

Biophysical Fluid Dynamics: The Respiratory System

Course number: 115433 / 115430

Also formerly known as :
Bio Fluid Mechanics

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<http://tsu7.wb.utwente.nl/~frans/frans2.htm>

Overview

When:

Tuesday 5e+6e+7e hr: plenary lecture (HC)

Thursday 1e+2e+2e hr: werkcollege (WC)

- 1) **Tuesday 19 April 5e t/m 7e hr (HC) , Thursday 21 April (1 t/m 3e)(WC)**
- 2) **Tuesday 26 April 5e t/m 7e hr (HC) , Thursday 28 April (1 t/m 3e) (WC)**
- 3) **Tuesday 3 May 5e t/m 7e hr (HC) , Tuesday 10 May (2 t/m 4e) (WC)**
- 4) **Tuesday 10 May 5e t/m 7e hr (HC) , Thursday 12 May (1 t/m 3e) (WC)**

- 5) **Tuesday 17 May 5e t/m 7e hr (HC) , Thursday 19 May (1 t/m 3e) (WC)**
- 6) **Tuesday 24 May 5e t/m 7e hr (HC) , Thursday 26 May (1 t/m 3e) (WC)**
- 7) **Tuesday 31 May 5e t/m 7e hr (HC) , Thursday 2 June (1 t/m 3e) (WC)**
- 8) **Tuesday 7 June 5e t/m 7e hr (HC) , Thursday 9 June (1 t/m 3e) (WC)**

Exam: open book

Overview

	Hr
Subjects:	s
1) Lungmodels	2
2) Pressure drop across the human lung	2
3) Convection and Diffusion	4
4) High Frequency Ventilation	2
5) Forced expiration: Collapsible tubes	2
6) Surfactant Fluid mechanics	2
7) Aerosol transport and deposition in the human lung	4
8) Multigas washout (He, SF6), Lungs of other species	2
9) Lung function measurements	2

1) Lungmodels

a) **Deterministic**: average values

- lengths
- diameters
- angles
- number of tubes per generation

b) **Stochastic**: probability distributions en correlaties

1) Longmodels

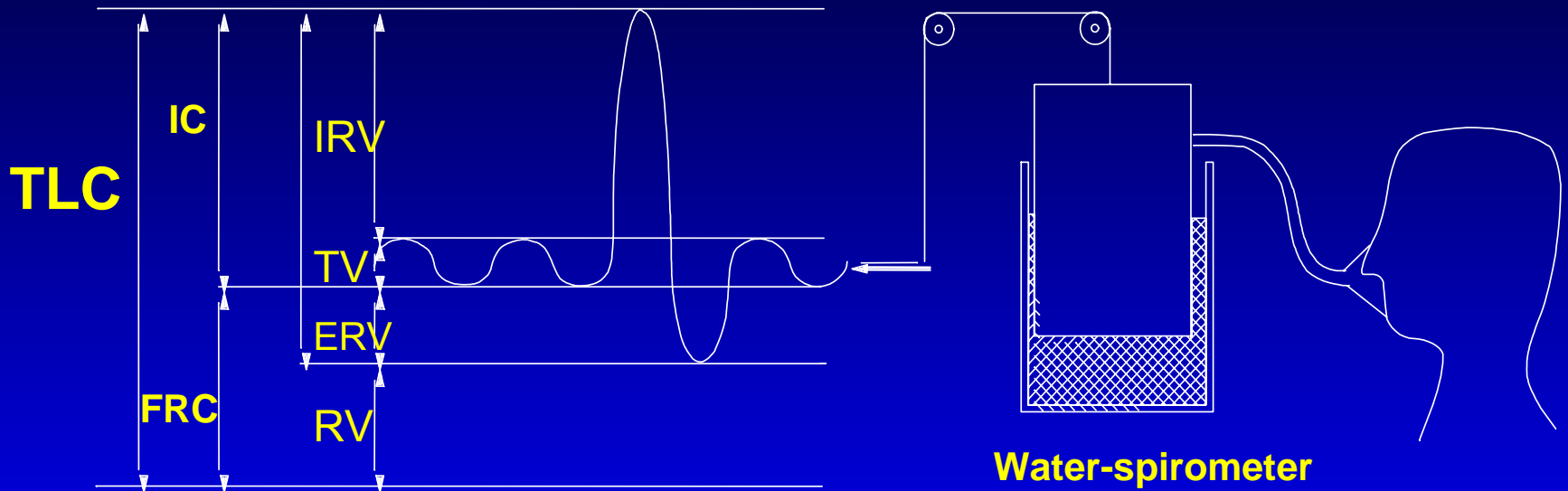
a) Deterministic

- Weibel 1963 (Springer, Berlin)
- Hansen & Ampaya 1975 (J.Appl.Physiol 38)
- Yeh & Shum 1980 (Bull. Math. Biol.)
- James 1988 (Wiley, NY)
- Heafeli-Bleuer & Weibel 1988 (Anat.Recor 220)
-

b) Stochastic

- Raabe 1976 (Lovelace report LF-53)
- Koblinger & Hofmann 1985 (Phys. Med. Biol. 30)
- Koblinger & Hofmann 1990 (J. Aerosol Sci. 21)


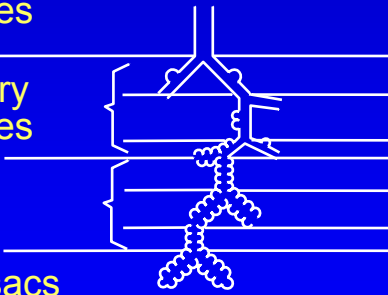
Definitions lungvolumes



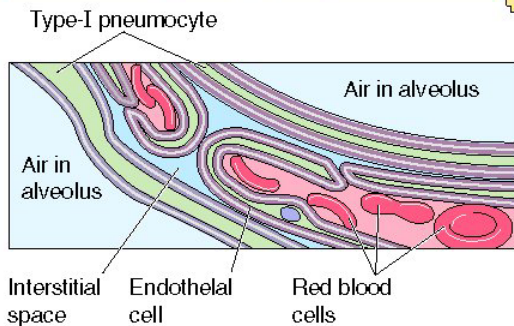
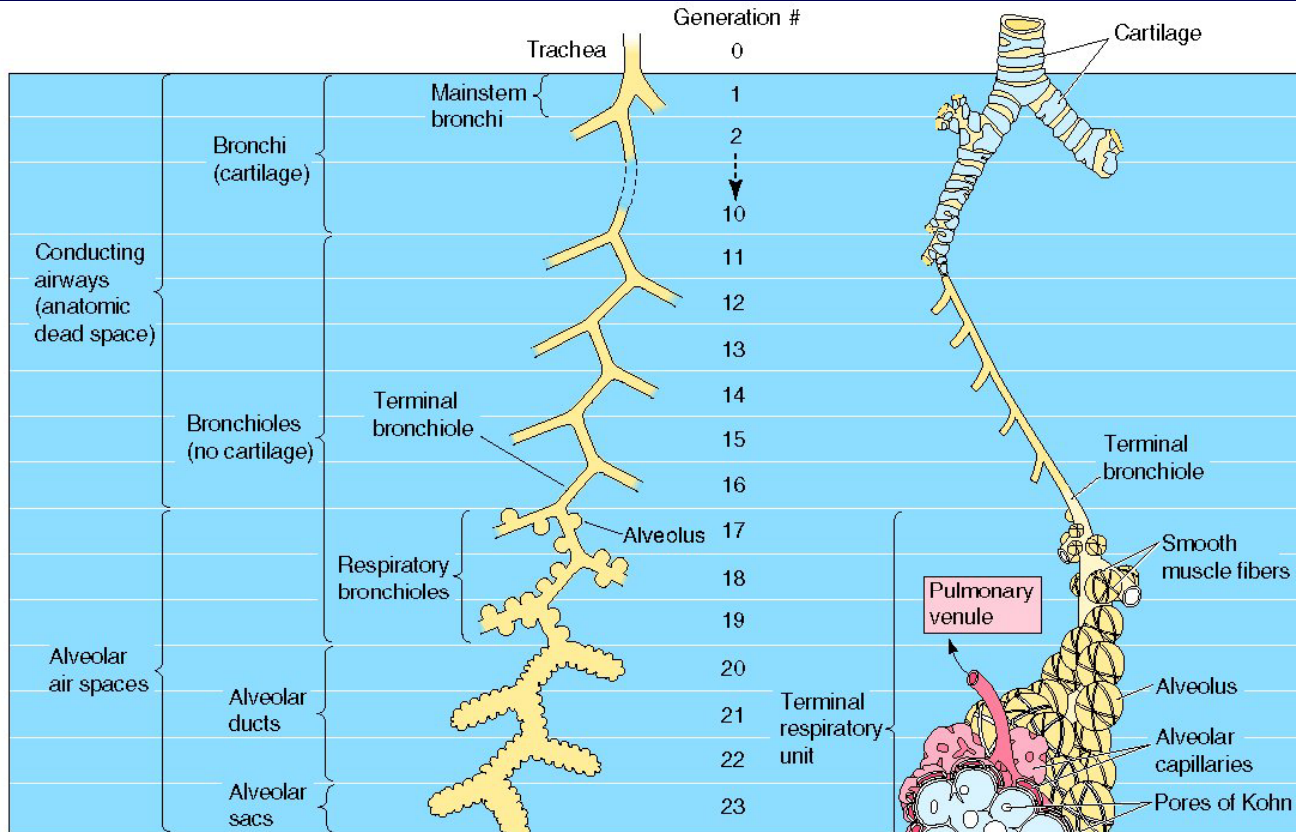
TLC	= Total Lung Capacity	(6 litre)
FRC	= Functional Residual Capacity	(3 litre)
RV	= Residual Volume	(1.8 litre)
TV	= Tidal Volume	(0.5 litre)
IC	= Inspiratory Capacity	(3 litre)
IRV	= Inspiratory Reserve Volume	(2.5 litre)
ERV	= Expiratory Reserve Volume	(1.2 litre)

Example of deterministic model

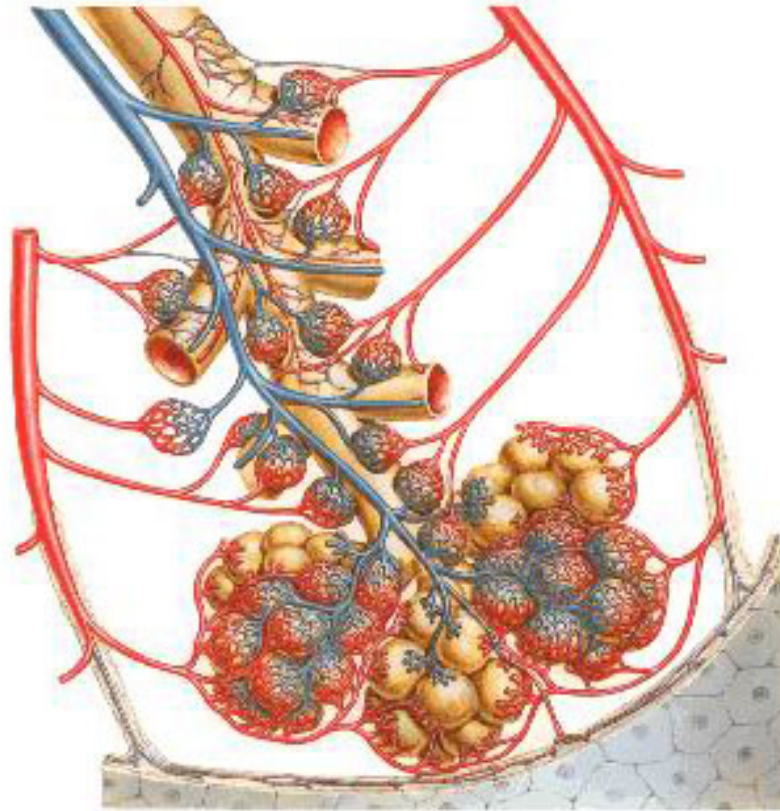
n = generation number

Conducting zone	Trachea		n
			0
	Bronchi		1
			2
			3
			4
	Bronchioles	5	
	Terminal Bronchioles	16	
Respiratory zone	Respiratory Bronchioles		17
			18
	Alveolar ducts		20
	Alveolar sacs Alveoli		23

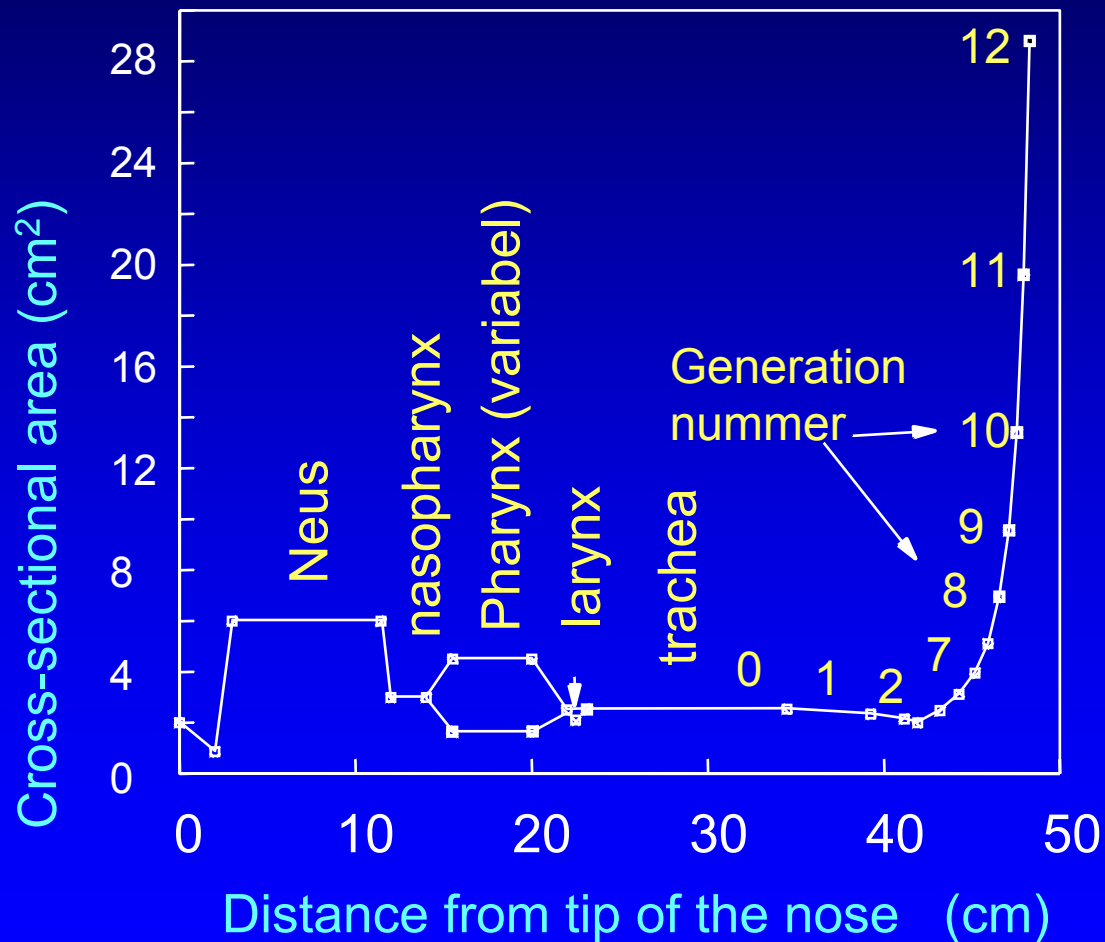
“Weibel” Lungmodel



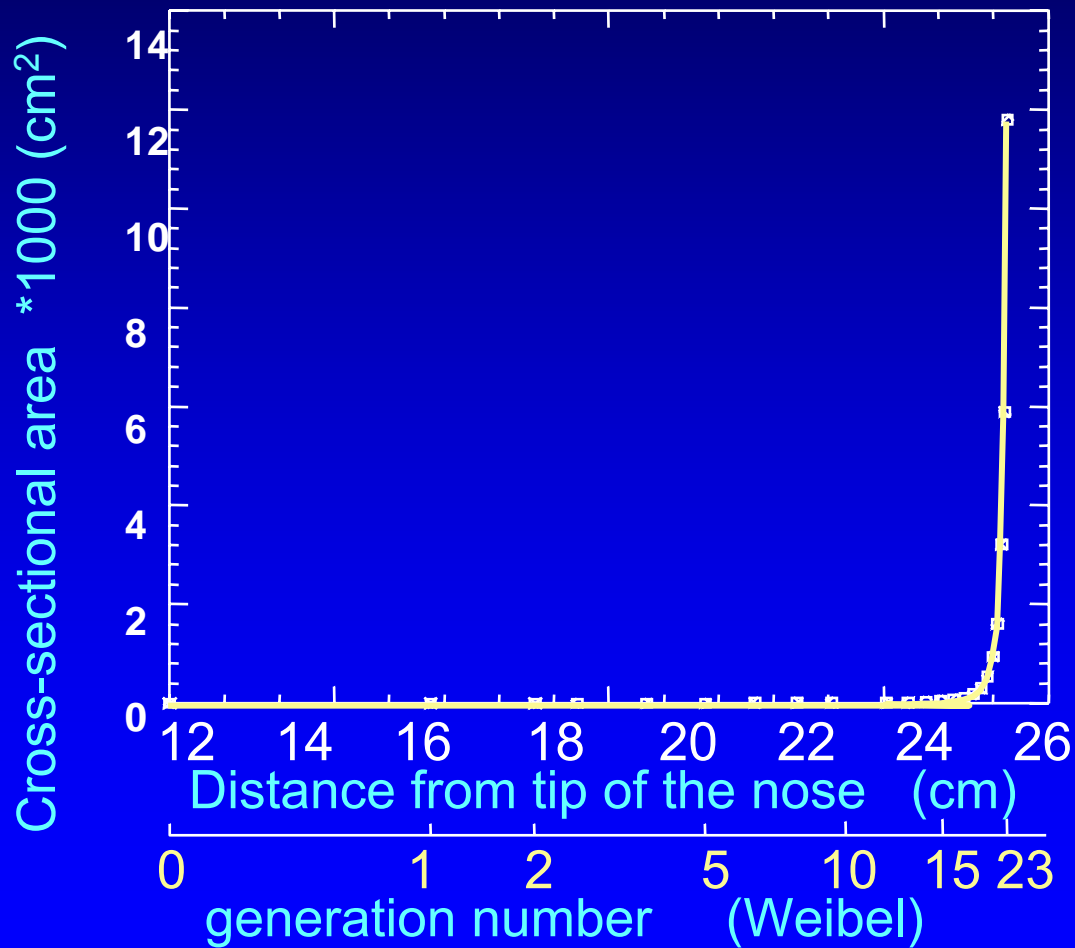
Intrapulmonary Blood Circulation Schema



1D model – cross-sectional area



1D model – cross-sectional area



Optimal dividing tube

A Cost-function is:

$$F = \dot{Q}\Delta p + K\pi a^2 L = \frac{8\mu L}{\pi a^4} \dot{Q}^2 + K\pi a^2 L$$

$$\frac{\partial F}{\partial a} = -\frac{32\mu L}{\pi a^5} \dot{Q}^2 + 2K\pi a L = 0$$

so

$$a = \left(\frac{16\mu}{\pi^2 K} \right)^{\frac{1}{6}} \dot{Q}^{\frac{1}{3}}$$

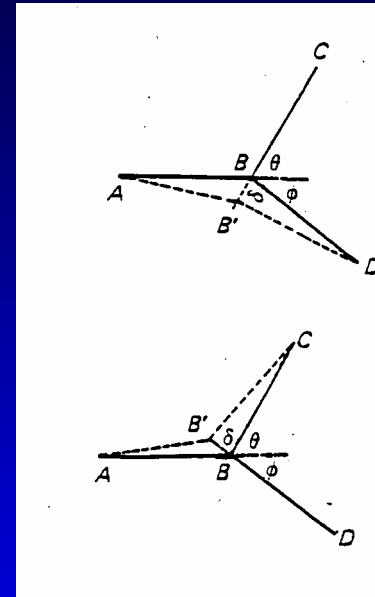
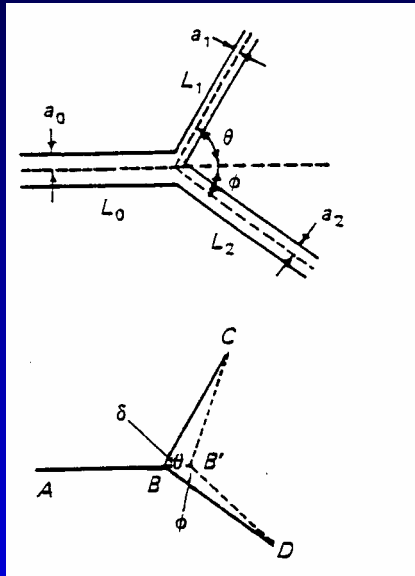
The minimal value of F becomes:

$$F_{\min} = \frac{3\pi}{2} K L a^2$$

Branching tube:

$$P_{\min} = \frac{3\pi K}{2} (a_0^2 L_0 + a_1^2 L_1 + a_2^2 L_2)$$

Optimal dividing tube



B in the direction of CB, yields:

$$\delta L_0 = \delta, \delta L_1 = -\delta \cos \theta, \delta L_2 = -\delta \cos \phi$$

So

$$\delta P = \frac{3\pi K}{2} \delta (a_0^2 - a_1^2 \cos \theta - a_2^2 \cos \phi)$$

With a minimal value for:

$$a_0^2 = a_1^2 \cos \theta + a_2^2 \cos \phi$$

Optimal dividing tube:

Displacement CB' gives:

$$\delta L_0 = -\delta \cos \theta, \delta L_1 = \delta, \delta L_2 = -\delta \cos(\theta + \phi)$$

So
$$\delta P = \frac{3\pi K}{2} \delta \left(-a_0^2 \cos \theta + a_1^2 + a_2^2 \cos(\theta + \phi) \right)$$

With a minimal value for:

$$-a_0^2 \cos \theta + a_1^2 + a_2^2 \cos(\theta + \phi) = 0$$

Displacement in the direction of DB yields as optimum

$$-a_0^2 \cos \theta + a_1^2 \cos(\theta + \phi) + a_2^2 = 0$$

From the three formulas for the optima one can derive:

$$\cos \theta = \frac{a_0^4 + a_1^4 - a_2^2}{2a_0^2 a_1^2} \quad \cos \phi = \frac{a_0^4 - a_1^4 + a_2^2}{2a_0^2 a_2^2} \quad \cos(\theta + \phi) = \frac{a_0^4 - a_1^4 - a_2^2}{2a_1^2 a_2^2}$$

Optimal dividing tube:

With the fact that: $\dot{Q}_0 = \dot{Q}_1 + \dot{Q}_2$ so : $a_0^3 = a_1^3 + a_2^3$

(also known as the law of Murray) the final result is:

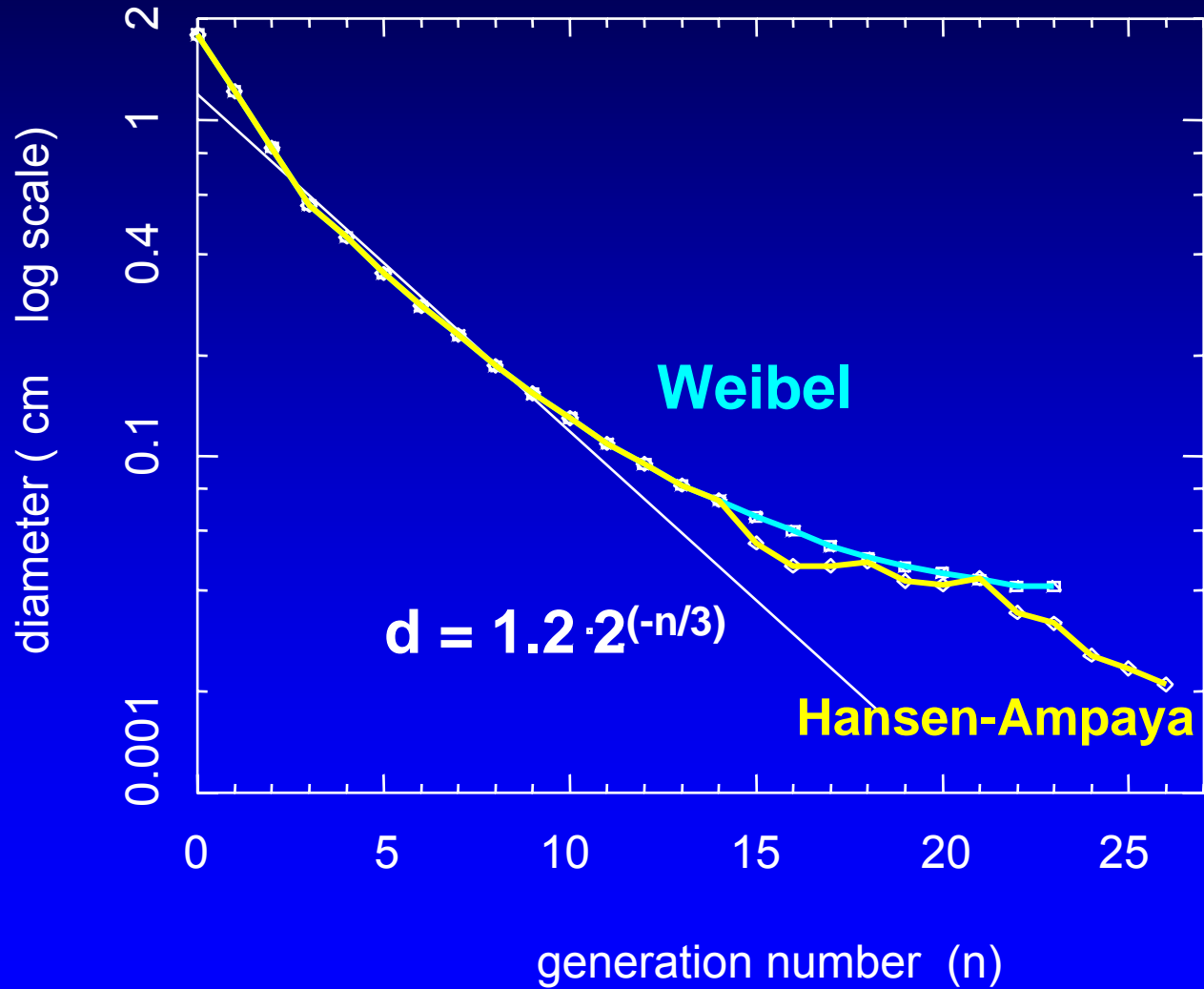
$$\cos \theta = \frac{a_0^4 + a_1^4 - (a_0^3 + a_1^3)^{\frac{4}{3}}}{2a_0^2 a_1^2}$$

Some special cases:

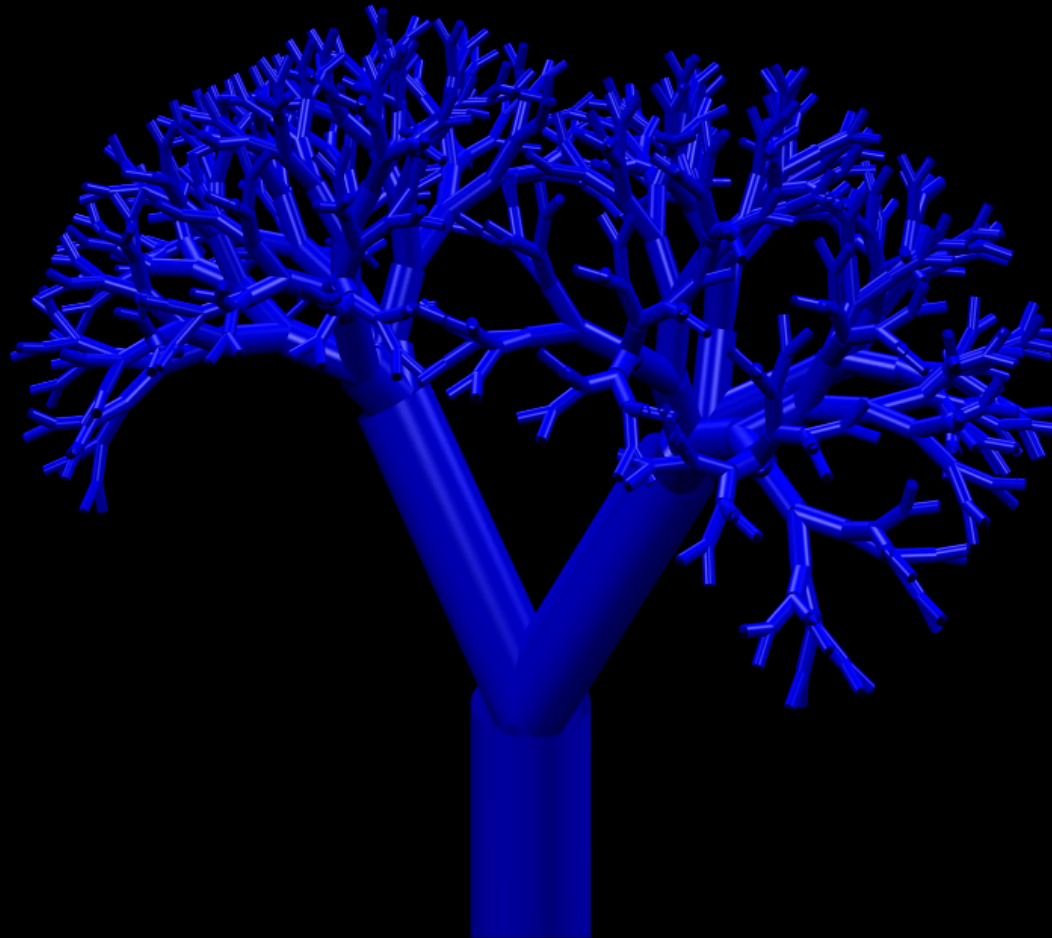
- 1) Consider $a_2 \gg a_1$ This results in: $a_2 = a_0$ en $\theta = \pi/2$, $\phi=0$
- 2) Take $a_1 = a_2$ one yields $a_1/a_0 = 2^{-1/3} = 0.794$ and $\cos \theta = 0.794$ so
 $\theta = \phi = 37.5^\circ$

Aorta ($r = 1.5$ cm) till capillary ($r = 5 \cdot 10^{-4}$ cm) yields with
 $a_0/a_n = (0.794)^n$ that $n=30$. This implies $2^{30} = 10^9$ tubes which is close
to reality.

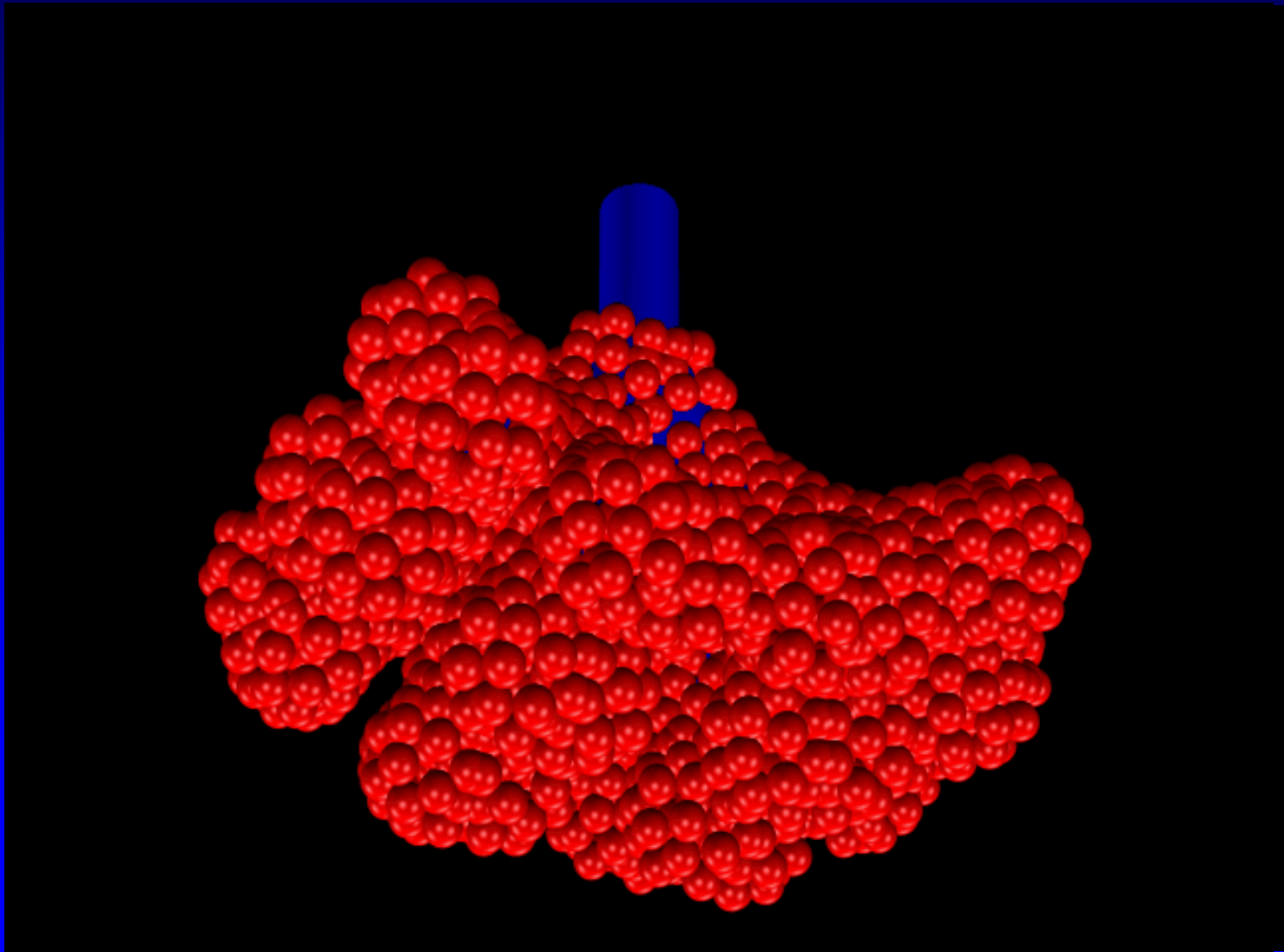
“Optimal” diameter

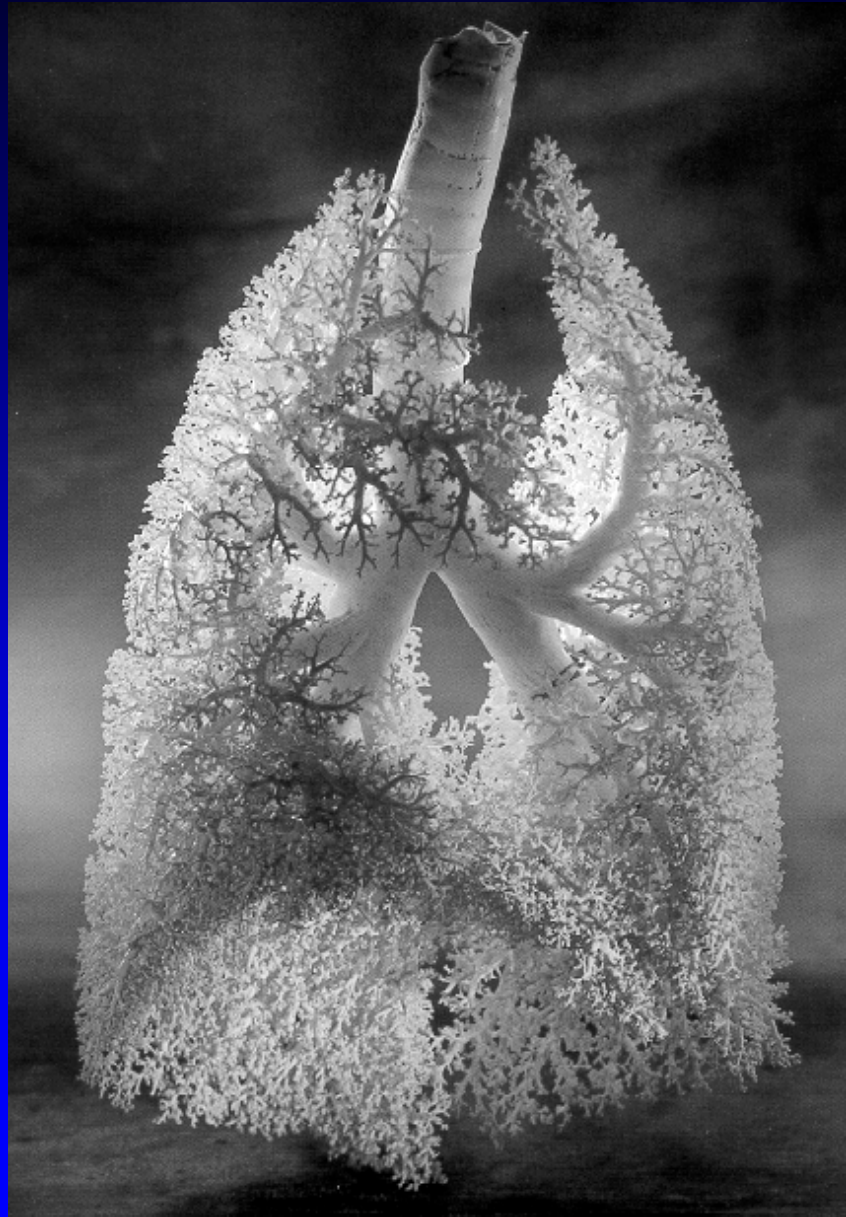


3-D model, the first 10 generations



3-D model, the last 5 generations





“the components”

Optimalisation of:

1) Air pump

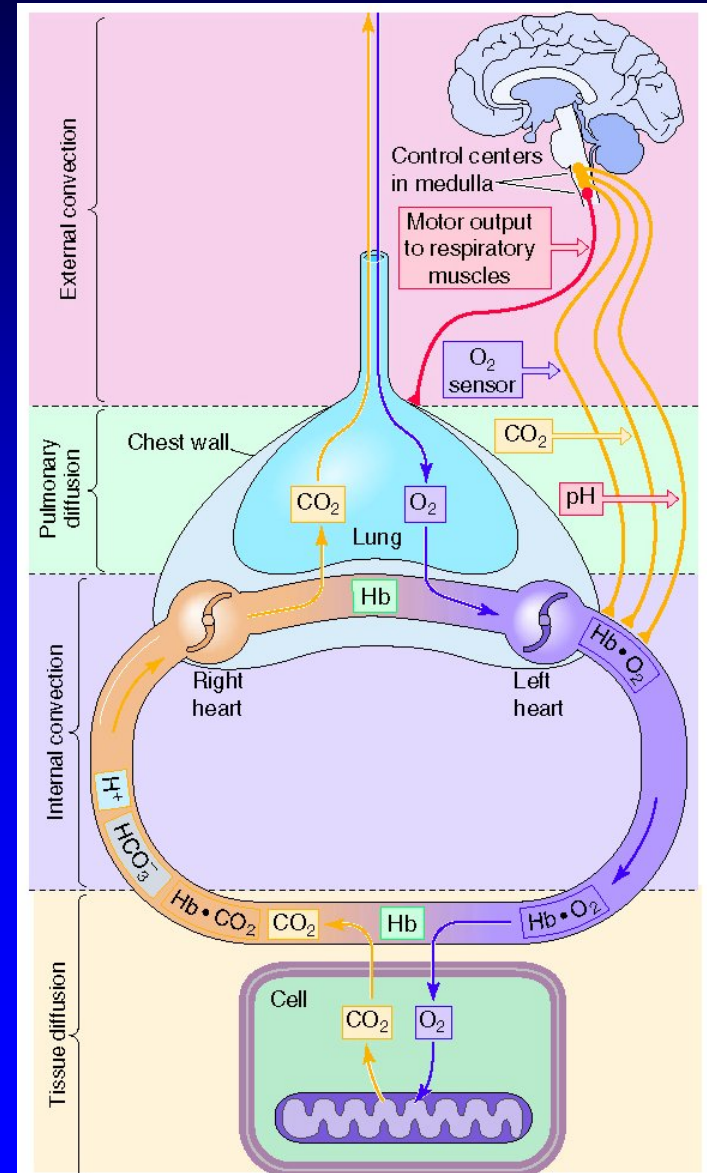
2) O₂ and CO₂ transport:
65 times more O₂ bound by
Hb than by saline

3) Gas exchange area

4) Circulatory system

5) Local regulation for \dot{V}/Q

6) central regulation (CNS)



Terminology

Respiratory mechanics

C	Compliance
f	breathing frequency
P,p	pressure
R	Resistance
V	Gas volume
\dot{V}	Flow

Subscripts

A	Alveolar
aw	airway
B	Barometric

Gas-exchange

C	Concentration /content
D	Diffusion capacity
F	fraction
\dot{Q}	blood flow (perfusion)
R	gas exchange ratio
S	saturation (haemoglobine)
\dot{V}	Ventilation

a	arterial
c	(lung) capillary
E	expired
I	inspired
v	venous
\bar{v}	mixed venous

Alveoli

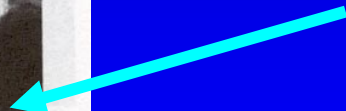
Number
300 - 450·10⁶

Surface area
50- 100 m²

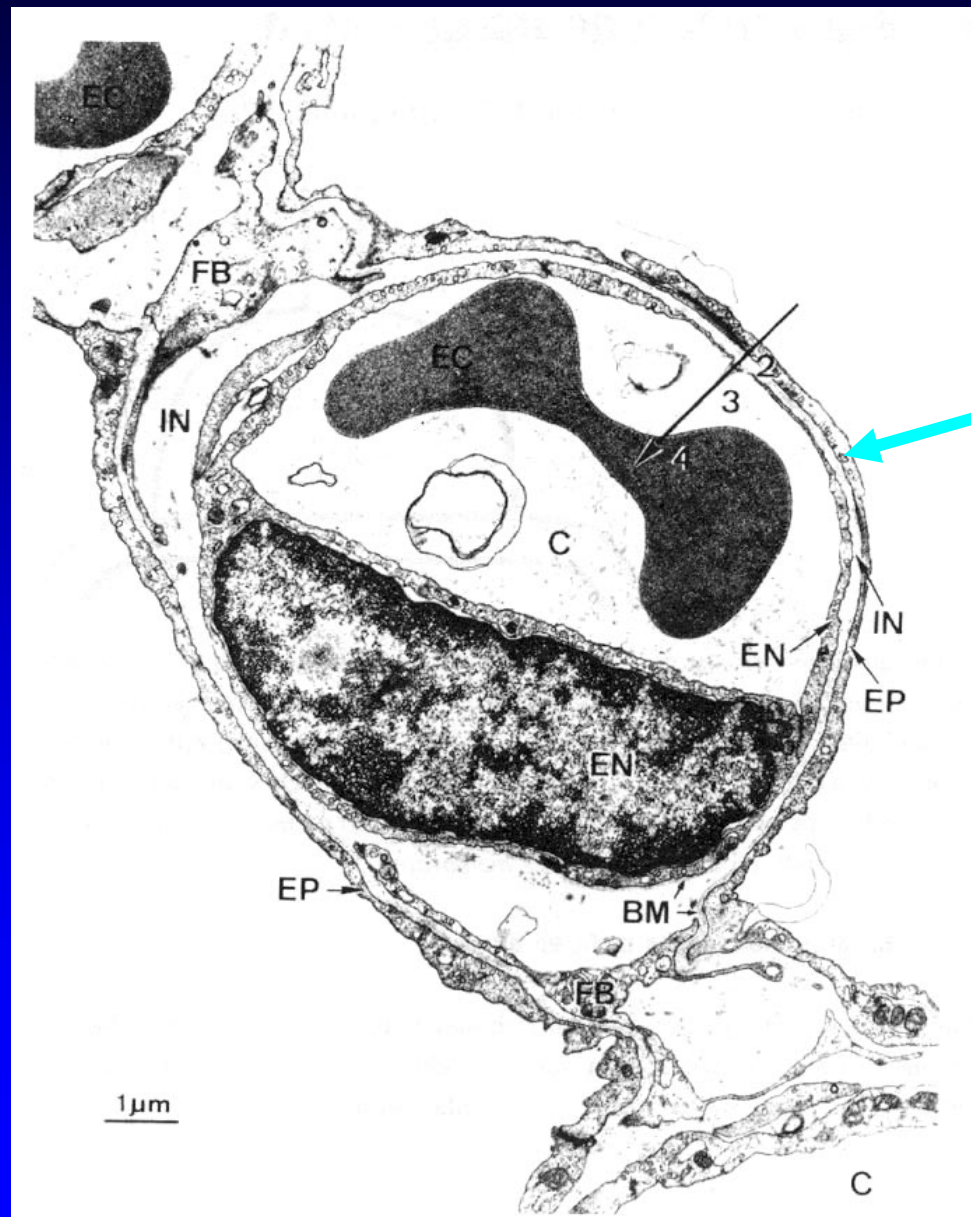
Volume
4 - 6 litre



Diameter
75-300 μm



EM-foto longcappilair



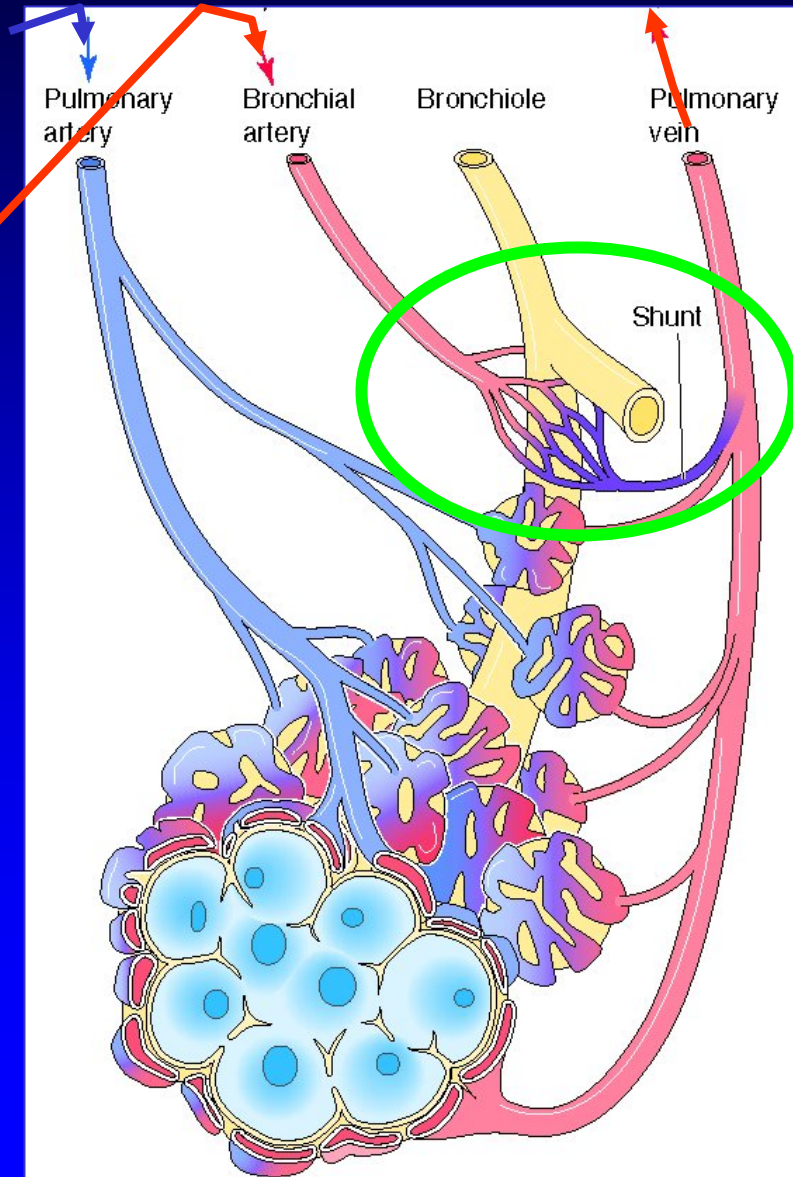
0.5 μm

Bloodflow in lungs

Oxygen-poor blood from right hart to alveoli

Oxygen rich blood from the left hart to the airways

lungcapillary
Diameter 8 μm
Length 10 μm
Duration 0.75 s
(passing 3 alveoli)



All the
(Oxygen rich)
blood back to
the left hart

Respiratory system : extra functions

1) smell

to prevent eating of poisoned food

2) heating

if air and pulmonary blood would be cold and be heated in the circulation, air bubbles would be formed (lung-emboli) due to the poor solubility

3) humidification

prevention of dry out of the alveoli

4) Filtering

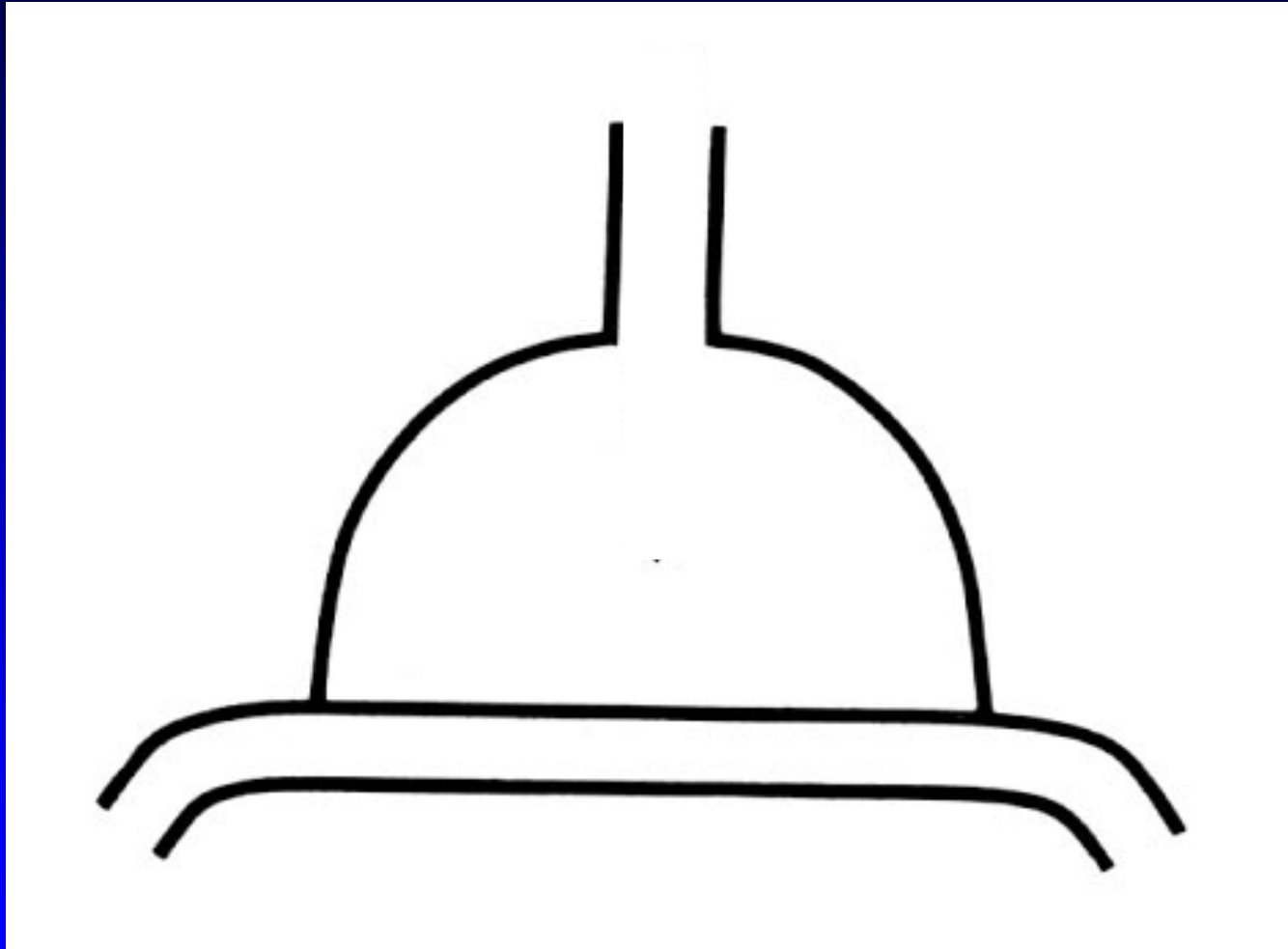
impaction from large particles $> 10 \mu\text{m}$

impaction+sedimentation 2- $10 \mu\text{m}$

Brownian diffusion 0.5 - $2 \mu\text{m}$ (80% again exhaled)

Breathing through the nose is more effective

Simple: West lungmodel



the Reality



Problems with lungmodels

Inter- en intra subject variability:

- pathological anatomical cast not at FRC
- correction by scaling
 - linear (Yu & Diu 1982, [Am.Ind.Hyg.Ass 43](#))
 - non-linear (Habib 1994, [J. Appl. Physiol. 77](#))

To few models, almost/no pathological models

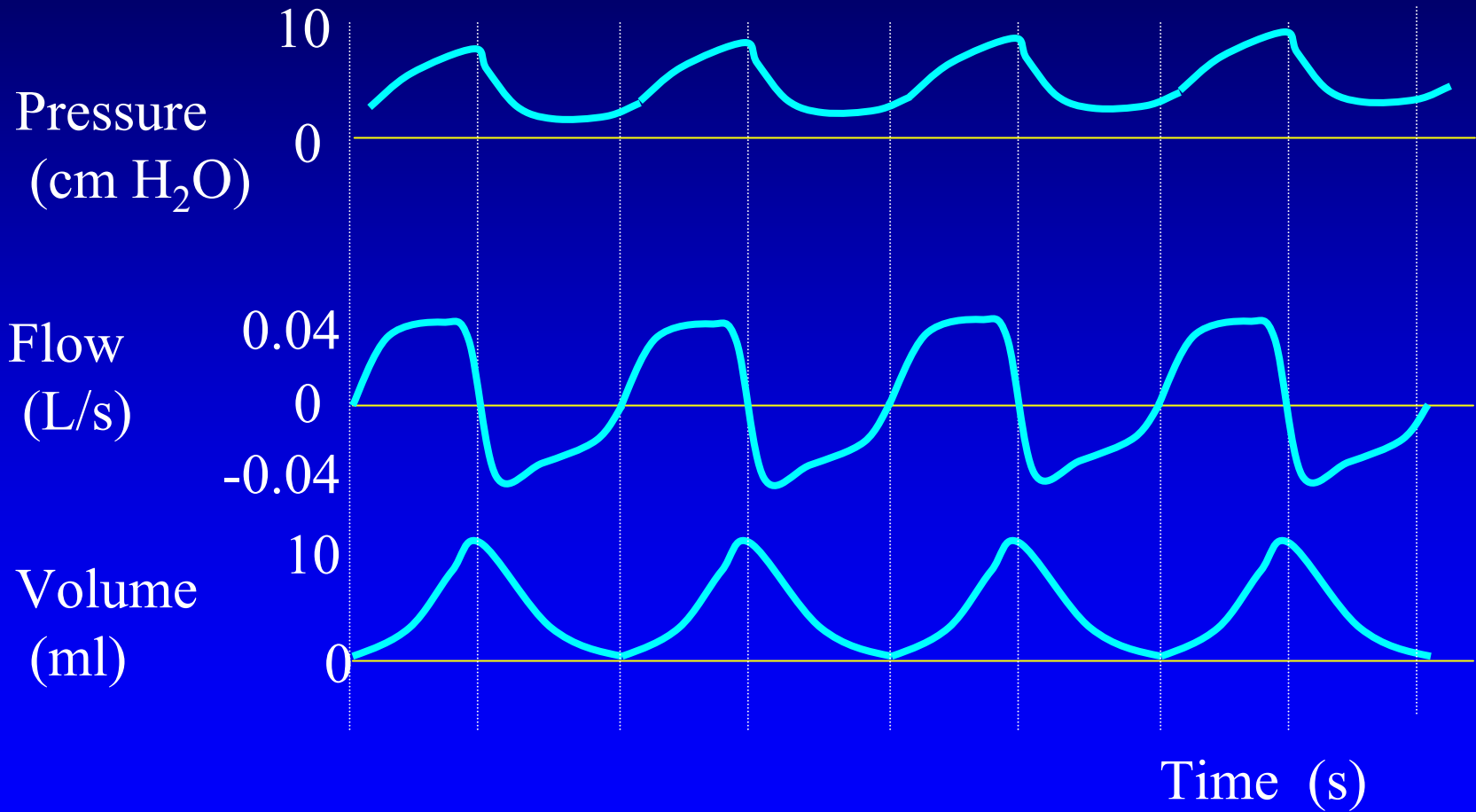
Lungmechanics

Compliance

Resistance

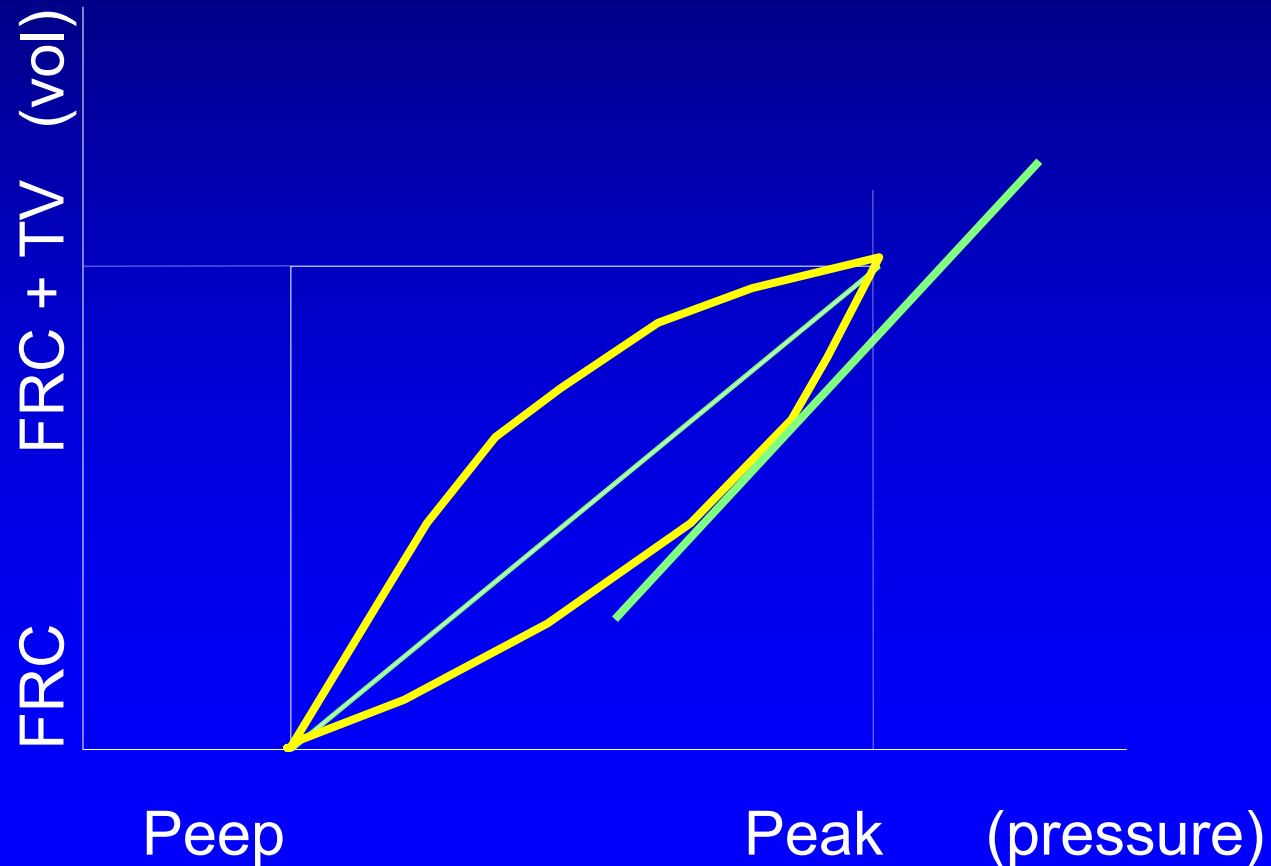
Work of breathing

Basic signals: P, \dot{V} , V



Compliance definition

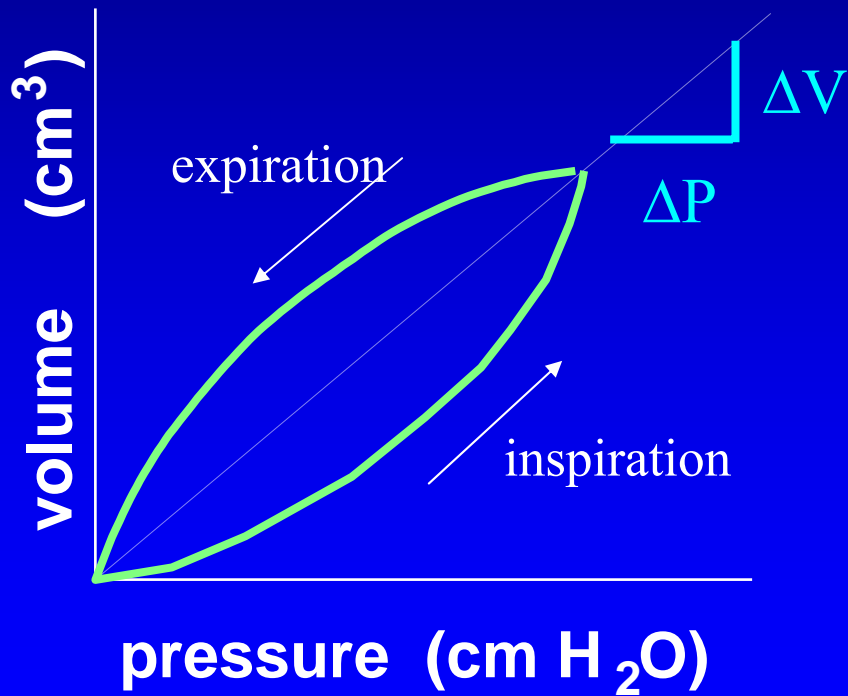
$$\text{Compliance} = \Delta V / \Delta p \quad 1/C_{\text{tot}} = 1/C_L + 1/C_{\text{airw}}$$



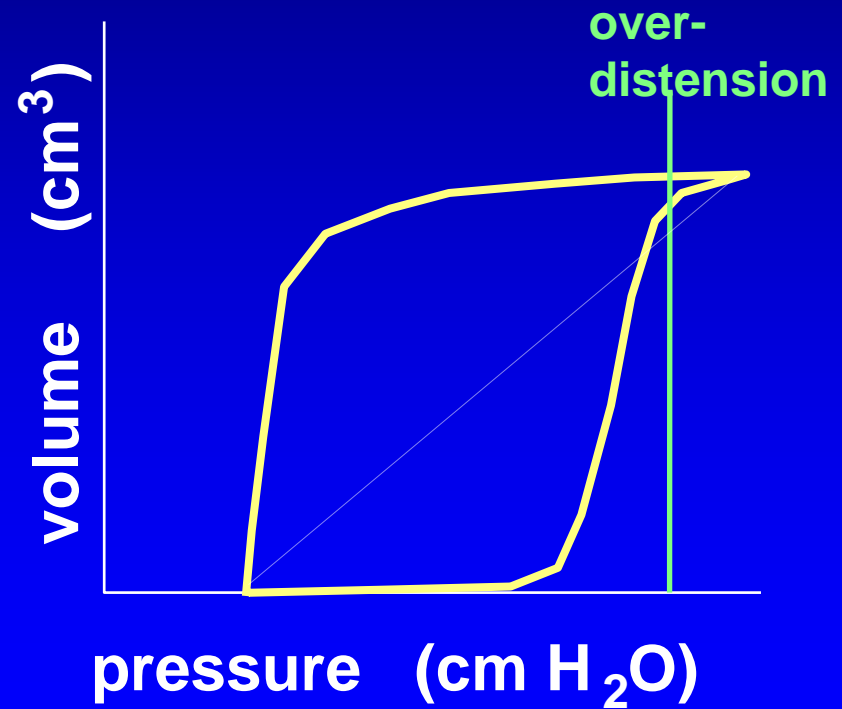
Pressure - Volume curve

$$\text{Compliance} = \Delta V / \Delta P$$

Normal



RDS



Pressure - Volume curve

Tracheal versus

Y-piece measurements

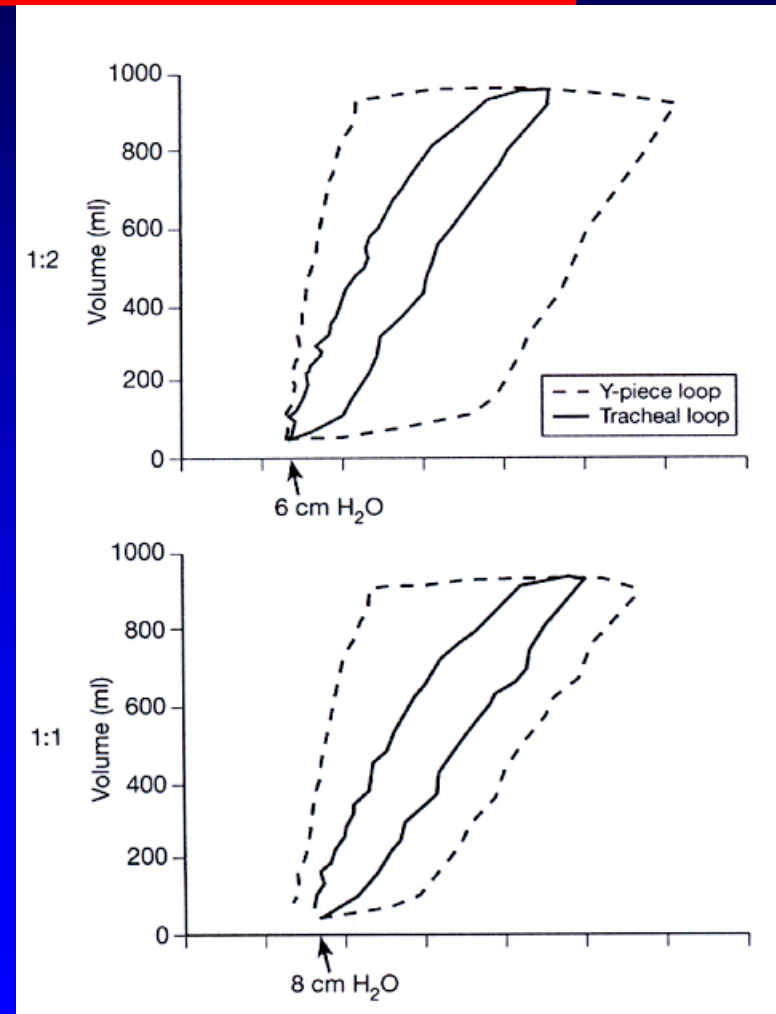
Place of loop:

I : E ratio

Width of loop:

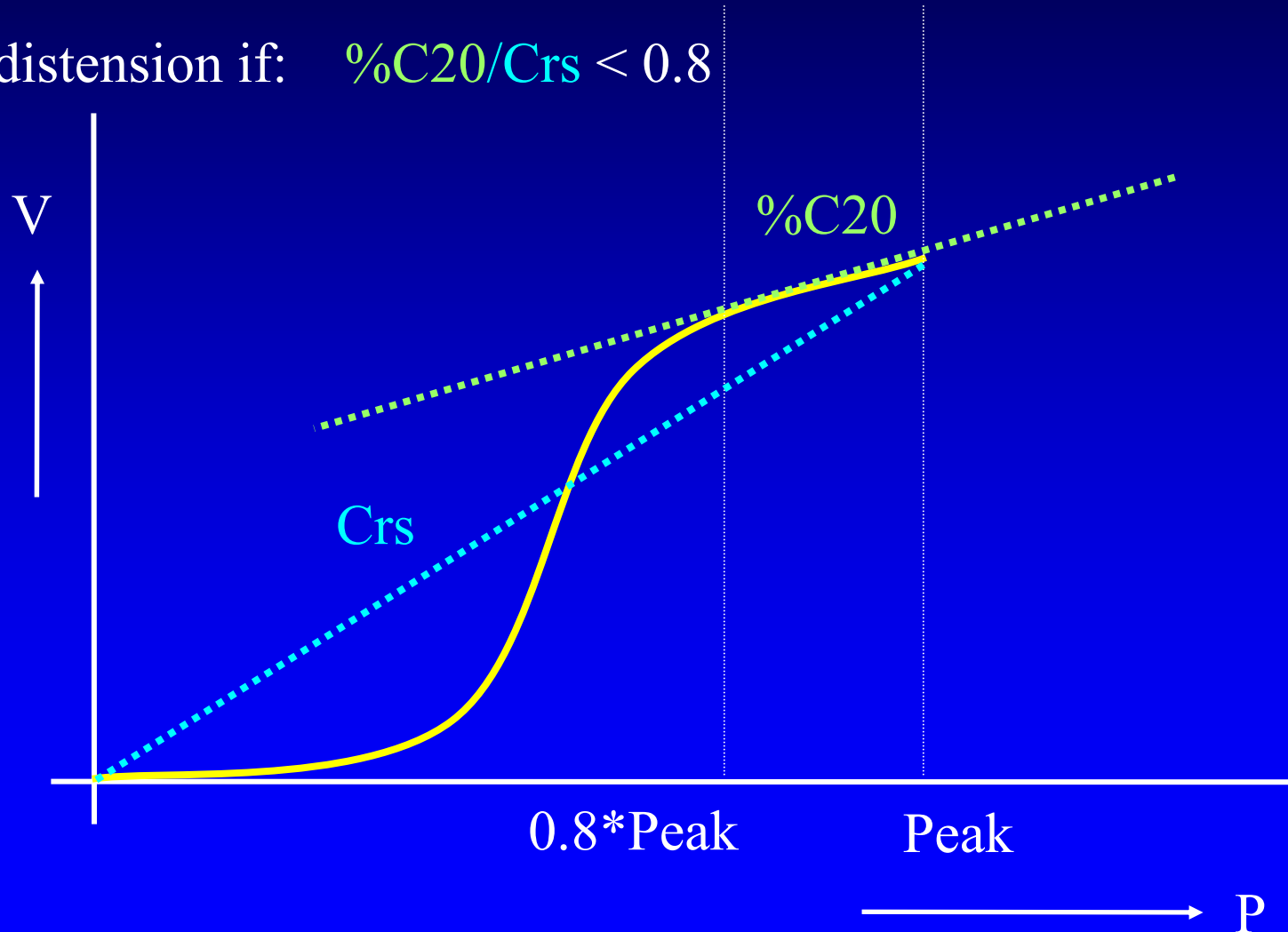
tube resistance

flow



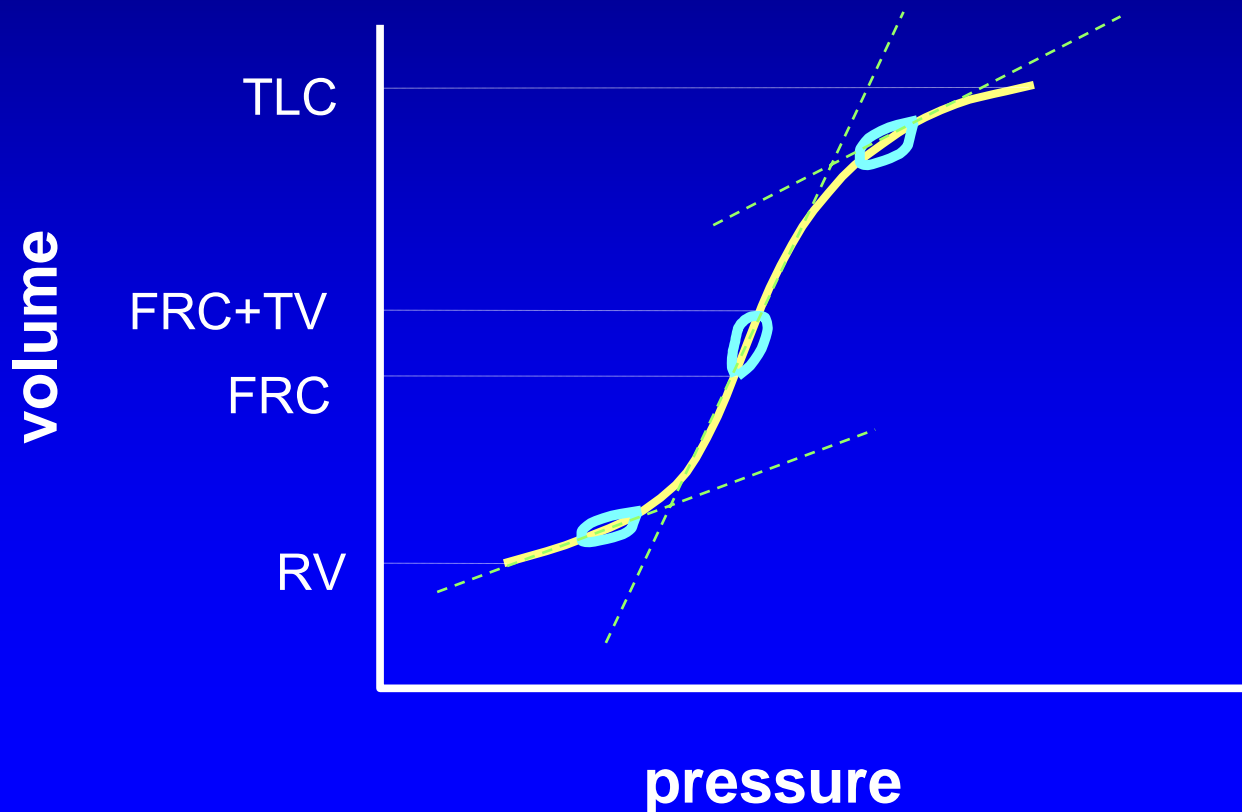
Pressure - Volume curve

Overdistension if: $\%C20/Crs < 0.8$



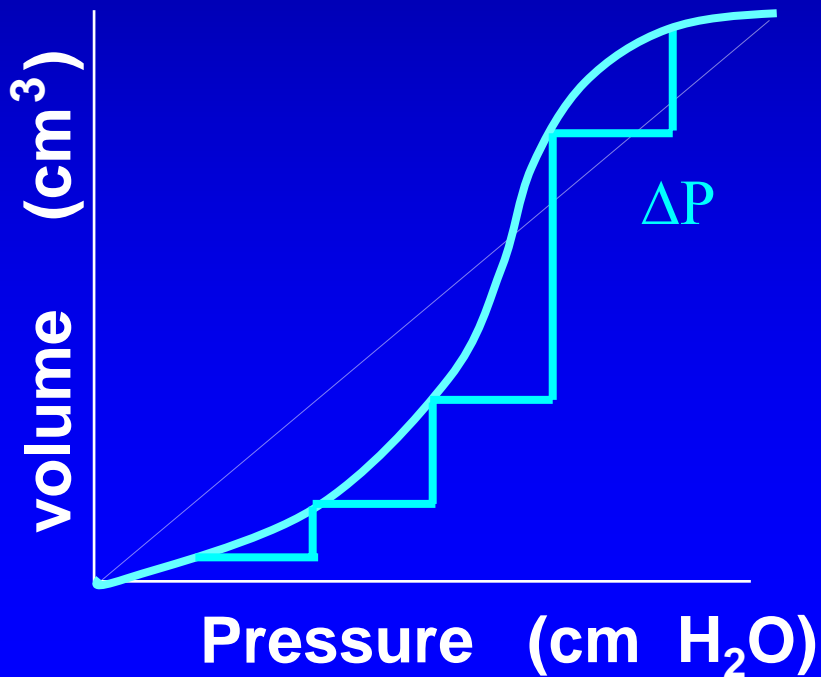
“Optimal” Compliance

Optimal lung volume
Minimal work of breathing



Difficulties when optimising

- 1) (Alveolar) distension versus recruitment
(increased FRC) versus (increased PaO₂)
- 2) Reciprocal summation of compliance



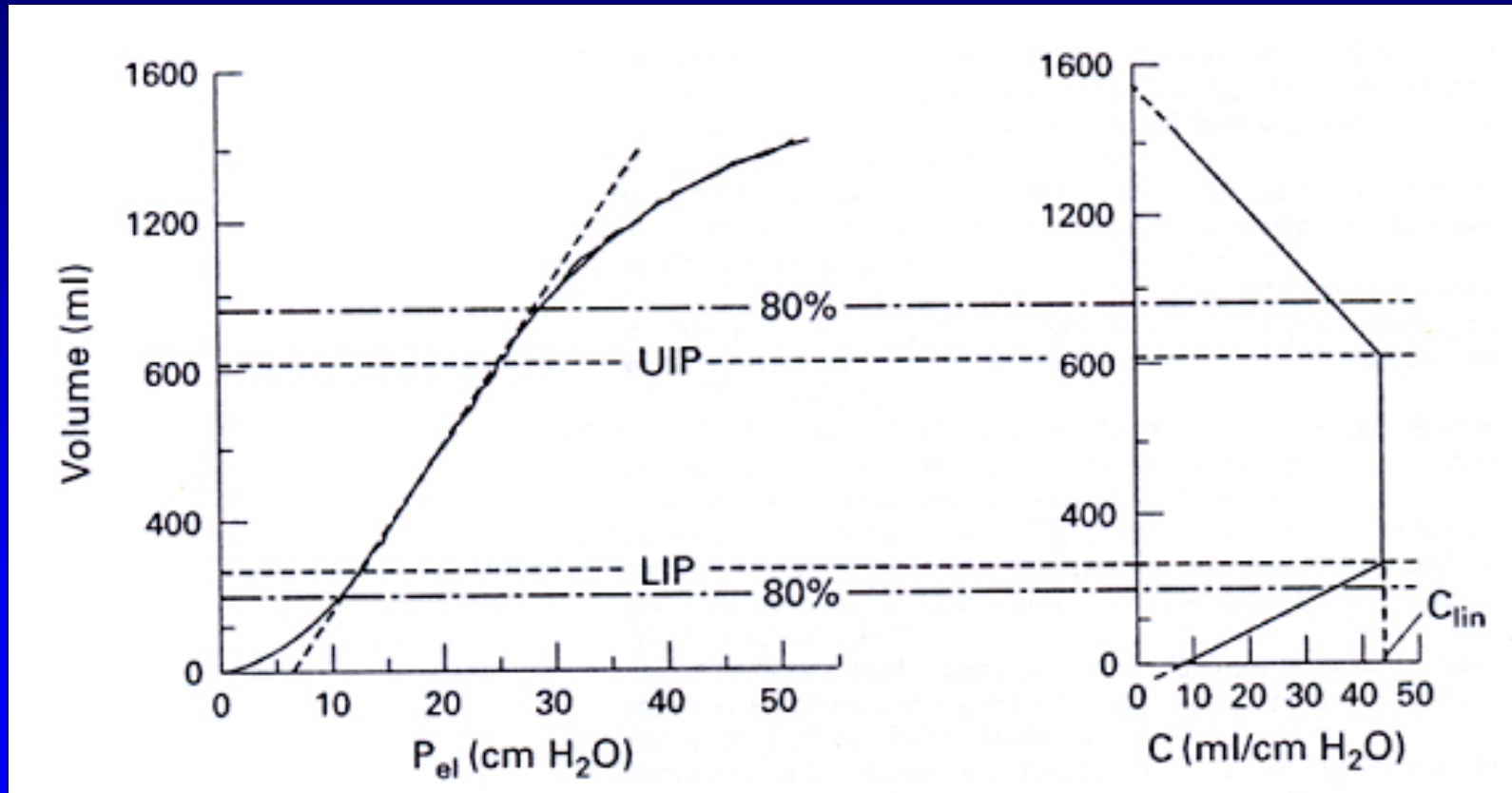
$$\frac{1}{C_{rs}} = \frac{1}{C_{chestwall}} + \frac{1}{C_{lung}}$$

For instance :

$$\frac{1}{0.2} = \frac{1}{1} + \frac{1}{0.25}$$

Pressure - Volume curve

Compliance is a function of the lung volume



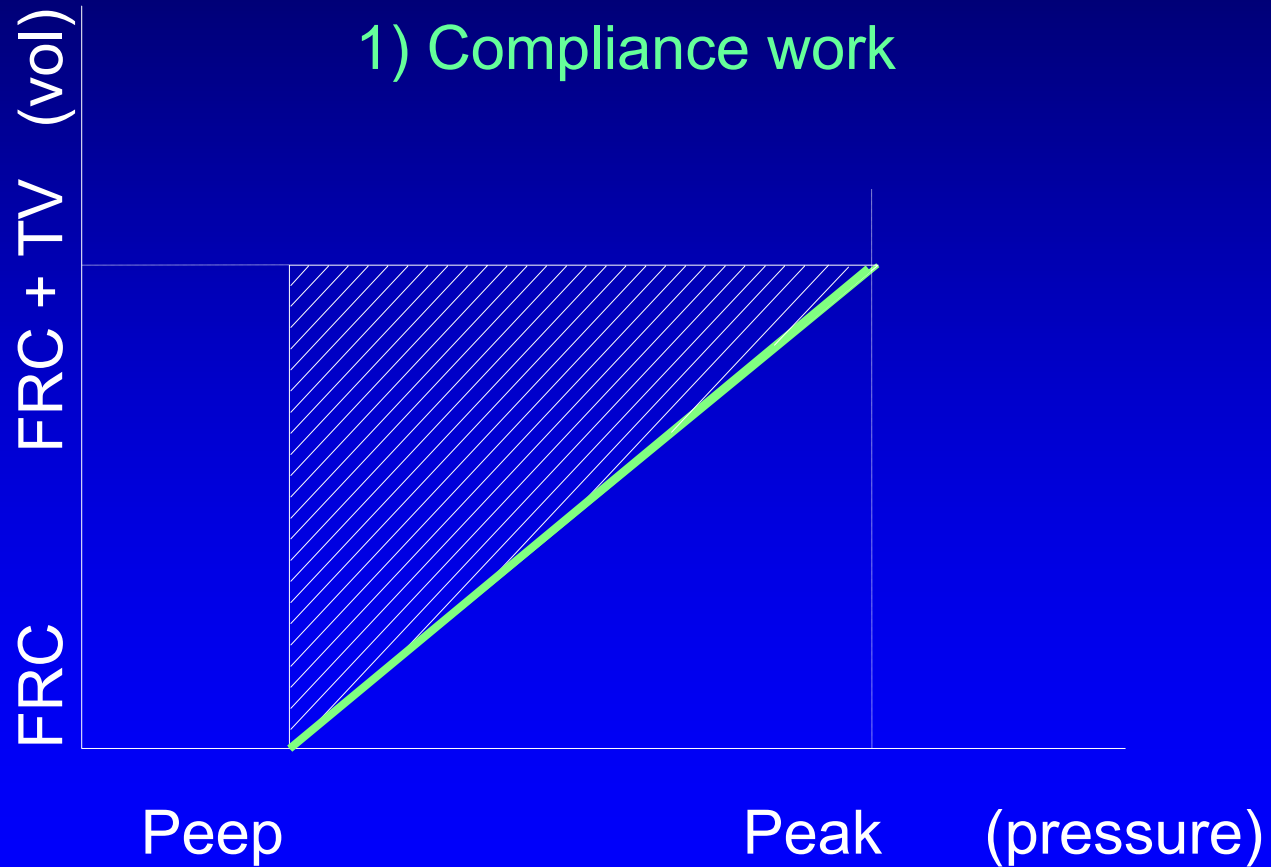
Resistance

$$\text{Resistance} = \text{pressure/flow} = p/Q = \frac{8 \mu l}{\pi r^4}$$

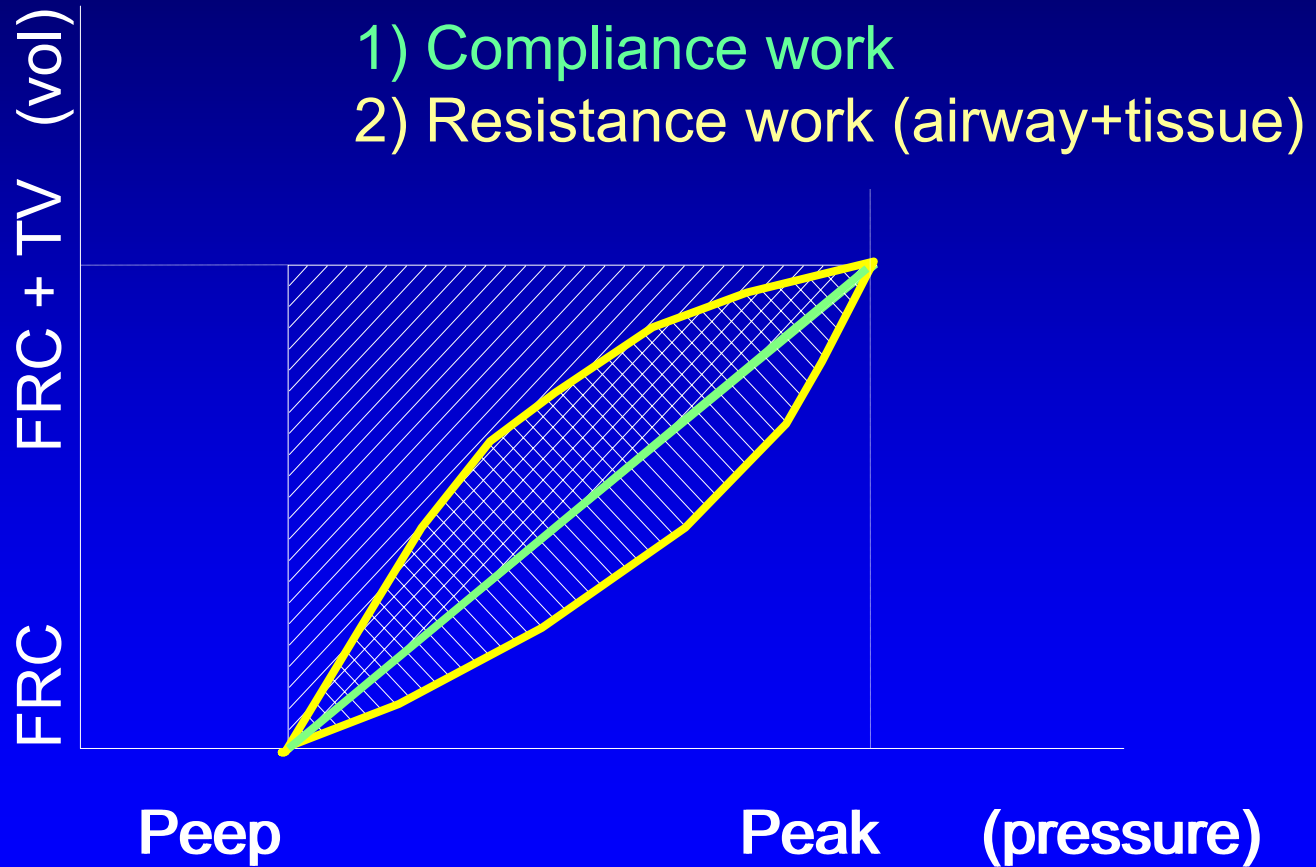
Rrs = Resistance respiratory system

Resistance mainly in first 5 airway generations.
Therefore small airway disease not detectable by
resistance measurements

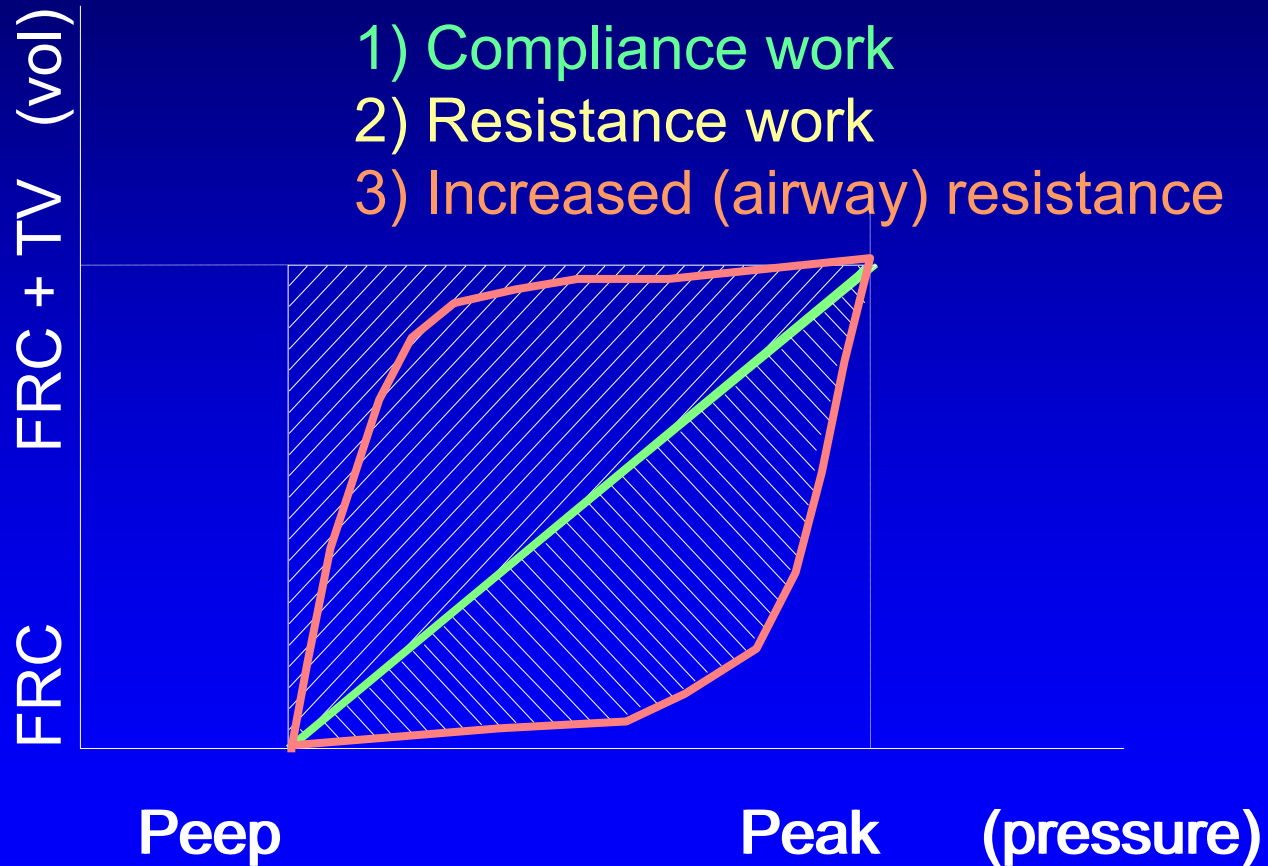
Work of breathing



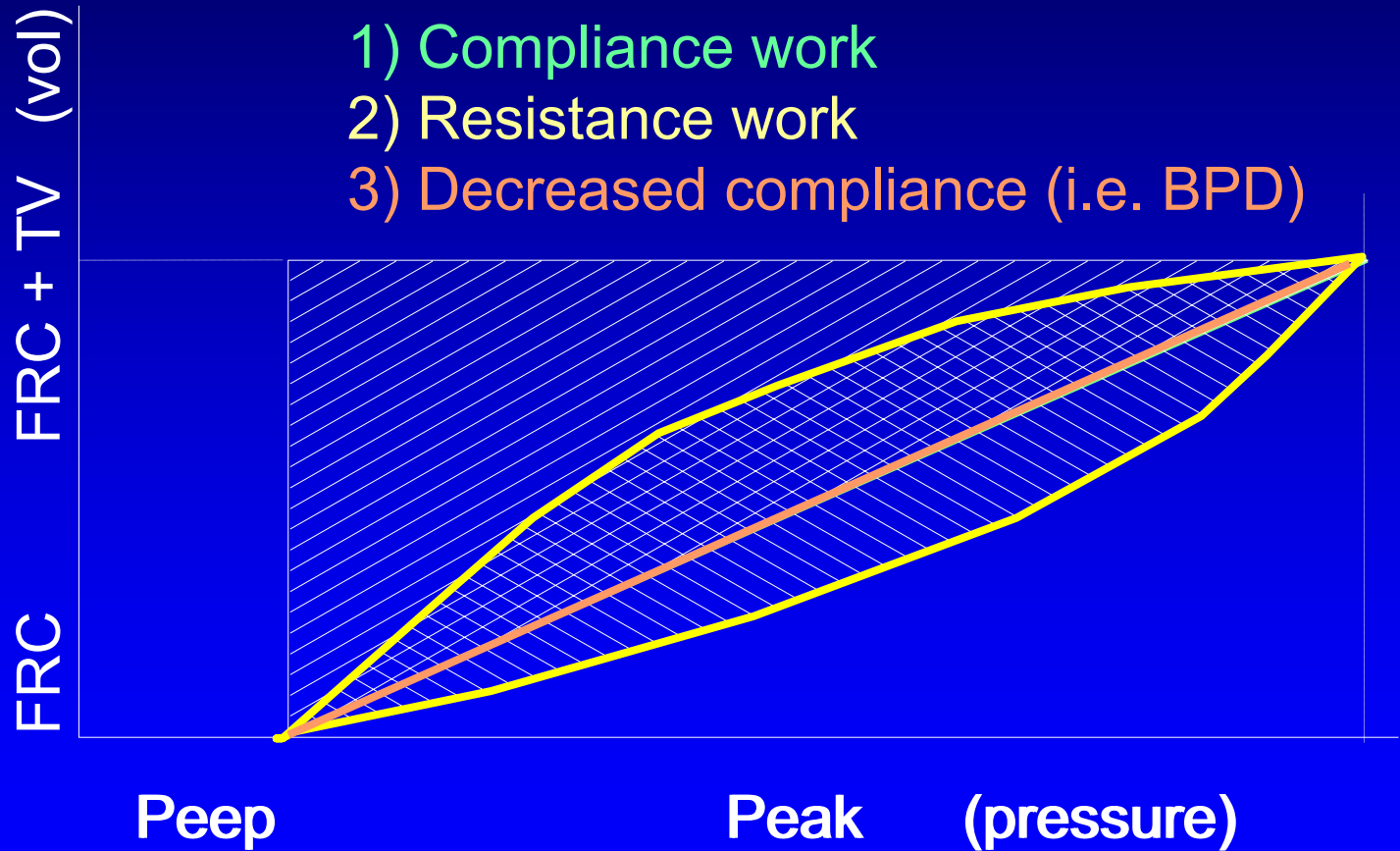
Work of breathing



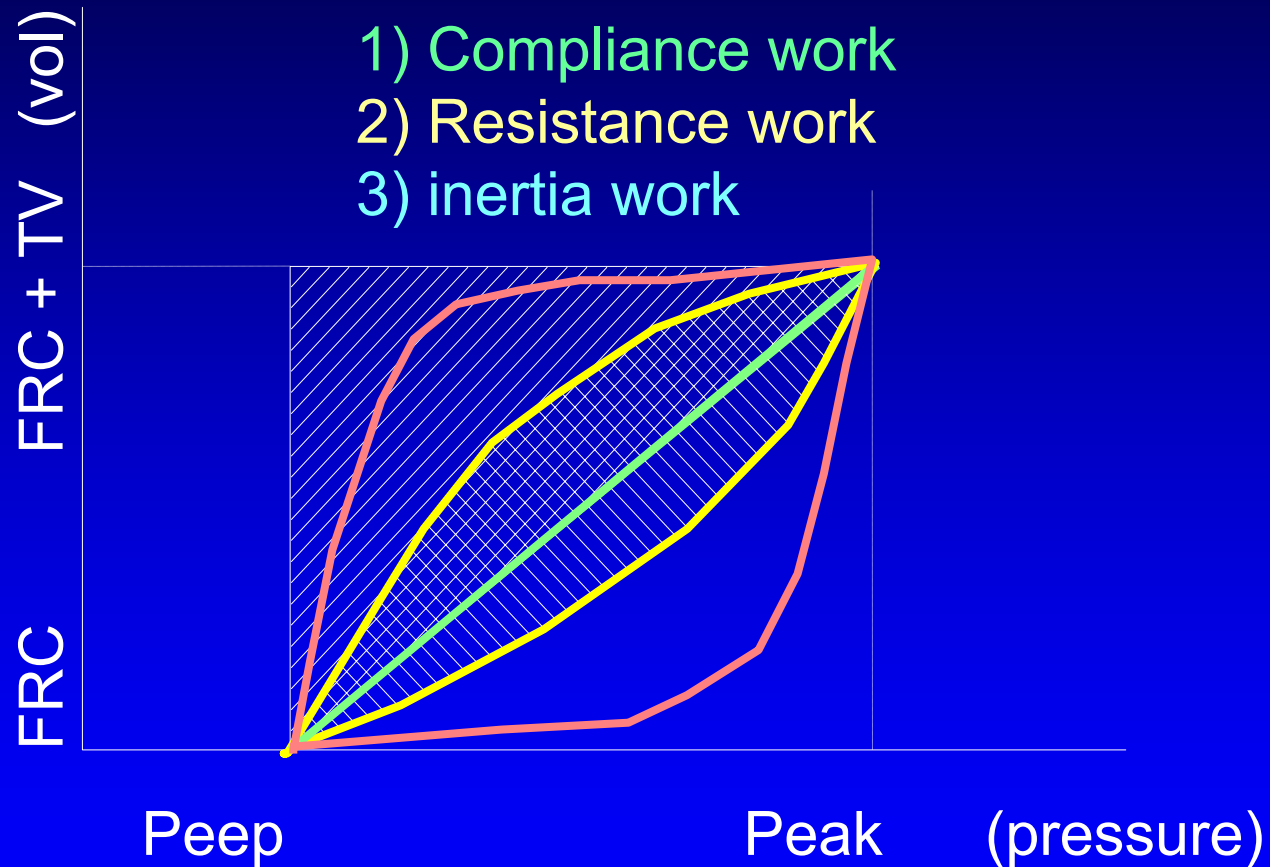
Work of breathing



Work of breathing



Work of breathing

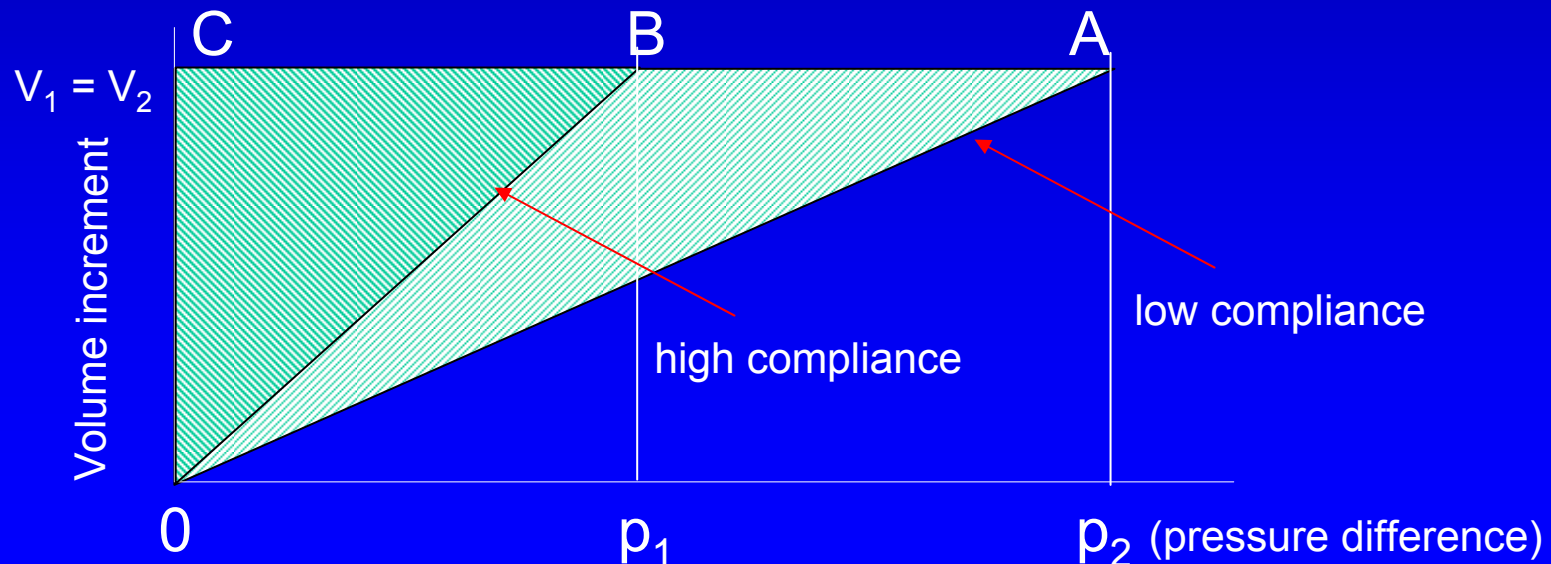


Work of breathing

$$\text{Work} = \text{Force} \cdot \text{distance} \quad W = F \cdot dx$$

$$\text{Force} = \text{pressure} \cdot \text{area} \quad \text{so} \quad W = p \cdot A \, dx = p \cdot dV$$

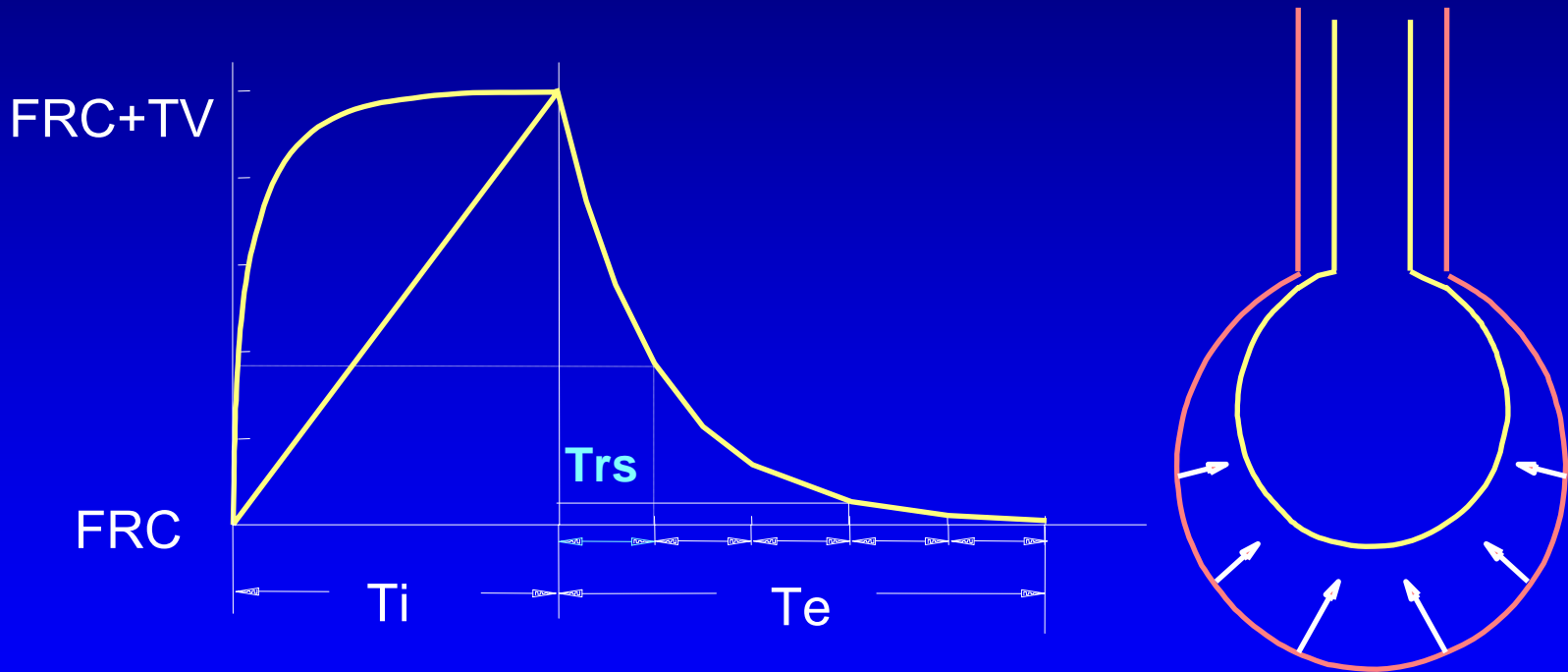
$$W_{\text{tot}} = W_{\text{compl}} + W_{\text{airw}} + W_{\text{tissue}} + W_{\text{inertia}}$$



Time constant

Time-constant = Resistance x Compliance

$$T_{rs} = R_{rs} \times C_{rs} = 0.1 \times 1.0$$



Work of breathing

$$W_{\text{tot}} = W_{\text{compl}} + W_{\text{airw}} + W_{\text{tissue}} + W_{\text{inertia}}$$

Work of breathing (compliance term)

$$W_{\text{compl}} = \int_{t=0}^{t=\frac{1}{2f}} p dV dt = \frac{TV^2 RR}{2C}$$

Airway resistance

$$R_p = \frac{8\mu l}{\pi r^4}$$

Röhler's equation

$$P_{\text{tot}} = P_{\text{el}} + P_{\text{res}} + P_{\text{in}}$$

$$P = EV + R\dot{V} + I\ddot{V}$$

$$P = EV \Rightarrow C = \frac{1}{E} = \frac{\Delta V}{\Delta P}$$

$$R = \frac{P}{\dot{V}}$$

P = Pressure

V = Volume

\dot{V} = Flow

\ddot{V} = Acceleration

E = Elasticity

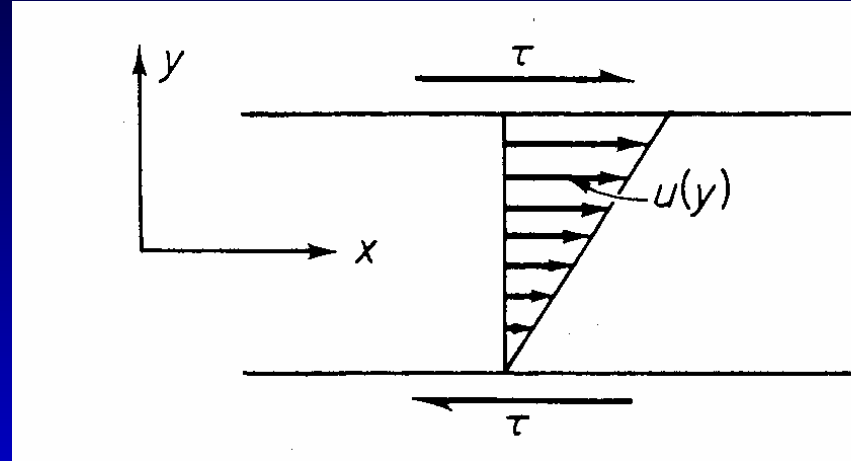
R = Resistance

I = Inertia

C = Compliance

Viscosity (Newton)

$$\tau = \mu \frac{du}{dy}$$



The viscosity μ has as dimension Ns/m^2

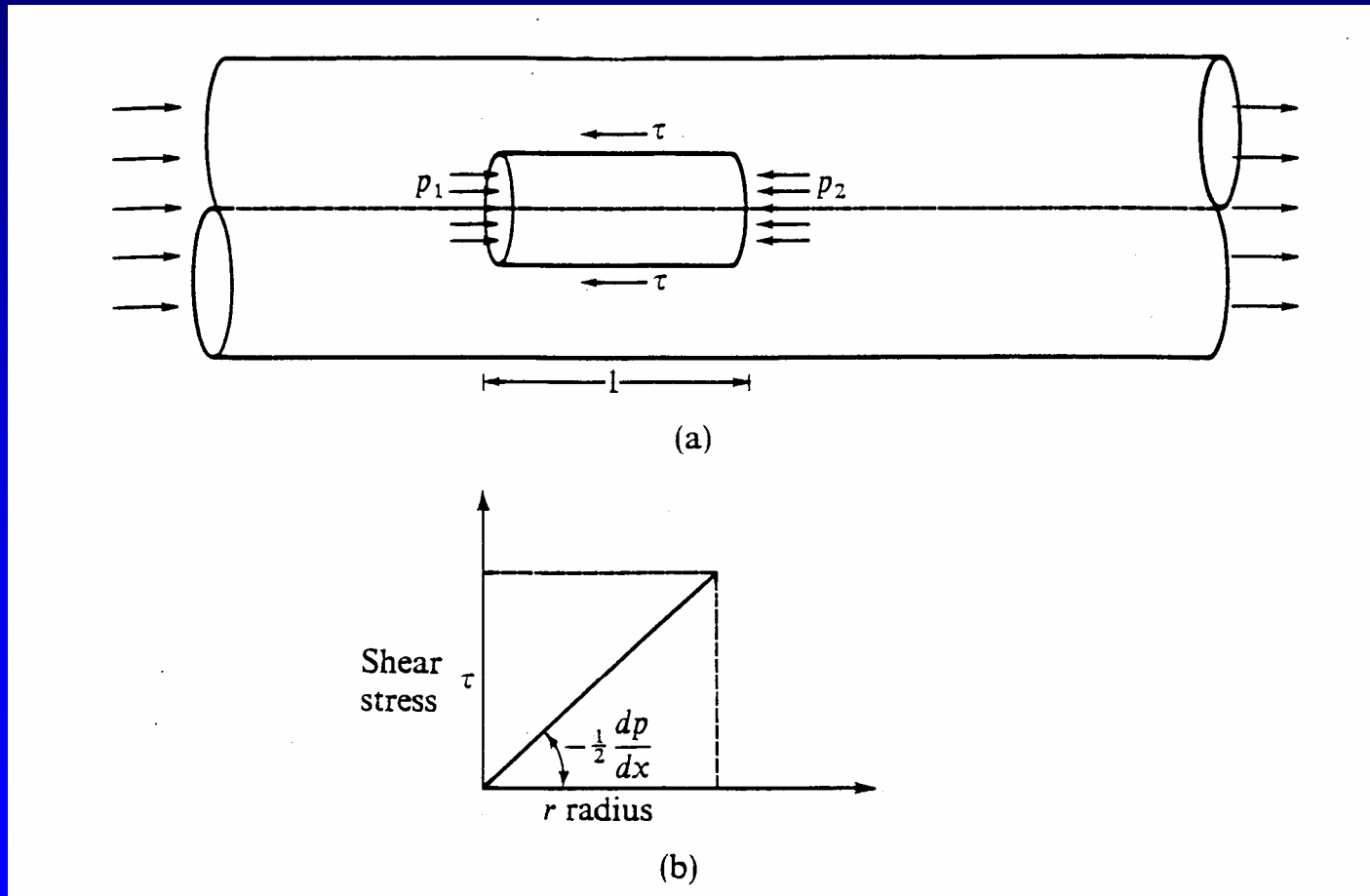
Poiseuille: poise (P), 1 poise = 0.1 Ns/m^2

Air = $1.8 \cdot 10^{-4} \text{ P}$

Water = $0.01 \text{ P} = 1 \text{ cP}$

Poiseuille

Stationary laminar tube flow without entree-effects



Poiseuille

Assumptions: the flow is place and time-independent, axis-symmetrical, and there is no slip at the wall.

$$\tau \cdot 2\pi r dx = \pi r^2 dp$$

so

$$\tau = \frac{r}{2} \frac{dp}{dx}$$

Together with a constitutive equation (which relates shear stress τ with the velocity gradient) a closed set of equations is obtained.

Newtonian fluid per definition :

$$\tau = \mu \frac{du}{dr}$$

substitution gives:
$$\frac{du}{dr} = \frac{r}{2\mu} \frac{dp}{dx}$$

so

$$u = \frac{r^2}{4\mu} \frac{dp}{dx} + B$$

Poiseuille

The constant B can be derived from the boundary condition which states that there is no slip at the airway wall so $u=0$ if $r=a$, which yields:

$$u = -\frac{1}{4\mu} (a^2 - r^2) \frac{dp}{dx}$$

Which is a parabolic flow.

The **flowrate** through the tube is:

$$\dot{Q} = 2\pi \int_0^a u r dr = -2\pi \int_0^a \frac{r}{4\mu} (a^2 - r^2) \frac{dp}{dx} dr = -\frac{\pi a^4}{8\mu} \frac{dp}{dx}$$

(law of Poiseuille)

Poiseuille

So the average velocity is Q/A with:

$$\dot{Q} = -\frac{\pi a^4}{8\mu} \frac{dp}{dx}$$

$$u_m = -\frac{a^2}{8\mu} \frac{dp}{dx}$$

Which gives

$$\dot{\gamma} = -\left. \frac{du}{dr} \right|_{r=a} = \frac{1}{2} \frac{a}{\mu} \frac{dp}{dx} = -\frac{4u_m}{a}$$

Apparant viscosity

The law of Poiseuille is: $\frac{\Delta p}{\Delta L} = \frac{8\mu}{\pi a^4} \dot{Q}$, so:

$$\mu = \frac{\Delta p}{\Delta L} \frac{\pi a^4}{8} \frac{1}{\dot{Q}}$$

μ = apparant viscositeit

μ_0 = the viscosity of an (Newtonian) fluid

$\mu_r = \mu / \mu_0$ = relative viscosity

Normal respiration/ventilation

Convection (laminar/turbulent)

Diffusion

Characteristic dimensionless numbers

Several forces can work on an elementary fluid particle. We can distinguish convective inertia forces, time dependent inertia forces, viscous forces, pressure forces and body-forces.

Compare the convective inertia forces with the viscous forces for a fluid with density ρ , velocity U and characteristic length L . The ratio of the convective inertia forces and the viscous forces becomes:

$$\frac{\text{convective inertia force}}{\text{viscous force}} = \frac{\rho U^2 / L}{\mu \frac{U}{L^2}} = \frac{\rho U L}{\mu} = \frac{U L}{\nu} = \text{Re}$$

with $\nu = \mu / \rho$ the kinematic viscosity

Characteristic dimensionless numbers

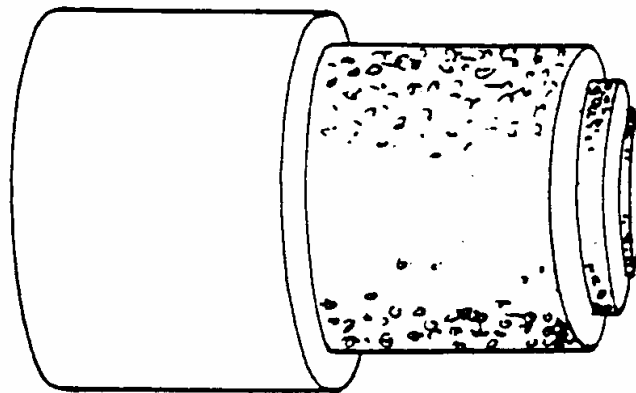
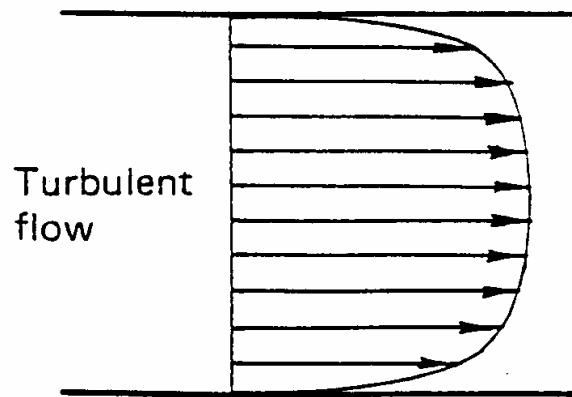
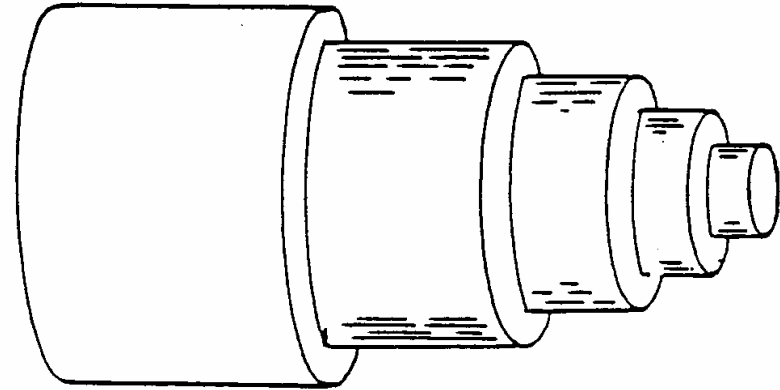
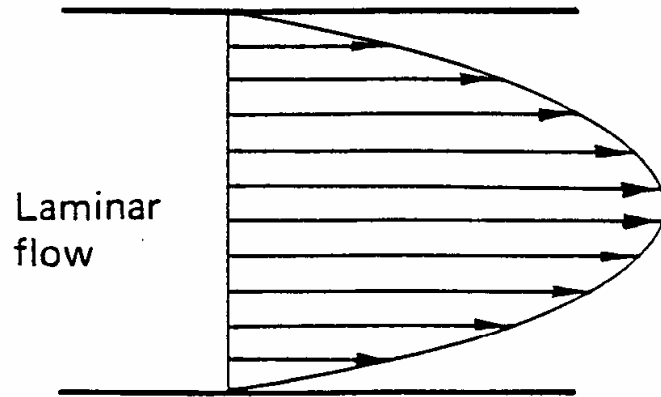
Take the ratio from the time dependent mass inertia forces and the viscous forces (with ω as characteristic frequency)

$$\frac{\text{tijdsafhankelijk massa traagheidskracht}}{\text{visceuze kracht}} = \frac{\rho \omega U}{\mu \frac{U}{L^2}} = \frac{\rho \omega L^2}{\mu} = \frac{\omega L^2}{\nu} = \text{Stokes getal}$$

This is better known as the Womersley number α , which is the square root of the Stokes number, in which r is a characteristic length:

$$\alpha = r \sqrt{\frac{\omega}{\nu}}$$

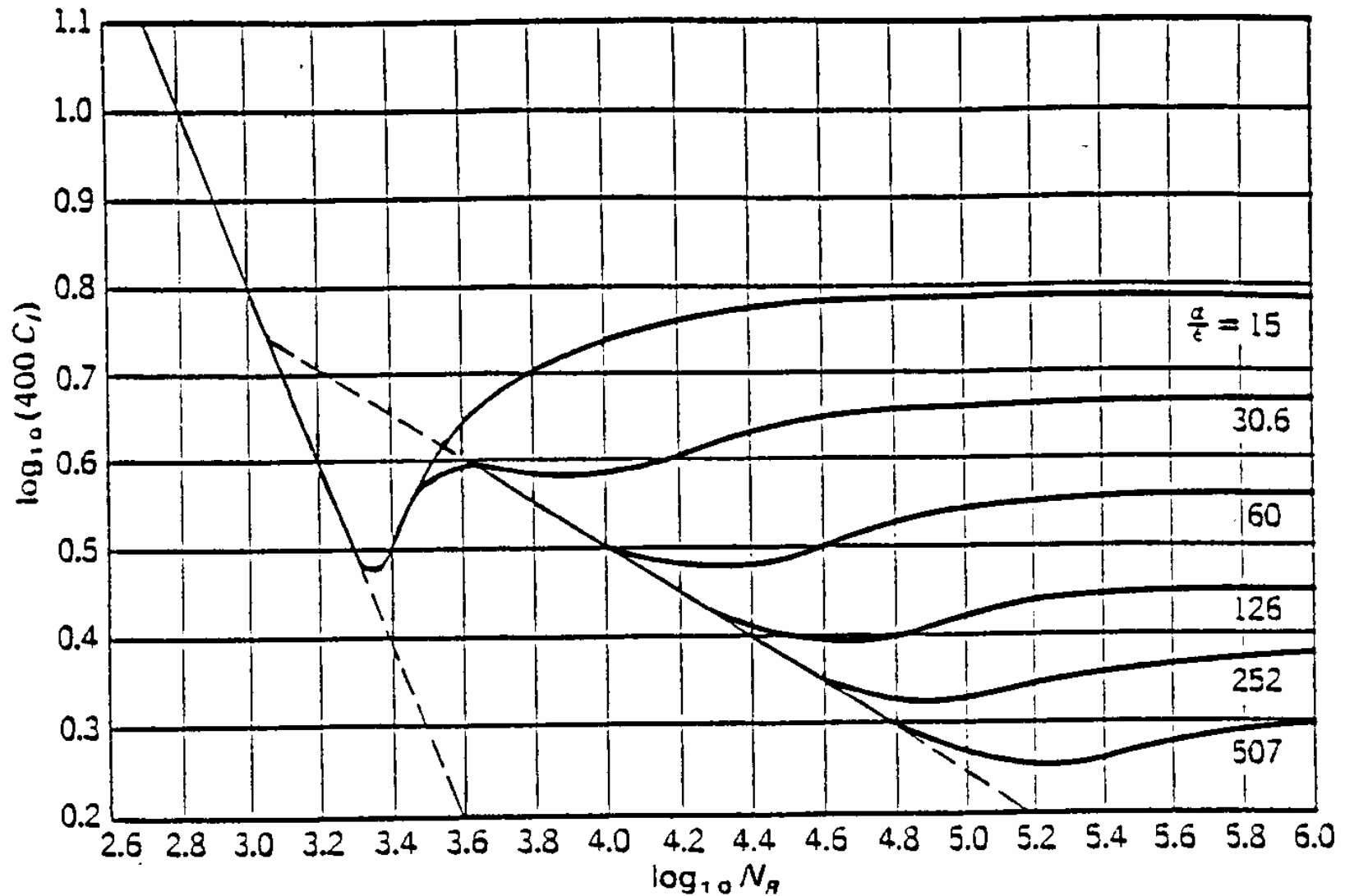
Laminar-Turbulent



Velocity profile

Sliding shell analog

Laminar-Turbulent



Diffusion

Kinetic gas-theory:

$$u = \sqrt{\frac{8KNT}{\pi W}}$$

K = Boltzmann constant = $1.3807 \cdot 10^{-23}$ (Joule/K)

T = Temperature (K)

N = number of Avogadro = $6.02214 \cdot 10^{23}$

W = weight of 1 mol (kg)

At room temperature $T = 293$ K this results in $u = 460$ m/s

The mean free path length is around $9.8 \cdot 10^{-8}$ m

Respiration

a) **Mathematical:**

- Block / Sinusoidal

b) **Normal:**

- measured experimentally, average fit

c) **Pathological:**

- measured experimentally, average fit

Breathing 1-D

Flow through a tube: law of mass-conservation
 density * velocity * cross-sectional area = constant

$$r_0 = 0.8 \text{ cm}$$

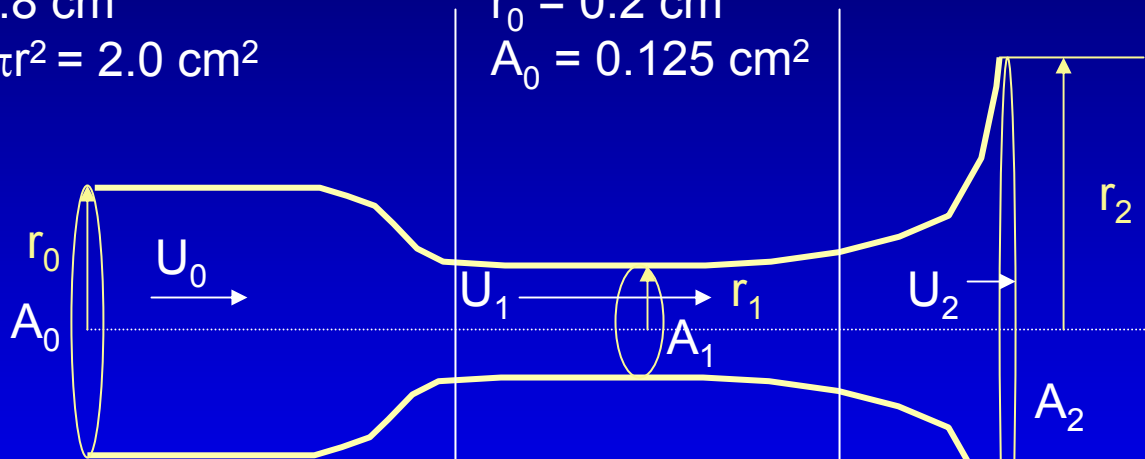
$$A_0 = \pi r^2 = 2.0 \text{ cm}^2$$

$$r_0 = 0.2 \text{ cm}$$

$$A_0 = 0.125 \text{ cm}^2$$

$$r_0 = 80 \text{ cm}$$

$$A_0 = 20000 \text{ cm}^2$$



$$Tv = 500 \text{ cm}^3$$

$$RR = 12 \text{ so } 1 \text{ breath} = 5 \text{ sec}$$

$$V_0 = 500/2.5 = 200 \text{ cm}^3/\text{s}$$

$$U_0 = 200/2 = 100 \text{ cm/s}$$

$$U_1 = 200/0.125$$

$$= 1600 \text{ cm/s}$$

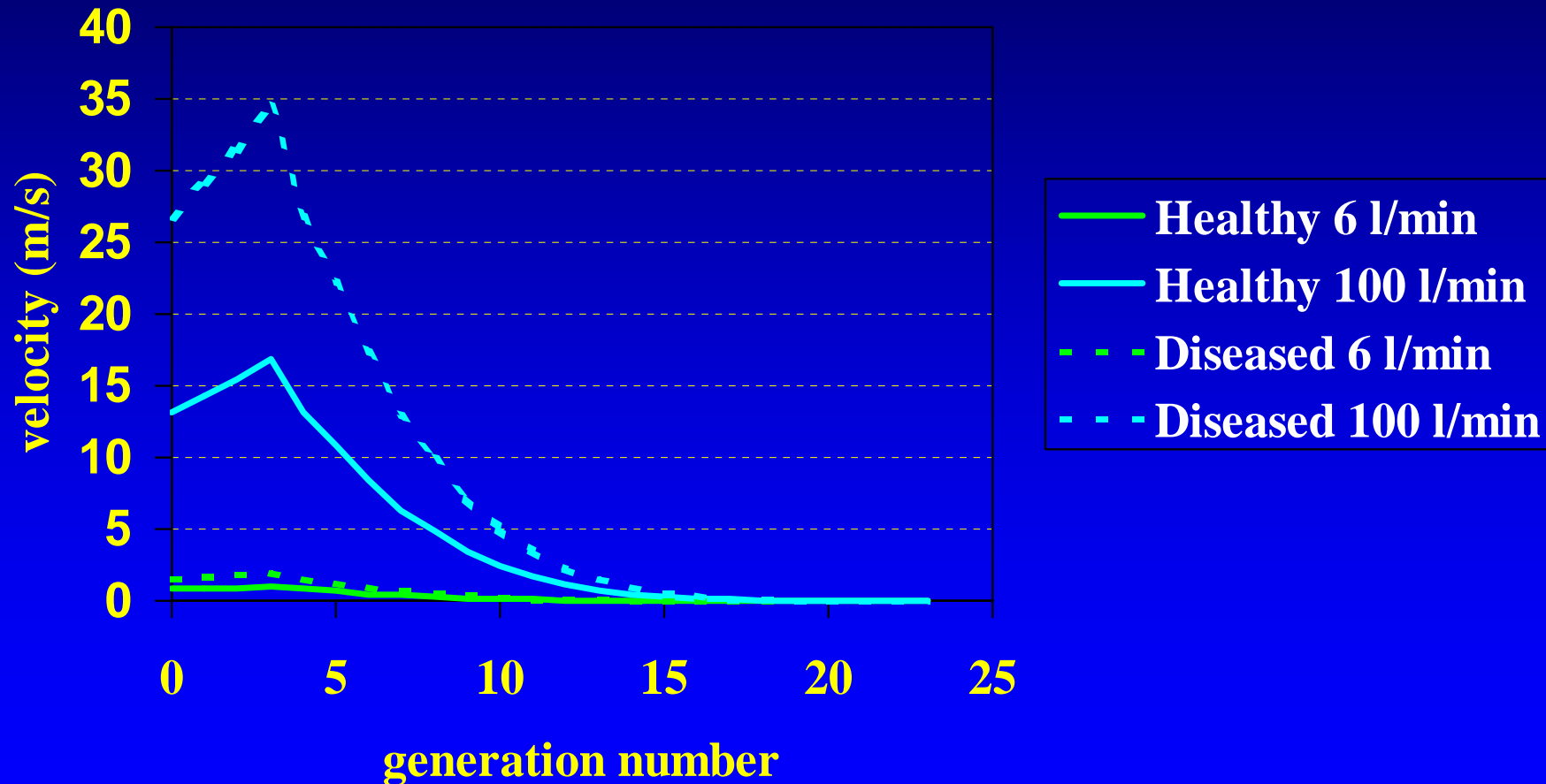
$$U_2 = 200/20000$$

$$= 0.01 \text{ cm/s}$$

Respiration 1-D

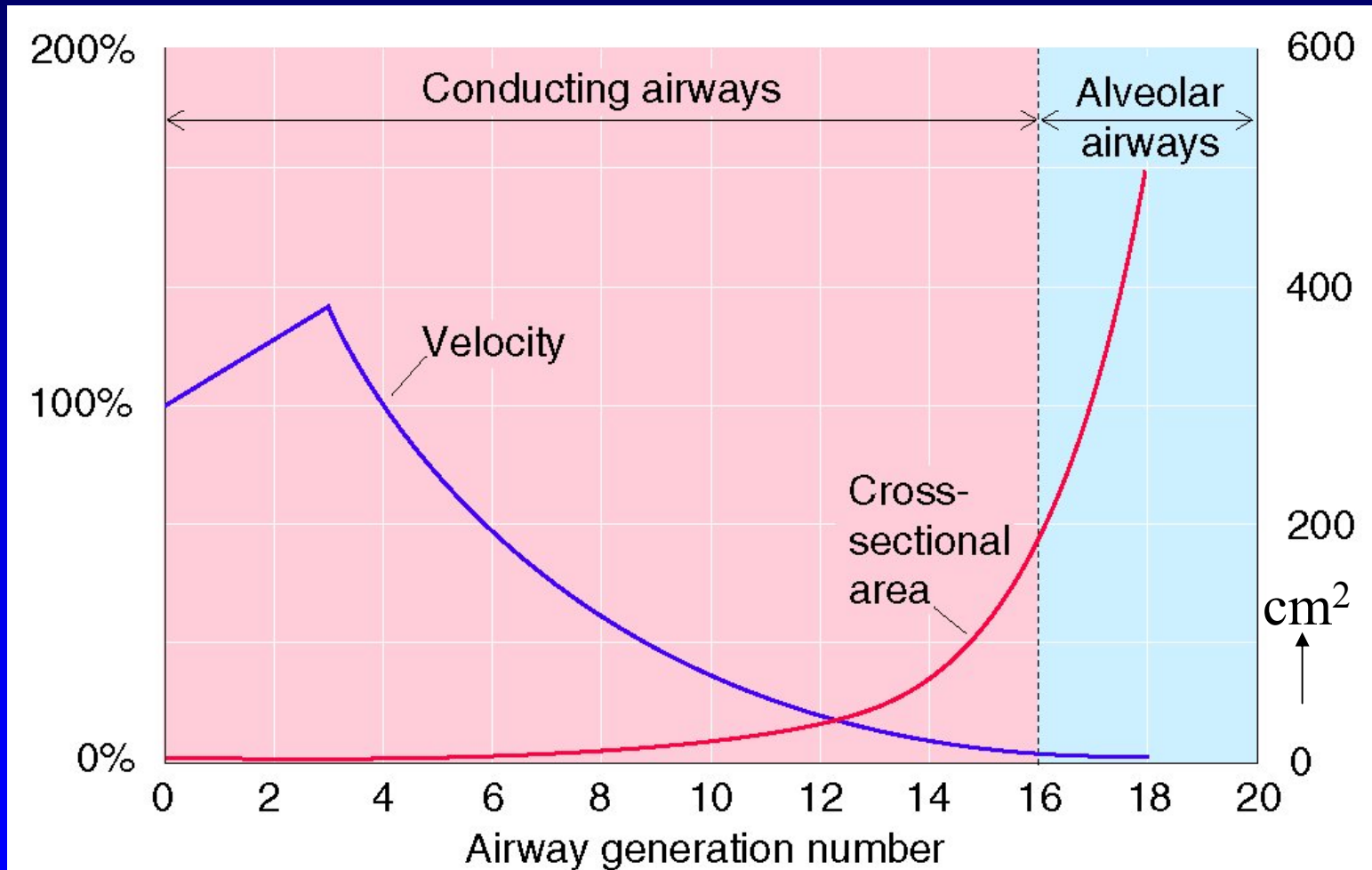
Healthy = Weibel model 1963

Diseased = Idem, but diameter airways 30% reduced



Velocity in the human airways

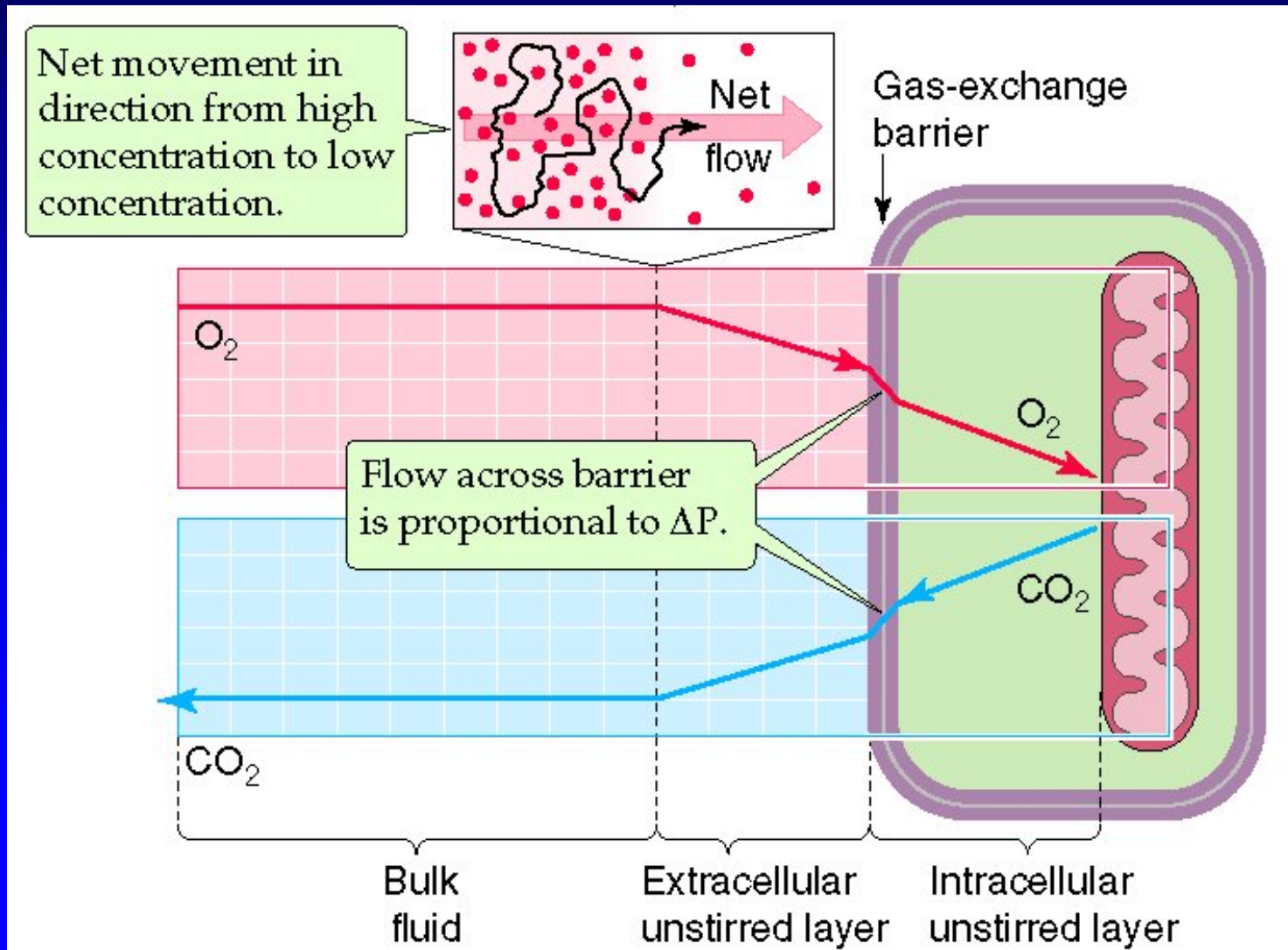
1 atm = 101.3 kPa = 760 mm Hg = 10 m H₂O



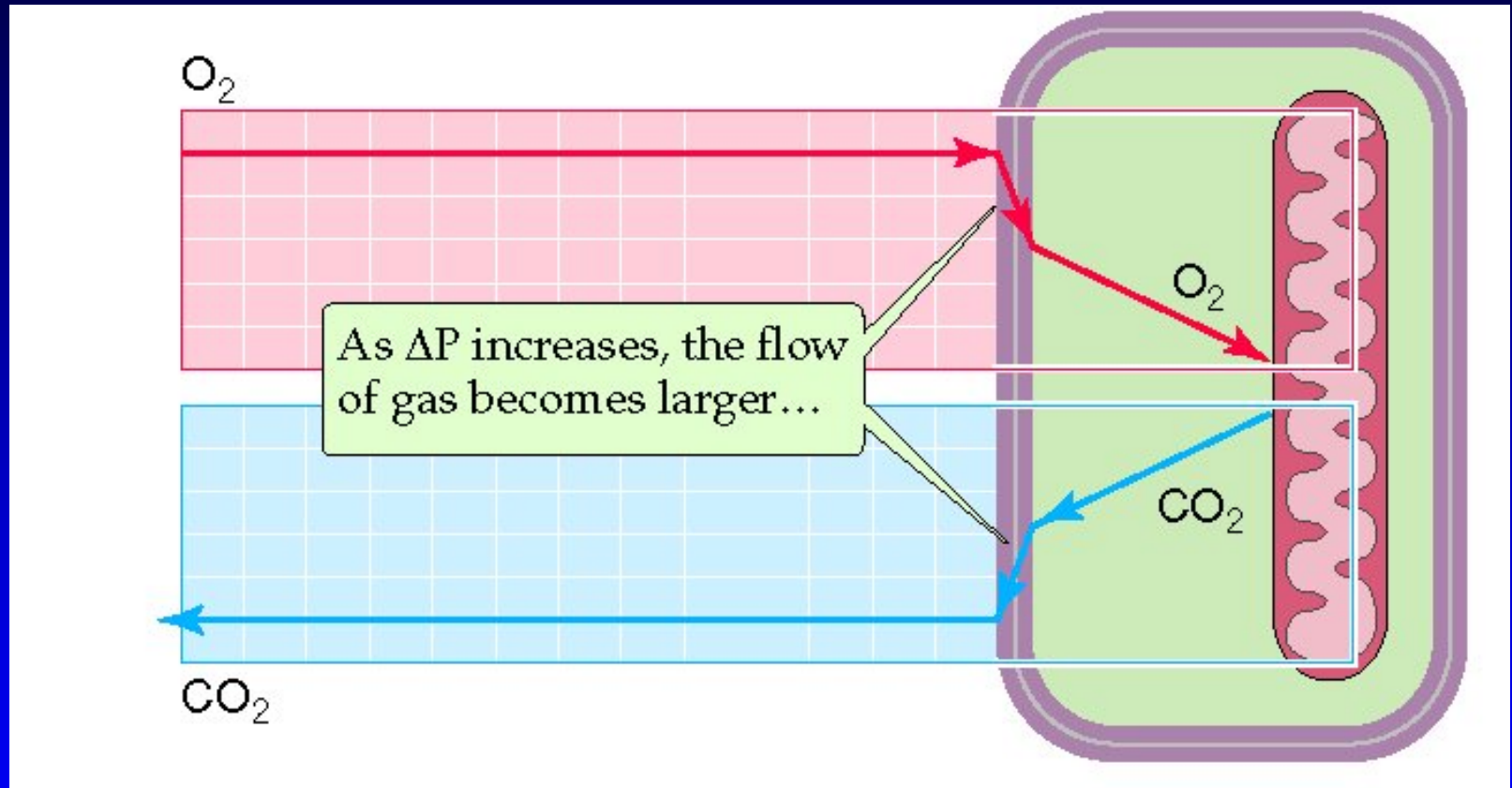
One cell without convection

Diffusion: the law of Fick

Flow $\propto \Delta P$



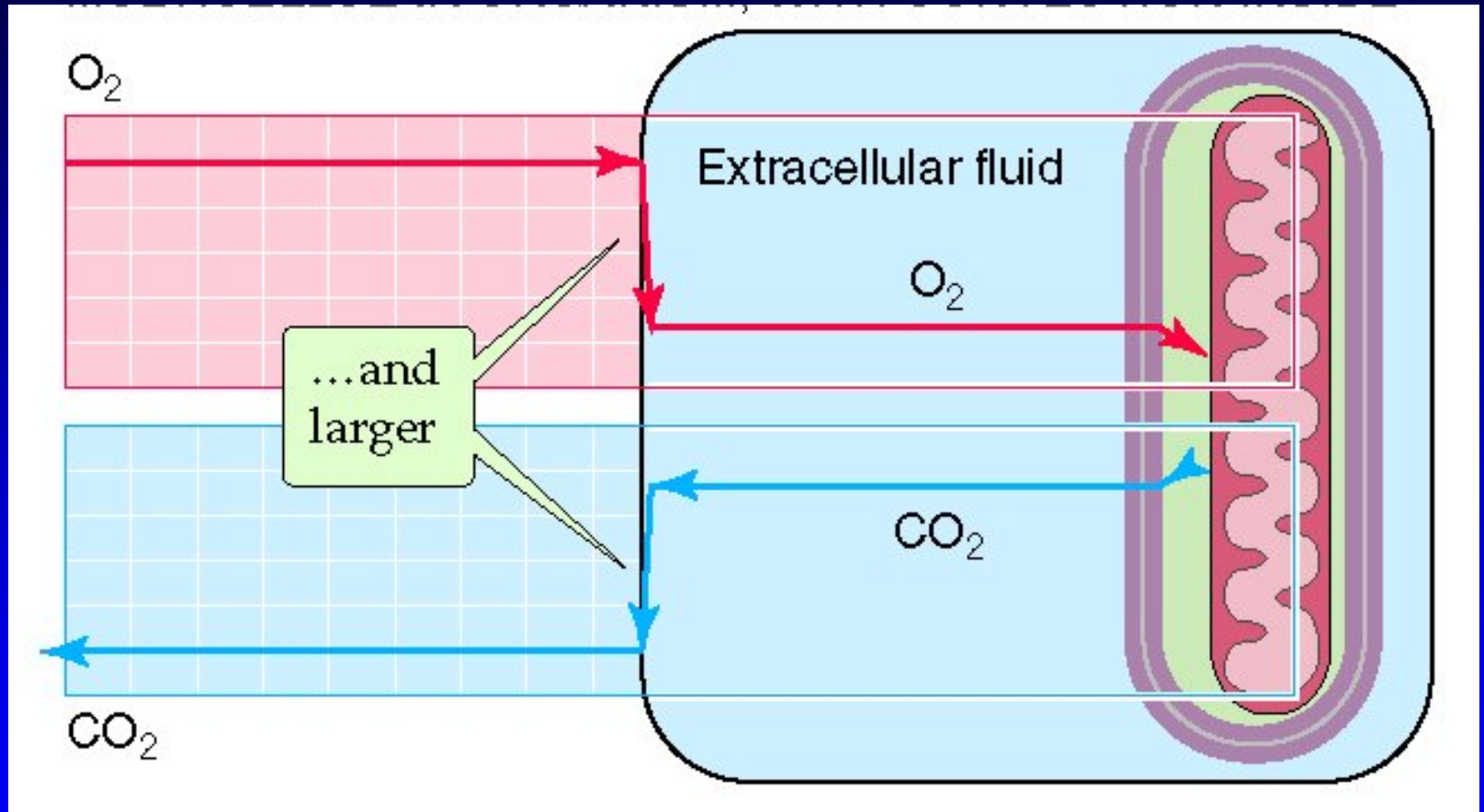
One cel with convection outside



Without convection: max size = 1 mm,
 H_2O at $25^\circ C$ has a PO_2 of 154 mmHg (low solvability)

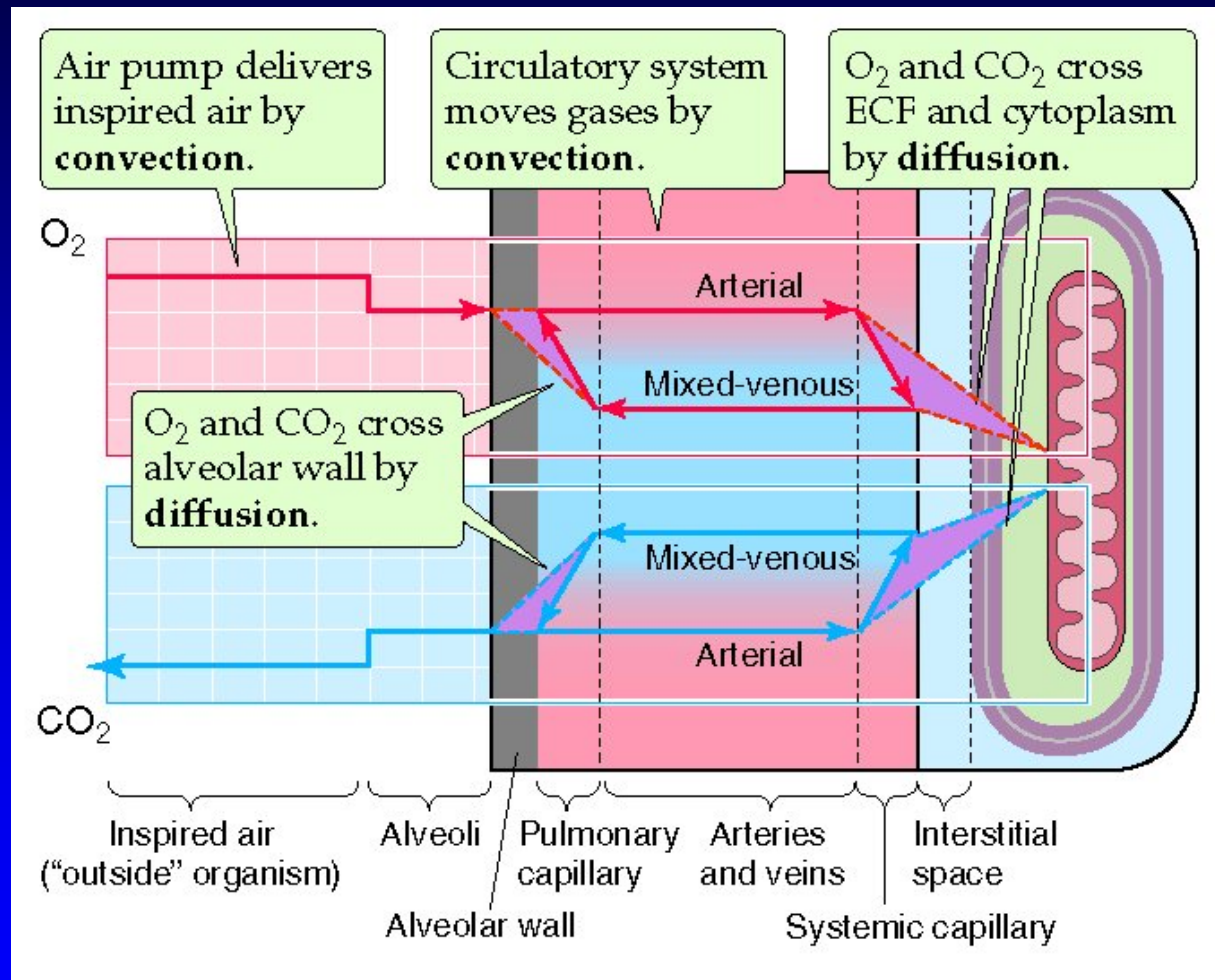
Example: one cel with cilia

More cells: 2-sided convection



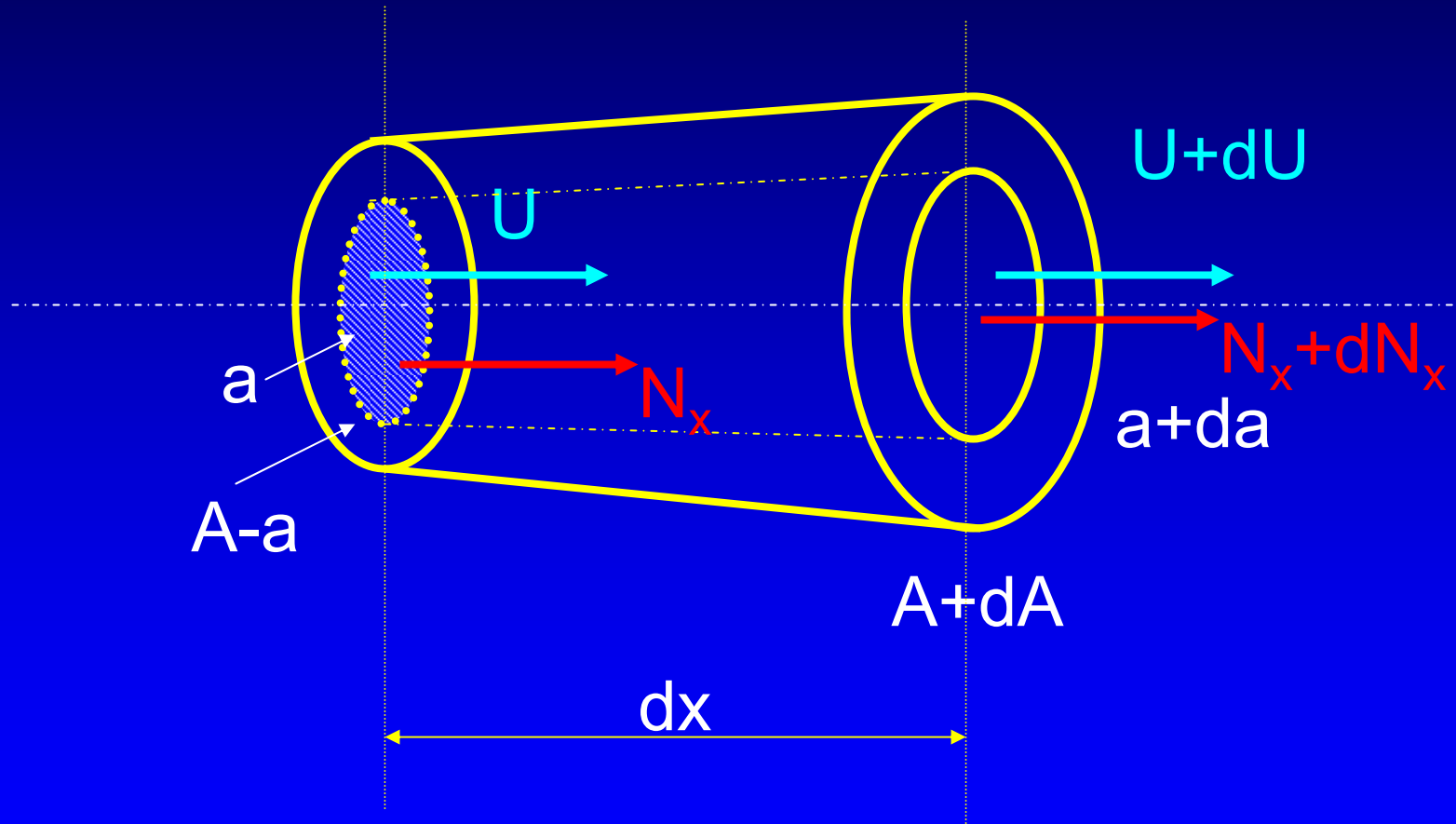
Shell: pumps 16000 ml H_2O to extract 1 ml O_2
Fish: more efficient: 400:1

More cells with a hart (“4 chambers”)



Air contains 210 ml O₂ per litre instead of 35 ml O₂ per litre water
Human 6000ml / 250 ml = 40:1

1D Convection-diffusion equation



1D Convection-diffusion equation

Consider the change of concentration in a volume element

$$\frac{\partial}{\partial t} \left[\frac{(A + (A + dA))}{2} dx c \right] = a N_x - (a + da)(N_x + dN_x) + AUc - (A + dA)(U + dU)(c + dc) + Q \left[\frac{(A + (A + dA)) dx}{2} \right]$$

Omitting higher order terms yields:

$$Adx \frac{\partial c}{\partial t} = -N_x da - adN_x - AUdc - AcdU - cUdA + QAdx$$

With the law of mass conservation:

$$\rho UA = \text{const. so } AU = \text{const. so } AdU + UdA = 0 \text{ so } AdU = -UDA$$

Two terms cancel, and after division by Adx the result is:

$$\frac{\partial c}{\partial t} = -\frac{N_x}{A} \frac{da}{dx} - \frac{a}{A} \frac{\partial N_x}{\partial x} - U \frac{\partial c}{\partial x} + Q$$

with

$$N_x = -D \frac{\partial c}{\partial x}$$

this results in:

$$\frac{\partial c}{\partial t} = +\frac{D}{A} \frac{da}{dx} \frac{\partial c}{\partial x} + D \frac{a}{A} \frac{\partial^2 C}{\partial x^2} - U \frac{\partial c}{\partial x} + Q$$

1D Convection-diffusion equation

$$\frac{\partial c}{\partial t} + U \frac{\partial c}{\partial x} - \frac{D}{A} \frac{\partial a}{\partial x} \frac{\partial c}{\partial x} - D \frac{a}{A} \frac{\partial^2 c}{\partial x^2} = Q$$

c = concentration O_2 / CO_2

x = length scale in flow direction

t = time

U = convection speed

D = diffusion coefficient

a = cross-sectional area without alveoli

A = as above but with alveoli

Q = source/sink

1D Convection-diffusion equation

$$\frac{\partial c}{\partial t} + R(x, t) \frac{\partial c}{\partial x} - S(x) \frac{\partial^2 c}{\partial x^2} = 0$$

$R \gg S \Rightarrow$ 1-D wave speed equation:

$$\frac{\partial c}{\partial t} + R(x, t) \frac{\partial c}{\partial x} = 0$$

With solution (assume $R = \text{constant}$):
($R =$ wave speed)

$$c = f(x - Rt)$$

If $S \gg R$ the diffusion equation:

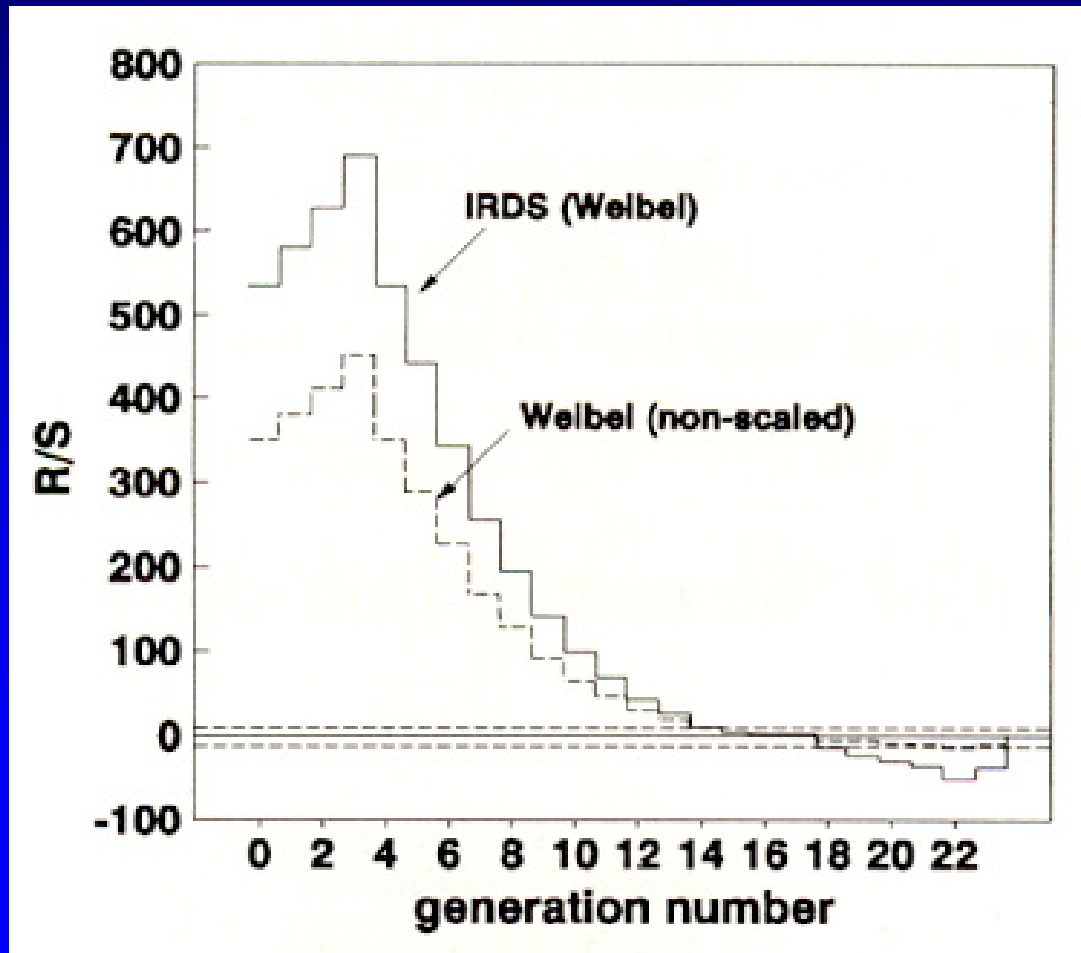
$$\frac{\partial c}{\partial t} - S(x) \frac{\partial^2 c}{\partial x^2} = 0$$

With solution

$$c(x, t) = \frac{M}{2\sqrt{\pi St}} e^{-\frac{x^2}{4St}}$$

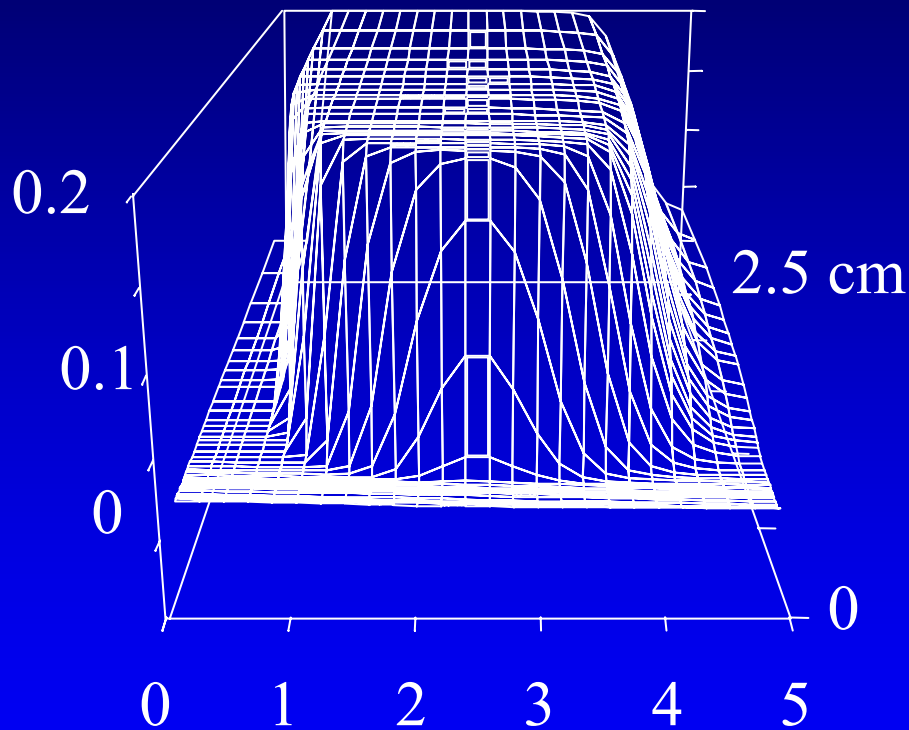
1D Convection-diffusion equation

The importance of R and S

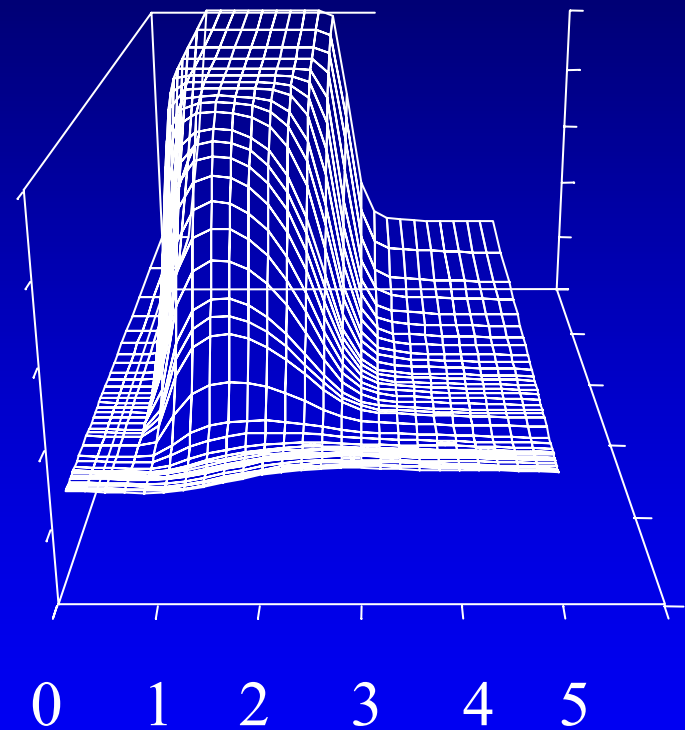


O₂ end-alveolar with and without diffusion

without diffusion

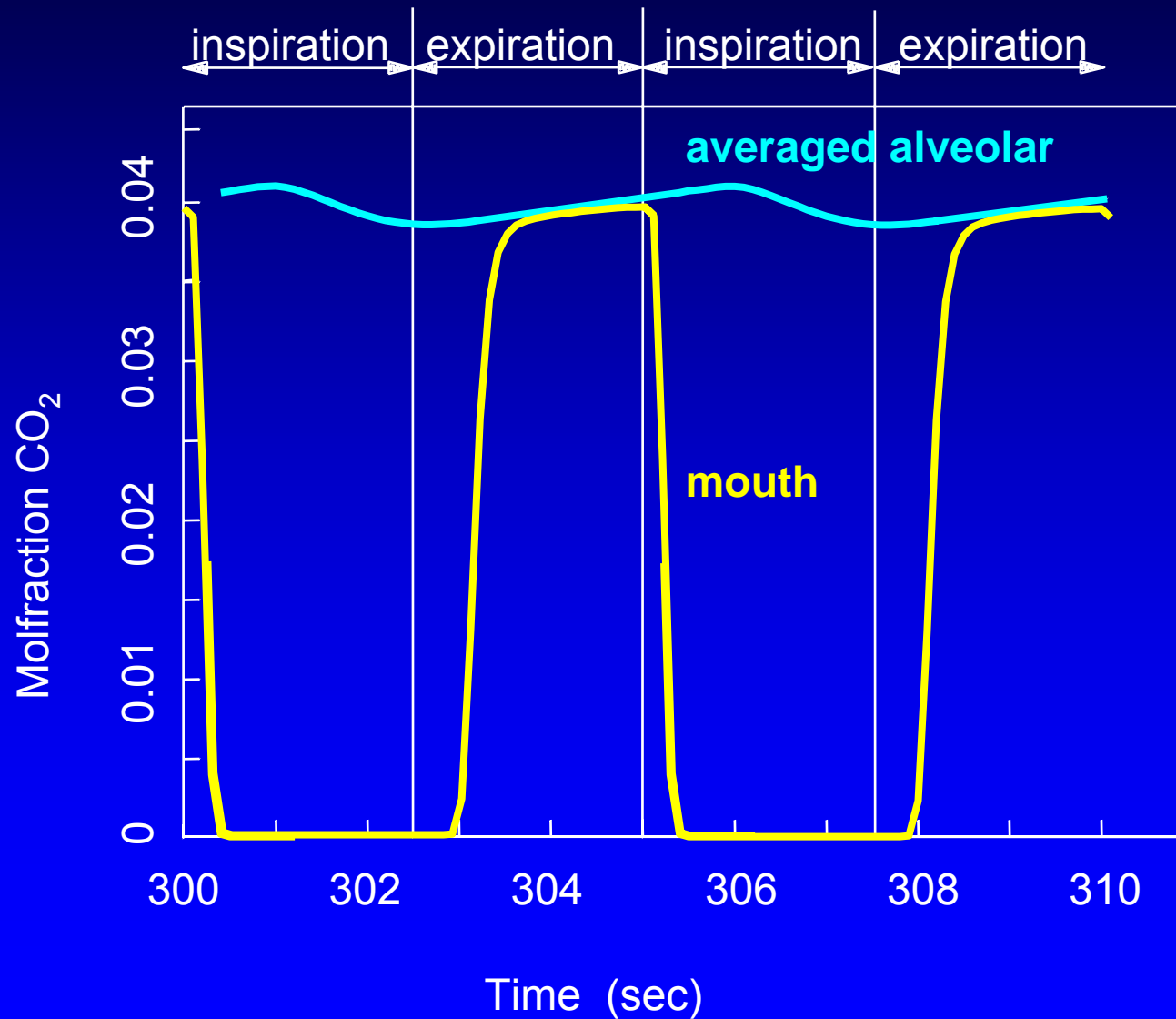


with diffusion

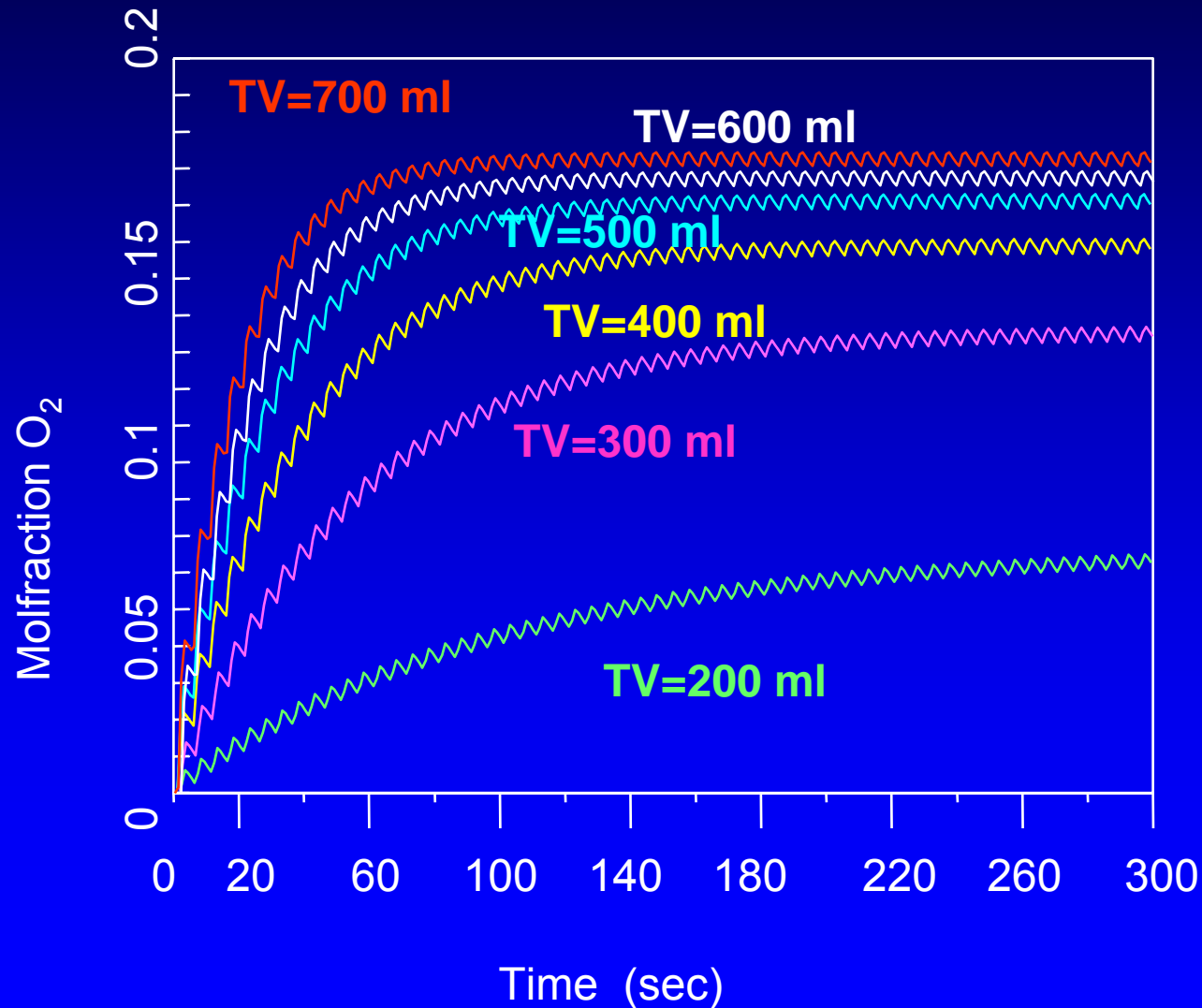


time (sec)

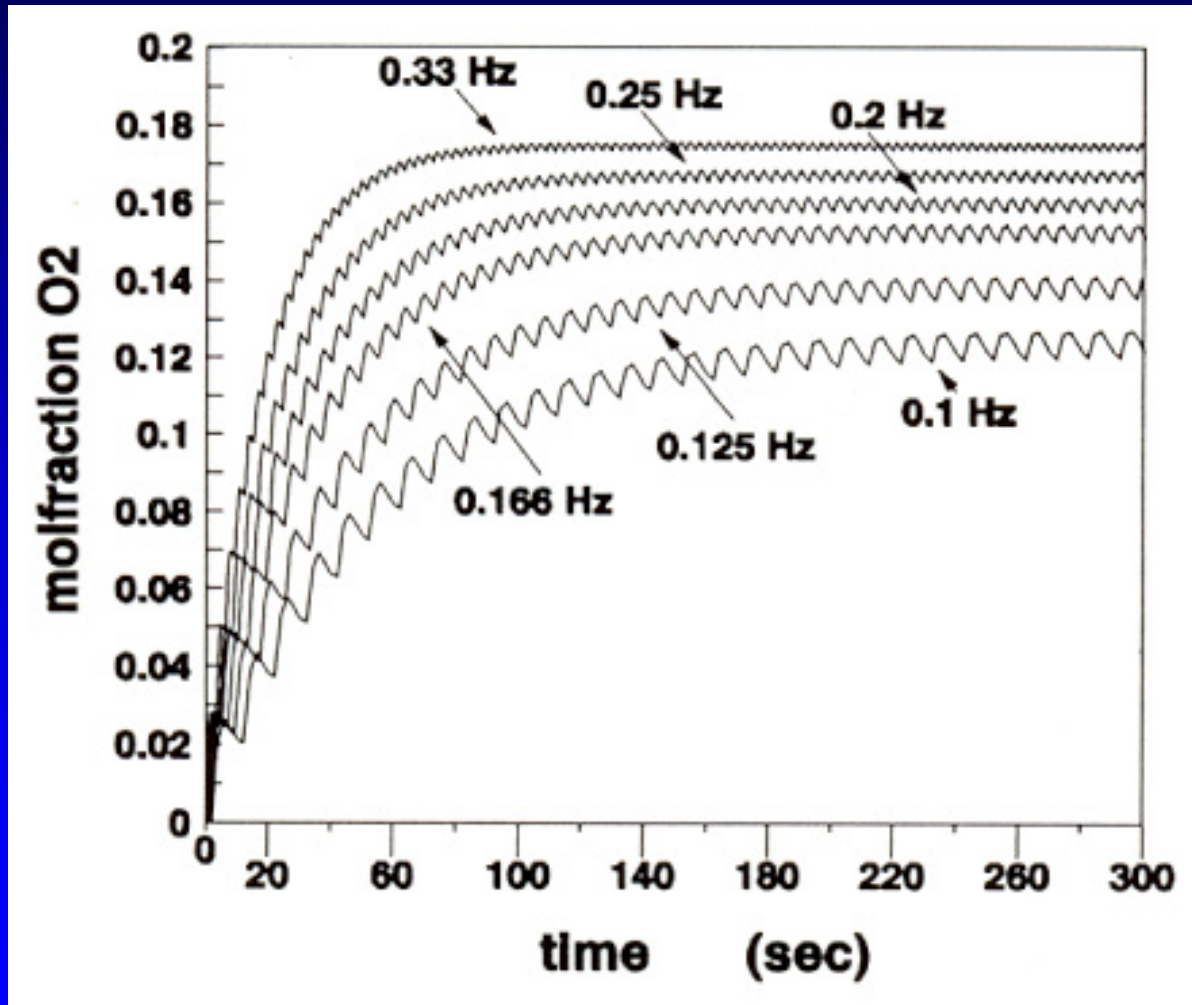
CO₂ molfraction at mouth and alveoli



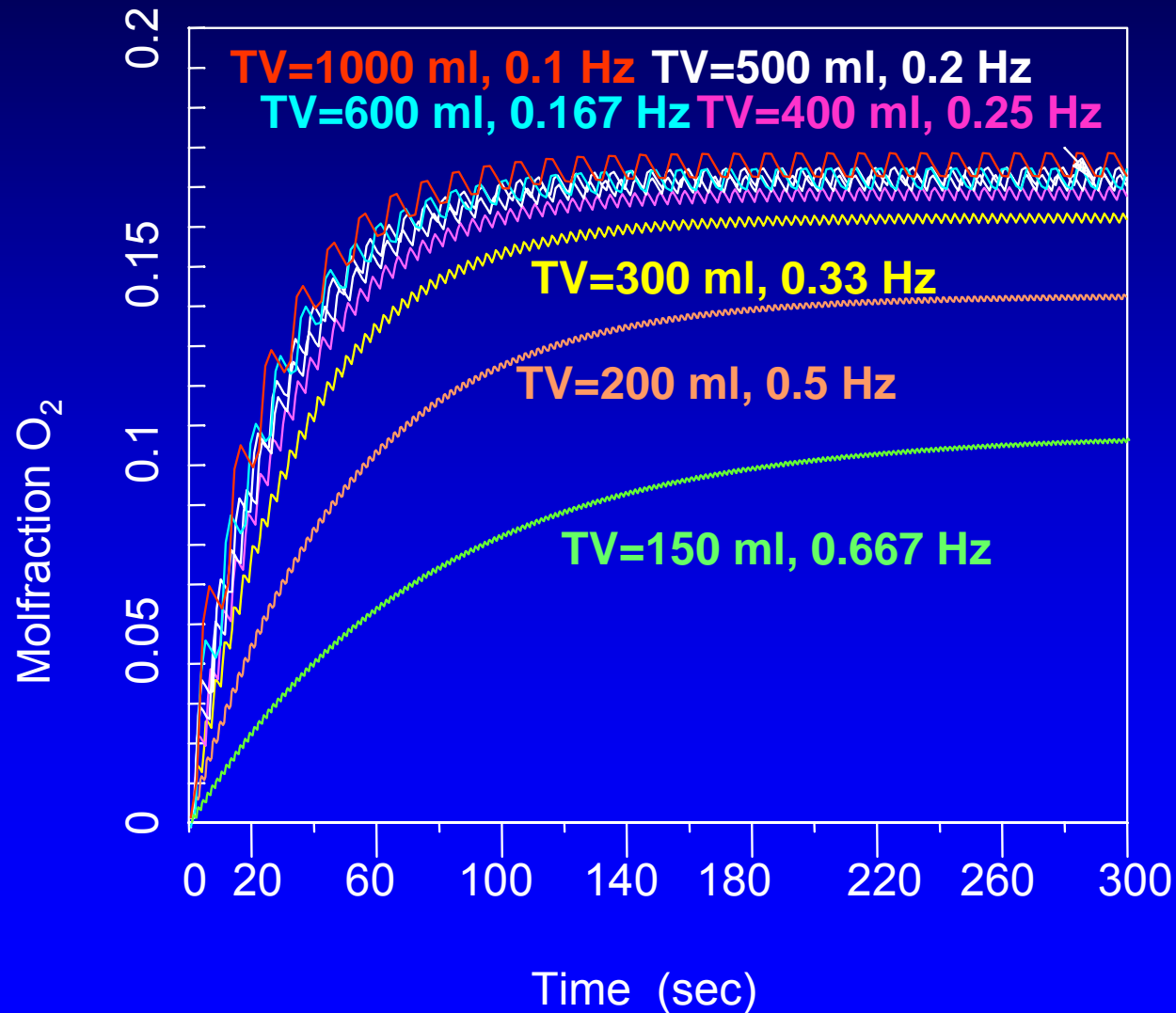
Constant Frequency (0.2 Hz)



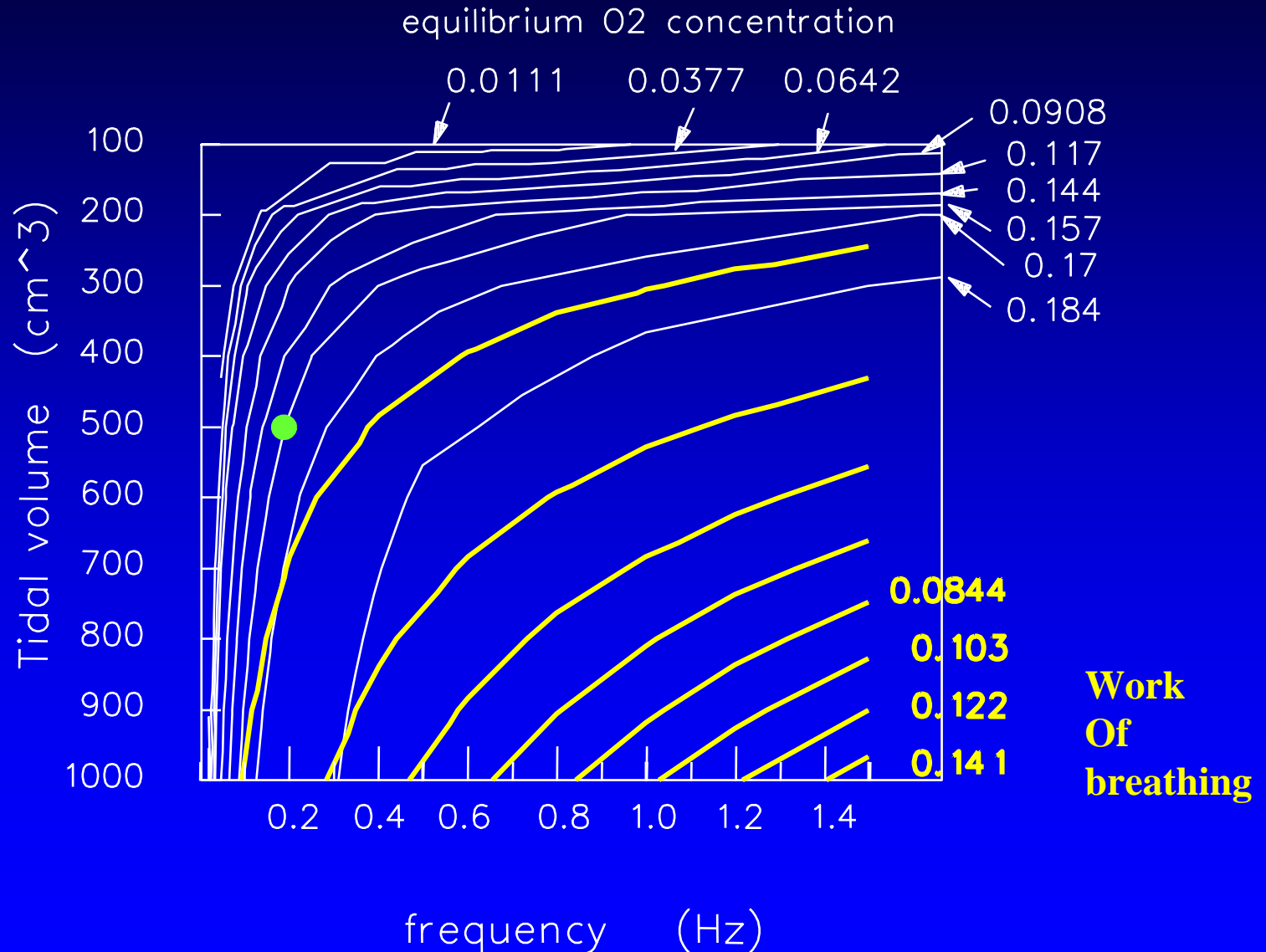
Constant Tidal Volume (500 ml)



Constant Minutevolume

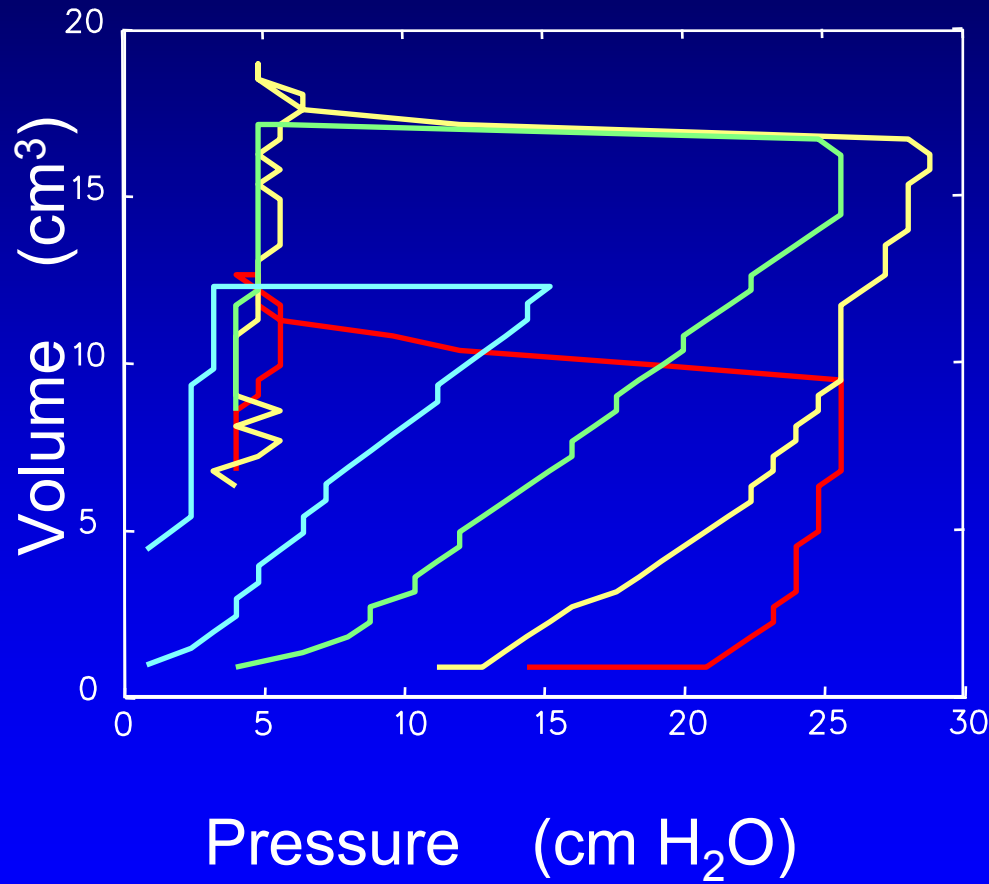


Equilibrium O₂-work of breathing



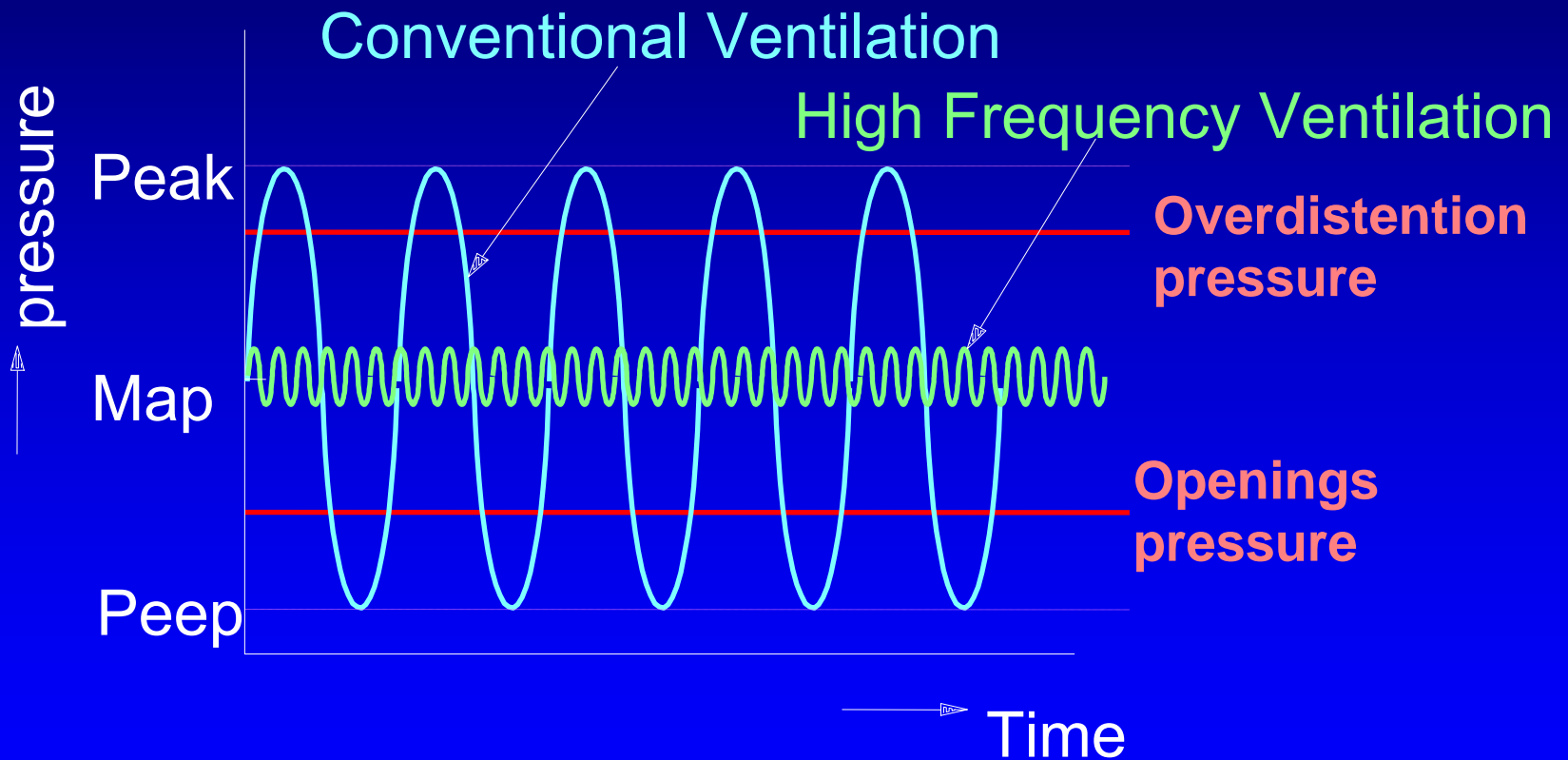
Why HFV: Effect surfactant on P-V curve

Premature neonate with Respiratory Distress Syndrome



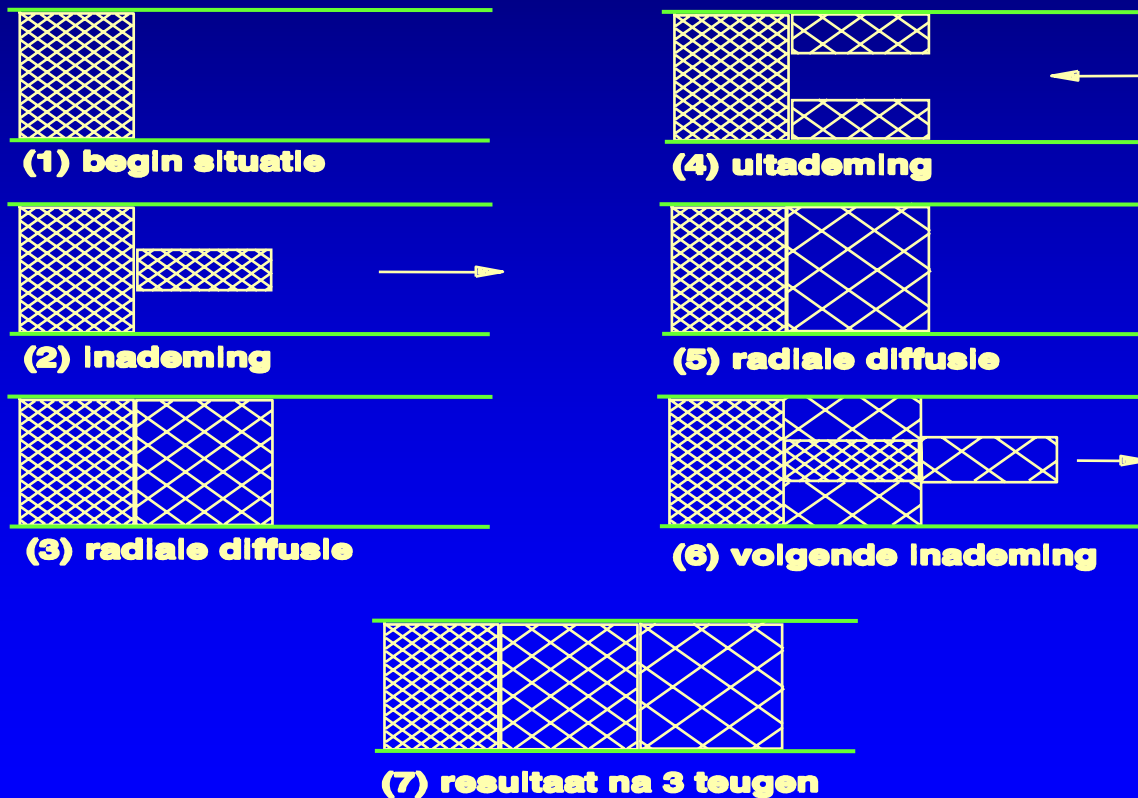
1/2 hr before therapy
1/2 hr after therapy
6 hr after therapy
before extubation

Conventional - High Frequency Ventilation



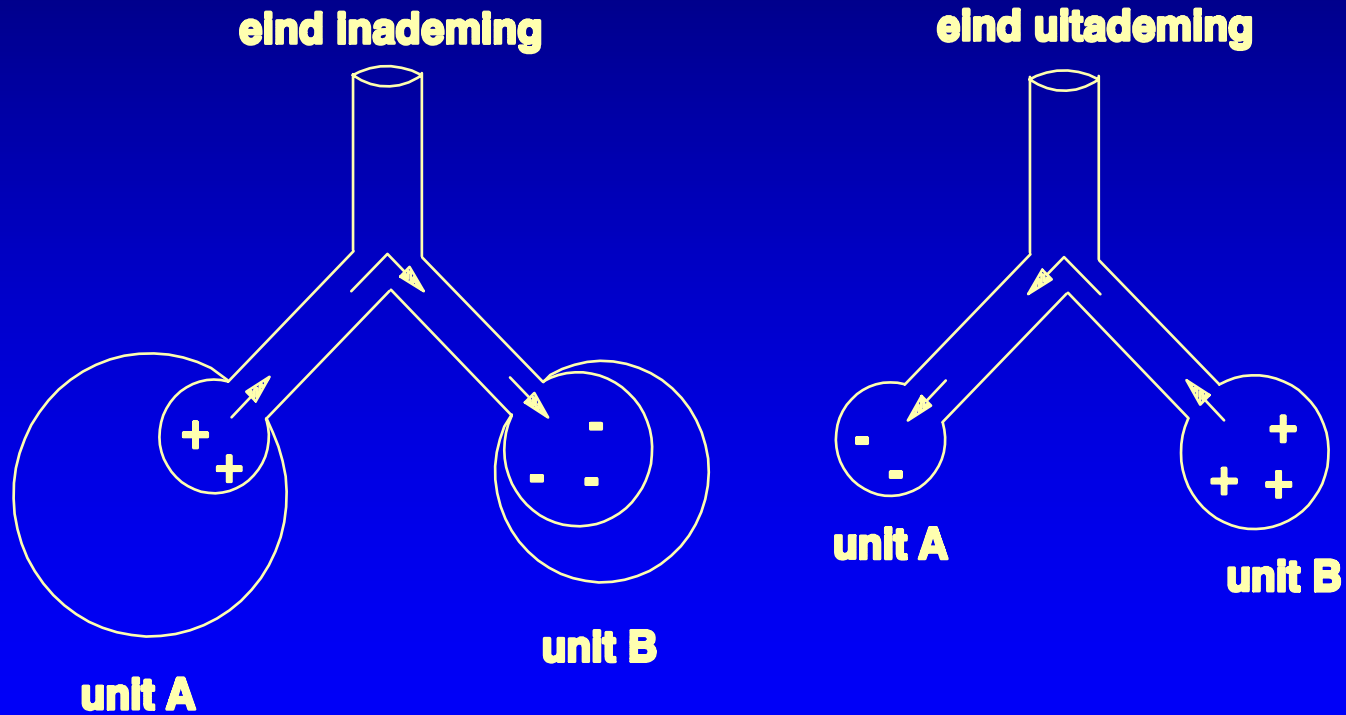
Flow mechanism HFV

- Taylor diffusion



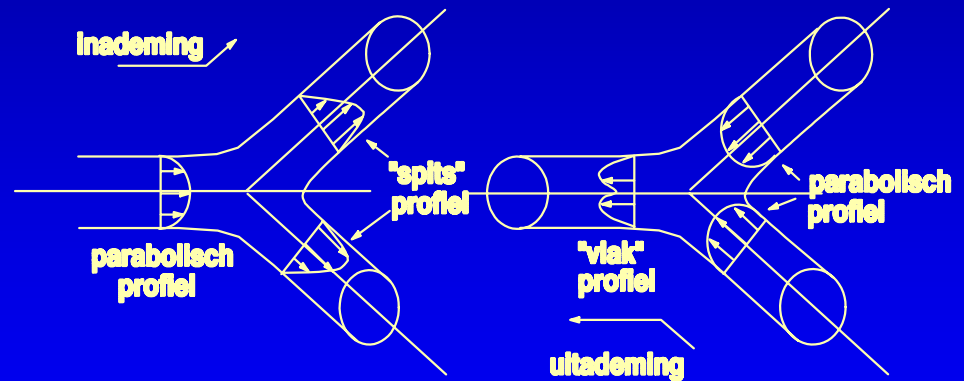
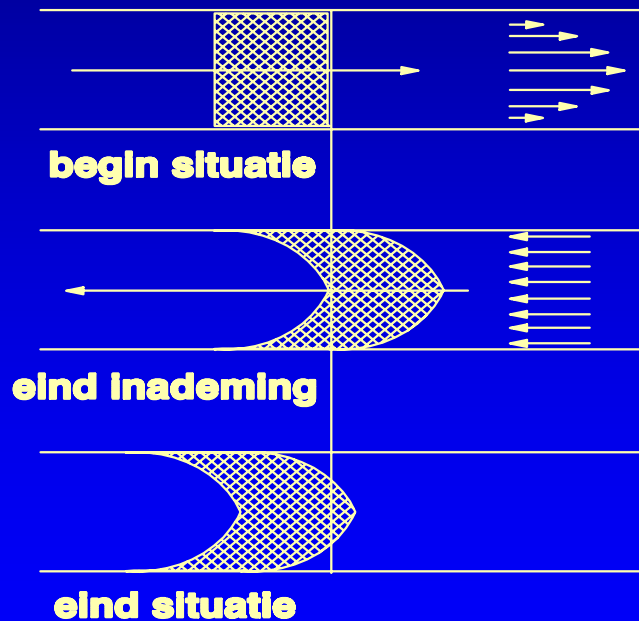
Flow mechanism HFV

- Pendelluft



Flow mechanism HFV

Difference in- and expiratory flow profiles



1D Convection-diffusion HFV equation

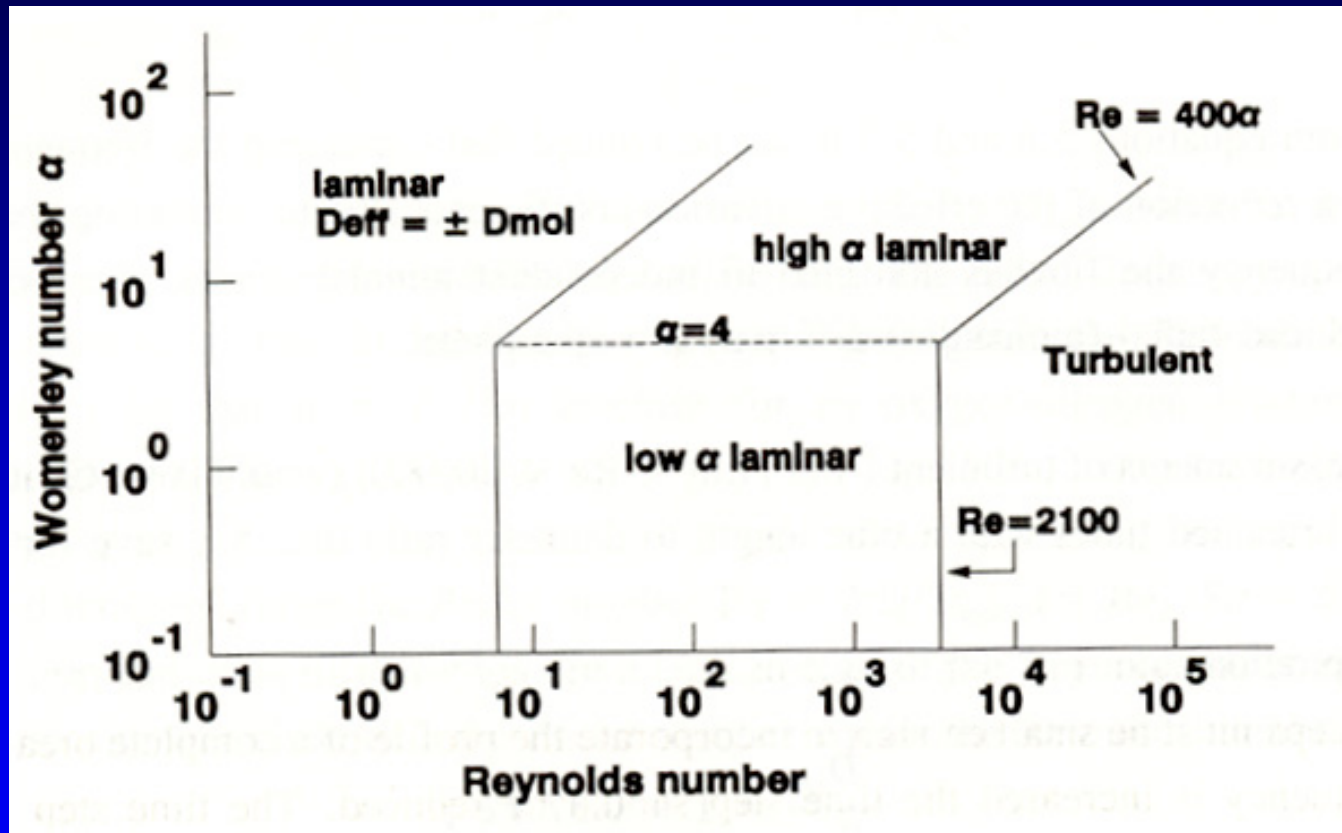
Normale respiration / conventional ventilation

$$\frac{\partial c}{\partial t} + U \frac{\partial c}{\partial x} - \frac{D}{A} \frac{\partial a}{\partial x} \frac{\partial c}{\partial x} - D \frac{a}{A} \frac{\partial^2 c}{\partial x^2} = Q$$

High Frequency Ventilation

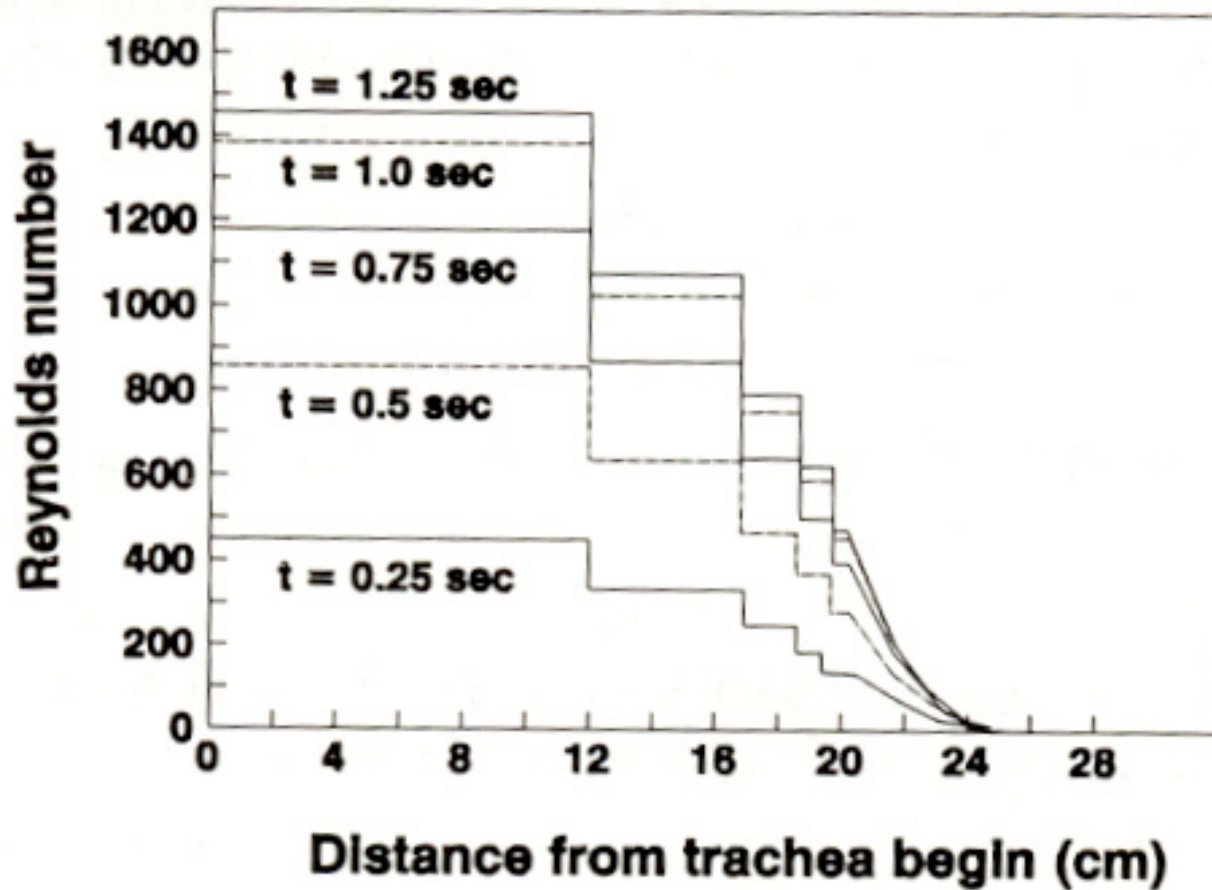
$$\frac{\partial c}{\partial t} + U \frac{\partial c}{\partial x} - \frac{D_{eff}}{A} \frac{\partial a}{\partial x} \frac{\partial c}{\partial x} - D_{eff} \frac{a}{A} \frac{\partial^2 c}{\partial x^2} = Q$$

The “effective” Diffusion coefficient

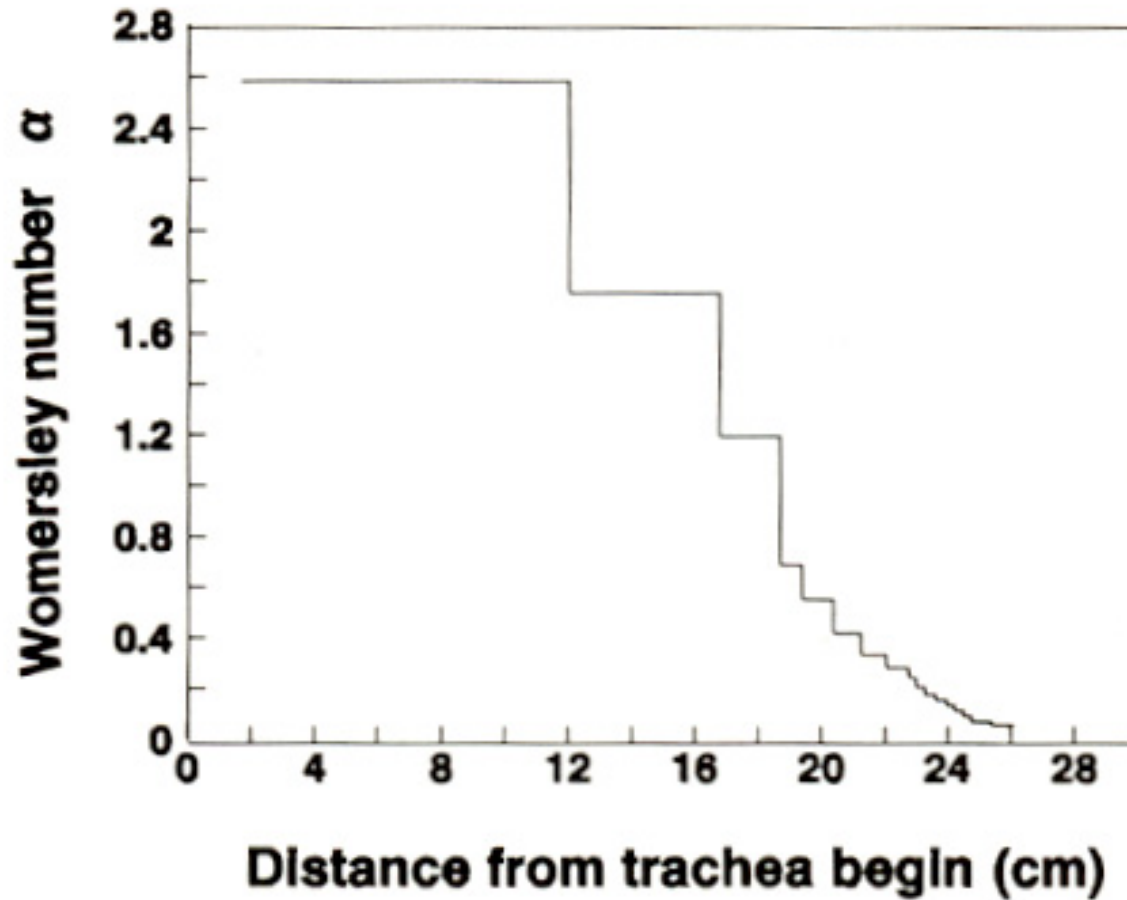


The 4 areas with different (semi-empirical) formula's for D_{eff}

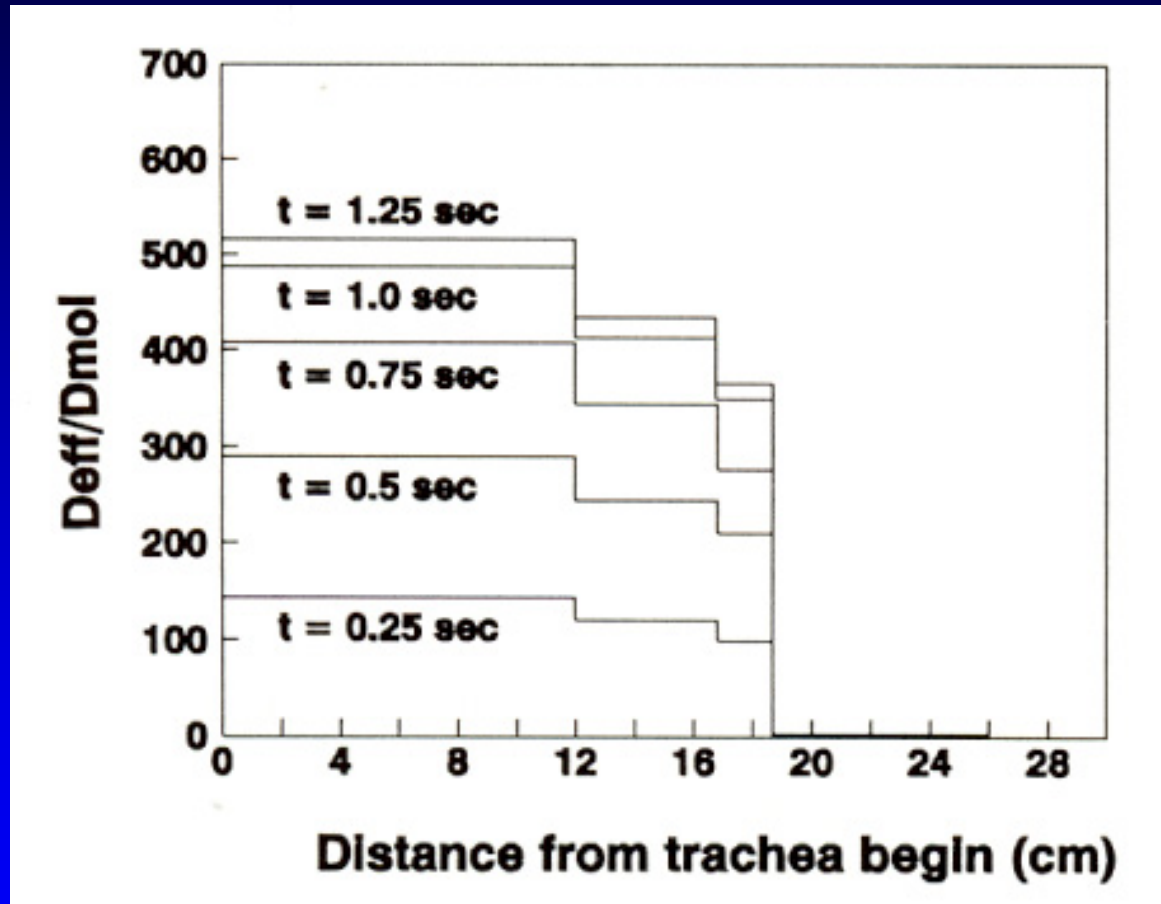
The Reynolds number (Re)



The Womersley number (α)

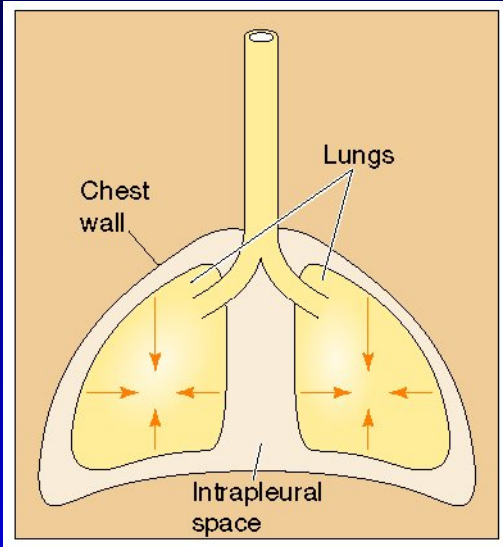


The “effective” Diffusion coefficient

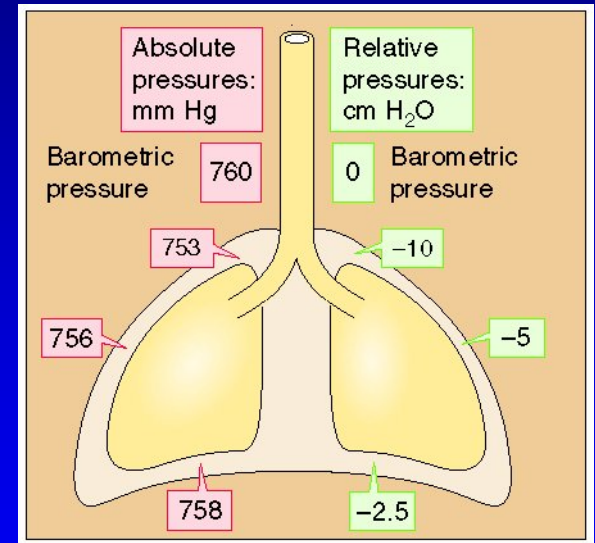
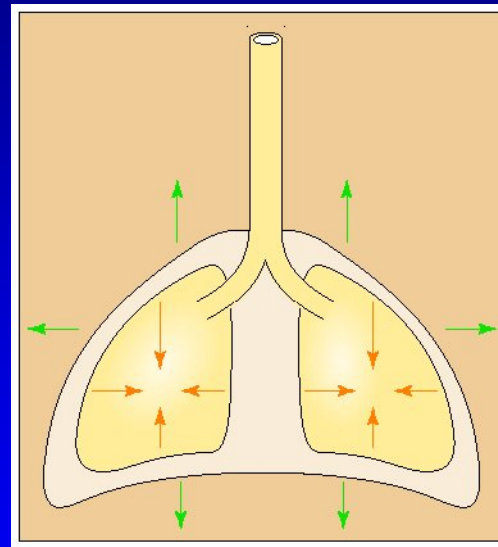
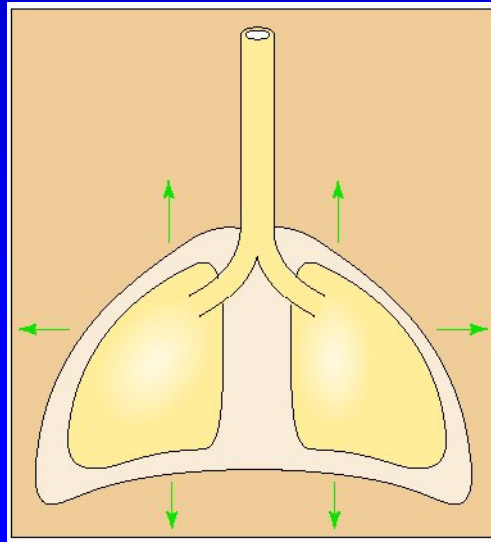


Result: The same kind of pictures as when $D_{eff}=D_{mol}$

Chest wall vs Lungs

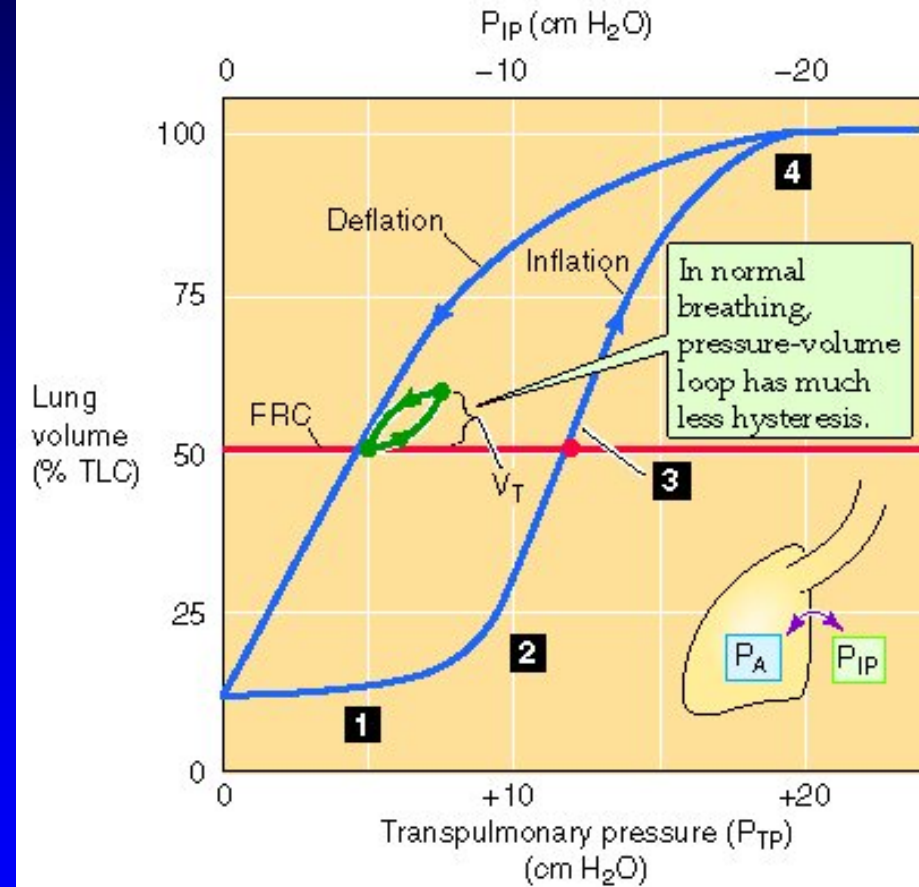
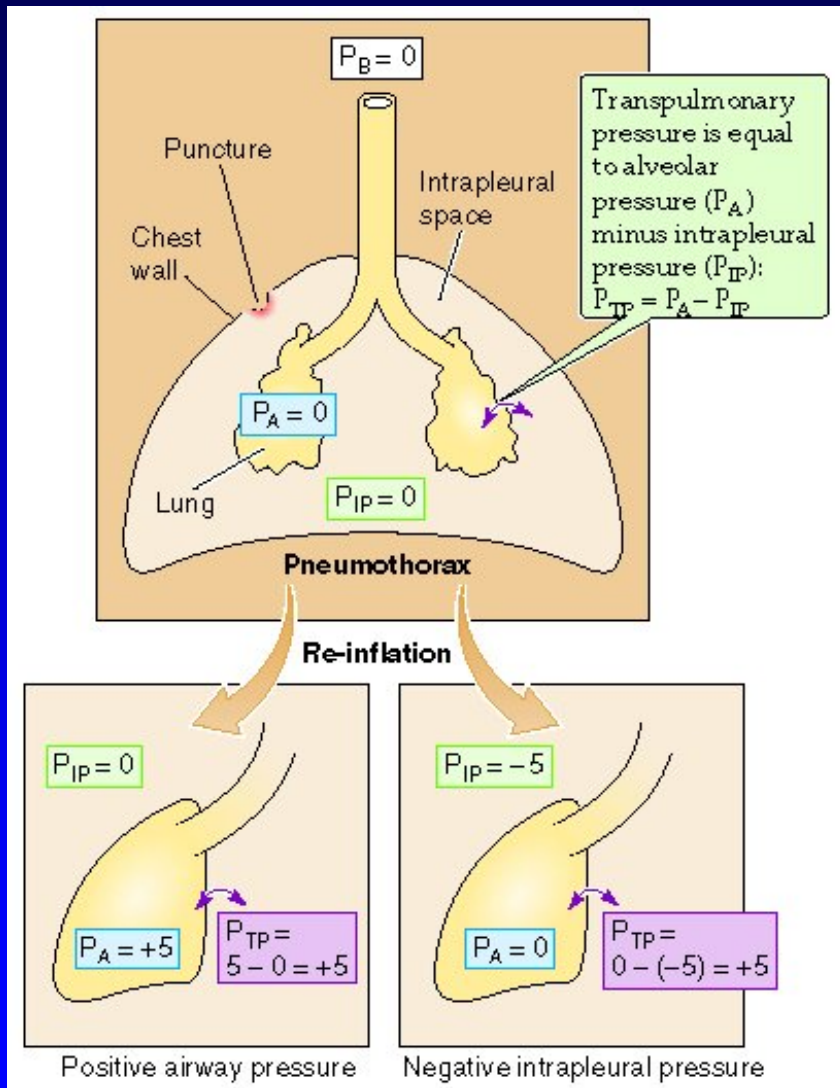


Chest wall: outwards
- muscles

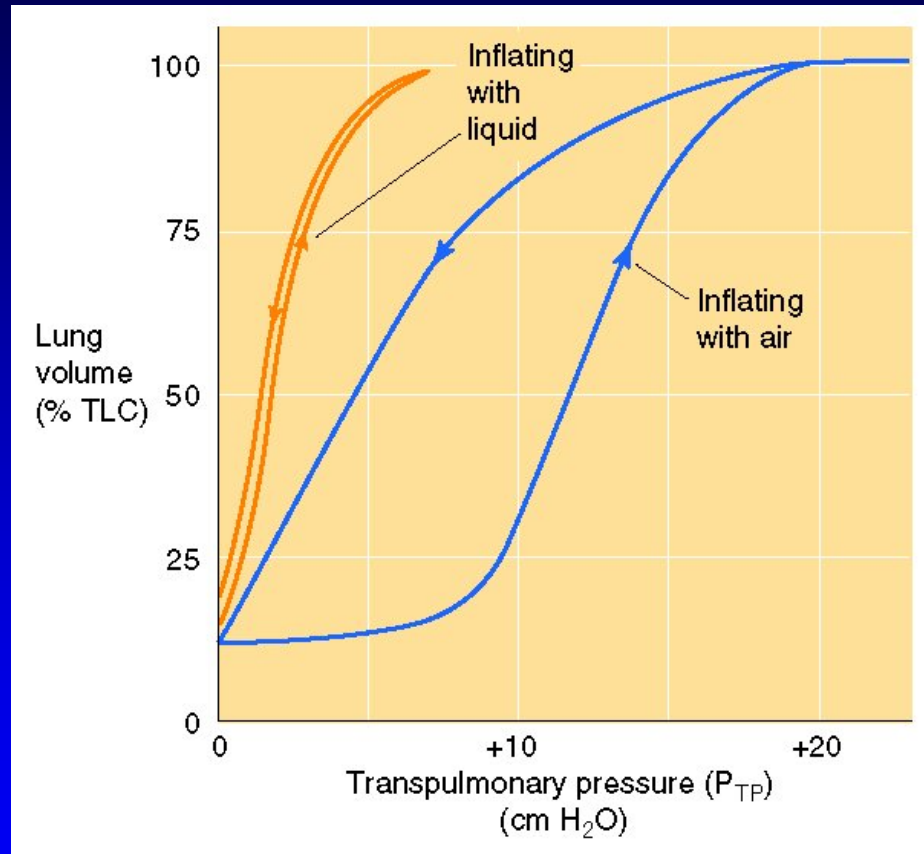


Lungs : inwards
- elastic tissue forces
- surface tension

Pneumothorax



PV loop with air / water



In absence of surface tension the compliance of the respiratory system is improved!

Surfactant and SP-A

Lipids 90%

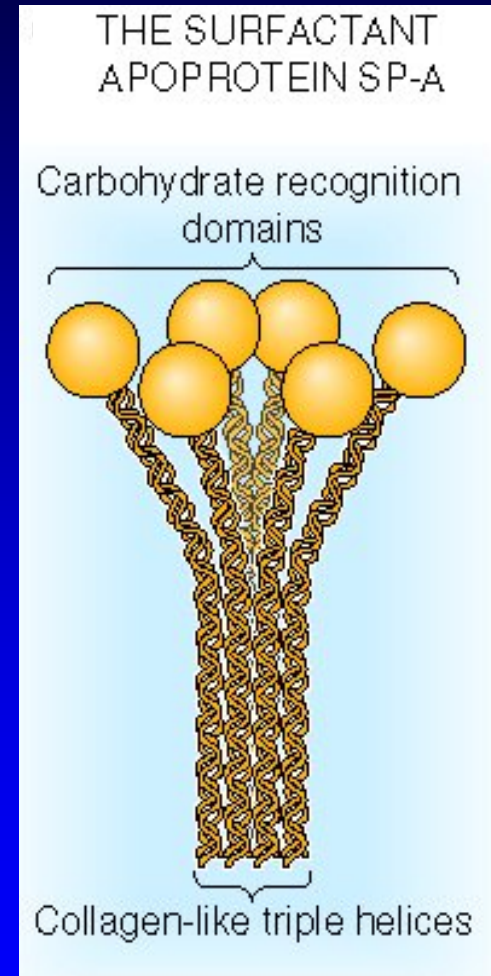
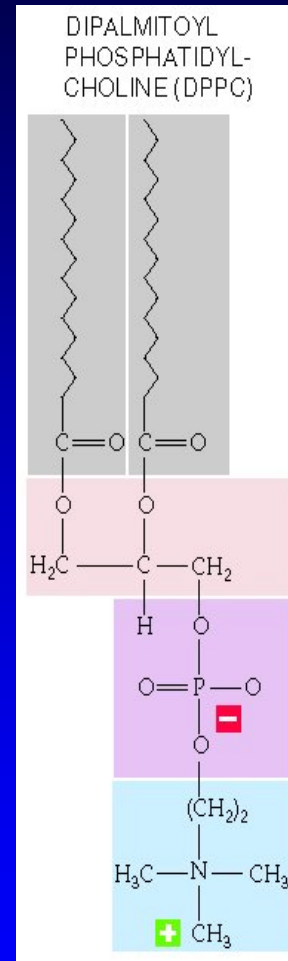
- DPPC
- PG (glycerol)
- PE (ethanolamine)

(reduce γ)

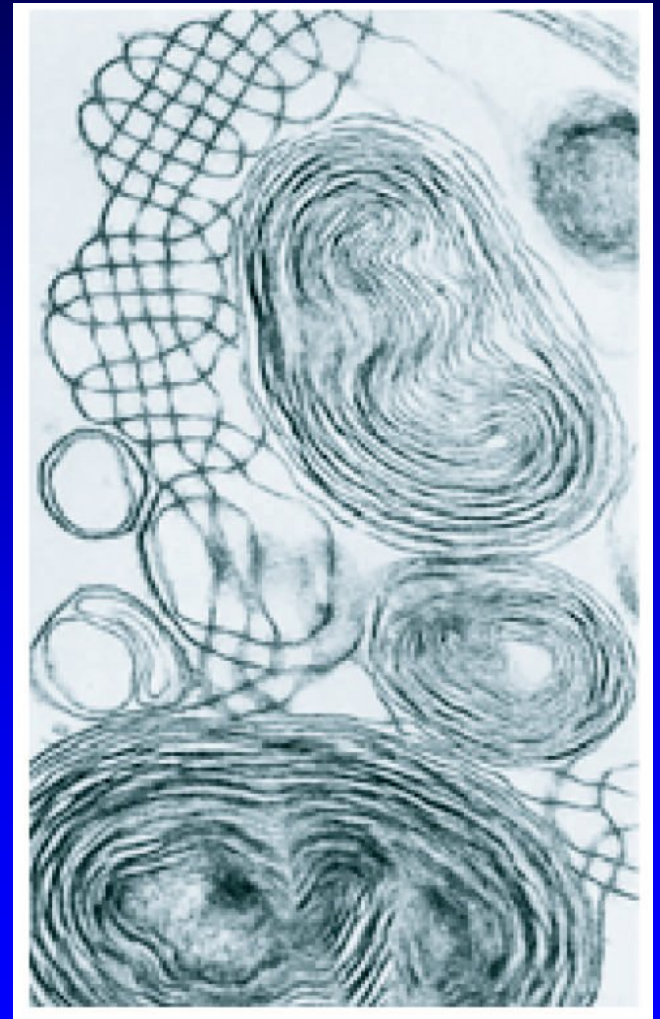
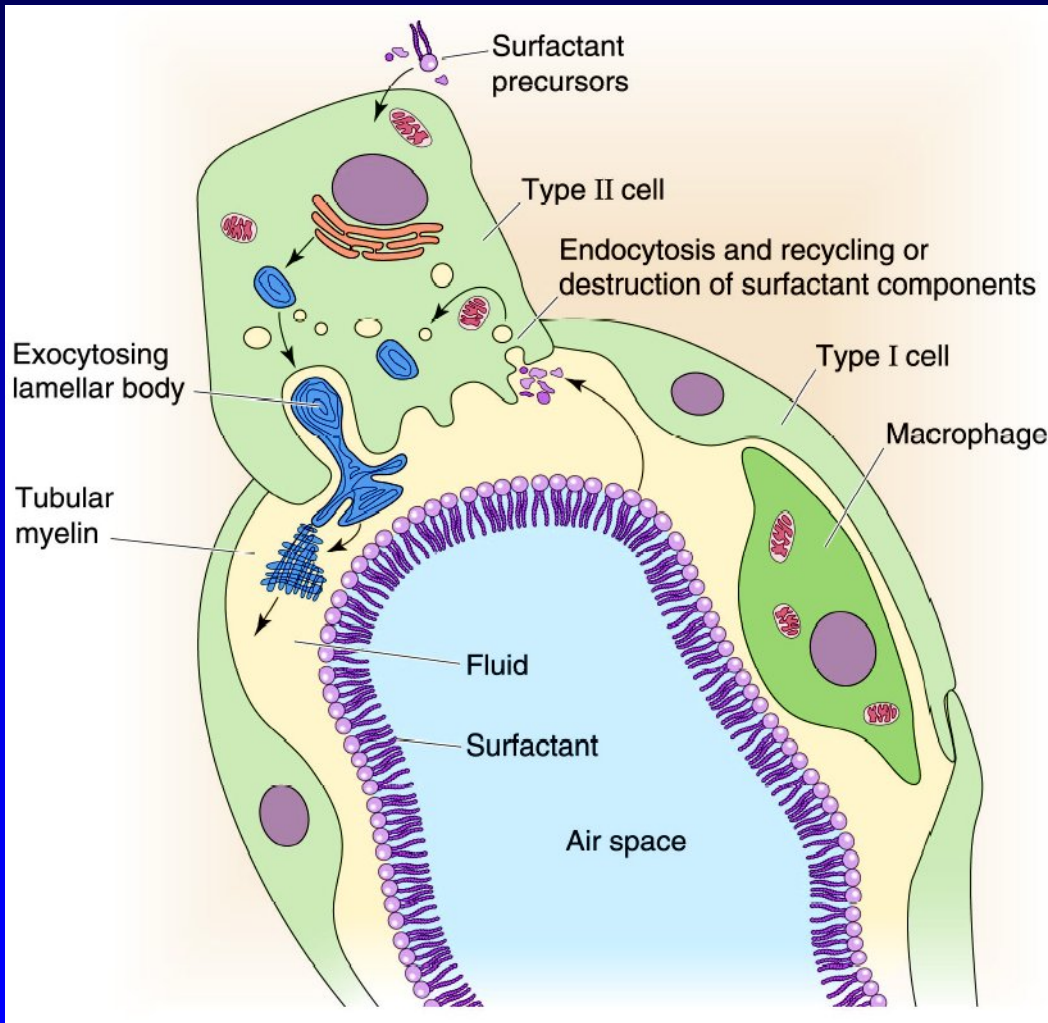
Proteins

- SP-A
- SP-B
- SP-C
- SP-D

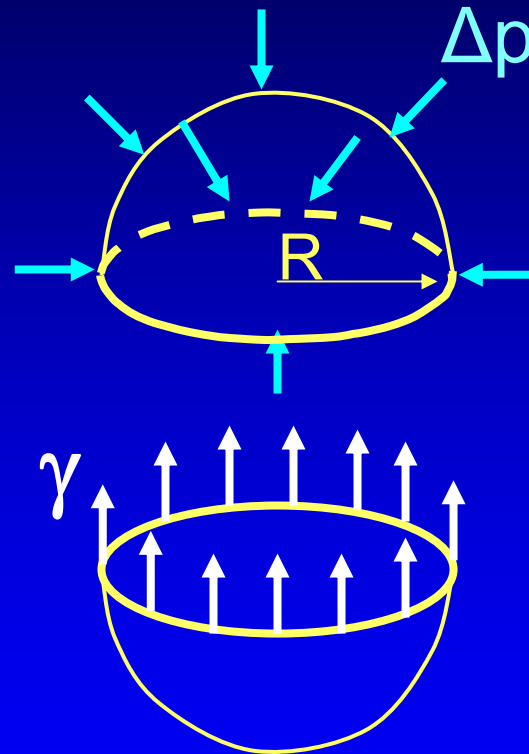
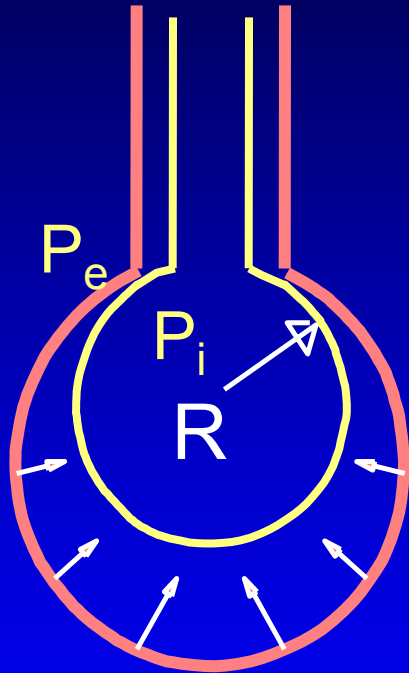
(transport, (re)generation, defense system)



Surfactant production



Law of Laplace (sphere)

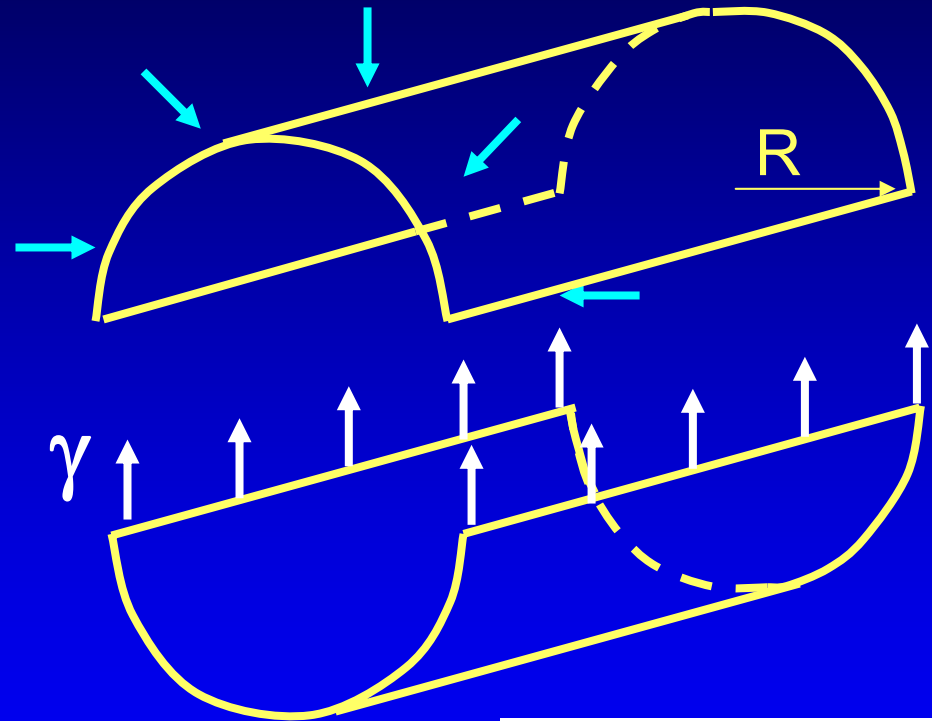
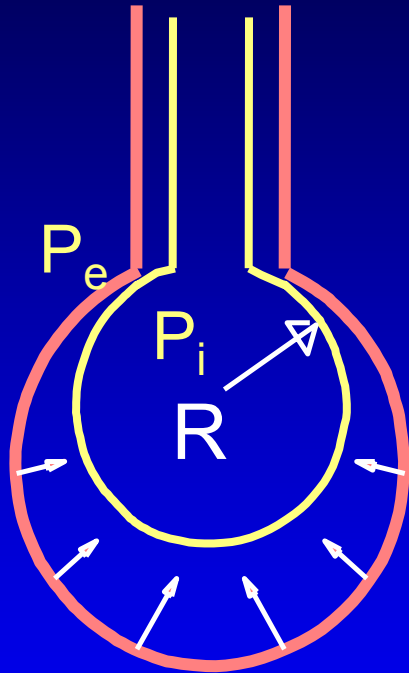


$$\Delta p \pi R^2 = 2\pi R \gamma$$

$$\Delta p = P_e - P_i = \frac{2\gamma}{R}$$

If $R = 0 \Rightarrow \Delta p = \infty$

Law of Laplace (tube)



$$\Delta p = \frac{\gamma}{R}$$

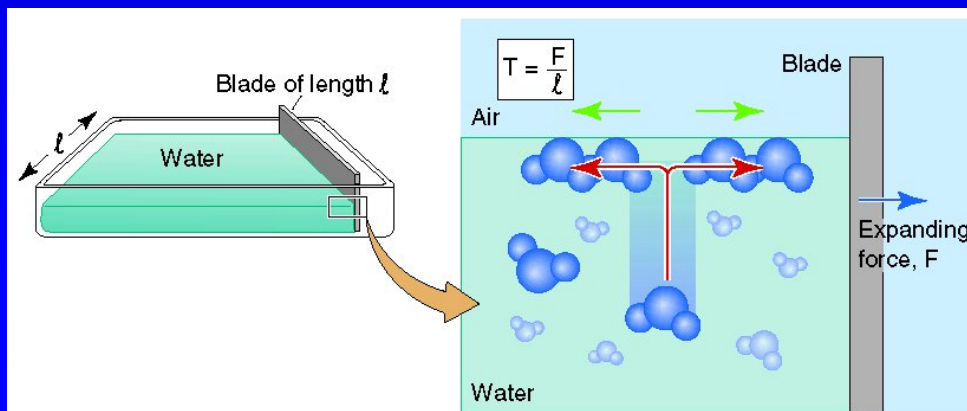
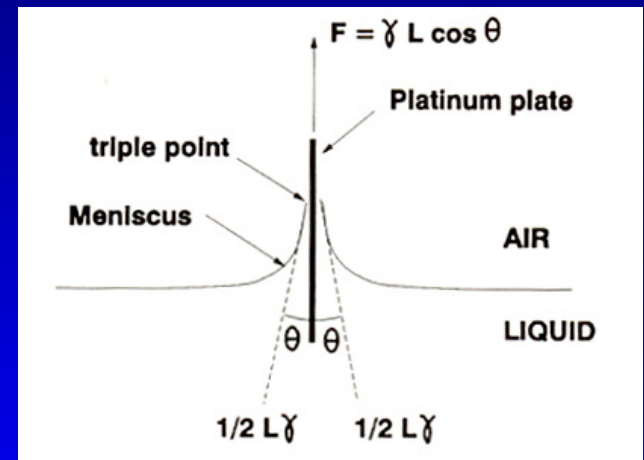
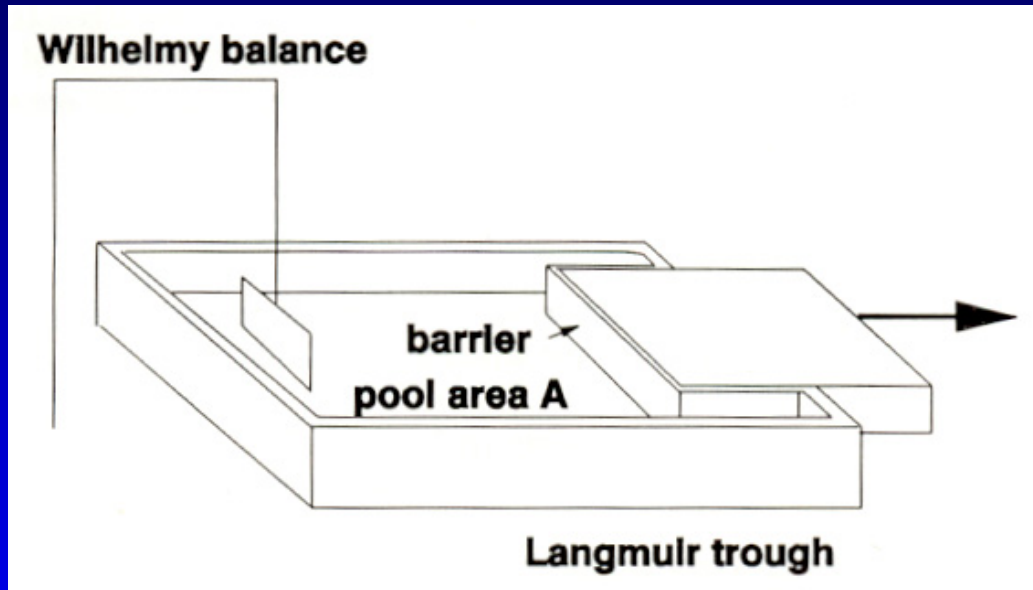
$$\Delta p l 2R = 2l\gamma$$

If $R = 0 \Rightarrow \Delta p = \infty$

Surfactant measurement

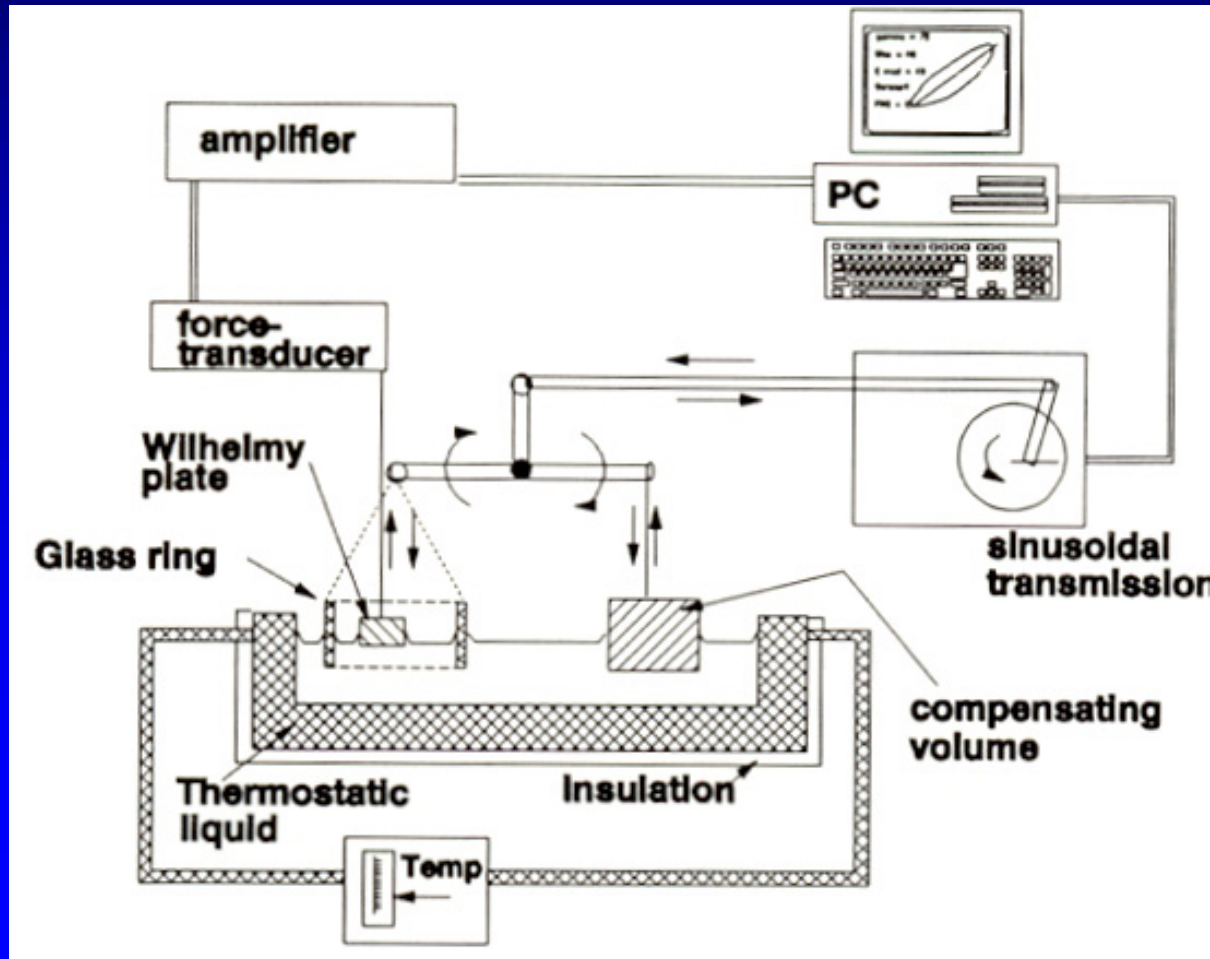
Langmuir trough with

Wilhelmy balance



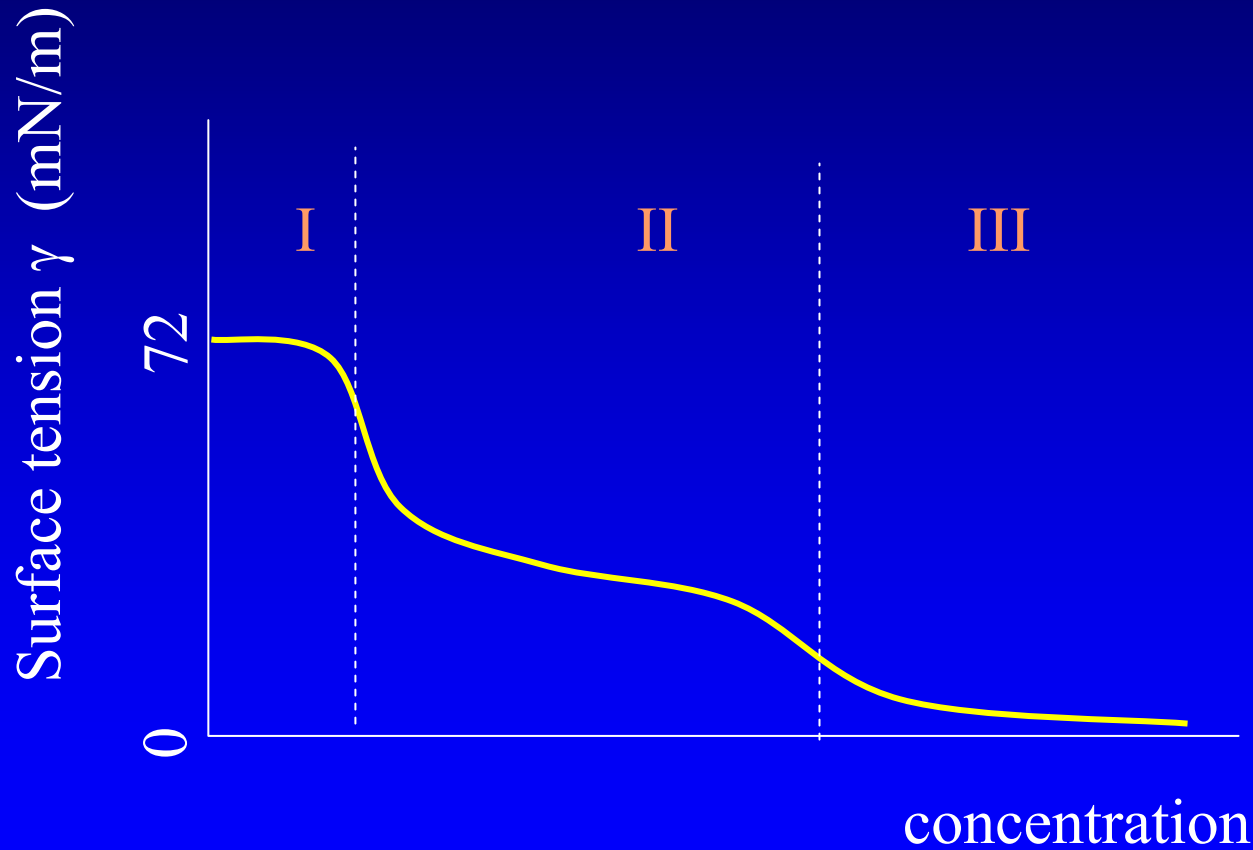
Surfactant measurement 2

Advanced system (nowadays: captive bubble)

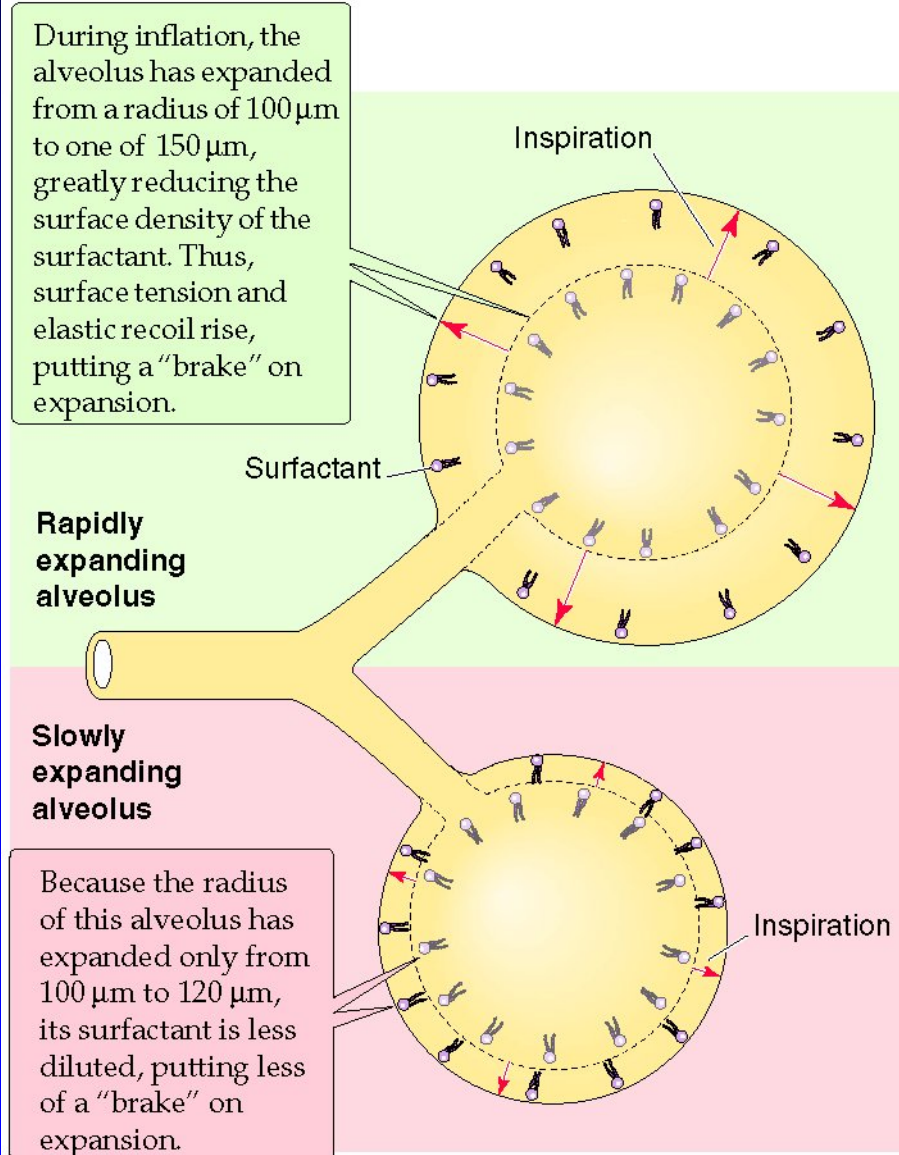


Surfactant measurement 3

Advanced system (nowadays: captive bubble)



Surfactant stabilisation

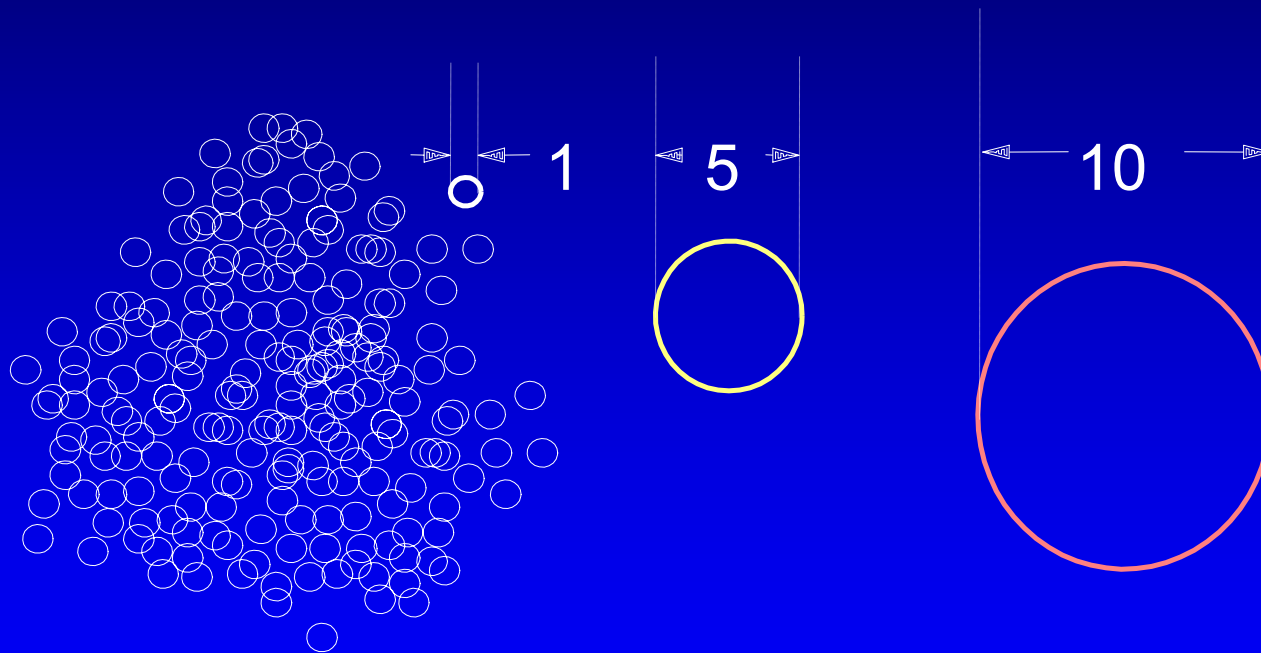






Aerosols

MMAD = Mass Median Aerodynamic Diameter



Aerosols

GSD = Geometric Standard Deviation

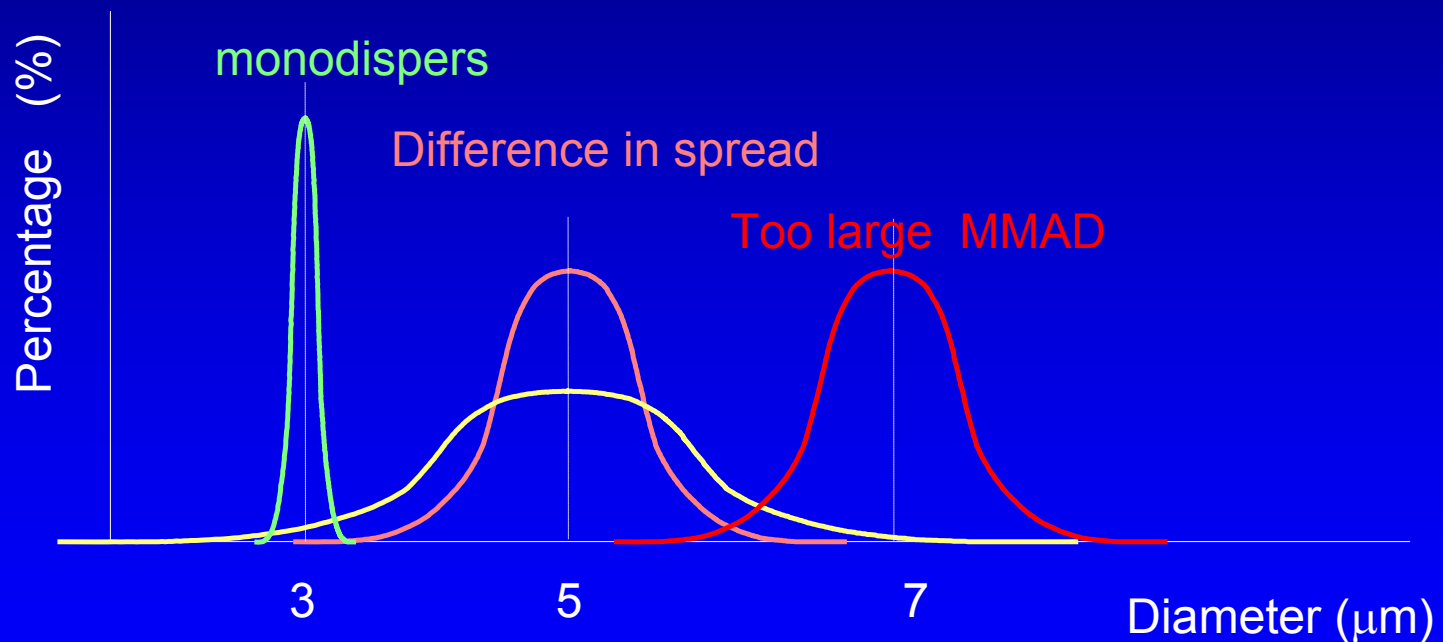
$$\text{GSD} = \frac{D_{84\%}}{D_{50\%}} = \frac{D_{50\%}}{D_{16\%}}$$

$D_{50\%}$ = median diameter

$D_{84\%}$ = that diameter at which 84% of the particles has a smaller diameter

MMAD + spread

respirable fraction = the particles which enter the target area (e.g. the lungs)



CFC-HFA Aerosols



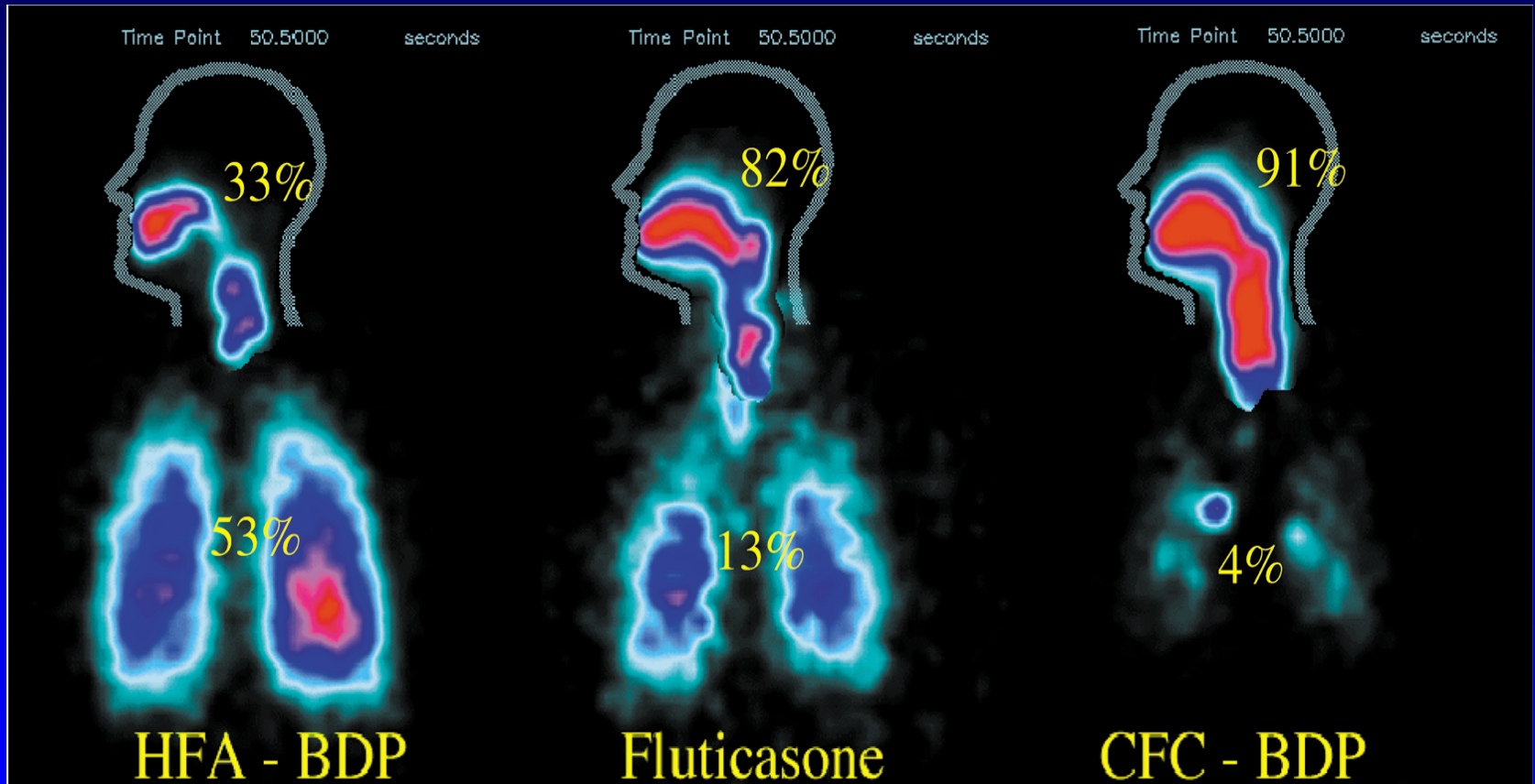
**CFC (salbutamol)
(Ventolin)**



**HFA (salbutamol)
(Airomir)**

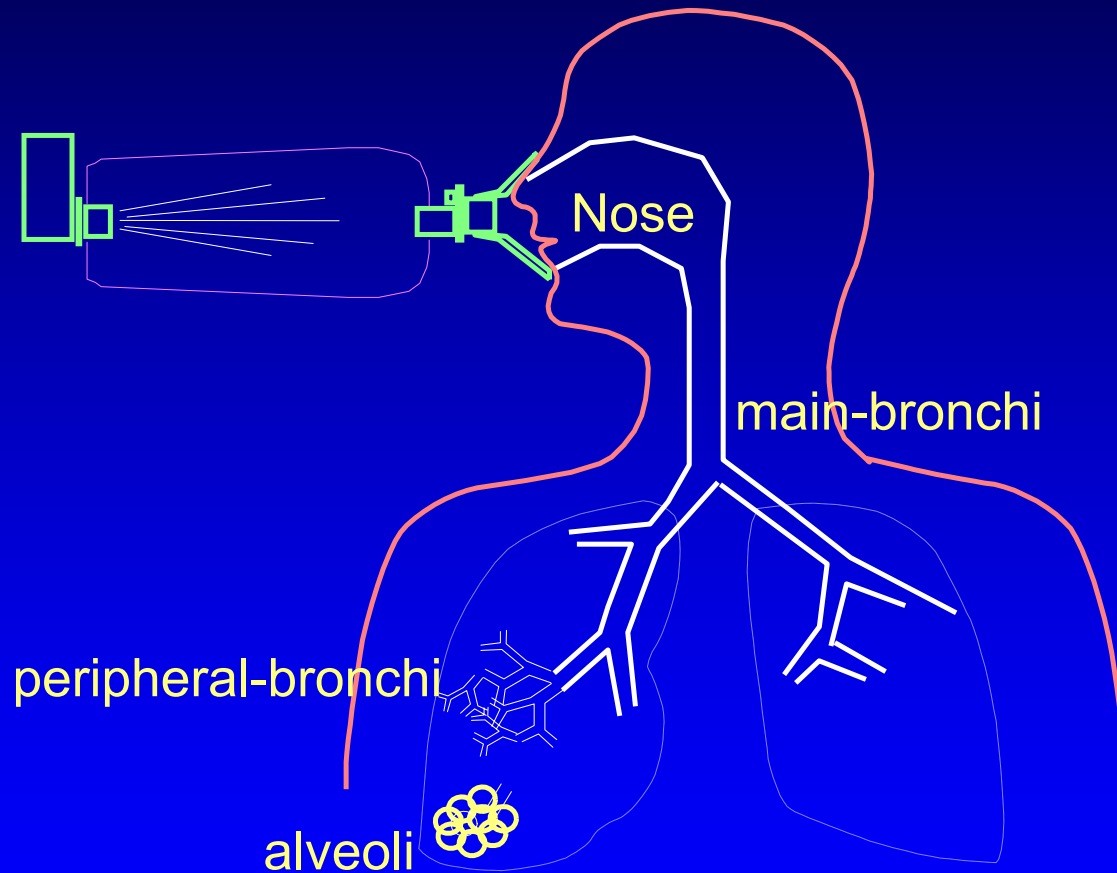
Comparison of deposition in the same subject

Adult



Leach CL et al. Presented at the ATS, 2000

What does an aerosol encounter



Mathematical modelling

Experimental fit

semi-empirical equations for deposition in parts of the lung as function of velocity and particle size (vb Stahlhofen 1989, [J. Aerol. Med. 2](#))

Advantages:

- “simple equations”
- fast calculations
- results fit with experiments (are based on them)

Disadvantage

- “course outcomes” where deposition occurs (nasal, extra-thoracal, bronchi and alveolair)

Law of Stokes

Descending velocity depends on

- size of the particles
- density difference
- viscosity
- shape of the particle

For a non-moving sphere

$$F_z = 4/3 \pi r^3 \rho_b g$$

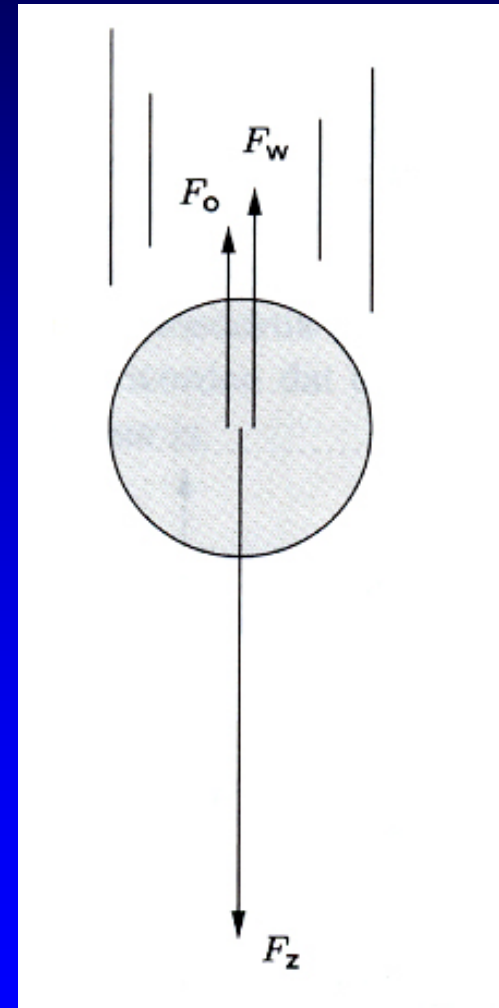
$$F_o = 4/3 \pi r^3 \rho_v g$$

Resulting Force $F_z - F_o$

If moving, there is friction F_w

This force works opposite to the direction of movement

$$F_{\text{tot}} = F_z - F_o - F_w$$



Law of Stokes

Law of Stokes: a sphere falls in an infinite medium

$$F_w = 6\pi\eta r v$$

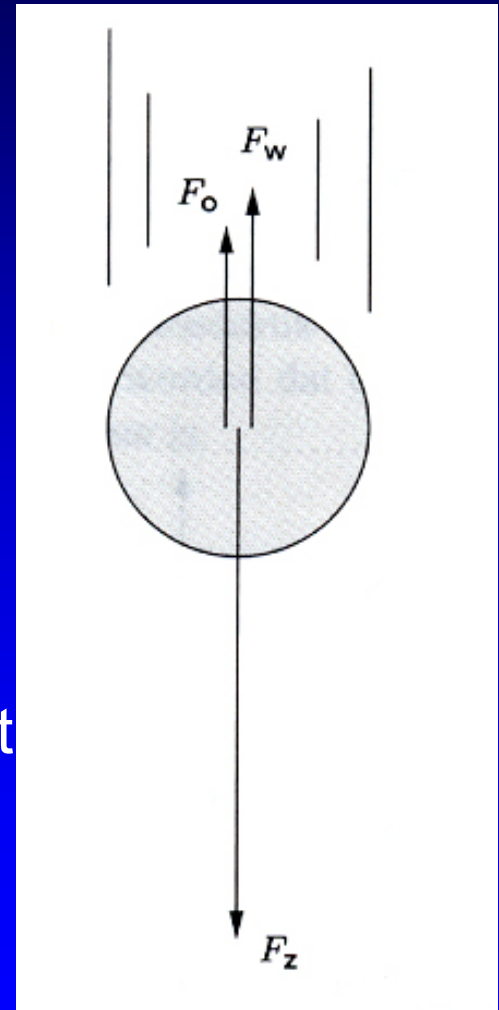
F_w increases with increasing velocity

On a certain moment:

$$F_{\text{tot}} = F_z - F_o - F_w = 0$$

So no net force anymore.

Therefore no acceleration, so $v = \text{constant}$



Law of Stokes

With $F_w = F_z - F_o$ follows:

$$6\pi\eta r v = \frac{4}{3} \pi r^3 (\rho_b - \rho_v) g \quad \text{so}$$

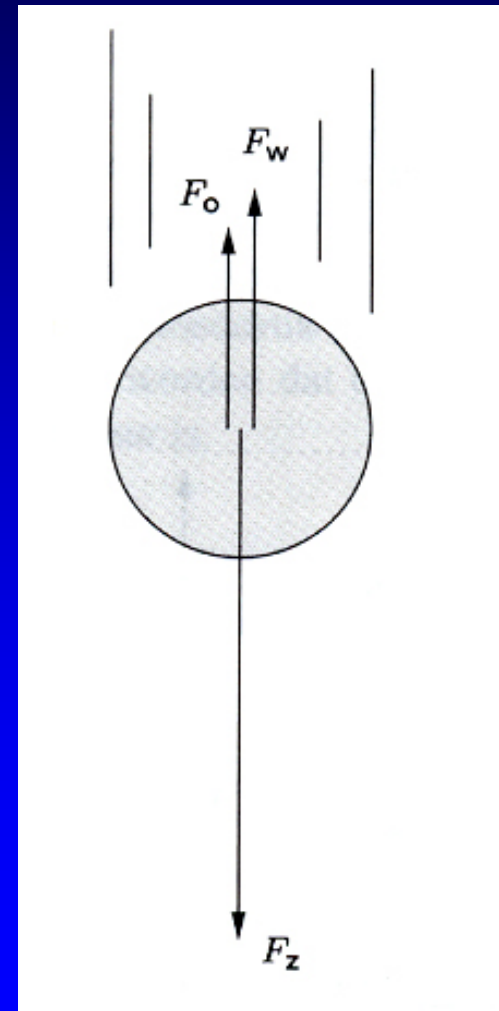
$$v = \frac{2}{9} \frac{r^2 (\rho_b - \rho_v) g}{\mu}$$

v depends quadratically on r

Very small particles: very low v

Use a centrifuge

(for instance for red blood cells)



The dragcoefficient

A drag force D can be defines as

$C_d = f(Re)$ with $Re = V \cdot d / \nu$

ρ = density (kg/m^3)

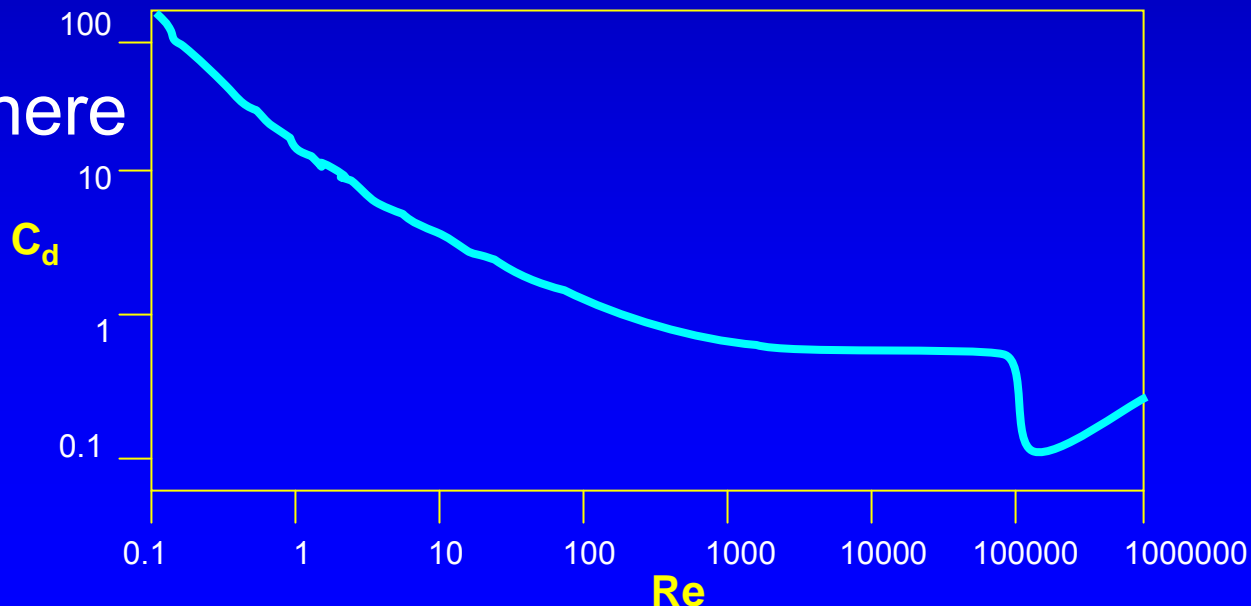
V = velocity (m/s)

S = surface area (frontal or “wetted”) (m^2)

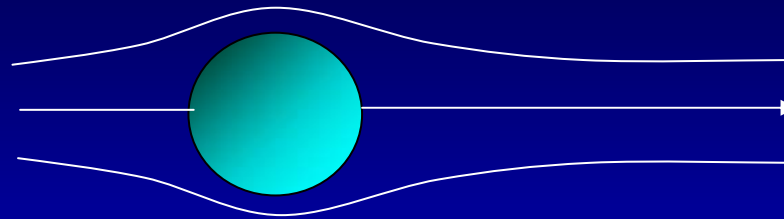
$$D = C_d \frac{1}{2} \rho V^2 S$$

Eg: Sphere

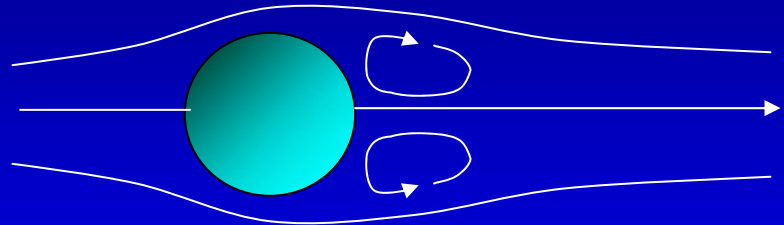
S =frontal



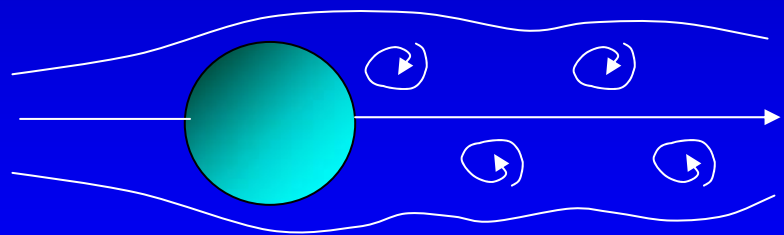
Flow patterns



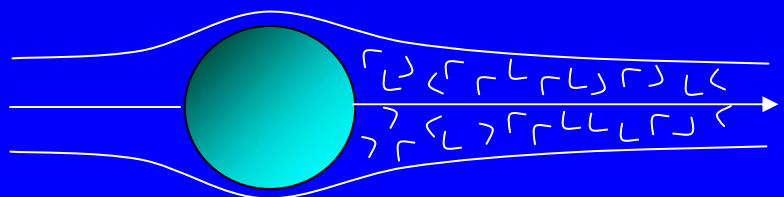
$Re < 10$



$10 < Re < 40$



$40 < Re < 200.000$



$Re > 200.000$

Drag

Resistance due to friction (parallel to the flow)

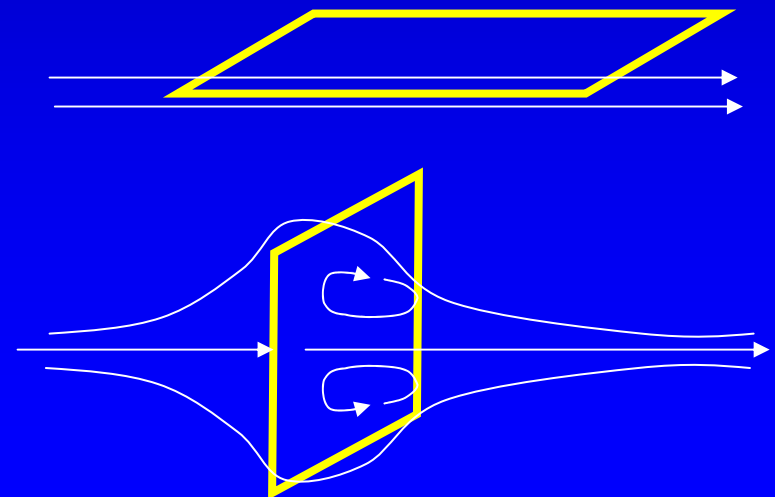
Low Re + surface area in flow direction is important

Resistance due to wake, energy loss (pressure drag)

High Re + surface area perpendicular to flow is important

E.g. infinitely long flat plate (S = “wetted area”)

Re	$C_{d \text{ parallel}}$	$C_{d \text{ perpendicular}}$	Ratio
1	6.2	9.2	1.5
10	1.1	1.9	1.7
100	0.13	1.22	9.2
1000	0.042	1.00	24
10000	0.013	0.98	74
100000	0.0042	0.98	230
1000000	0.0013	0.98	740



Mathematical modelling

1- D equation

Convection-diffusion equation with deposition term

$$\frac{\partial C}{\partial t} = \frac{a}{A} D \frac{\partial^2 C}{\partial x^2} + \frac{1}{A} \frac{\partial(aD)}{\partial x} \frac{\partial C}{\partial x} - U \frac{\partial C}{\partial x} - \frac{L}{A}$$

C = concentration of the aerosol/gas

t = time

x = depth in the lung (normally x=0 is begin trachea)

a = cross-sectional area without alveoli

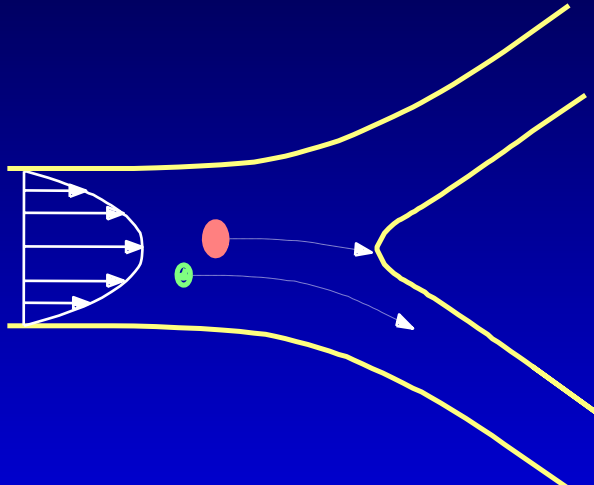
A = same with alveoli

D = diffusion-coefficient = $D_b + D_a$
= Brownian diffusion+convective dispersion

U = (convective) velocity at place x en time t

L = deposition function = $L_i + L_s + L_d$
= inertial impaction + sedimentation+ diffusion

Impaction



Grote deeltjes $> 5\mu\text{m}$

Vooral in:

- Bovenste luchtwegen
- Hoofd bronchiën
- Voorzetkamers

$$L_i = 1.3 \frac{CAU}{l} (Stk - 0.0001)$$

$$L_i = 0$$

$$Stk \geq 0.0001$$

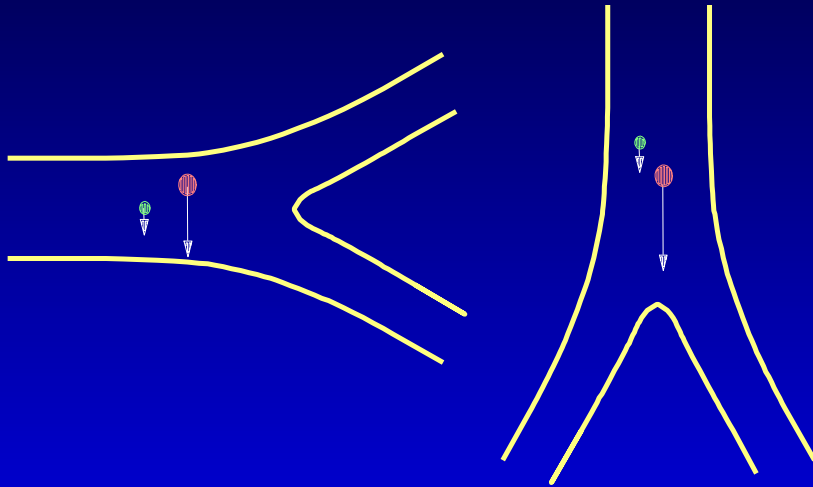
$$Stk < 0.0001$$

$$Stk = \frac{\rho_p d_p^2 U}{18\mu d}$$

ρ_p = dichtheid van het aërosol deeltje
 d_p = diameter van het aërosol deeltje
 μ = dynamische viscositeit van lucht
 d = lengtemaat (luchtweg diameter)

Taulbee & Yu 1975 J.Appl.Physiol.38

Sedimentatie



Grote deeltjes
Vooral in
perifere bronchiën

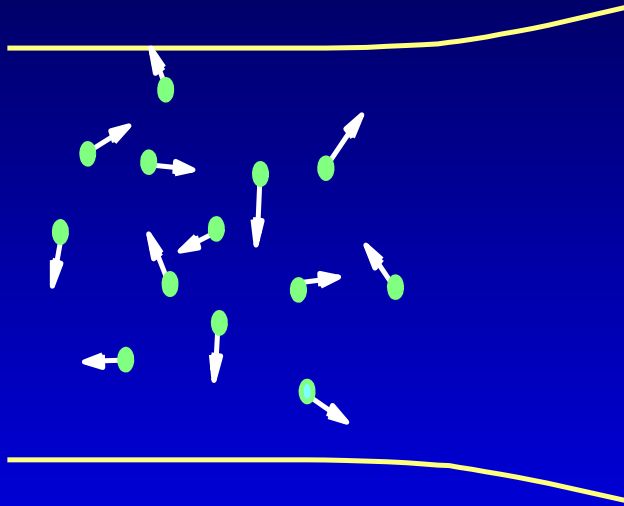
$$L_s = \frac{CAU}{l} \left(1 - e^{-\frac{2n_z v_s \sqrt{a/\pi}}{AU}} \right)$$

n_z = aantal luchtwegen in generatienummer z

v_s = sedimentatiesnelheid van het aërosol deeltje =

$$= \frac{\rho_p d_p^2}{18\mu} g$$

Diffusie



Kleine deeltjes $< 0.1 \mu\text{m}$

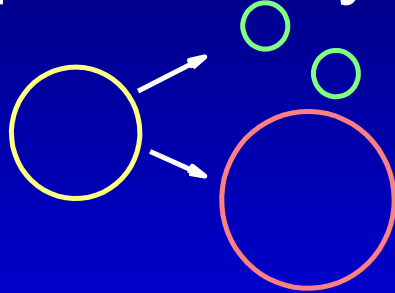
Vooral in
perifere bronchiën
alveoli

$$L_d = \frac{CAU}{l} \left(1 - e^{-\frac{36D_b l n_z}{AU}} \right)$$

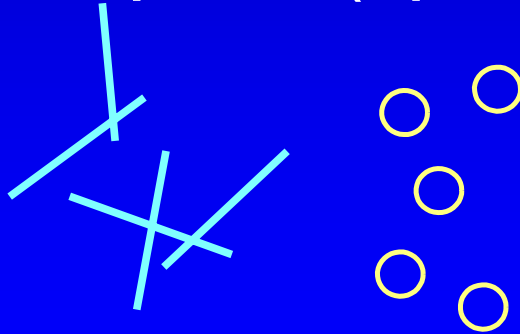
D_b = brownse diffusiecoëfficiënt

Not modelled

- Electrostatic forces
- hydrophobic, hydrophilic



- interception (sphere - fibre)



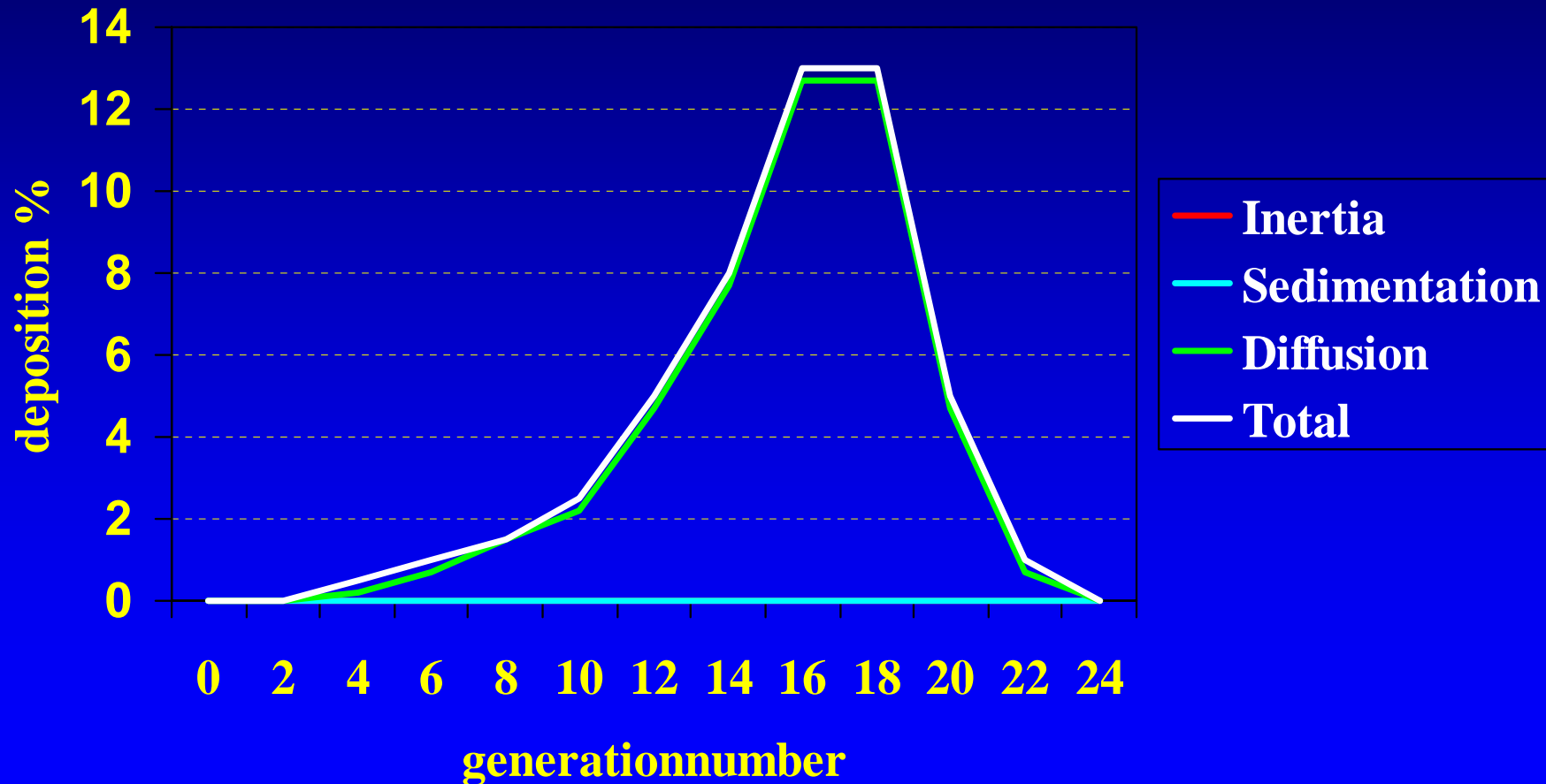
Displacement in 1 s (μm)

Diameter	Sediment	Inertial *	Diffusion	Total
25	18203	1893	1,5	20098
10	2912	303	2,3	3217
5	740	76	3,3	819
2	124	12	5,3	141
1	33	3	7,8	44
0,5	9,5	0,8	11,9	22
0,2	2,2	0,12	22,3	25
0,1	0,9	0,03	39,2	40
0,05	0,4	0,008	73,0	73
0,02	0,14	0,001	174,5	175
0,01	0,07	0,0003	344,0	344

* initial velocity of 1 m/s

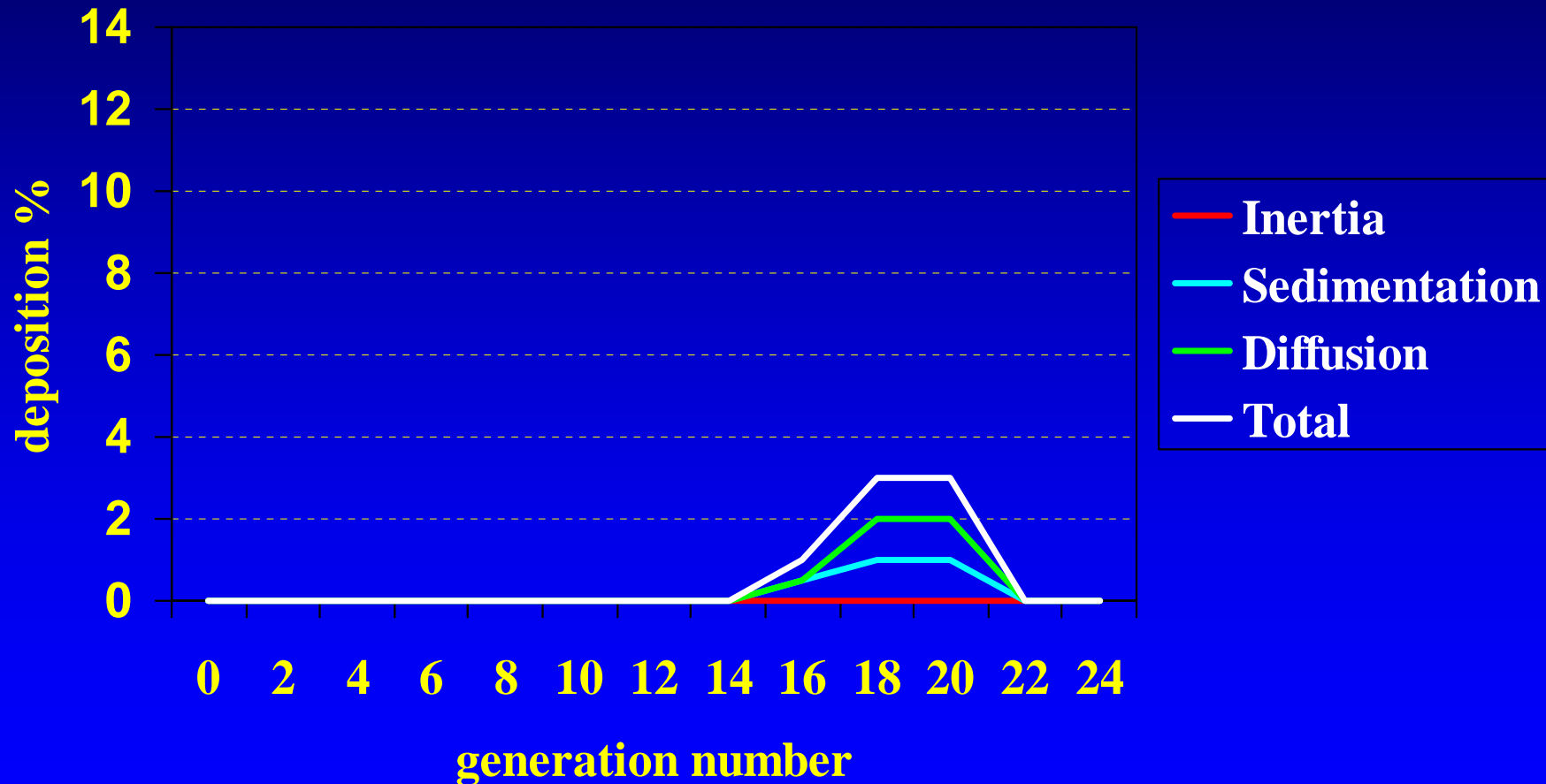
Results $d = 0.01 \mu\text{m}$

TV=500 ml, $t_i=t_e=2\text{s}$, mouth-breathing, 1 breath
total deposition = 83%



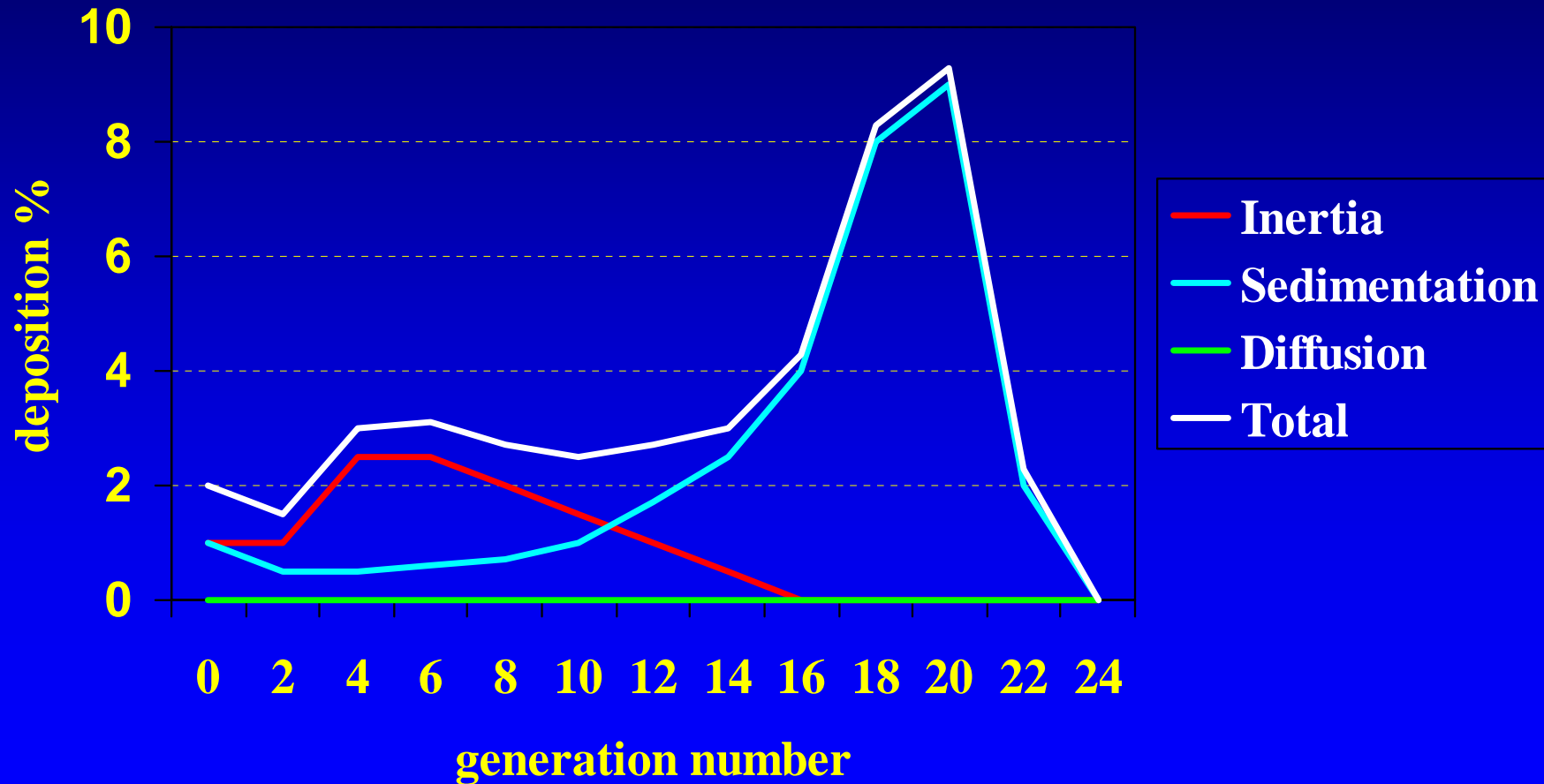
Results $d = 0.5\mu\text{m}$

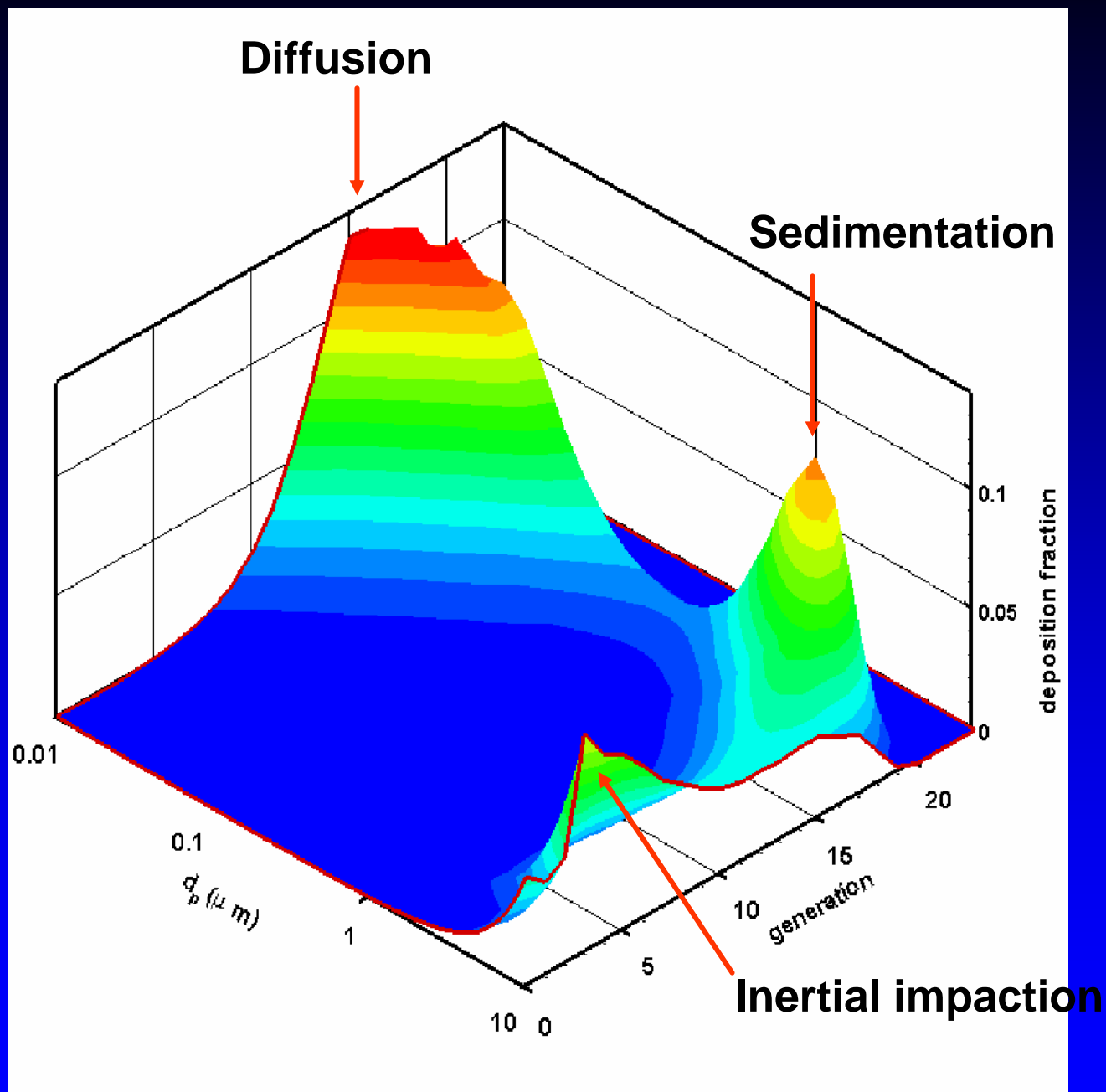
TV=500 ml, $t_i=t_e=2\text{s}$, mout-breathing, 1 breath
total deposition = 8.3%



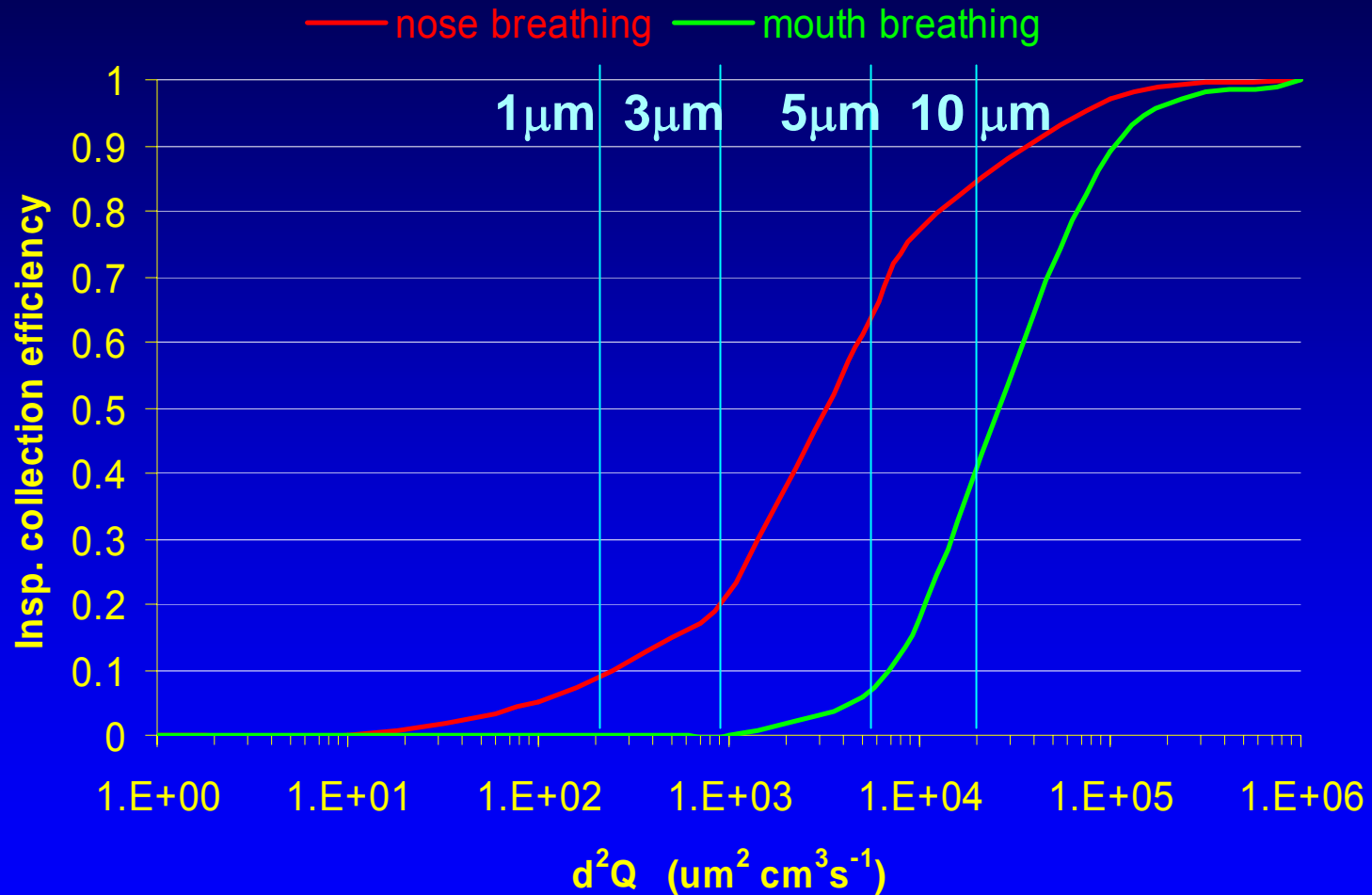
Results $d = 5.0 \mu\text{m}$

TV=500 ml, $t_i=t_e=2\text{s}$, mouth-breathing, 1 breath
total deposition = 81%



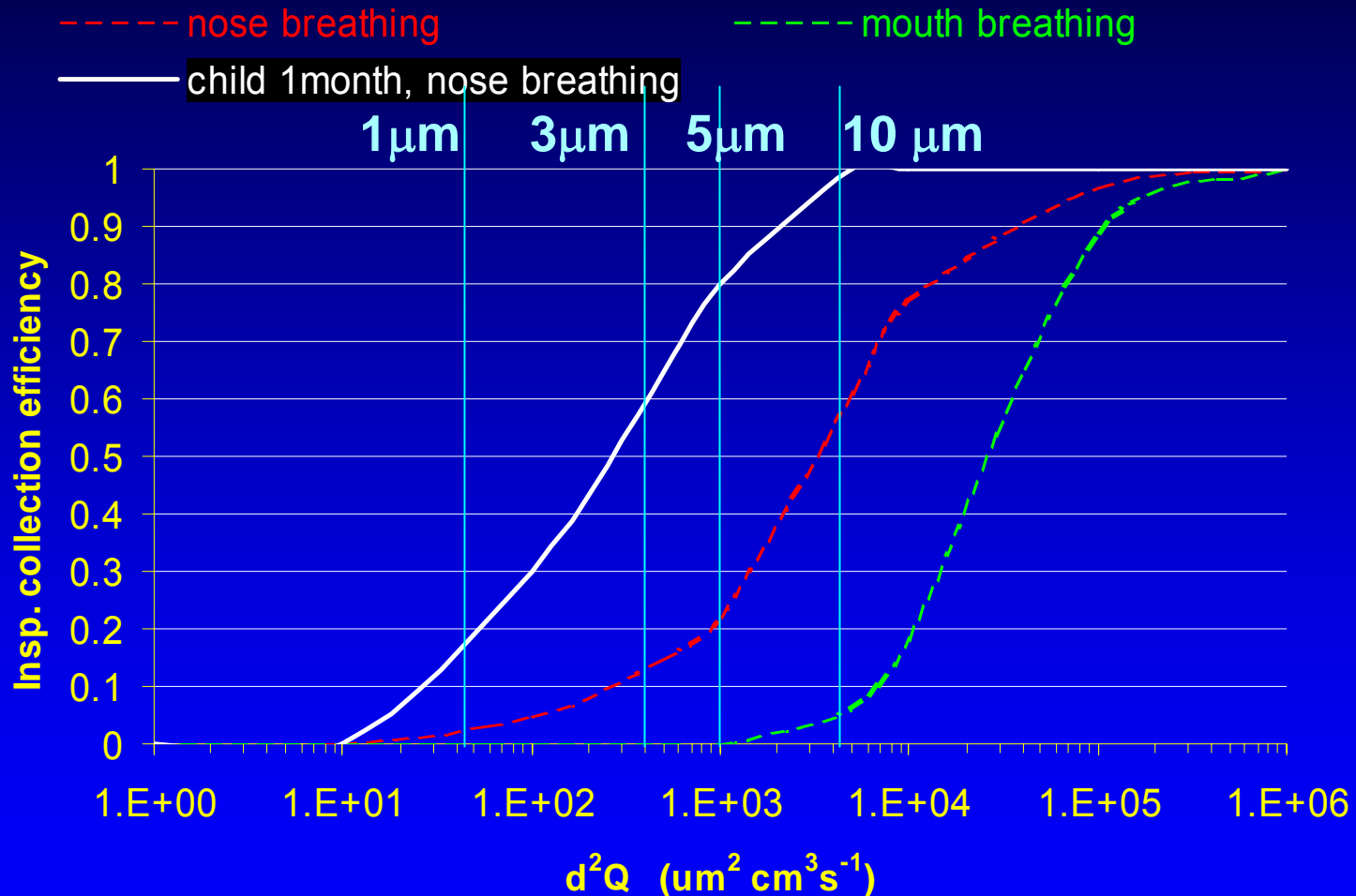


Deposition in upper airways (adults)



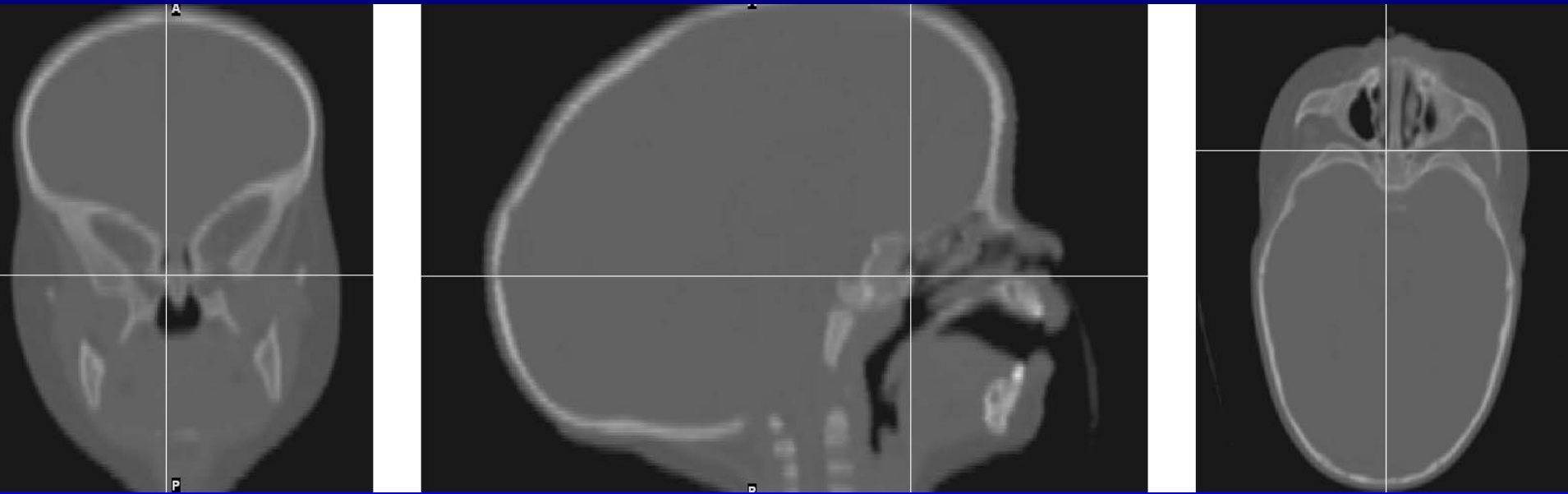
Schulz H, Brand P, Heyder J, Chapter 5: Particle deposition in the respiratory tract, Lung Biol. In Health and Disease 2000 Vol 143

Deposition in upper airways (newborn)

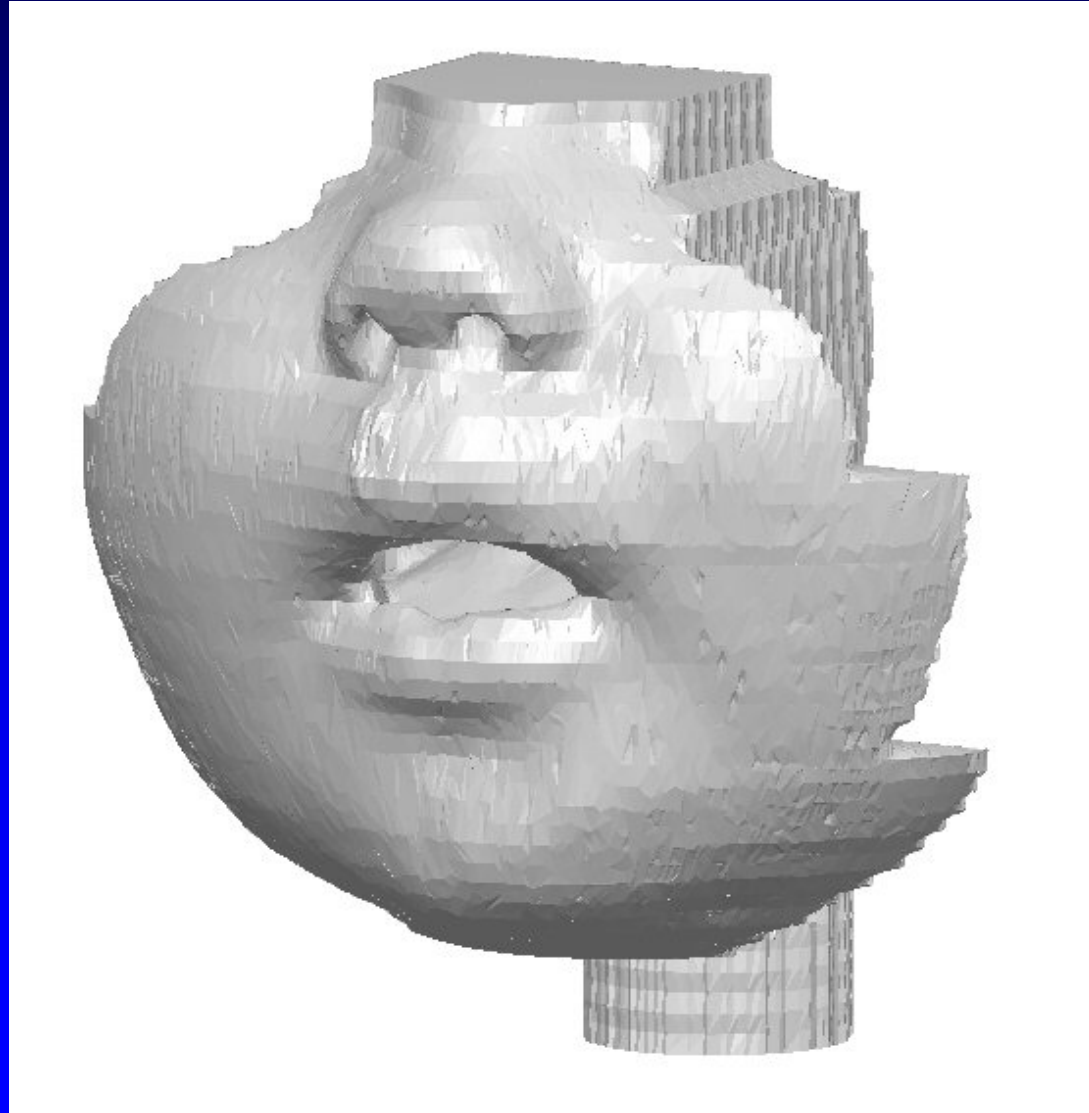


Phalen RF, Oldham MJ, Mautz WJ: Aerosol deposition in the nose as a function of body size, Health Physics 1989, 57 suppl1, 229-305

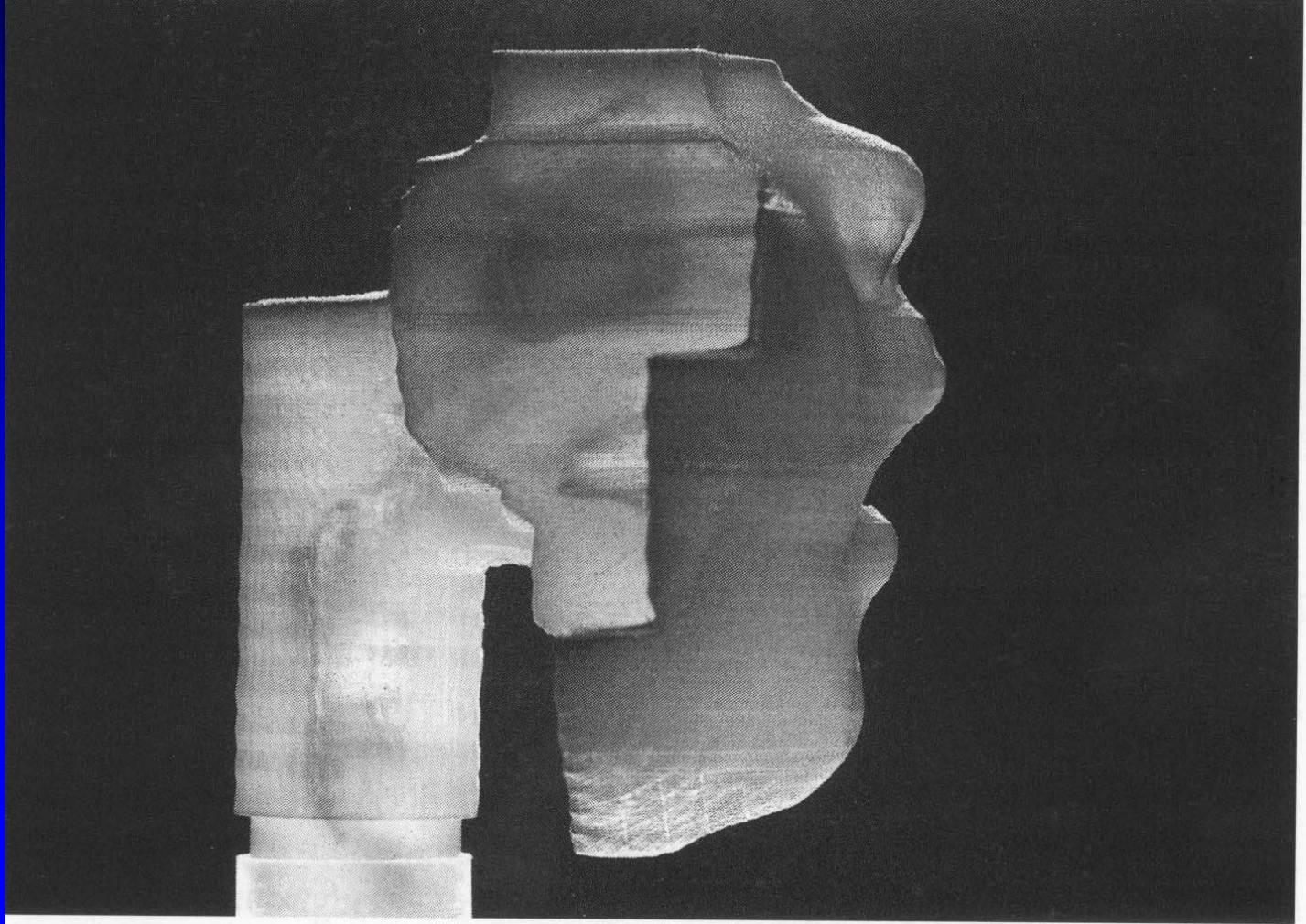
Example of actual research: CT- images of a child (9 months)



Stereo-lithographic reproduction

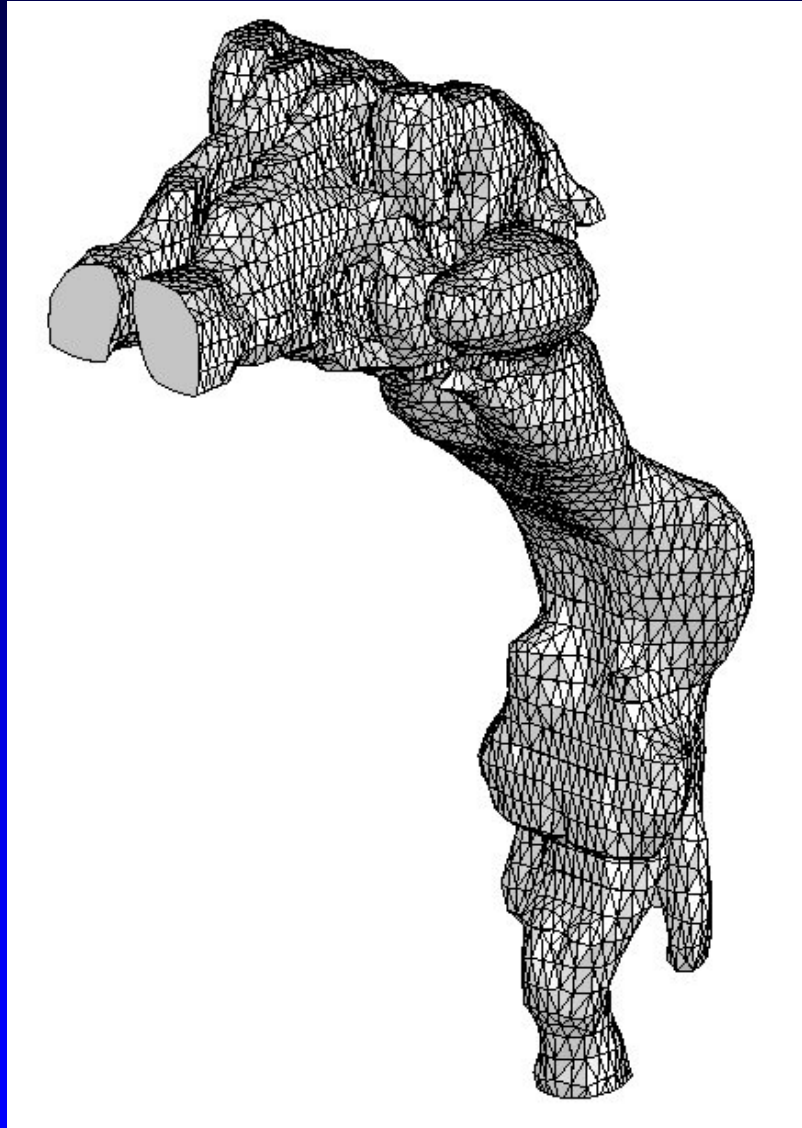


Model of 3D-CT scan, 9m, 10kg nasal



Janssens HM. JAM 2001, 14,435

CFD model (solved with CFX)



Lungfunction measurements

Flow-Volume measurement

Open systems (measure flow: integrated to obtain volume)

- Pneumotach (Fleisch/Lilly)
- Mass flow measurements (hot wire)
- Rotameter
- Ultrasound
-

Closed systems (direct volume measurement)

- (Wet) spirometer
- Dry rolling seal
-

ATP – BTPS correction, calibration, linearisation

Classic normal lungfunction : F-V curve

PEF = Peak Expiratory Flow

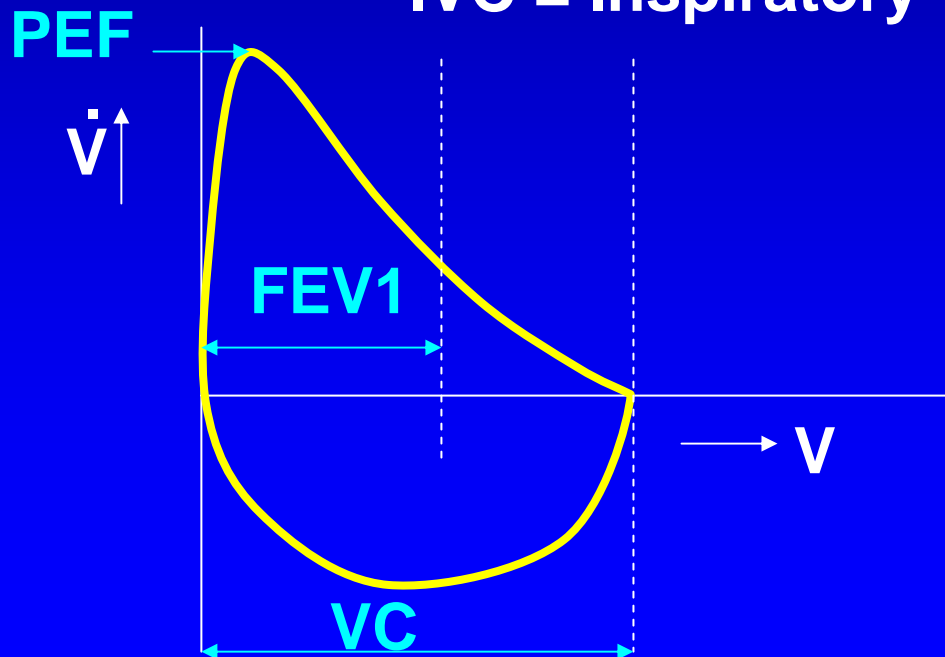
FEV1 = Forced Expiratory Volume in 1 second

VC = Vital capacity

FVC = Forced Vital Capacity

EVC = Expiratory Vital Capacity

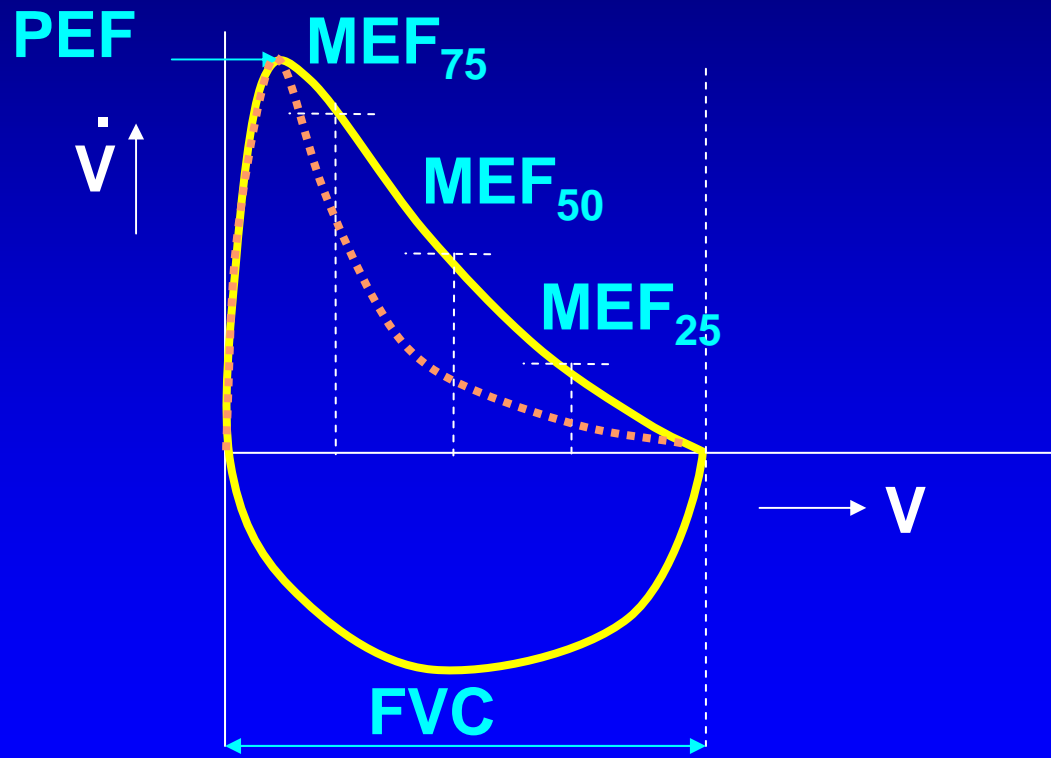
IVC = Inspiratory Vital Capacity



Classic normal lungfunction

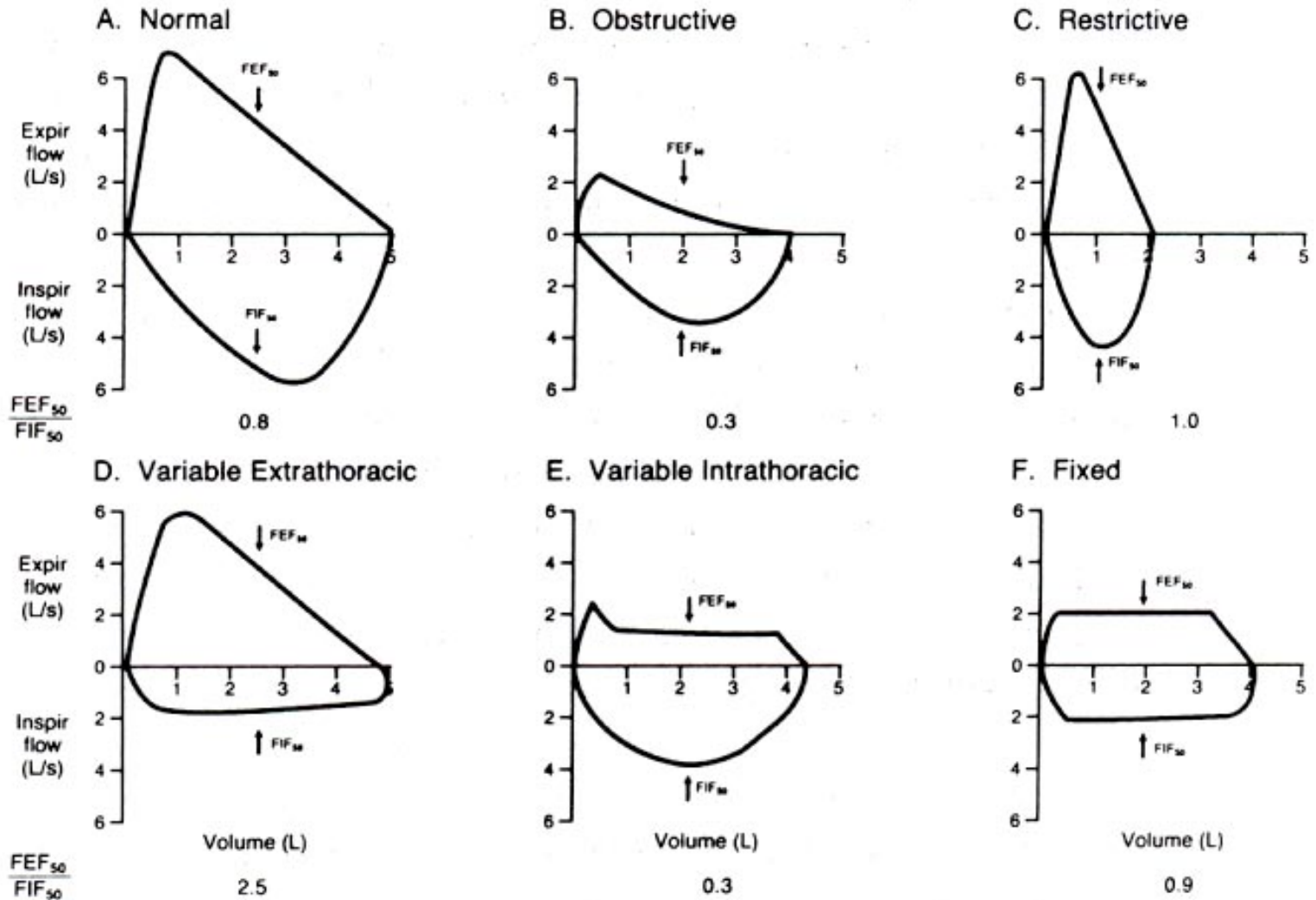
MEF = Maximal Expiratory Flow

Subscript = How much of the FVC can still be expired

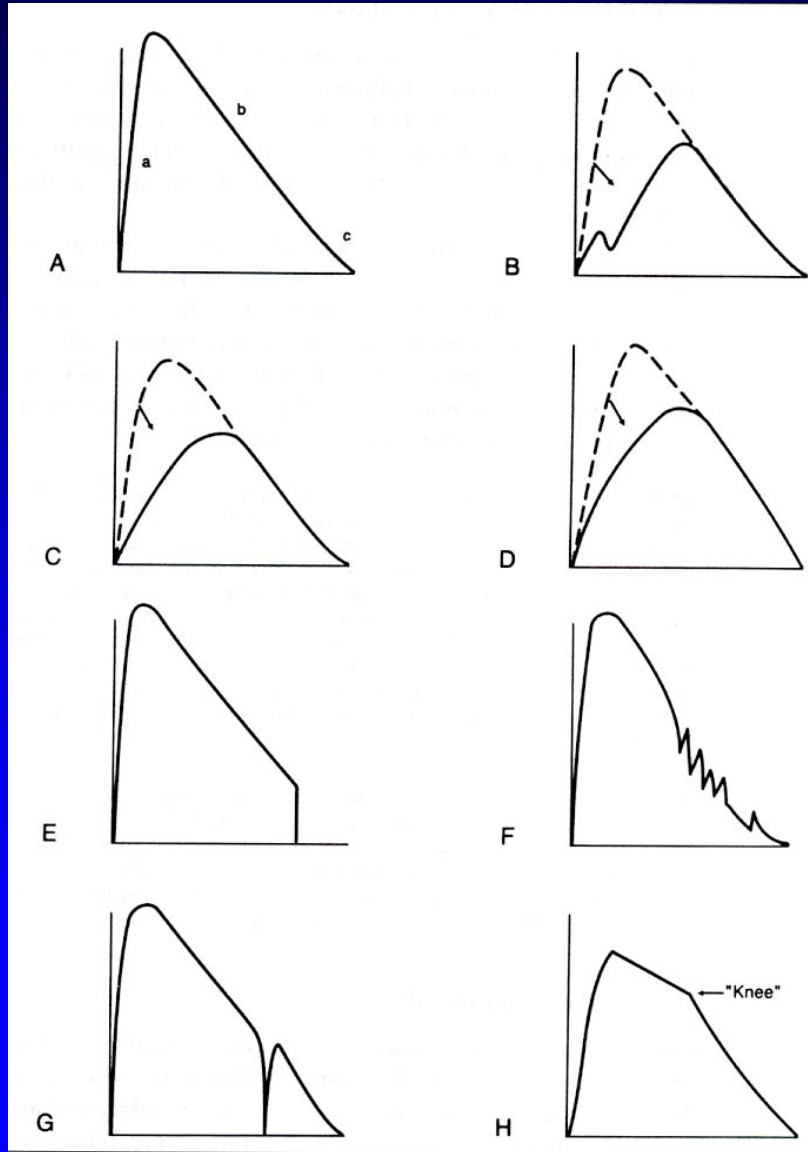


To quantify small airway obstruction

F-V patterns



FV mistakes



- a) good
- b) Hesitation at start
- c) sub maximal begin exp
- d) "rainbow" curve (repr.)
- e) early end
- f) cough
- g) temporary pause at exp.
- h) good, mostly not-smoking young adult

Peak Expiratory Flow

Circadian rhythm

Highest value normally around 12:00

If the variation over the day (=highest – lowest value)

> 20% from the average value from that day (adult)

> 31% from the average value of that day (for a child)

**Then there might be a variable airway obstruction
(Asthma)**

FEV1/VC, FEV1 (obstructive)

ERS Criteria:

1) Normal:

as well FEV1/VC as VC are in their normal range

2) Obstructive:

FEV1/VC is below normal

%pred FEV1 \geq 100% physiological variance

%pred FEV1 $<$ 100 en \geq 70 Mild

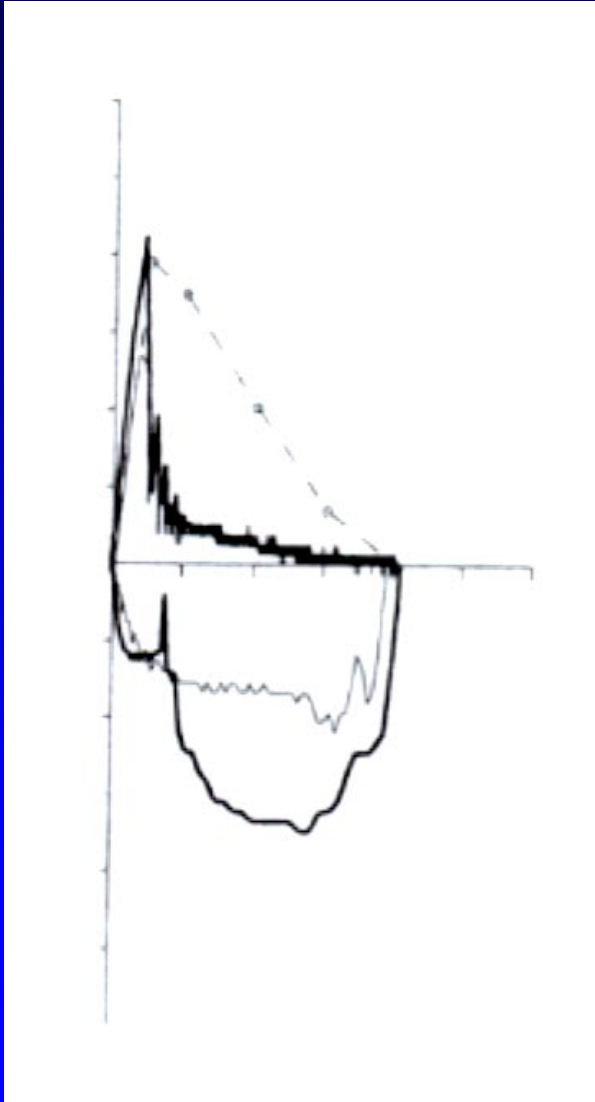
%pred FEV1 $<$ 70 en \geq 60 Moderate

%pred FEV1 $<$ 60 en \geq 50 Moderate severe

%pred FEV1 $<$ 50 en \geq 34 severe

%pred FEV1 $<$ 34 very severe

Normal PEF (obstructive)



Man 1.74 m, 69 year, BMI 33

FEV1/VC 34 (75)

FEV1 1,50 (2.99) 50%

VC 4.42 (4.03) 110%

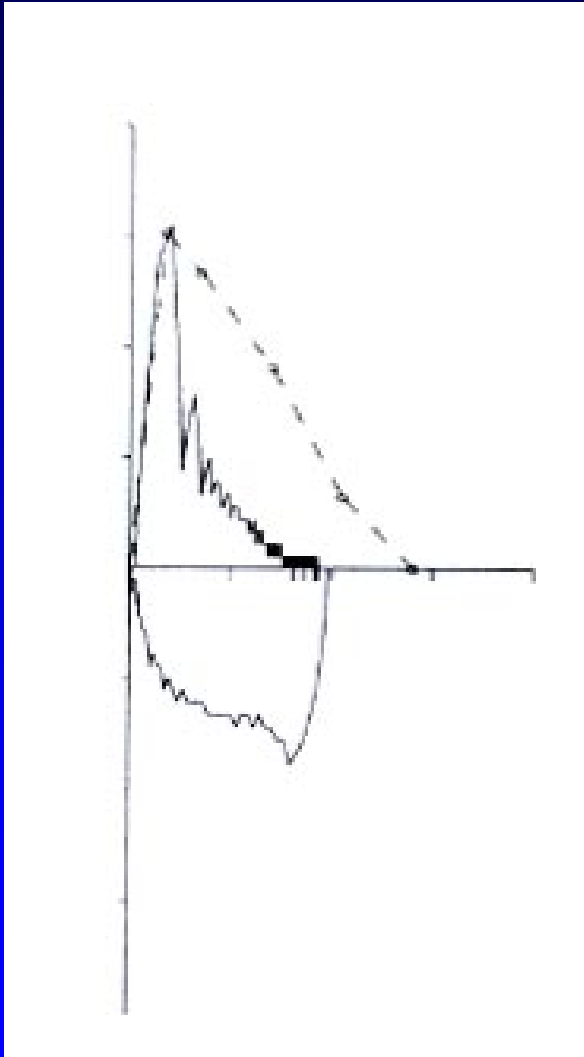
TLC 8.3 (6.8) 121%

RV 3.9 (2.6) 150%

RV/TLC 41 (47)

FRC/TLC 58(65)

Normal PEF (restrictive)



Woman 1.65 m, 61 year, BMI 29

FEV1/VC 72(78)

FEV1 1.40 (2.35) 59%

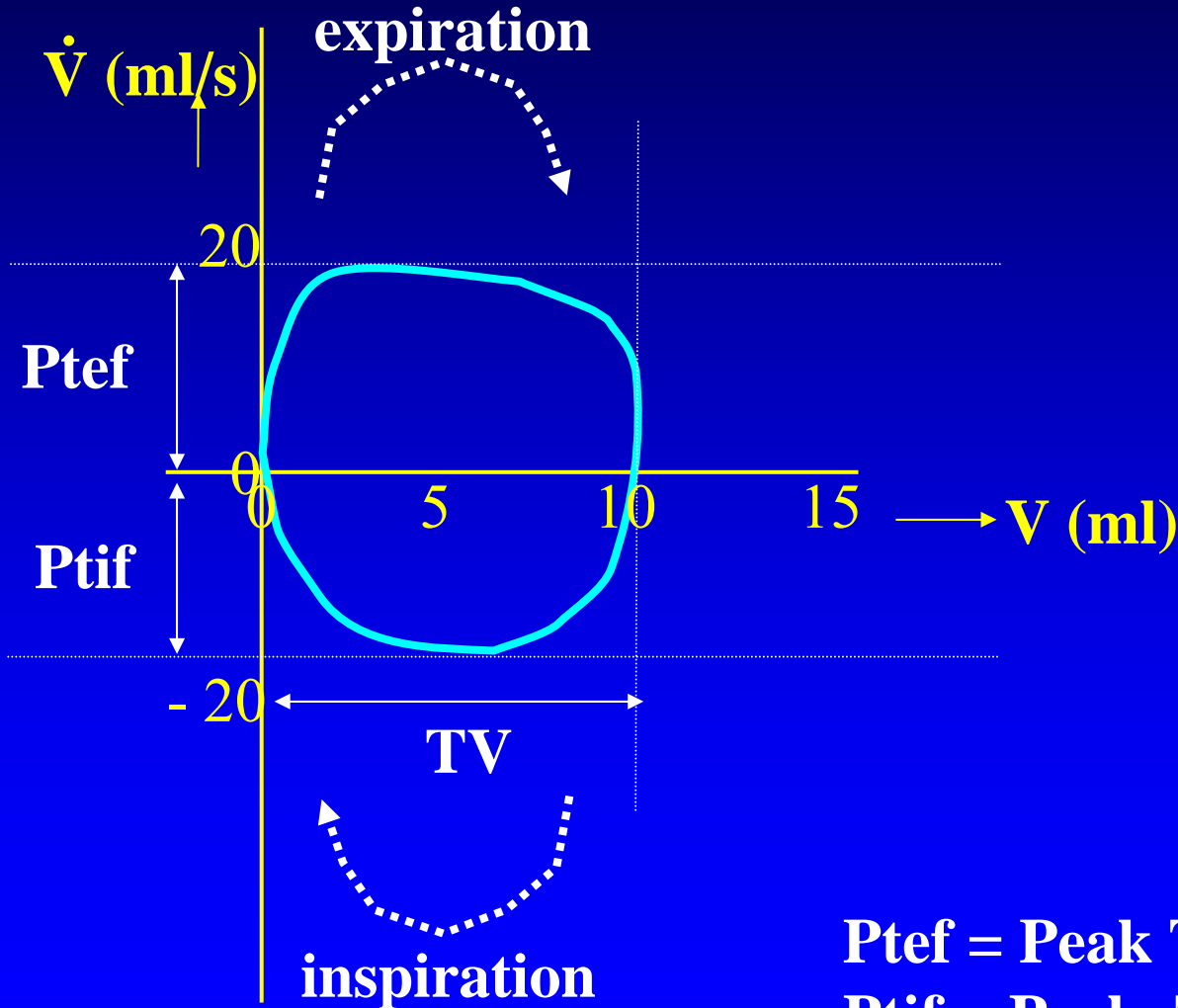
VC 1.95 (2.78) 70%

TLC 3.4 (5.0) 68

RV/TLC 40 (43)

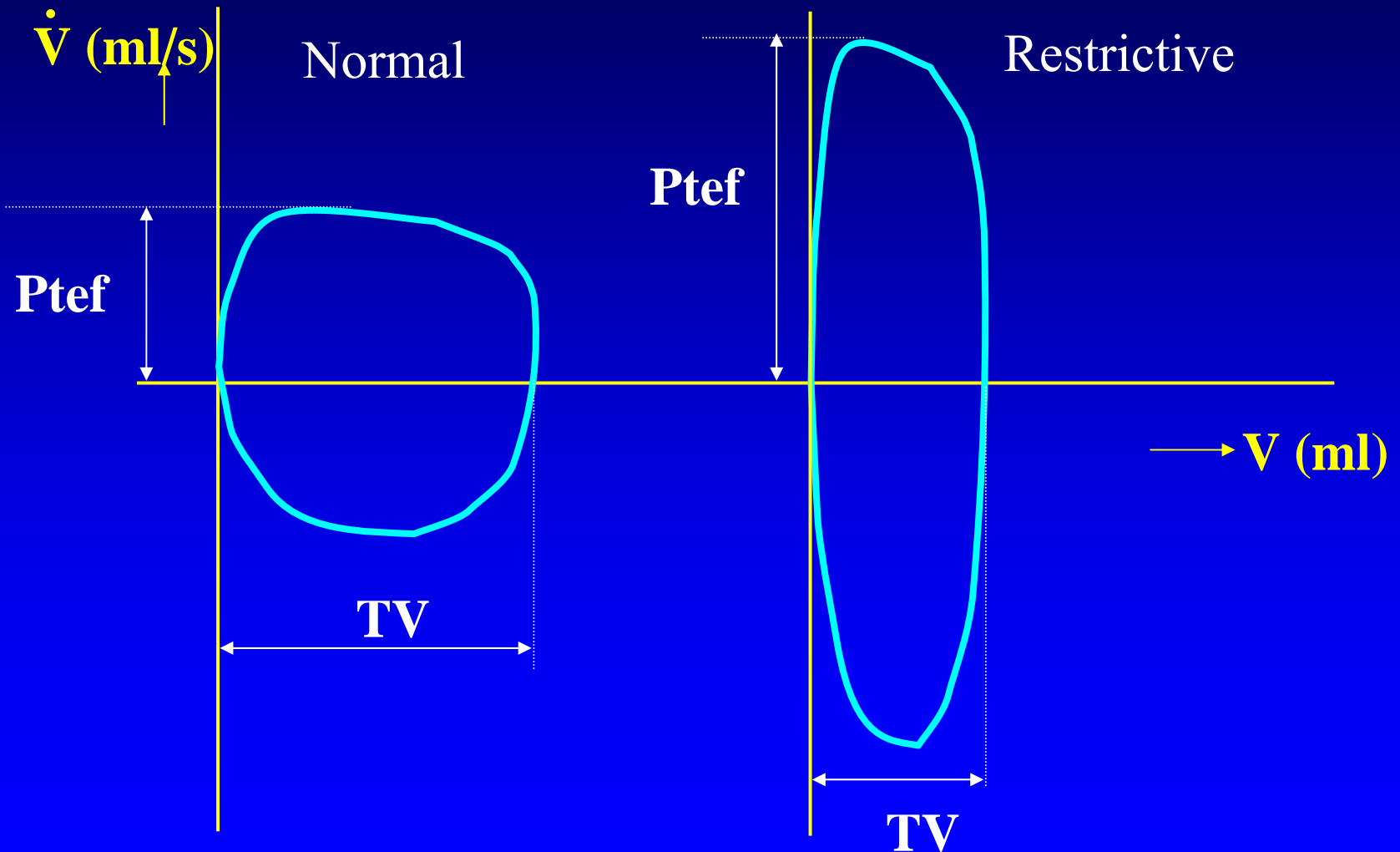
FRC/TLC 59(55)

Flow - Volume curves (tidal)

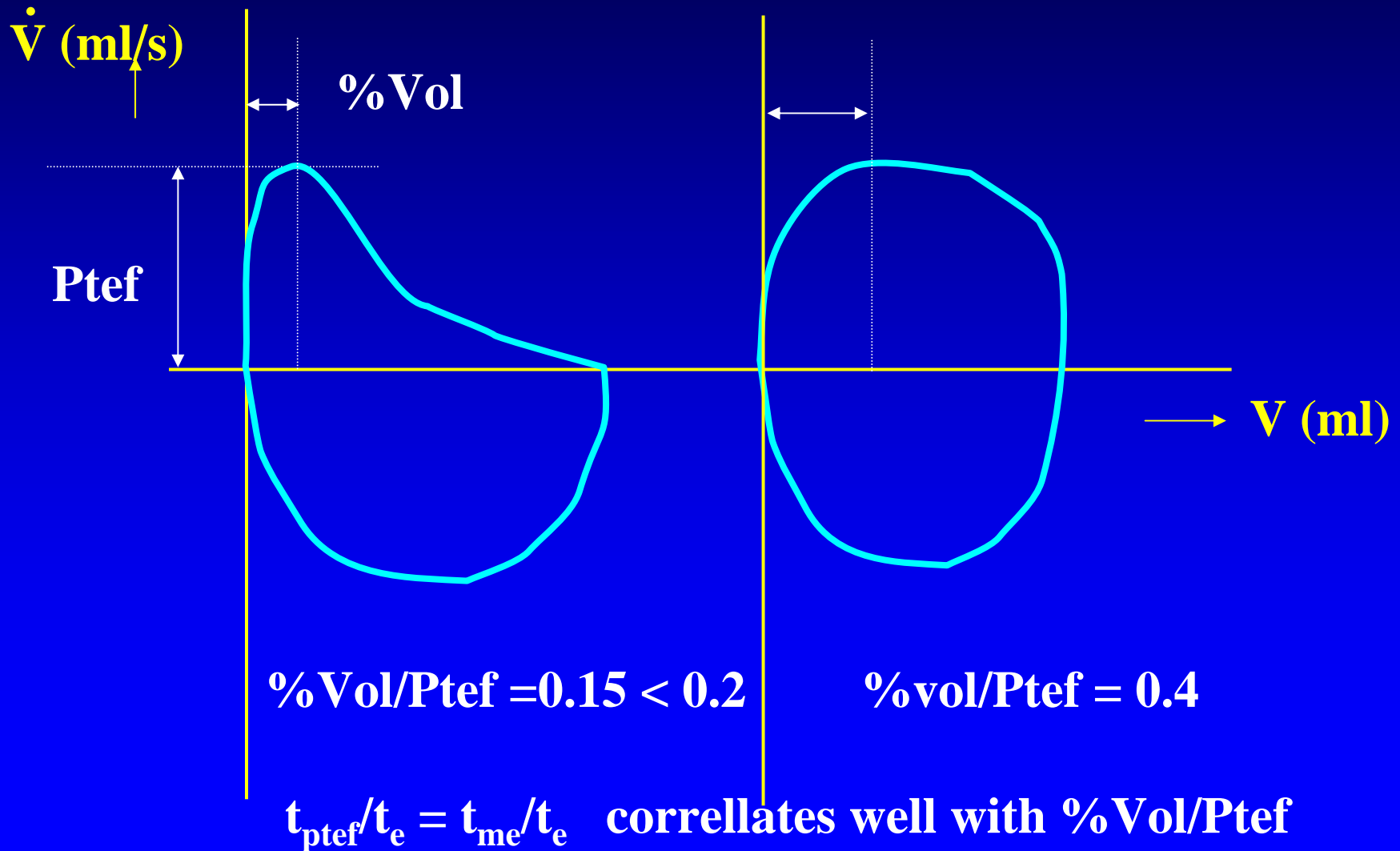


Ptef = Peak Tidal Expiratory Flow
Ptif = Peak Tidal Inspiratory Flow

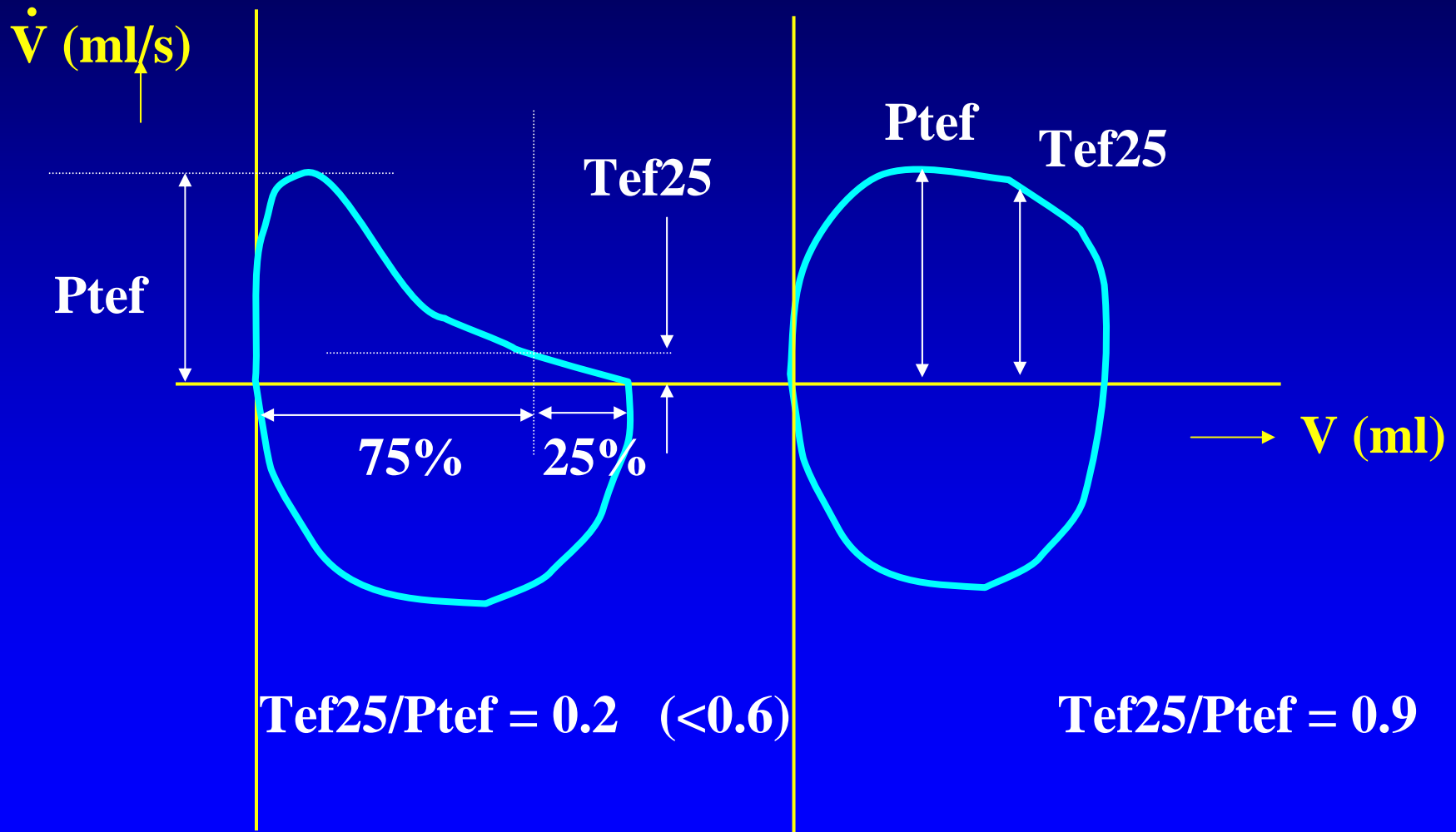
Restriction: Ptef/TV



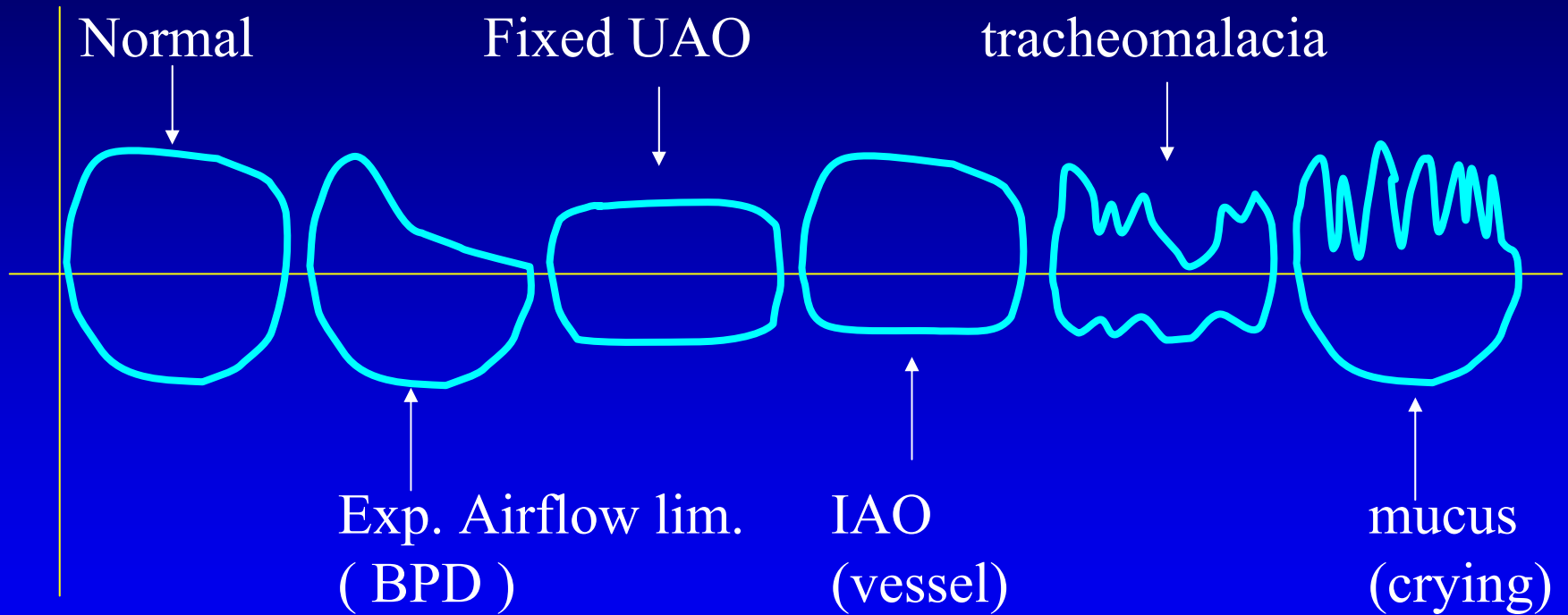
Obstruction 1) %Vol/Ptef



Obstruction 2) Tef25/Ptef



Flow - Volume curves



UAO = Upper airway obstruction

IAO = Intrathoracic airway obstruction

Static Lungvolumes

TLC elevated (hyperinflation)
FRC elevated (hyperinflation), lowered (obesitas)
RV

He wash-in
SF₆ wash-in / wash-out
N₂ wash out
Body-plethysmograaf (Bodybox)

Difference between bodybox and wash in/ out methode
- not ventilated parts of the lung (trapped air)

TLC, VC (restrictive)

ERS Criteria:

3) Restrictive based on TLC:

%pred TLC <LLN but ≥ 70	Mild (LLN~80)
%pred TLC < 70 and ≥ 60	Moderate
%pred TLC < 60	Moderate severe

If TLC is not measured, indicated by VC:

%pred VC <LLN but ≥ 70	Mild (LLN~80)
%pred VC < 70 and ≥ 60	Moderate
%pred VC < 60 and ≥ 50	Moderate severe
%pred VC < 50 and ≥ 34	Severe
%pred VC < 34	Very severe

Reversibility on salbutamol (ERS/ATS)

ERS

FEV1 after medication (% pred) – FEV1 before medication (%pred)

More than 12% and more than 200 ml
(NB: primary practitioners mostly 9%!)

ATS

FEV1 after medication more than 12% increase of base value (and more than 200 ml)

Example COPD:

FEV1 predicted 4 litre, before medication 2 litre, after 2.4 l

ERS:	$2.4 / 4 - 2 / 4 = 60\% - 50\% = 10\%$	not reversible
ATS:	$2.4 / 2 - 1 = 120\% - 100\% = 20\%$	reversible !

Transferfactor (diffusion capacity)

CO binds to blood

Measurement methods single breath / rebreathing

Transfer factor = TLCO

Transfer coefficient = $K_{CO} = TLCO / VA$

(often referred as specific diffusion capacity)

VA = alveolar volume

Pathological < 80-70%

Metacholine / Histamine provocation

Provocation with allergens is the “standard” method to identify asthma

PC20/PD20 = that dose which results in a decrease in FEV1 of 20%

If that dose is lower than 8 mg/ml (PC20) or 7.8 μ mol (PD20) then positive

Several methods:

Tidal breathing-method, dosimeter, Yan method etc

Other “medication”: adenosine-5-monophosphate (AMP)

Physical stimuli: cold air, exercise, non-isotonic aerosols

Resistance measurements

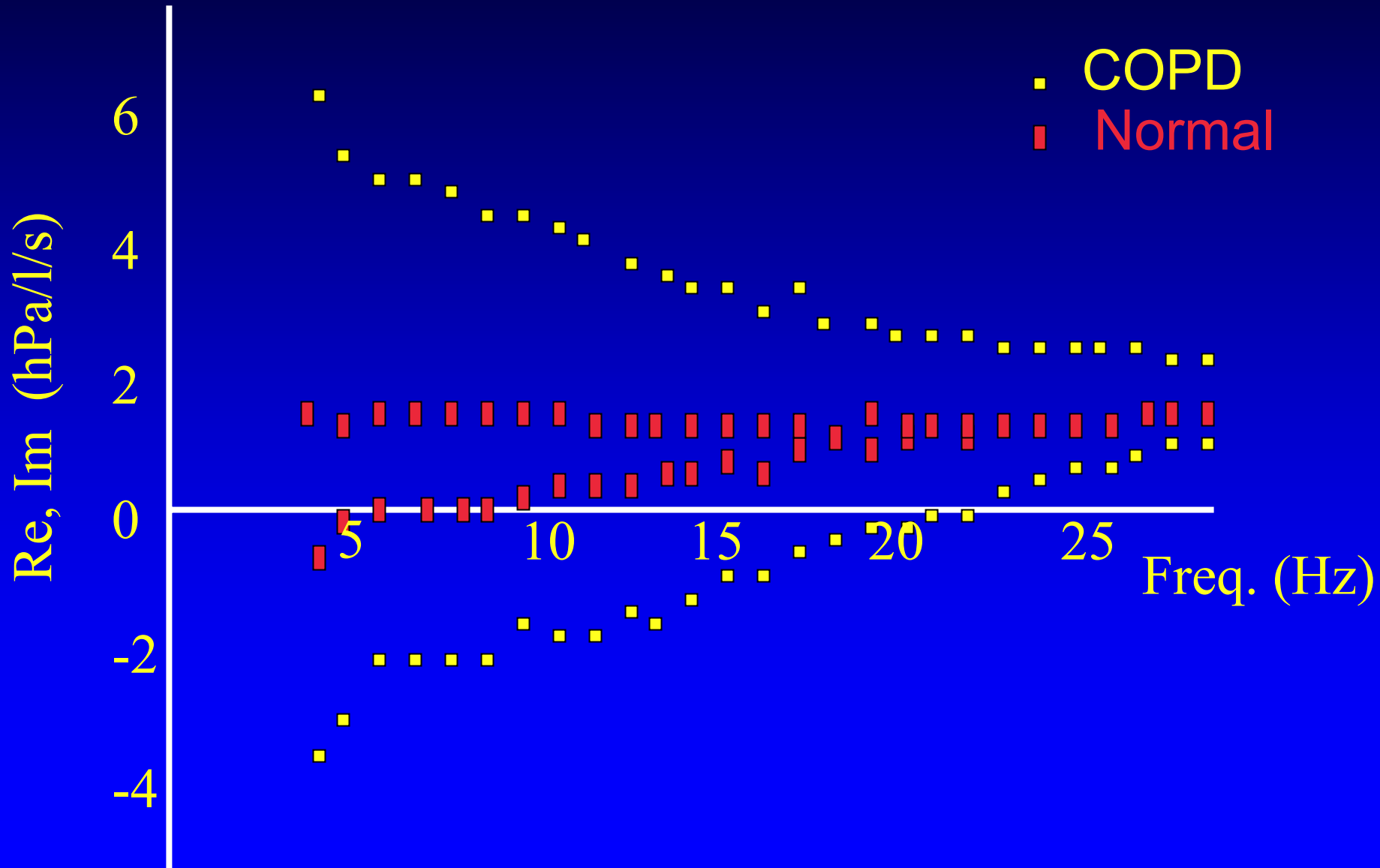
Body plethysmograph

Rint (interruption-technique)

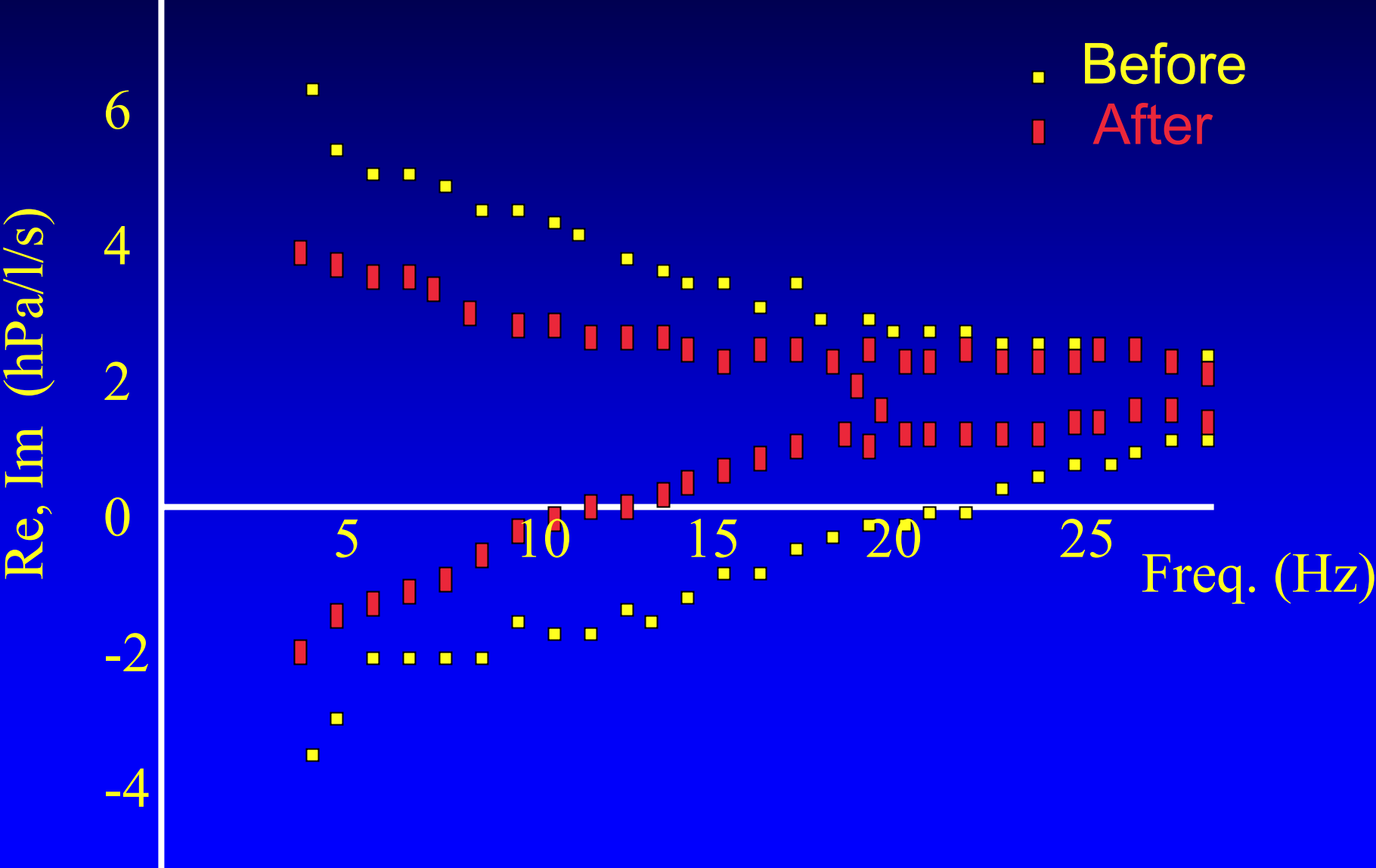
FOT – IOS (Forced Oscillation Technique)

Oesophagus balloon

FOT (COPD against Normal)



COPD before and after Atrovent



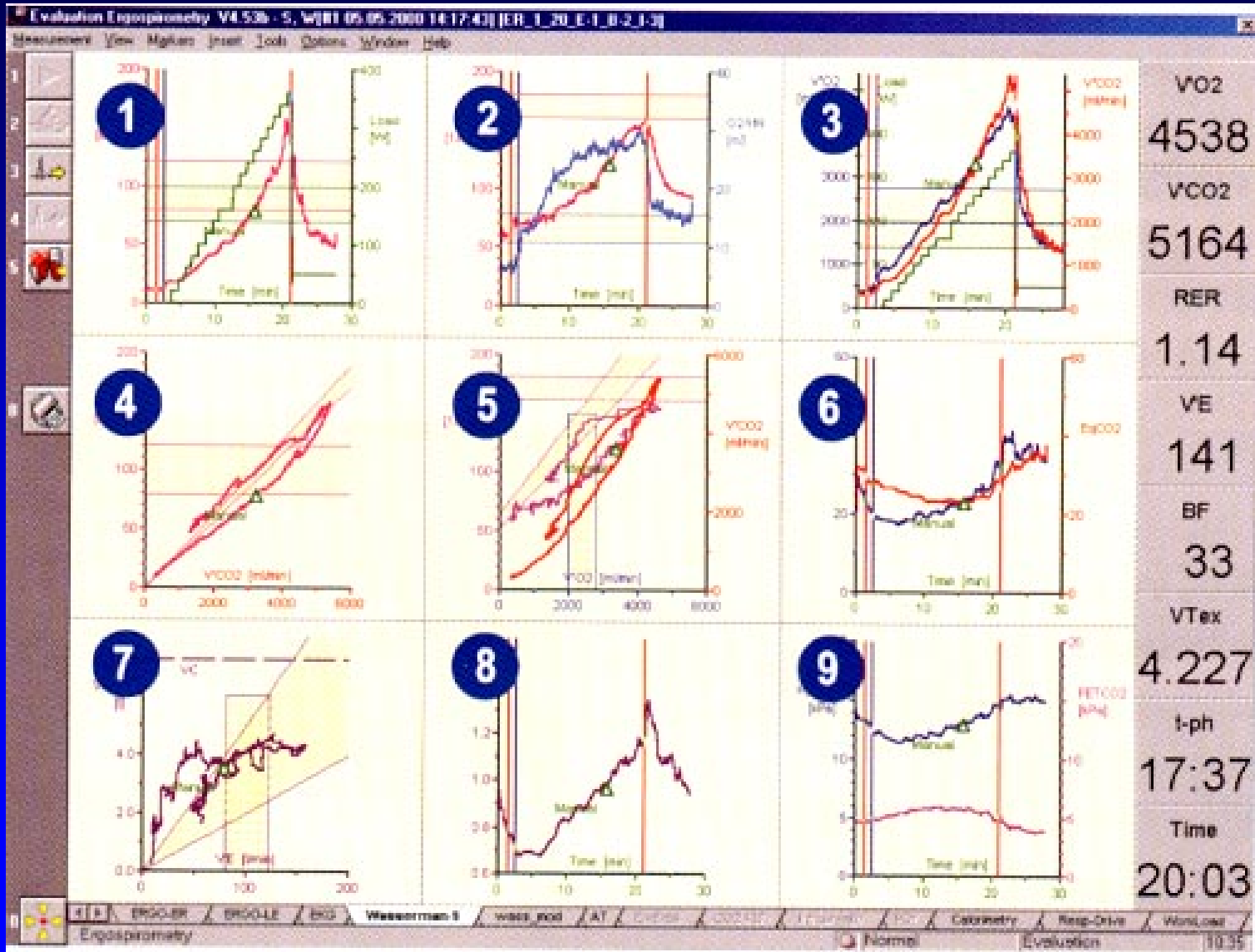
Hyperventilation

- 1) “Nijmeegse” questionnaire > 23
- 2) Provocation (3 min $\text{FetCO}_2 < 2.5\%$) : 3 minutes own frequency (does a fly-wheel effect occur ?)
- 3) Recognizing complaints

Ergometry: Treadmill / Cycle



Nine panel plot



“New” lungfunction tests

Mostly non-invasive to tell about peripheral diseases

Forced Oscillation Technique / Impulse Oscillation Tech.

Exhaled gases

- NO	> 16 ppb	inflammation
- CO	0-10 ppb	non-smoker
	11-20	moderate smoker
	20	smoker

Exhaled breath Temperature

EMG measurements

“Newest” lungfunction tests

Mostly non-invasive to tell about peripheral diseases

(Functional) HRCT

N₂ Multibreath Washout techniques

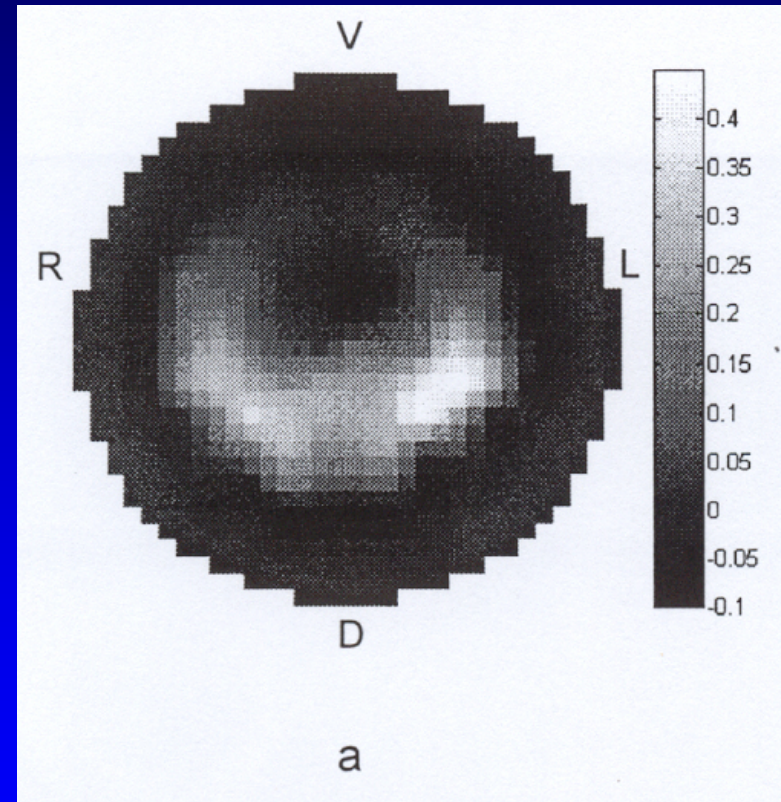
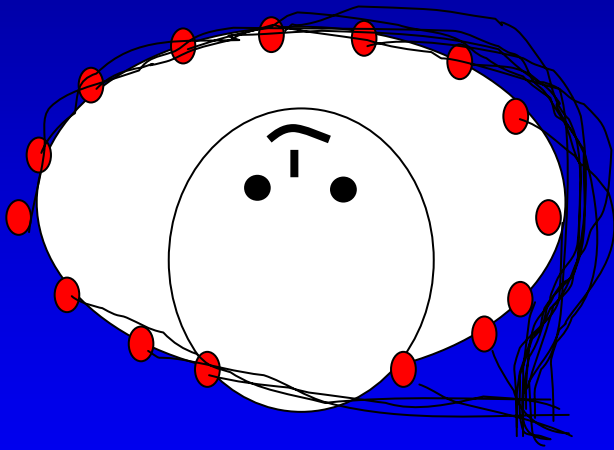
Electric Impedance Tomography (EIT)

Polarised Helium

Breath condensates

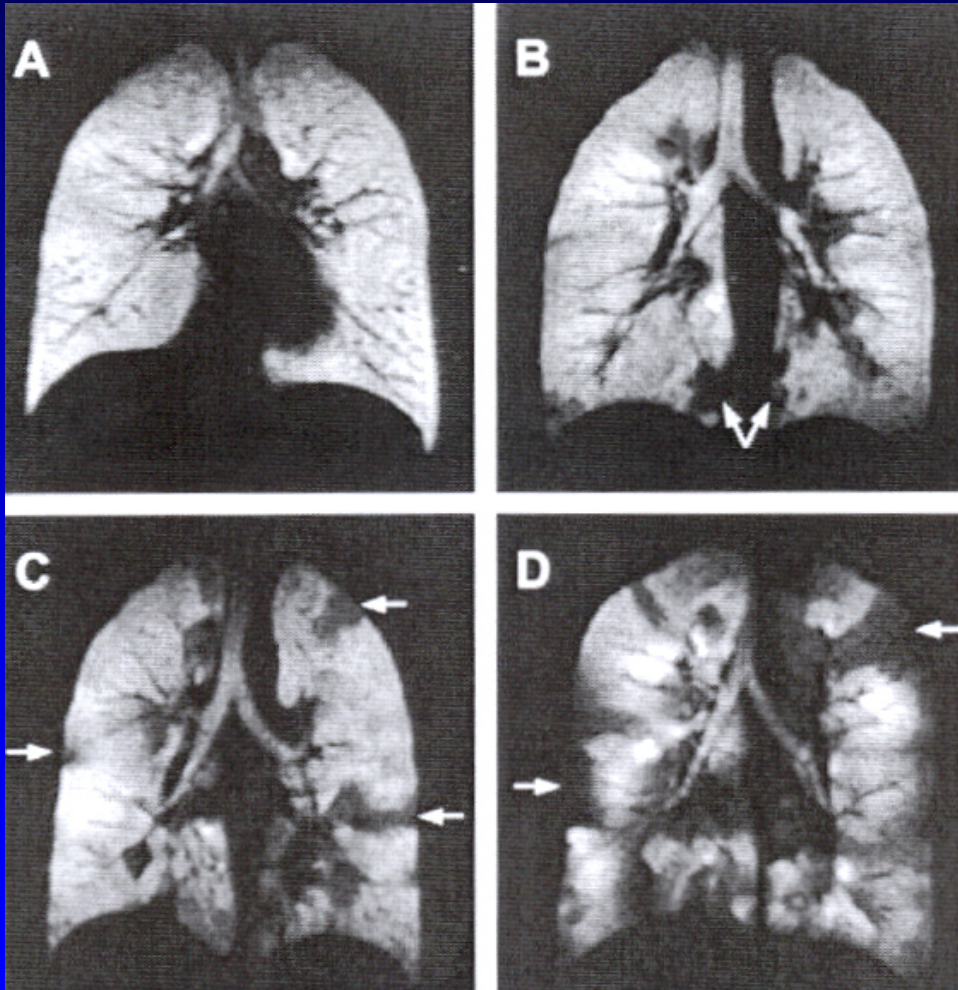
.....

Electric Impedance Tomography



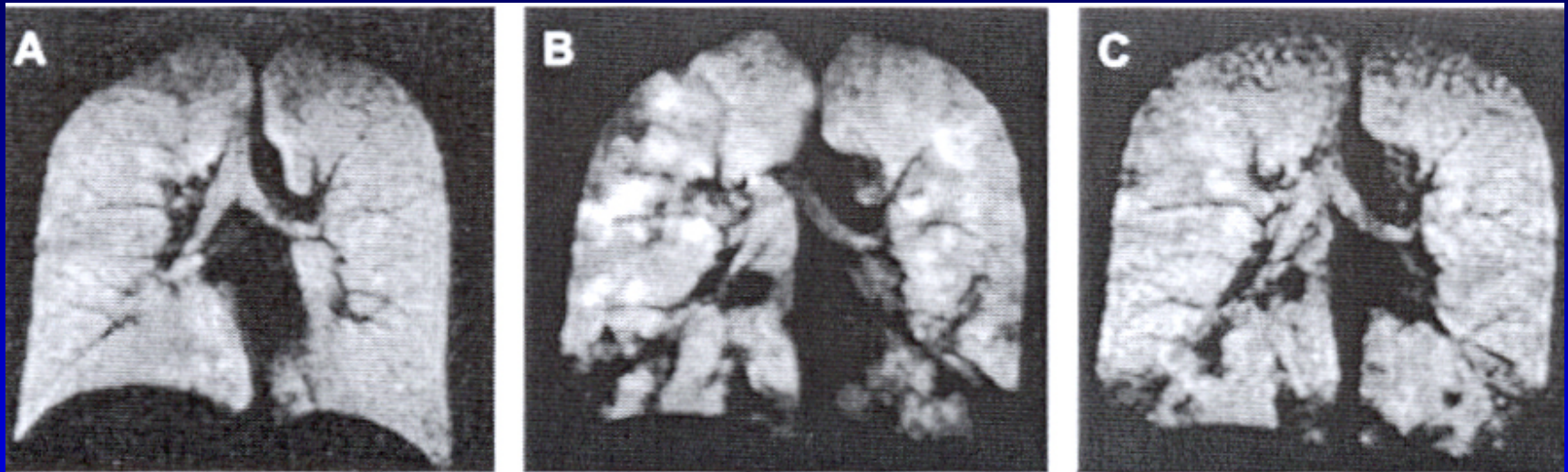
- + cheap
- + easy
- + fast
- results only in one cross-section
- low resolution

Polarised Helium



- a) Normal lung
- b) Mild asthma
- c) Moderate
- d) Severe

Polarised Helium



- a) Mild asthma (baseline FEV1=118%)
- b) After Metacholine challenge (FEV1=73%)
- c) After albuterol

Which lung function parameter ?

Simple

for doctor and patient
cheap

Reliable

reproducible results
normal values available

Smart

Use patient as its own control

- changes over time
- changes under treatment

Conclusion

- 1) There are many outcomes and methods**
- 2) No clarity which outcome and method is standard**
- 3) Increasing number of non invasive diagnostic and bio-chemical markers**

Literature: Longfunctie-onderzoek: Technieken, toepassingen, interpretaties, M. Demedts, M. Decramer 1998

Conclusions 2: The future

Minimize lung damage by optimal patient monitoring and measurement

New techniques for (early) detection of : peripheral diseases and ventilation in-homogeneities

Optimise treatment and medication (like aerosolised drugs) to treat inflamed areas

FEV₁ is still the golden standard but detects changes on macro scale. We have to find a new one.

New parameters are important and searched after, since lungfunction lost in (early) life is never regained

