The Physiologic Basis of DLCO testing

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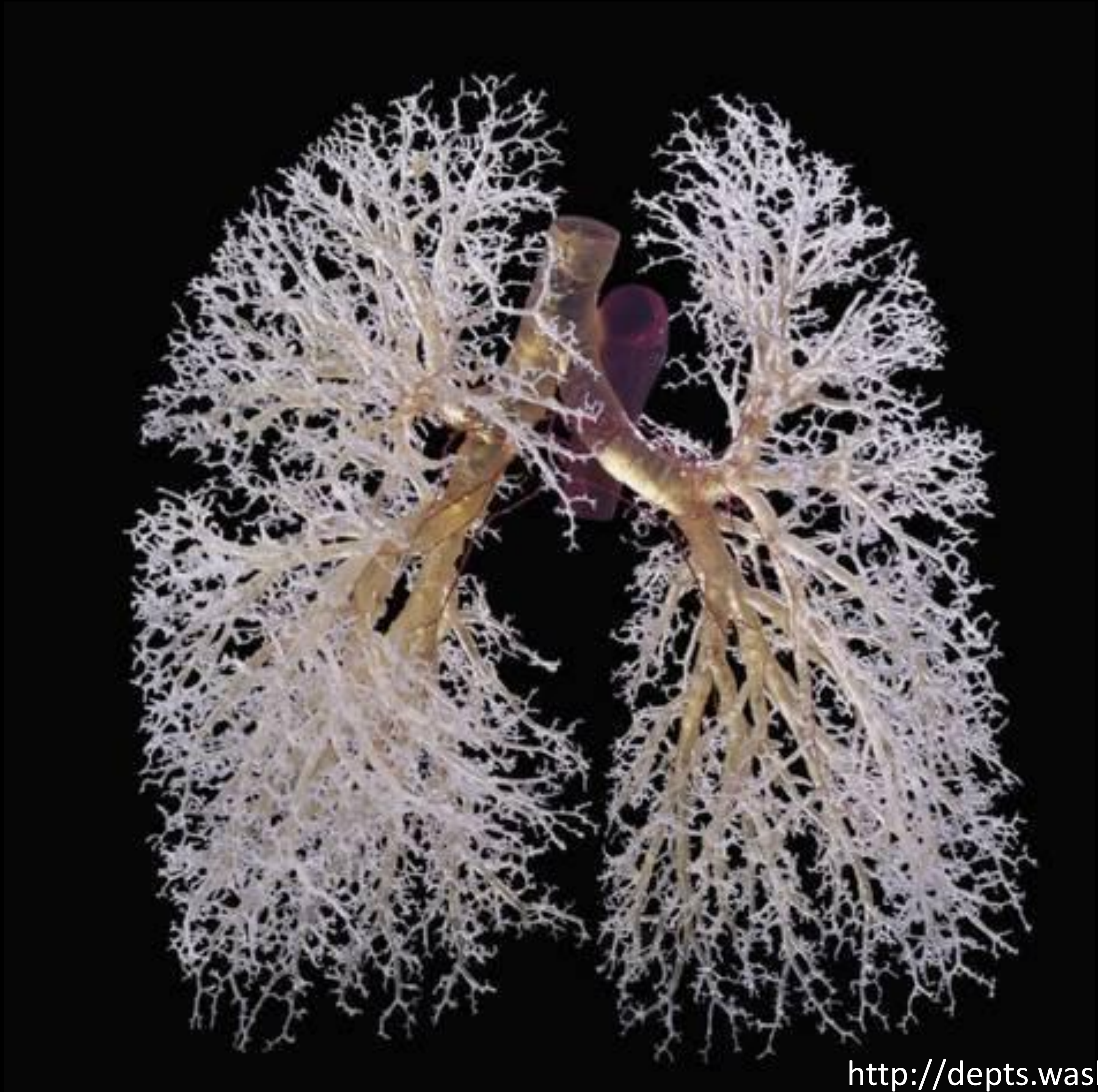
Objectives

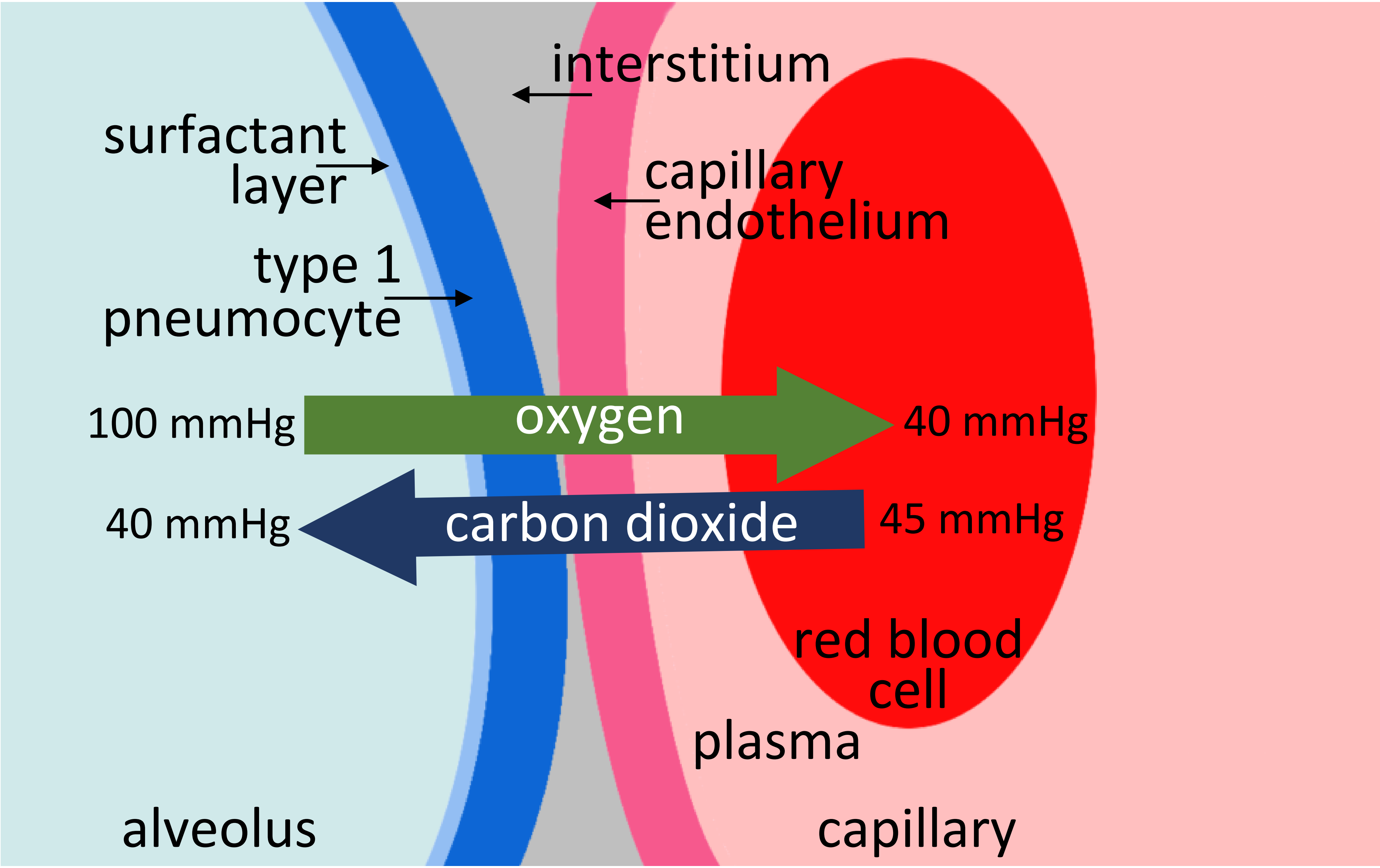
- Review gas transport from inhaled gas to the rest of the body body
- Review the methods of measuring gas exchange
- Review the principles of the DLCO test
- Review physiologic factors that affect DLCO

Gas exchange pathway

1. Transport from the mouth through the airways of the lung to the alveoli by convective and diffusive gas flow and mixing
2. Diffusion across the surfactant layer and the Type 1 pneumocytes which form the alveolar wall
3. Diffusion through the interstitium between the alveolar wall and the capillary wall
4. Diffusion across the pulmonary capillary endothelium
5. Diffusion through the plasma to the red blood cell
6. Diffusion across the red blood cell membrane
7. Diffusion through the red blood cell cytoplasm to the Hb molecule
8. Binding with a Hb molecule
9. Transport via the circulatory system to the rest of the body

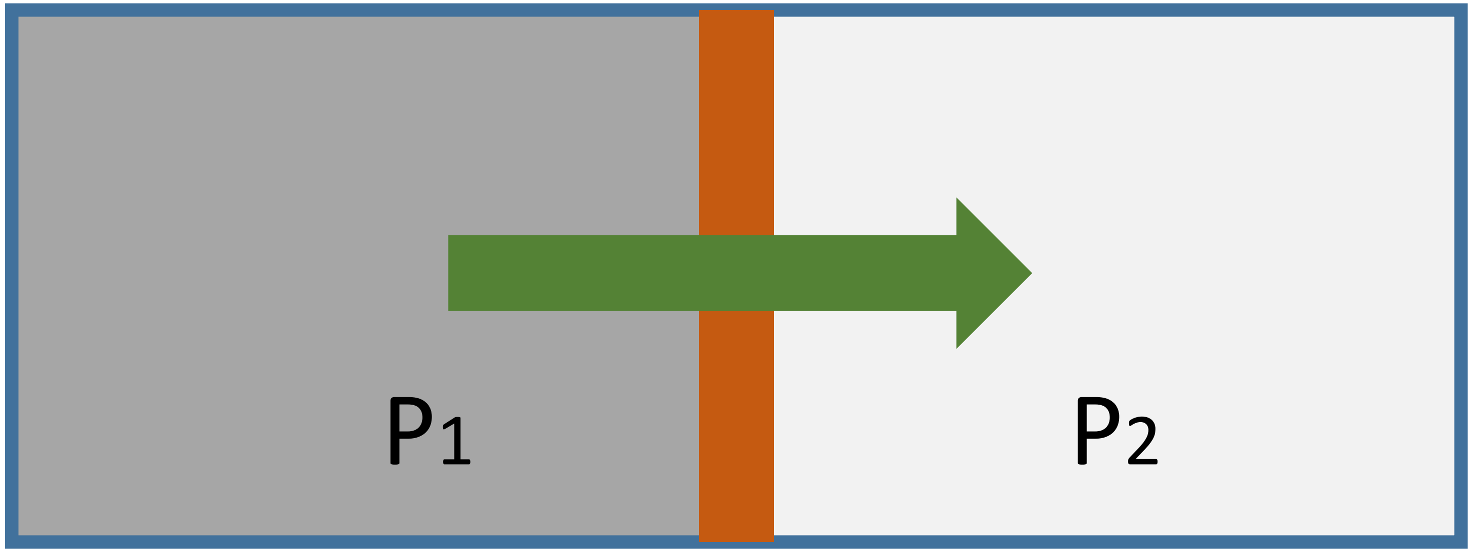


http://depts.washington.edu/envh/lung.html


interstitium
surfactant layer
type 1 pneumocyte
capillary endothelium
100 mmHg
oxygen
40 mmHg
40 mmHg
carbon dioxide
45 mmHg
red blood cell
plasma
alveolus
capillary

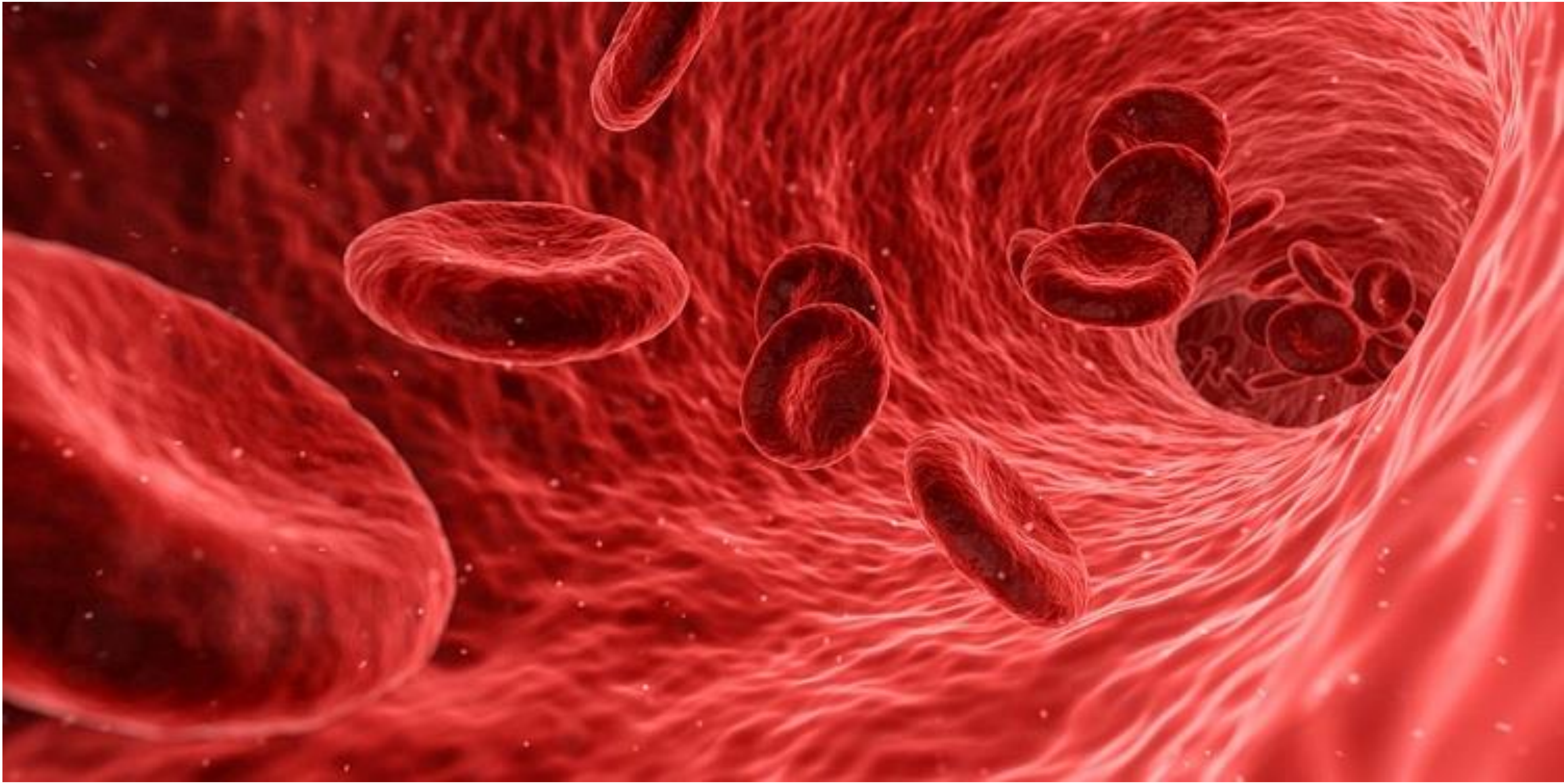
Fick's Law of Diffusion

diffusive gas flow α Area × Diffusivity × (P_1 – P_2) / Thickness

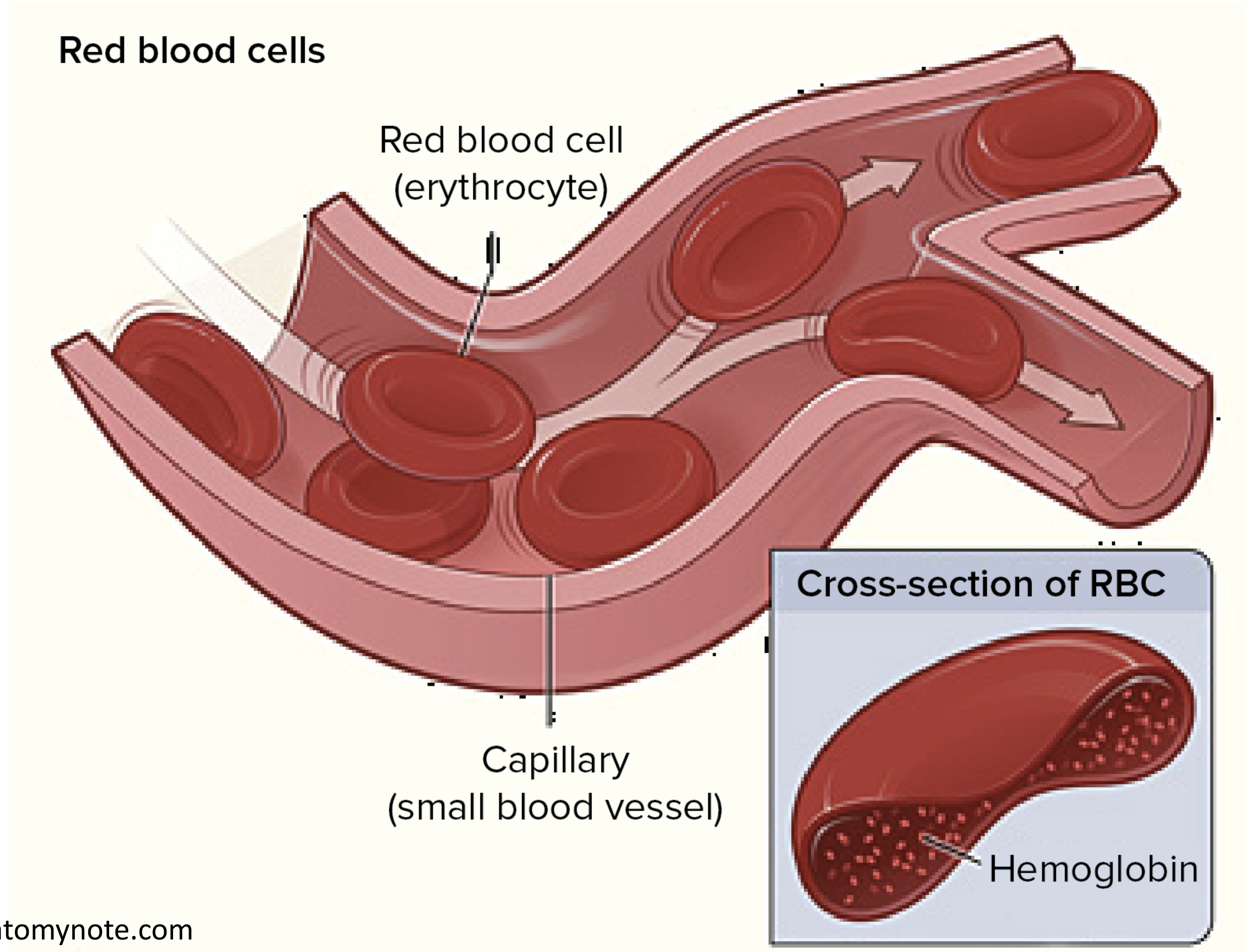


diffusivity
CO_2 ~ 20 × O_2

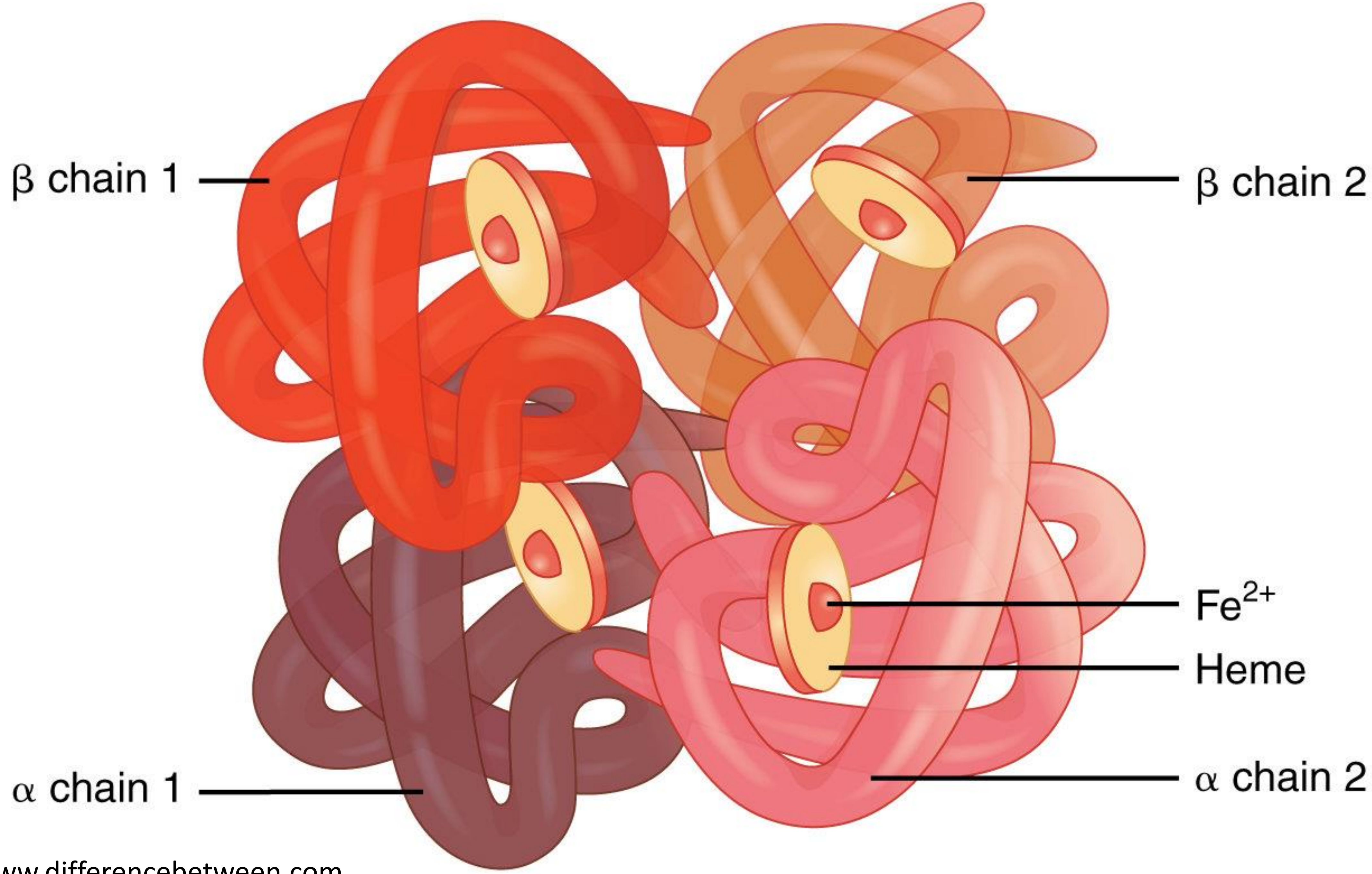
The diffusivity of a gas molecule is equal to its solubility divided by the square root of its molecular weight



https://www.easyways.net



https://www.anatomynote.com



β chain 1
β chain 2
Fe^{2+}
Heme
α chain 1
α chain 2

Hemoglobin transport

- 15 gm Hb in 100 mL of blood with a PO_2 of 100 mmHg carries 20 mL of oxygen in contrast to 0.3 mL of oxygen dissolved in 100 mL of plasma
- The hemoglobin molecule simultaneously carries O_2 and CO_2, but not at the same binding sites.
- the affinity of hemoglobin for CO_2 is greater when it is not combined with oxygen (Haldane effect)
- carbaminohemoglobin has a decreased affinity for O_2 (Bohr effect)

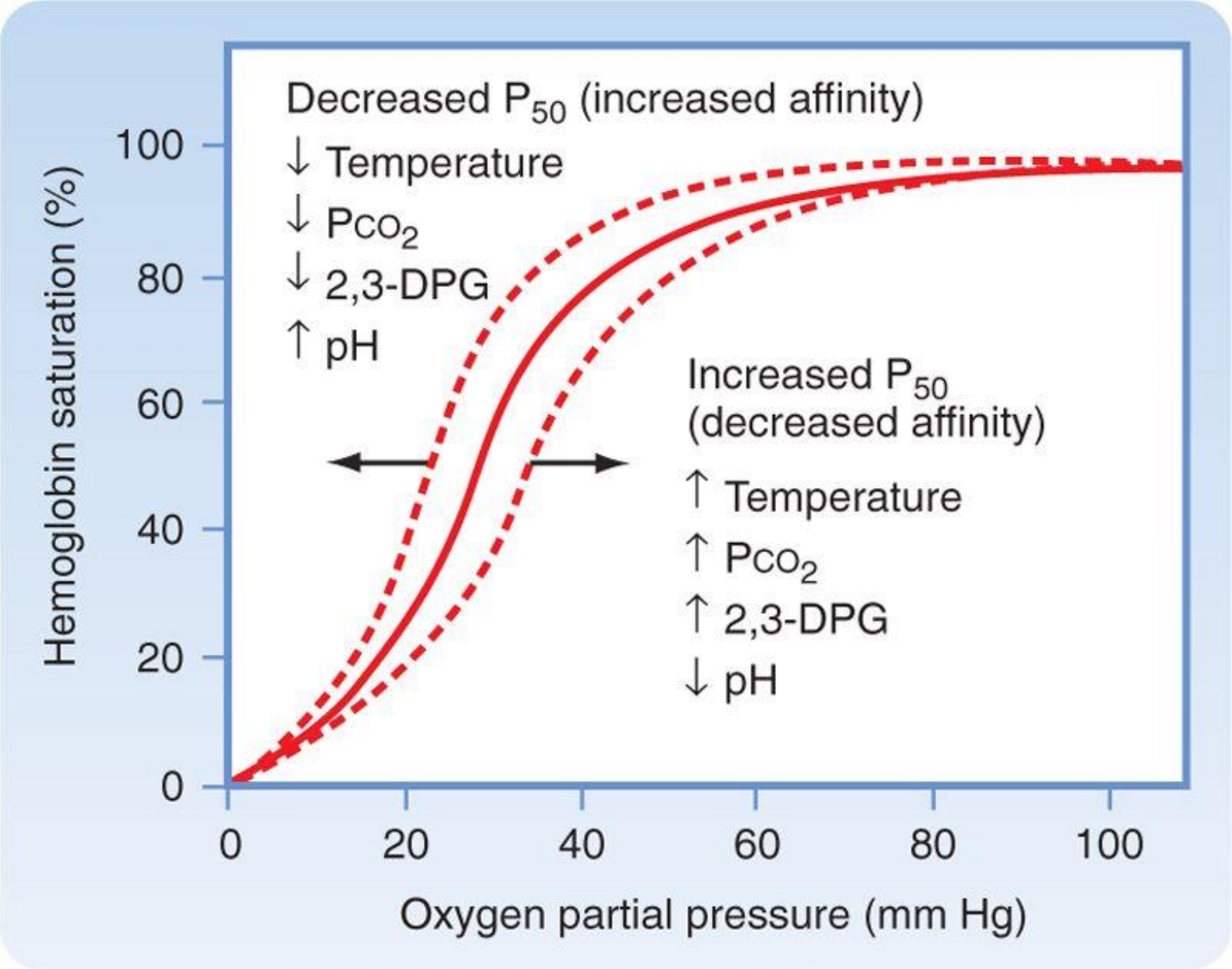
As oxygen molecules successively bind with heme groups, the hemoglobin molecule physically changes its shape, causing it to reflect and absorb light differently when it is oxygenated than when it is deoxygenated. This phenomenon is responsible for the bright red color of oxygenated hemoglobin and the deep purple color of deoxyhemoglobin

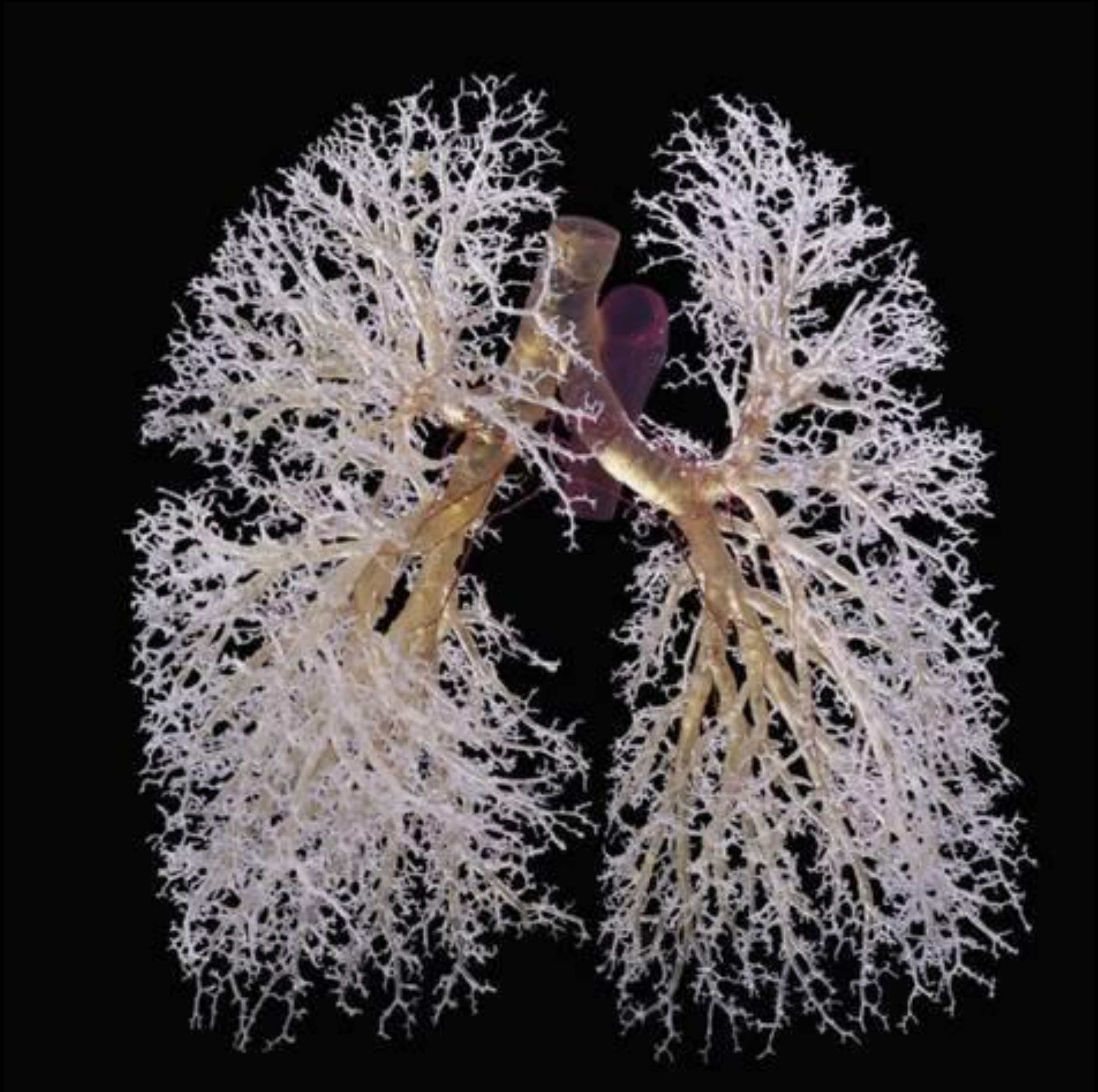
But carboxyhemoglobin is bright cherry red!

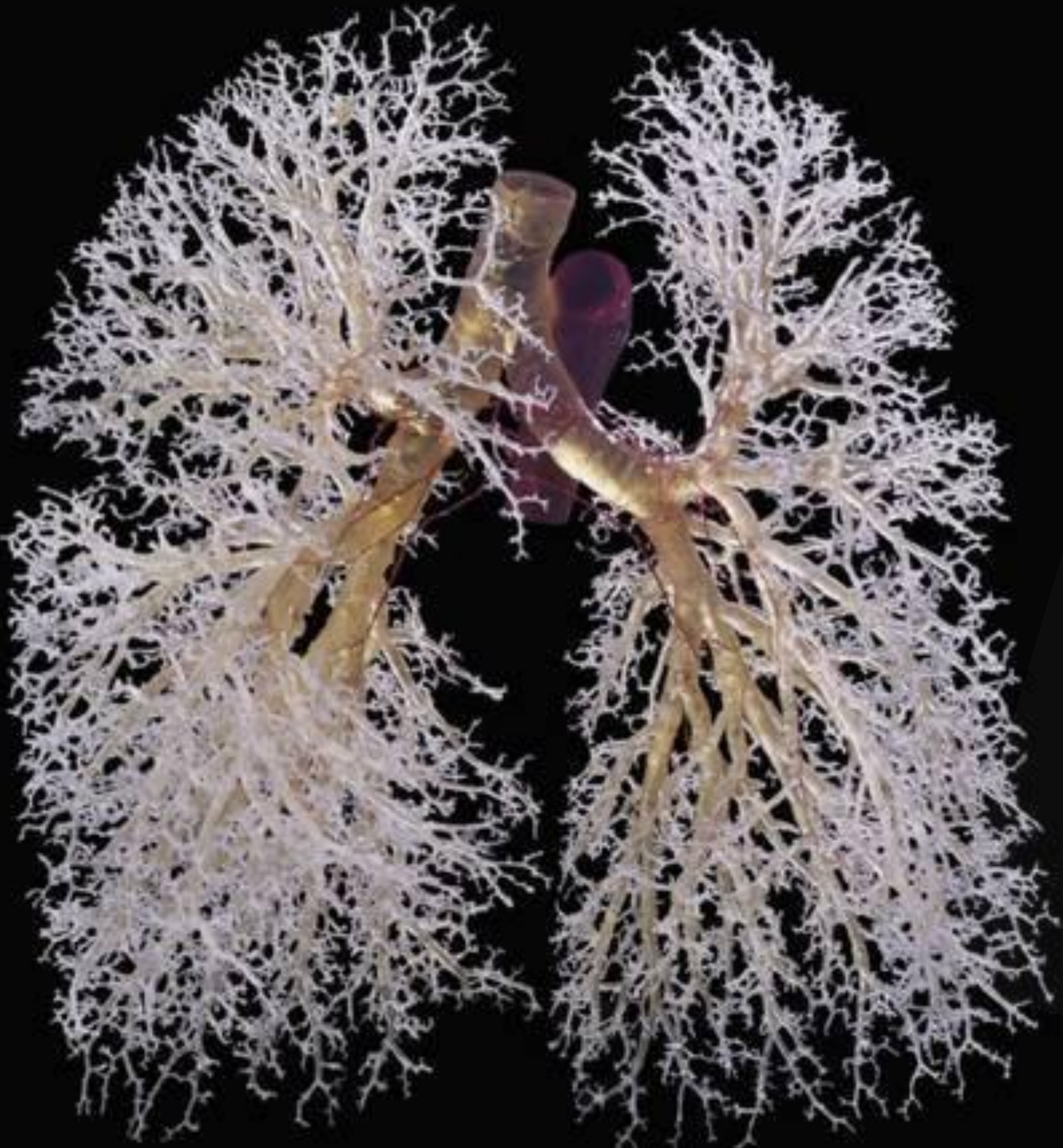
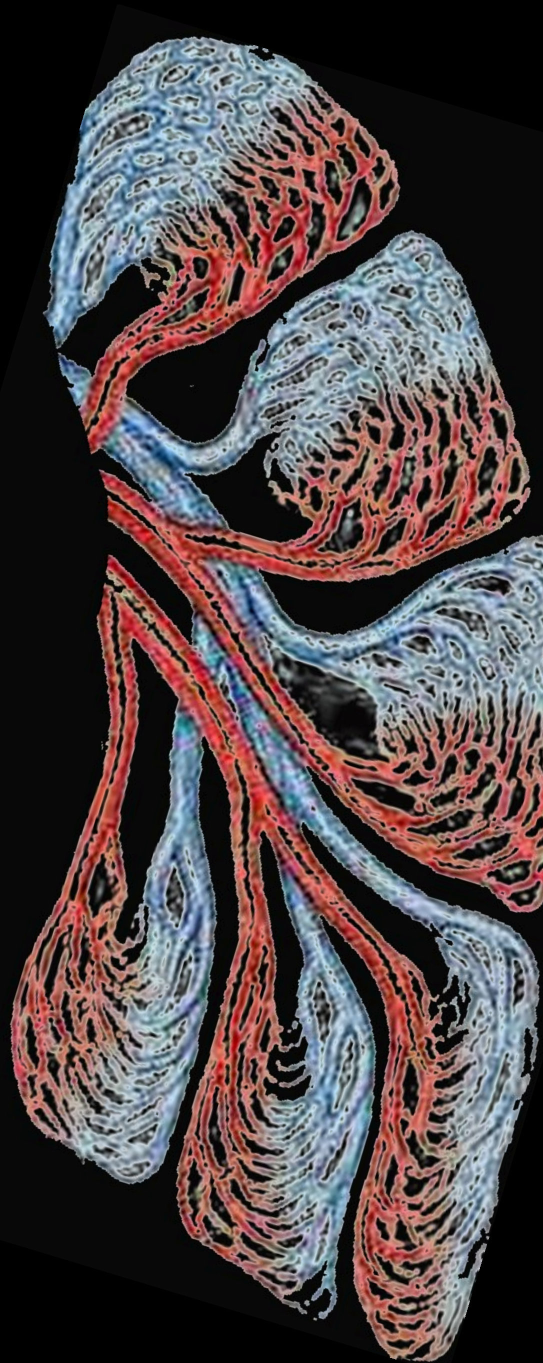
https://www.quora.com

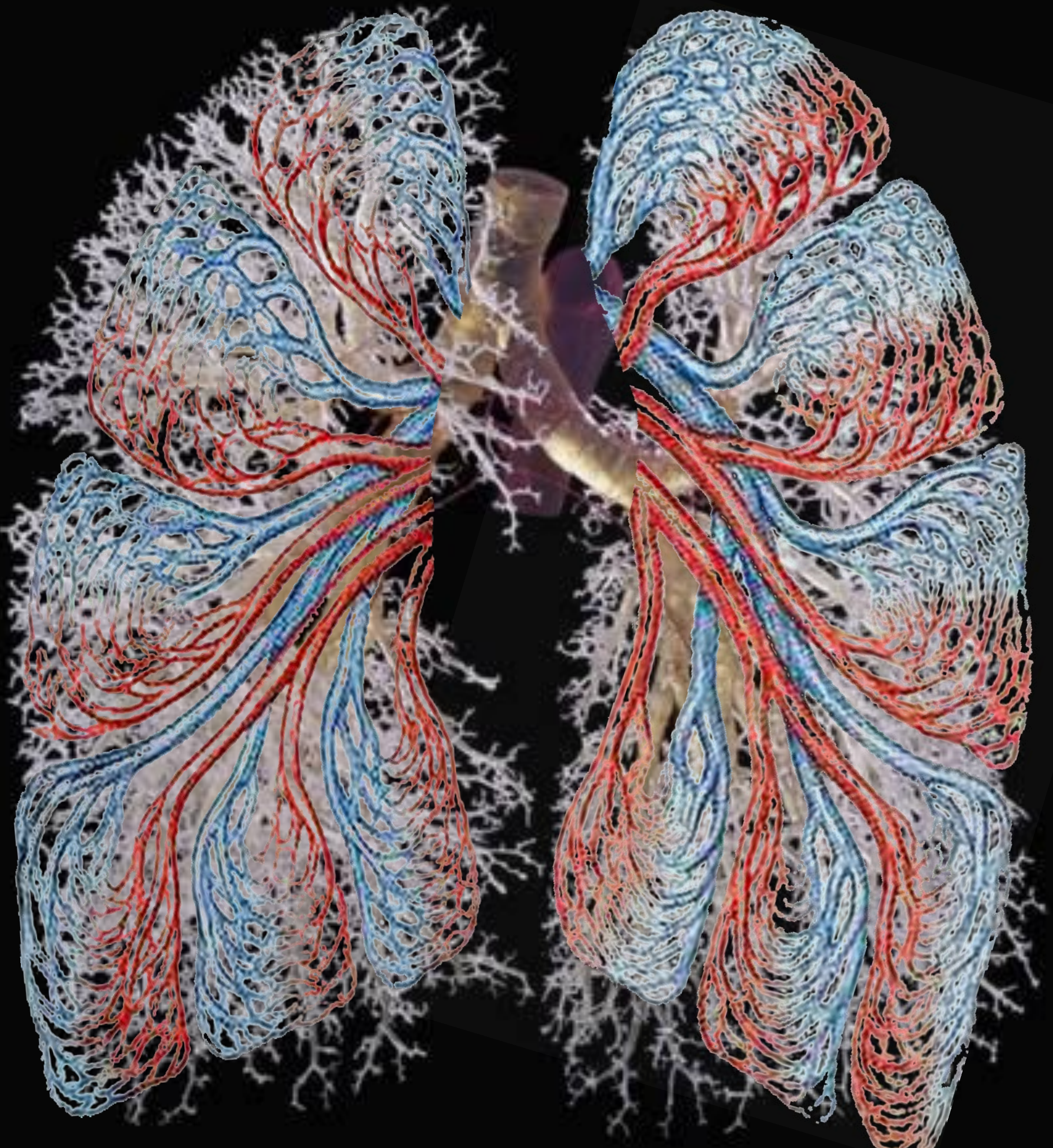
Pulse Oximetry (the 5th vital sign)

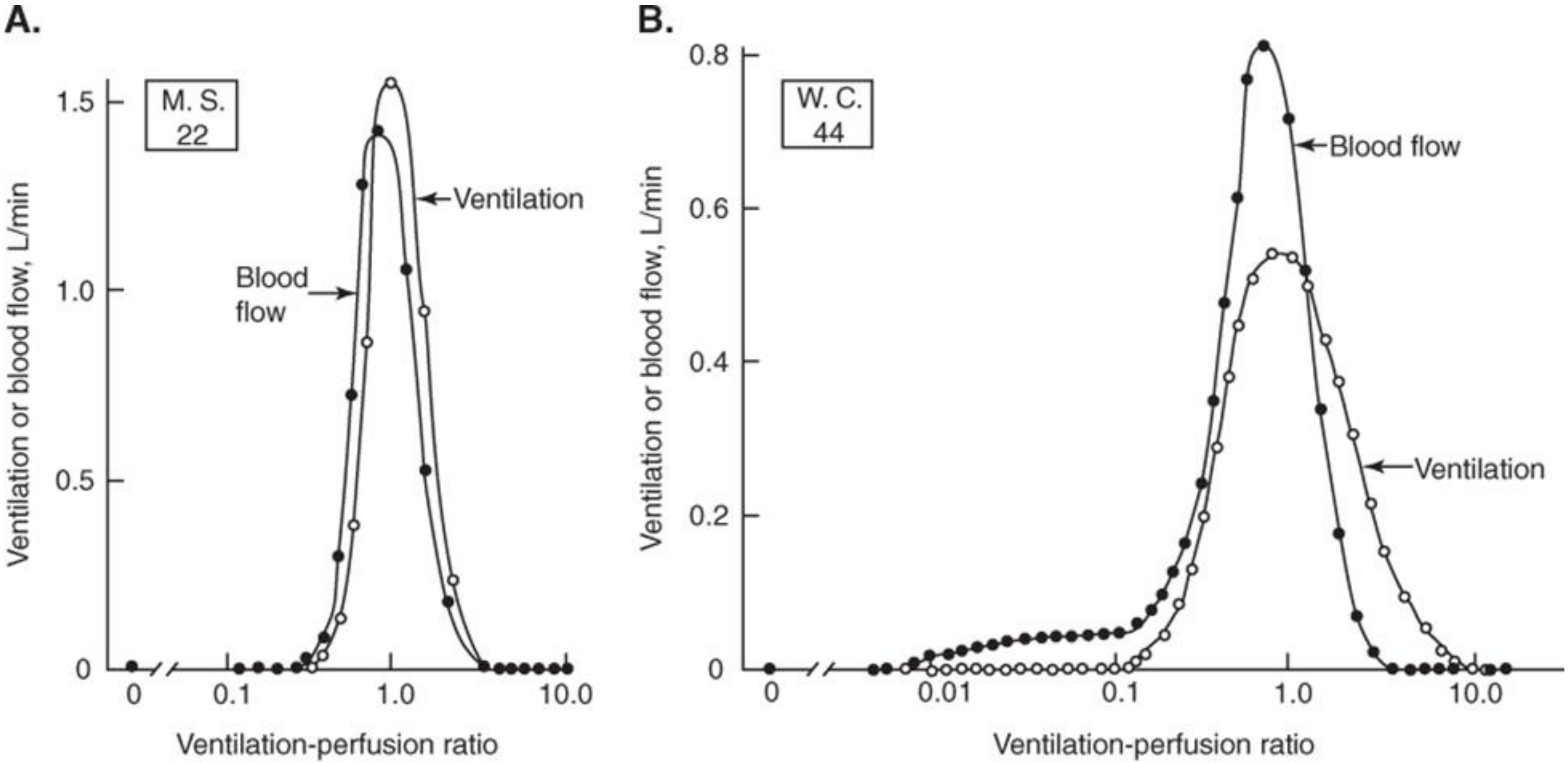
- Based on the change in colour of Hb that occurs when reduced Hb is oxygenated
- Different colours affect the absorption of different wavelengths of light
- Standard pulse oximetry does not distinguish COHb from O_2Hb
- While PaO_2 is the preferred measure of gas exchange from the lung to the bloodstream, SpO_2 is a better measure of oxygenation of the tissues
- Arterial blood gas measurements provide data from a single time point while SpO_2 can be continuously monitored, including in ambulatory patients


Decreased P_{50} (increased affinity)
↓ Temperature
↓ P_{CO_2}
↓ 2,3-DPG
↑ pH
Increased P_{50} (decreased affinity)
↑ Temperature
↑ P_{CO_2}
↑ 2,3-DPG
↓ pH
100
80
60
40
20
0
Hemoglobin saturation (%)
0
20
40
60
80
100
Oxygen partial pressure (mm Hg)

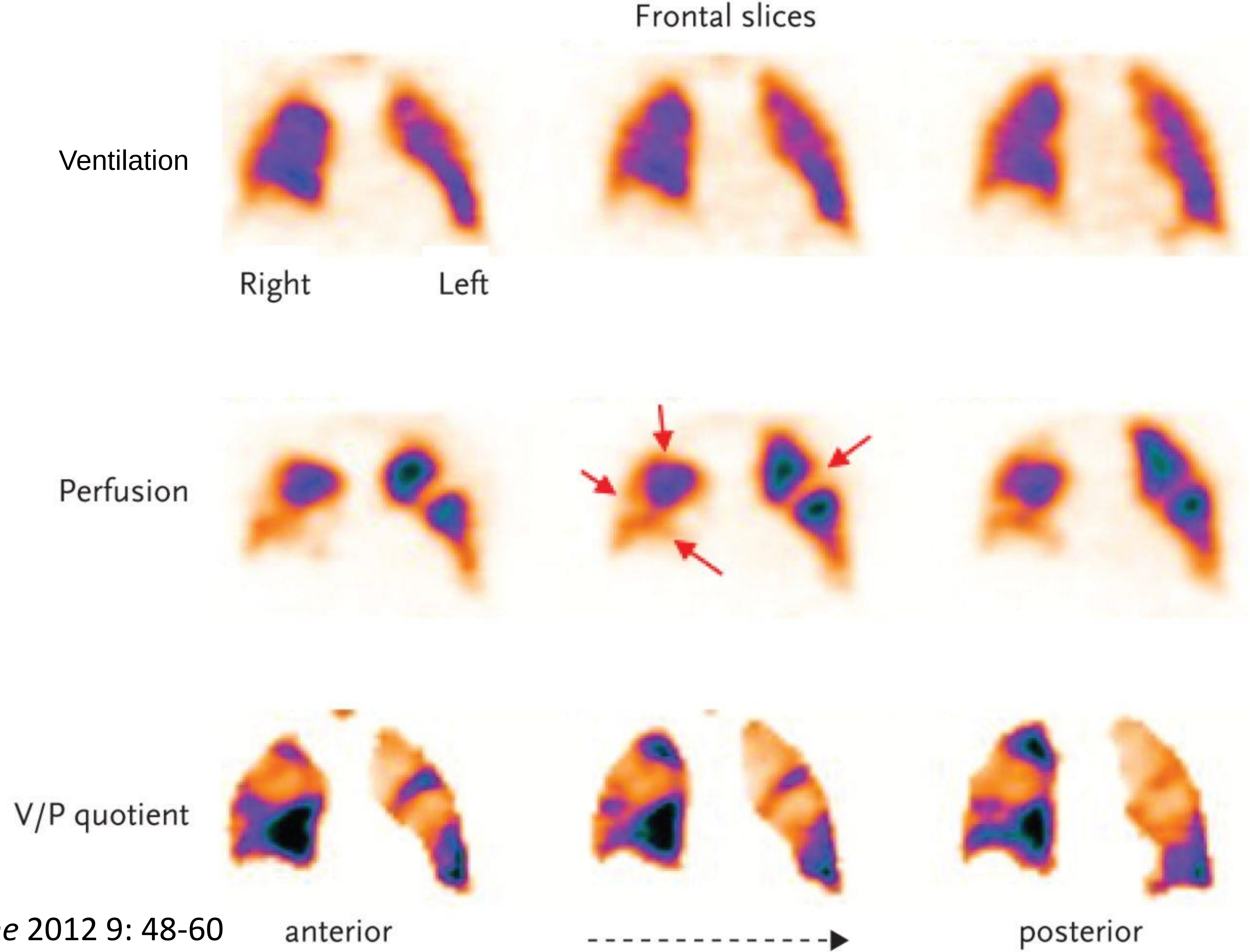






Distribution of $\dot{V}_A/\dot{Q}$ ratios. Results from a 22-year-old healthy subject are shown in the left panel and from a 44 year-old with COPD in the right panel



M Bajc. *Breathe* 2012 9: 48-60

Ventilation-Perfusion matching

The normal lung has a distribution of $\dot{V}_A/\dot{Q}$ units around one. This distribution is relatively tight in normal subjects and the differences that do exist are largely explained by the greater effects of gravity on the vertical distribution of perfusion than on ventilation. As a consequence a small alveolar-arterial difference ($P_{A\text{-}a}O_2$) exists in normal subjects.

Ventilation-Perfusion matching

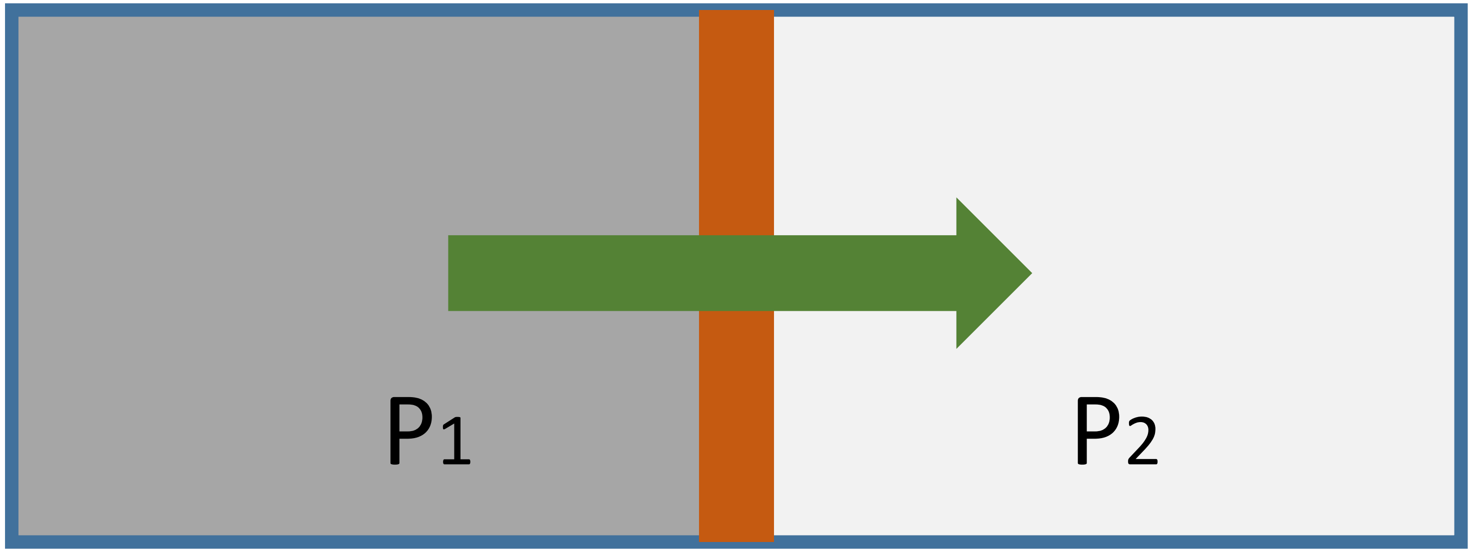
Vascular smooth muscle modulation is an important mechanism to assist in matching perfusion to ventilation. This is largely controlled by oxygen and is a locally mediated response of the pulmonary vasculature to the decrease in P_AO_2 which occurs when ventilation to the alveolar unit is reduced. This local hypoxic vasoconstriction serves to reroute blood flow to better ventilated units.

An alveolus is not a balloon

- There are 200 to 800 million alveoli in adult humans, depending on the size of their lungs. The blood-gas barrier has been estimated to have an area in the order of 100 m^2 at TLC in a typical adult and a thickness that varies from 200 nm to 2000 nm.
- At TLC an alveolus will have a diameter of about 100 µm
- Mixing within an alveolus can take several seconds

An alveolus is not a balloon

diffusive gas flow α Area × Diffusivity × (P_1 – P_2) / Thickness



diffusivity
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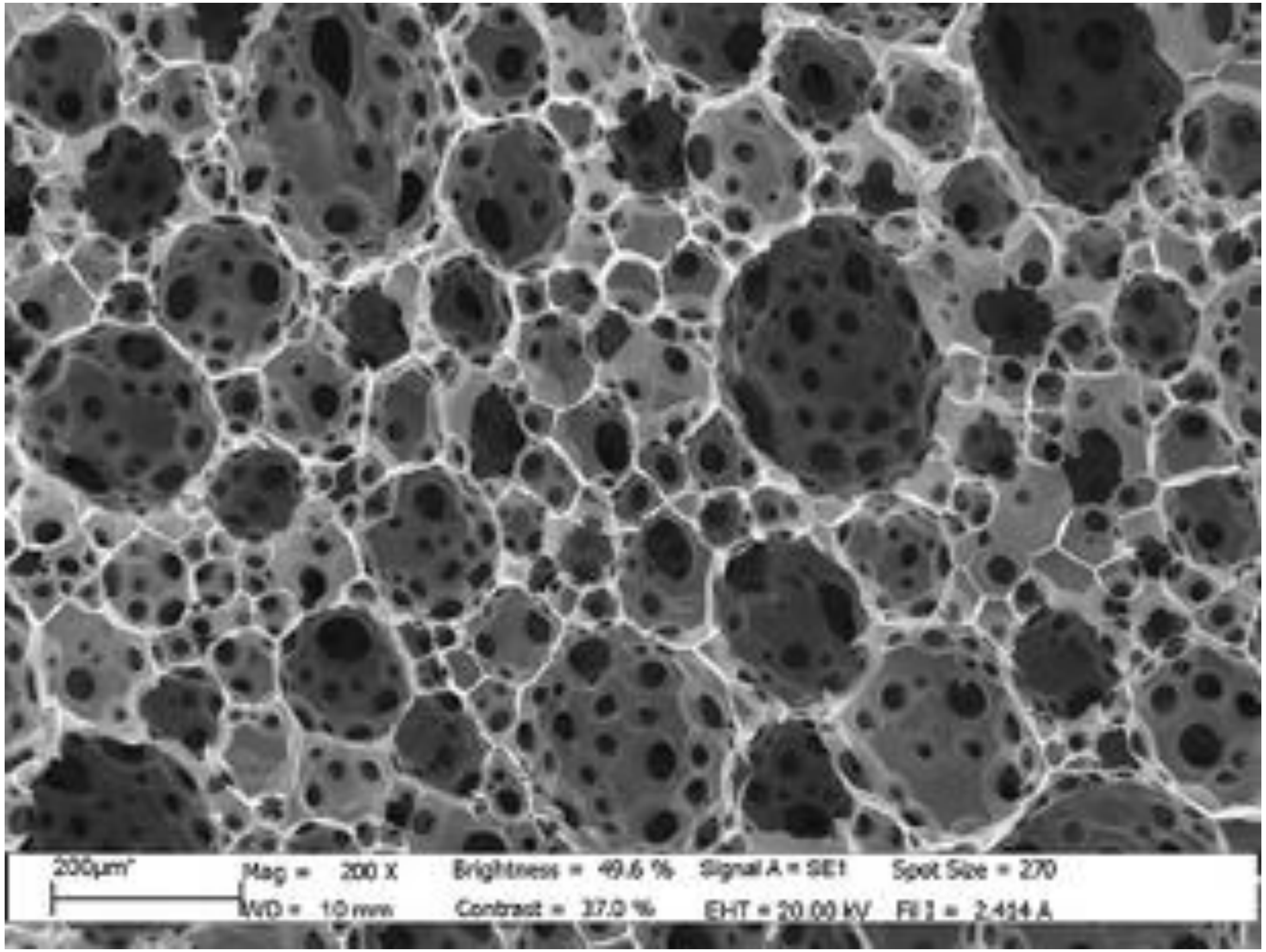
The diffusivity of a gas molecule is equal to its solubility divided by the square root of its molecular weight

An alveolus is not a balloon

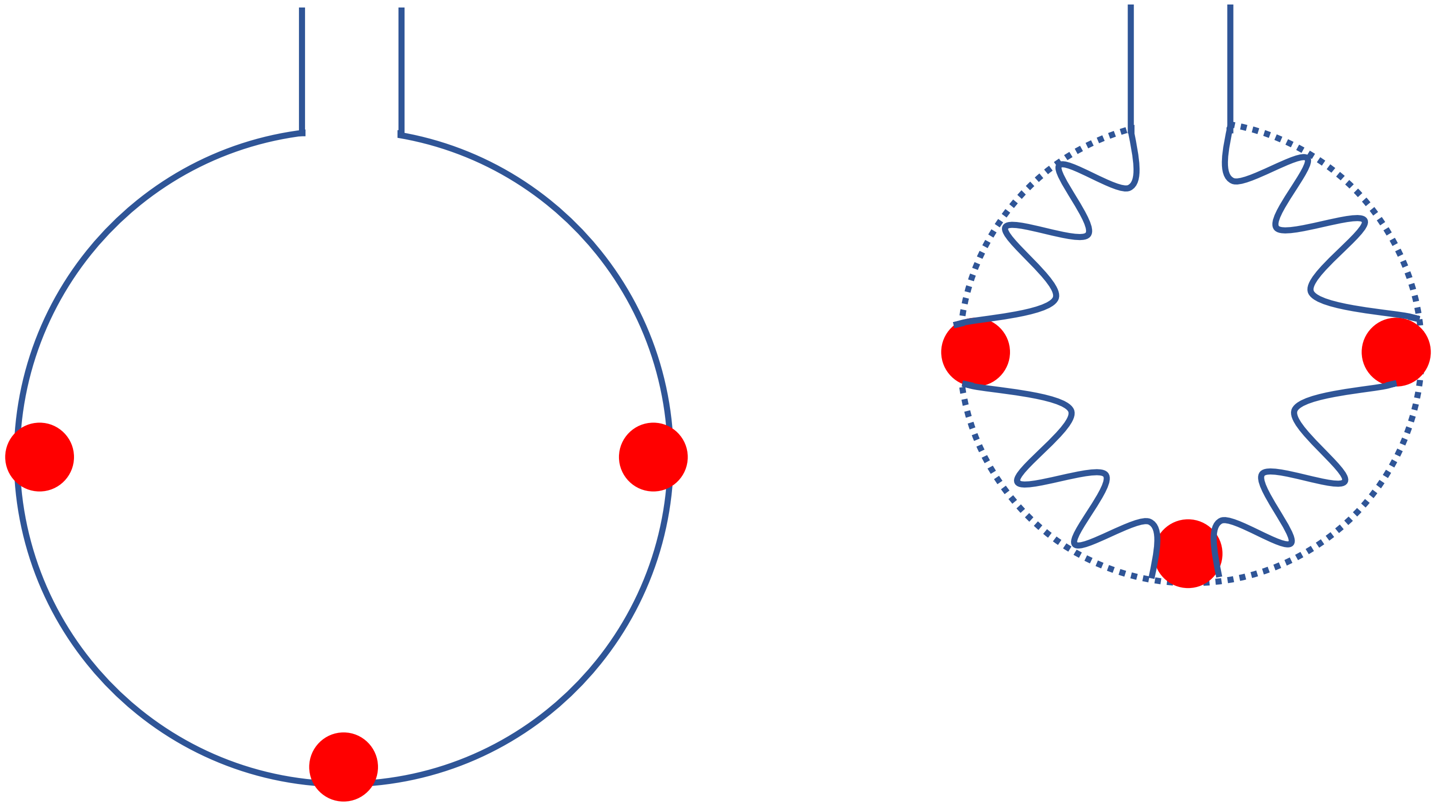
Pores of Kohn



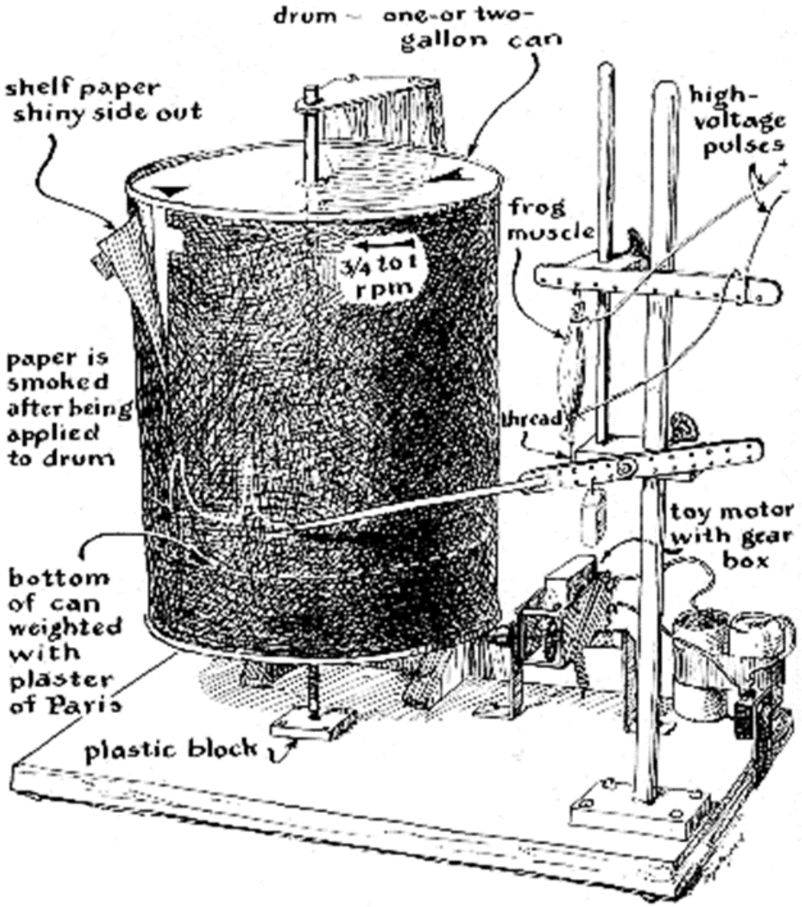
A Barbetta. Soft Matter, 2010 1785–1792

An alveolus is not a balloon

Alveolar septal folding and capillary bulging



How do we measure gas exchange?



How to measure gas exchange

flow = driving pressure / resistance

steady state flow = flow of gas inhaled – flow of gas exhaled

driving pressure = alveolar – pulmonary capillary partial pressure of the gas

for oxygen the pulmonary capillary partial pressure would be very difficult to measure

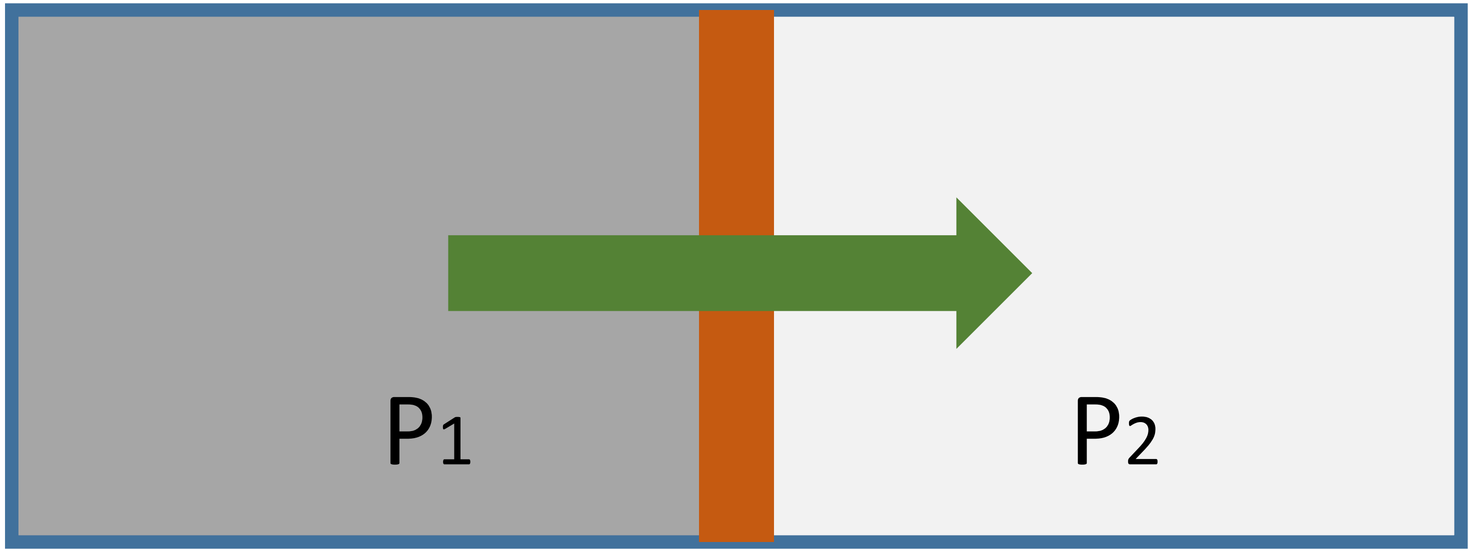
Why use CO to measure gas exchange?

- The affinity of CO for Hb is about 230 times the affinity for O_2 O_2
- CO molecules that cross into the pulmonary capillaries are quickly and tightly bound to Hb so that the pulmonary capillary partial pressure of CO is assumed to be zero

[but really it isn’t]

Why use CO to measure gas exchange?

diffusive gas flow α Area × Diffusivity × (P_2 - P_1) / Thickness



The molecular weight and the solubility of CO are both a little lower than that of O_2, with the net result that Fick's Law predicts CO transport across a membrane will be about 83% of O_2 transport at the same driving pressure.

Why use CO to measure gas exchange?

flow = driving pressure / resistance

conductance = 1 / resistance

DLCO = conductance = flow / driving pressure

flow = [CO inhaled – CO exhaled – CO left in the lung] / time

driving pressure = alveolar partial pressure of CO

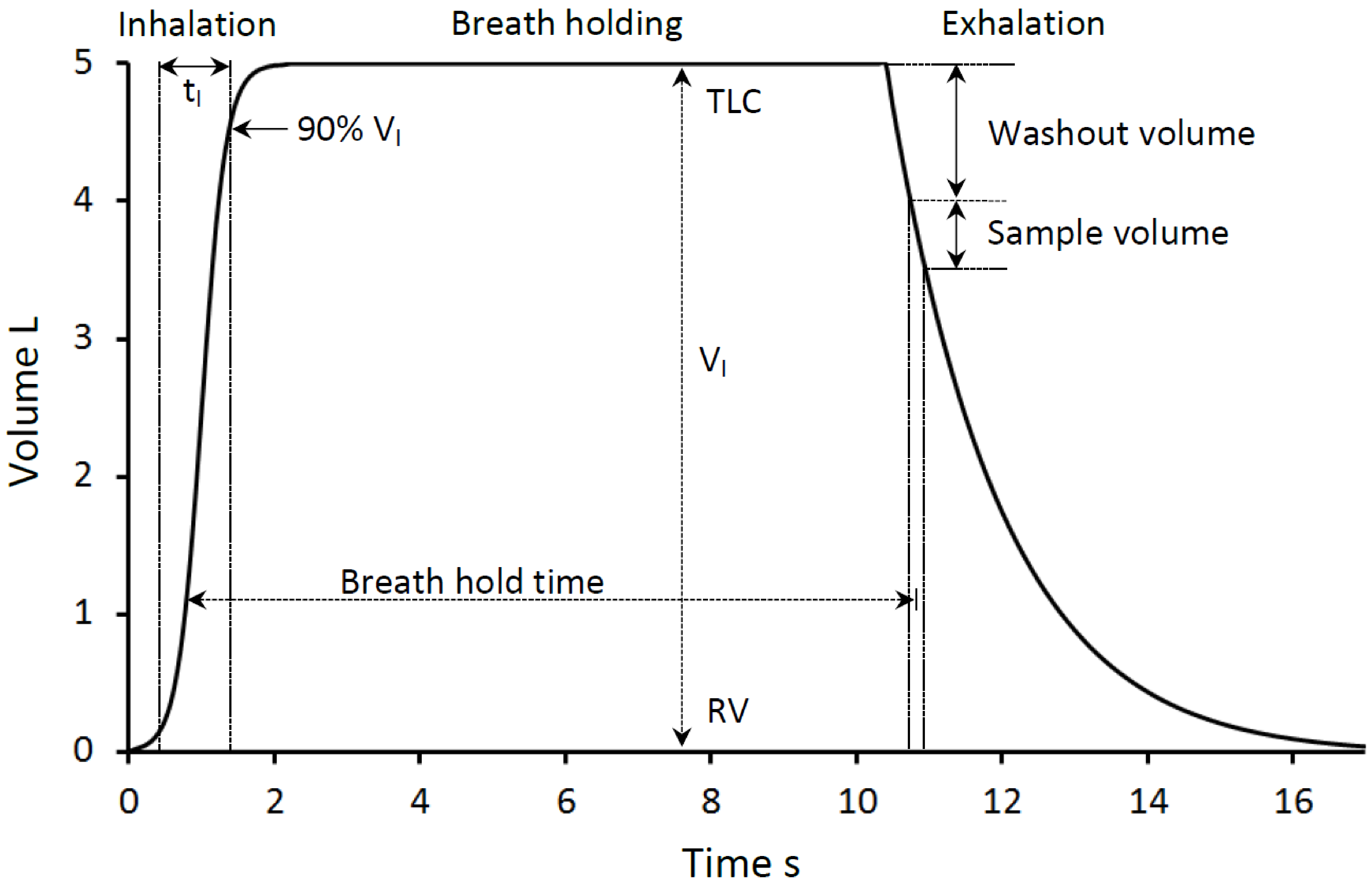
= alveolar CO concentration x barometric pressure

Why use CO to measure gas exchange?

Krogh equation

$$d_{\mathrm{CO}} = \frac{V}{p} \cdot \frac{\log C_0 - \log C_t}{t}$$

Marie Krogh. The diffusion of gases through the lungs of man. *J Physiol (London).* 1914


Inhalation
Breath holding
Exhalation
t_I
90% V_I
TLC
Washout volume
Sample volume
V_I
Breath hold time
RV
Volume L
Time s
0
1
2
3
4
5
0
2
4
6
8
10
12
14
16

Limitations

- A single value is reported equivalent to the DLCO in a balloon model that would explain the observed CO uptake
- A small sample of exhaled gas is not representative of a heterogeneous lung
- High coefficient of variation
- It’s not just diffusion. It’s not a capacity. It should be called TRANSFER FACTOR instead of diffusing capacity

Factors affecting DLCO – physical

- Breath hold time
- Inspired and expired flow rates
- Inspired O_2 concentration
- Barometric pressure
- COHb (back pressure and anemia effects)
- Valsalva or Müller manoeuvre

Factors affecting DLCO - physiological

- Hb (anemia or polycythemia)
- Increase or decrease in blood flow (exercise, position)
- Alveolar volume (restrictive or neuromuscular)
- Ventilation-perfusion mismatch (embolism)
- Pulmonary edema
- Static blood in lung
- Pulmonary capillary bed disorders

Summary

Gas exchange is a complex process.

However, the use of DLCO to quantify the rate of gas exchange, although simplified and subject to various sources of variation, remains a useful tool in the assessment of pulmonary function.

Acknowledgement:

Much of the information in this talk is contained in a new textbook to be published this fall:

Pulmonary Function Testing - Principles and Practice;
D. Kaminsky and C. Irvin, editors
Springer International Publishing;

Chapter 7, Gas Exchange
B Graham, N MacIntyre, Y-C Huang.

CO trivia

- The binding of CO to one heme site increases O_2 affinity of the other binding sites in the Hb molecule
- This effect on hemoglobin O_2 affinity explains why the formation of 50% COHb causes more severe tissue hypoxia than when various forms of anemia cause the reduction of hemoglobin concentration to half the normal concentration