Pathophysiology of Hypoxia

NeoHemodynamics 2018

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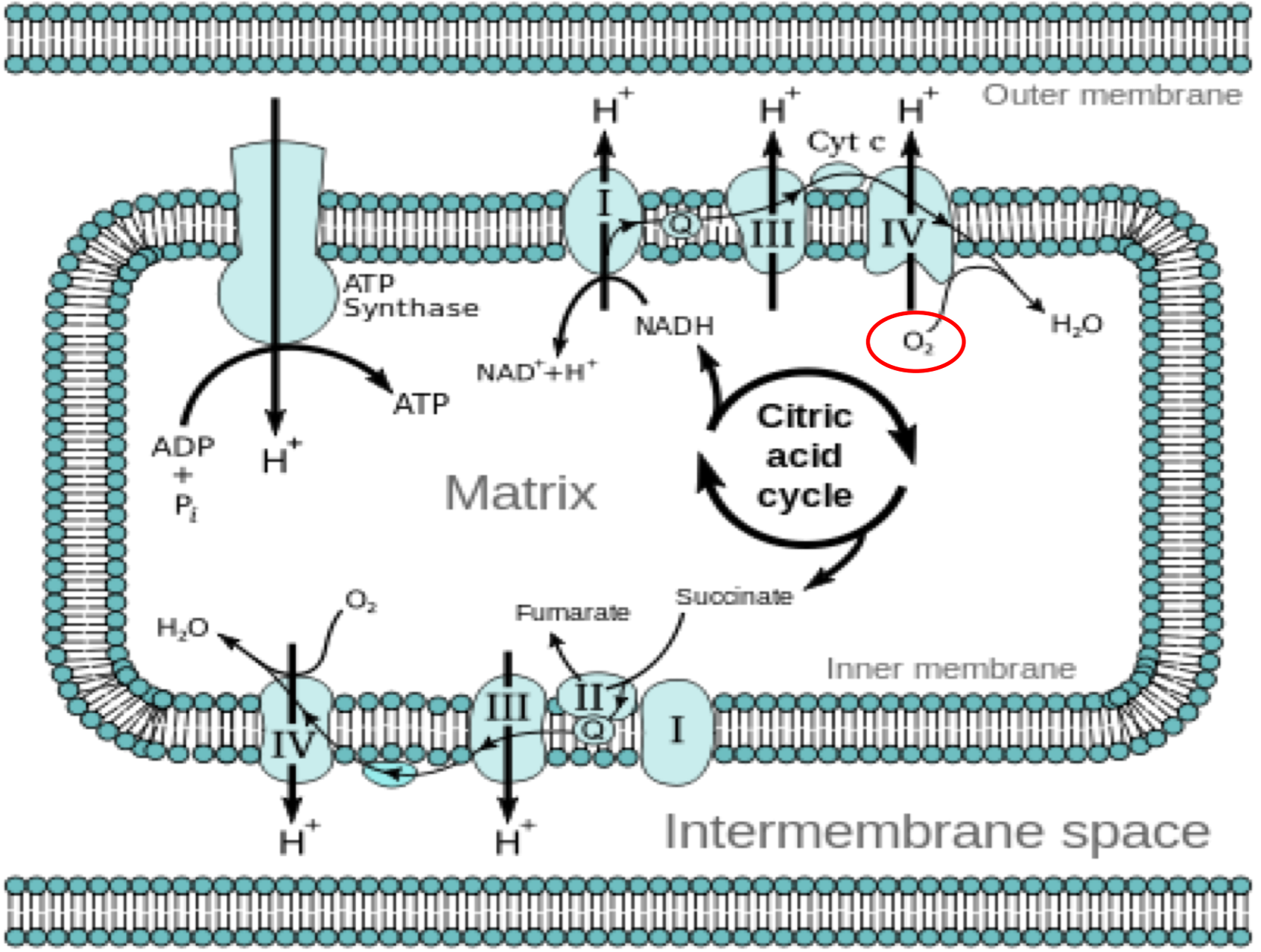
Objectives

- To examine four types of hypoxia that occur in the ICU, and in utero
- To review strategies to identify and manage each type of hypoxia
- To understand how the fetus and the neonate can adapt to low oxygen delivery



- Mitochondria thrive on oxygen
- *All* of it is consumed by cytochrome oxidase, the last enzyme (complex IV) in the electron transport chain
- Oxygen is required to create the H^+ gradient that drives aerobic ATP production
- This one step is why we breathe, and why the blood transports oxygen

What's enough for you may not be enough for me

- **Physioxia:** when oxygen delivery neatly matches oxygen demand
- The oxygen tension of physioxia varies from tissue to tissue
- Where demand increases, the threshold DO2 (oxygen delivery) required to maintain physioxia also increases
- **Hypoxia** is when DO2 is insufficient to supply the demand set by VO2 (metabolic utilization)

	pO_2	
	mmHg	%
Air	160	21.1
Inspired air (in the tracheus)	150	19.7
Air in the alveoli	110	14.5
Arterial blood	100	13.2
Venous blood	40	5.3
Cell	9.9–19	1.3–2.5
Mitochondria	<9.9	<1.3
Brain	33.8 ± 2.6	4.4 ± 0.3
Lung	42.8	5.6
Liver	40.6 ± 5.4	5.4 ± 0.7
Kidney	72 ± 20	9.5 ± 2.6
Muscle	29.2 ± 1.8	3.8 ± 0.2

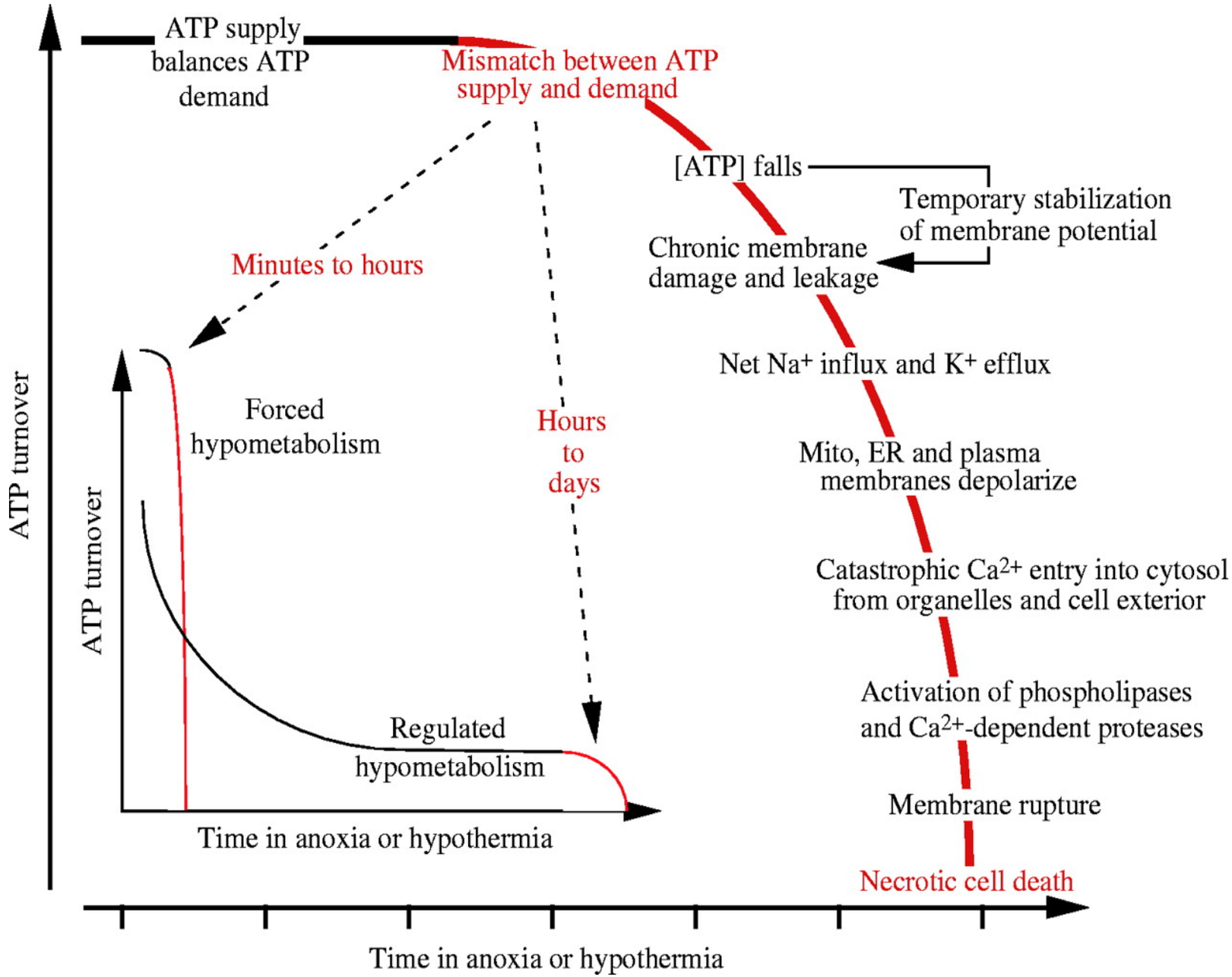
AJ Carreau, Cell Mol Med 2011

- **Cellular hypoxia**

- **Cell death**

Or, hypoxia is a Bad Thing

- Cellular hypoxia
- Adaptive metabolism, redistribution of blood flow
- Anaerobic metabolism
- Energy deficit
- Lactic acid accumulation
- Metabolic acidosis
- Pulmonary vasoconstriction
- Systemic vasodilation
- Loss of cerebral autoregulation
- Receptors and enzymes stop functioning properly
- Cell membrane pump dysfunction
- Cell lysozymes release digestive enzymes
- Escape of circulating toxins
- Capillary endothelial damage
- Cell death… ouch.

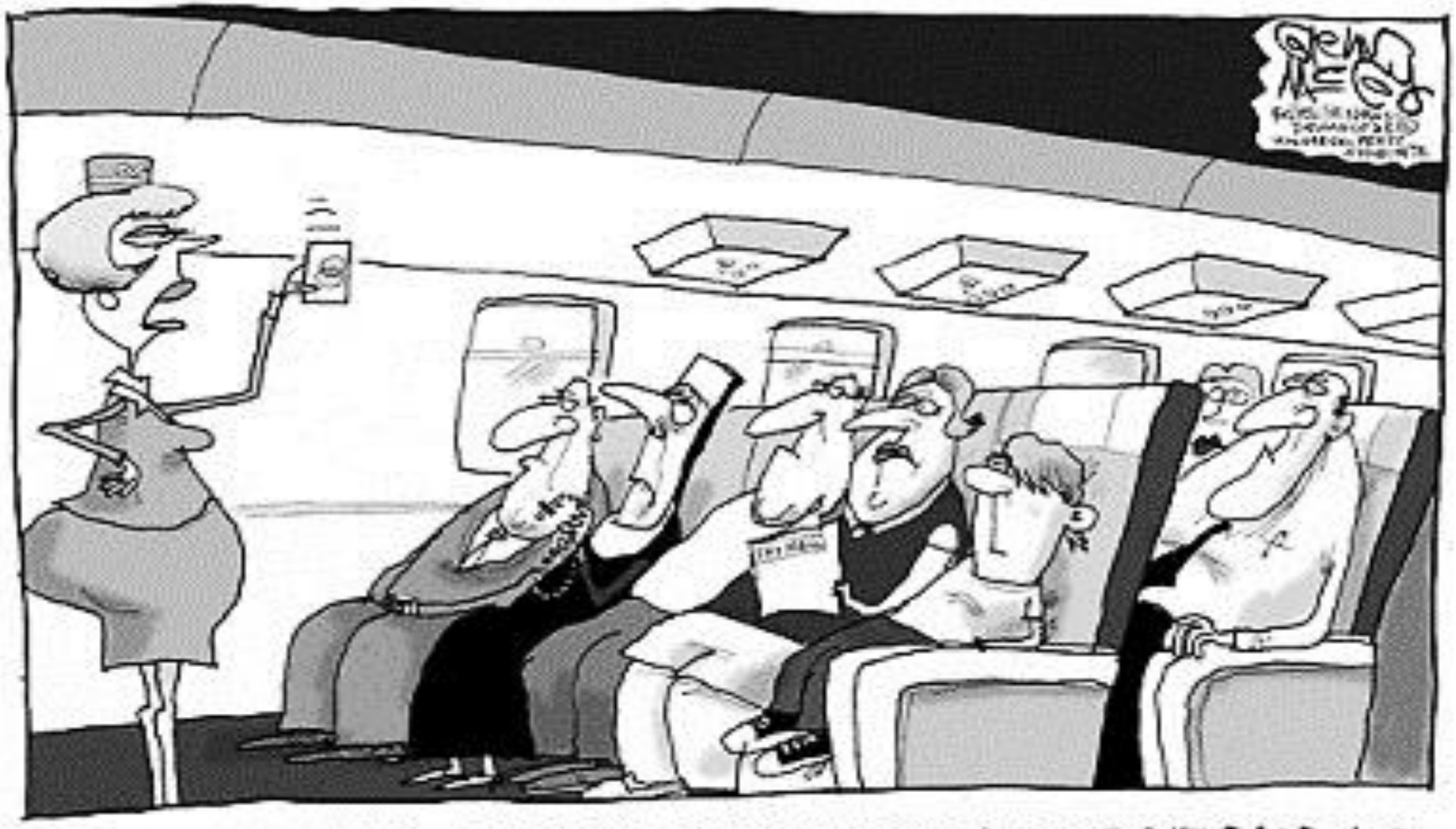


RG Boutilier, J Exp Biol 2001

Types of Hypoxia

- **Hypoxemic**
  - Insufficient oxygen supply or uptake
  - Inadequate hemoglobin saturation
- **Anemic**
  - Reduced O_2 carrying capacity of blood
- **Circulatory**
  - Blood (and thus O_2) not reaching tissues
- **Metabolic / Histotoxic**
  - Cells cannot use the delivered O_2

Hypoxemic Hypoxia



Review: Alveolar Gas Equation

$$P_AO_2 = (O_2 \text{ tension} \times P_{atm}) - (CO_2 \text{ produced})$$

Alveolar partial pressure of O_2 $= (F_iO_2 \times (760 - 47)) - (P_aCO_2 / 0.8)$

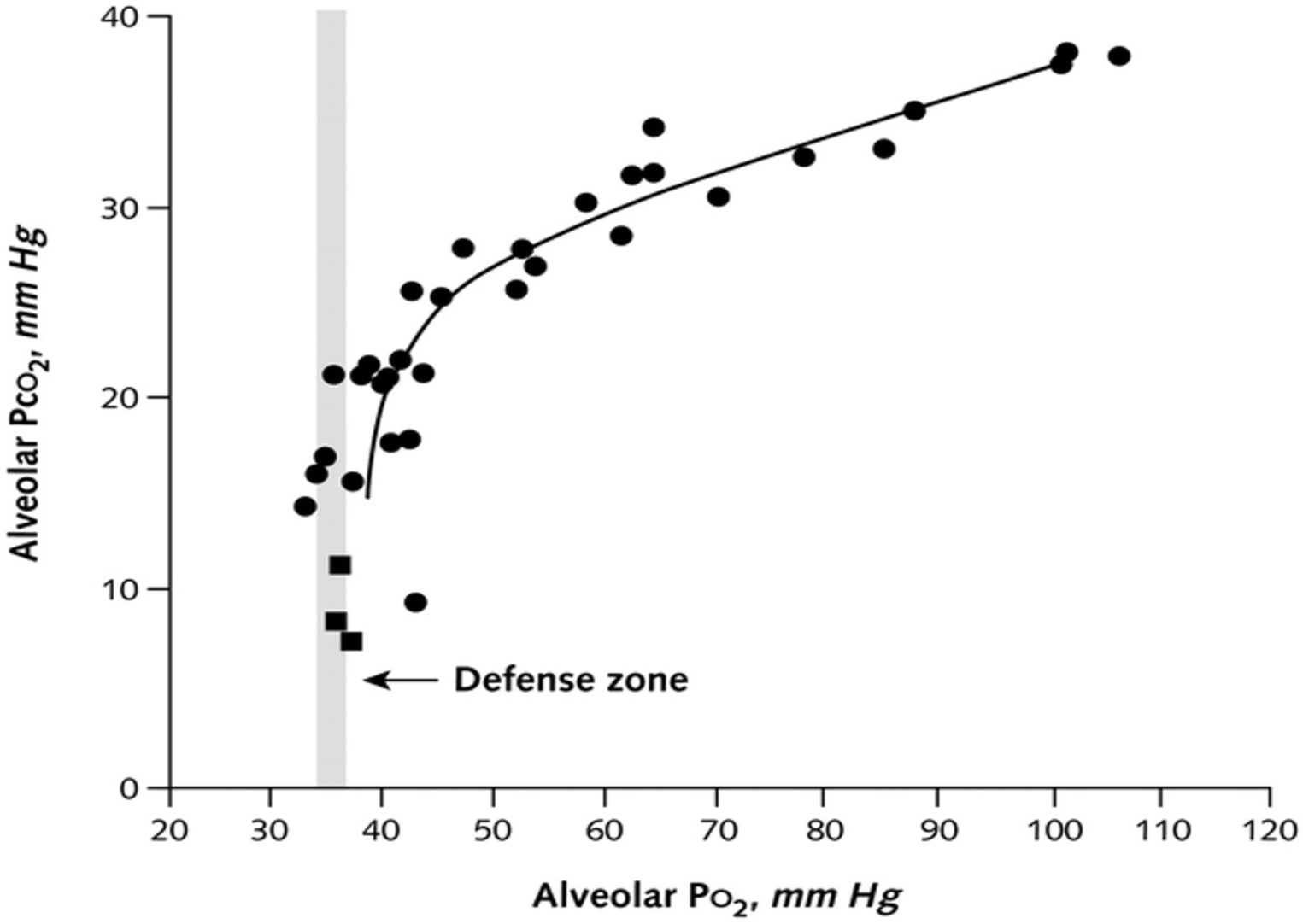
assuming sea level

assuming 100% humidity in alveoli

assuming a respiratory quotient (ratio of CO_2 released to O_2 absorbed) **of 0.8**

- Normal P_AO_2 is 150 – 50 = **100**
- A/a gradient = $P_AO_2 - P_aO_2$ (normally 5 –10, if no impediment to diffusion)
- P_aO_2 is typically around 95 in room air, around 660 in 100% O_2

Defence of Alveolar PO_2 by PCO_2



West, J. Ann Intern Med 2004;141:789-800

- ***Counterpoint example:*** Ventilated neonate, acute deterioration
- Arterial blood gas, on room air:

  pH 7.20 / PO2 45 / PCO2 85 / HCO3 29

  Can you estimate what is this patient's A/a gradient?

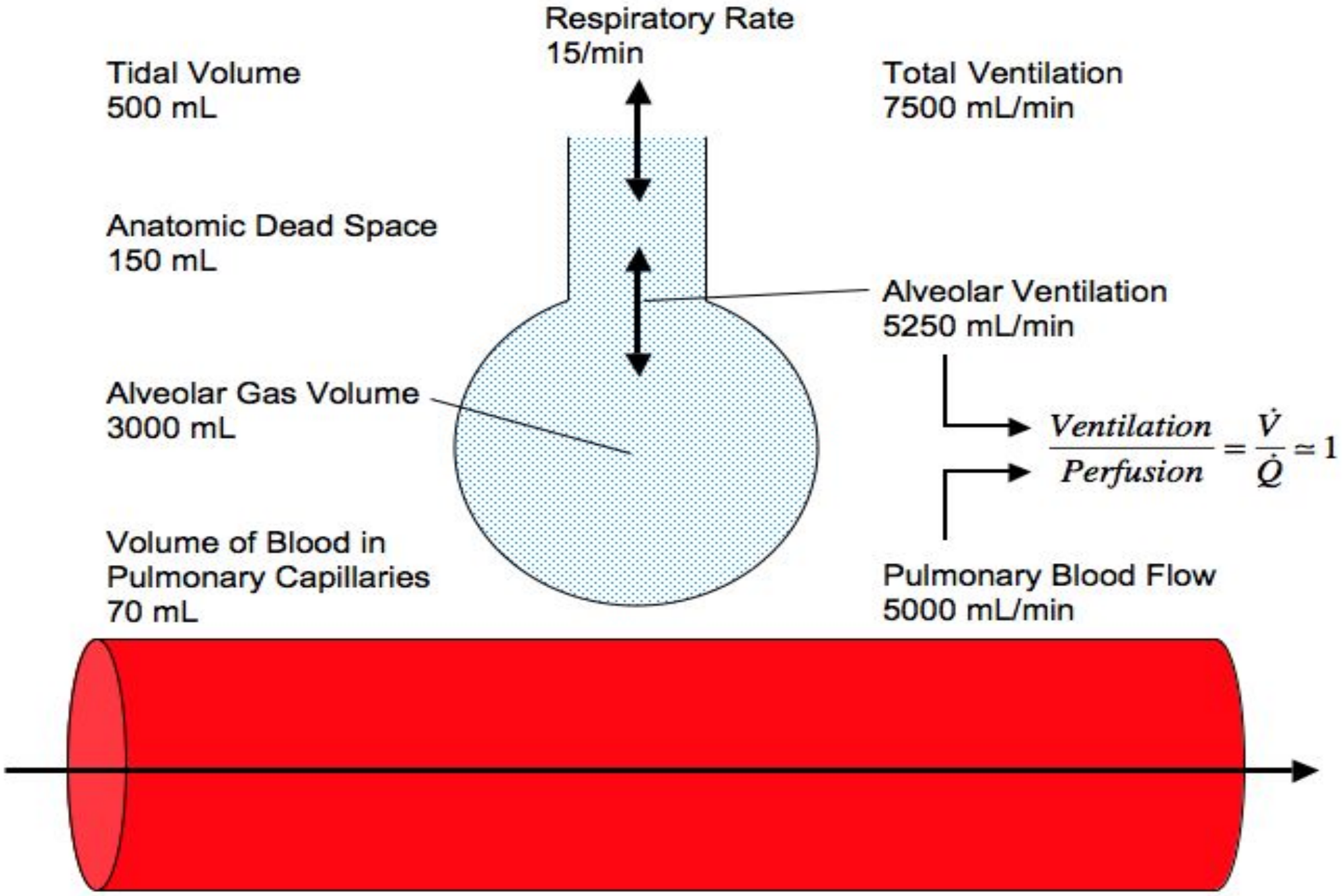
- What should the PAO2 be, in room air at sea level?

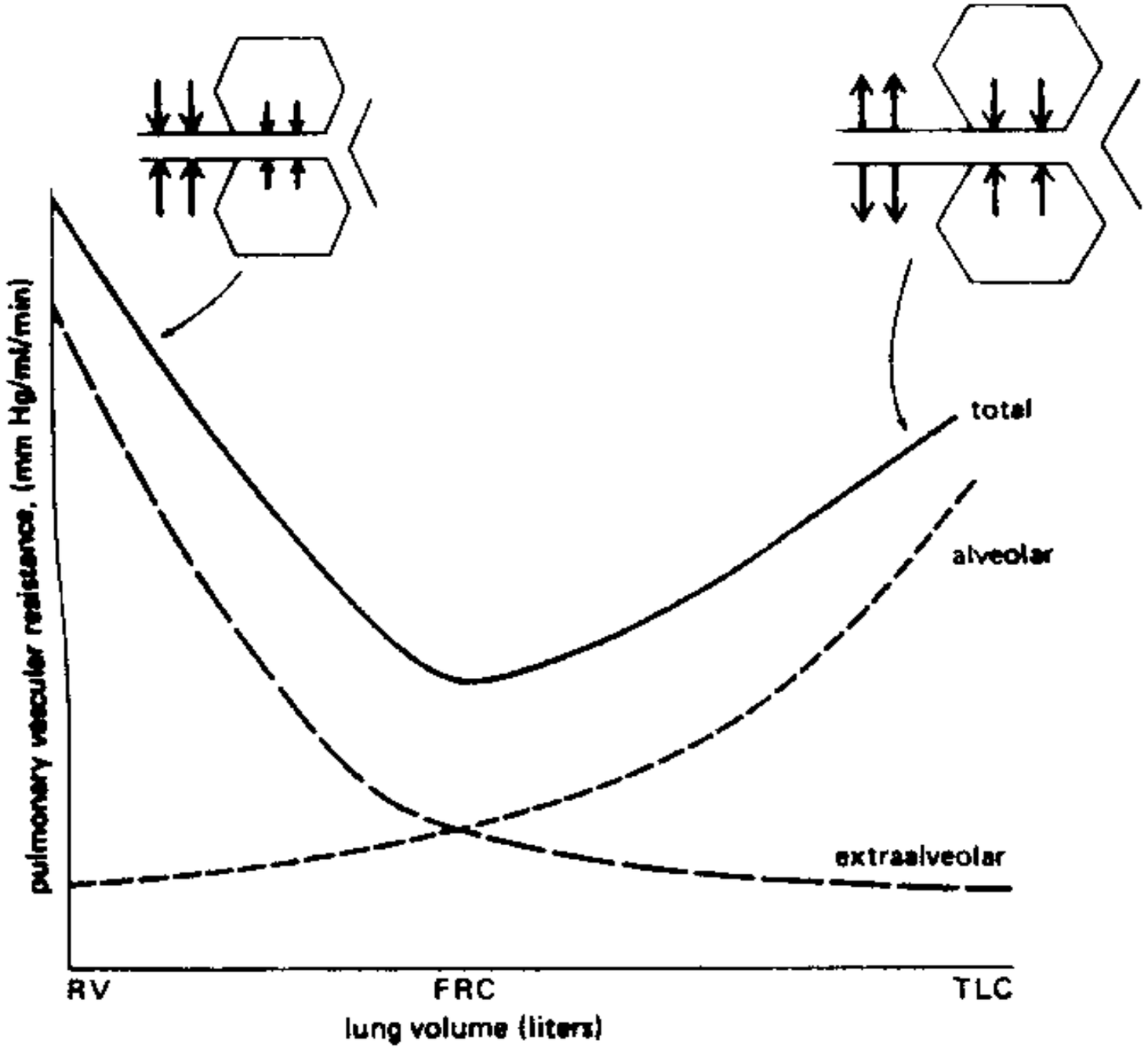
  (FiO2 x (760 - 47)) - (PaCO2 / 0.8)

  0.21 x 713 - 85 / 0.8 = 44

- A-a difference? *Negligible!*

- This low PaO2 is due to a sudden increase in PaCO2, crowding out the oxygen (ie. hypercapneic hypoxemia)

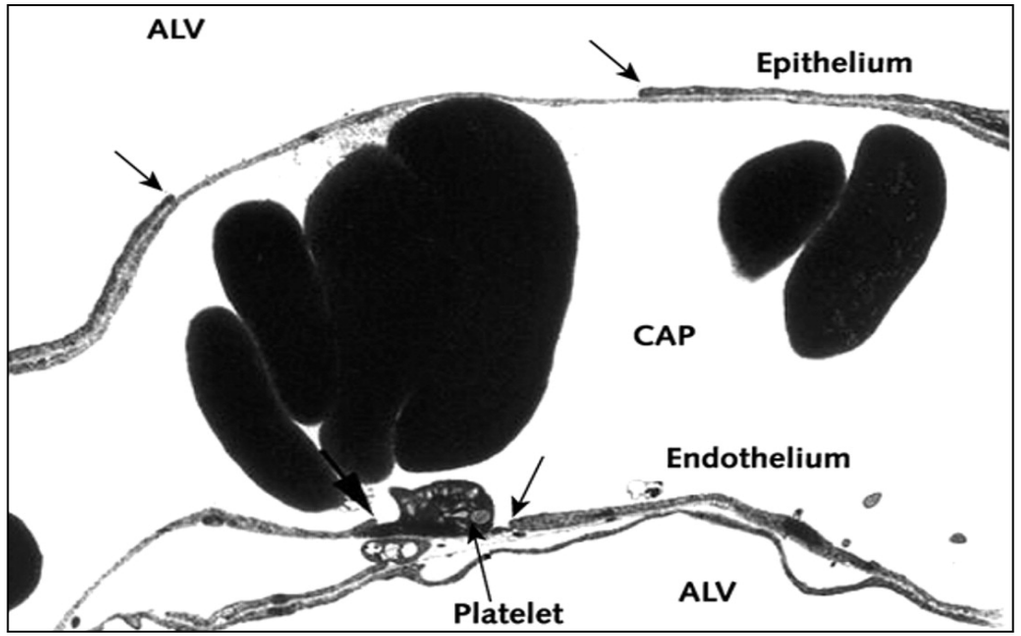

Respiratory Rate
15/min
Tidal Volume
500 mL
Total Ventilation
7500 mL/min
Anatomic Dead Space
150 mL
Alveolar Ventilation
5250 mL/min
Alveolar Gas Volume
3000 mL
$\frac{Ventilation}{Perfusion} = \frac{\dot{V}}{\dot{Q}} \simeq 1$
Volume of Blood in
Pulmonary Capillaries
70 mL
Pulmonary Blood Flow
5000 mL/min

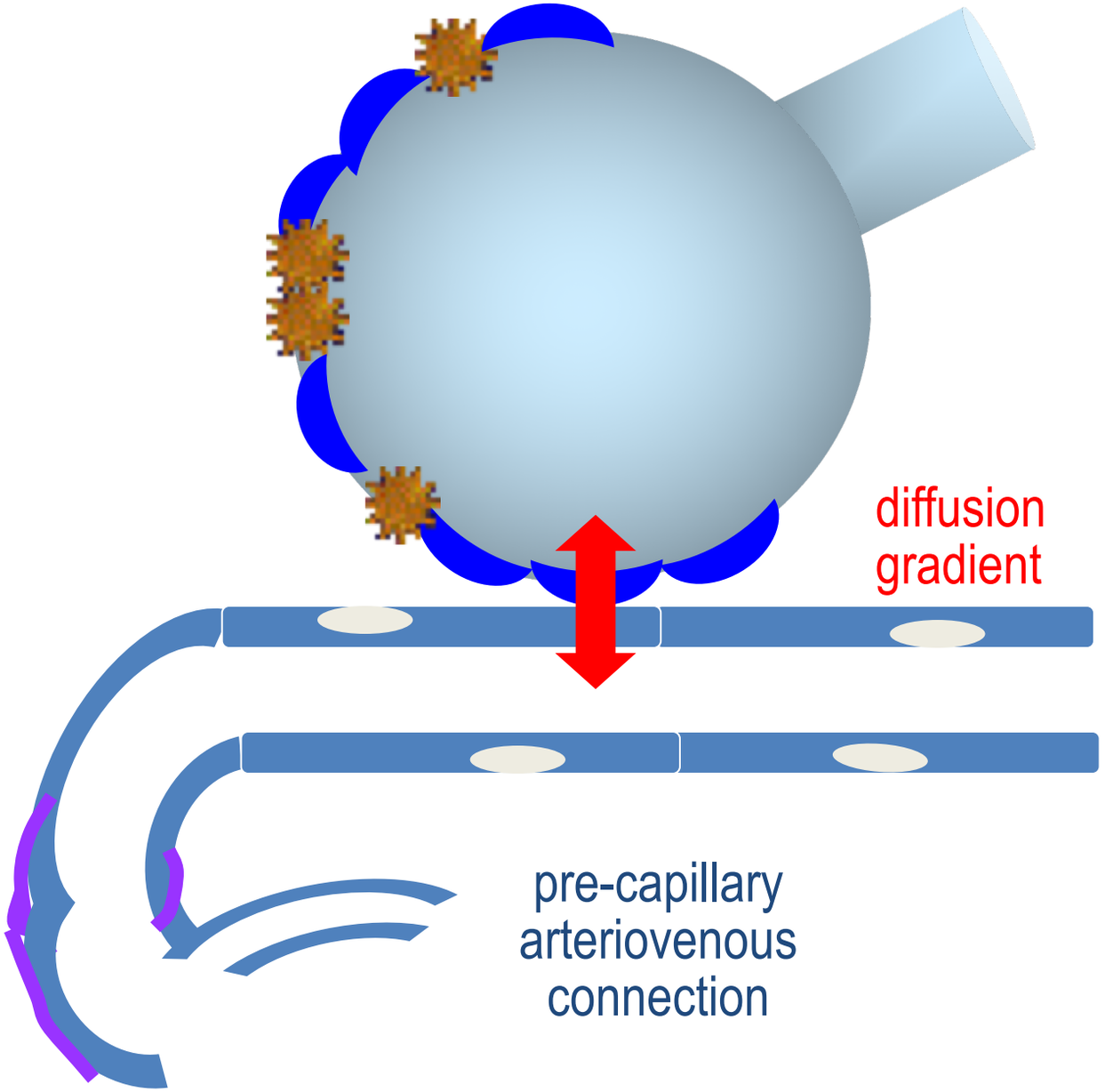


Effects of Lung Volume on Resistance to Pulmonary Flow

Pulmonary vascular resistance is lowest near the FRC, increases at both high and low lung volumes

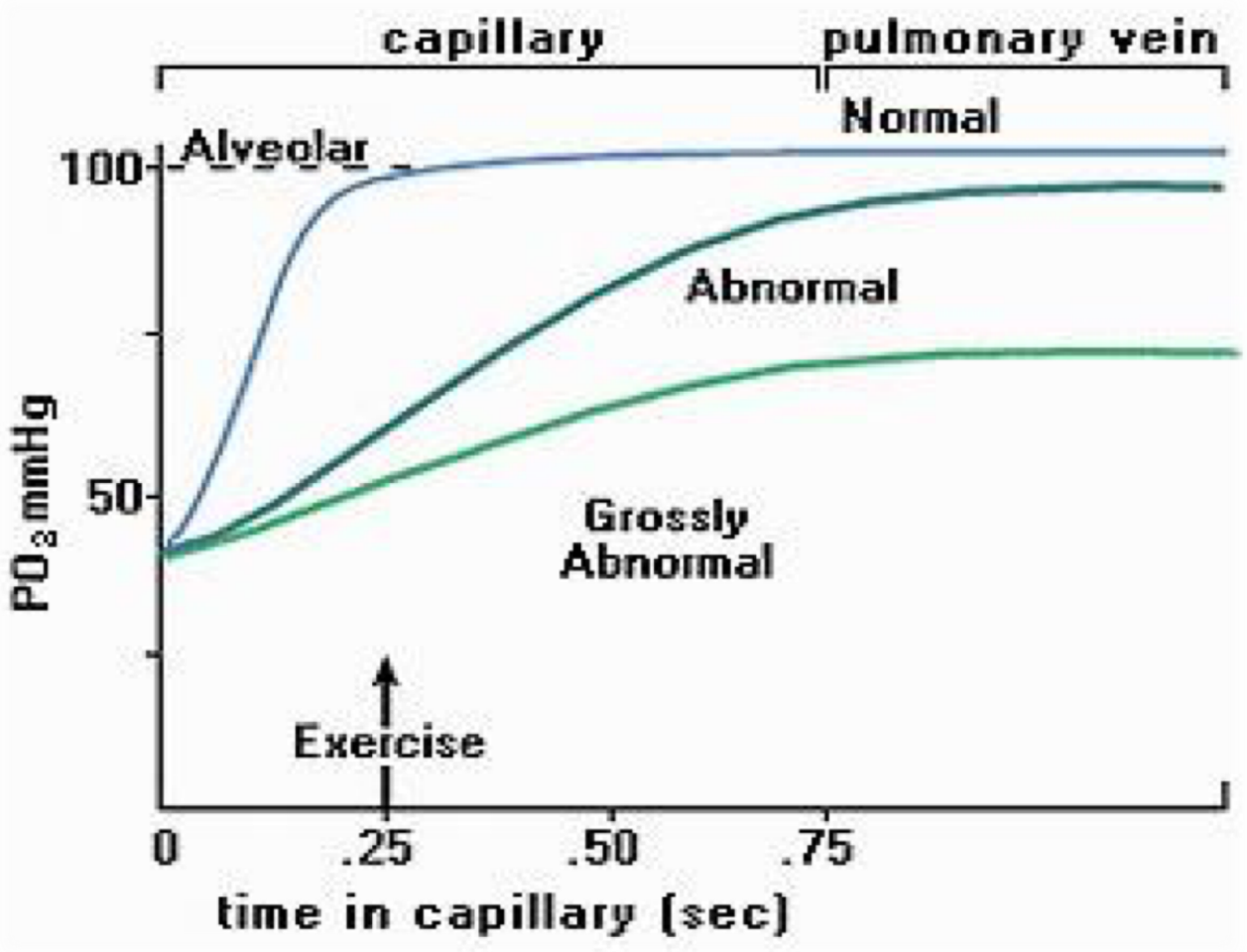
Alveolar Capillary Interface





A diffusion gradient *is* a Bad Thing

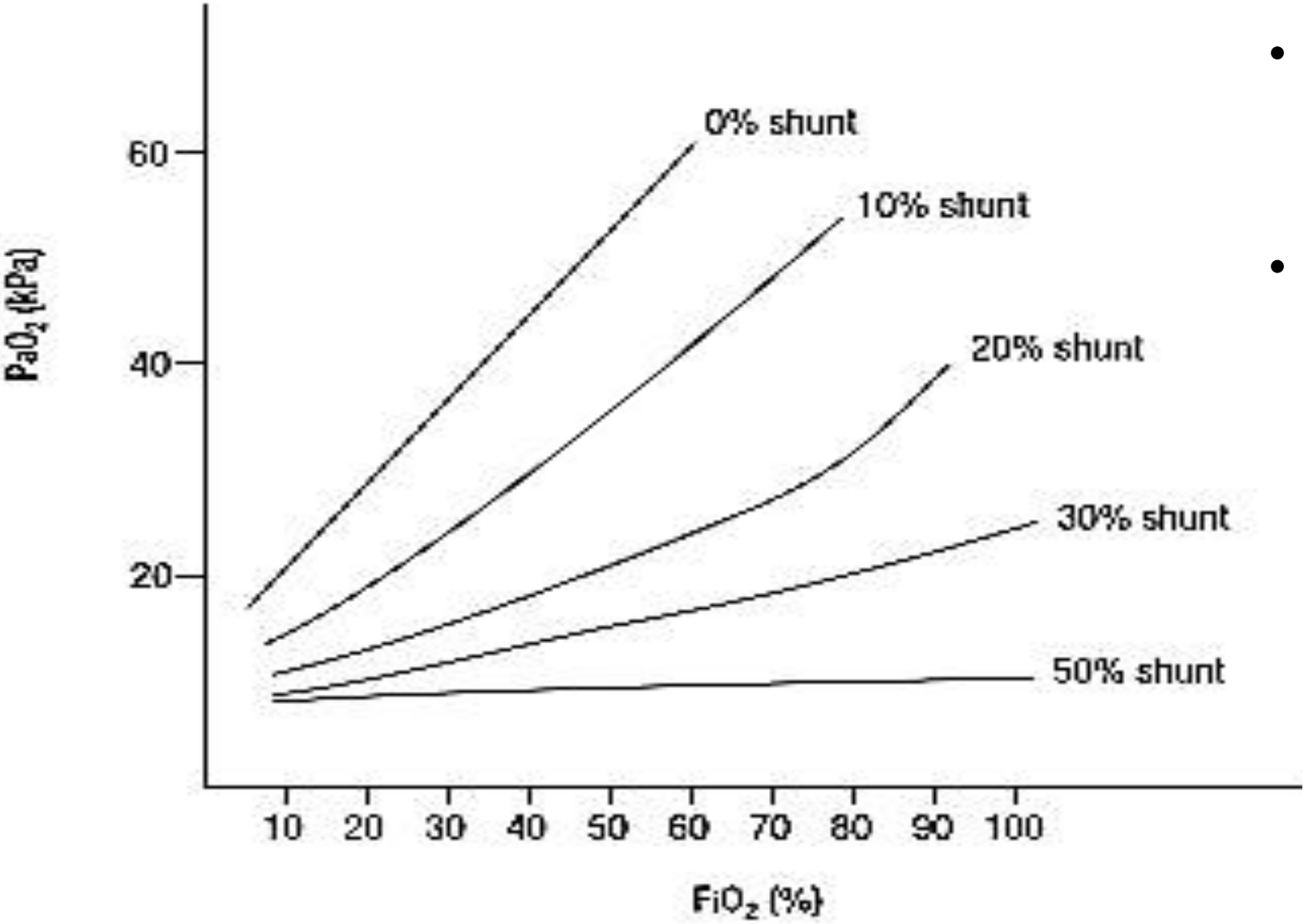
- Adult lung gas exchange surface area ~ 70 m^2
- Alveolar capillary diffusion distance = 0.4 µm



Blood transiting the lung has to equilibrate at the gas exchange surface, within the time it takes to pass through the lung

Transit time ~ 1 sec (as fast as 0.5 sec if cardiac output is increased)

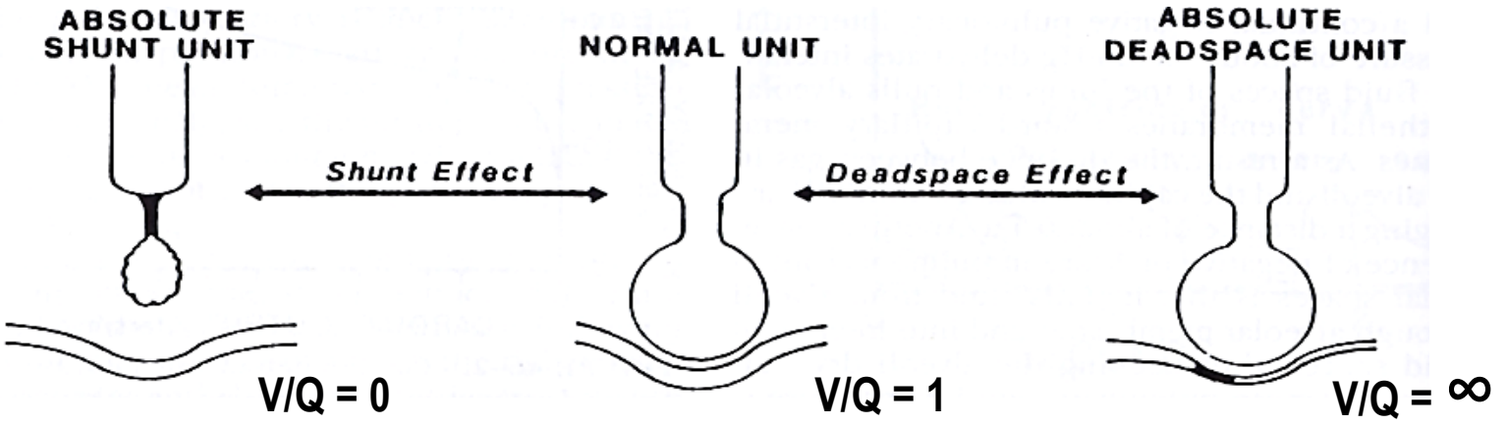
V : Q Mismatch



Shunt physiology:

- Where there's a shunt, for a given drop in sat, the arterial PO_2 falls *more than predicted*
- When PAO_2 is high (eg a trial of 100% O_2), the PaO_2 just doesn't go up as much as it should; and a *small decrease* in alveolar oxygen causes a *large decrease* in arterial PaO_2

V : Q Mismatch

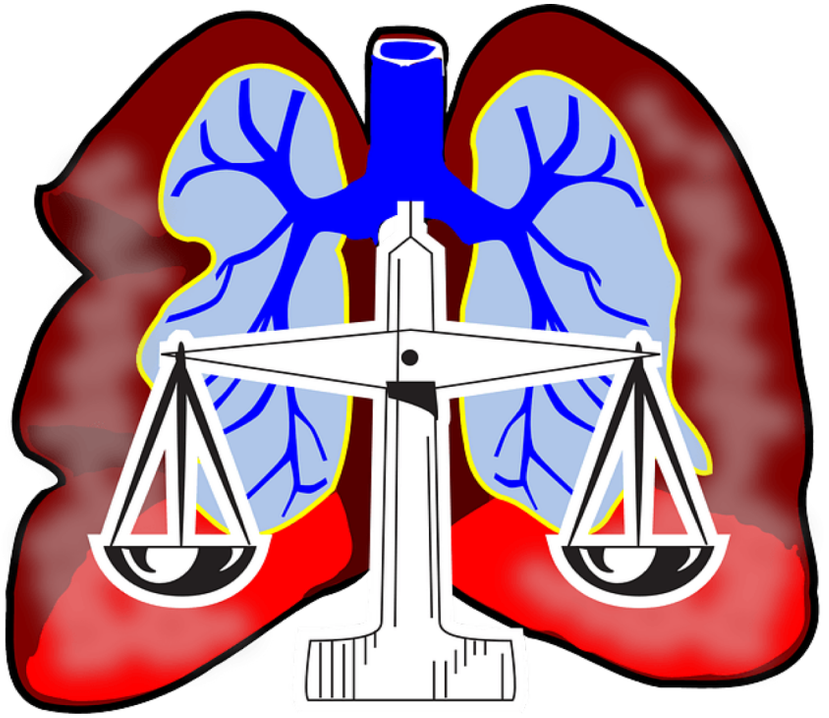


- **How?**

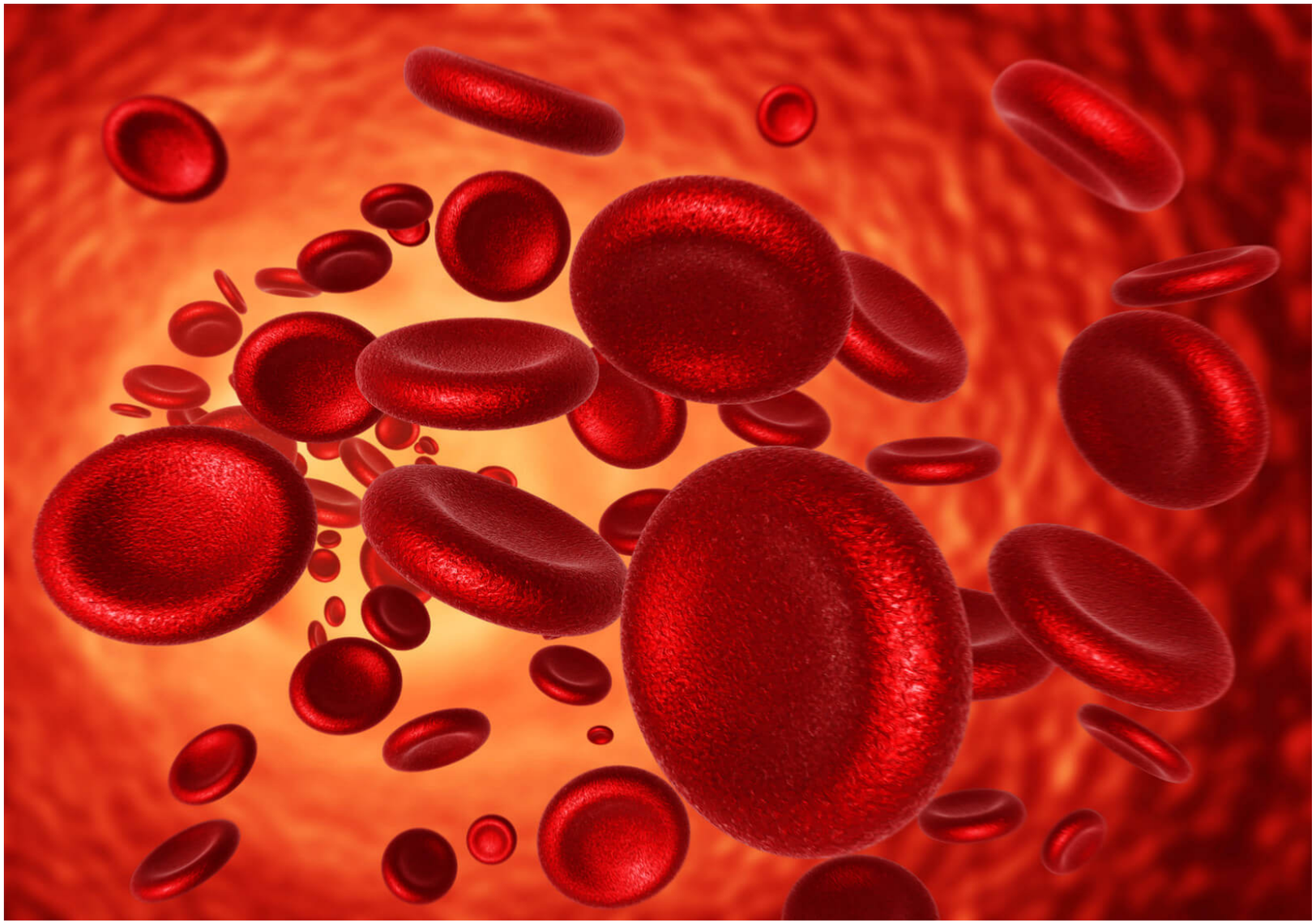
- In presence of V:Q scatter, well aerated alveoli with a **high** V/Q ratio are on a flatter part of the hemoglobin dissociation curve than collapsed alveoli with a **low** V/Q
- More blood goes through areas of low V:Q
- The *increase in O2 content* associated with an increase in PaO2 is smaller than the *decrease in O2 content* associated with a decrease in PaO2 of the same magnitude, because the hgb dissociation curve is steeper in low V:Q areas – which get more blood flow
- Thus, the beneficial effect of high V/Q on oxygen content is not enough to compensate for the adverse effect of low V/Q on oxygen content
- In V/Q mismatch, PaO2 **drops** relative to FiO2, and is lower than the SaO2 predicts

Strategies to determine contribution of V/Q mismatch

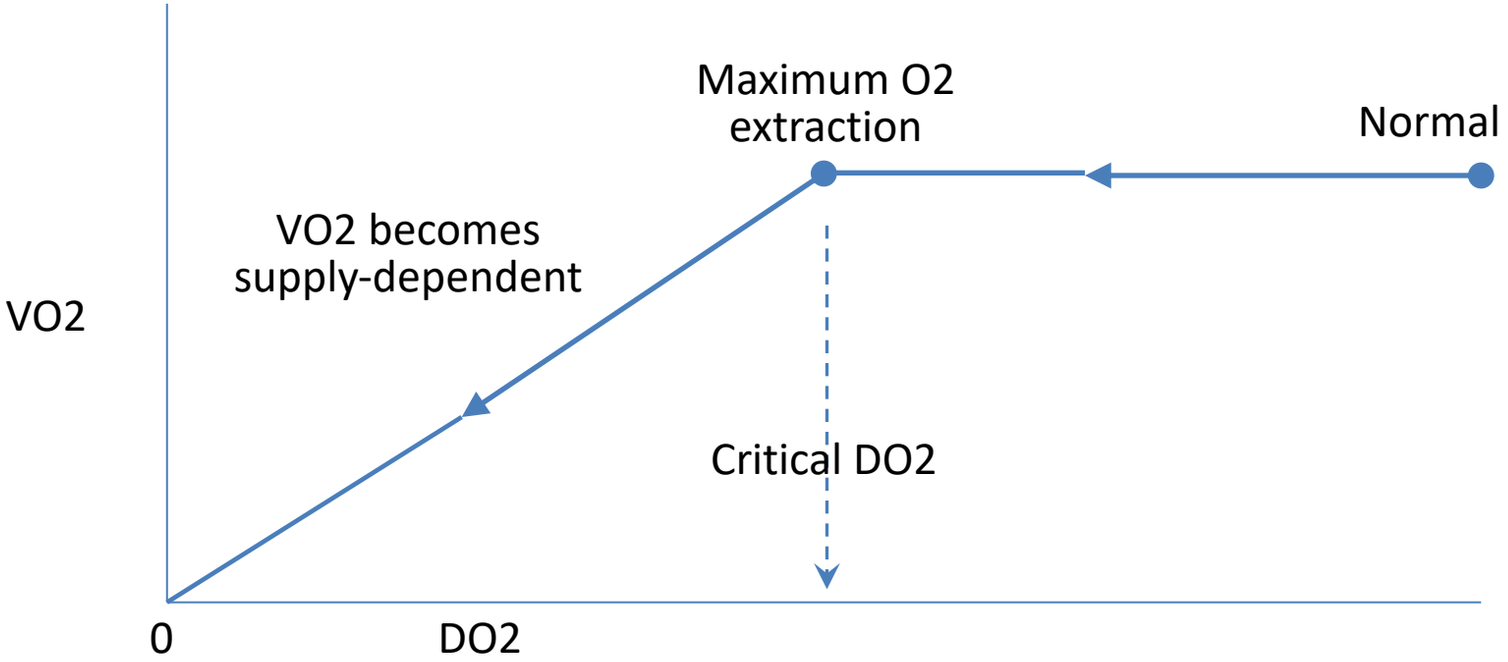
- Increase the FiO2 – then map out PaO2 versus SaO2
- Try a position change – if PaO2 increases when V:Q is transiently rearranged, then V:Q mismatch is a major element of the pathophysiology
- Recruitment maneuver
- Trial of increased PEEP – with caution (you can compress pulmonary arteries and *worsen* V:Q)



Anemic Hypoxia



Metabolic Rate: VO2 = DO2 x [SaO2 – SvO2]



- Under normal circumstances, DO2 is ***4 x*** the VO2
- When SaO2 is near 100%, this relationship leads to a SvO2 of approx 75%, and overall oxygen extraction of approx 25%
- Oxygen extraction increases as DO2 falls
- Below a critical point, VO2 depends upon oxygen delivery – a linear relationship of VO2 with DO2 is pathological

Relative effects of changes in PaO2, Hgb and cardiac output (Qt) on DO2

(Patient with hypoxemia, anemia, reduced cardiac output, and global tissue hypoxia)

	FIO_2	PaO_2 (kPa)	SaO_2 (%)	Hb (g/l)	Dissolved O_2 (ml/l)
Normal*	0.21	13.0	96	130	3.0
Patient†	0.21	6.0	75	70	1.4
↑FIO_2	0.35	9.0	92	70	2.1

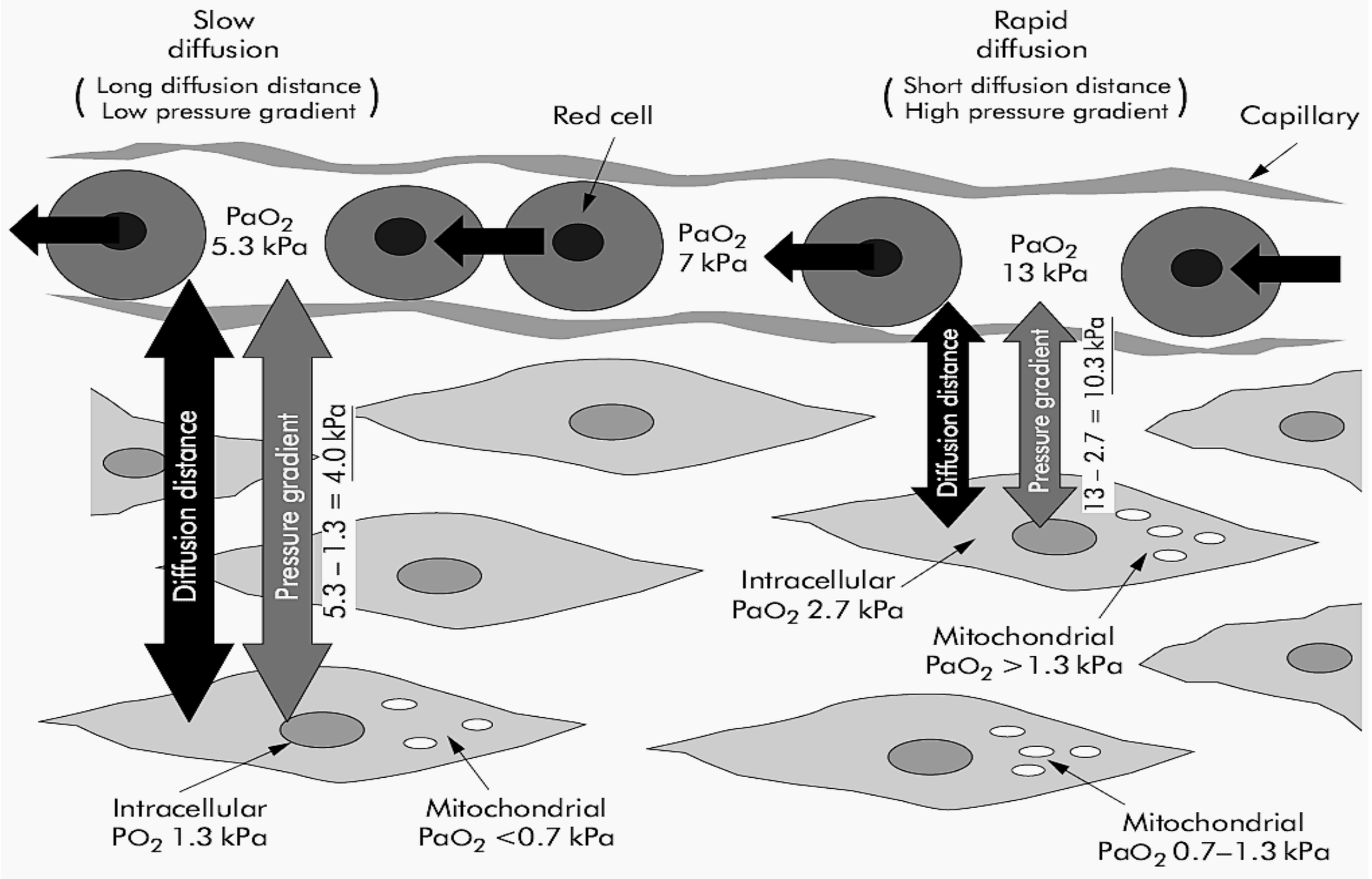
	CaO_2 (ml/l)	Qt (l/min)	DO_2 (ml/min)	DO_2 (% change)‡
Normal*	170	5.3	900	0
Patient†	72	4.0	288	– 68
↑FIO_2	88	4.0	352	+ 22

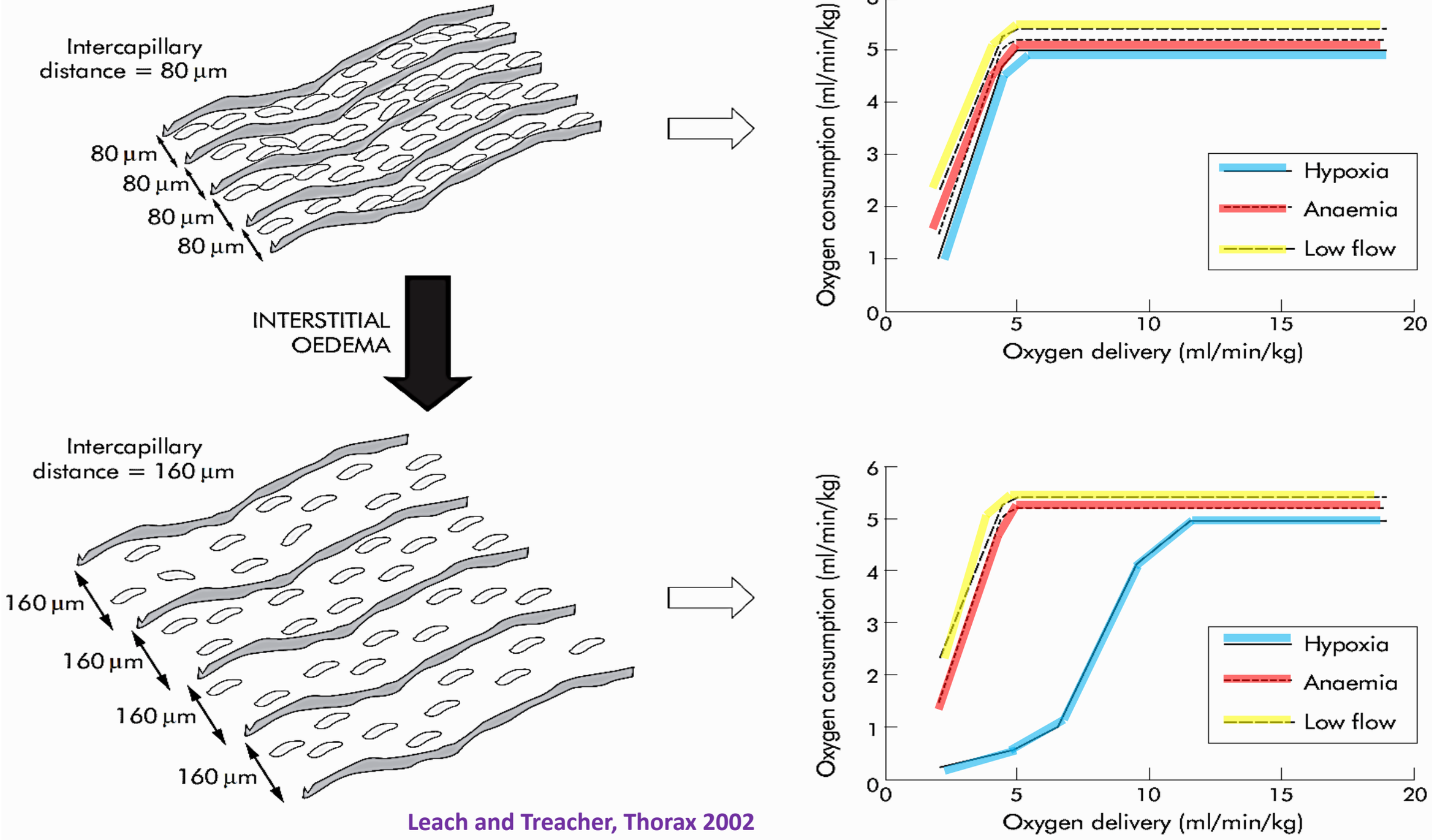
Leach and Treacher Thorax 2002

Strategies to optimize oxygen carrying capacity

- Transfuse!
- Optimize cardiac output
- Watch intravascular volume
- Polycythemia and sludging is also dangerous

Circulatory Hypoxia


Slow
diffusion
(Long diffusion distance
Low pressure gradient)
Rapid
diffusion
(Short diffusion distance
High pressure gradient)
Red cell
Capillary
PaO2
5.3 kPa
PaO2
7 kPa
PaO2
13 kPa
Diffusion distance
Pressure gradient
5.3 – 1.3 = 4.0 kPa
Diffusion distance
Pressure gradient
13 – 2.7 = 10.3 kPa
Intracellular
PaO2 2.7 kPa
Mitochondrial
PaO2 > 1.3 kPa
Intracellular
PO2 1.3 kPa
Mitochondrial
PaO2 <0.7 kPa
Mitochondrial
PaO2 0.7–1.3 kPa

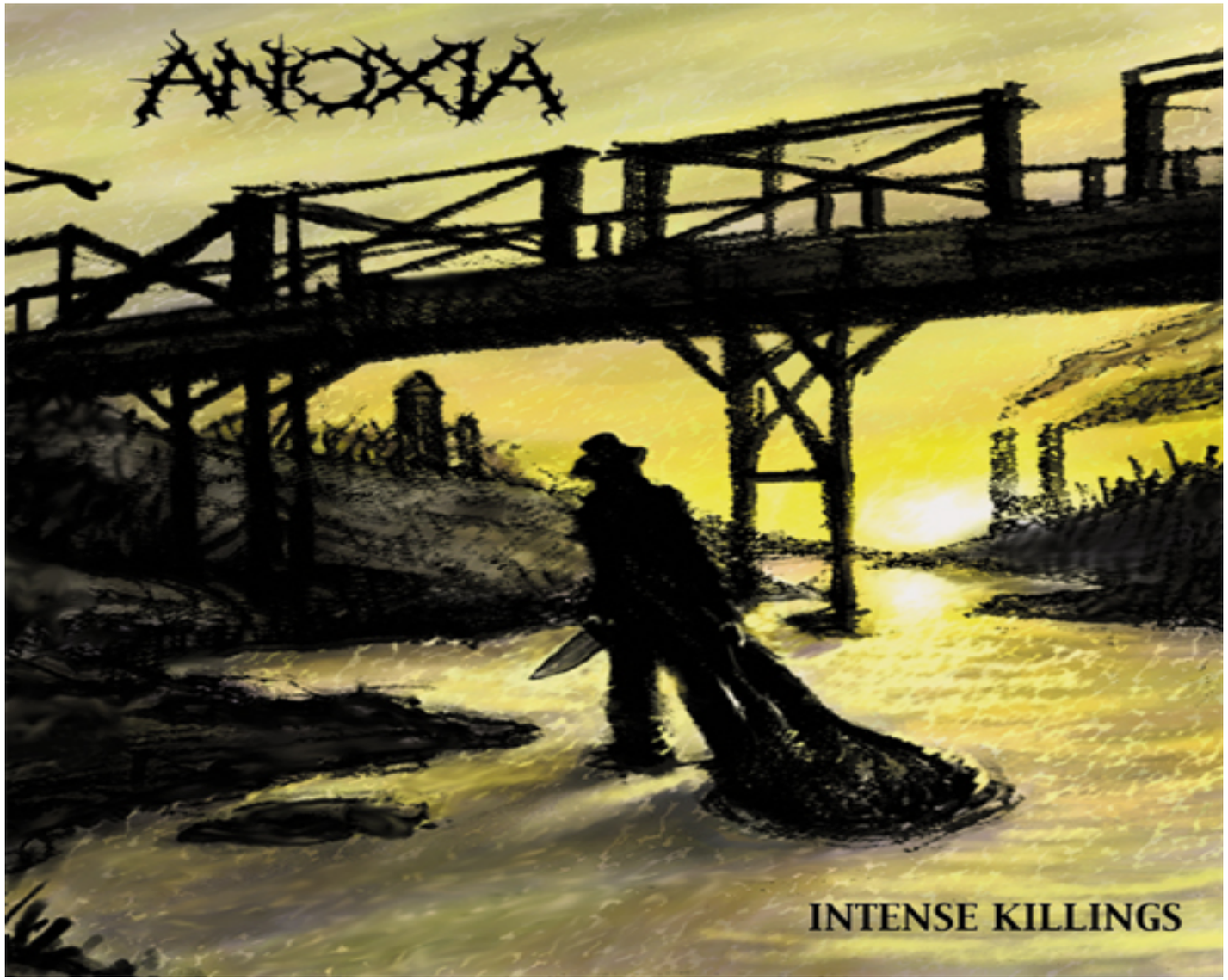


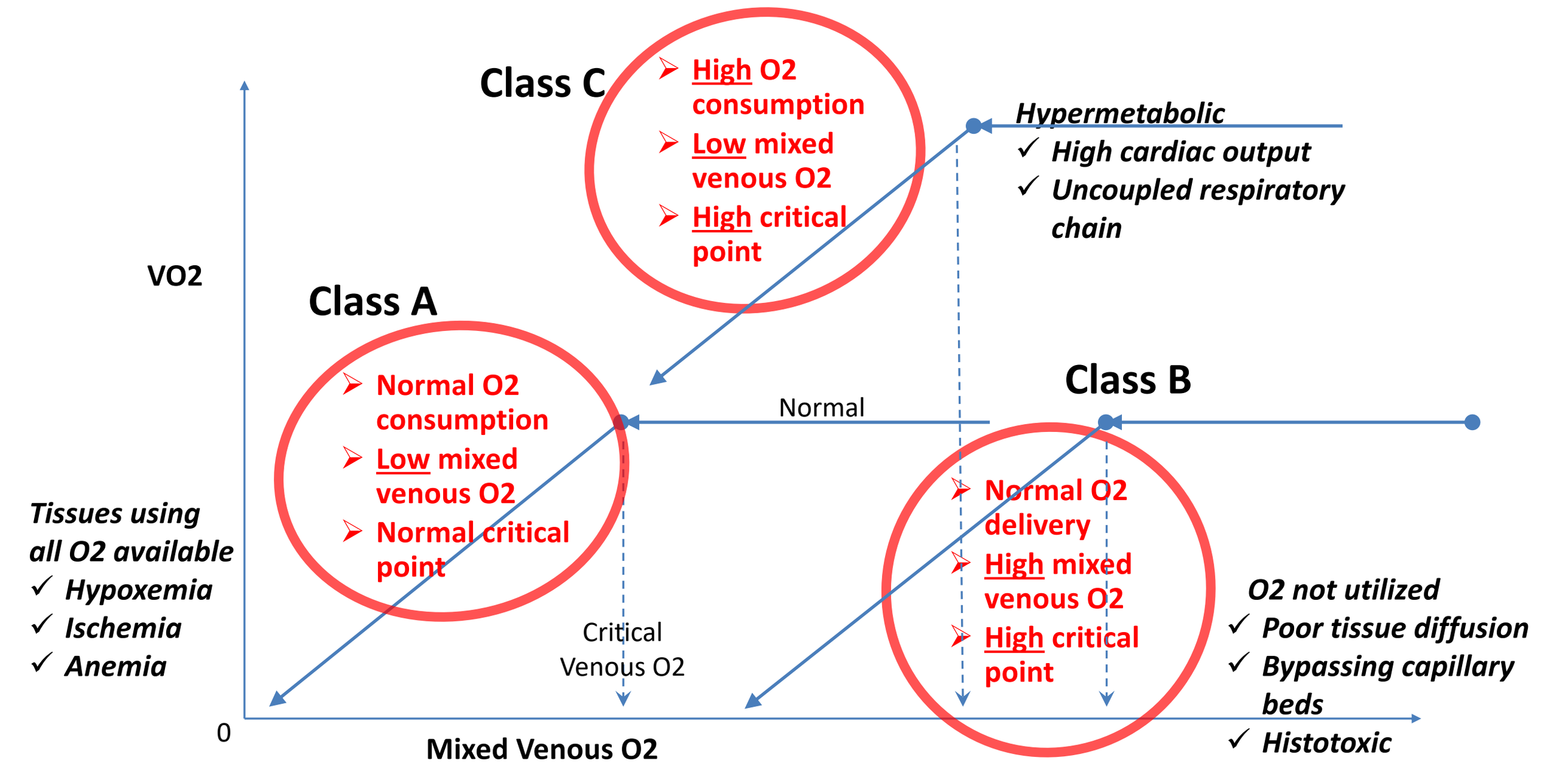
Leach and Treacher, Thorax 2002

Strategies to recognize tissue diffusion gradient

- Diffusion gradients in tissue are at least as important as pulmonary gradients
- In a hypoxemic state (but not in anemia or low flow states), the PO2 gradient driving diffusion is gravely impaired
- Tissue edema impairs O2 diffusion – impaired diffusion means less capillary oxygen is utilized – so higher residual O2 in venous blood
- Measured tissue O2 saturation (by NIRS) may be increased; VO2 will be lower, and A-V O2 difference will be lower
- Check perfusion index – it decreases in tissue edema

Metabolic (Histotoxic) Hypoxia





Siggaard-Andersen, Acta Anaesth Scand 1995

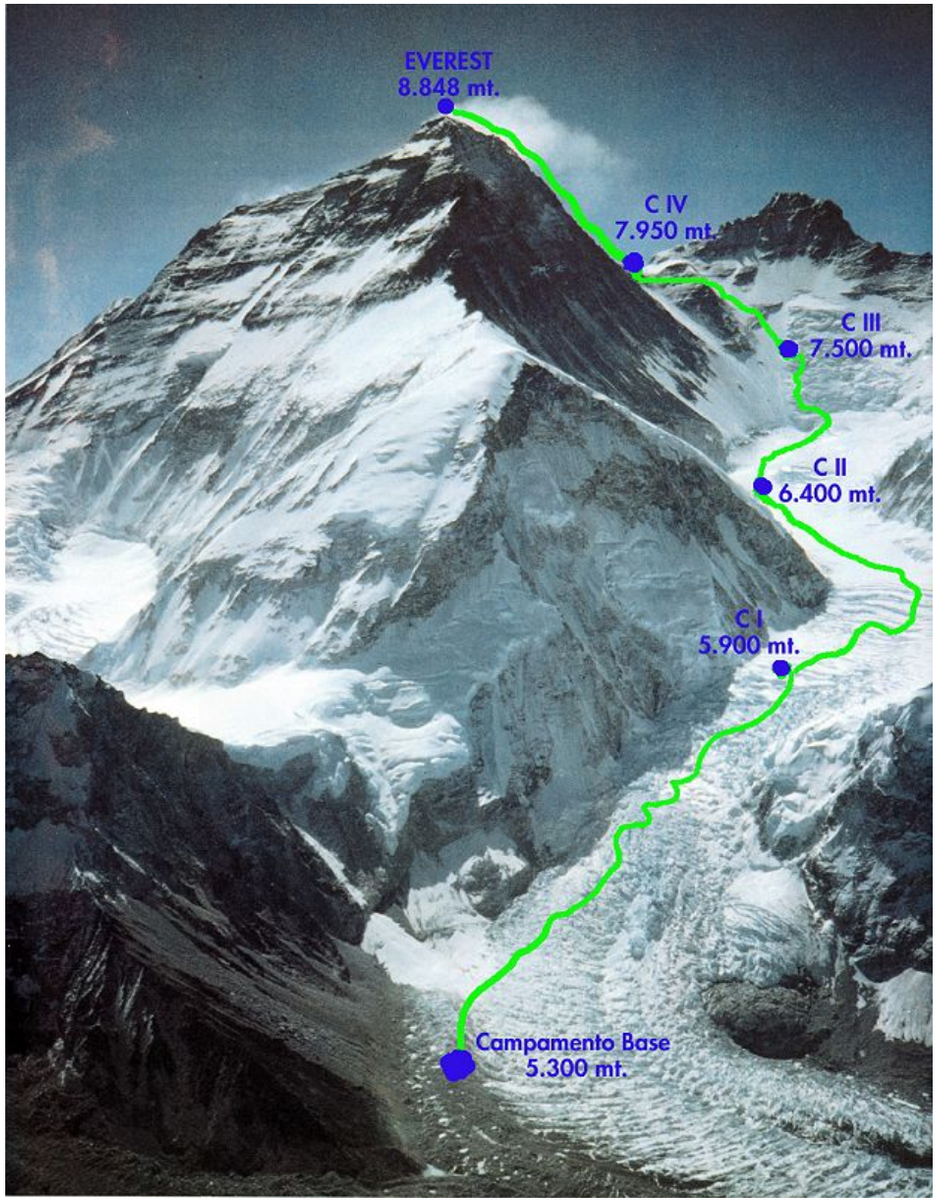
Strategies to determine tissue metabolic activity

- Measure a mixed venous O2; measure serum lactate; and estimate tissue oxygen utilization using NIRS
- Is oxygen consumption low or high?
- Can you increase venous O2 by increasing oxygen delivery?
  - If it makes no difference, likely class A or C (all additional oxygen will be consumed by avid tissue)
  - If venous O2 also goes up, likely Class B

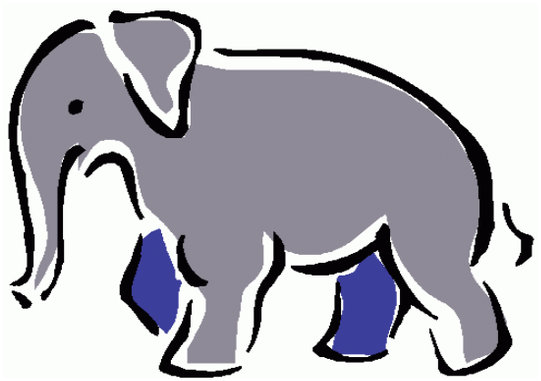
Fetal Oxygenation: The Everest in Utero

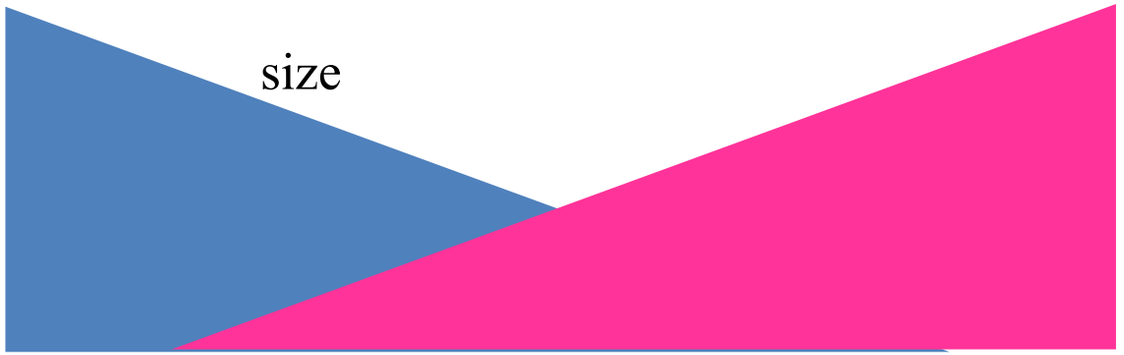
- Fetal oxygen tension:
  PaO_2 25-40 mmHg
  PvO_2 15 mmHg
  (corresponds to that encountered at 8000m)

So how is the fetus so well protected against hypoxia?



Deviation from Metabolic Rate Allometry





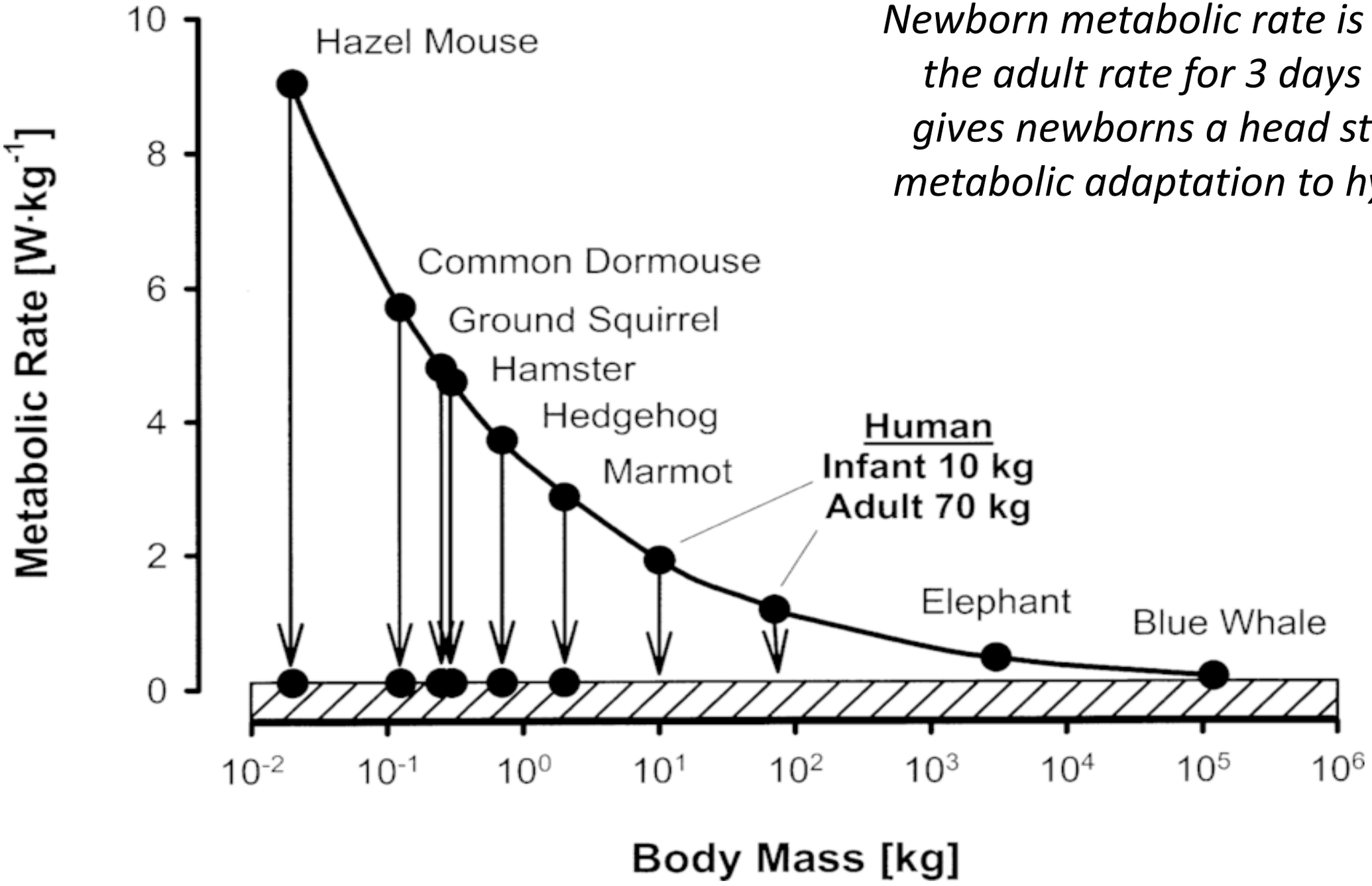
Escape from the metabolic size relationship: the fetus behaves like an organ of the mother, therefore has lower (maternal) metabolic rate

Immediately after birth, infant retains maternal metabolic rate – this is protective in cases of perinatal hypoxia (VO_2 determines tissue PO_2)

Metabolic rate increases to reflect actual size gradually over first three days of life

Singer D, Comp Biochem Physiol 2007

Newborn metabolic rate is low like the adult rate for 3 days – this gives newborns a head start on metabolic adaptation to hypoxia!



Pink is a happier colour…

Pink may avert a lot of problems…
but of course not all of them.

Questions?