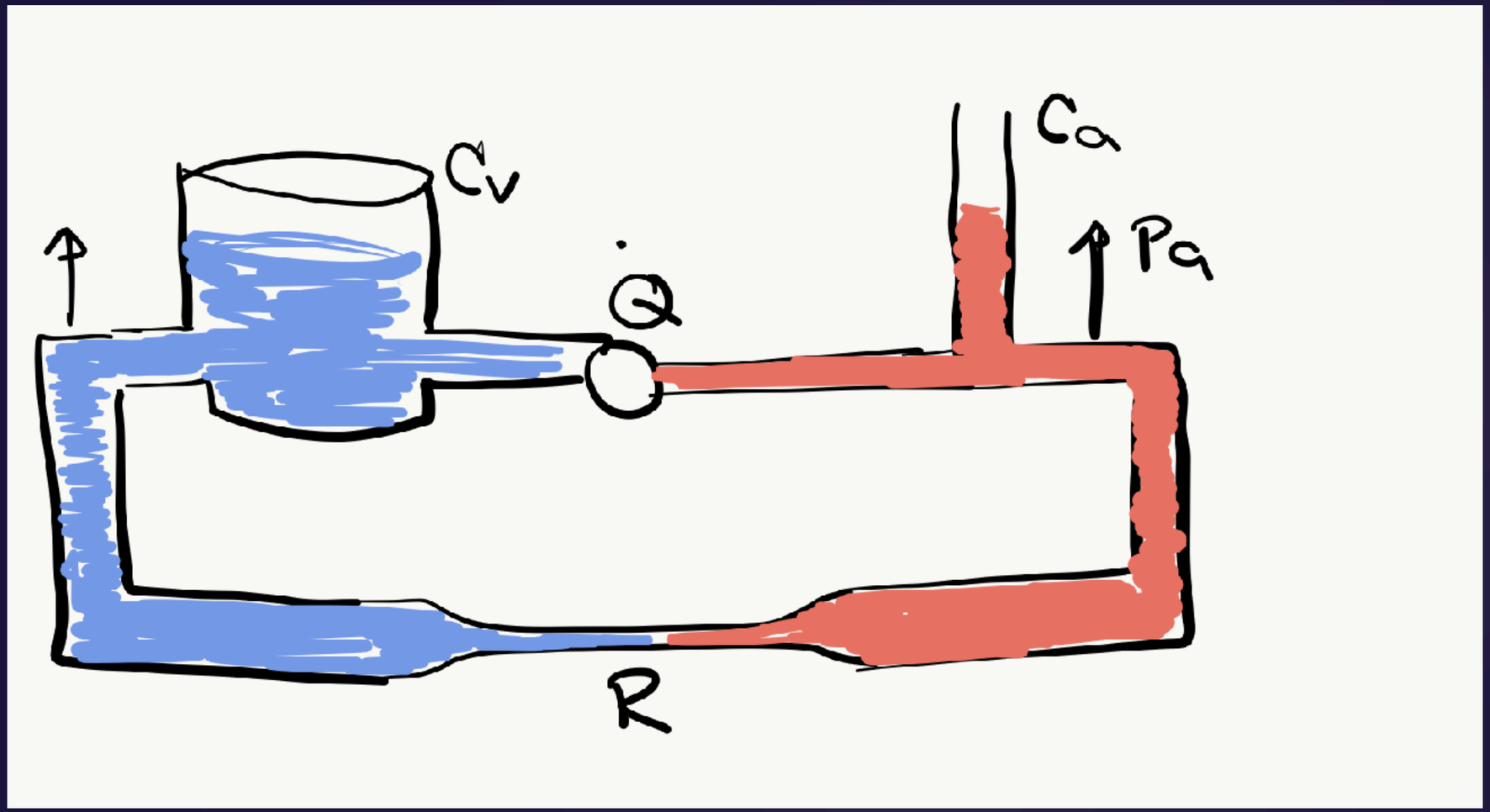
Venous Blood Retuen

- 75% of blood in venous system
- Acts as a reservoir

Venous Return Blood Flow

- Represents the blood flow from the venous capacitance bed to the right heart
- Slope of the venous return curve represent resistance to venous return

Mean Systemic Filling Press



MSFP

- X-axis intercept is determined by patient's volume status as well as capitance
- Venous return governed by press gradient between Pmsf - RAP

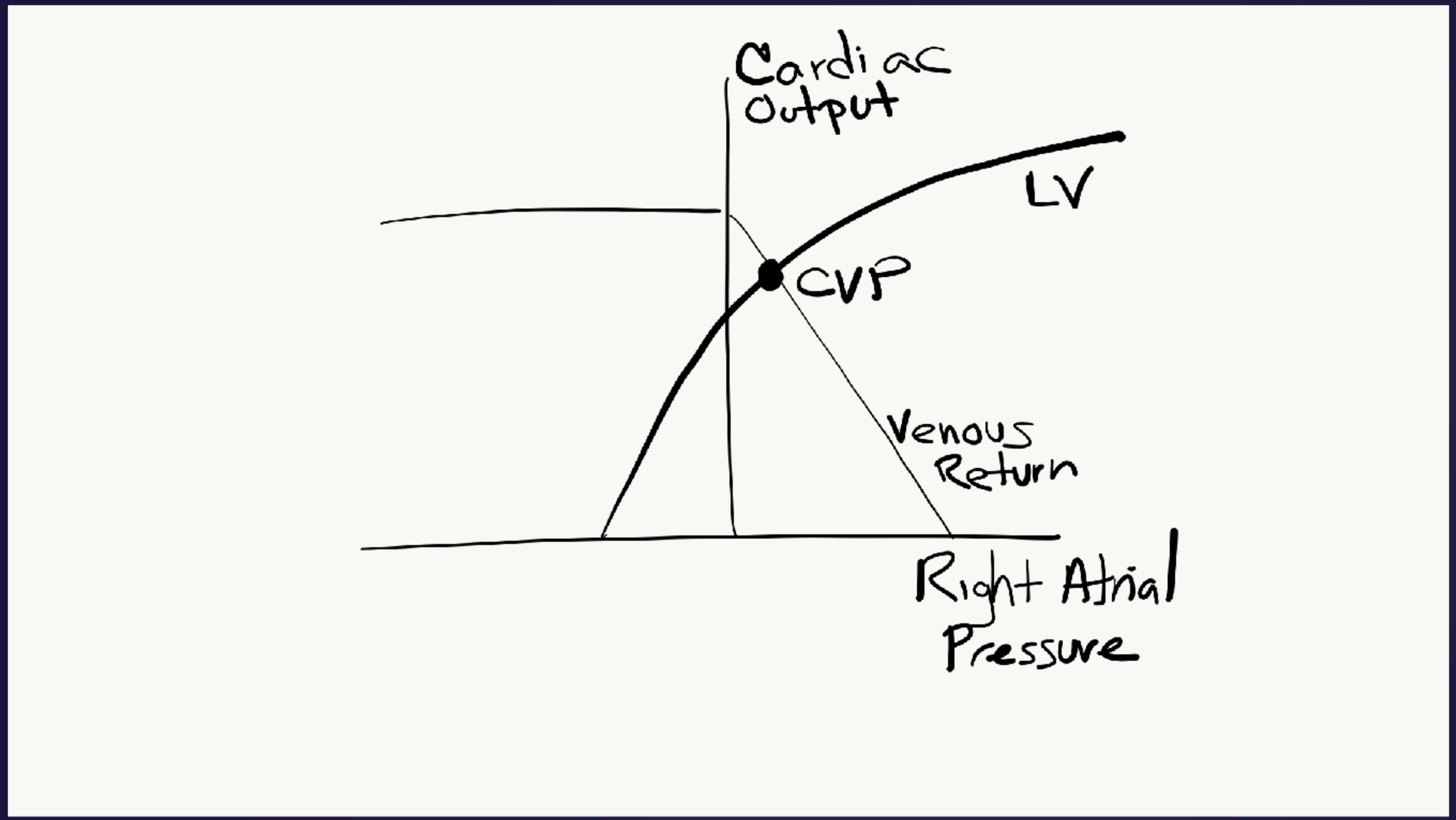
Changes in MSFP

- Sepsis shifts blood to unstressed volume
- Volume expansion goes first to unstressed then stressed
- Vasoconstrictors generally increased stressed volume

Stressed and Unstressed

- Unstressed = Filling up the blood vessels without causing intravascular pressure
- Stressed = volume that stretches blood vessels (Pmsf)

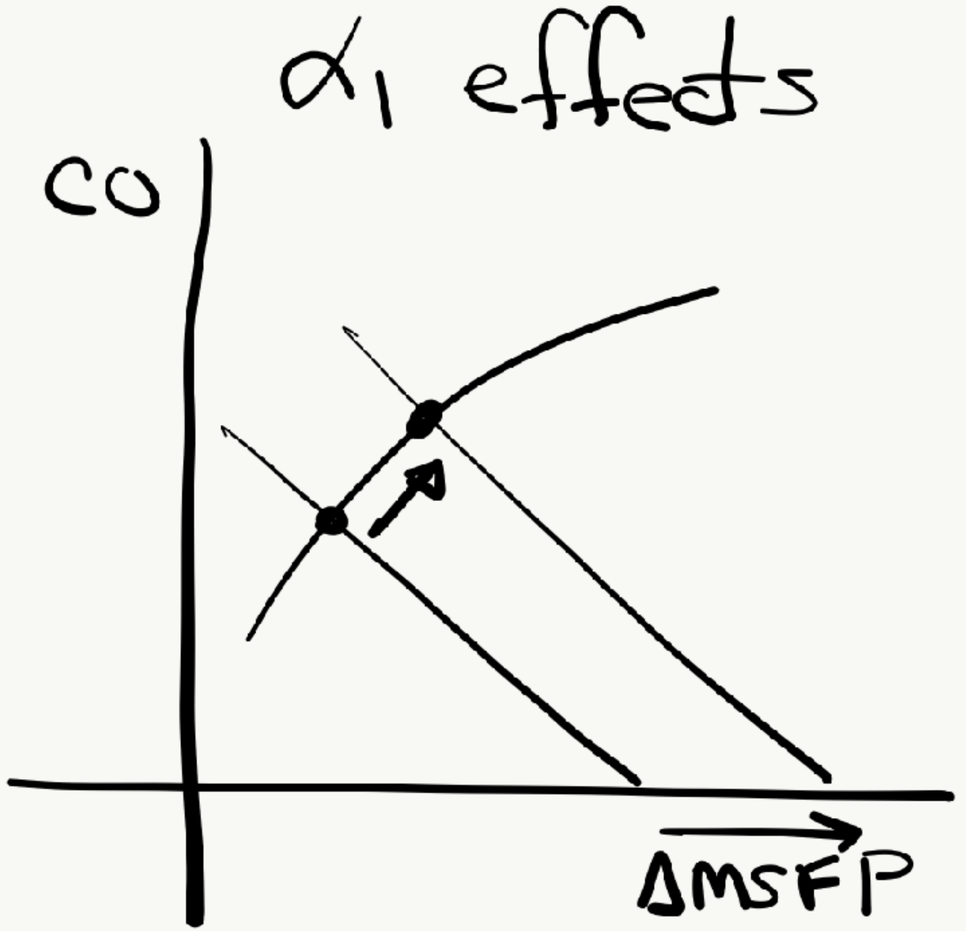
Guyton Diagram



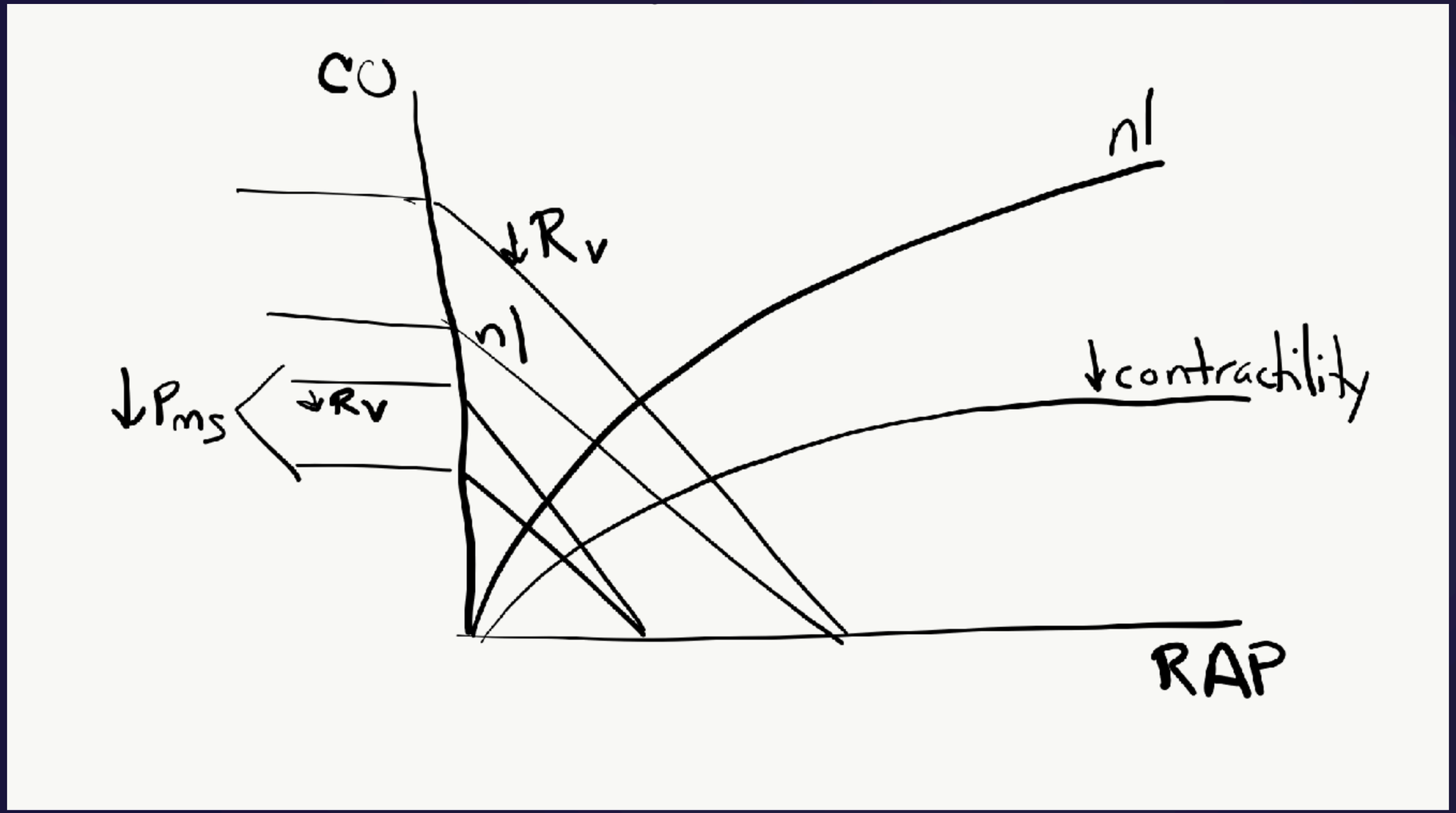
Cardiac Output

- LV flow = RV flow
- Used to seeing
  - CO = SV x HR = (MAP - RAP) / SVR
- But instead can thing about it as
  - CO = (Pmsf - Pcvp) / Rven
- The only way cardiac function can affect CO is altering RAP

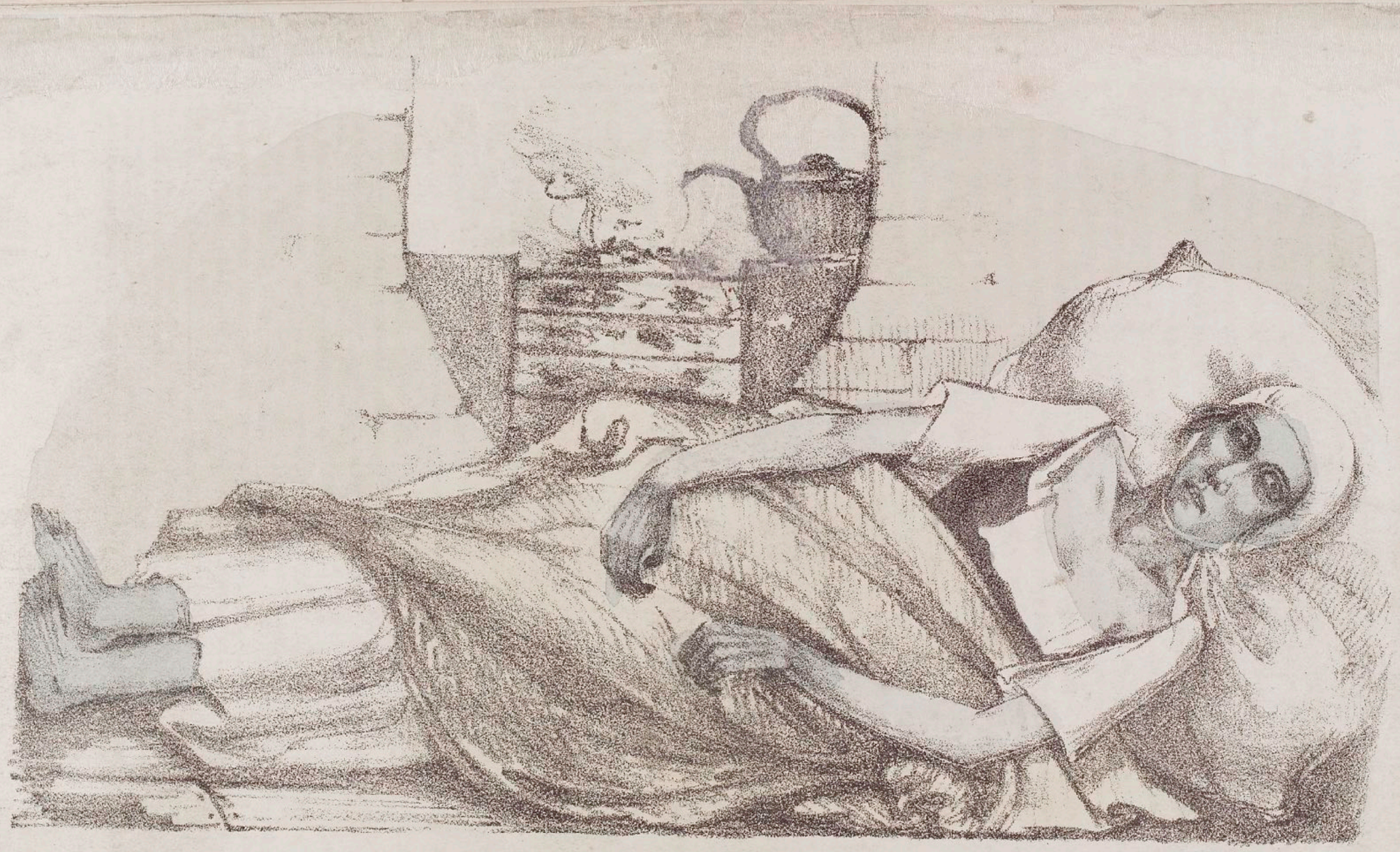
Alpha Effects



Effect in Septic Shock



Fluids



BLUE STAGE OF THE SPASMODIC CHOLERA.

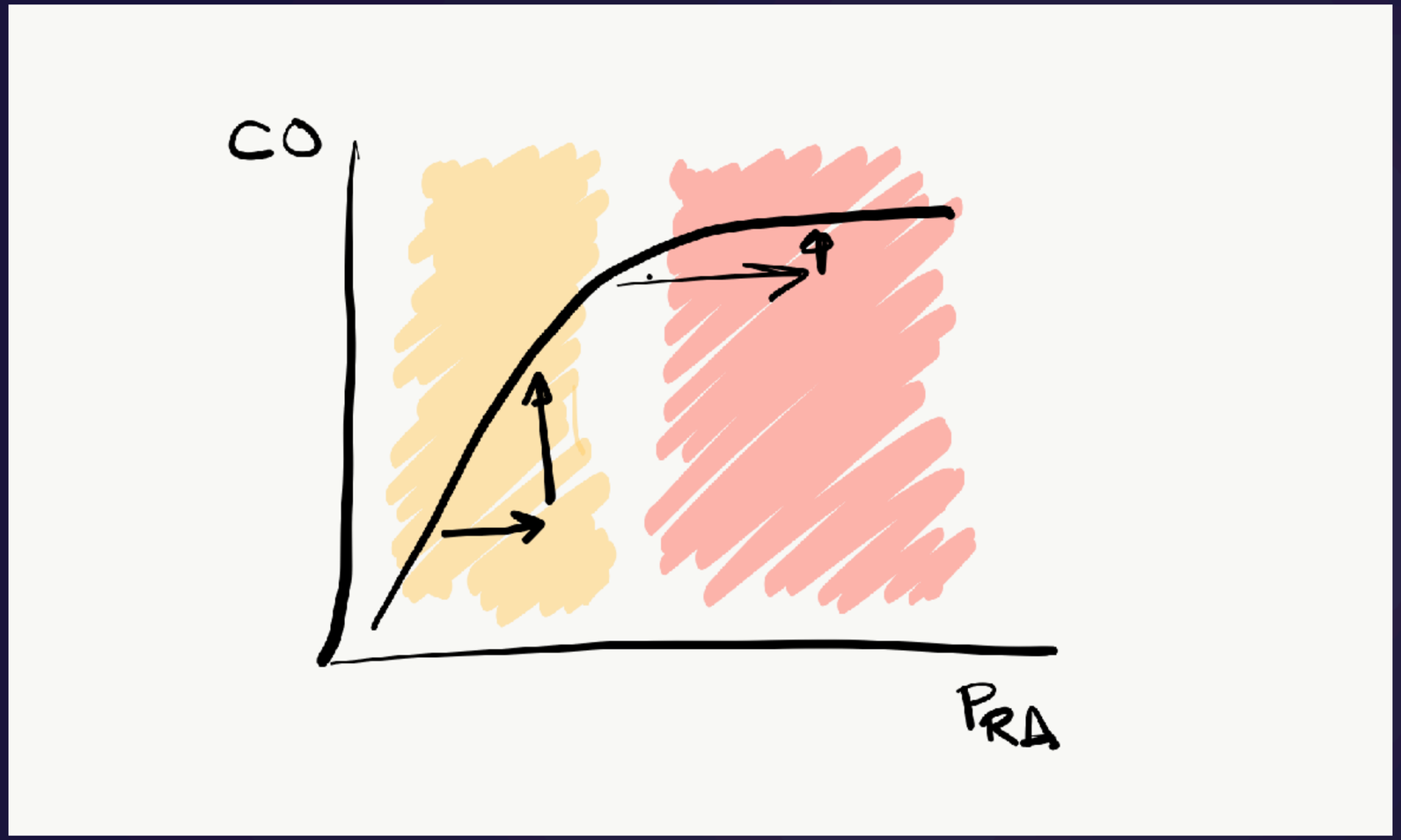
Sketch of a Girl who died of Cholera, in Sunderland, November, 1831.

Published at the Lancet Office, 7[illegible] Strand

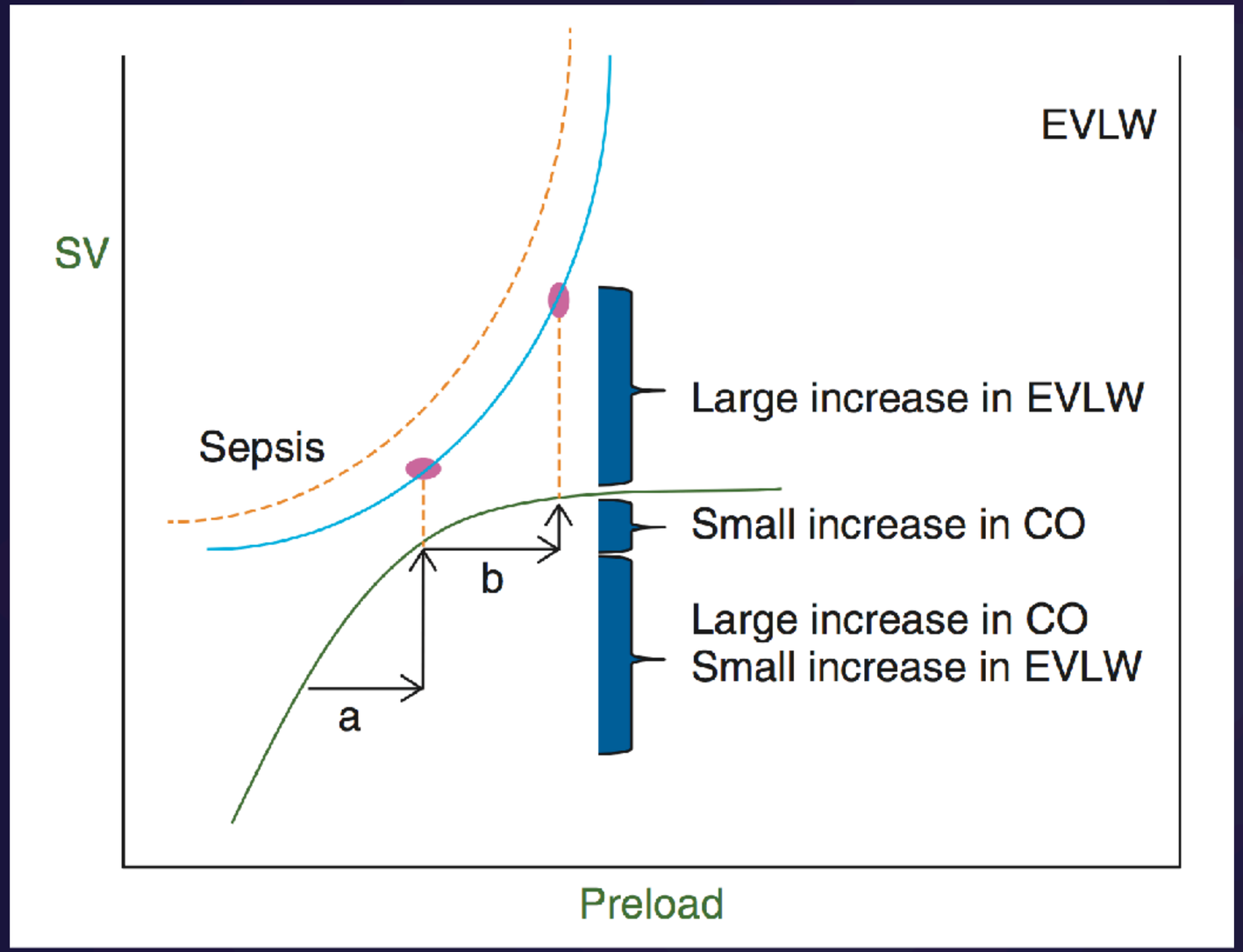
Fluid Responsive

- So lets change the stressed volume by giving fluids
- 500 mL fluid bolus crystalloid
- +10% SV is fluid responsive
- Repeat

Diminishing Returns



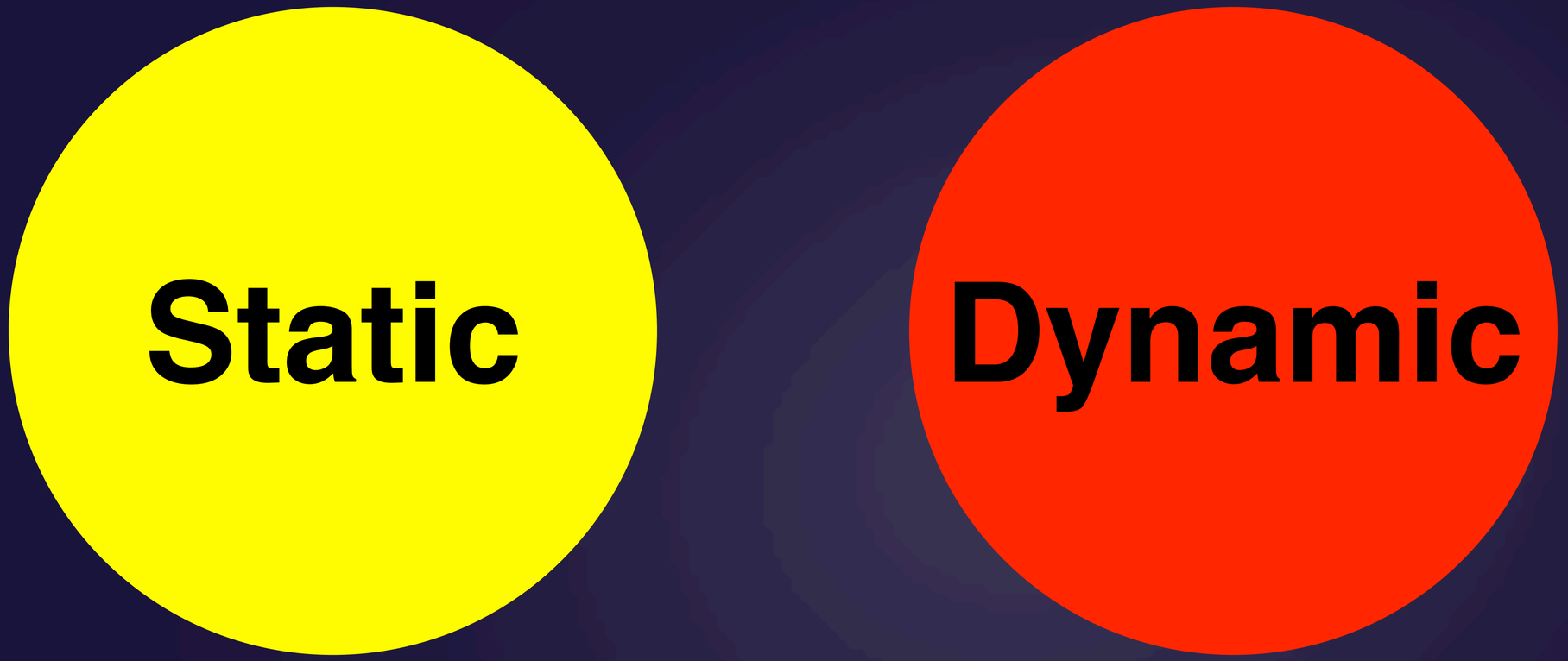
Diminishing-Accelerating Effects



When you have hemodynamically unstable patient

Give all the fluid they need …

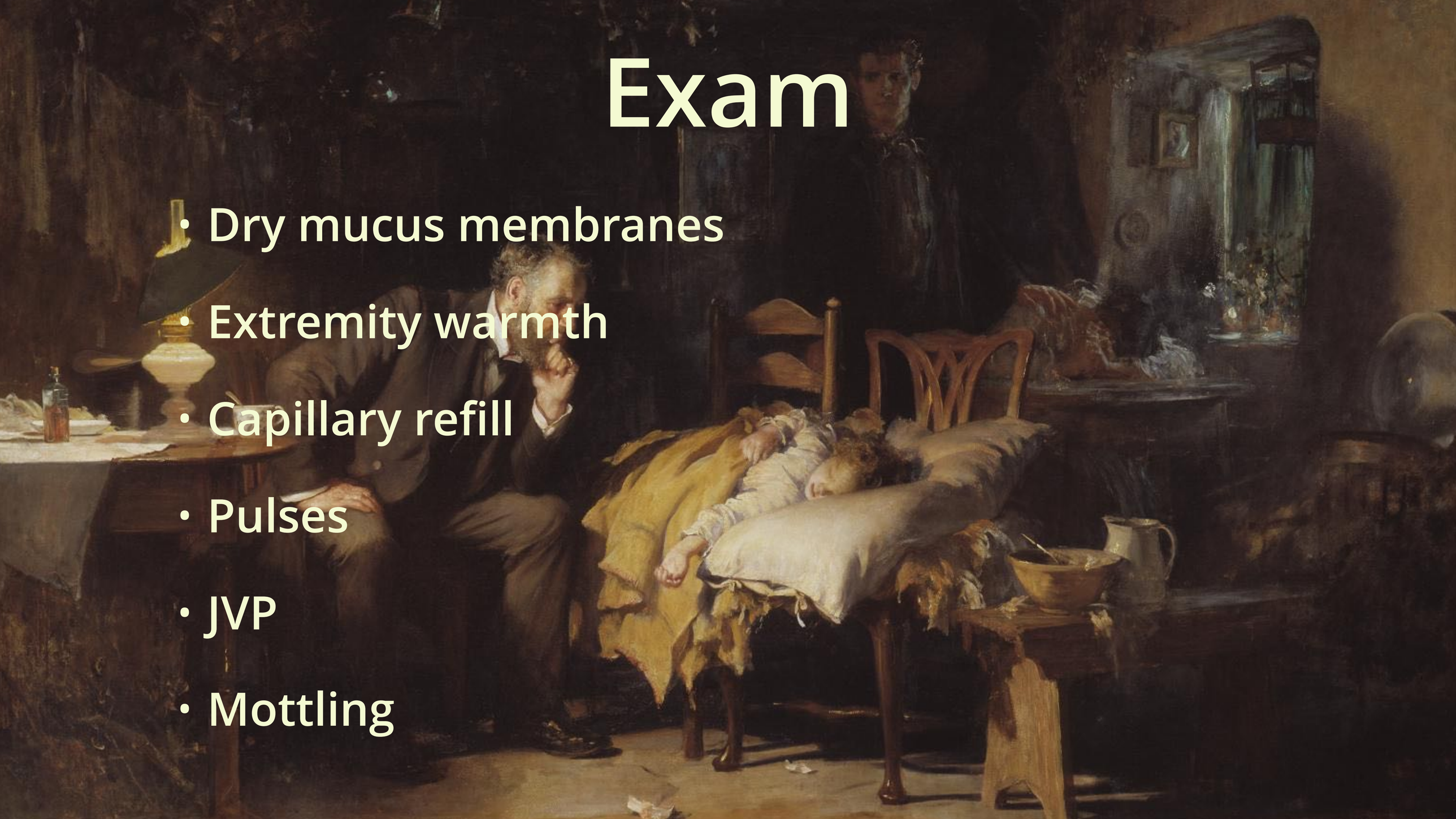
but not one drop more.


Static
Dynamic

Hypotensive

- Hemodynamically unstable is not a good indication
- BP does not correlate with fluid responsiveness
- Only 50% will repsond to fluid challnge

Exam



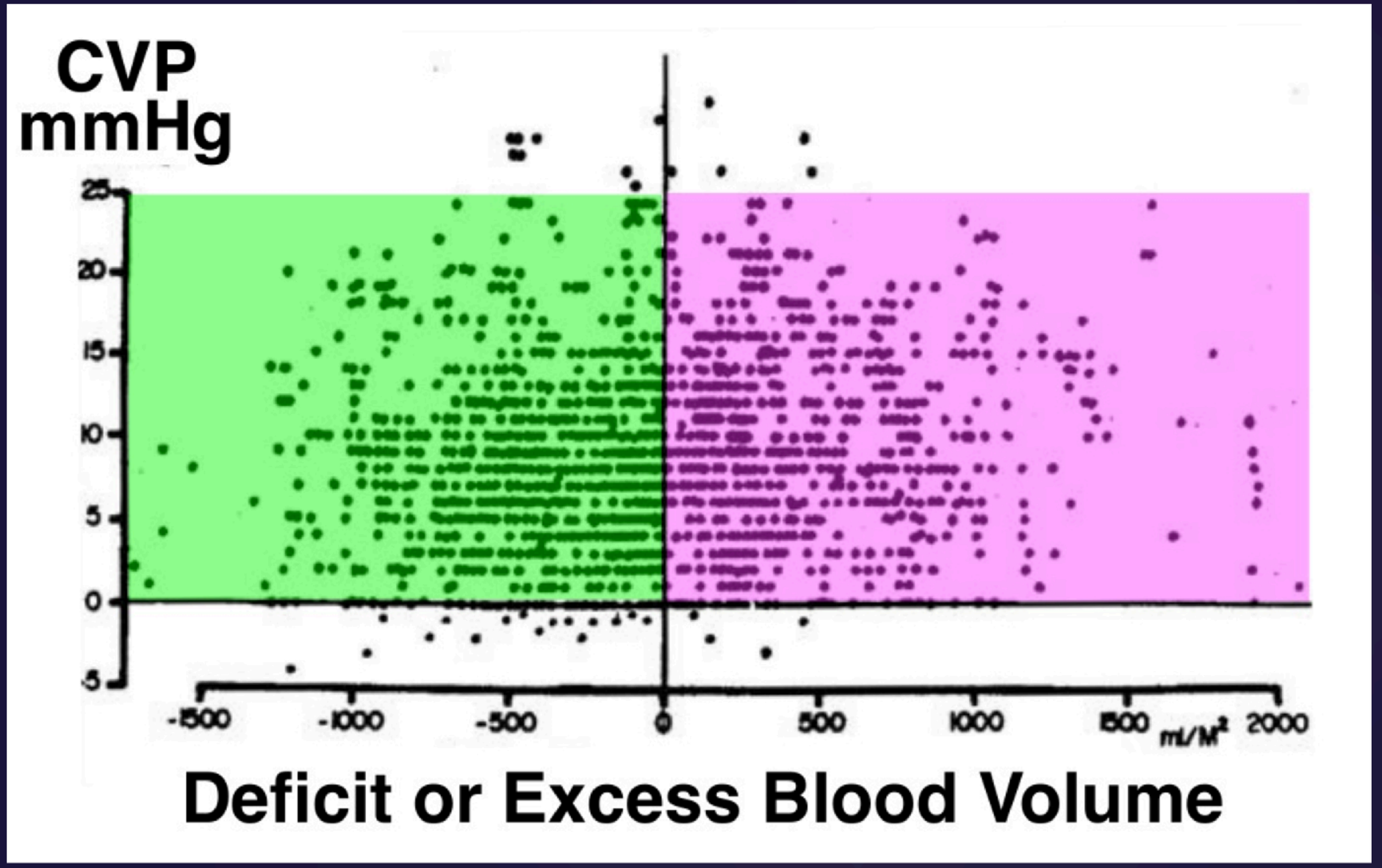
- Dry mucus membranes
- Extremity warmth
- Capillary refill
- Pulses
- JVP
- Mottling

Objective Measurements

- BUN/Creatinine
- Lactate
- Urine output
- Central venous saturation

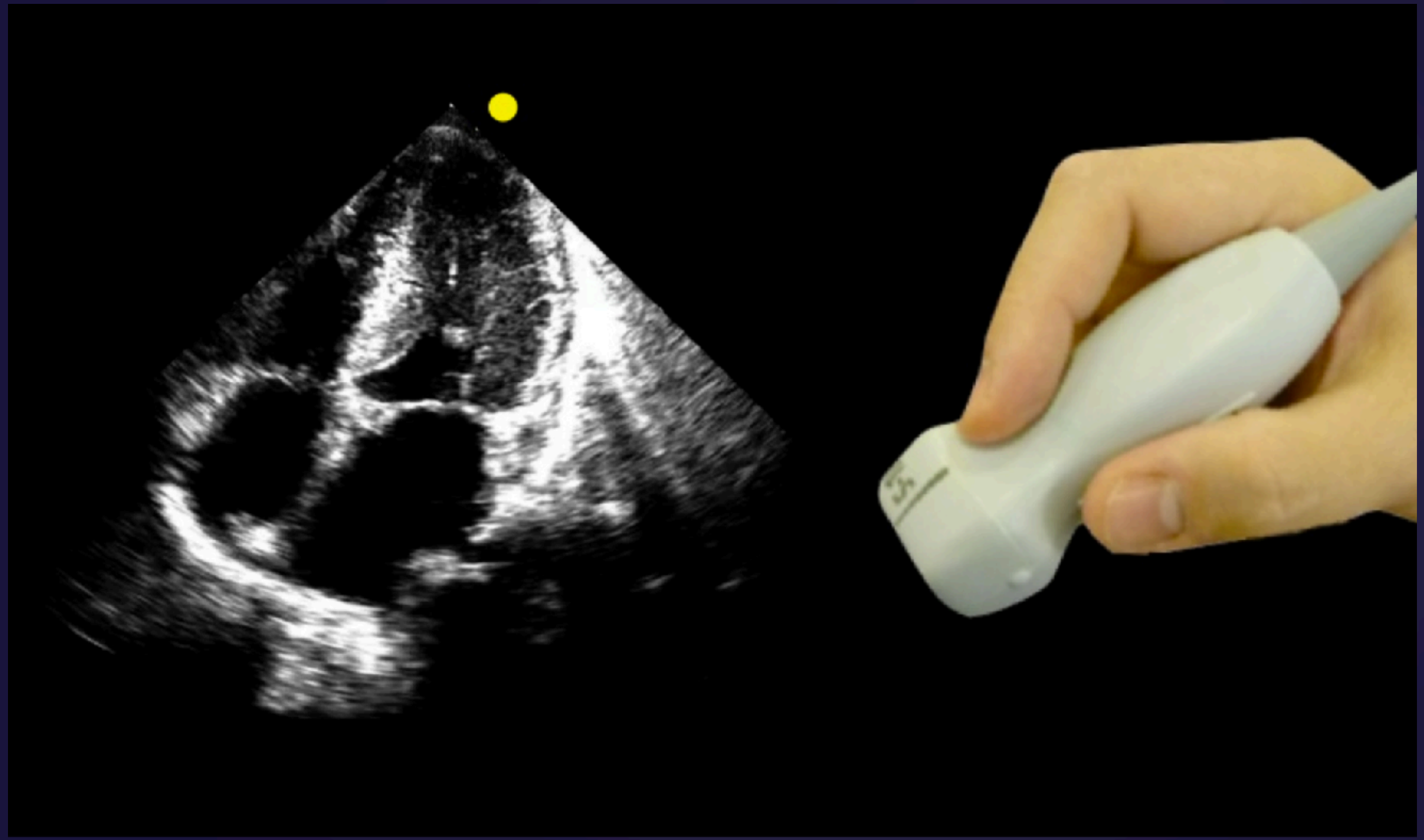
Invasive

- PAC
- CVP
- Pulse counter monitoring
- Thranspulmonary Thermodiltuion
- Aortic bood flow


CVP
mmHg
25
20
15
10
5
0
-5
-1500
-1000
-500
0
500
1000
1500
2000
ml/M²
Deficit or Excess Blood Volume

Noninvasive

- Ultrasound
  - IVC ~ CVP
- Bioimpedance



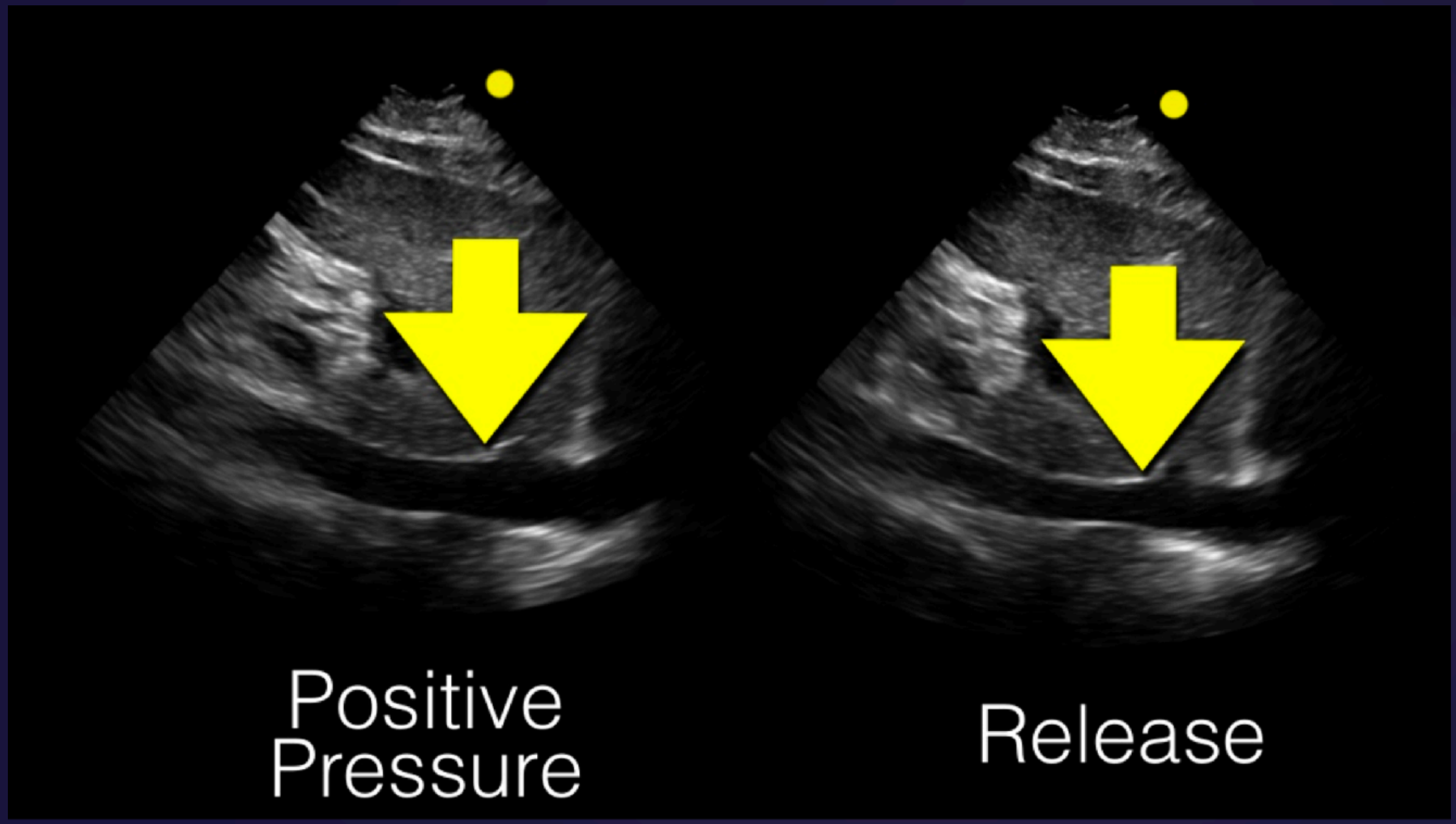
Static Indices

- IVC in spontaneous breathing patient ~CVPMaybe only useful at extremes
- What
- May only hold true at extreme

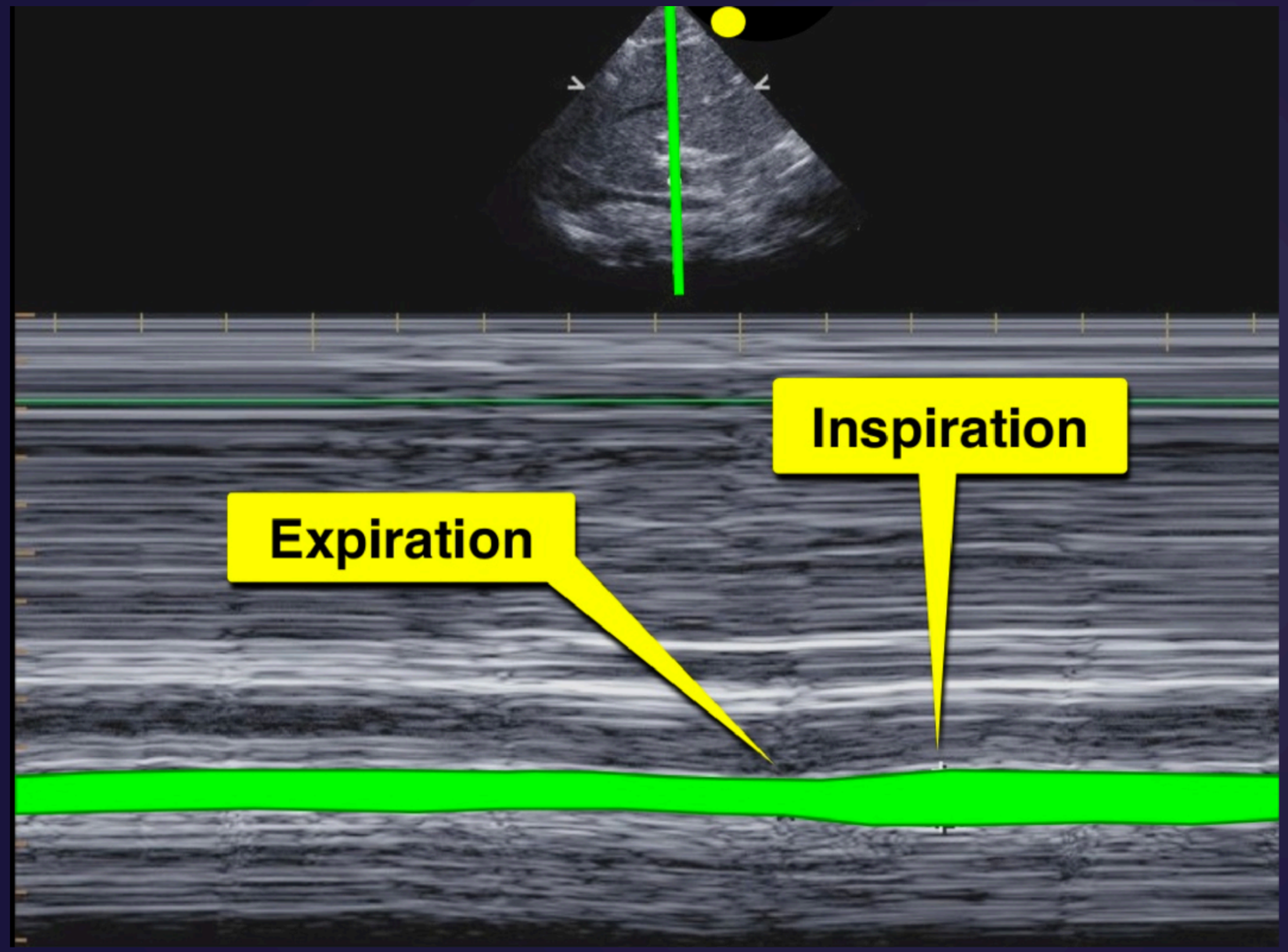
Dynamic

- Very accurate
- RElY on interaction of respiratory cycle and cardiac preload
- Requires mechanical ventilation

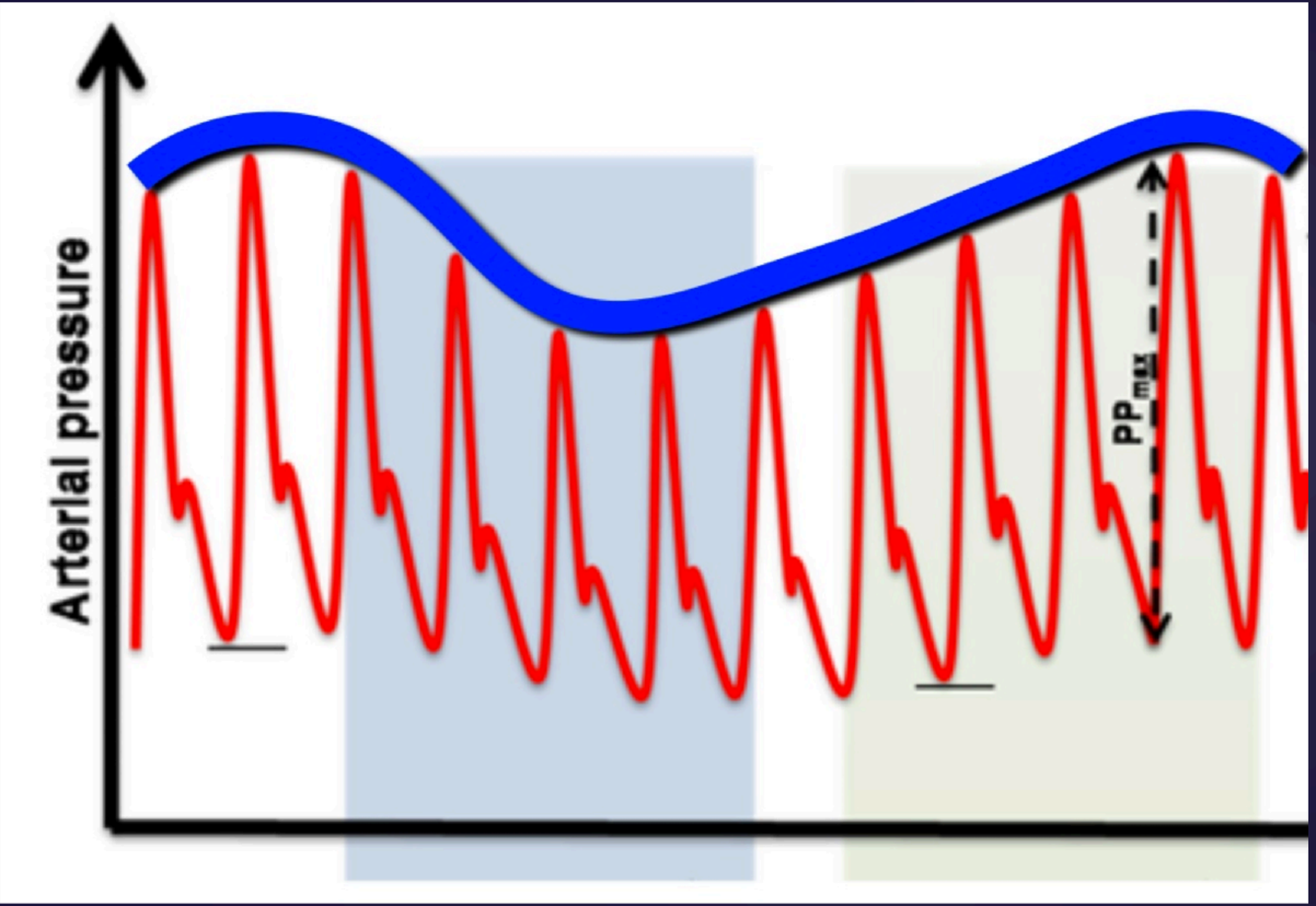
IVC Distensibility

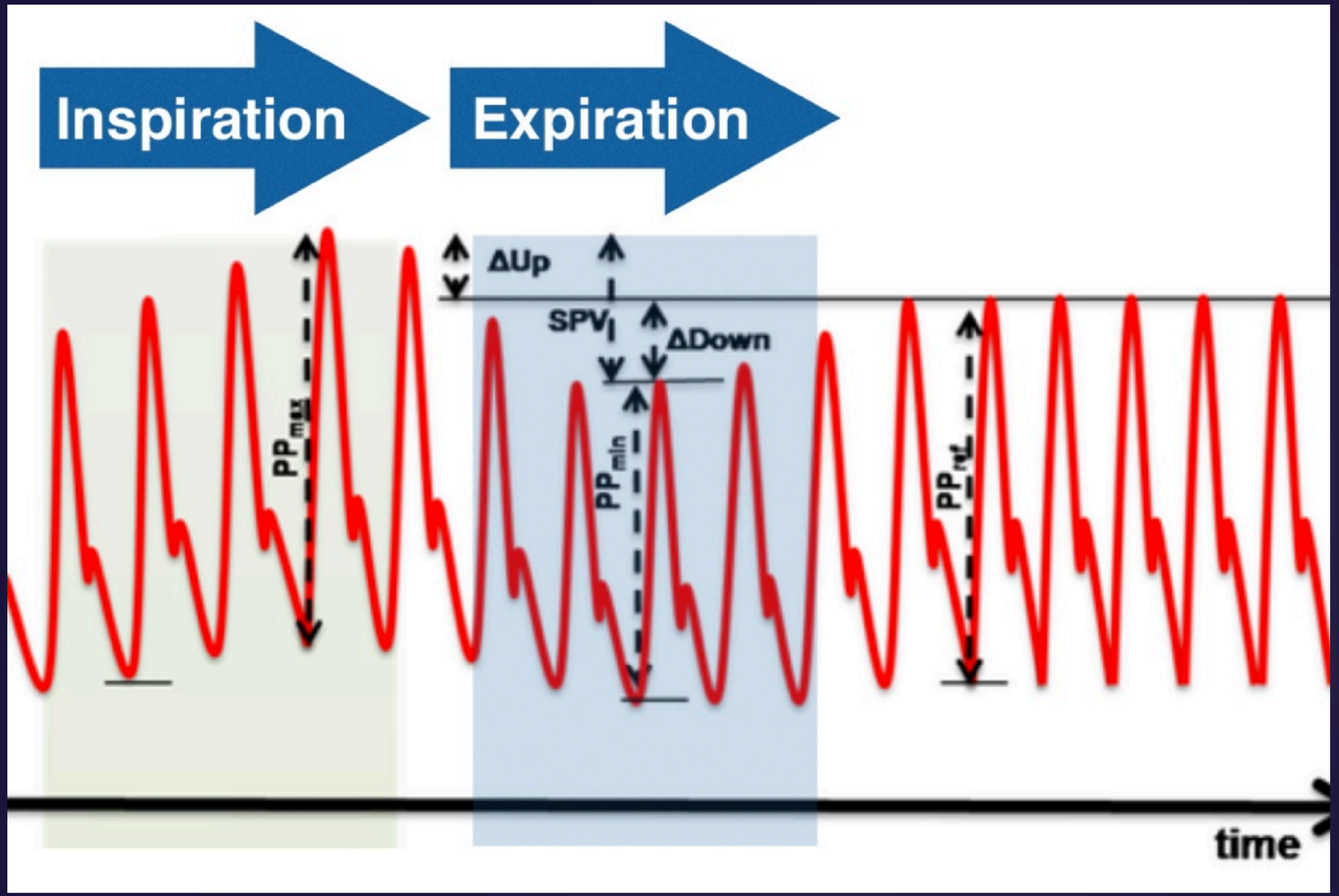


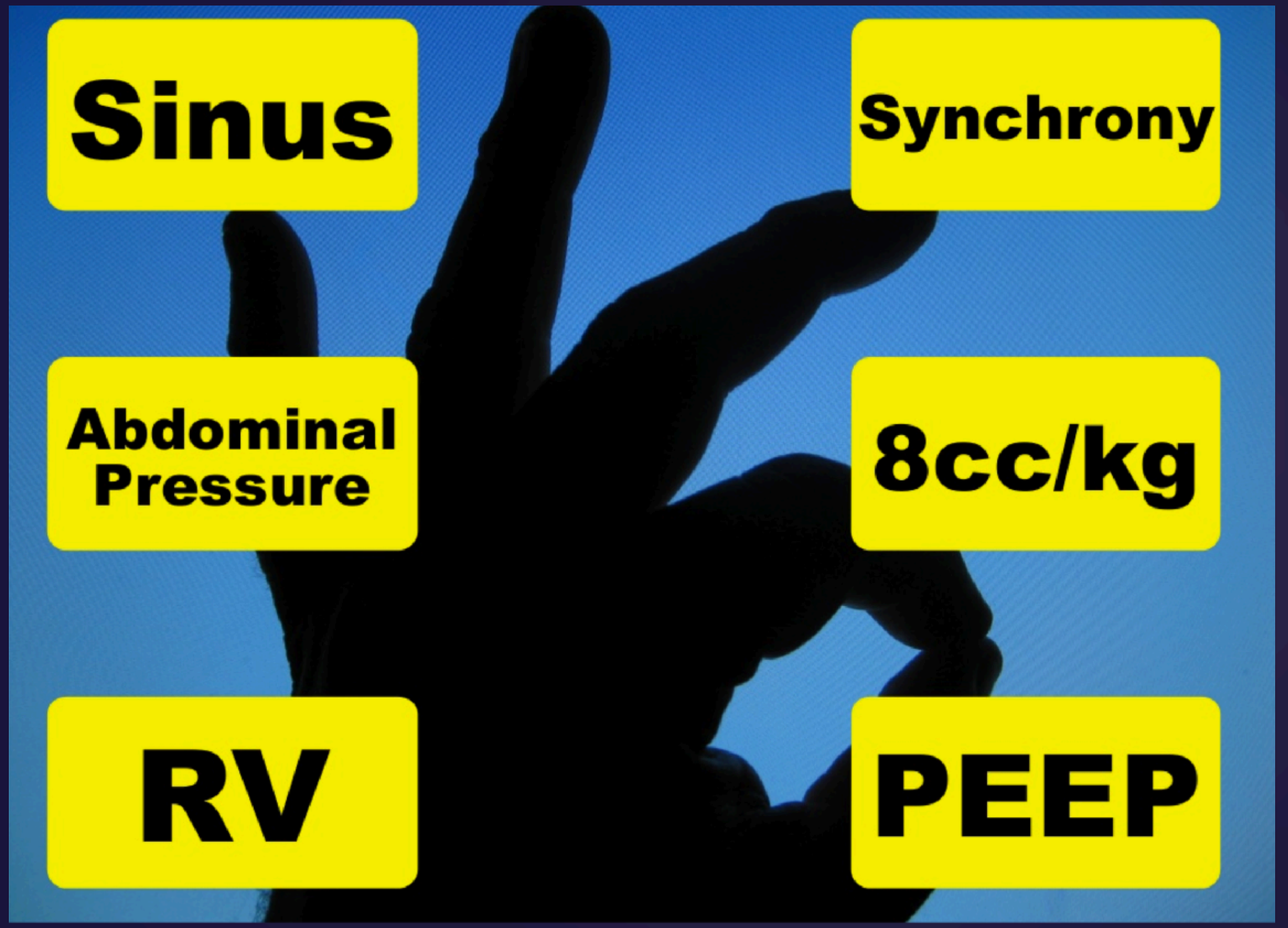
IVC Distensibility



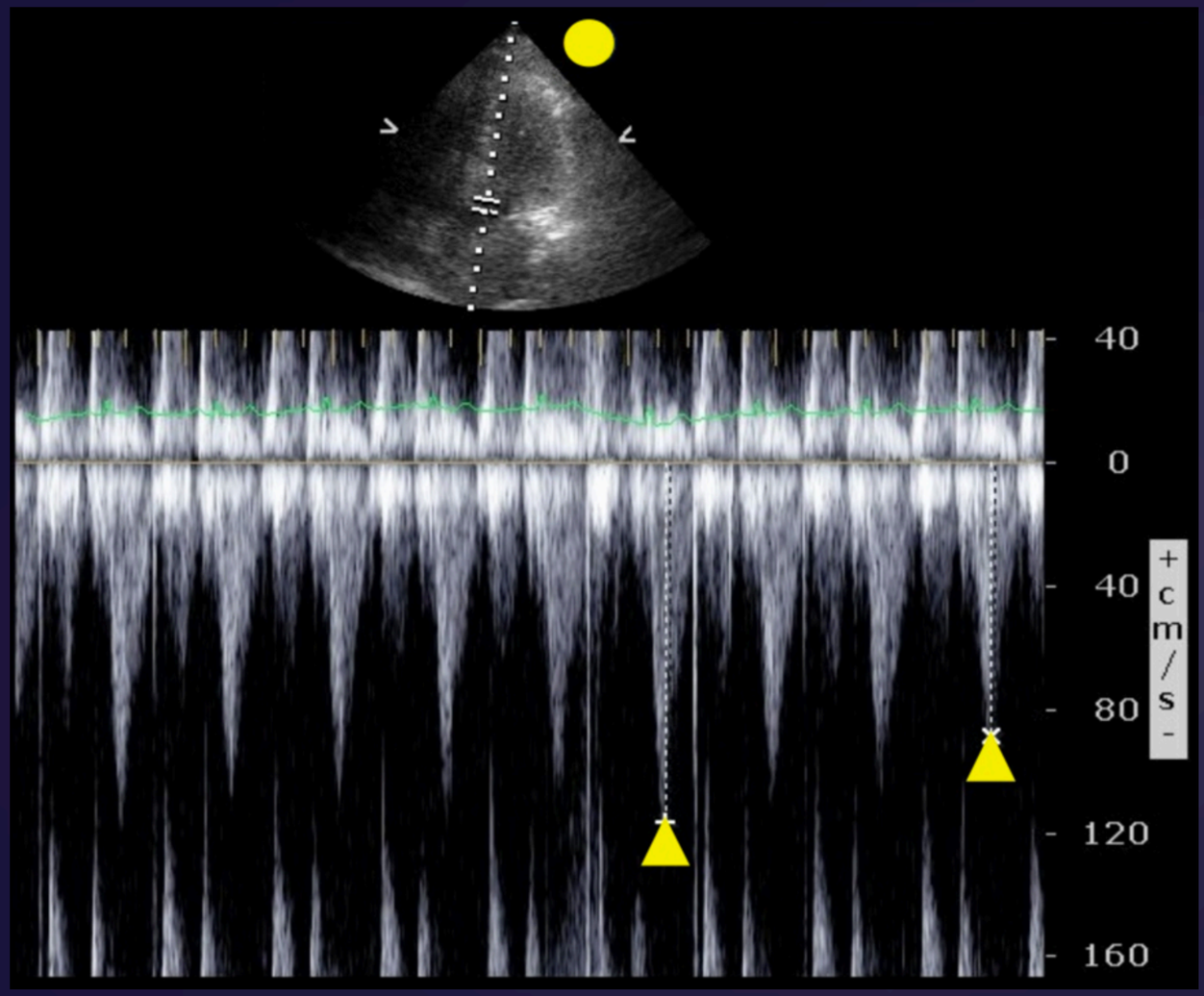
Pulse Pressure Variation




Inspiration
Expiration
ΔUp
SPV
ΔDown
PP
PP
PP
time


Sinus
Synchrony
Abdominal Pressure
8cc/kg
RV
PEEP

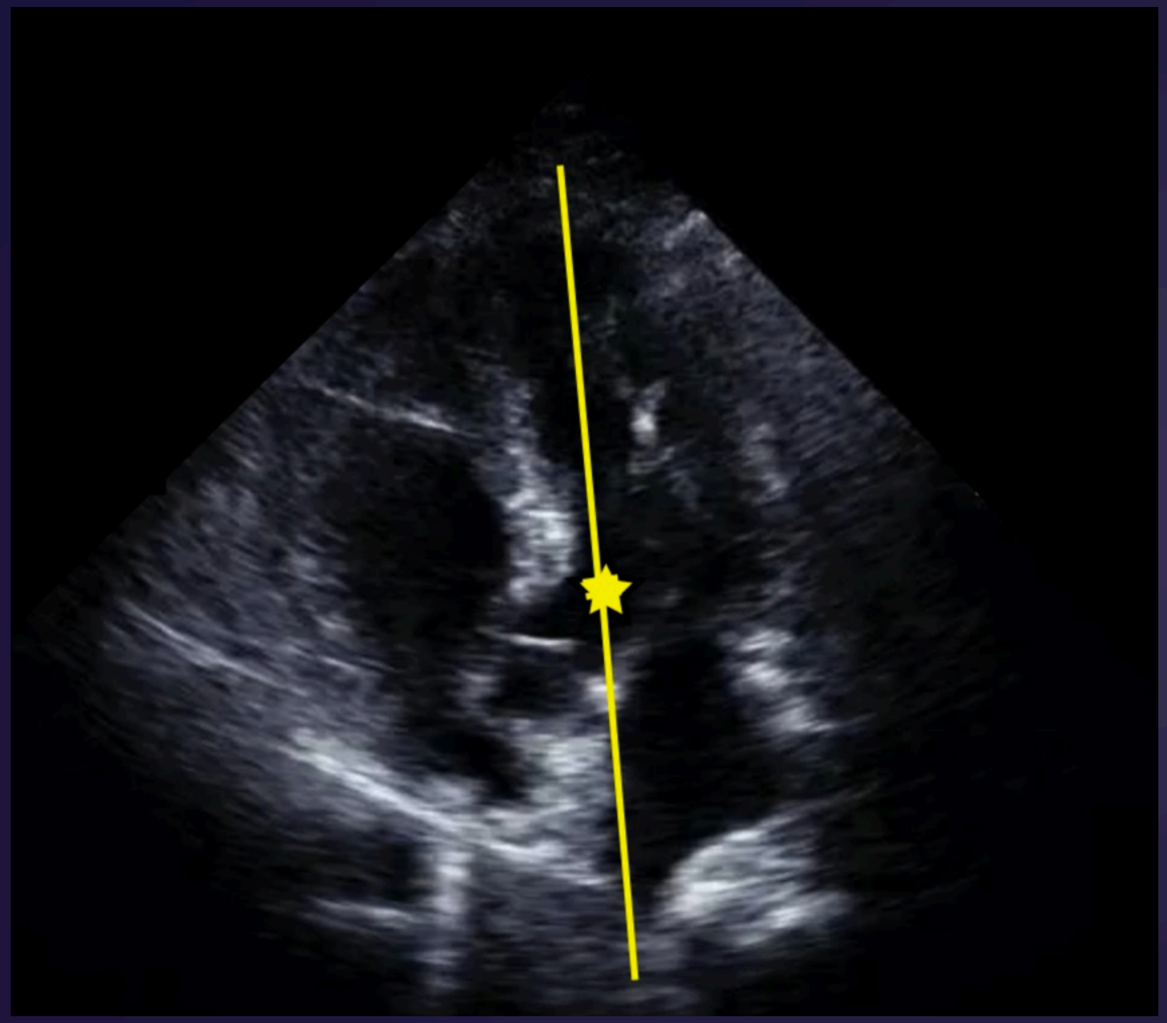
Aortic Blood Flow

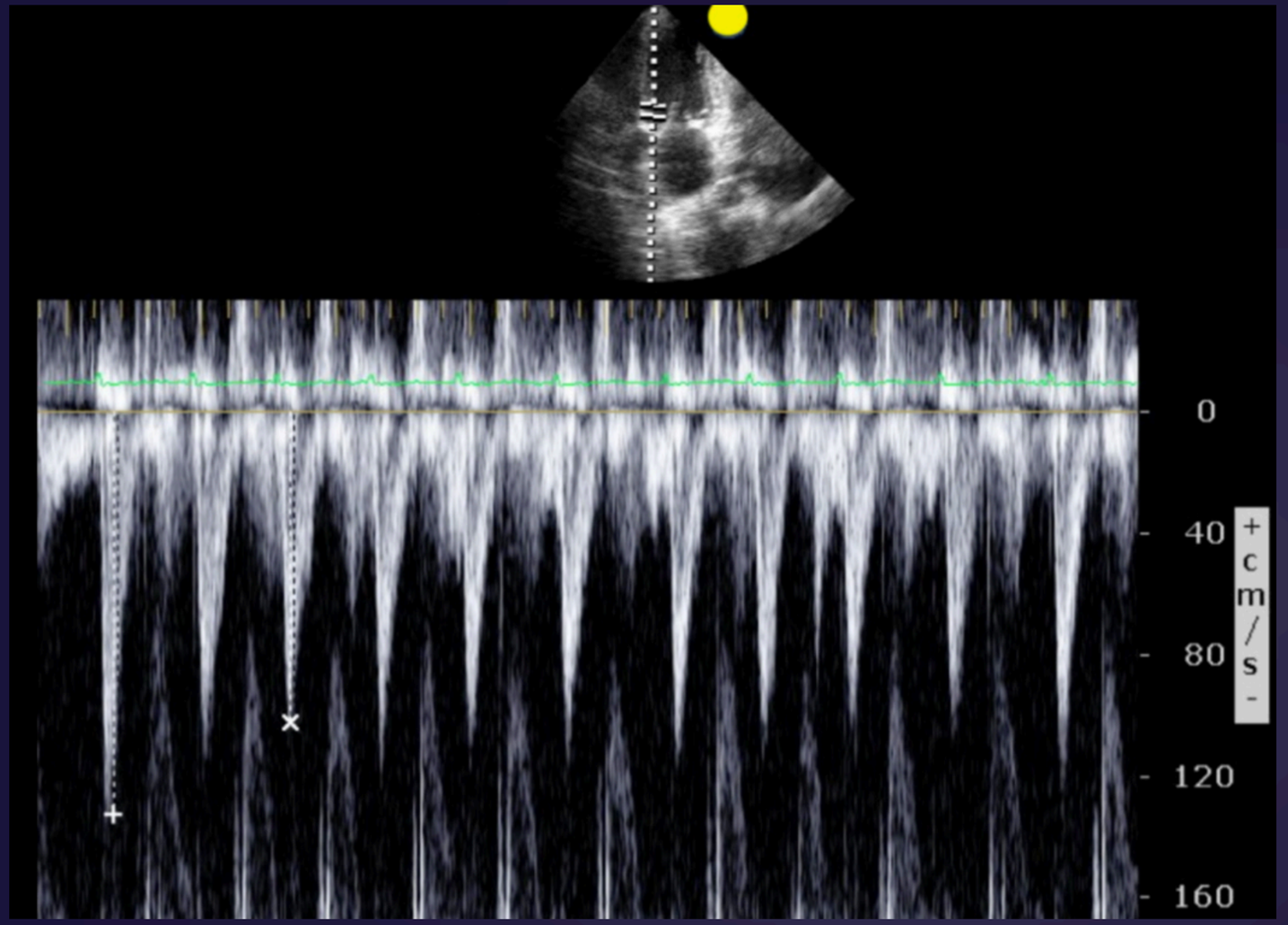


End Expiratory Occlusion

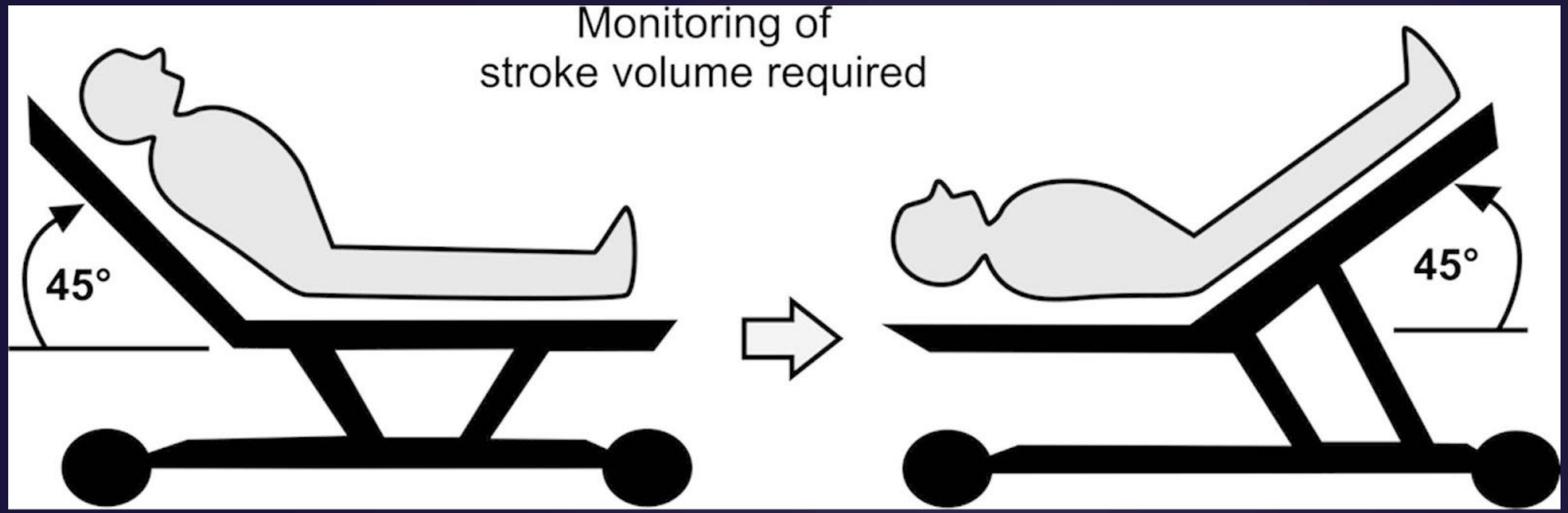
Stroke Volume

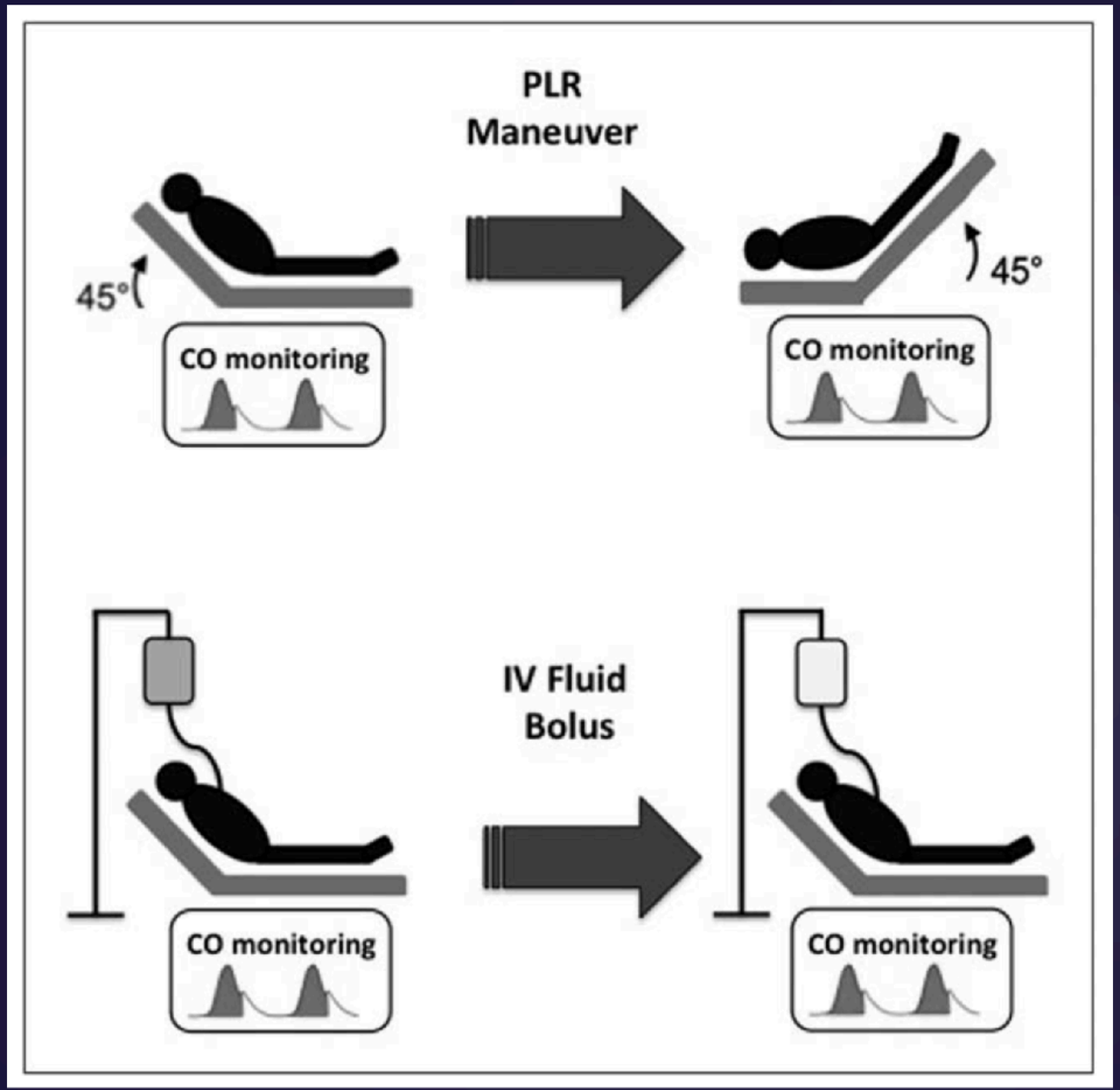
LVOT
Diameter




0
40
80
120
160
+
c
m
/
s
-

Passive Leg Raise




PLR
Maneuver
45°
CO monitoring
45°
CO monitoring
IV Fluid
Bolus
CO monitoring
CO monitoring

- Static pressure and volume parameters (ROC ~0.5–0.6)
  - CVP
  - PAOP
  - IVC/SVC diameter
  - Flow corrected time
  - Right ventricular end-diastolic volume
  - Left ventricular end-diastolic volume
  - SVC/IVC variation during mechanical ventilation
- Dynamic techniques based on heart–lung interactions during mechanical ventilation (ROC ~0.7–0.8)
  - PPV
  - SVV
  - Pleth variability index
  - Aortic blood flow (Doppler or echocardiography)
- Techniques based on real or virtual fluid challenge (ROC~0.9)
  - PLR
  - Rapid fluid challenge (100–250 cc)

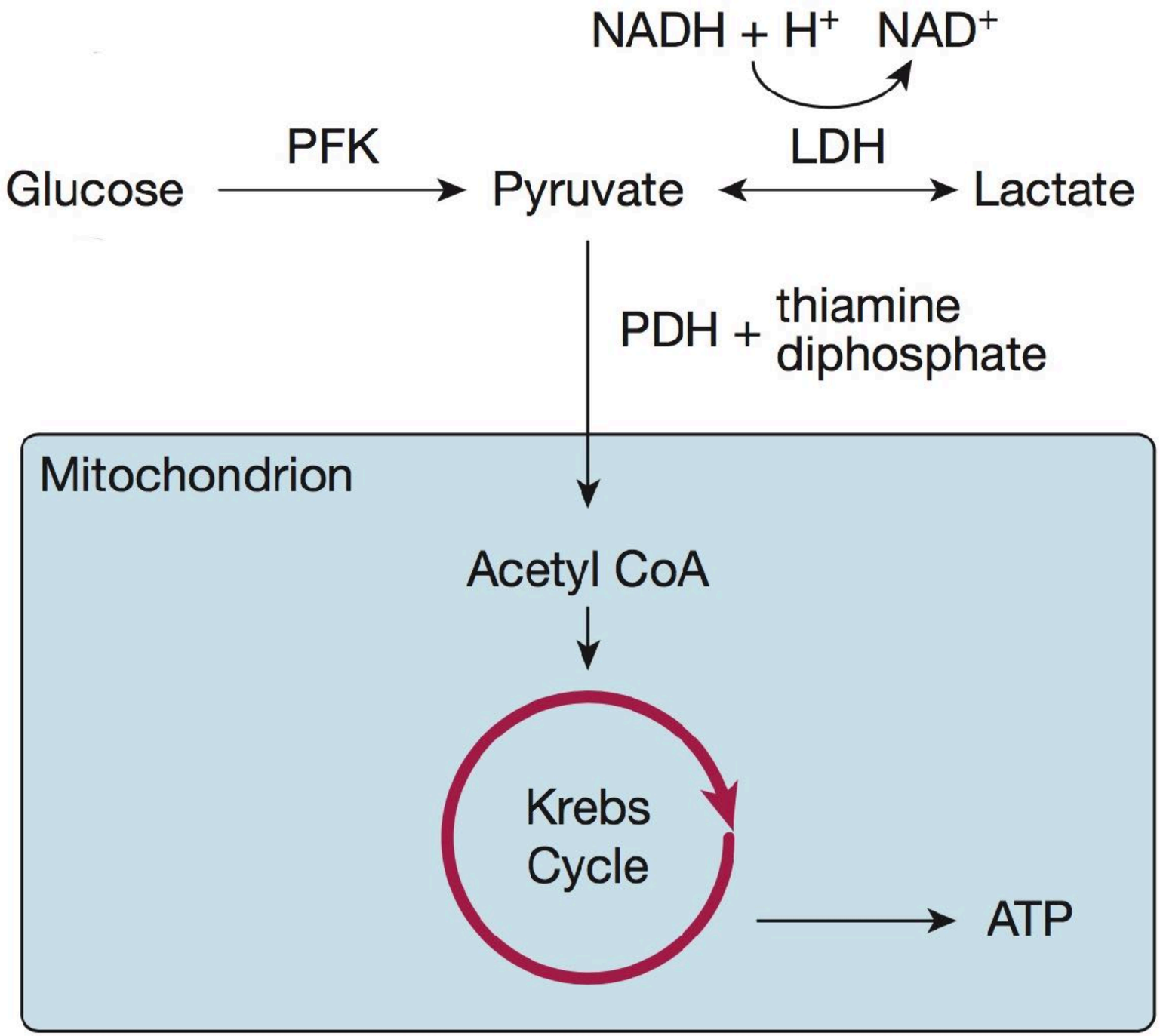
Lactate

Lactate Production

- It is not a “waste product” of anaerobic metabolism
- It is an important energy shuttle

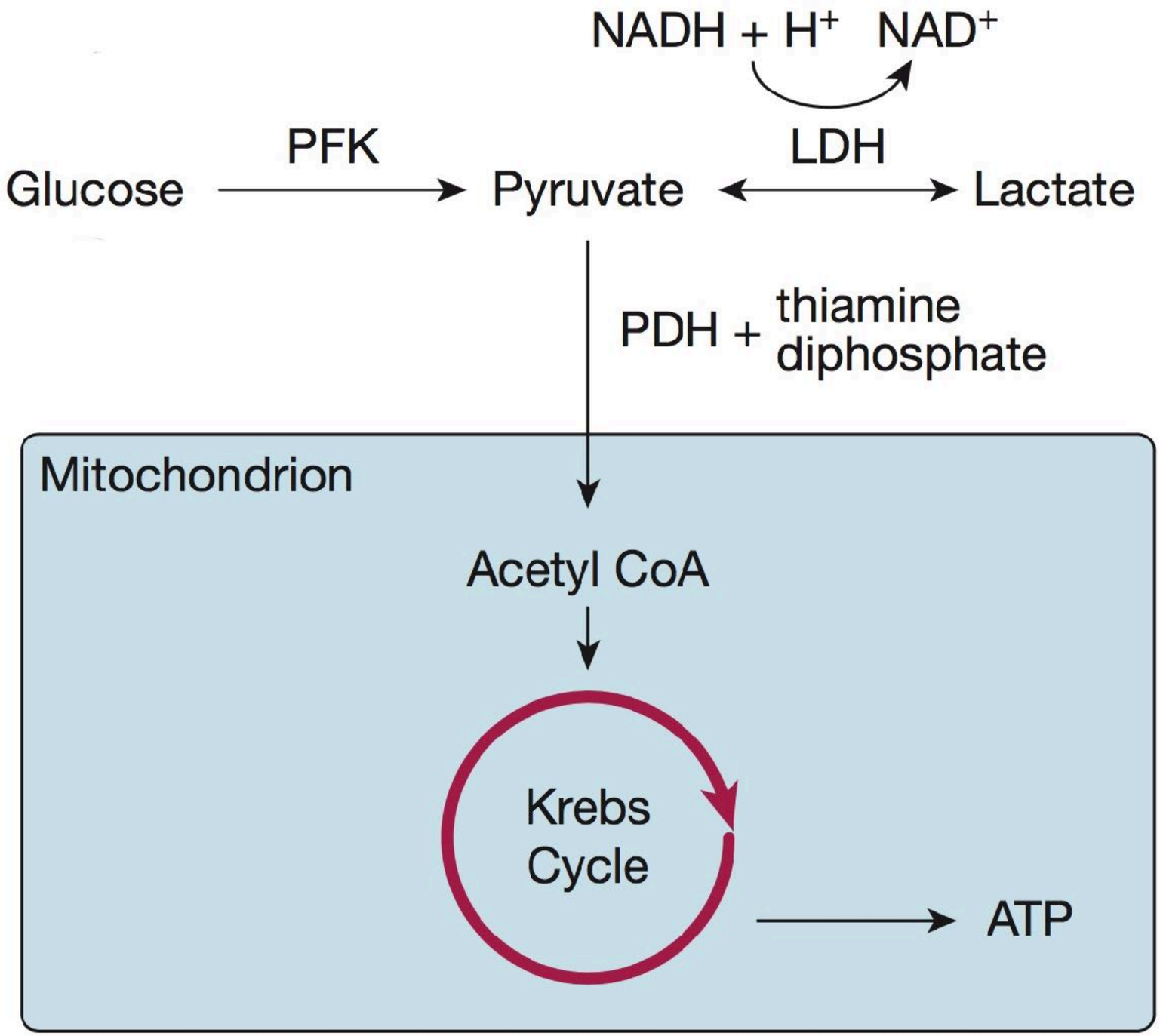
Normal Metabolism

- Lactate production arises mainly from skeletal muscle (25%), skin (25%), brain (20%), intestine (10%), and erythrocytes (20%).
- Glycolysis metabolizes glucose to pyruvate
- Under aerobic conditions, pyruvate is converted to Acetyl-CoA which enters the Krebs cycle to produce ATP by oxidation


NADH + H+
NAD+
PFK
LDH
Glucose
Pyruvate
Lactate
PDH + thiamine diphosphate
Mitochondrion
Acetyl CoA
Krebs Cycle
ATP

Normal Metabolism

- Pyruvate is also in equilibrium with lactate in the cytosol
- Bidirectionally catalyzed by LDH
- This requires NADH and H+
- Normal lactate:pyruvate ratio of approximately 10:1.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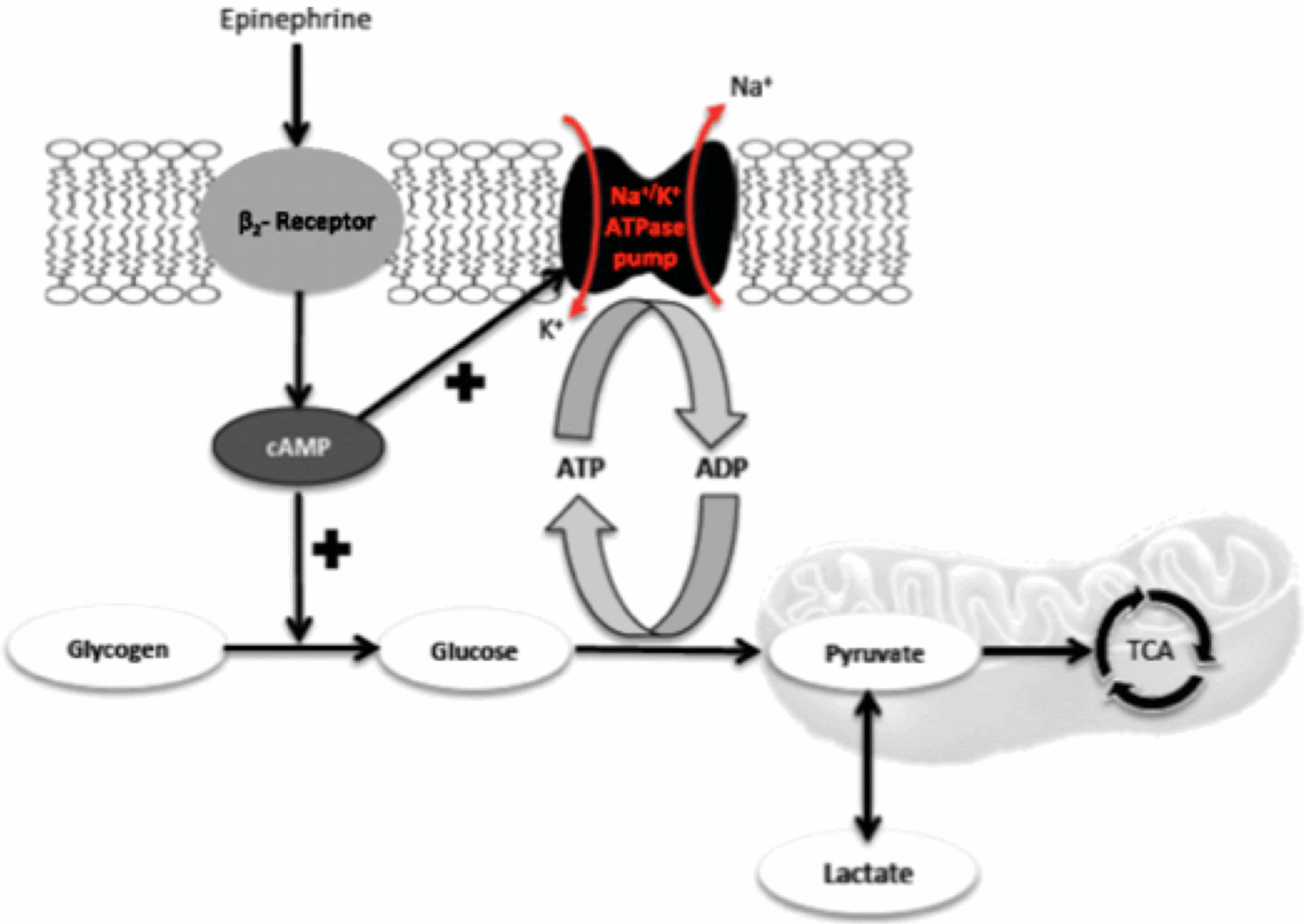
ATP

Normal Metabolism

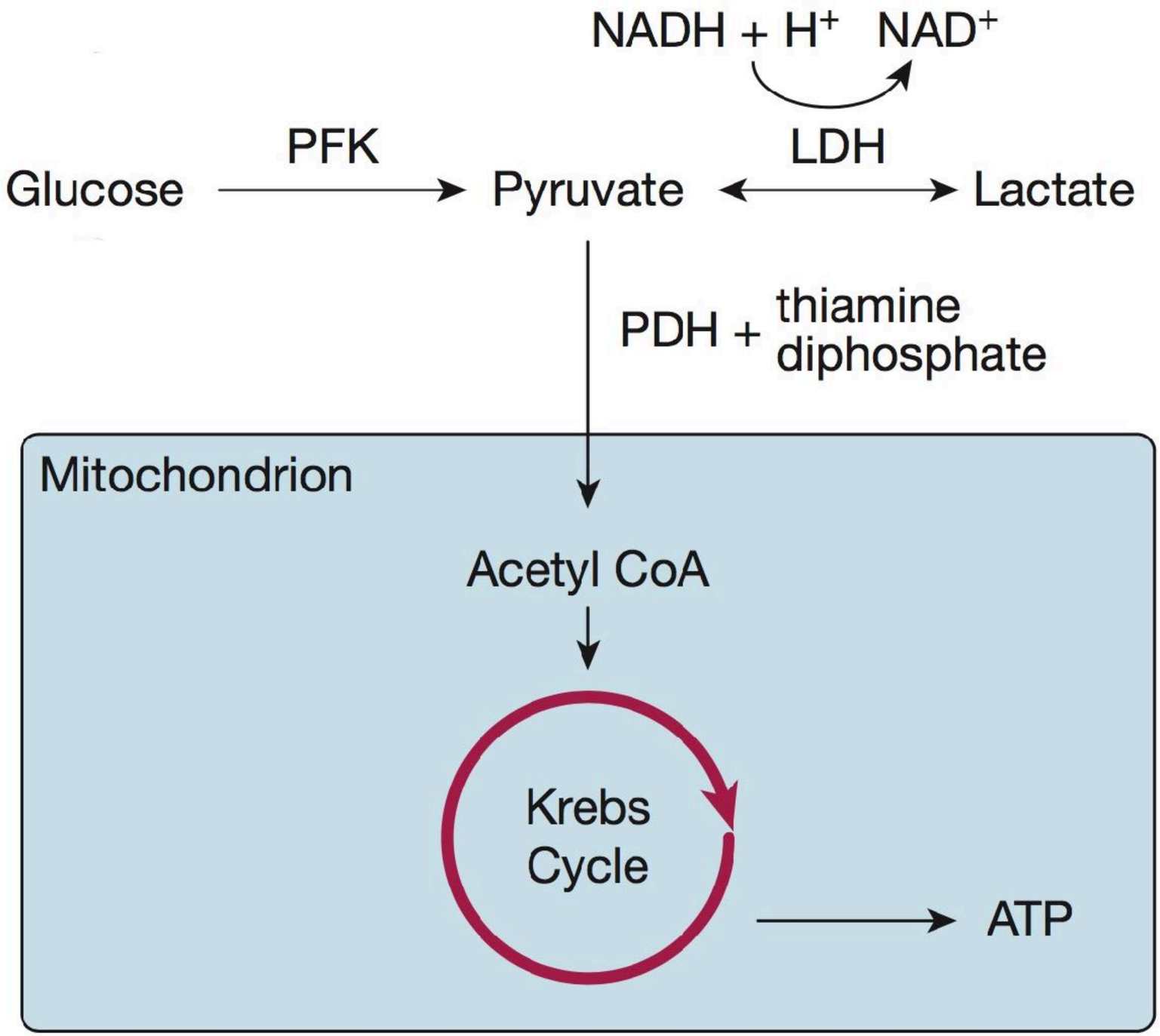
- There is also a glycolytic component that occurs in the cytosol
- Compliments the oxidative pathway.
- Beta2-adrenergic stimulates cAMP inducing glycogenolysis and glycolysis for ATP production
- Pyruvate is a byproduct
- Na^+/K^+-ATPase pump uses the ATP for much of the cellular work



Garcia-Alvarez *et al. Critical Care* 2014 **18**:503

Lactate Clearance

- Consumption by local or distant mitochondria for energy production
  - Via pyruvate and Krebs cycle
- Utilized as substrate for gluconeogensis
  - Cori cycle
- Metabolism occurs in the liver (60%) and kidney (30%)
- Urinary excretion threshold is 5-6 mmol/L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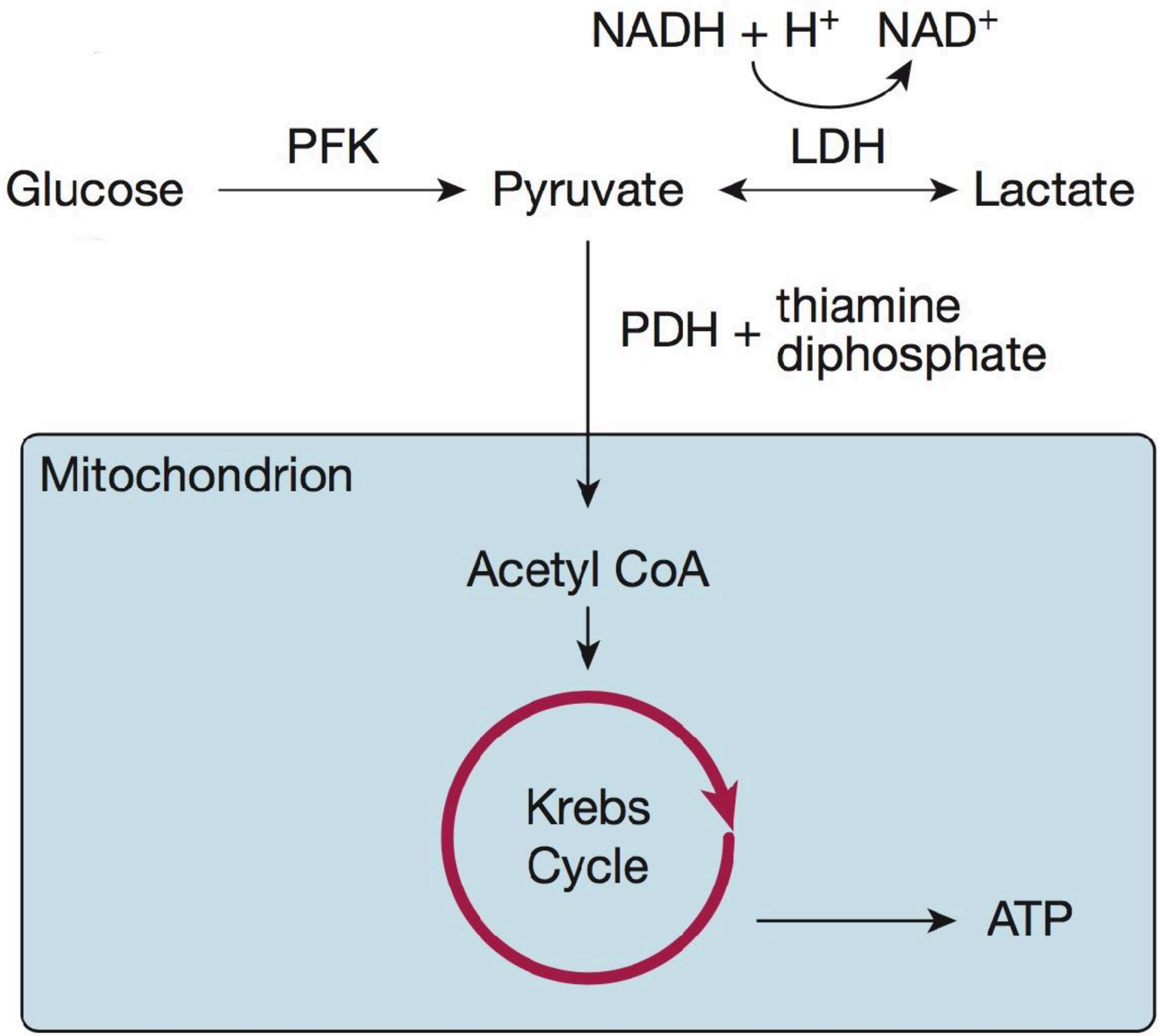
Abnormal Lactate Production

- Leukocytes also generate lactate during phagocytosis or when activated in sepsis.
- The lungs can create lactate during acute lung injury without tissue hypoxia
    - Accelerated glucose production in inflammatory lung tissue

Abnormal Lactate Production

- Anaerobic metabolism in hypoxic tissue
- Pyruvate cannot enter the Krebs cycle, so it is shunted to lactate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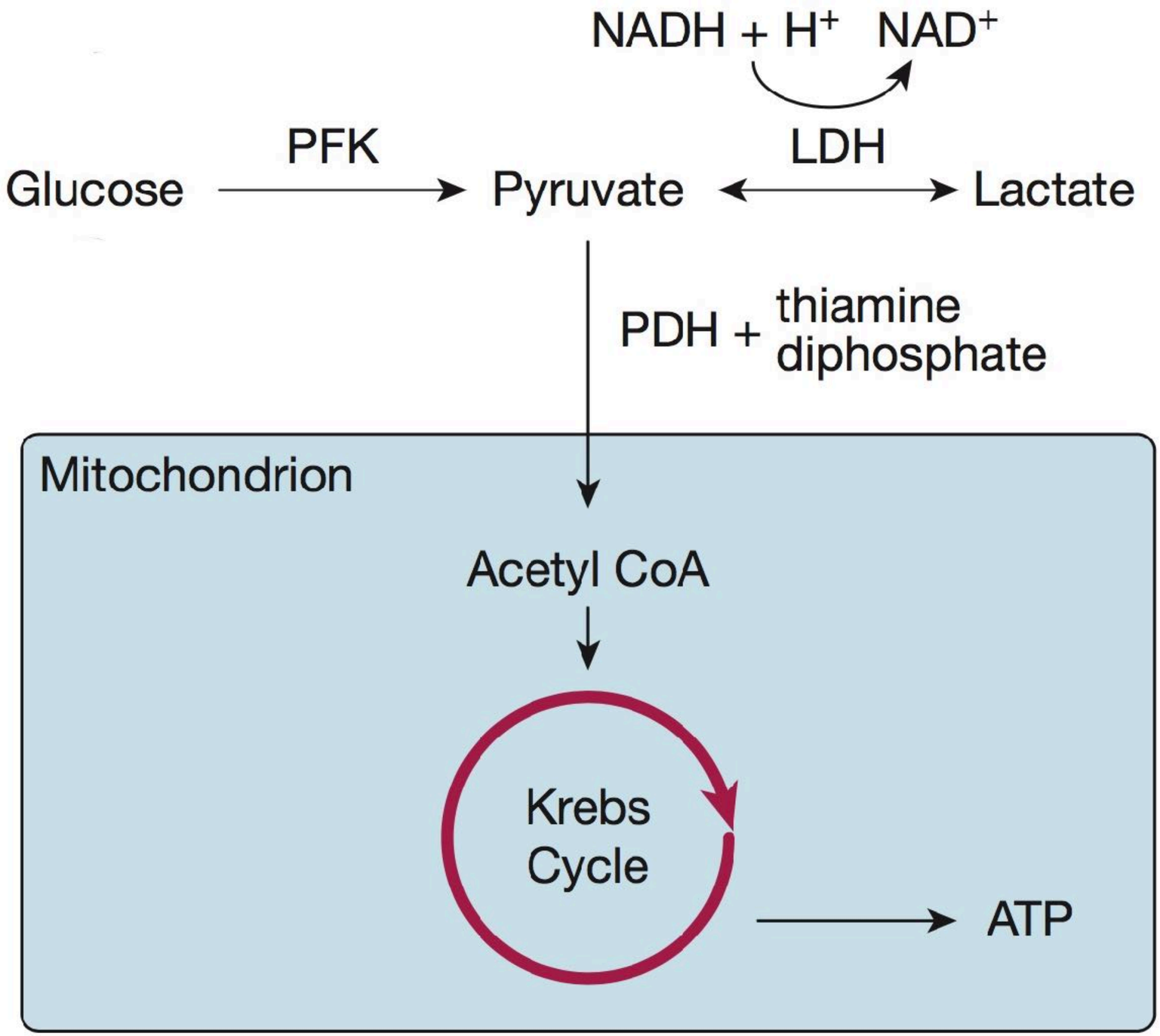
Increased Glycolytic Flux

- Severe exercise
- High work of breathing
- Catecholamine administration
- Sepsis
- Maintains normal lactate:pyruvate ratio if adequate oxygen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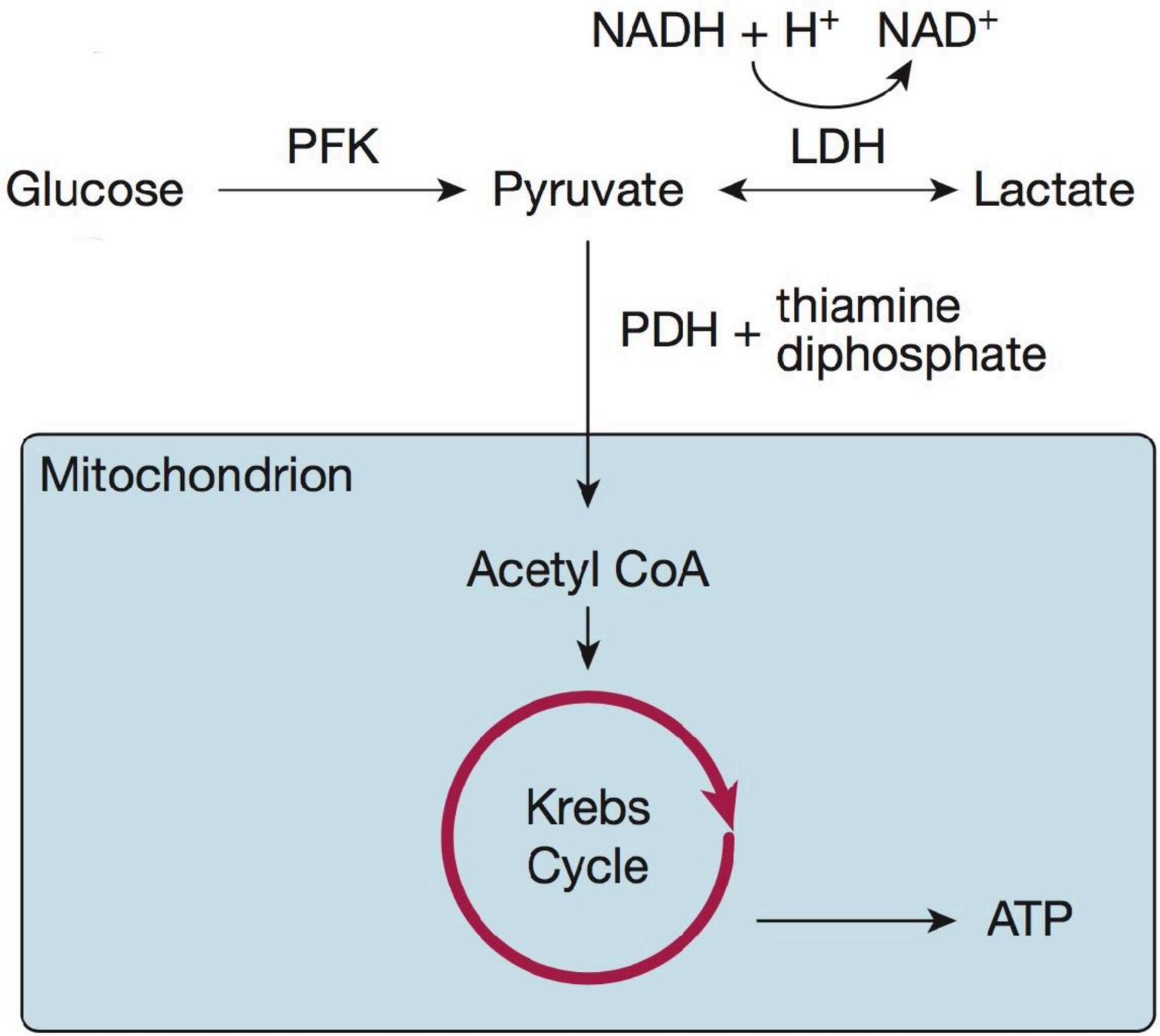
Impaired Clearance

- Elevated reducing environment (high NADH)
  - Ketoacidosis
  - Ethanol ingestion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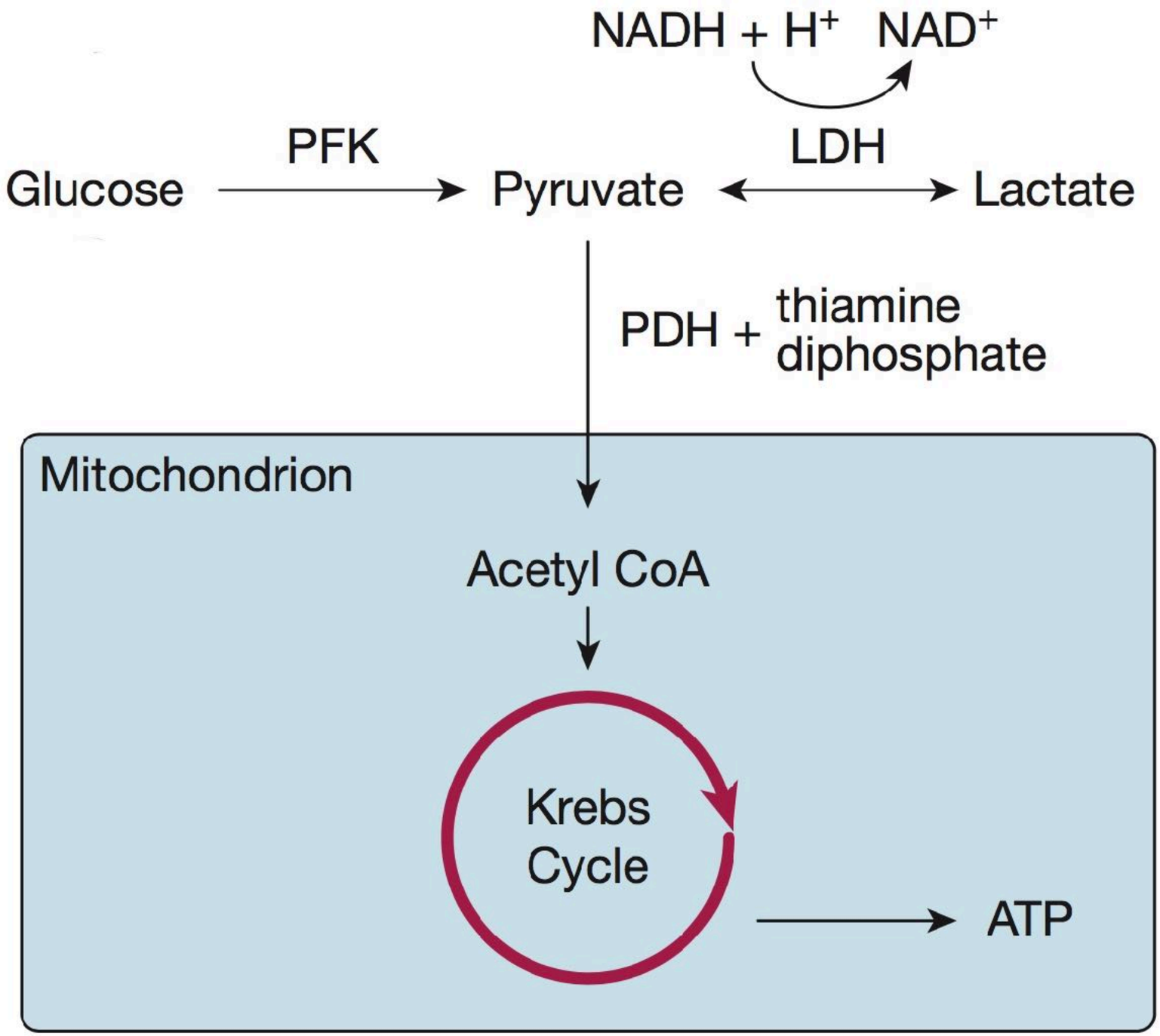
Hyperlactatemia

- Abnormal lactate/pyruvate ratio
- Occurs if pyruvate is prevented from entering Krebs cycle
  - Hypoxia (already mentioned)
  - Amount exceeds capability of mitochondria (excessive glycolytic flux)
  - Mitochondrial dysfunction (sepsis induced cytokines)
  - Thiamine deficiency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Sepsis Tissue Hypoxia Myth

- In sepsis, lacte is NOT produced by anaerobic metabolism
  - Septic patients have hyperdynamic circulation
- Mt Everest Climbers (PaO2 24, lactate normal)
- Oxygen delivery to tissues is adequate
  - P_aO2 100, P_vO2 40, $P_{cytosol}O2$ 5
  - But Mitochondrial threshold is 1
  - Critical oxygen delivery occurs at 3.8 mL/kg/min (CO 1.8 L/min)
- Studies trying to correct oxygen delivery fail to improve

Acidosis Production

- Glycolysis to pyruvate produces H+, pyruvate to lactate consumes H+
  - Stoichiometrically does not generate any net protons
- But lactic acid by p-chem must generate acidosis
- The key is that protons are consumed by a fully functional Krebs cycle that can keep up

Acidosis Production

- Hyperlactatemia without acidosis can persist as long as there is not a decreased Krebs cycle flux
- Acidosis generated by production of lactate occurs when lactate:pyruvate ratio is altered by failure of Krebs cycle

Lactate:Pyruvate Alteration besides Hypoxia

- Impaired Tissue Extraction
  - Microcirculatory dysfunction (vasodilation)
  - Inflammatory changes to enothelium
  - Regional and microregional oxygen delivery does not meet demand
  - Microthrombotic occluson
- Mitochondrial dysfunction
- Diminished clearance -- Hepatic dysfunction
- These dont improve with increased cardiac output or tissue oxygen perfusion.

Excessive Glycolytic Flux

- 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--changing ratio
- This is entirely aerobic

Lactate might be compensatory

- Lactate is not a toxin
- Lactate serves as efficient metabolic fuel for heart and brain in stress
- Depletion of lactate caused cardiovasular collapse
- Cardiac myocytes use lactate as fuel in some circumstances, such as during exercise, beta-adrenergic stimulation, and shock.
- Giving lactate as been shown to improve outcomes in CAB and HF patients

Measuring lactate

- Arterial and vensous 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

- Autnomic system and endogenous catecholamine response are variable
- Some patients have a weak response and immediately develop hypotension
- Other patients have a robust response supporting their blood pressure and thereby preventing hypotension
  - 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

Identification of Occult Shock

- This makes it useful for detection of occult shock
- 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
  - Used by Surviving Sepsis Campaign as arbitrary threshold for identifying cryptic shock
  - Lactate has a continuous curvilinear association with mortality
  - There is no elevation that is clearly safe
  - Intermediate concentrations (lactate 2-4) or even high-end normal range (1.4-2.3) still indicated a poorer prognosis than normal lactate concentrations

Lactate Clearance as marker of adequate resuscitation

- Rivers trial established EGDT in severe sepsis and septic shock
  - NEJM 2001
  - Used proprietary designs continuous ScvO2 as a target to assess than oxygen delivery was adeqaute
  - Intermittent measurement of ScvO2 correlated well

Lactate Clearnce

- Jones studied RCT of lactate clearance vs ScvO2
  - No difference between the two
  - 10% Clearance threshold
- Averaging out of ScvO2 is misleading
  - Even if there is tissue hypoperfusion
  - Following ScvO2 results in mismanagement.

Lactate Clearance

- 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 SvO2 (as a single variable)

Lactate Clearance

- 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.

Lactate Clearance

- We dont know if directing therapy at clearing lactate improves outcomes
- When looked at seperately, clearing they do not alter outcomes
  - ARISE, ProCESS studies
- 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.

What to Do

- Source control
- Antibiotics
- Reasonable amount fluids
- Vasopressors
- Reasses
  - Use lactate along with ScvO2, echo, VaCO2 difference, mental status, urine output, mottling

What if lactate is not clearing?

- It is not telling us that we did not fix anaerobic metabolism
- You need functioning liver and kidney
- Do nothing empirically

What if lactate is not clearing?

- If left ventricular dysfunction — give inotrope
- Low Cardiac Output
- Assess volume — give volume
- If Hgb low — give blood
- Look for ischemic/infarction tissue (ie regional lactate production)
  - Bowel ischemia/infarction
  - Limb arterial occlusion
  - Compartment syndrome

What if lactate is not clearing?

- Consider thiamine if malnourished to maximize aerobic metabolism
- Limit beta-adrenergic stimulation
  - Vasopressor choice
  - Esmolol
- Reduce skeletal muscle work
  - Mechanical ventilation for work of breathing
  - Paralytics
- Avoid hepatotoxins

Reference and Outline available at:

resusreview.com/resistanceJun17