Best of Brussels - 2010

Subjects covered

- Acute Heart Failure
- ARDS
- Pleural Effusions/Pneumothorax
- Cardiovascular
- Micro-circulation
- Renal
- Hepatic
- Infection
- Physiology
- Intra abdominal hypertension
- Pulmonary embolism

Acute Heart Failure

ED:Dyspnoea and/or other signs of congestion + elevated SBP (>150 mmHg)

Acute pulmonary oedema

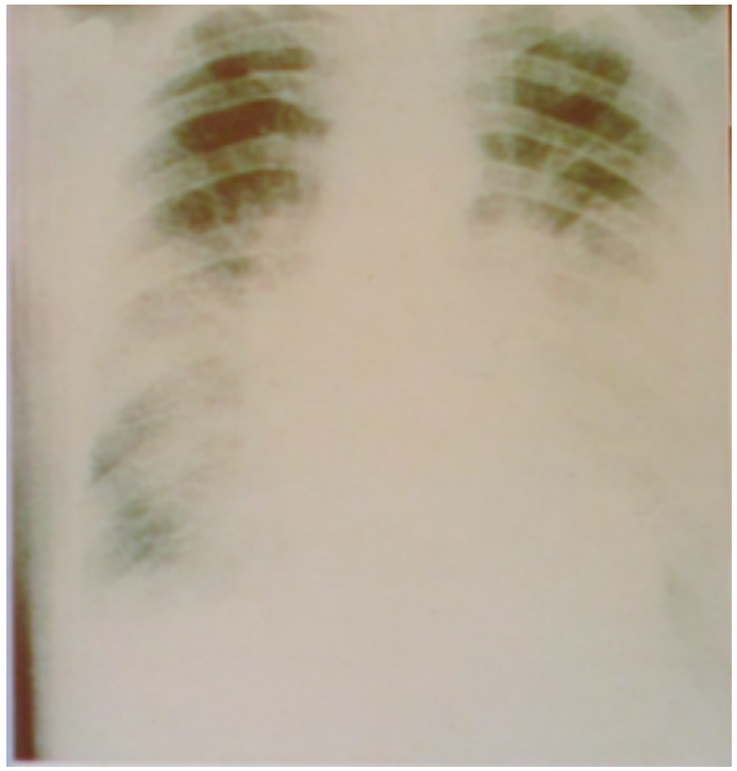
+

Dyspnoea develops abruptly
Diffuse pulmonary oedema

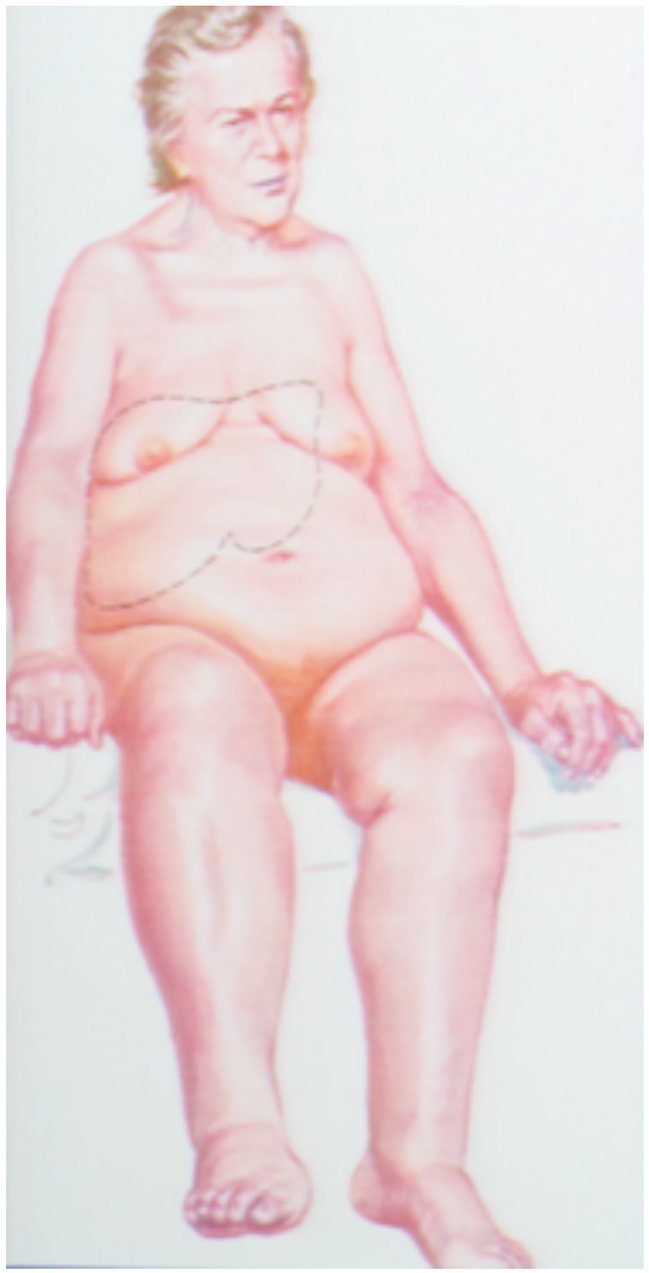
It is a <u>vascular</u> illness

+

Warning!
Patient is very often
normovolemic
or hypovolemic



HF clinic: Dyspnoea + SBP 100-150 mmHg



Decompensated chronic heart failure

+

Dyspnoea develops gradually

Gradual increase in body weight

Systemic oedema

Minimal pulmonary oedema

It is a systemic illness

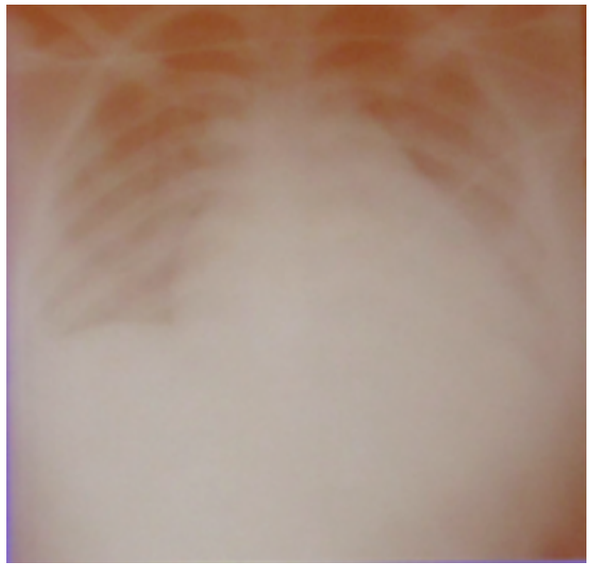
Possible renal dysfunction

Anaemia

Low albumin

Increased pulmonary congestion

Systemic congestion



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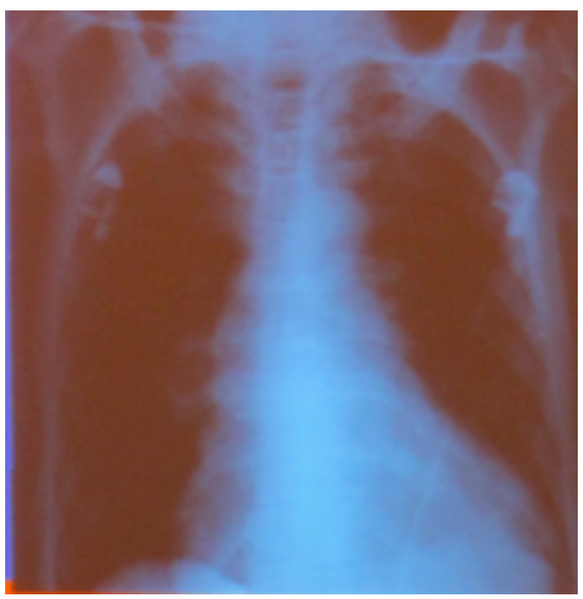


Acute heart failure

Clinical scenarios

- Clinical scenario 1 - Dyspnoea with elevated BP

  SBP >140
  Symptoms develop abruptly
  Predominantly diffuse pulmonary oedema
  Minimal systemic oedema (may be euvolaemic or hypovolaemic)
  Acute elevation of filling pressure often with preserved LVEF
  Vascular pathology

- Clinical scenario 2 - Dyspnoea with normal BP

  SBP 100-140
  Symptoms develop gradually, gradual increase body weight
  Predominantly systemic oedema
  Minimal pulmonary oedema
  Chronic elevation of filling pressure with increased venous pressure and increased PAP
  Organ dysfunction (renal impairment, liver dysfunction, anaemia, hypoalbuminaemia)

Acute heart failure

Clinical scenarios

- Clinical scenario 3 - Dyspnoea with low BP

  SBP < 100
  Rapid or gradual onset of symptoms
  Predominantly signs of hypoperfusion
  Minimal systemic nor pulmonary oedema
  Elevation of filling pressure
  2 subsets :
  clear hypoperfusion or cardiogenic shock
  No hypoperfusion/cardiogenic shock

- Clinical scenario 4 - Dyspnoea with signs of ASC

  Symptoms and signs of acute heart failure
  Evidence of ACS
  Isolated elevation of cardiac troponins is inadequate for CS4 classification

- Clinical scenario 5 - Isolated Right heart failure

  Rapid or gradual onset
  No pulmonary oedema
  Rt ventricular dysfunction
  Signs of systemic venous congestion

Algorithm for early hospital management of patients with acute heart failure

Management at admission

Initial 90 - 120 minutes

- Non invasive monitoring (SaO2, BP, temperature)
- 02
- Non invasive ventilation as indicated
- Physical exam
- Lab tests
- BNP or NT-pro-BNP when diagnosis uncertain
- ECG
- CXR

Mebazaa et al; CCM 2008; 36[Suppl.]:S129-S139

Algorithm for early hospital management of patients with acute heart failure

Initial 90 - 120 minutes

Treatment

- Clinical scenario 1 (SBP >140 mmHg): NIV and nitrates; diuretics rarely indicated
- Clinical scenario 2 (SBP 100-140 mmHg): NIV and nitrates; diuretics if systemic chronic fluid retention
- Clinical scenario 3 (SBP <100 mmHg): Volume loading with initial fluid challenge if no overt fluid retention; inotropes; PAC if no improvement; if BP fails to improve above 100 and hypoperfusion persists, consider vasoconstrictors
- Clinical scenario 4 (ACS): NIV; nitrates; cardiac cath lab, follow ACS guidelines (aspirin, heparin, reperfusion therapy; IABP
- Clinical scenario 5 (RVF): Avoid volume loading; diuretics if SBP>90 mmHg and systemic chronic fluid retention; inotropes if SBP <90 mmHg; if SBP fails to improve above 100, then begin vasoconstrictors

Algorithm for early hospital management of patients with acute heart failure

Initial 90 - 120 minutes

Treatment Objectives

- Decrease dyspnoea
- Improve well being
- Decrease heart rate
- Urine output > 0.5ml/kg/min
- Maintain/improve BP
- Restore adequate perfusion

Algorithm for early hospital management of patients with acute heart failure

Reassess frequently clinical and physical exam

Next 6 - 12 hours

If dyspnoea persists

Stay in the ER/ward

If SBP <100
Organ hypoperfusion
Rt ventricular failure
SaO2 <90% despite O2

ICU admission
ECHO if not recent
Central/arterial line
Additional diagnostic tests
Transfer to tertiary center

ARDS

ARDS - Definition

THE LANCET

[Close]

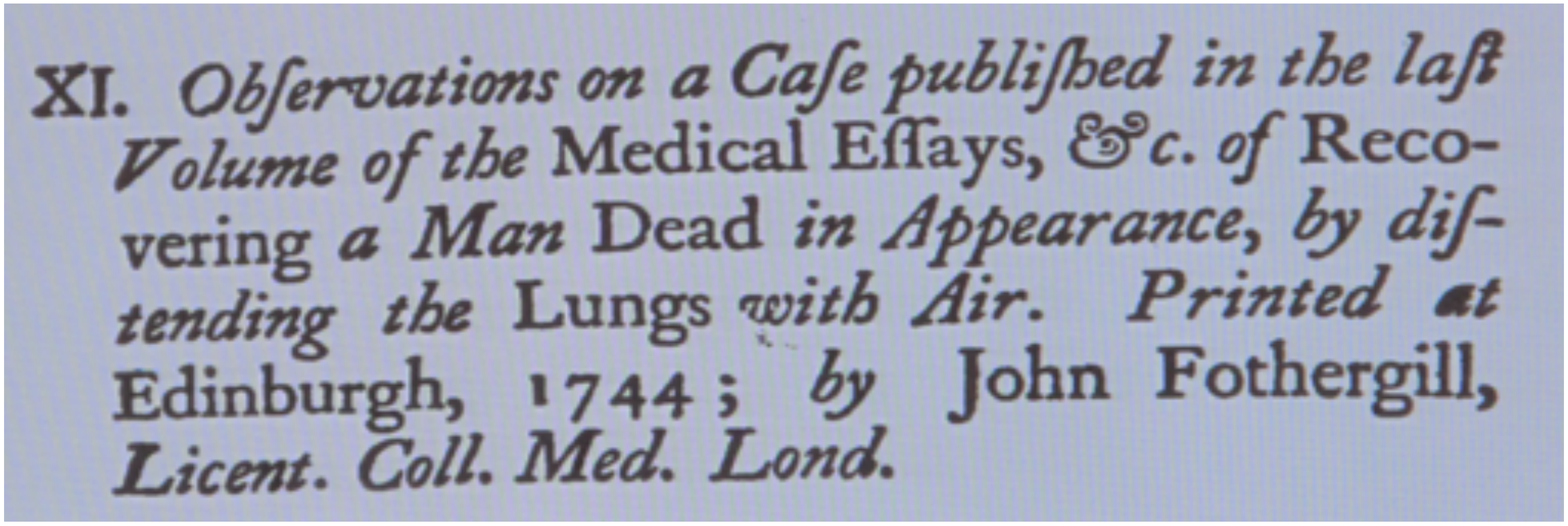
The Lancet, Volume 290, Issue 7511, Pages 319 - 323, 12 August 1967
doi:10.1016/S0140-6736(67)90168-7

ACUTE RESPIRATORY DISTRESS IN ADULTS

DavidG. Ashbaugh M.D. Ohio State , D. Boyd Bigelow M.D. Colorado , ThomasL. Petty M.D. Colorado , BernardE. Levine M.D. Michigan [1]

"The acute onset of severe respiratory distress and cyanosis that was refractory to oxygen therapy and associated with diffuse CXR abnormality and decreased lung compliance"

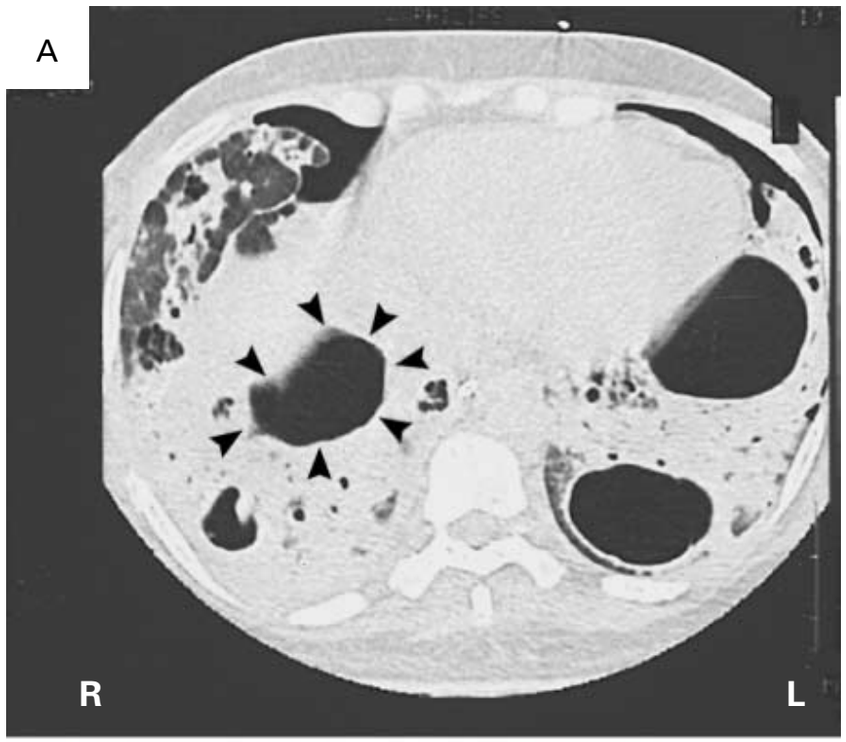
In fact the concept of ventilator induced lung injury is very OLD



XI. *Obſervations on a Caſe publiſhed in the laſt Volume of the* Medical Eſſays, *&c. of* Recovering *a Man* Dead *in Appearance, by diſtending the* Lungs *with Air. Printed at* Edinburgh, 1744; *by* John Fothergill, *Licent. Coll. Med. Lond.*

Philos Trans R Soc Med 43:275-281 1774

Ventilation induced lung injury



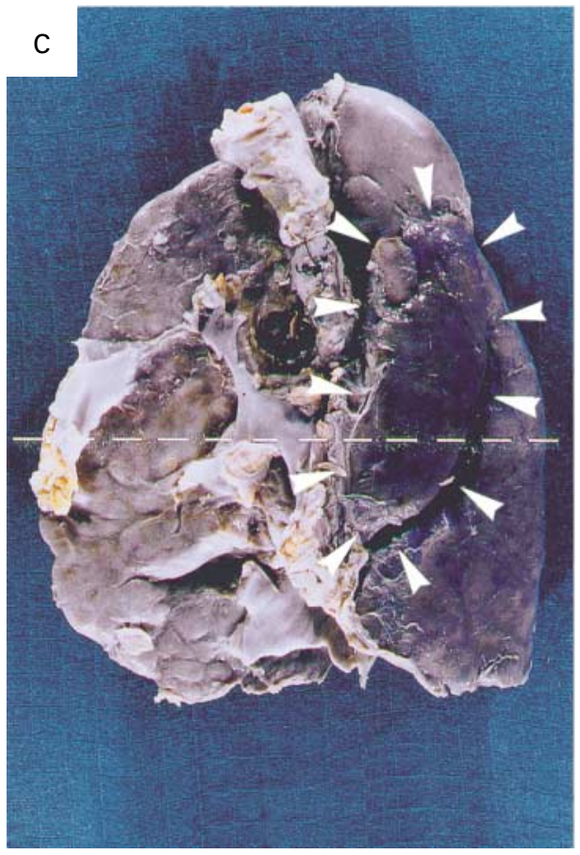
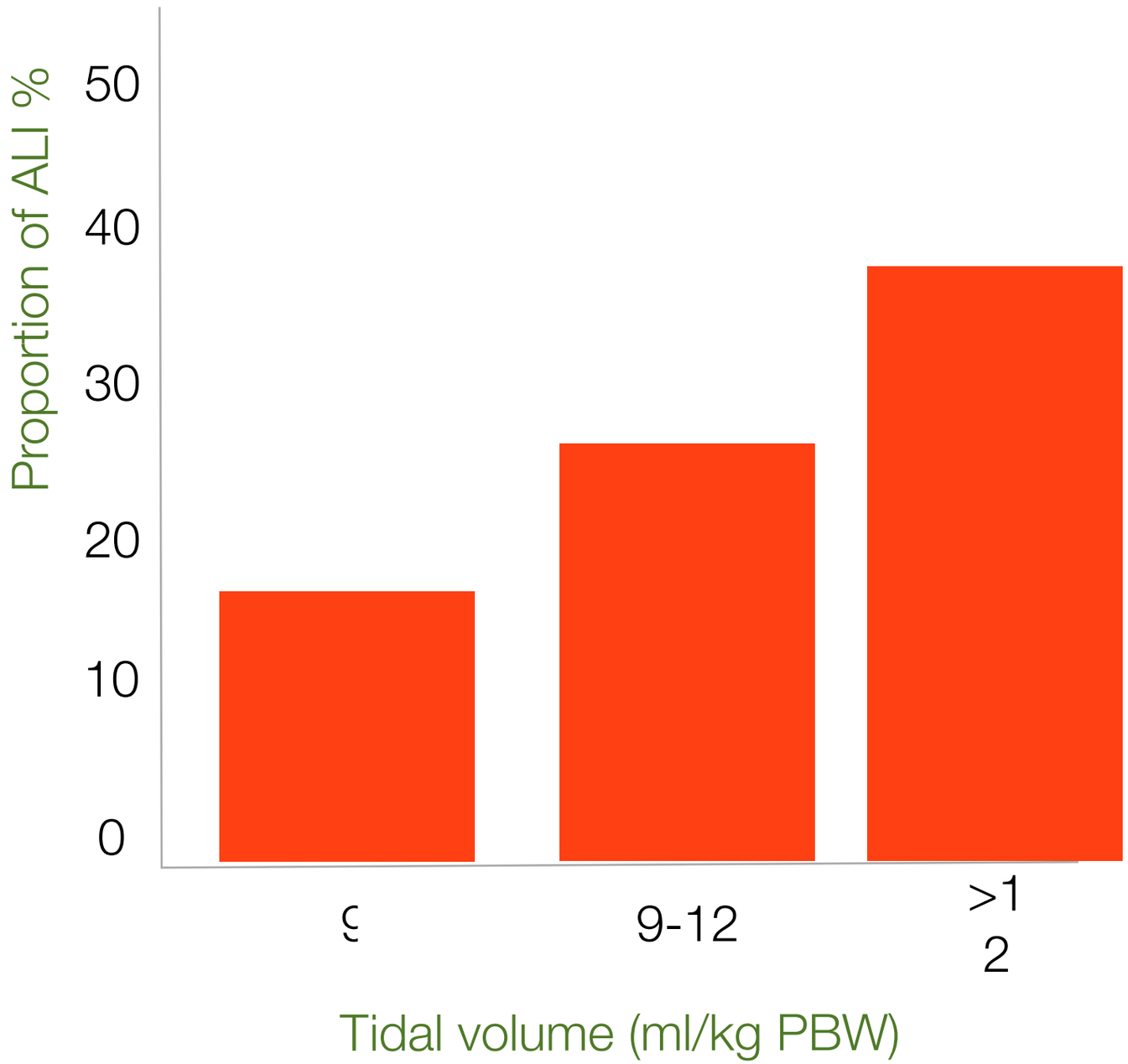


Figure 2. Lung Injury Caused by Mechanical Ventilation in a 31-Year-Old Woman with the Acute Respiratory Distress Syndrome Due to Amniotic-Fluid Embolism.
The patient had undergone mechanical ventilation for eight weeks with tidal volumes of 12 to 15 ml per kilogram of body weight, peak airway pressures of 50 to 70 cm of water, positive end-expiratory pressures of 10 to 15 cm of water, and a fractional inspired oxygen concentration of 0.80 to 1.00 in order to achieve a partial pressure of carbon dioxide that was less than 50 mm Hg and a partial pressure of oxygen that was 80 mm Hg or higher. Computed tomography (CT) performed two days before the patient died revealed a paramediastinal pneumatocele in the right lung (Panel A, arrowheads) and numerous intraparenchymal pseudocysts in the left lung (Panel B, black arrow, open circle, and asterisk).
At autopsy, both lungs were removed and fixed by intrabronchial infusion of formalin, alcohol, and polyethylene glycol at an insuf- flation pressure of 30 cm of water. Panel C shows the paramediastinal pneumatocele in the right lung (arrowheads); the horizontal broken line is the level of the CT section. Panel D shows a 1-cm-thick section of the left lung, corresponding to the CT section. Small pseudocysts are present (arrow), and two large pseudocysts (asterisk and open circle) have compressed and partially destroyed the parenchyma. The development of these lesions in a patient without a history of chronic lung disease indicates the harm that may result with the use of high tidal volumes and airway pressures. The photographs were kindly provided by Dr. Jean-Jacques Rouby, Hôpital de la Pitié–Salpêtrière, Paris.

Tobin M NEJM 2001

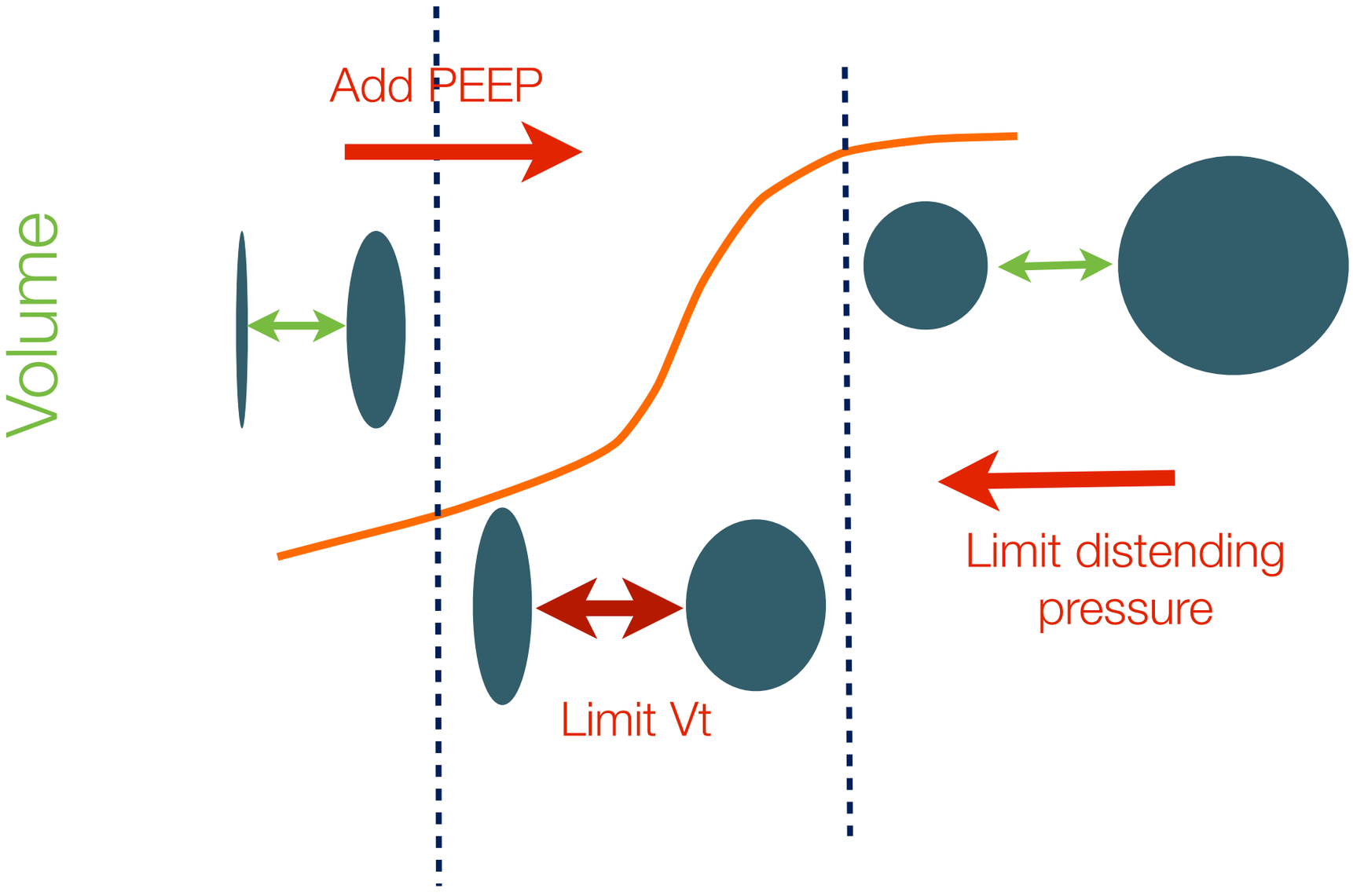
You can induce VILI- in **normal** lungs!



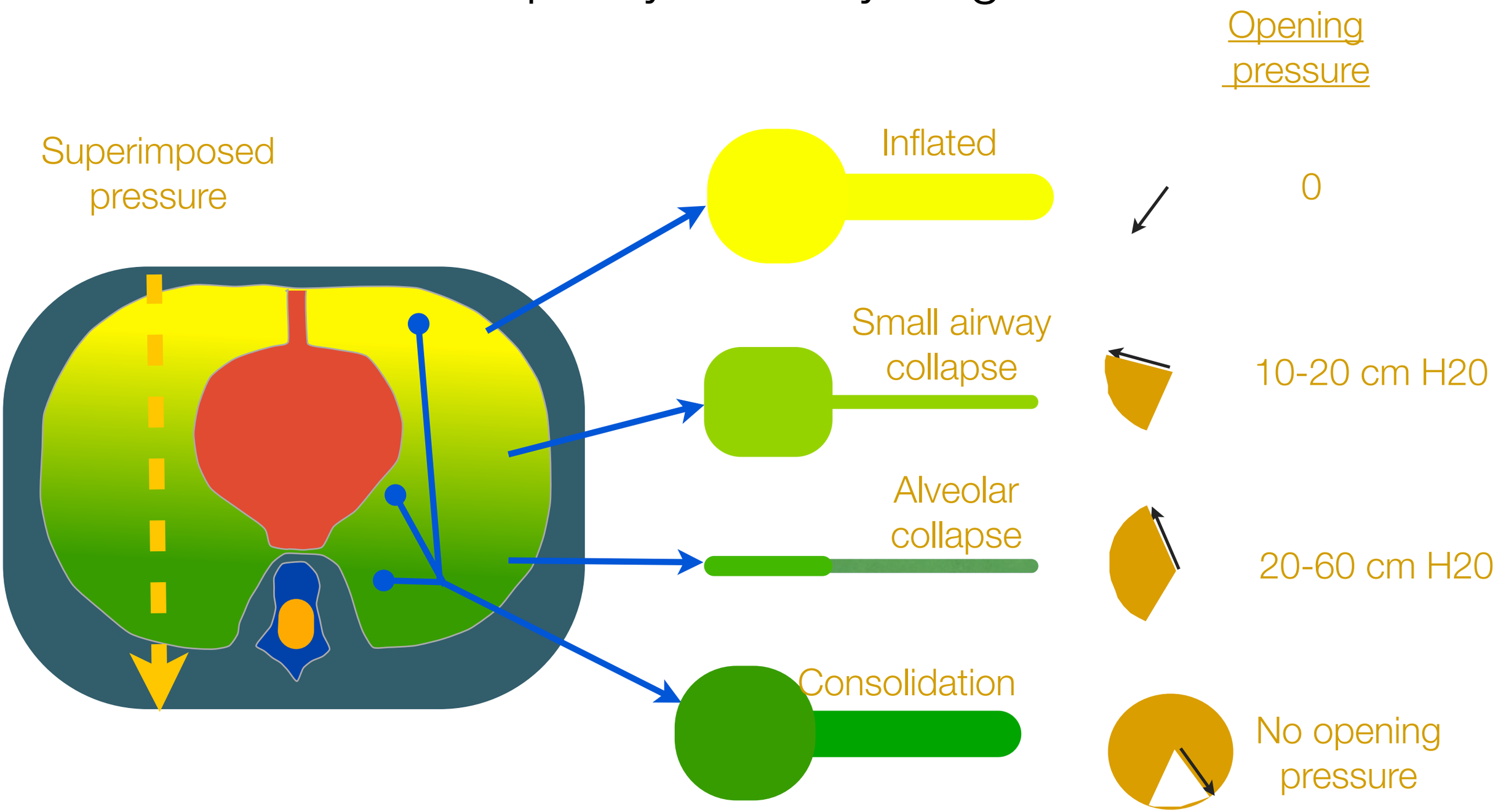
Gajic O. CCM 2004;32:1817

Preventing overdistension and under-recruitment injury

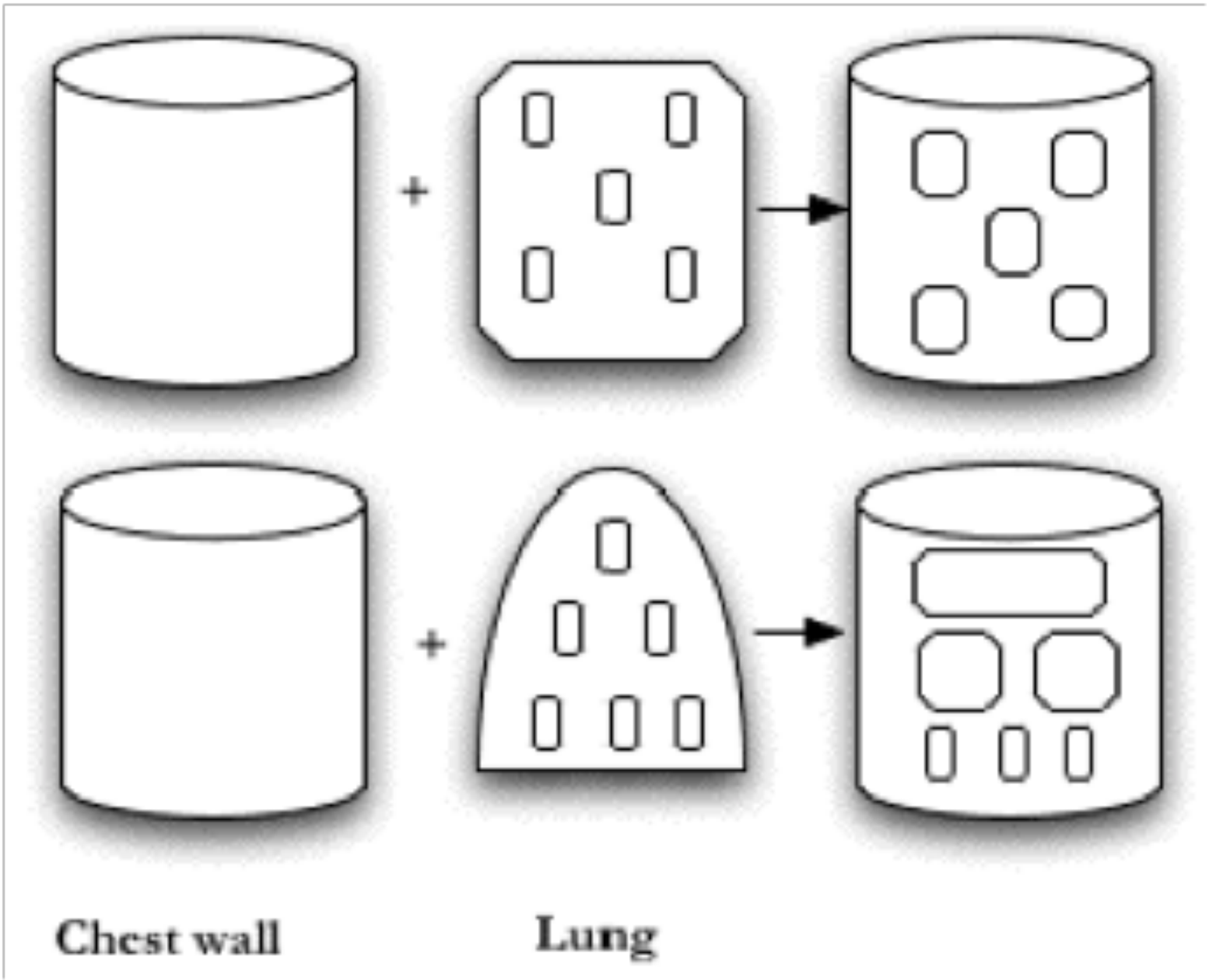
“Lung protective ventilation”



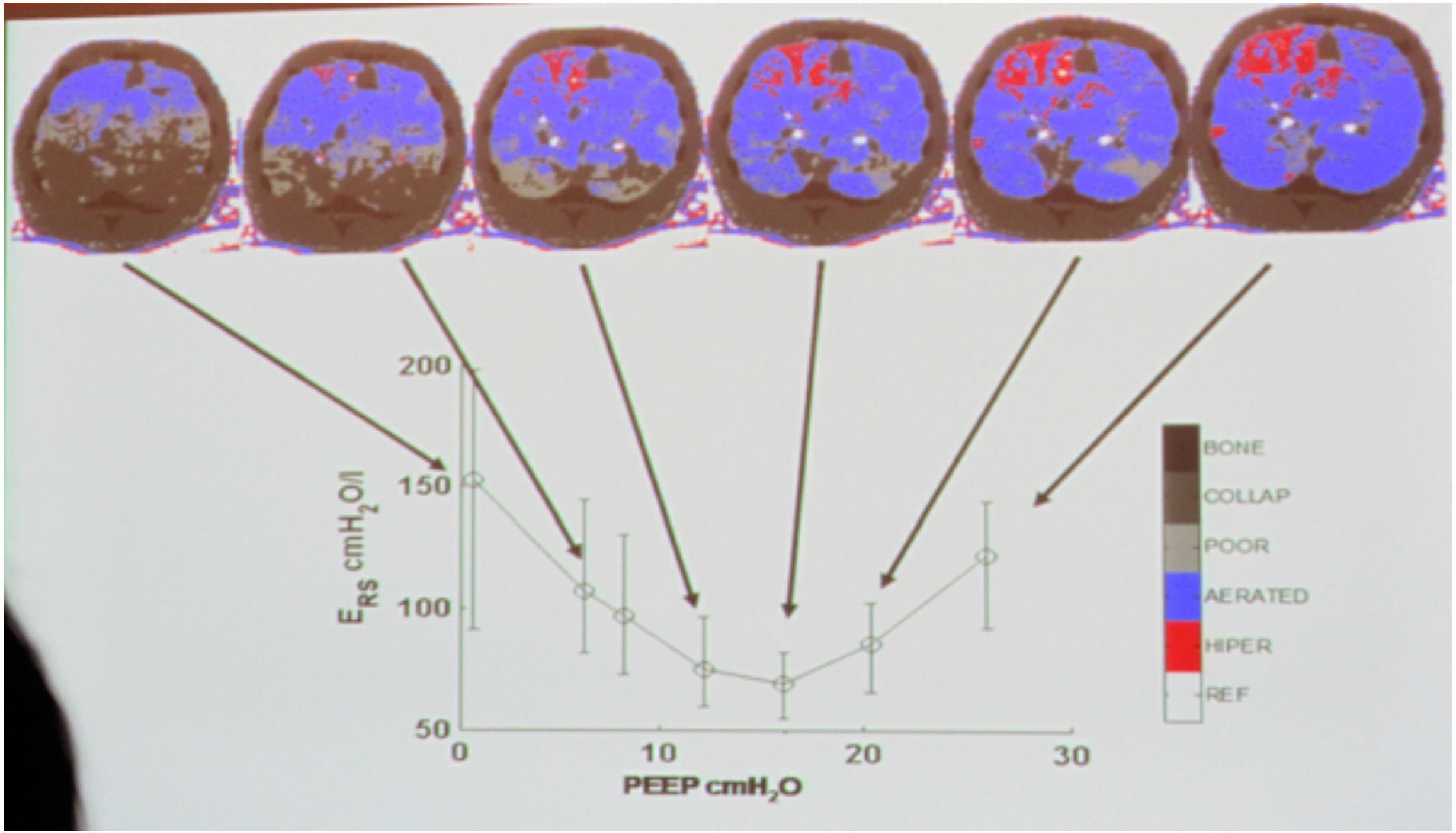
Trans-pulmonary pressure does NOT account for reduced capacity of “baby lung”



Ventilation induced lung injury

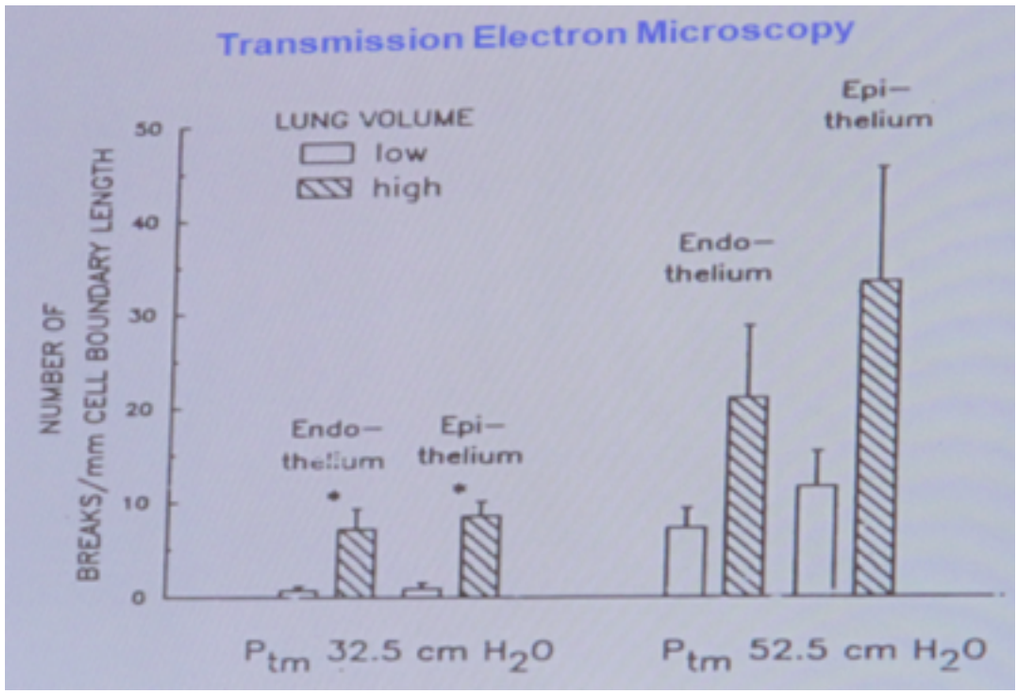


Elastance to titrate PEEP in ARDS



Carvalho AR et al. Intensive care medicine 2008 Dec; 34(12):2291-9

Endothelium and epithelium are injured at high lung volumes and pressures

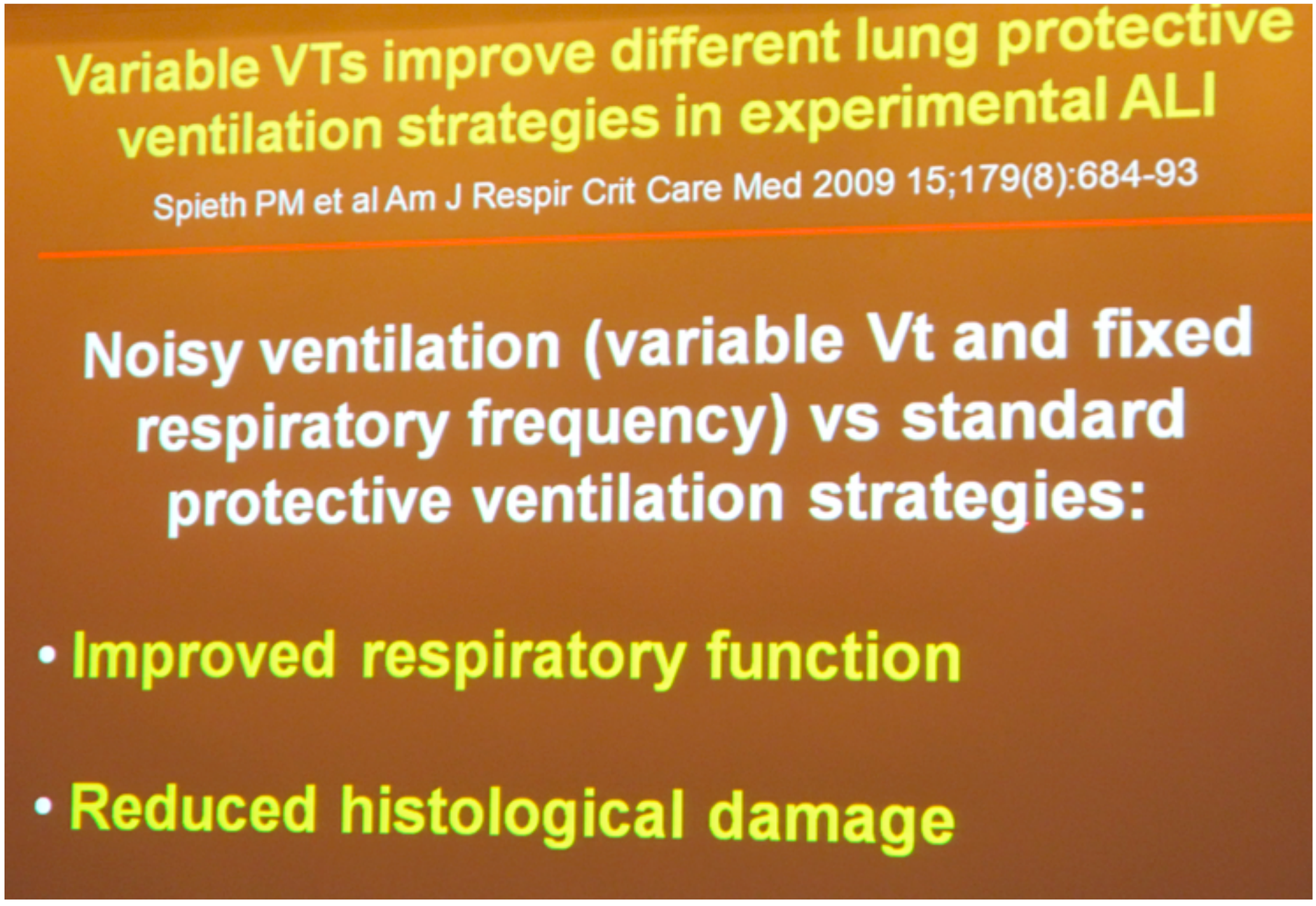


Fu Z et al J Appl Physiol 1992 73: 123-133

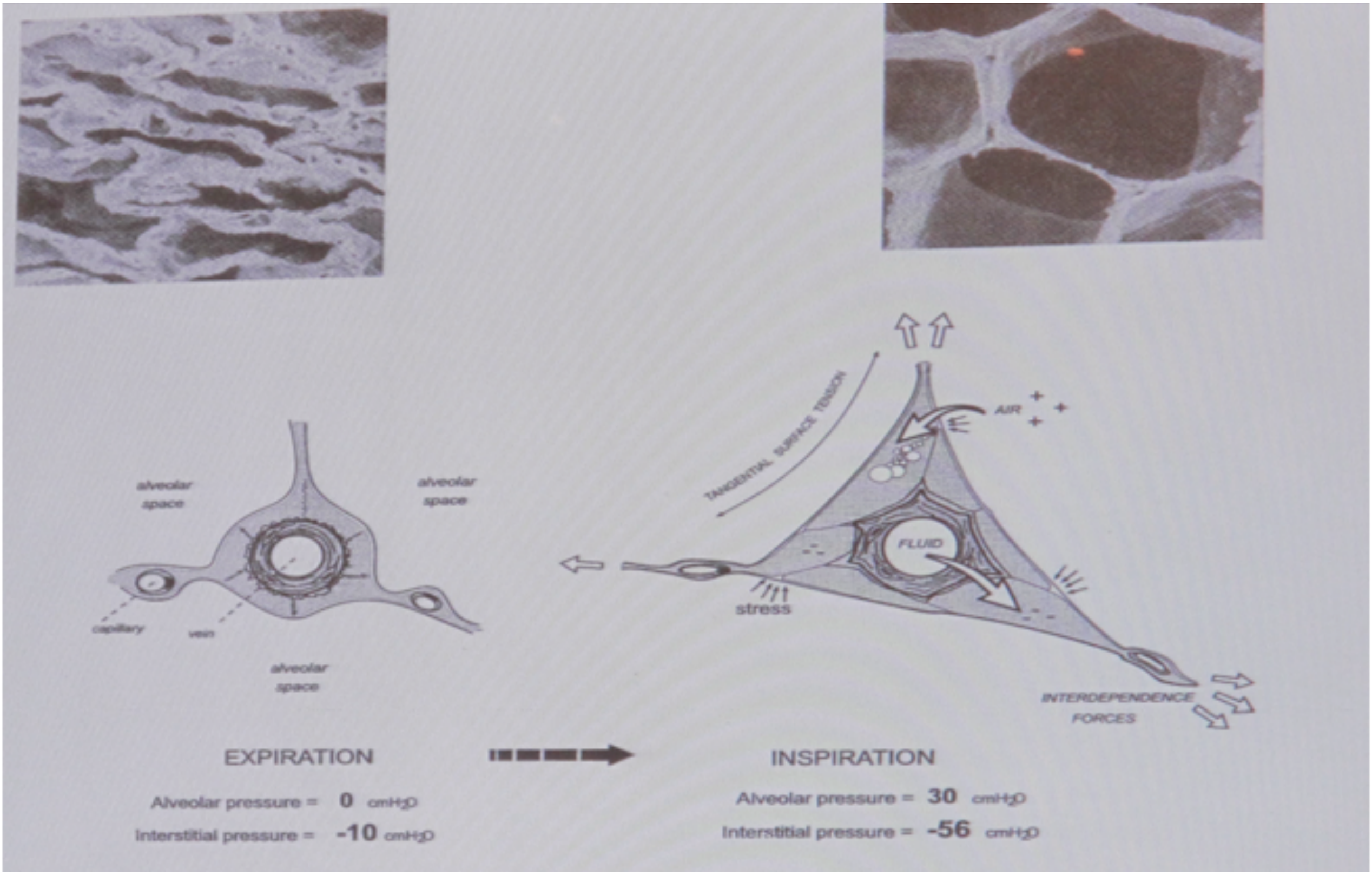
Between 1994 - 2003
we learned :

- ARDS Network low tidal volumes (despite PaO2)
- Intra-tidal recruitment/derecruitment
- Experimental protective effect of prone position on VILI

Variable ventilation

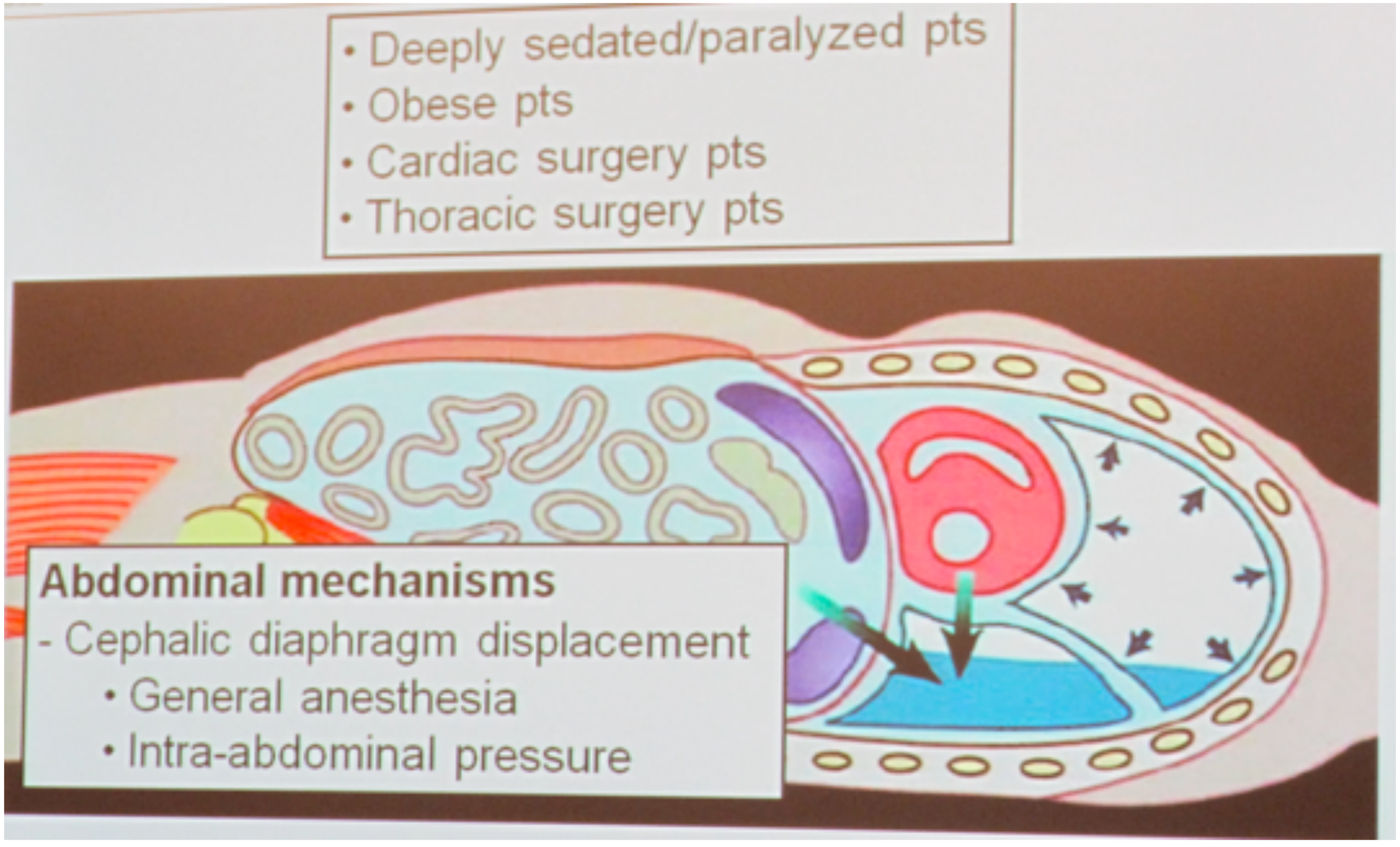


Ventilation induced lung injury



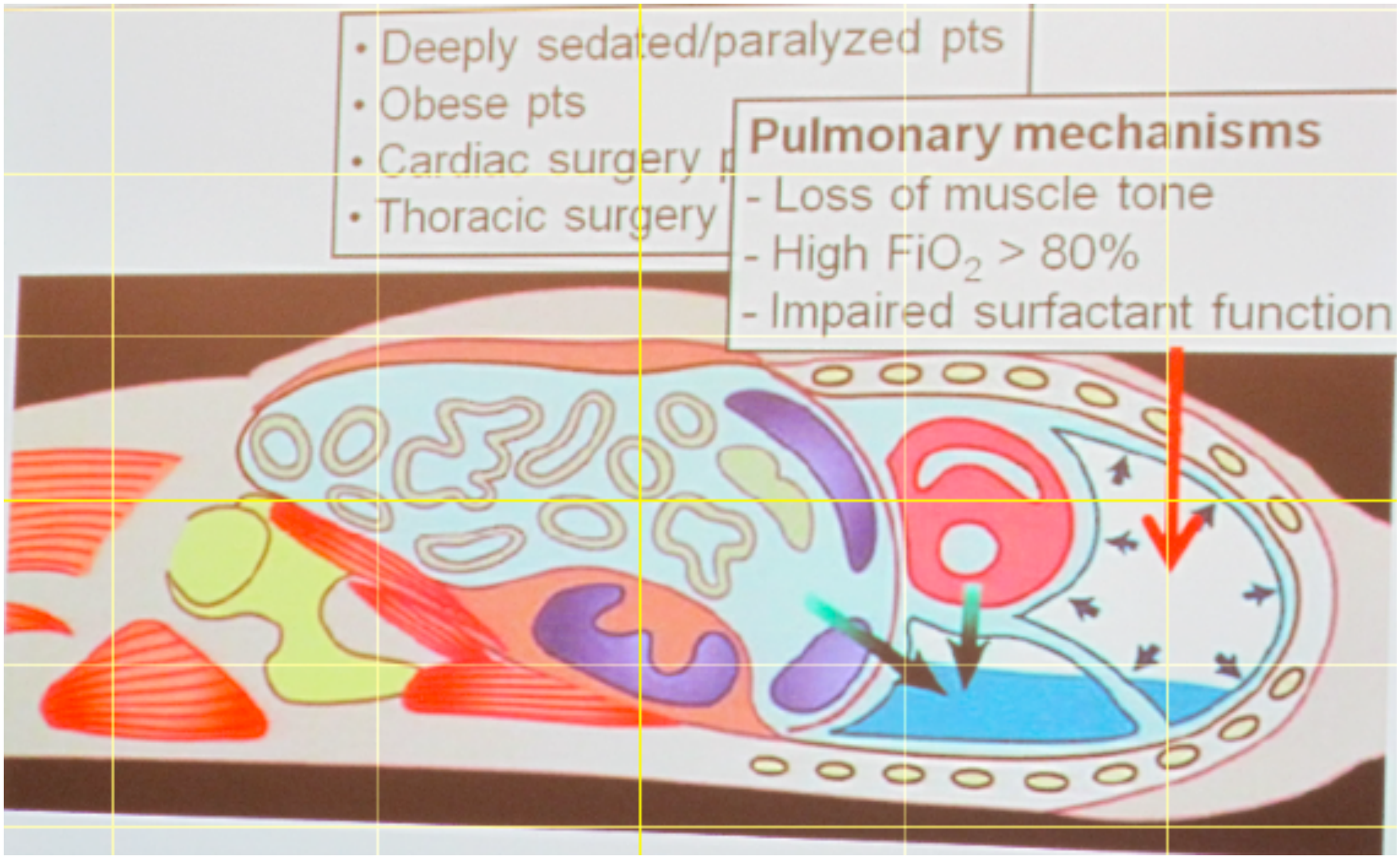
Marini & Amato “Mechanical Ventilation, Springer Verlag 2002

De-recruited lung



Duggan and Kavanagh Anesthesiology 2005, 102: 838-854

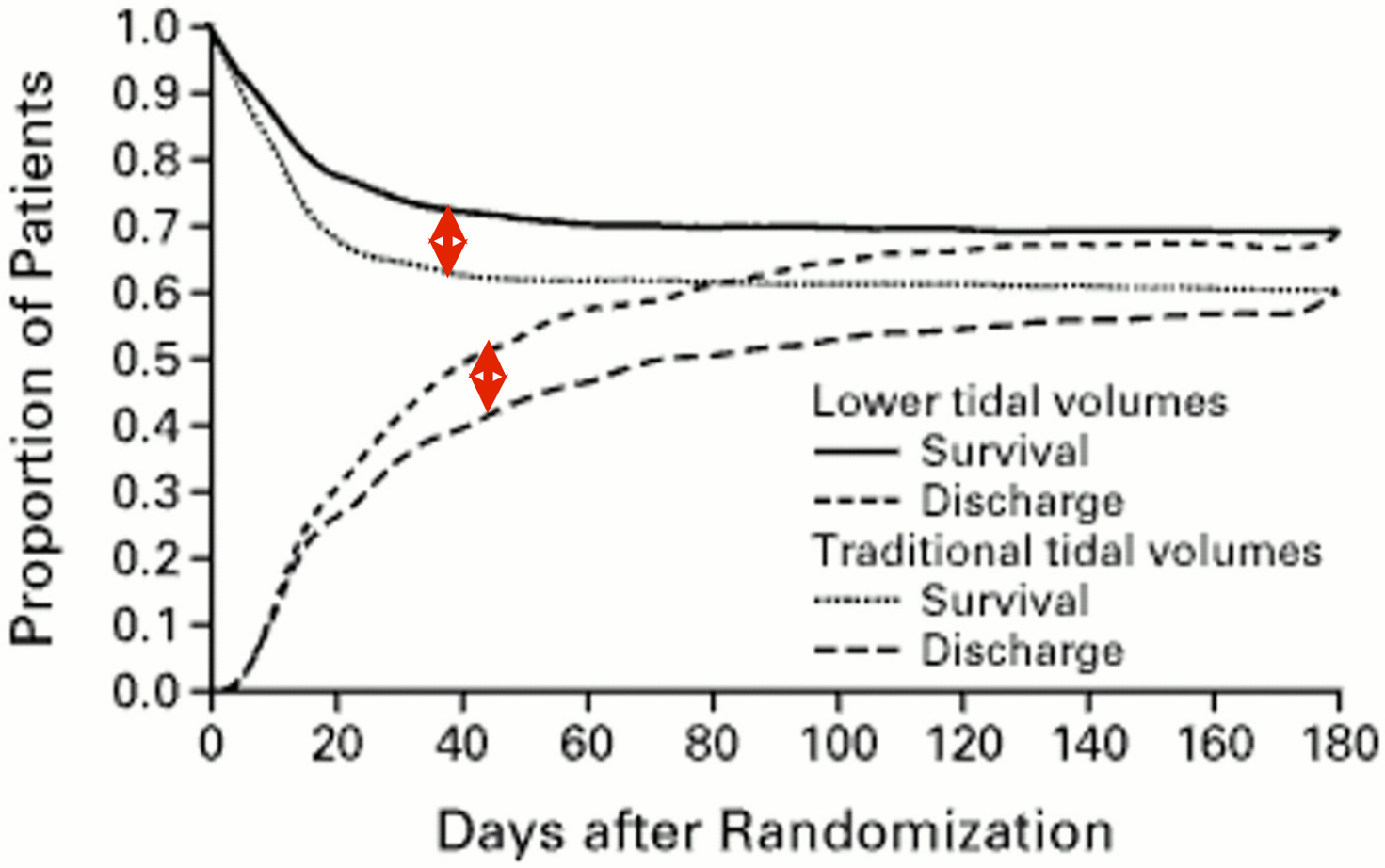
De-recruited lung



Duggan and Kavanagh Anesthesiology 2005, 102: 838-854

Low vs high tidal volumes in ARDS/ALI

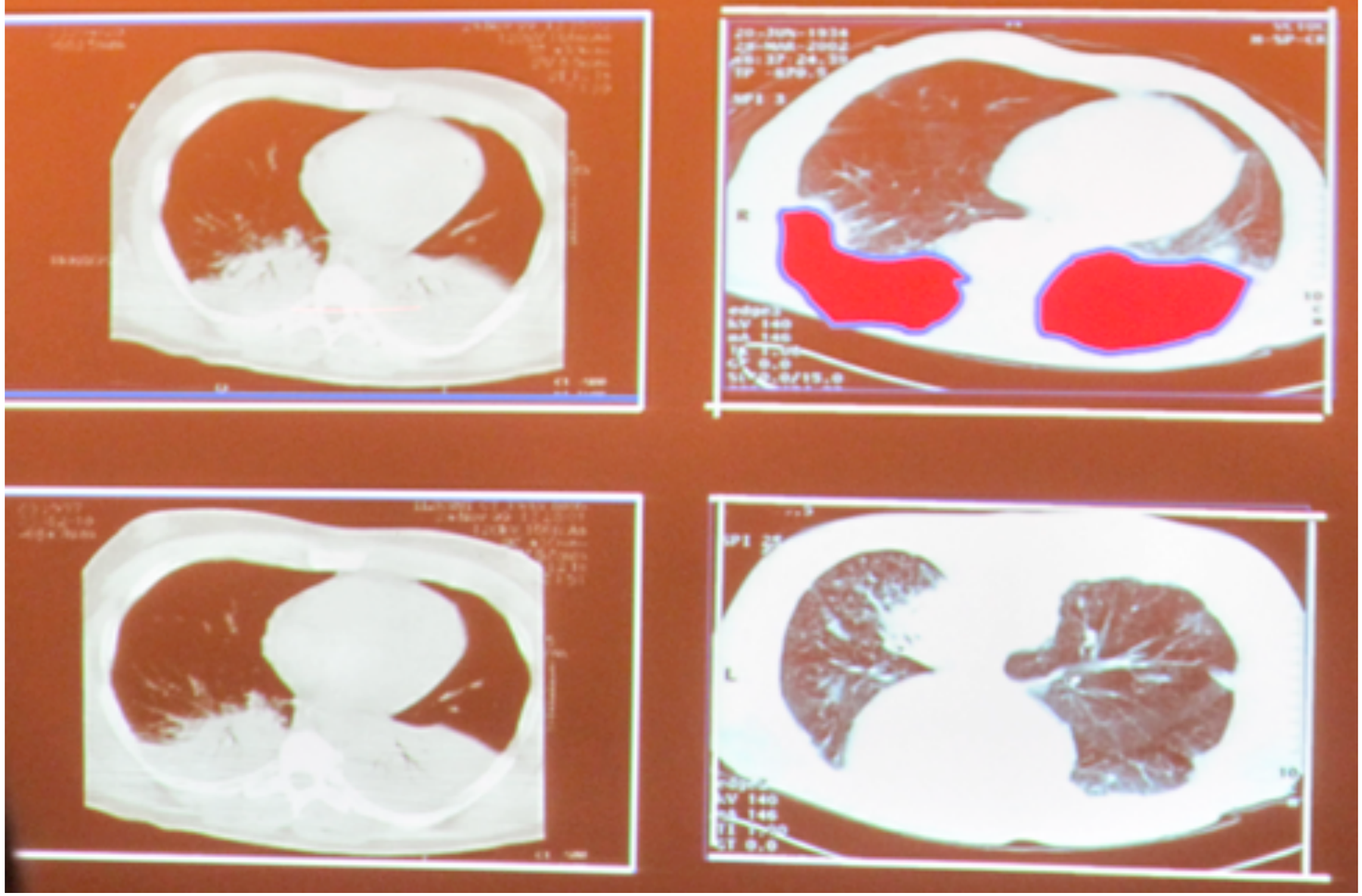
Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome



The NEW ENGLAND JOURNAL of MEDICINE

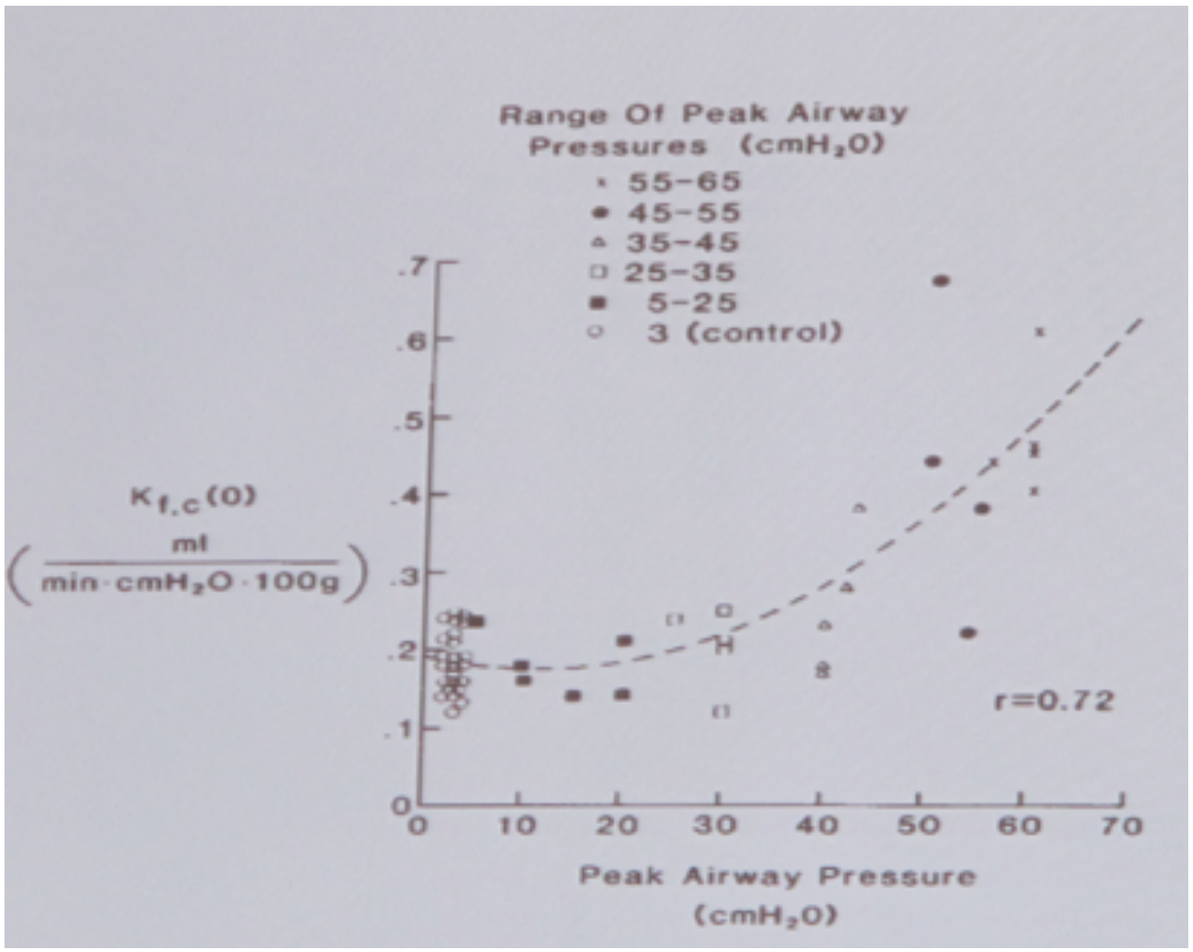
Prone position and recruitment

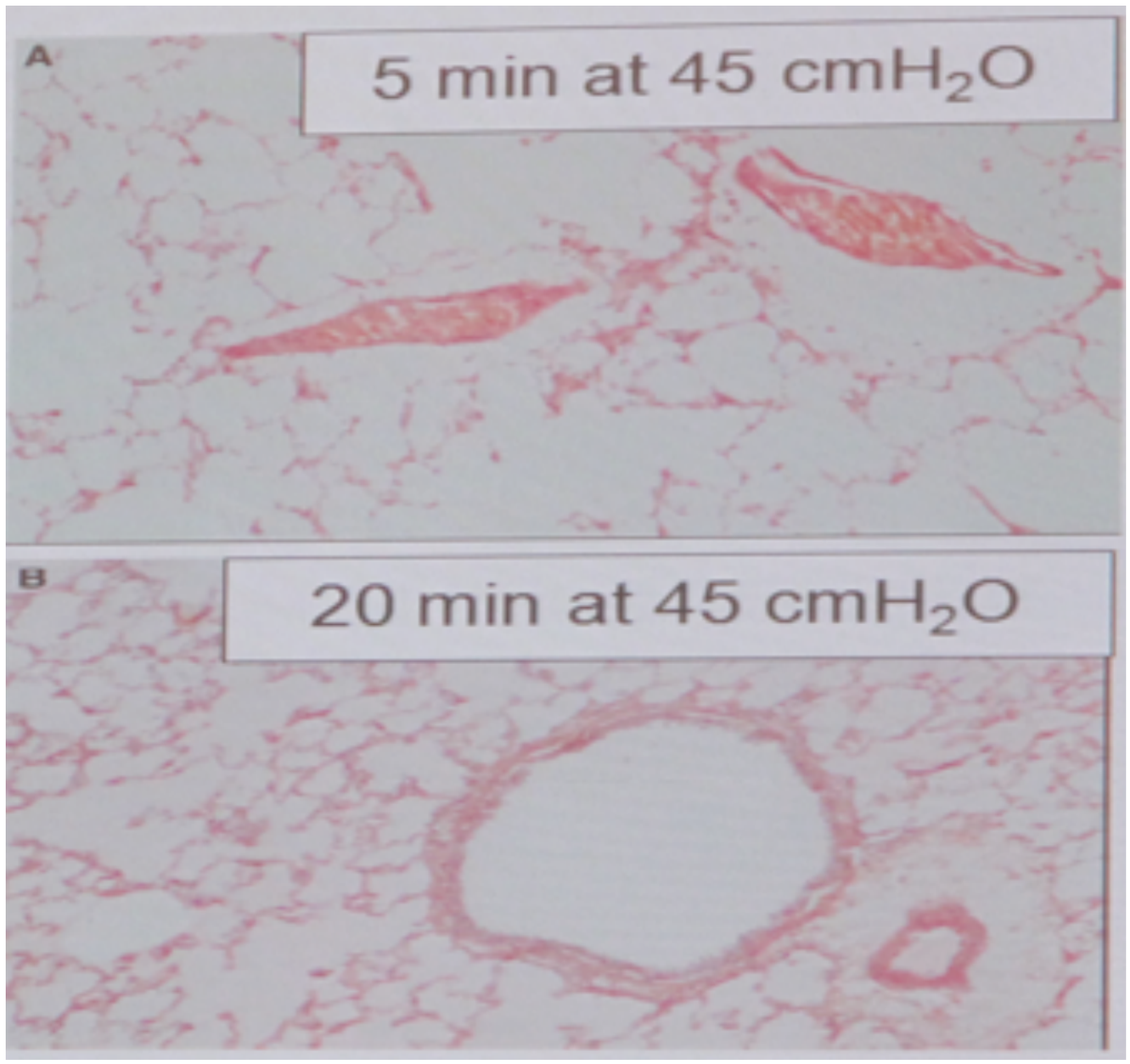
Pelosi P et al. Eur Respir J. 2002 Oct;20(4):1017-28



Ventilation induced lung injury

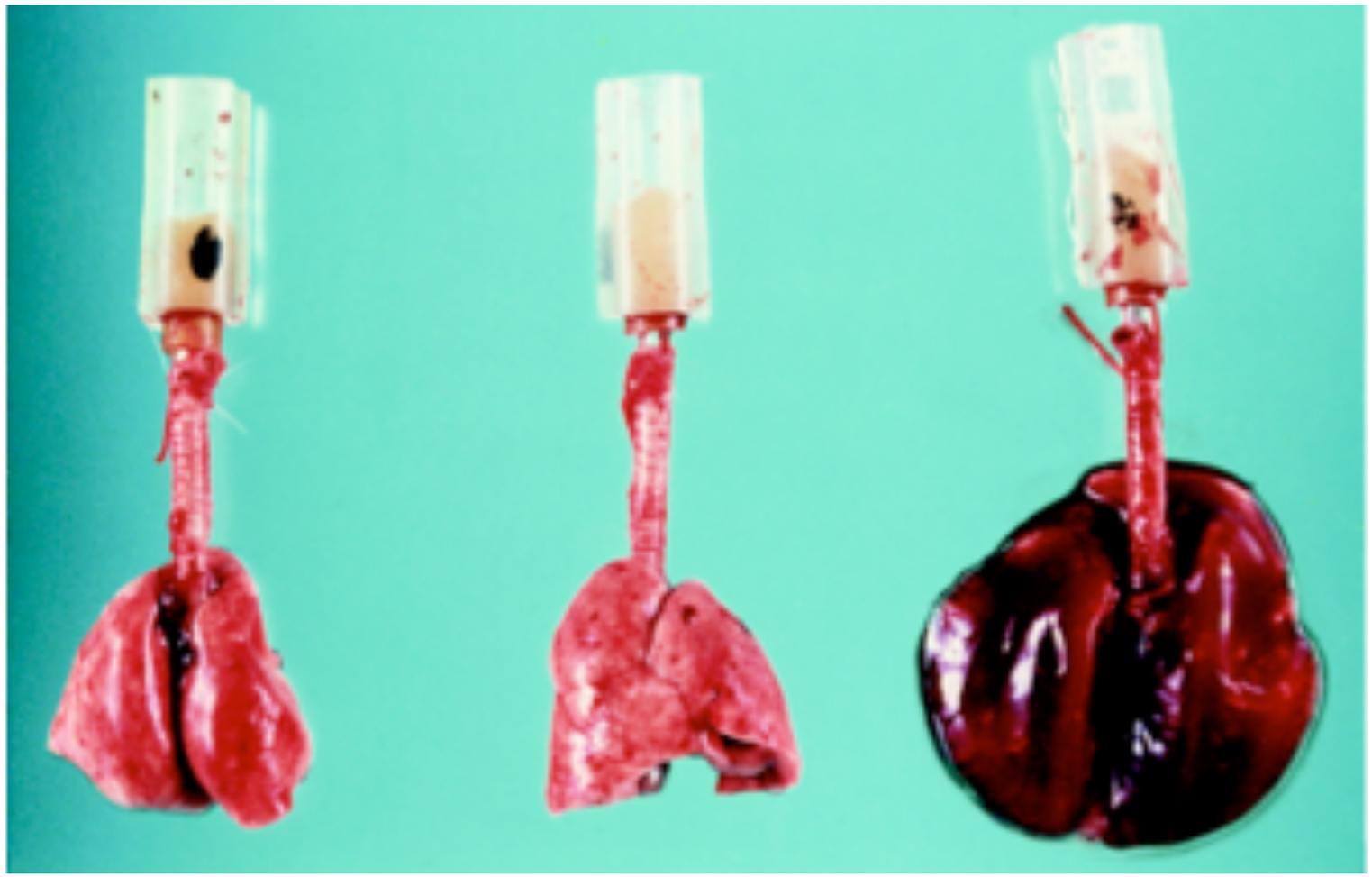
High airway pressures damage the healthy lung
= Barotrauma





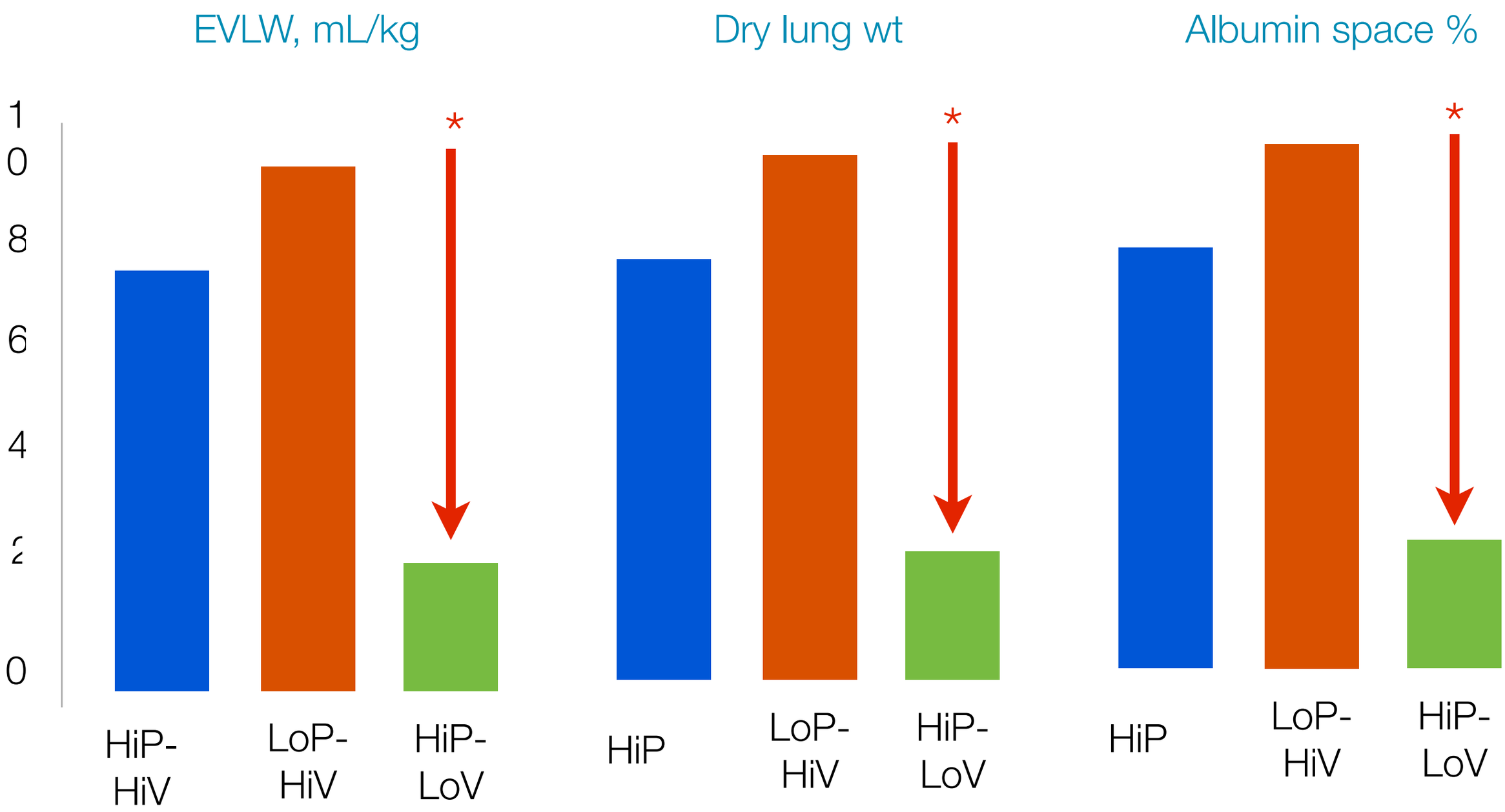
Parker et al JAP 1984, 57; 1809-1816

Effect of PIP of 45 cm H20



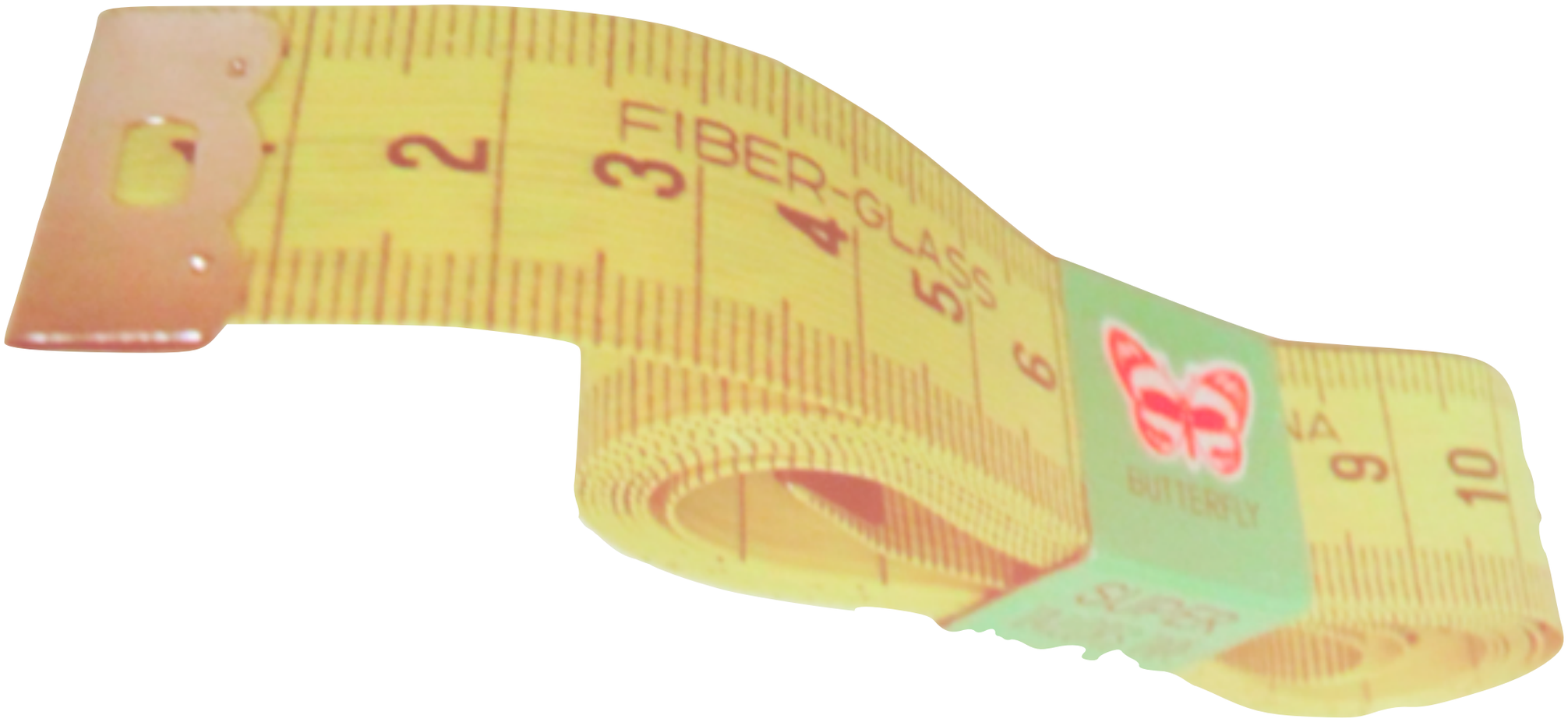
Control 5 min 20 min

VILI - Volutrauma or Barotrauma ?

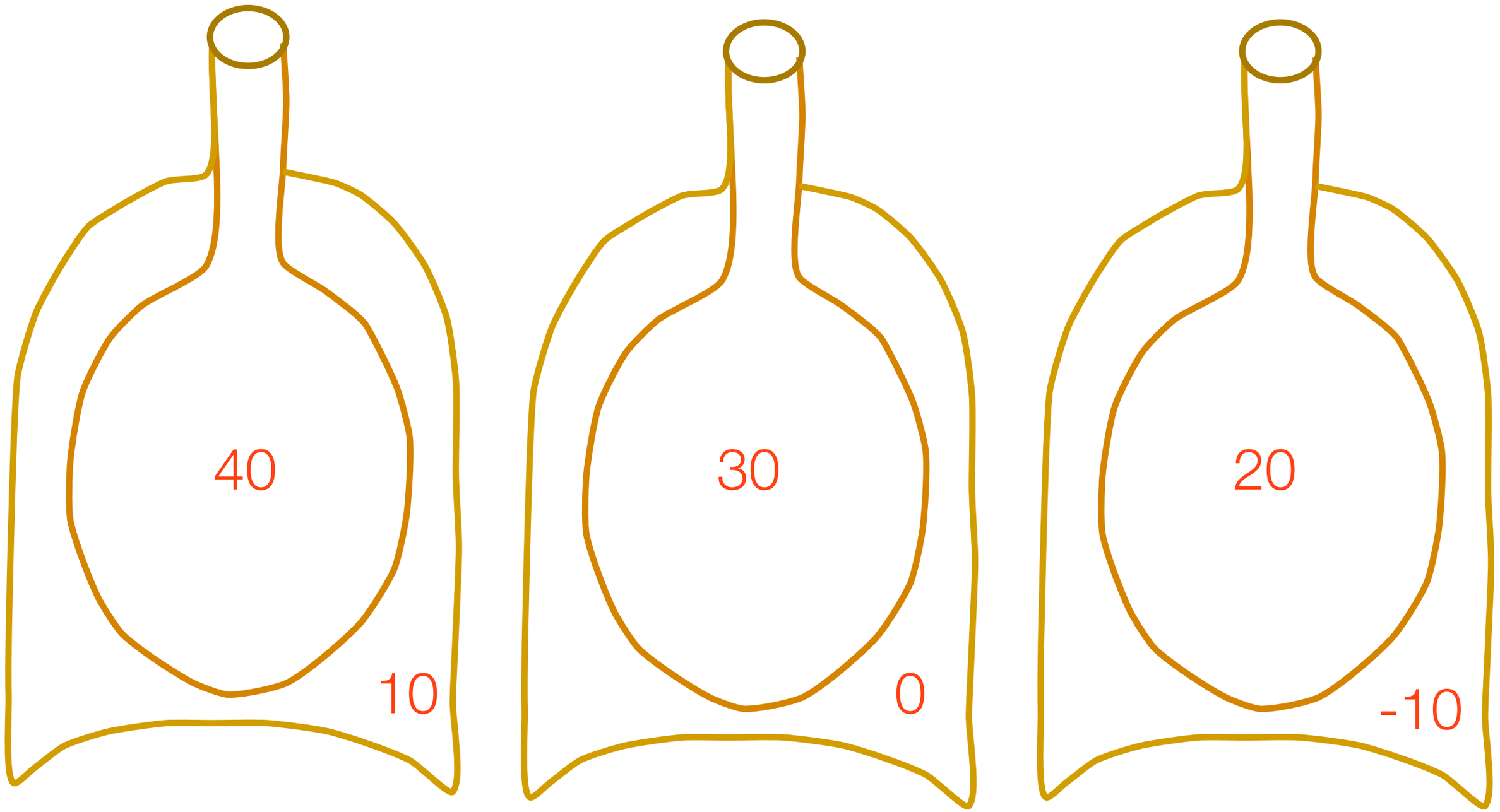


Dreyfuss D and Saumon G Am Rev Resp D 1988 137; 1159-1164

Don’t forget protective tidal volumes are based on ideal (or predicted) body weight, which are based on SEX and HEIGHT (NOT weight!!)


FIBER-GLASS
BUTTERFLY

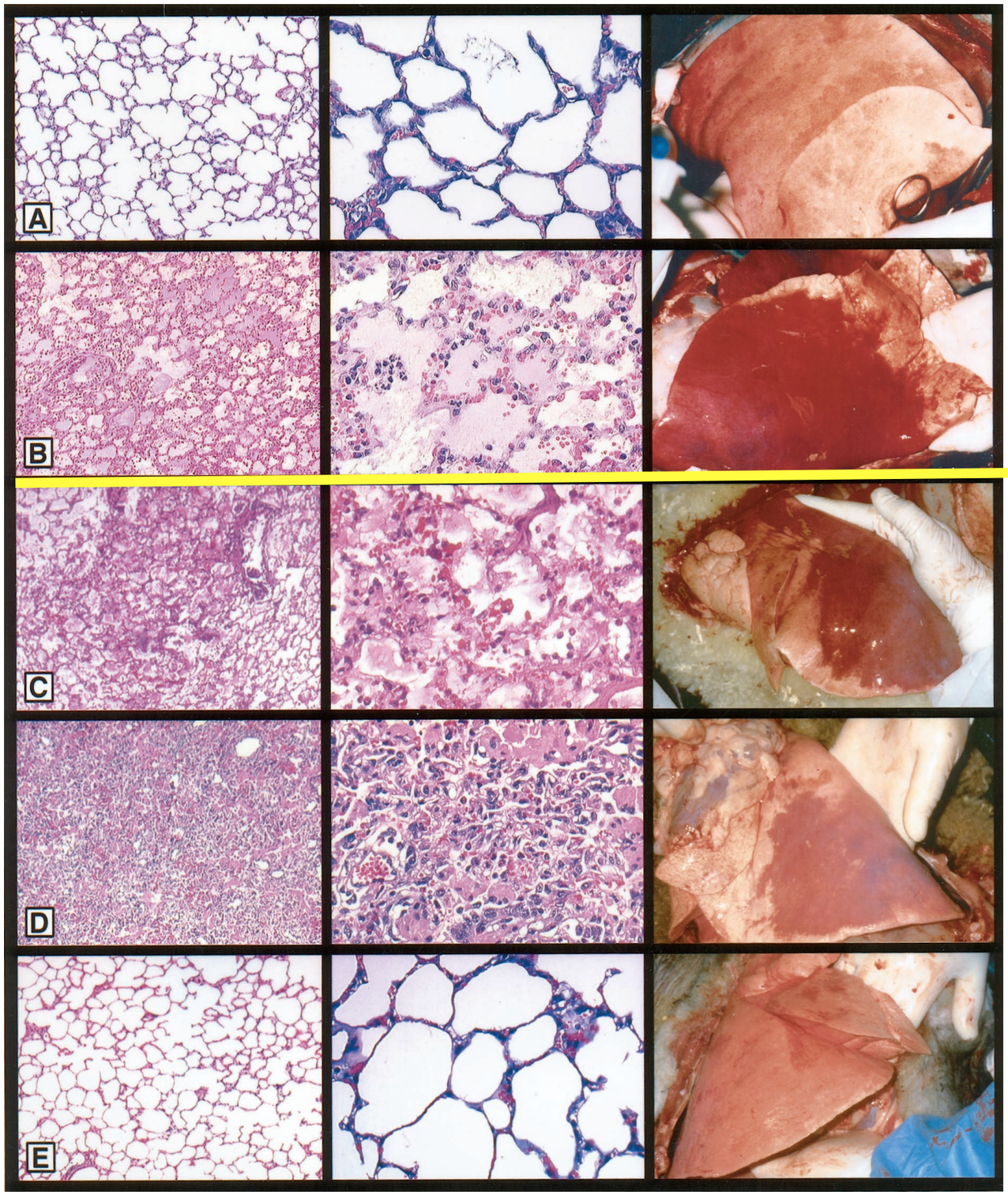
Which plateau pressure is safest?
...depends on chest wall stiffness and effort



IAH

Active inspiration

Why recruitment/PEEP ?



Low pressure
Control

High pressure
Normal rate

Normal f

Low f

High pressure
Extended I:E

High pressure
Short I:E

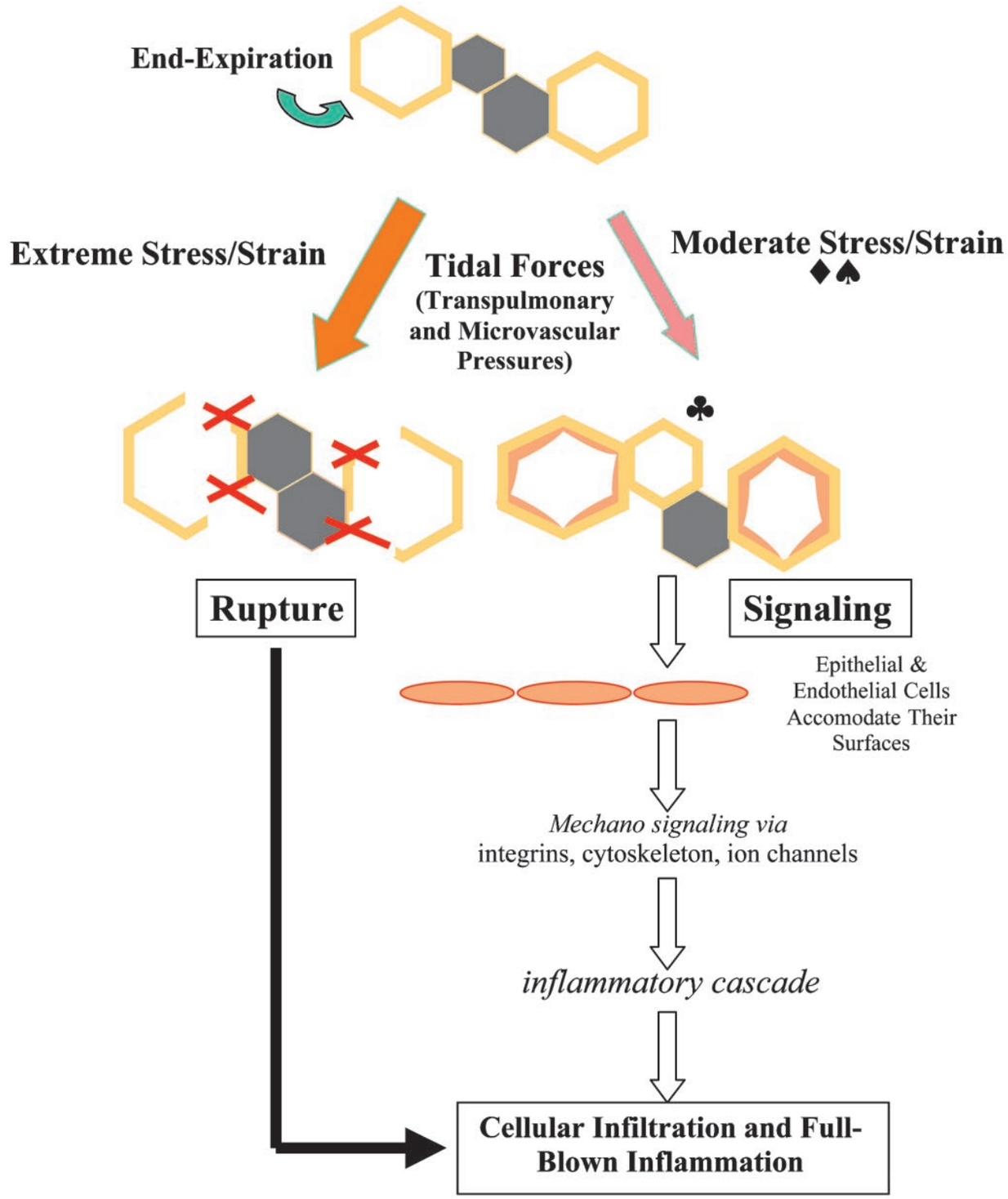
Stretch?

Shear?

High pressure
Low insp. flow

Rich J Trauma 2000

Pathogenesis of VILI



♦ Global stress/strain reduced by lowering Trans-Pulmonary Pressure (TPP)
♠ Local stress/strain less if TPP is more homogeneously applied (prone position)
♣ Local stress/strain reduced if PEEP "keeps open"

Vascular flow may be an important VILI co-factor

- Energy dissipation
- Vascular interdependence
- Endothelial shear

→ Cardiac output

→ Minute ventilation

Reducing O2 demand and ventilation targets may lower risk for VILI

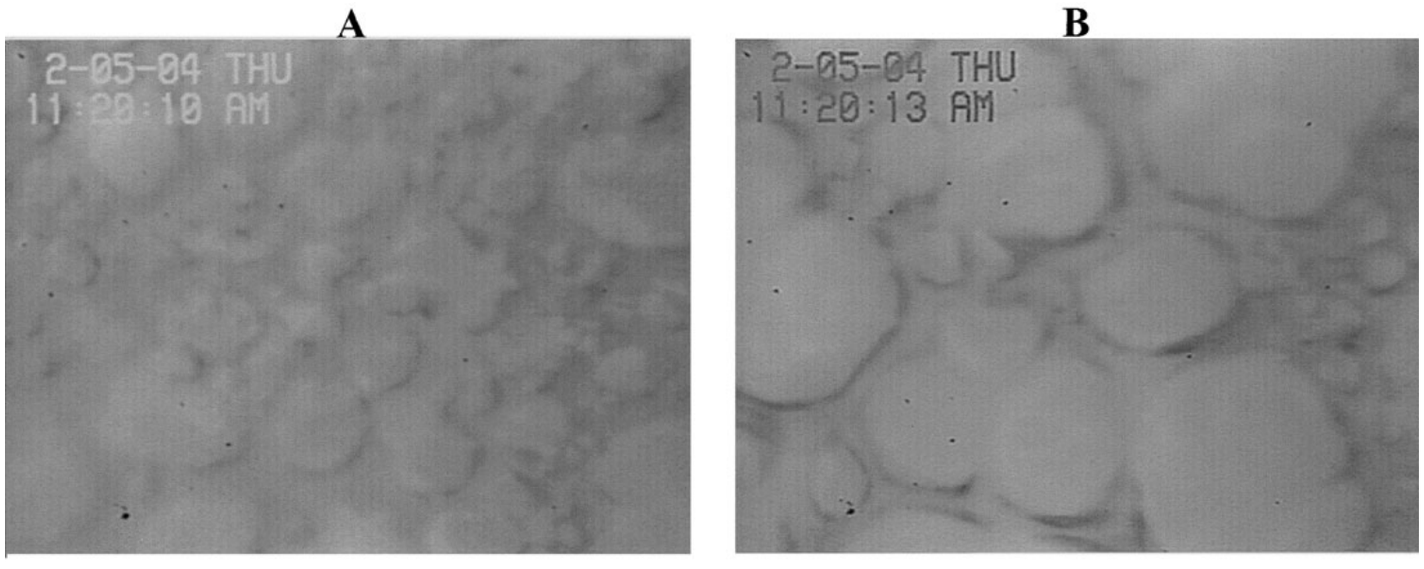
Hotchkiss, Brochard

Lung development and susceptibility to VILI

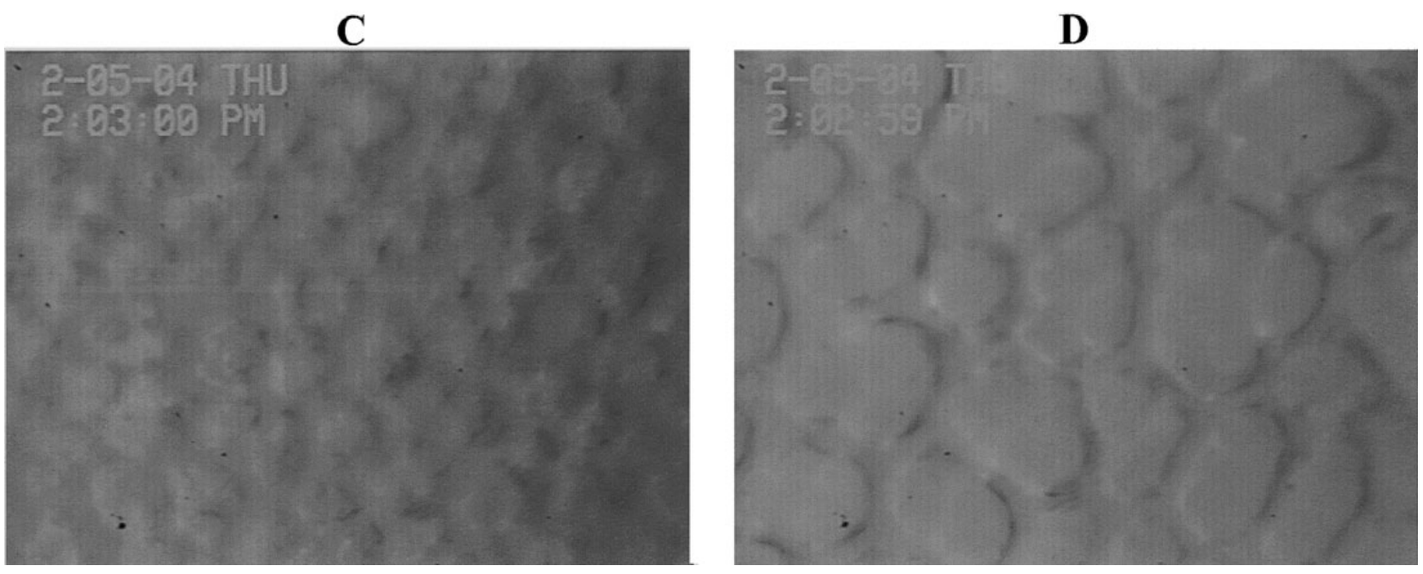
Expiration

Inspiration

Adult



Neonate

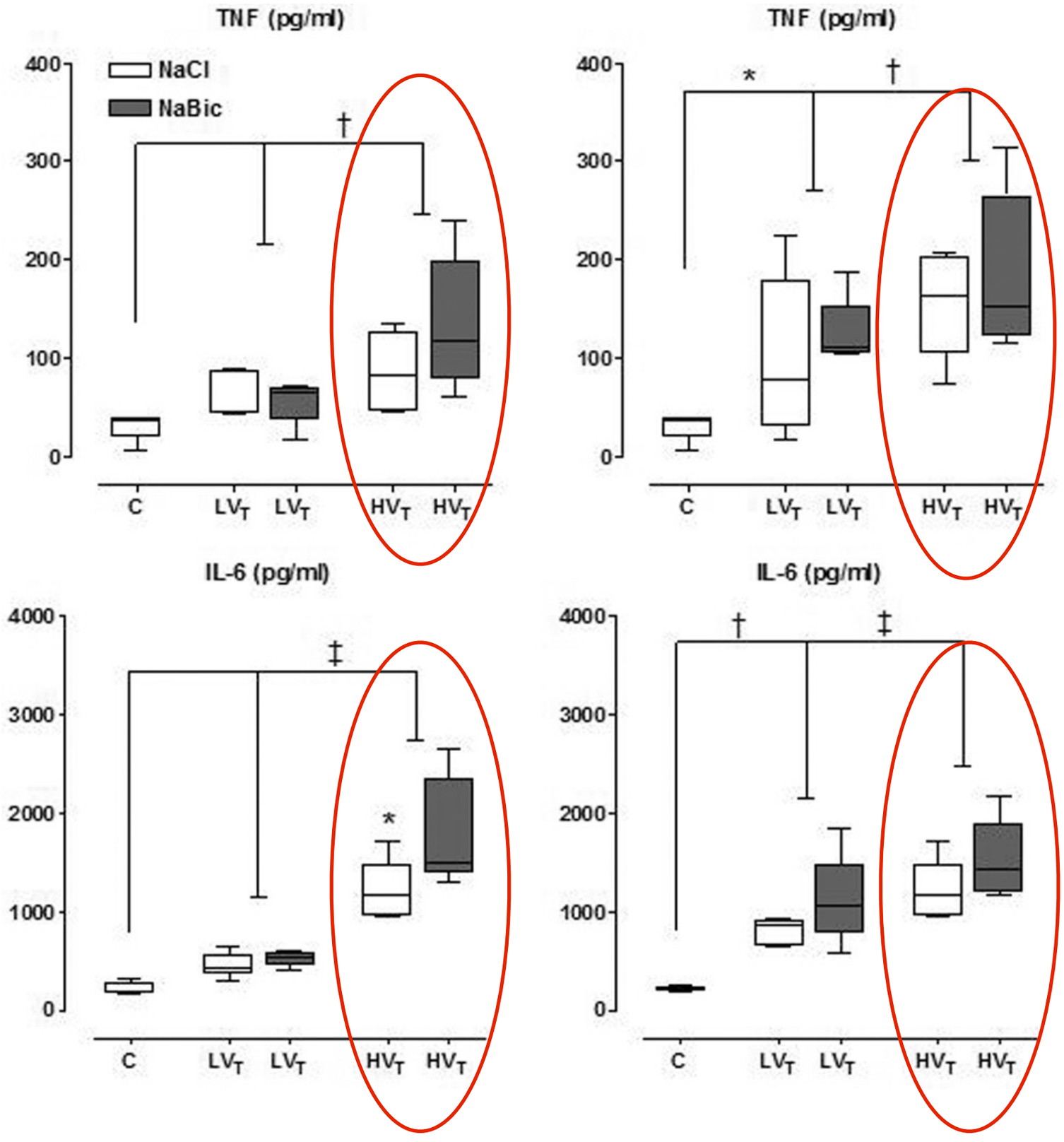


Note the end inspiratory alveolar size is more variable in the adult lung

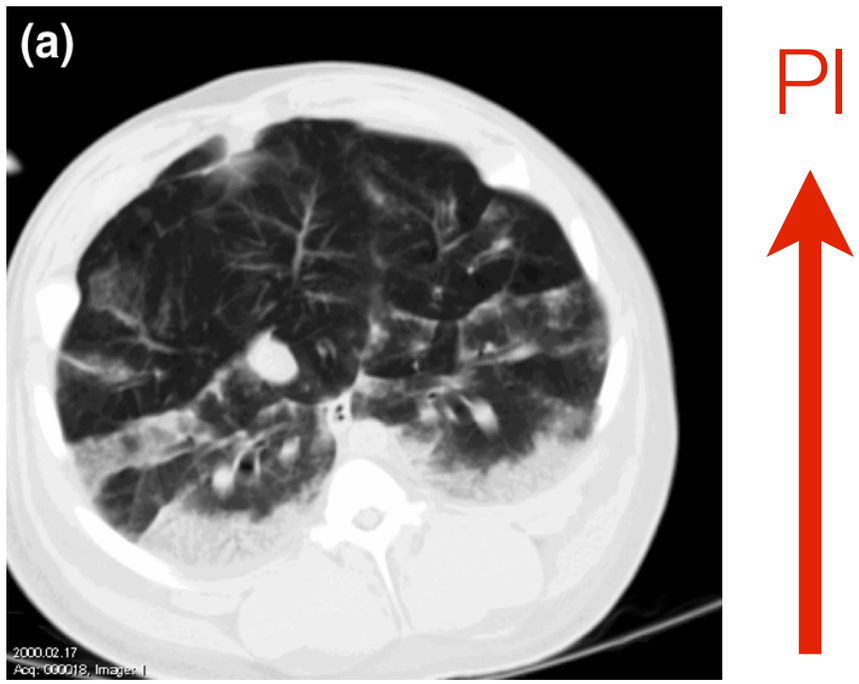
Cytokine responses to volutrauma in non-injured lungs in vivo

open boxes - no correction of metabolic acidosis

hatched boxes - correction of metabolic acidosis



Computed tomography of a lung region above the diaphragm in a pig with oleic acid induced lung injury during airway pressure release
ventilation/biphasic positive airway pressure (a) with and (b) without spontaneous breathing while maintaining airway pressure limits equal.



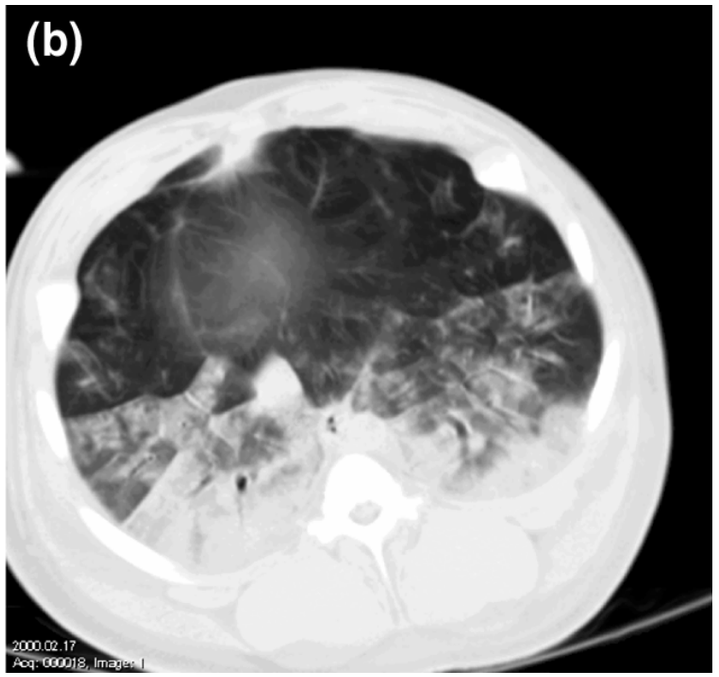
PI

- 15 cm H20

Pplat 30 cm H2O

active inspir effort

Transpulmonary pressure actually 45 cm H20



PpI

+ 15 cm H20

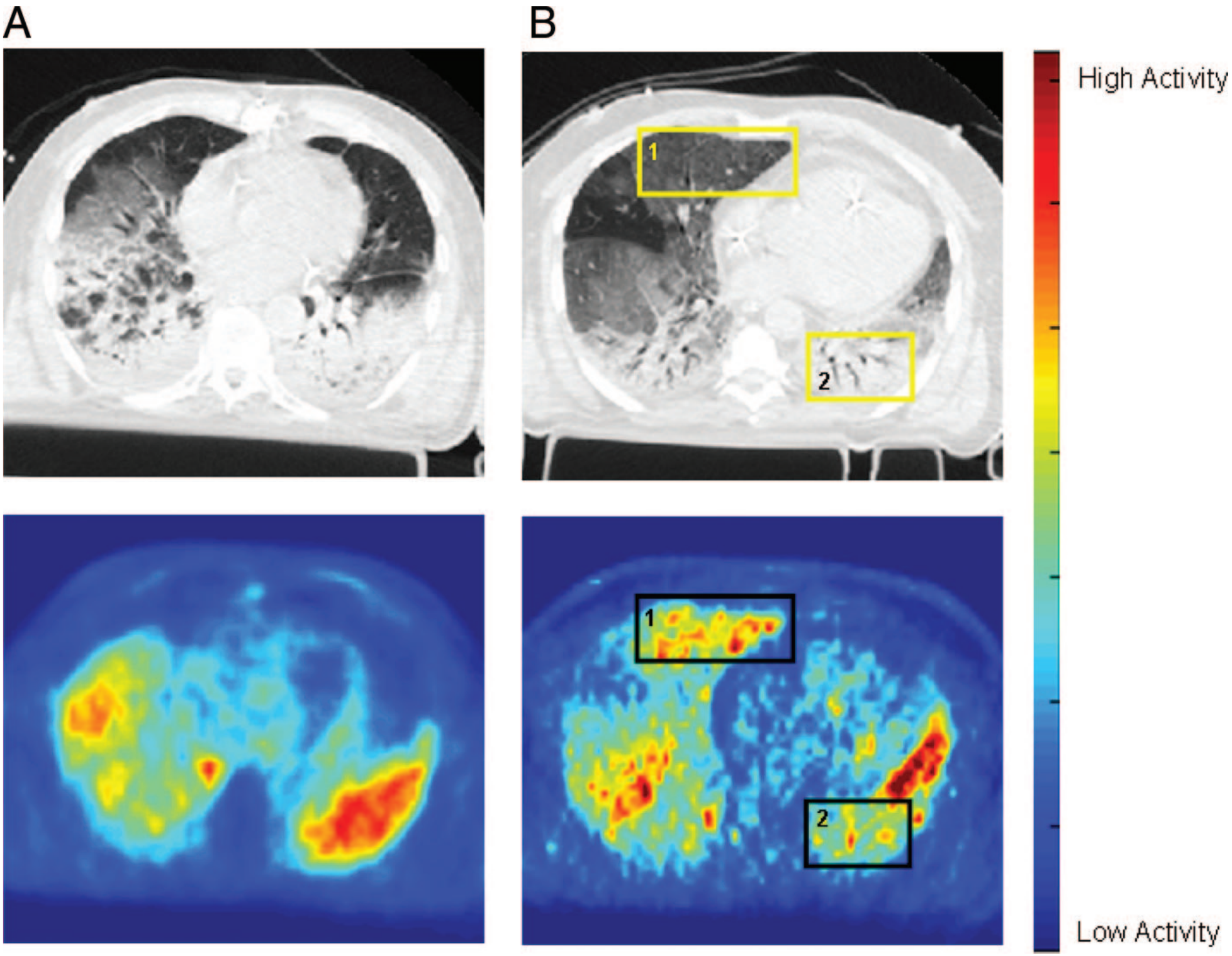
Pplat 30 cm H2O

decreased C_t

Transpulmonary pressure only 15 cm H20

Putensen and Wrigge, Crit Care 2004; 8:492-7

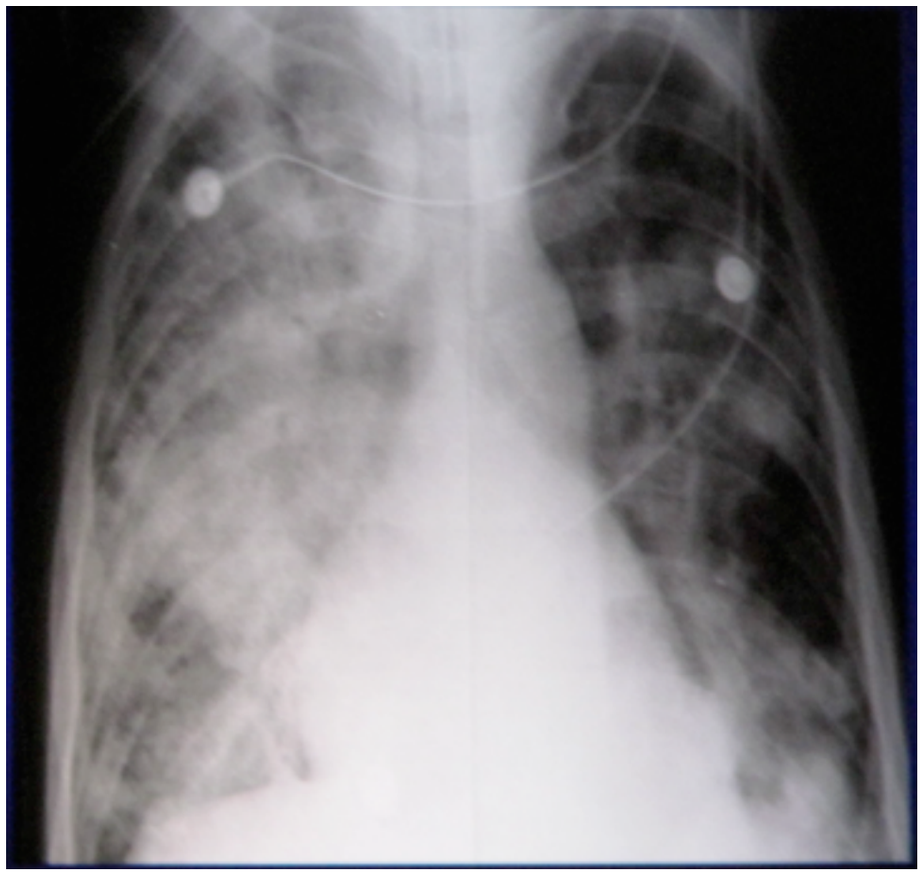
Lungs of patients with ARDS show diffuse inflammation in normally aerated regions on PET



Acute Lung Injury/ARDS

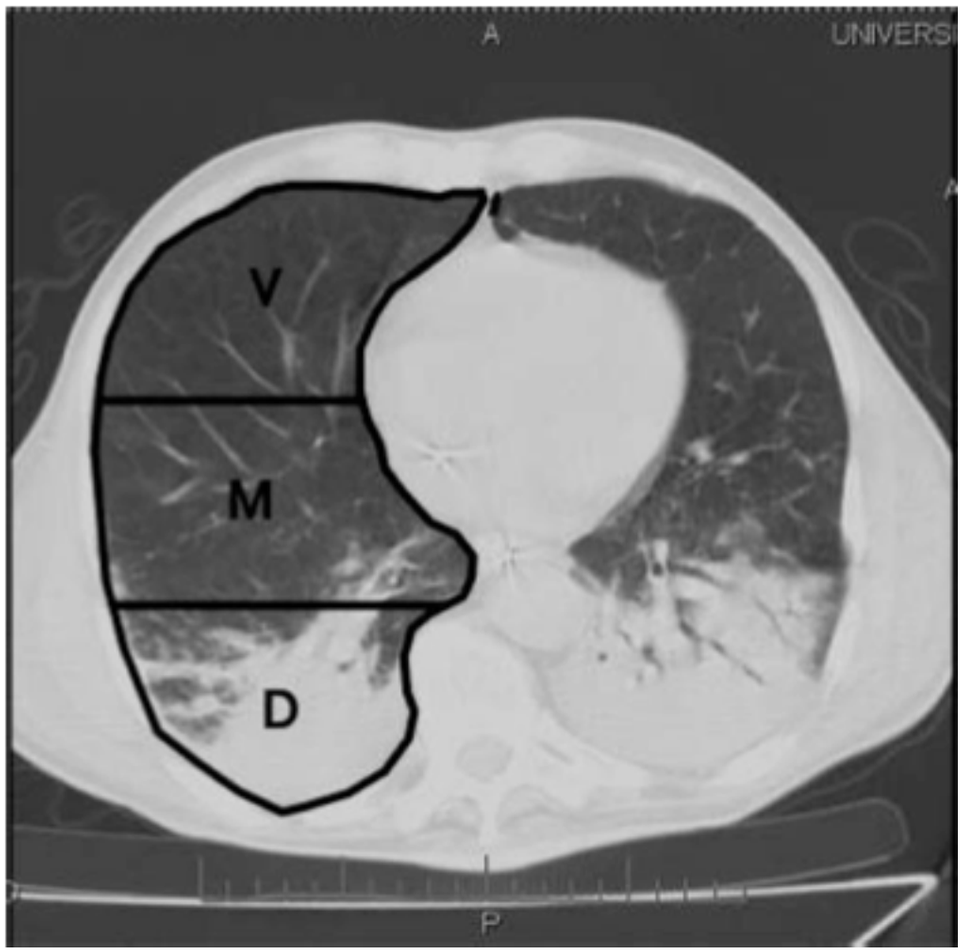
American-European consensus definition

- Acute onset after “at risk” dx
- Bilateral infiltrates on CXR
- PaO2/FiO2 < 40 (ALI)
- PaO2/FiO2 < 27 (ARDS)
- No left atrial hypertension
    - No evidence of CHF
    - Pwedge <=18 Hg



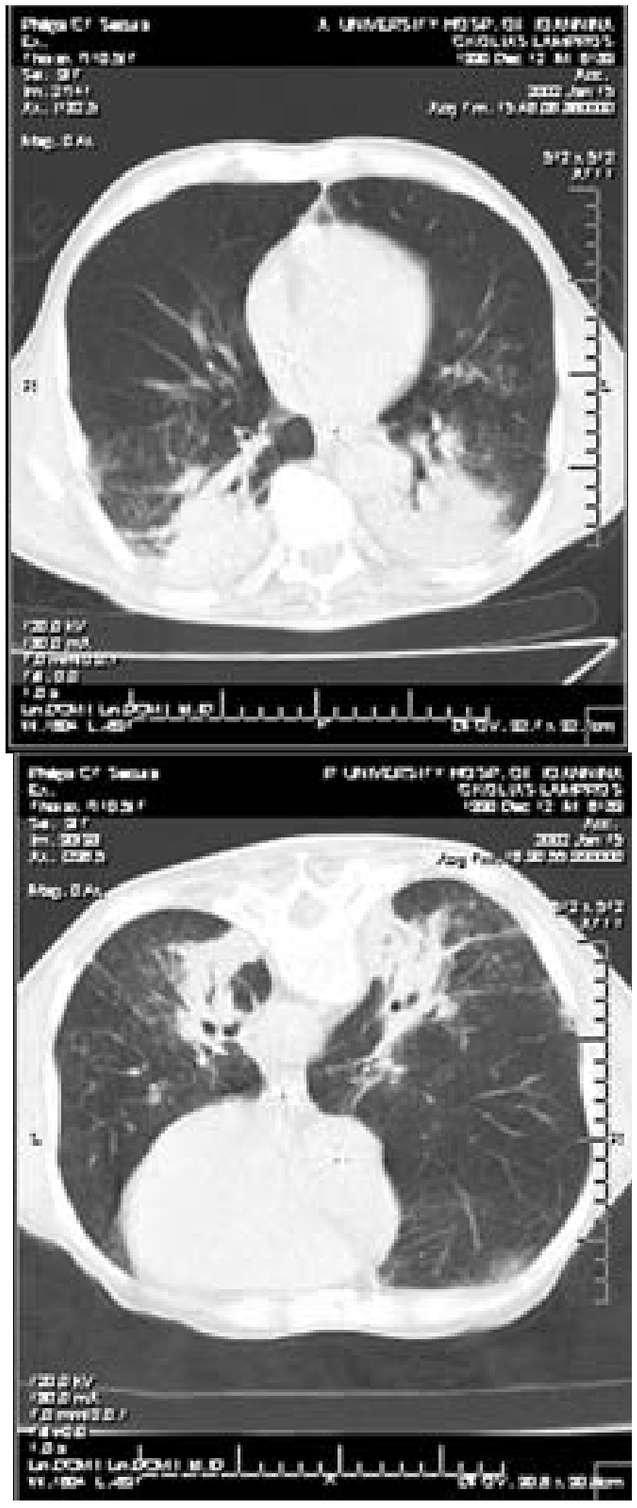
Bernard, et al. AJRCCM 1994; 149:818-24

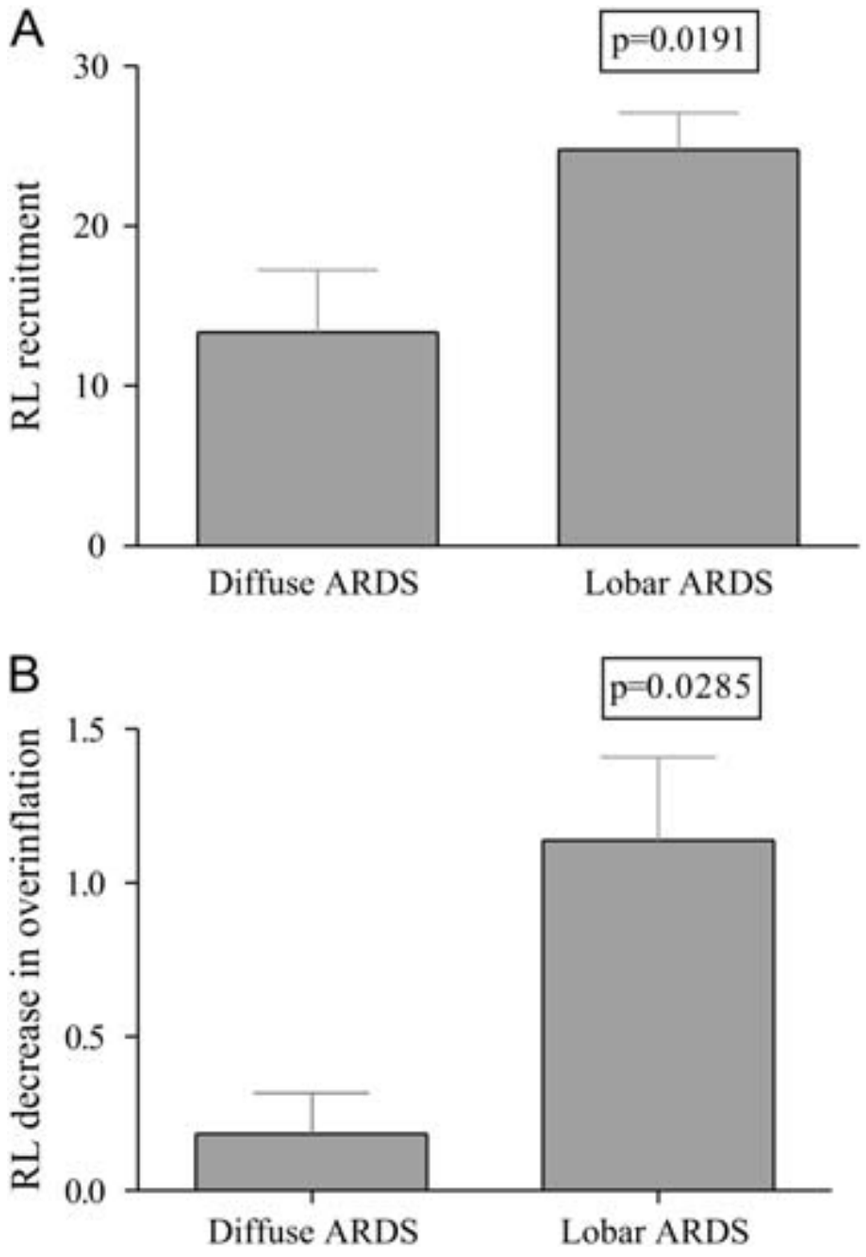
Prone ventilation



Volumetric analysis of CT scan. Each lung is divided into 3 equl sections

Prone ventilation - augments recruitment and prevents overdistension in ALI

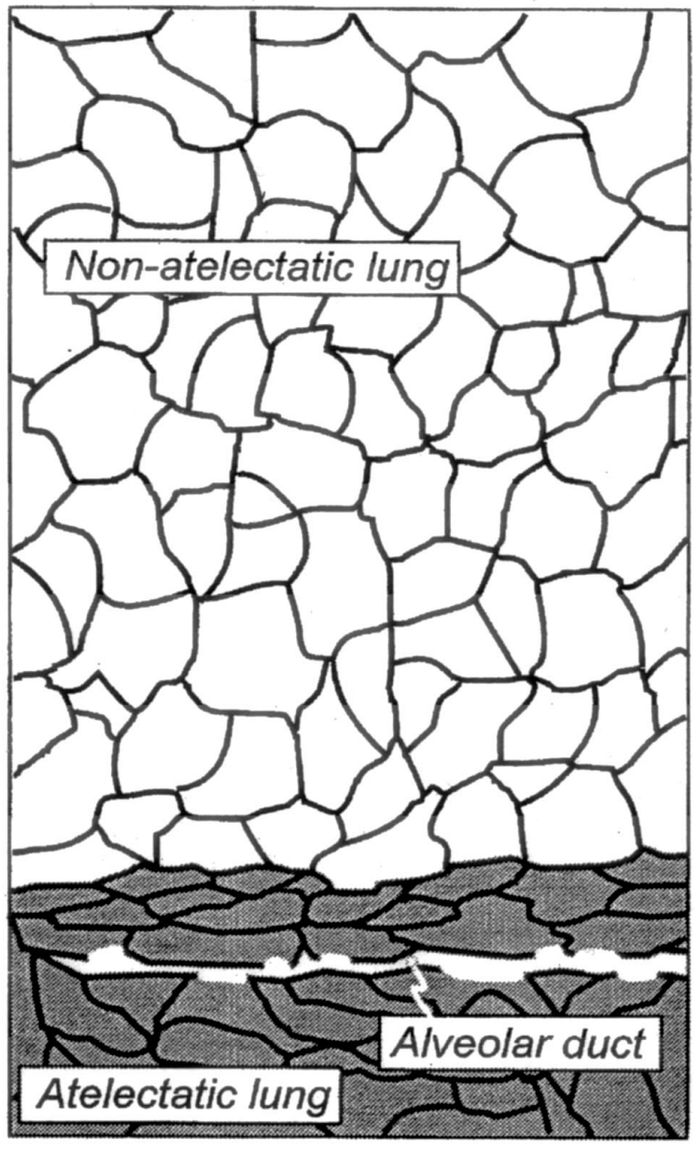




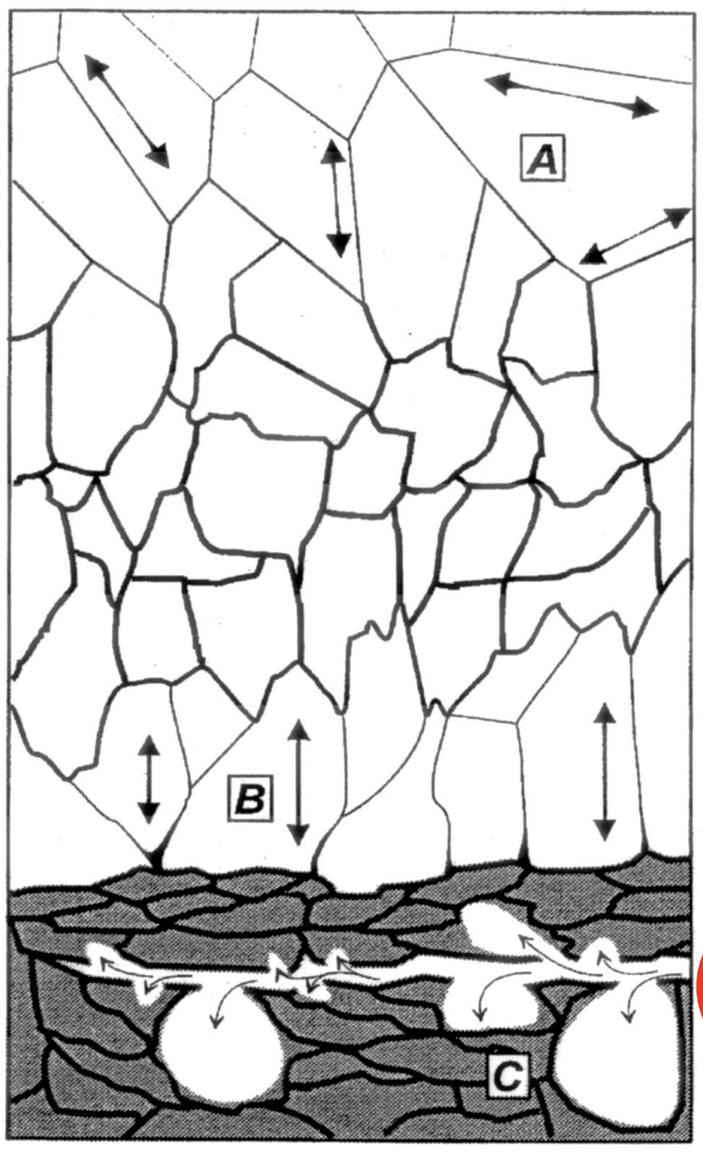
Differential response of diffuse and lobar ARDS to the prone position. Decrease in both the mass of nonaerated rt lung and overinflated areas is greater for lobar ARDS.

Galiatsou, et al. AJRCCM 2006; 174:187-197

ARDS



End-expiration



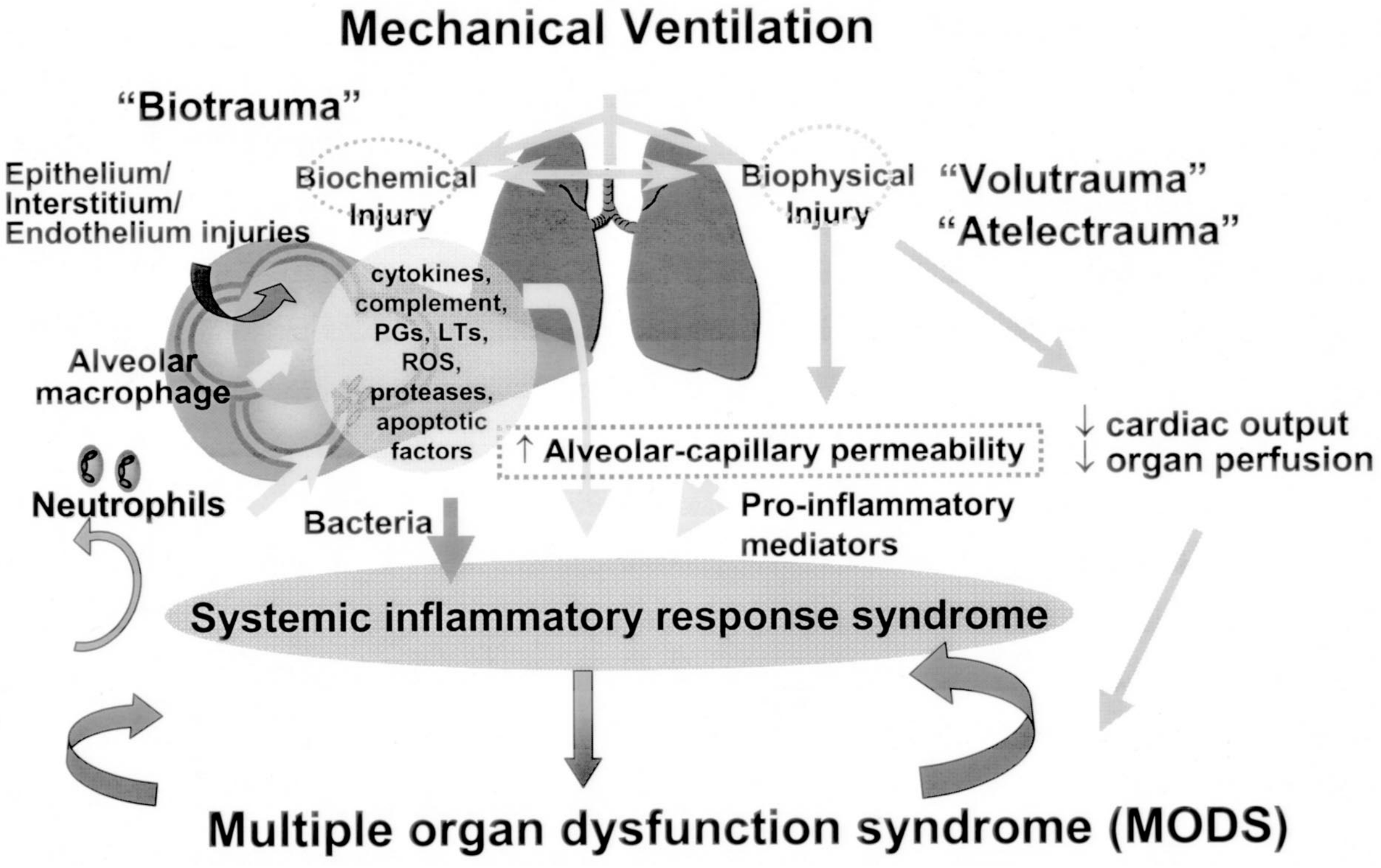
End-inspiration

overdistension
“volutrauma”

Recruitment/derecruitment
“atelectrauma”

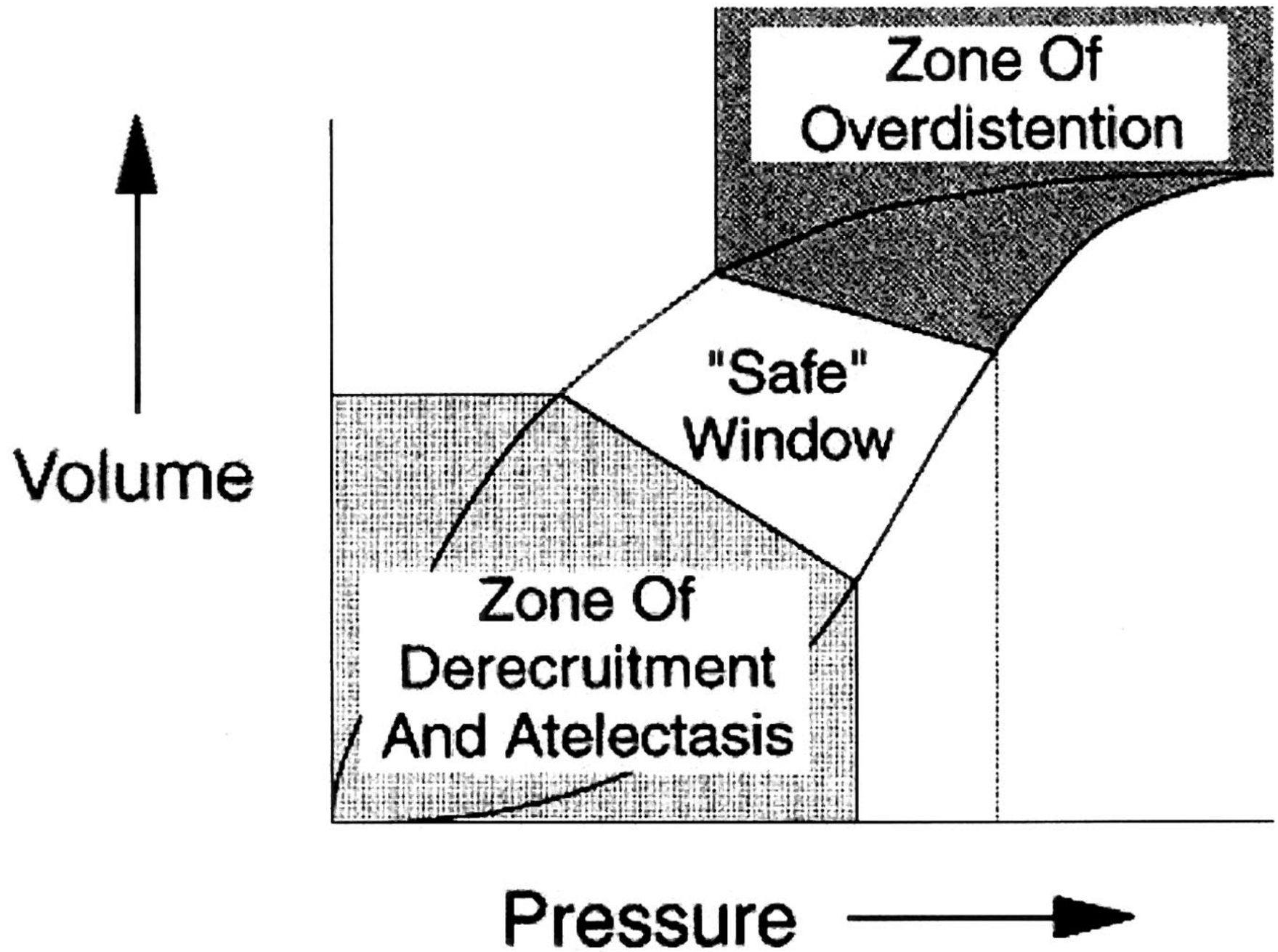
Imai et al. CCM 2005; 33: No.3 (Suppl.): S129-S134

ARDS

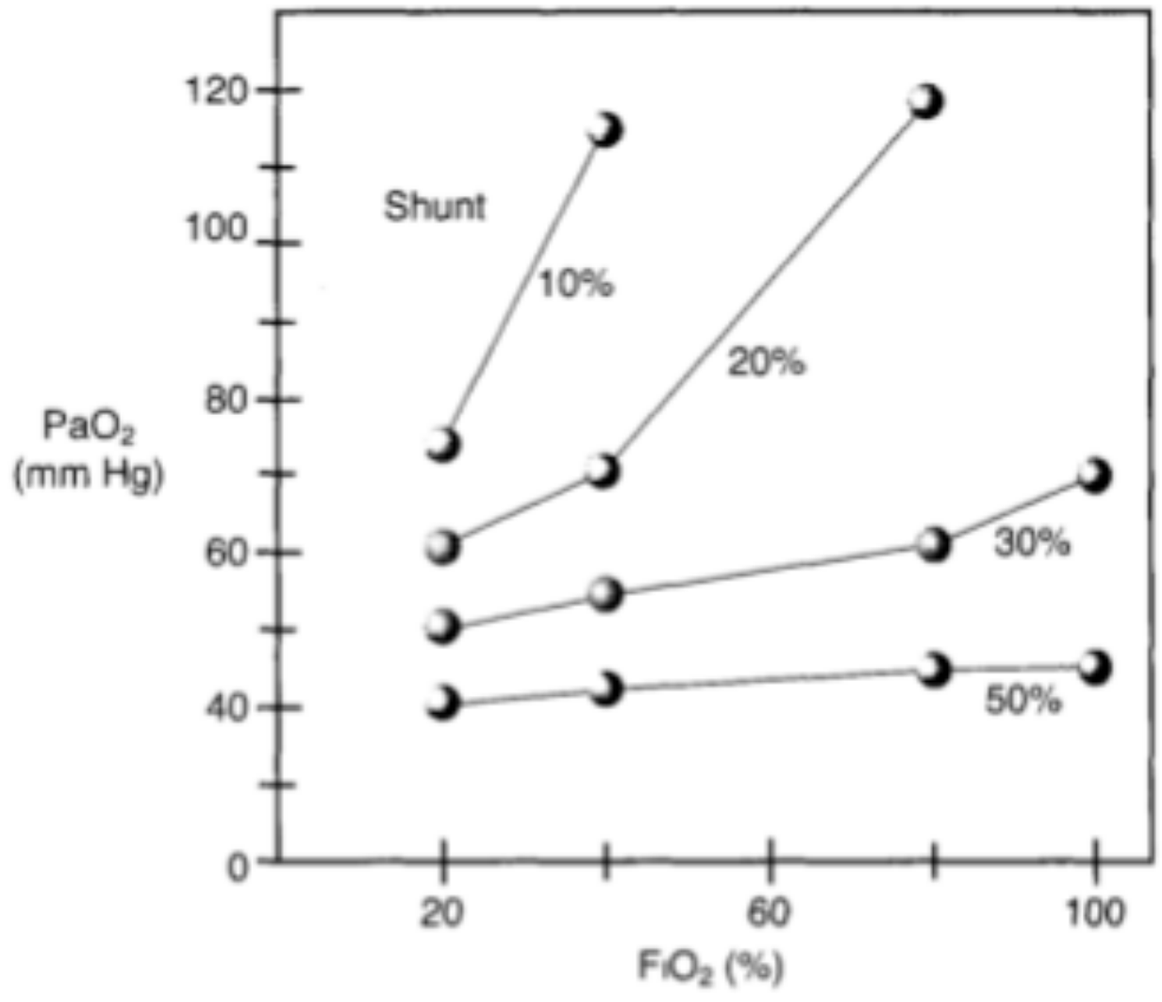


Imai et al. CCM 2005; 33: No.3 (Suppl.): S129-S134

ARDS



Imai et al. CCM 2005; 33: No.3 (Suppl.): S129-S134


120
100
80
60
40
0
PaO_2
(mm Hg)
Shunt
10%
20%
30%
50%
20
60
100
FiO_2 (%)

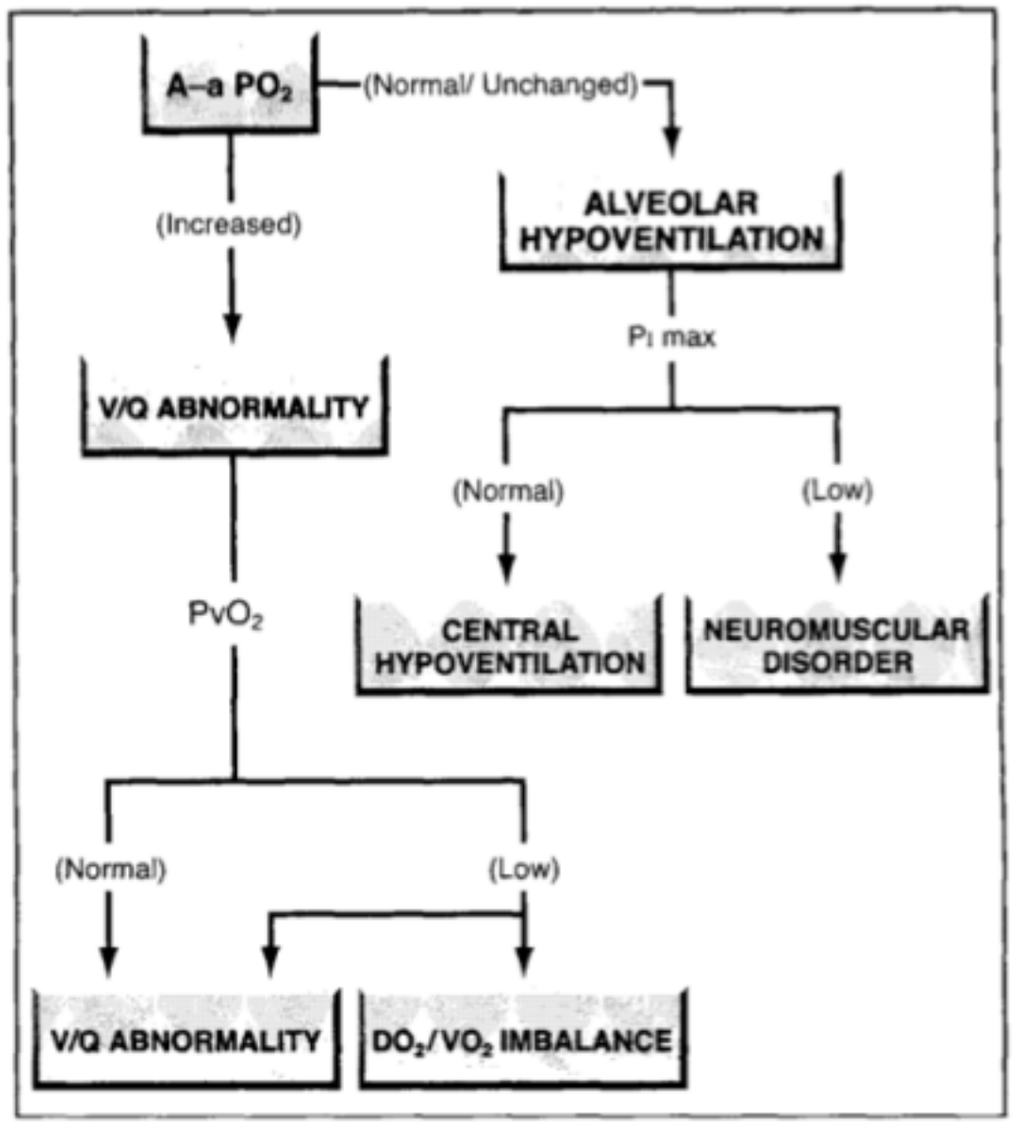
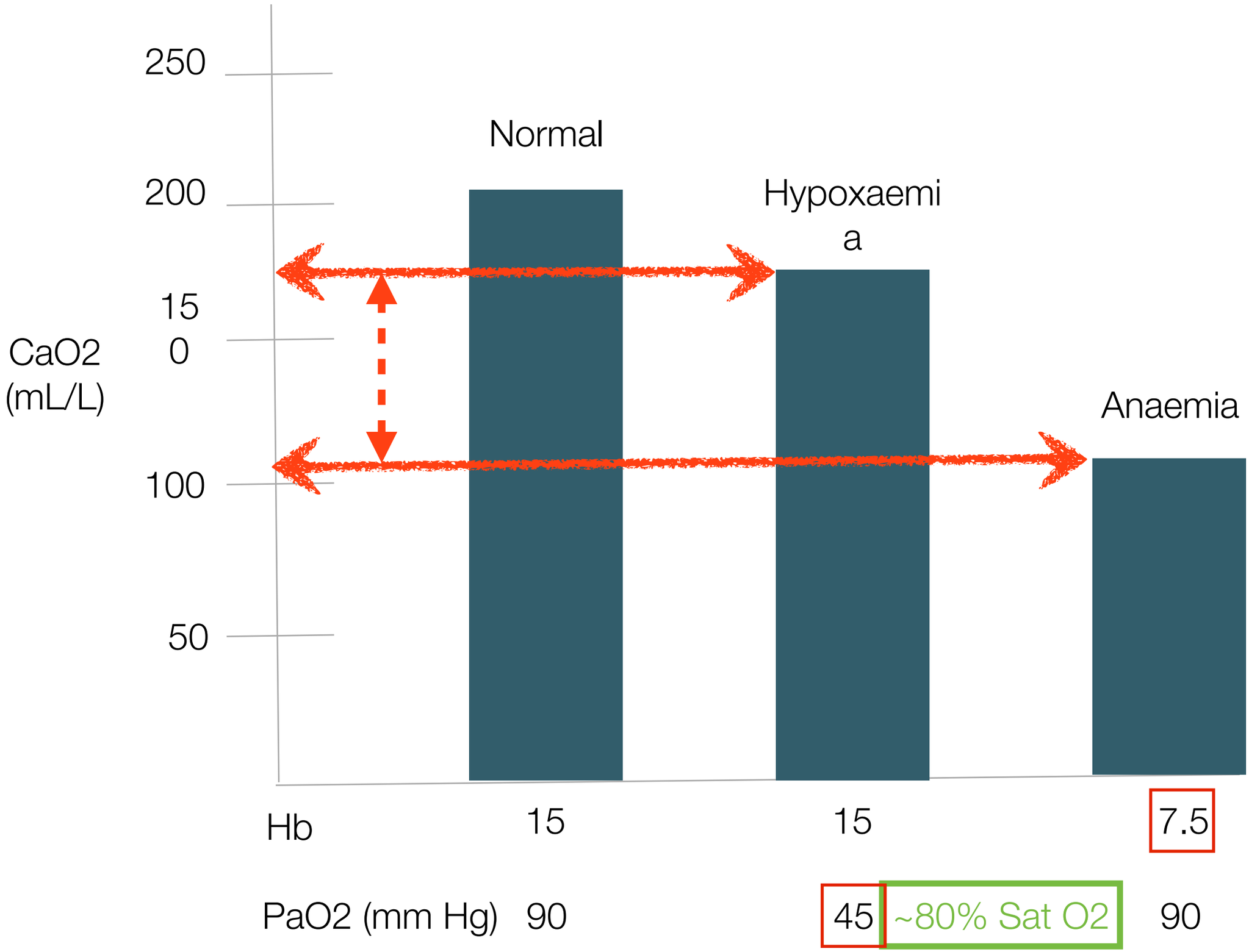
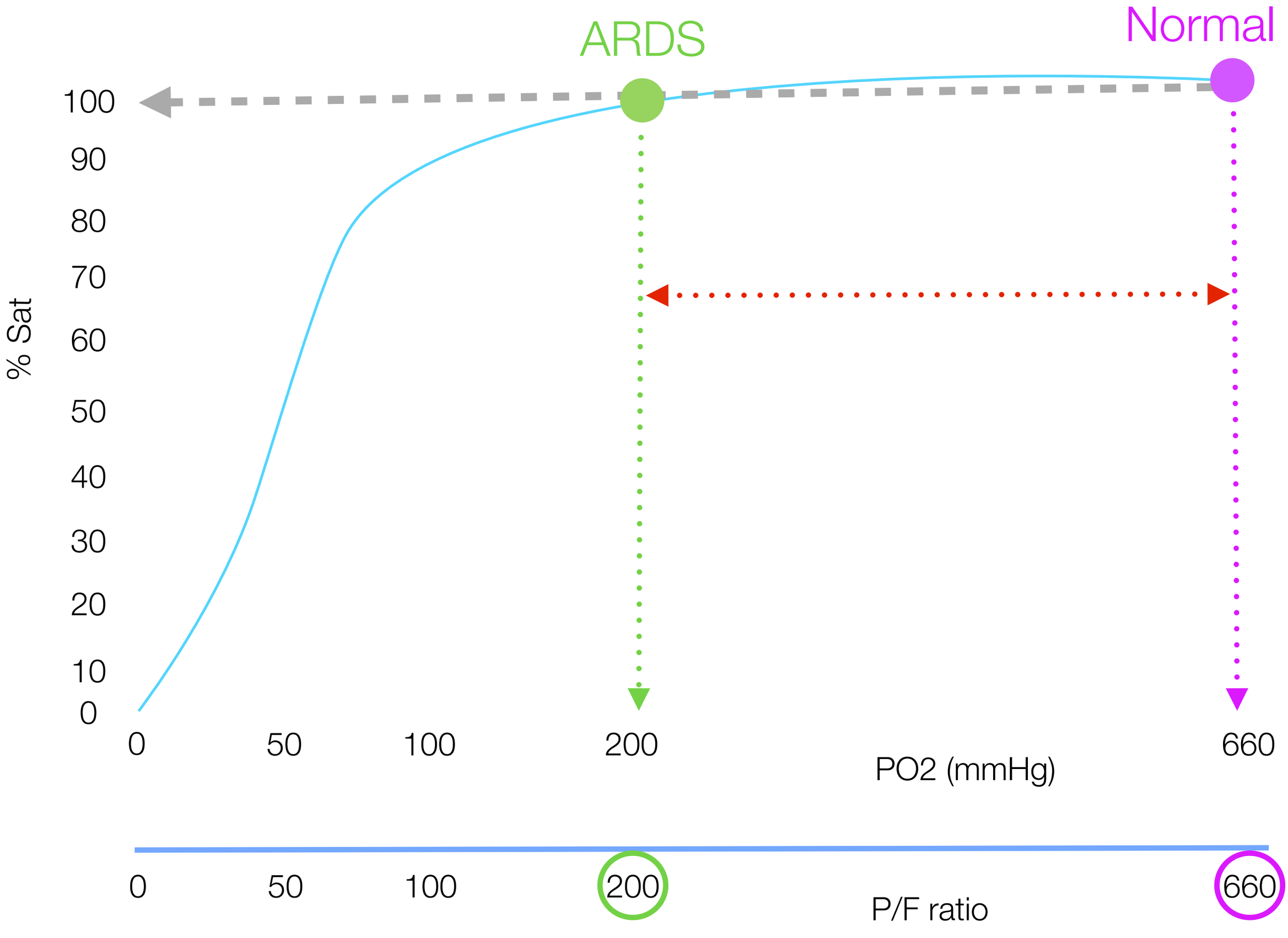


FIGURE 19.6 Flow diagram for the evaluation of hypoxemia.

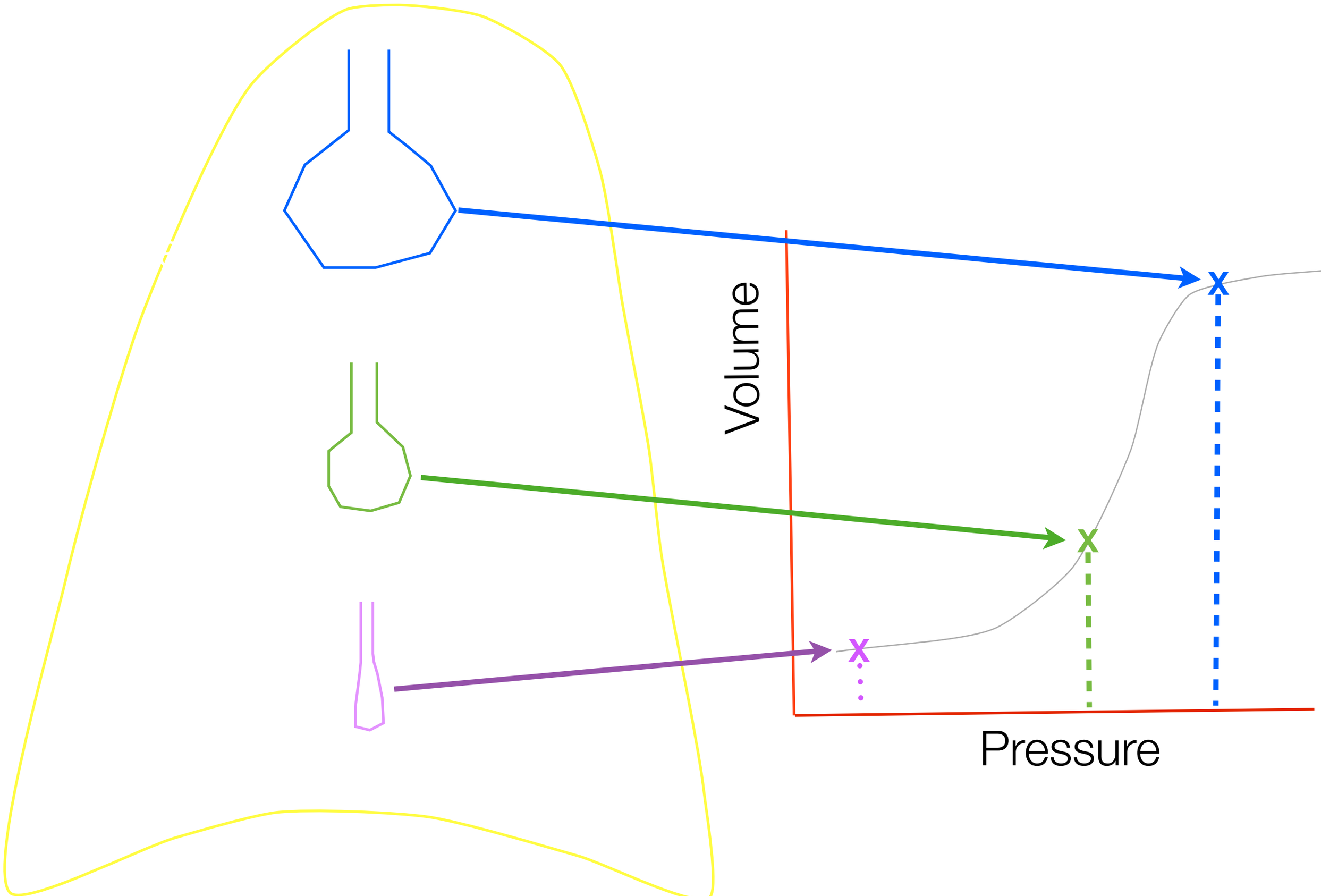
Effects of a equivalent 50% reduction in Hb and pO2 on **O2 content** in arterial blood



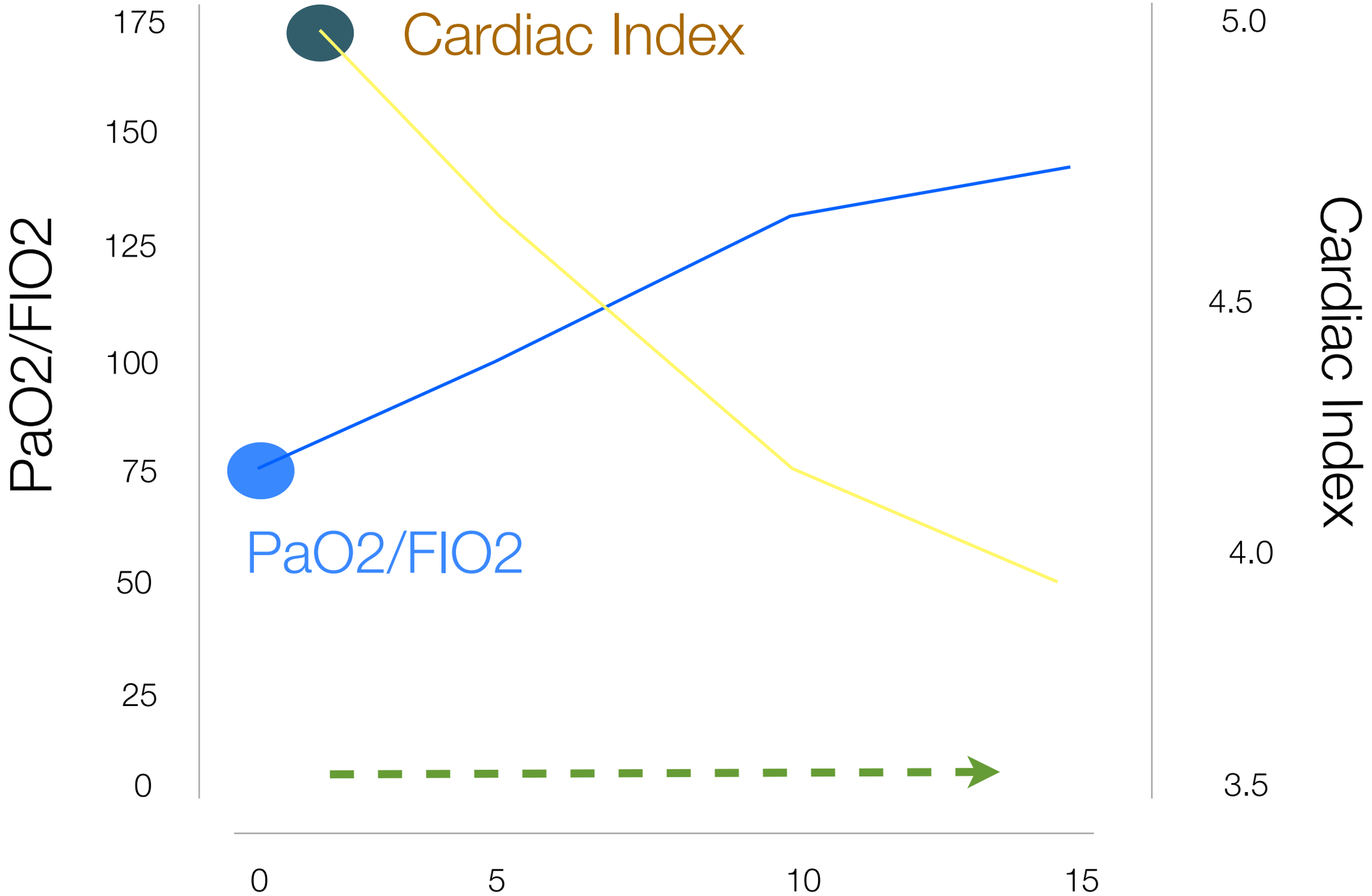
PaO2/FiO2 ratios (= P/F)- describes lung efficiency



Why recruitment/PEEP ?



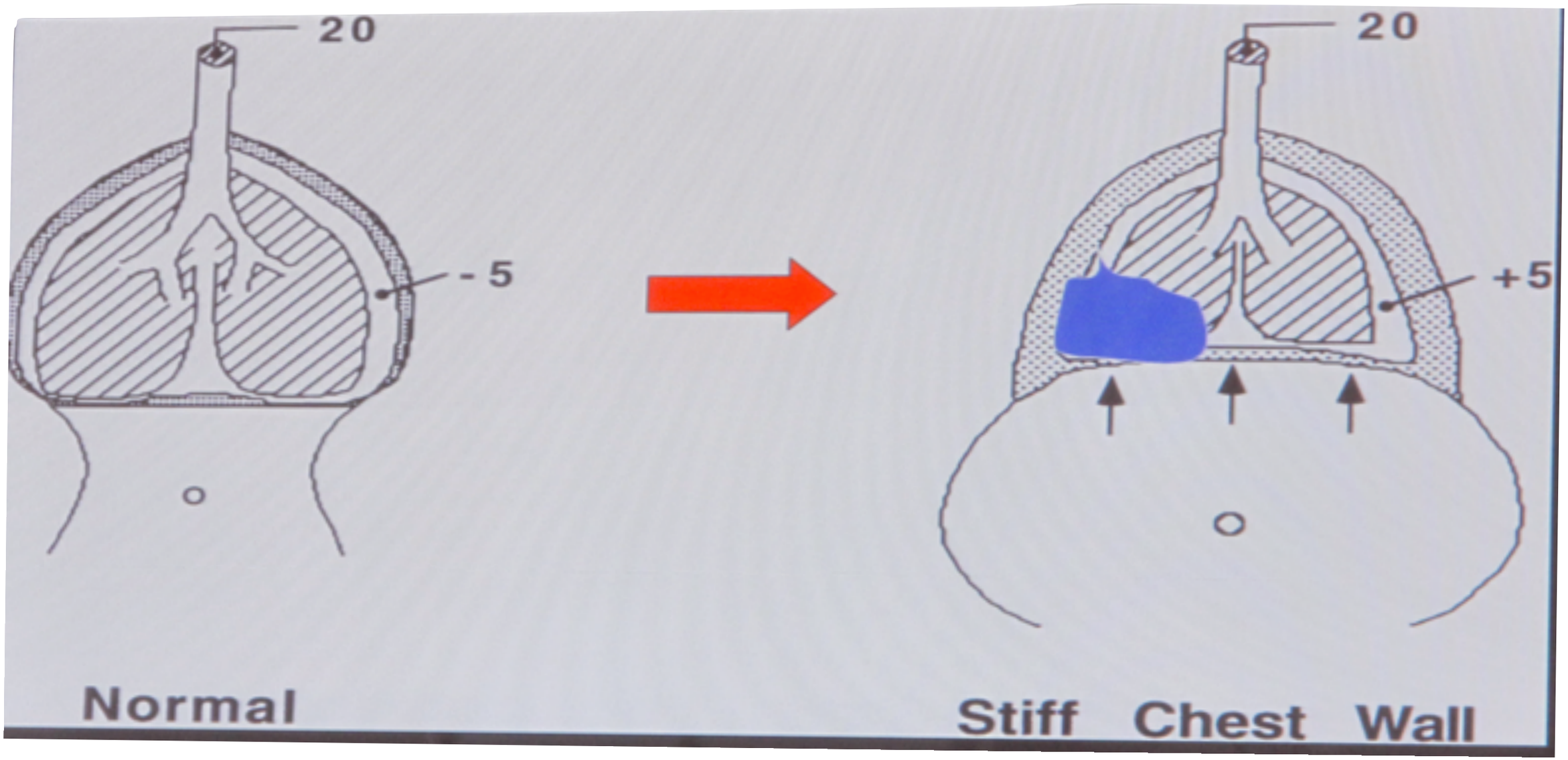
Effect of PEEP on lung efficiency vs. cardiac output



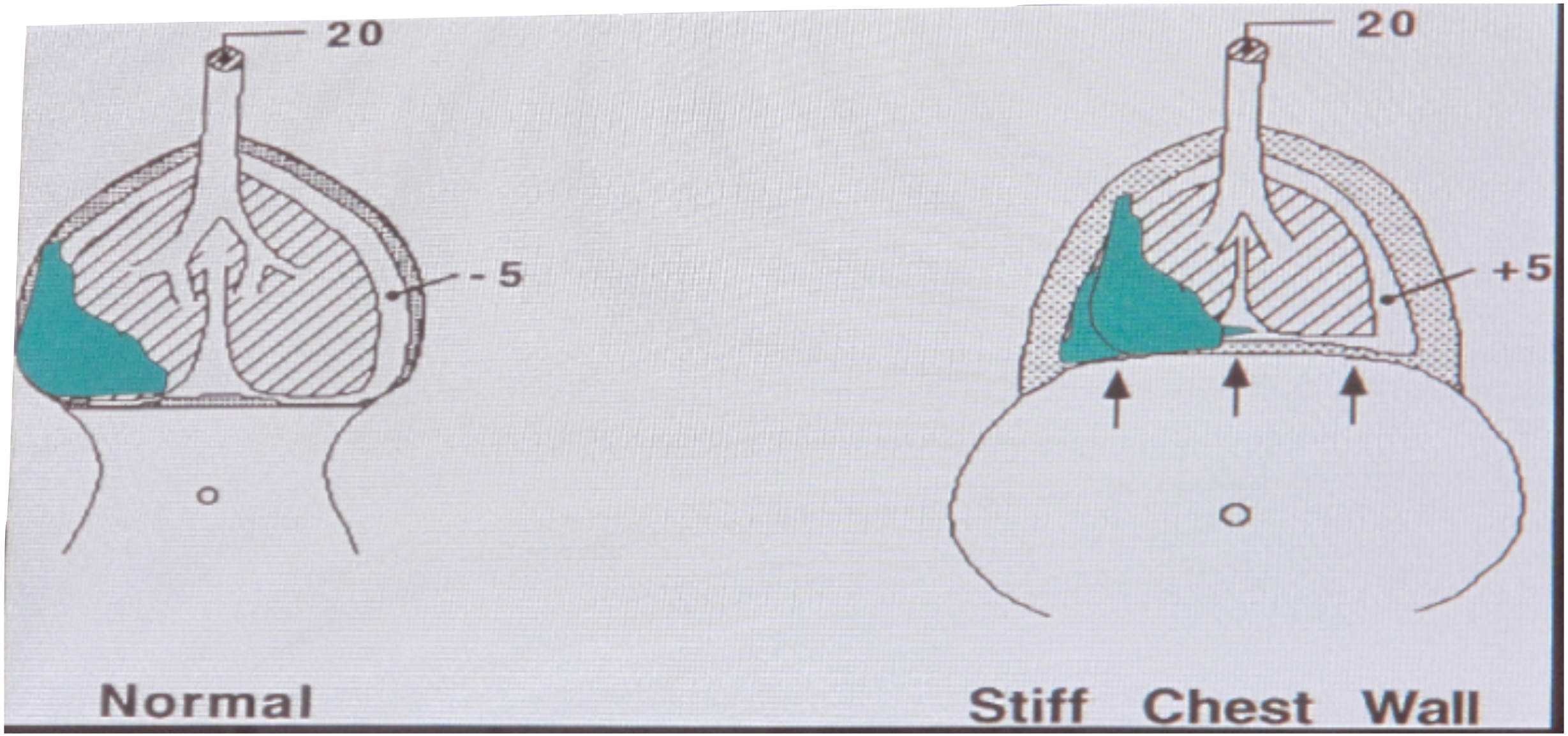
Crit Care Med 2003; 31: 2719-2726

Pleural Effusions/Pneumothorax

How does a pleural effusion influence mechanics during ventilation?

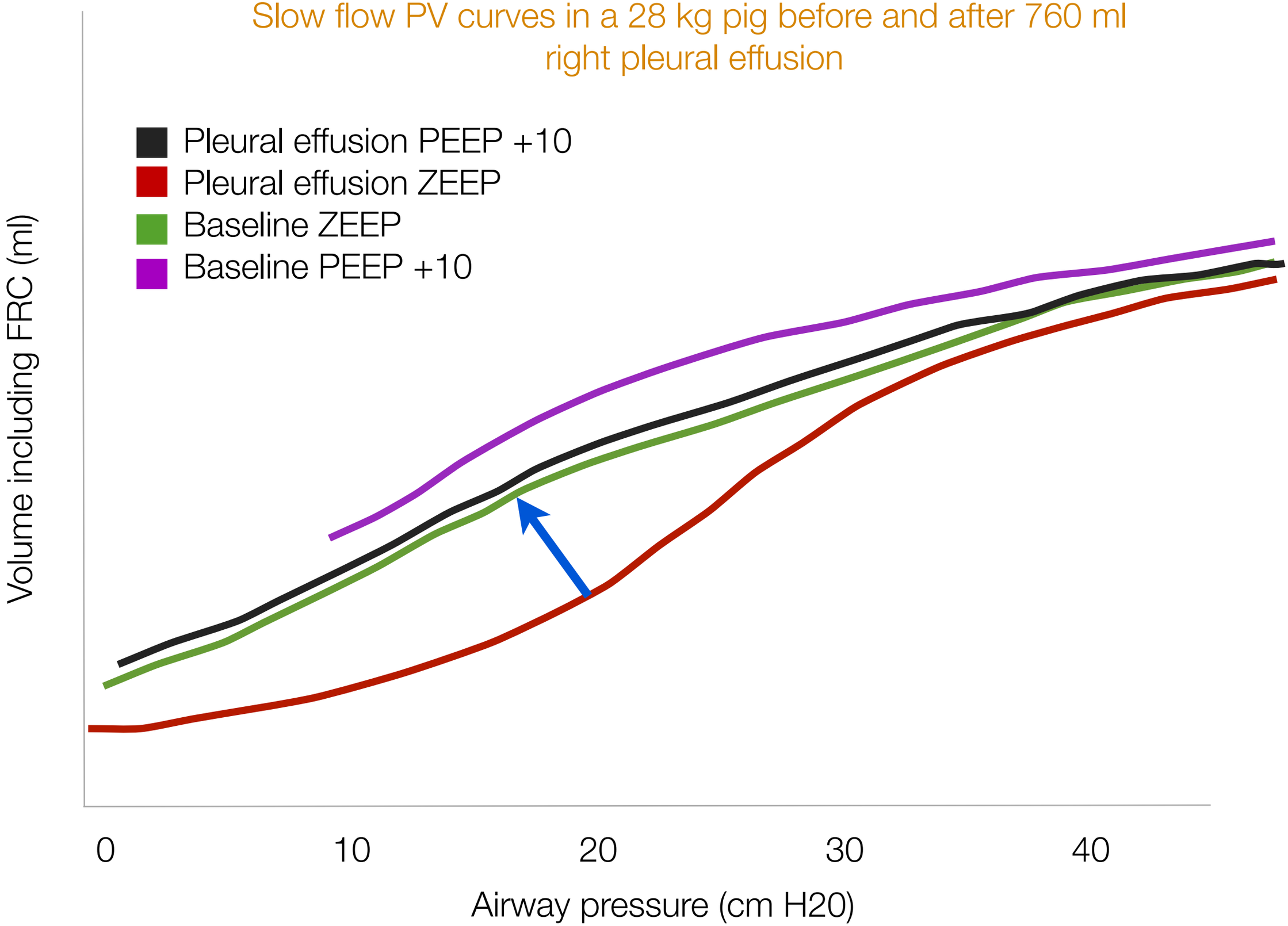


Always remove a pleural effusion?

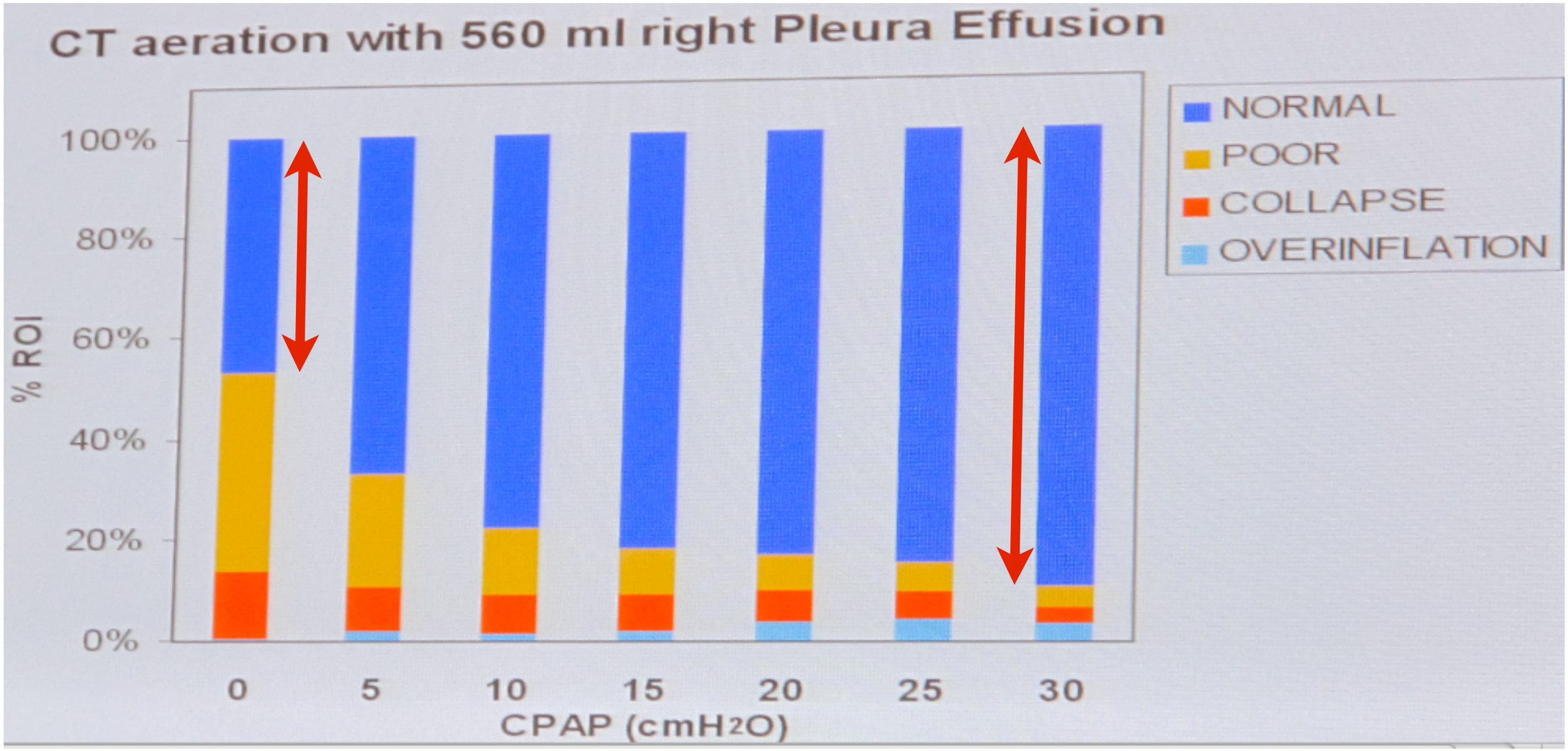


PEEP offsets pleural effusions

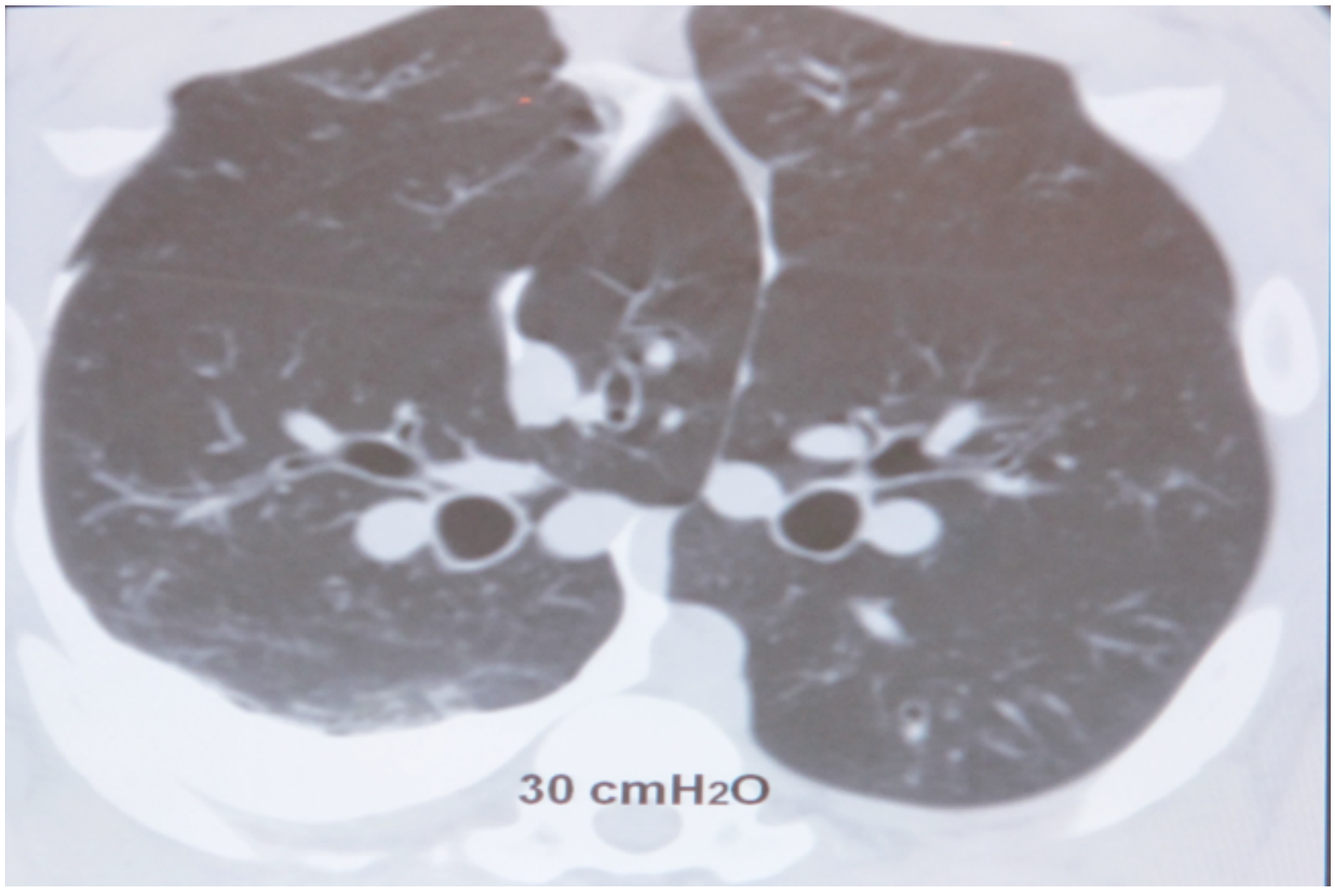
Slow flow PV curves in a 28 kg pig before and after 760 ml right pleural effusion



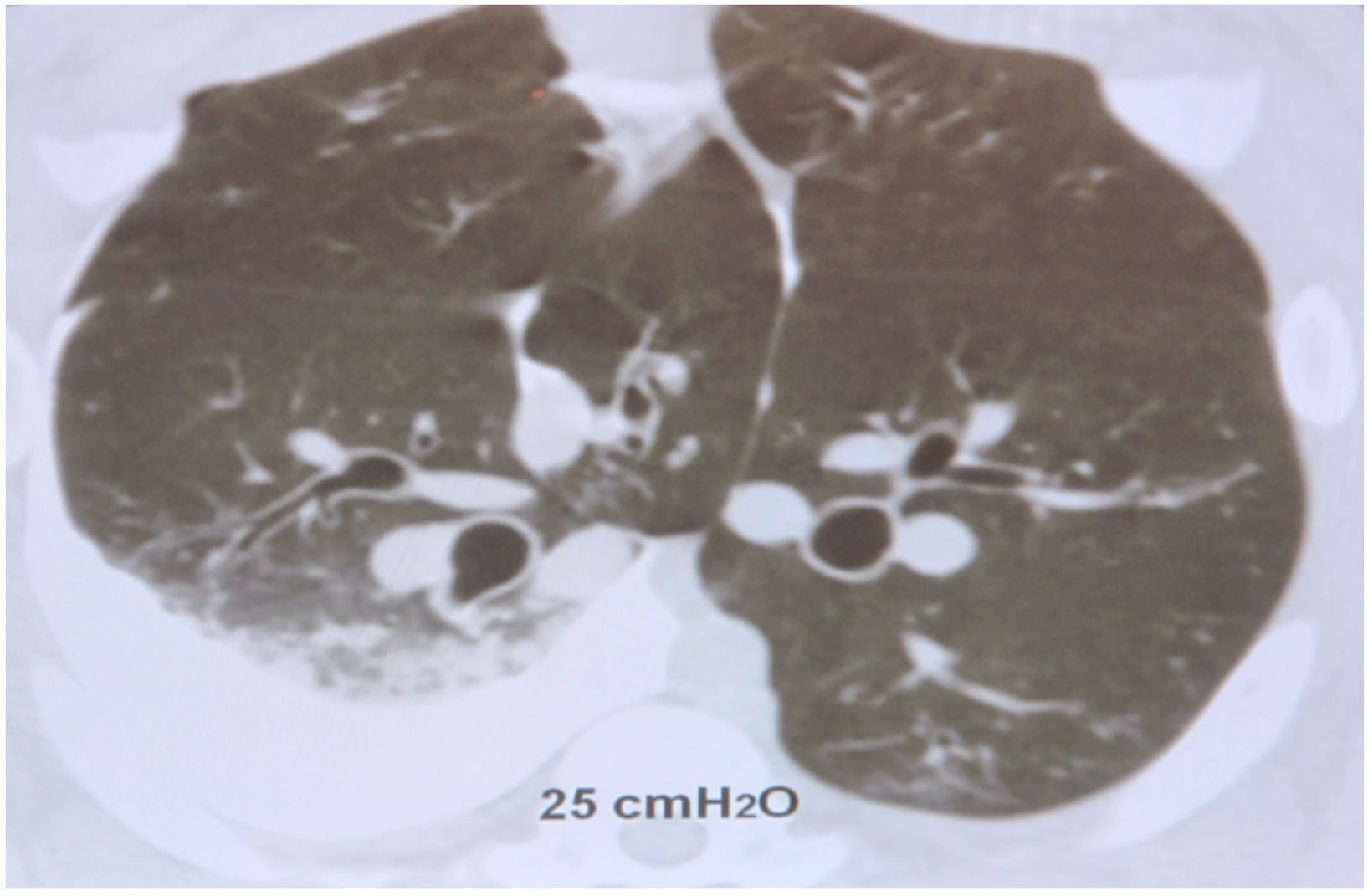
PEEP offsets pleural effusions



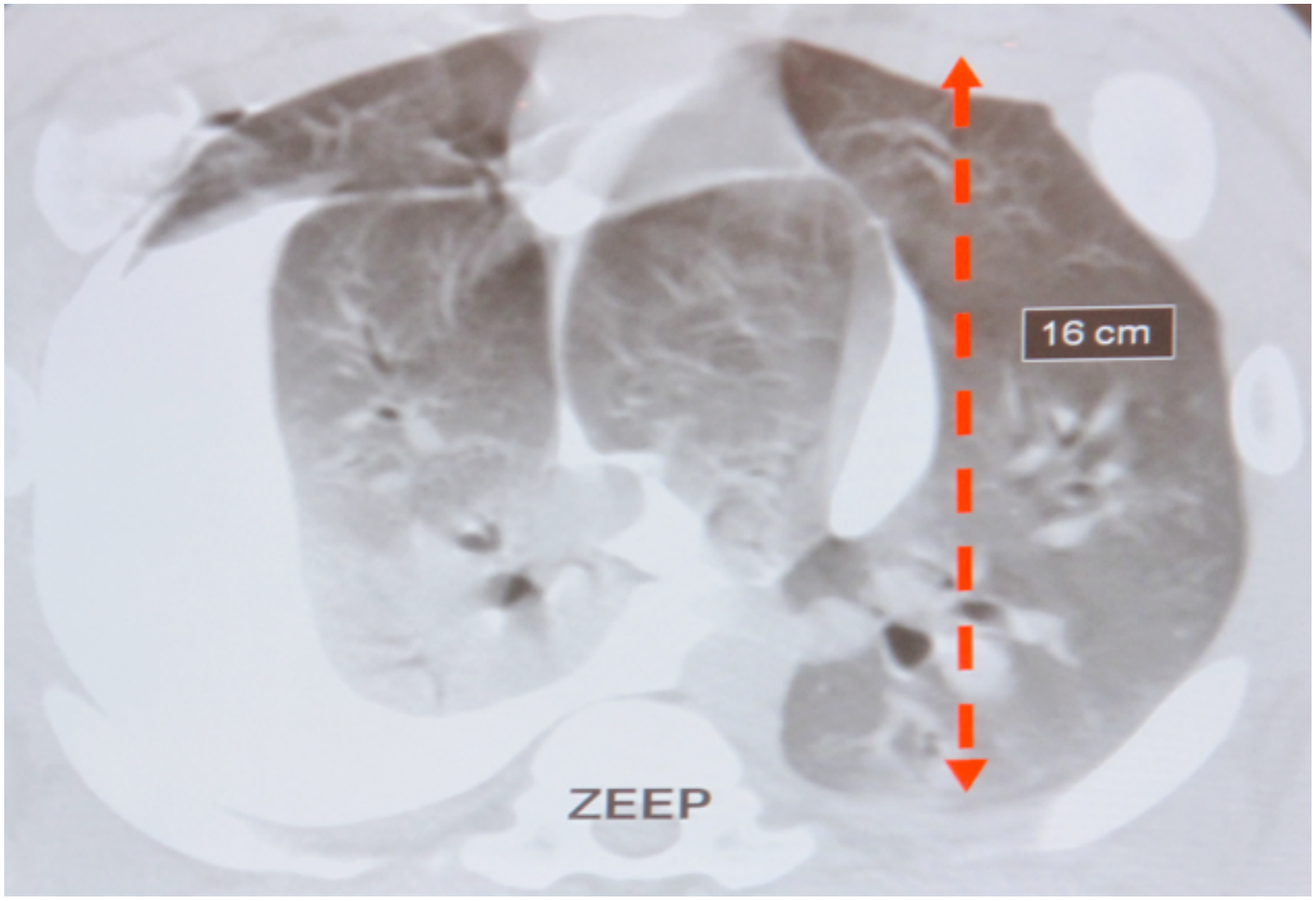
PEEP offsets pleural effusions



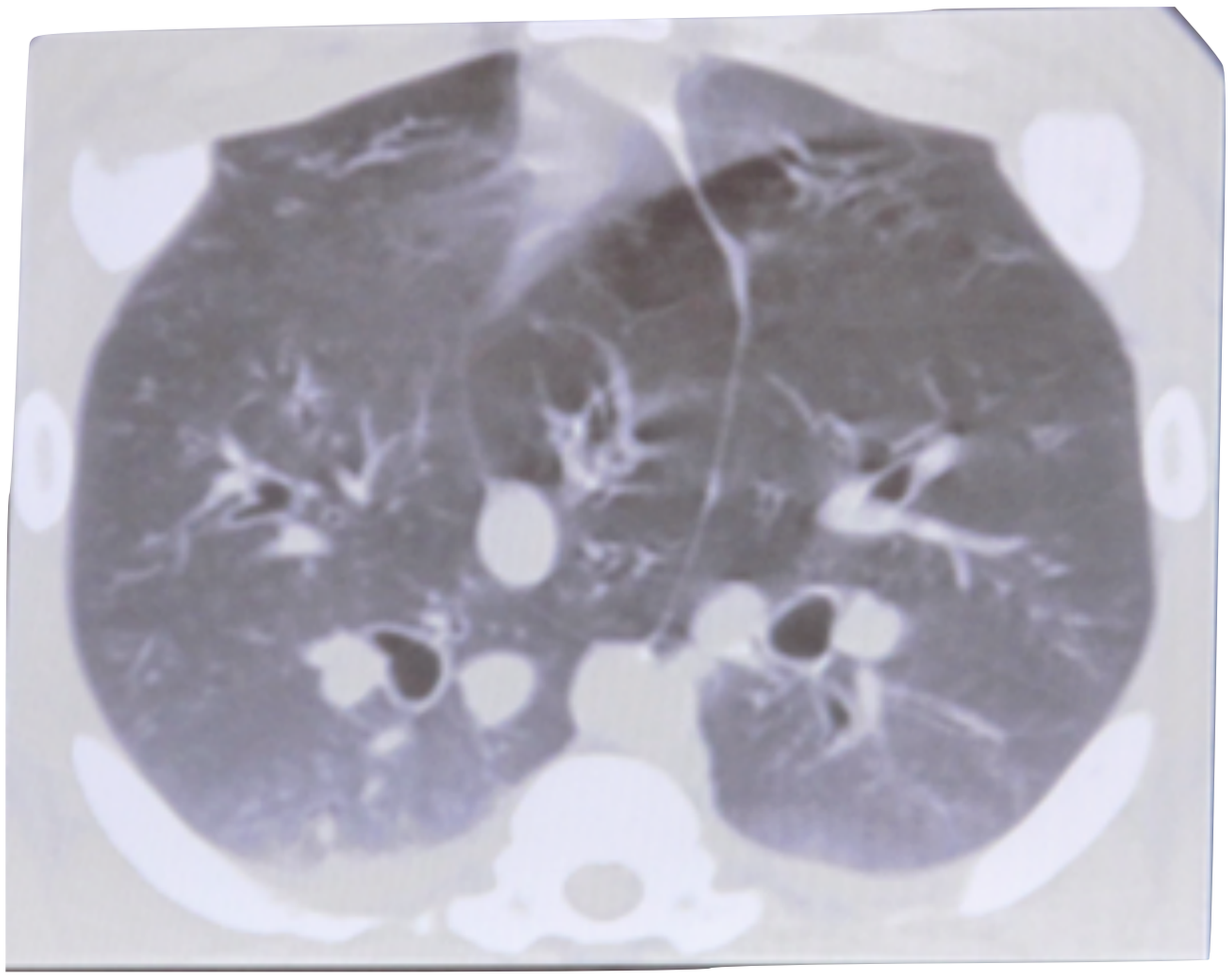
PEEP offsets pleural effusions

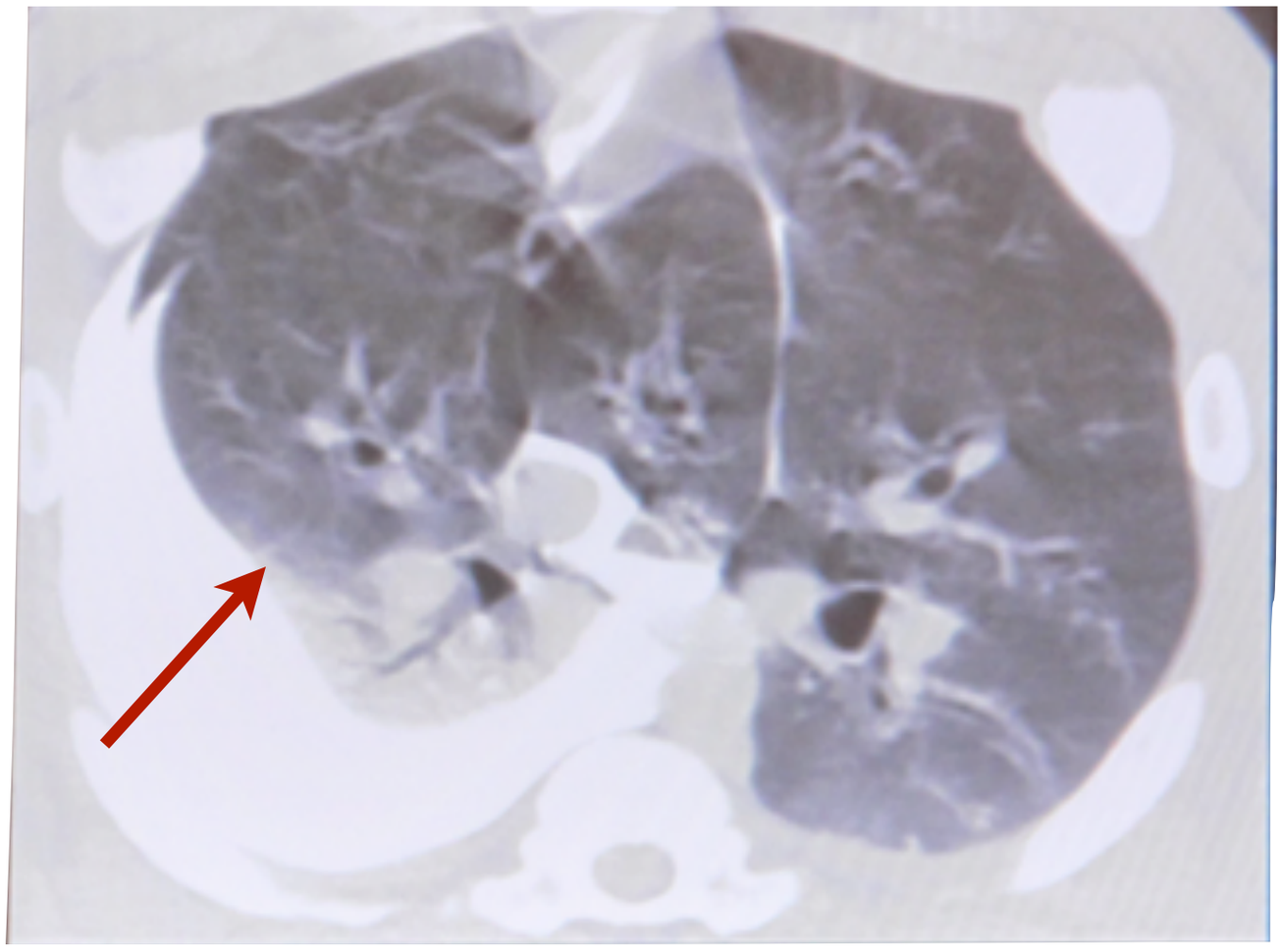


PEEP offsets pleural effusions

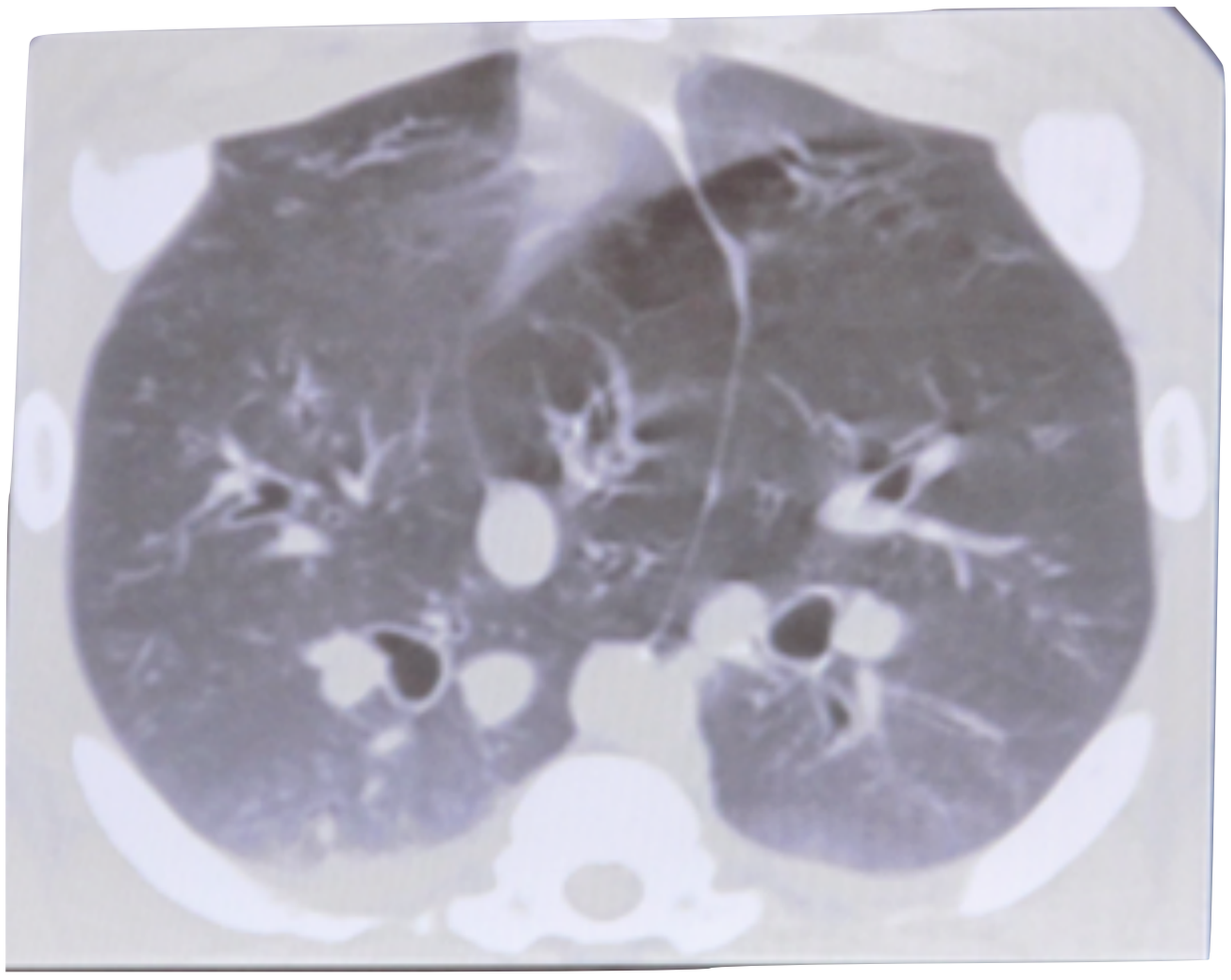


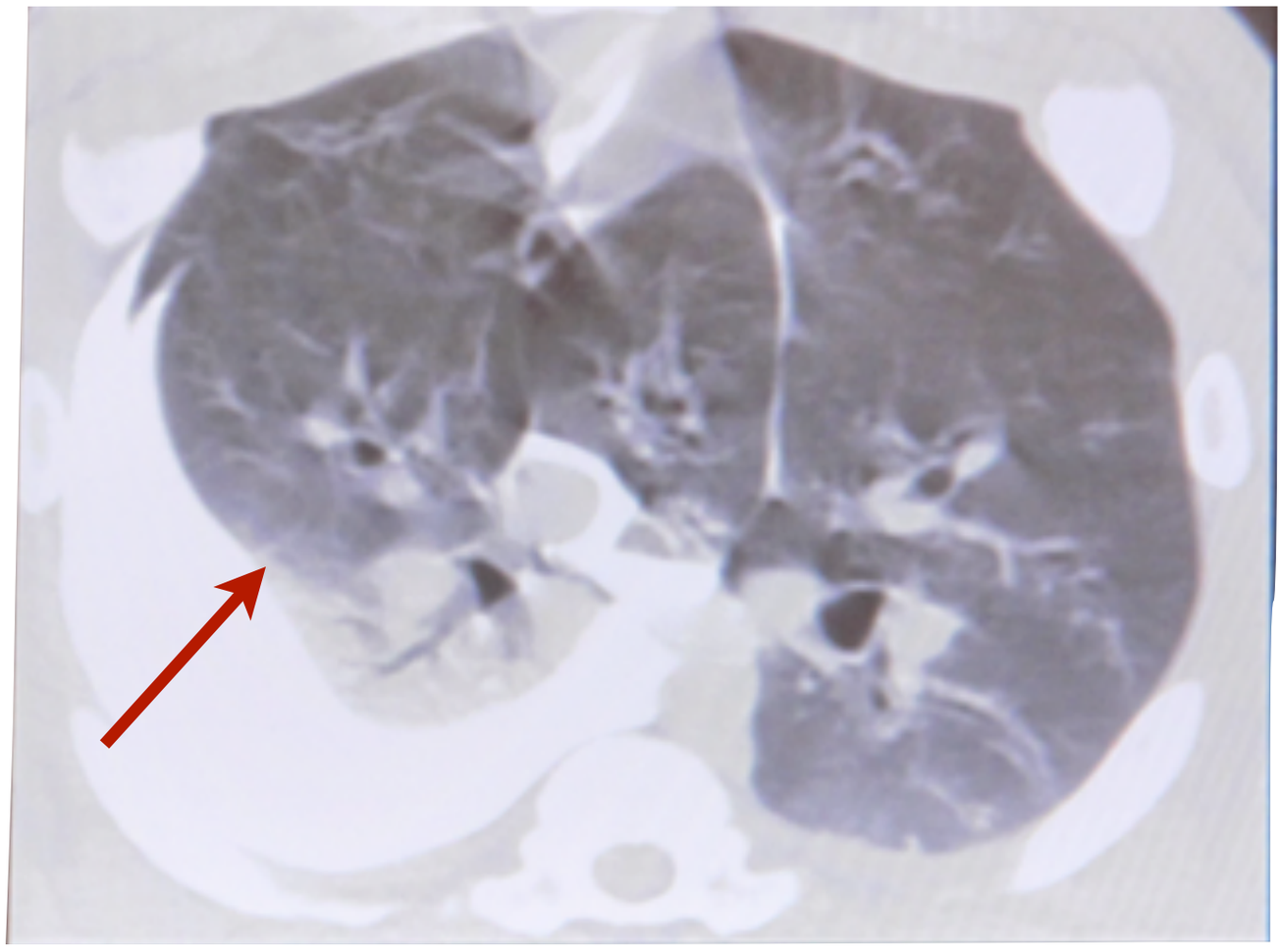
Local transpulmonary pressures?



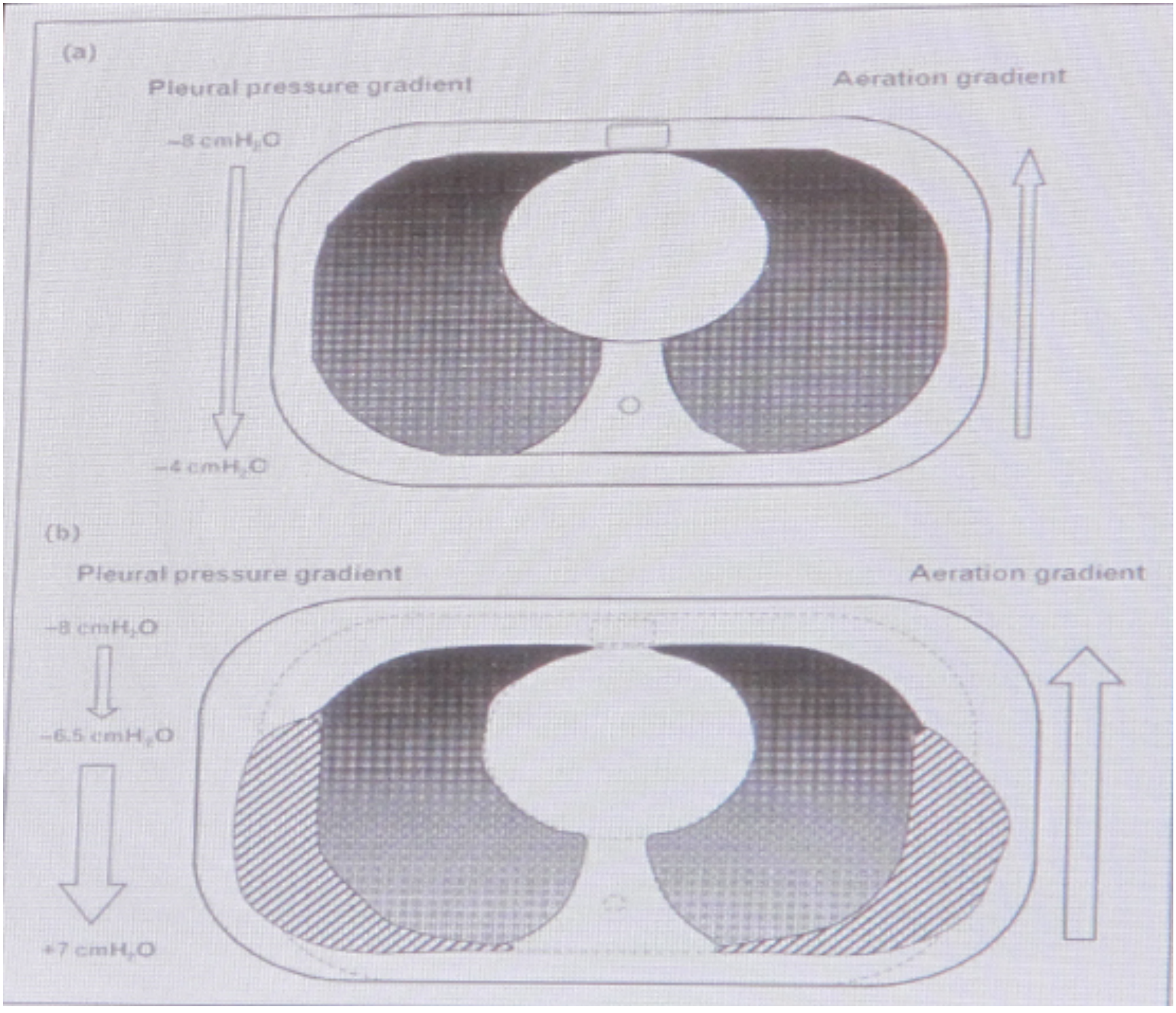


Global transpulmonary pressures (Paw-Poesoph).....**unchanged**





Normal chest wall expands > lung volume decreases



Pleural Effusions - lessons?

- Pleural effusions de-couples lung from chest wall and alters regional transmural pressures
- PEEP dramatically changes mechanical impact of pleural effusion
- Global lung behavior and regional stresses cannot be predicted from airway pressures alone.
- Intra-tidal recruitment of both the flooded and “dry” sides is the rule, especially with insufficient PEEP applied.

Pleural Effusions + Acute respiratory failure

Assess chest wall compliance

- Abdominal pathology
- Positive fluid balance-edema
- Intra-abdominal hypertension
- Esophageal pressure measurement

Low chest wall compliance

Consider drainage

Normal chest wall compliance

Perform recruitment manoeuvre

- Oxygenation improves
  - Increase PEEP +/- negative fluid balance
  - Consider drainage
- No change
  - Drainage not warranted

Pneumothorax

ACCP : distance from lung apex to cupola

- small: <3 cm apex-to-cupola distance
- large: >3 cm apex-to-cupola distance

BTS : distance from lung margin and the chest wall

- small: <2 cm
- large: ≥2 cm

Chest 2001: 119. 590
BMJ 1993: 307: 114

Drainage tube sizes

Small
- <=14 F

Moderate
- 16F to 22F

Large
- 24F to 36F

Chest 2001: 119. 590

Clinically unstable patients with large pneumothoraces

- Hospitalize and insert chest tube
- ACCP: moderate-sized chest tube (16F-22F)
    - though can use <=14F
- BTS recommends <=14F
- Large chest tube if one anticipates large air leak or requires positive-pressure ventilation

Chest 2001: 119. 590
BMJ 1993: 307: 114

Chest tube removal

- Should be removed in a staged manner
    - lung re-expansion on CXR
    - no air leak
    - H20 seal
    - repeat CXR 5-12 hrs later
        - some (47%) would clamp the tube for about 4 hrs
    - pull chest tube

Chest 2001: 119. 590

Parapneumonic effusions and empyema

- 40-57% of patients with bacterial pneumonia develop PPE
  - no clinical difference
- Associated with increased mortality
  - 3.4 - 7 fold
    - especially with delayed drainage
      - 3.4%->16%
- 10-20% of PPE will evolve into empyema
  - up to 58% overall mortality

Light et al. Am J Med 1980: 69: 507
Sahn ARRD: 1993: 148: 813

Microbiology

- Changing spectra
  - mixed infections
  - S. milleri ~27%
  - S. aureus ~21%
  - S. pneumoniae ~16%
  - anaerobes ~15%
    - Bacteroides spp., Peptostreptococcus
  - GN aerobes
    - E.coli, Klebsiella spp., Pseudomonas spp., Haemophilus influenza
    - miscellaneous: Actino spp., Nocardia spp.
  - Not identified - 33%

Light et al. Am J Med 1980: 69: 507
Sahn ARRD: 1993: 148: 813

A word on catheter size

- No RCTs
- Tubes < 10F have failure rate up to 23% in patients with empyema
- Small bore (<=14F) tubes equivalent to larger bore tubes & causes less pain
- SITE is much more important than SIZE

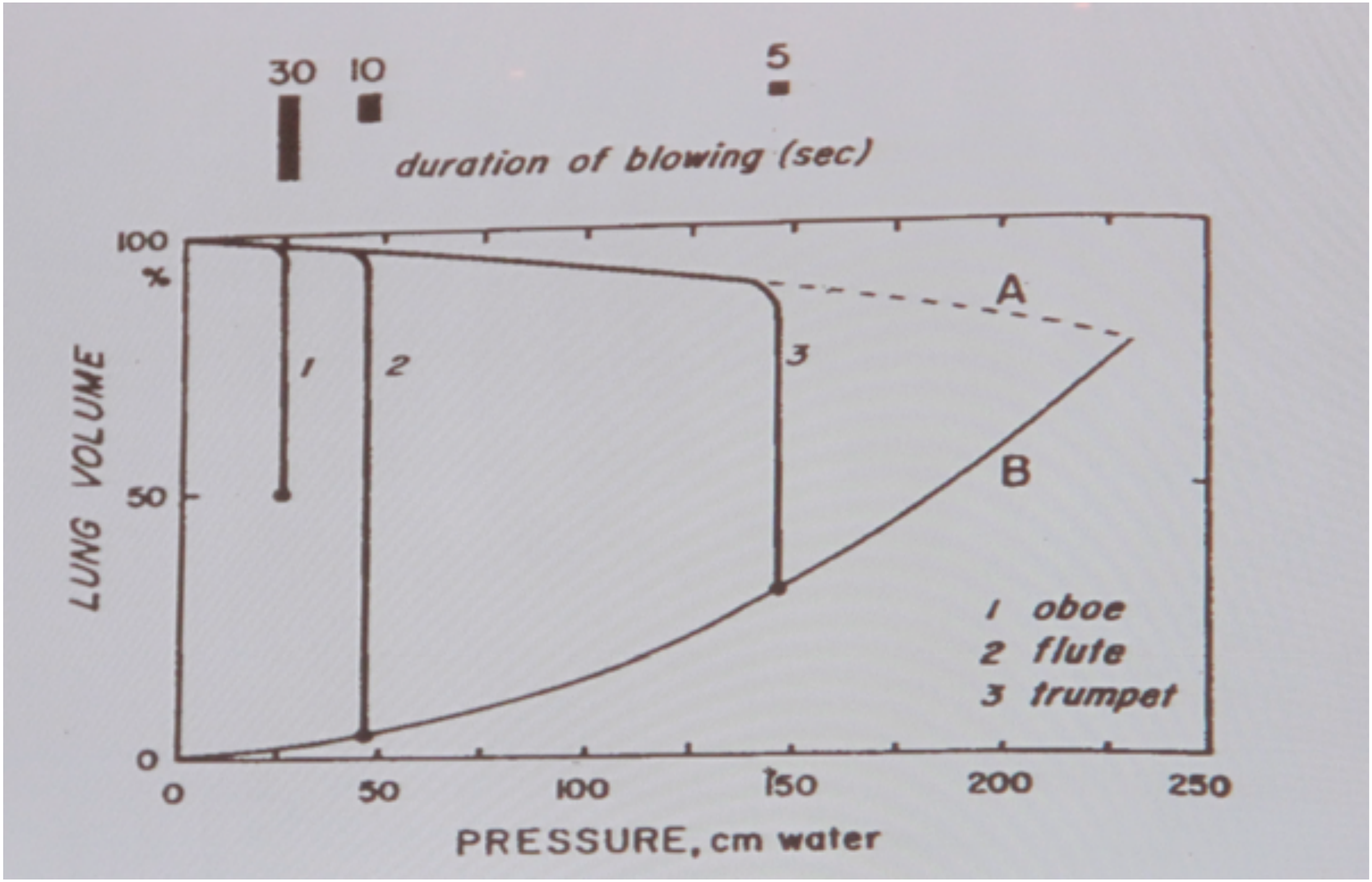
Davies et al. Thorax 2003: 58:183
Rahman et al. Chest 2010, 137:536

Cardiovascular

Intra-thoracic presure

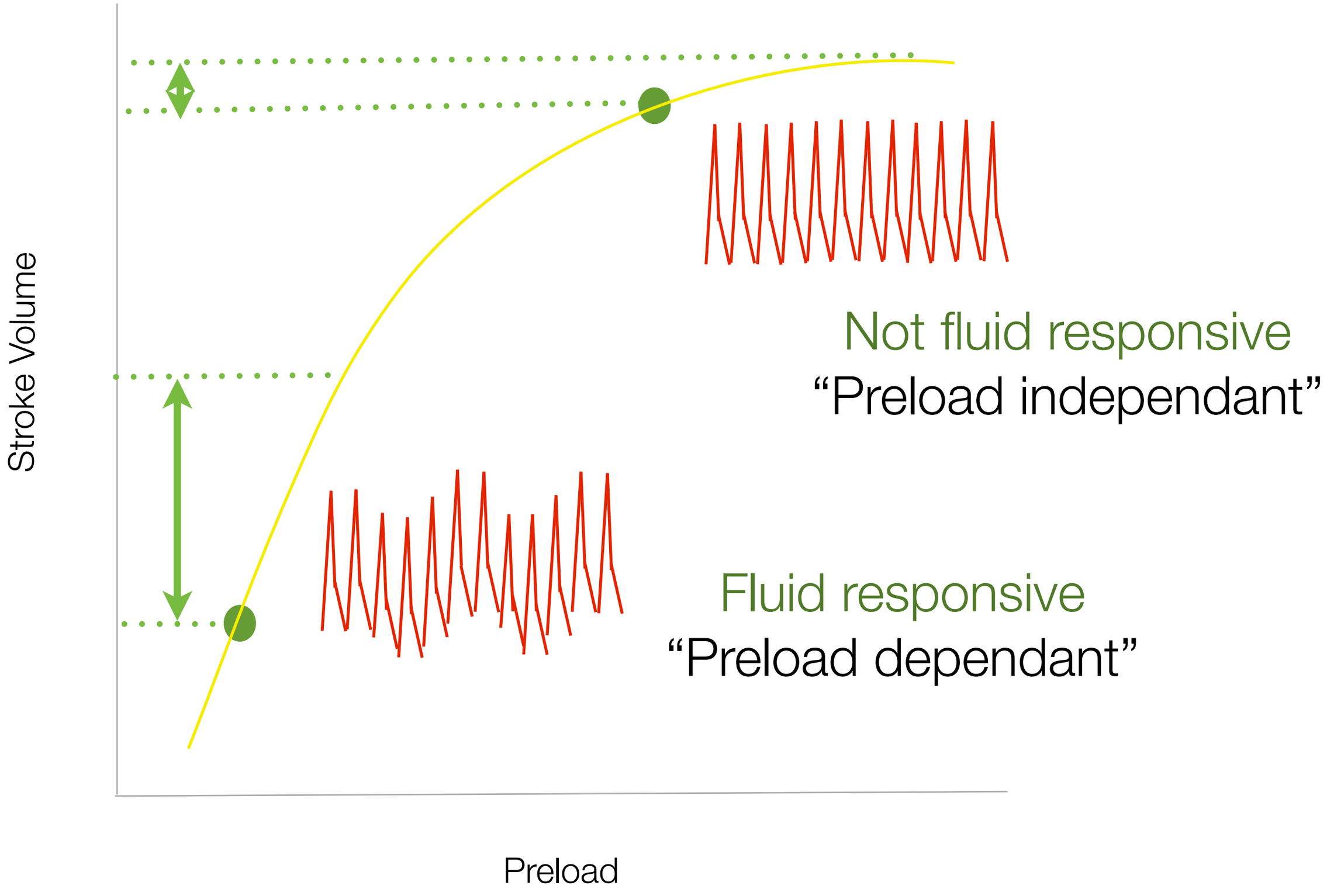
Nature 1969; 221 :
1199-1204

Intra-thoracic presure

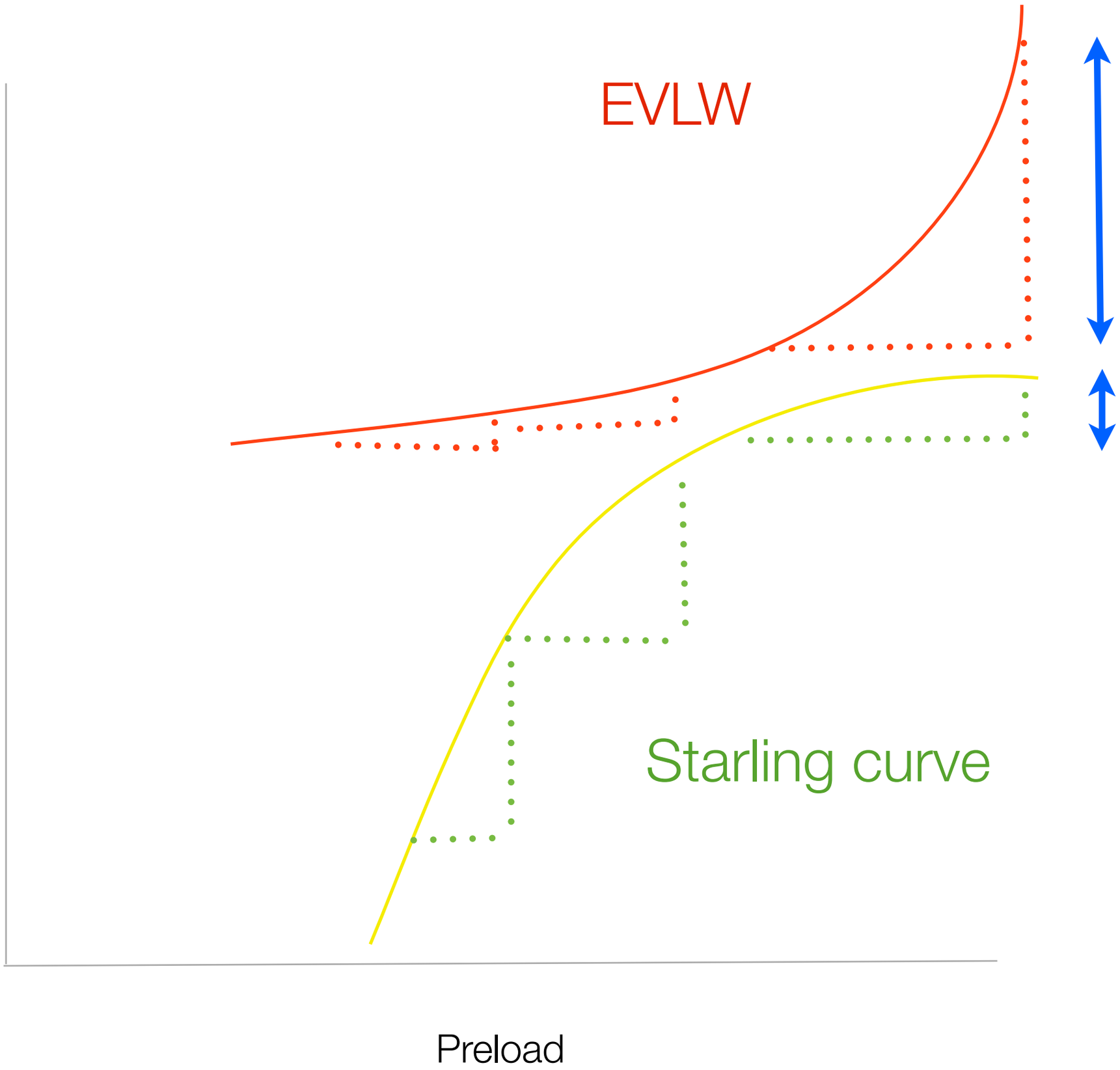


Nature 1969; 221 :
1199-1204

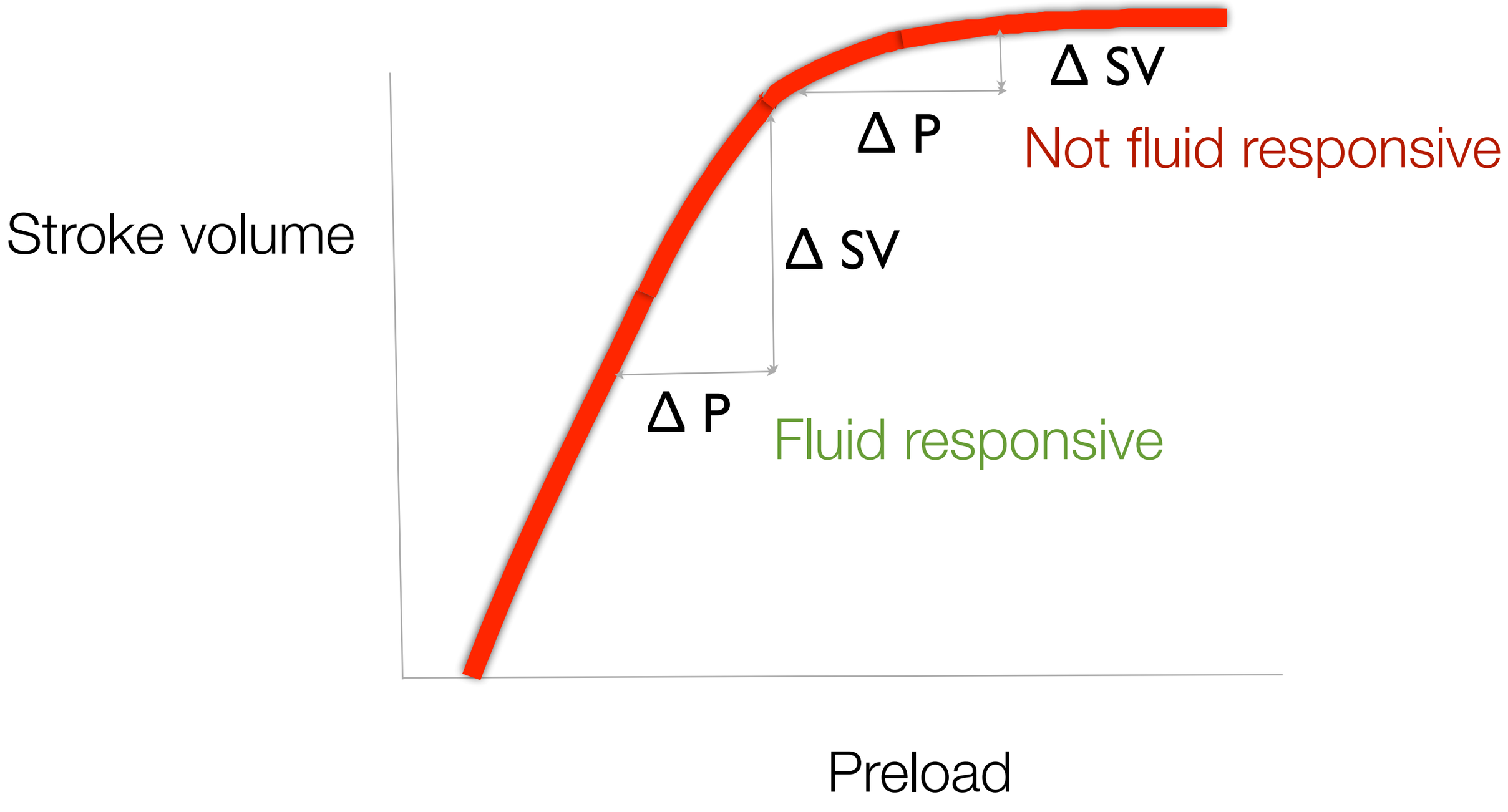
Preload Dependence Optimization



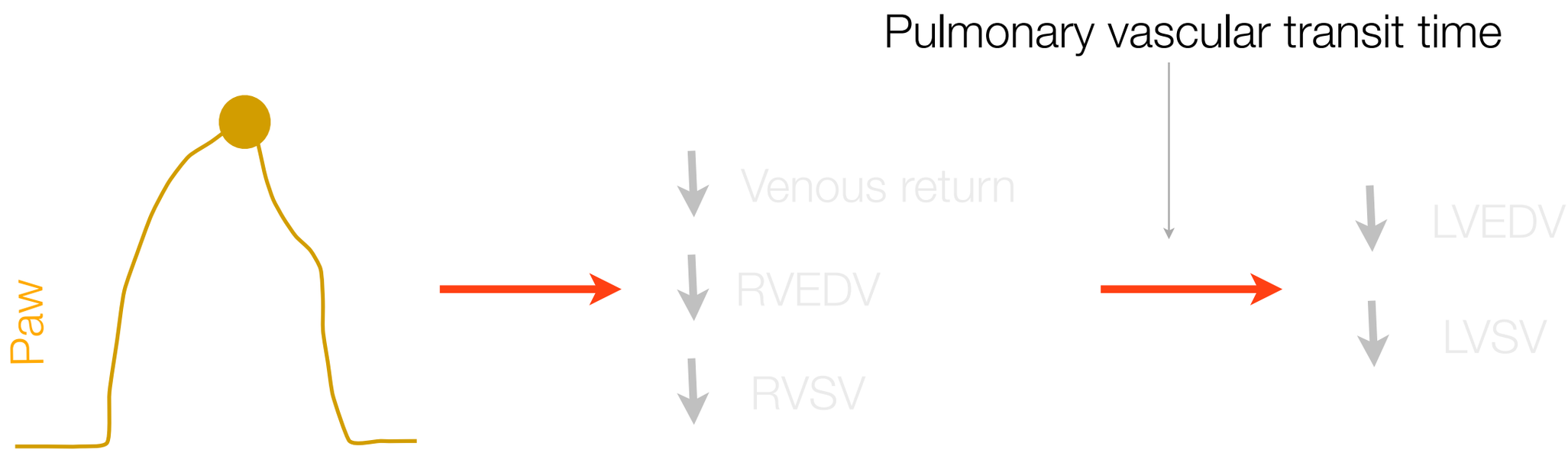
Why fluid responsiveness matters



Fluid responsiveness - means where is patient on the Starling curve?



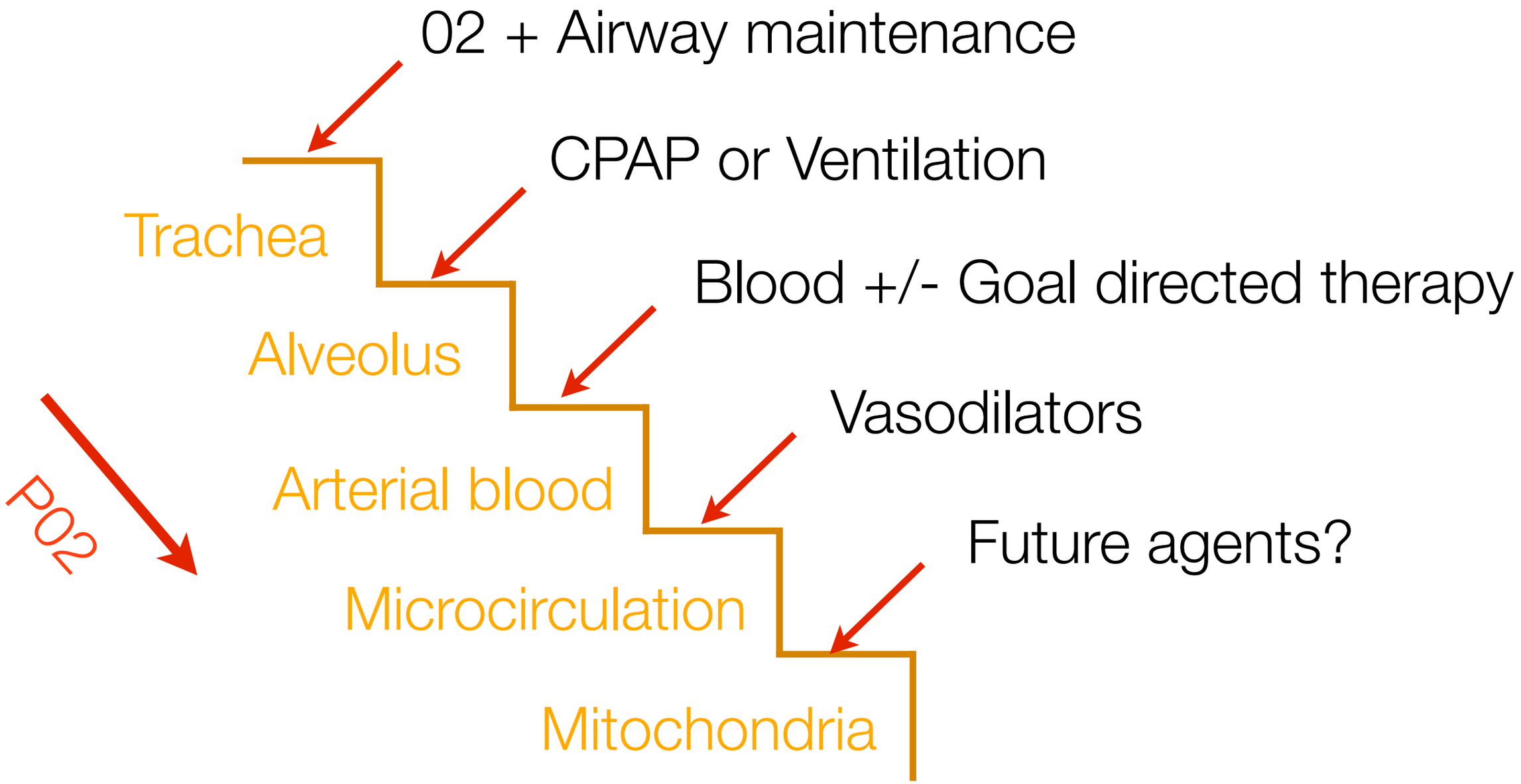
Mechanical Ventilation



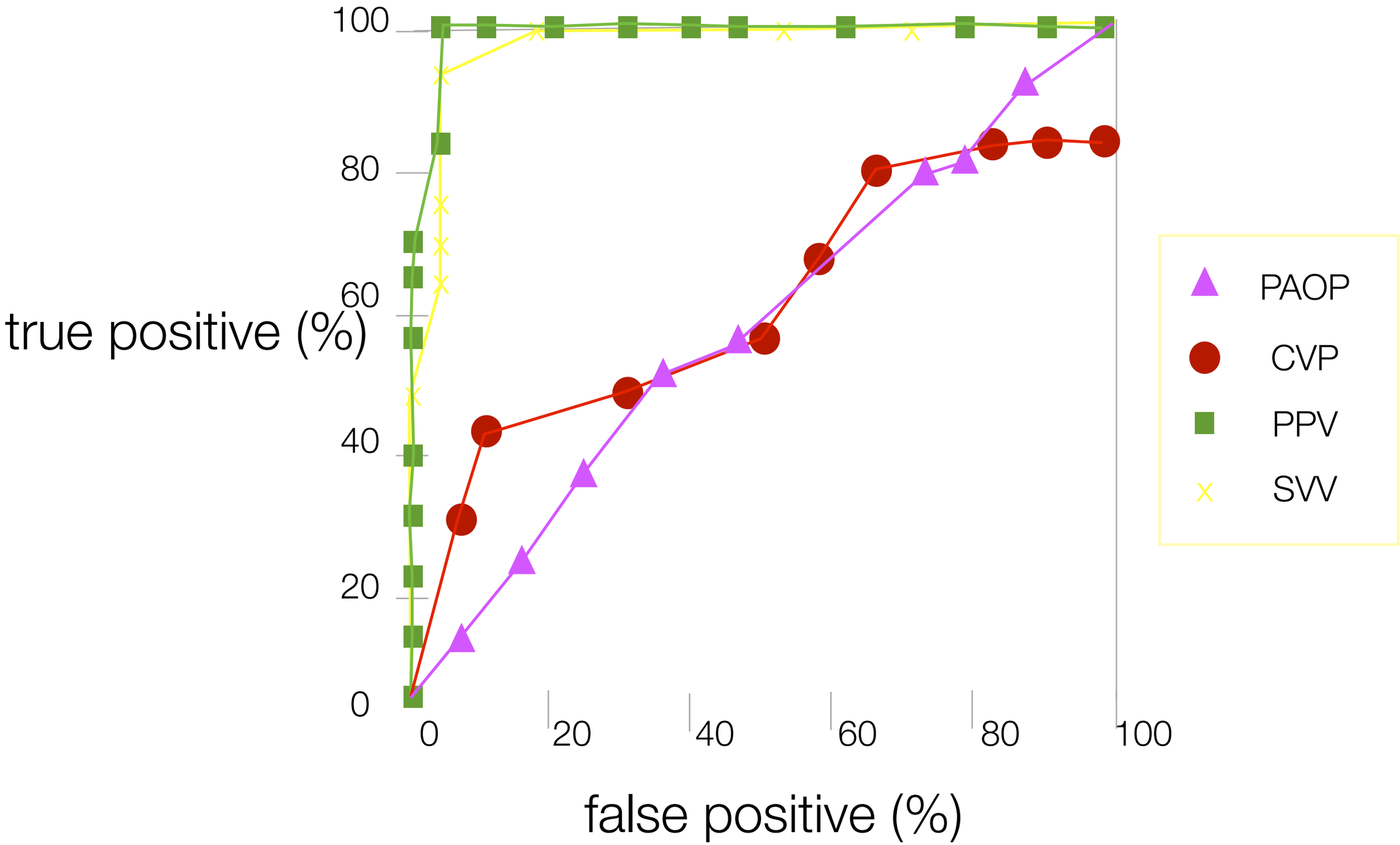
Respiratory variations in LV stroke volume

Static parameters vs. Dynamic parameters

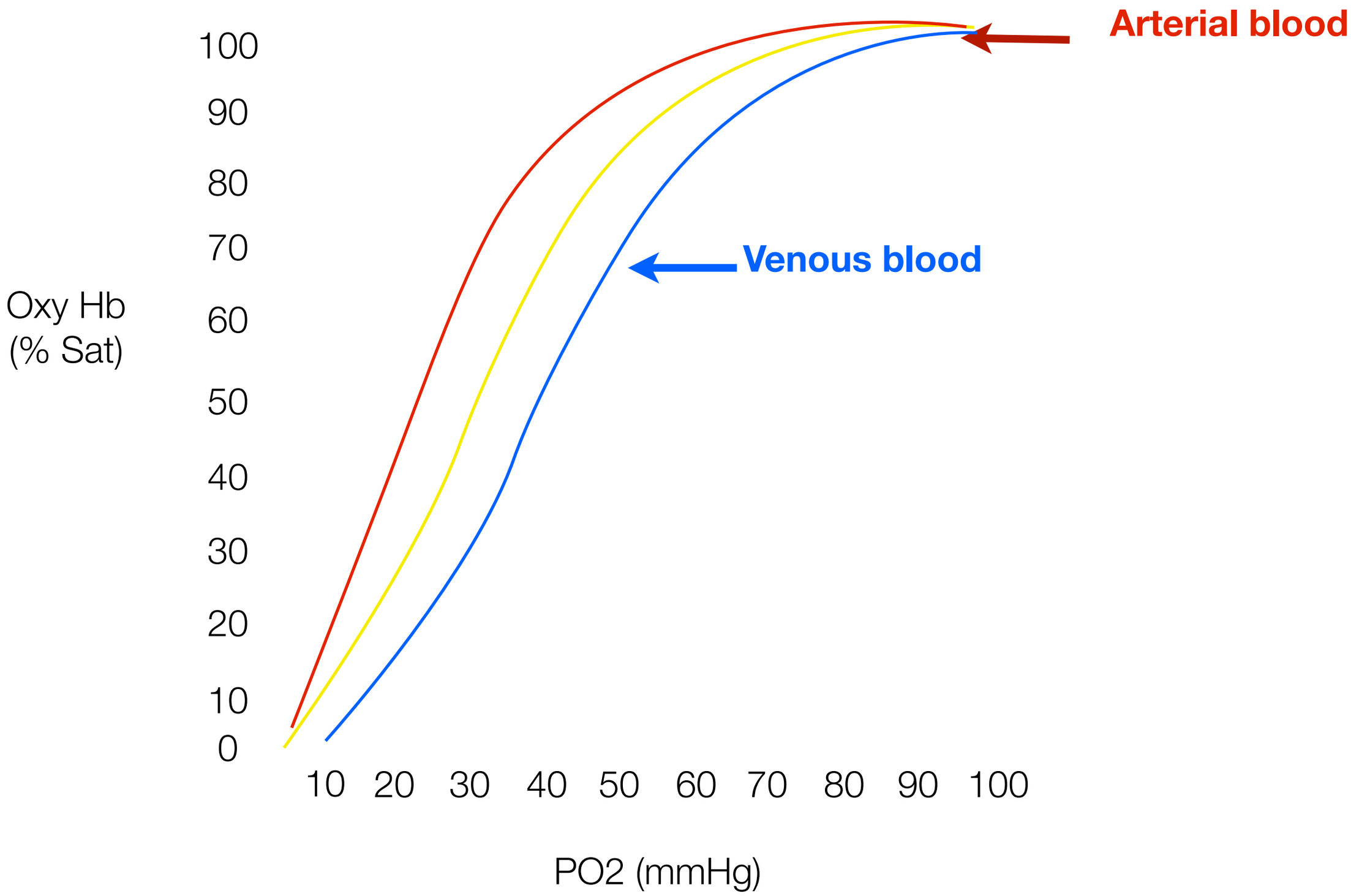
Maximising 02 delivery : O2 Cascade



Let’s recap, what works ?



Effect of shift in O2 dissociation curve on arterial and venous 02 saturation

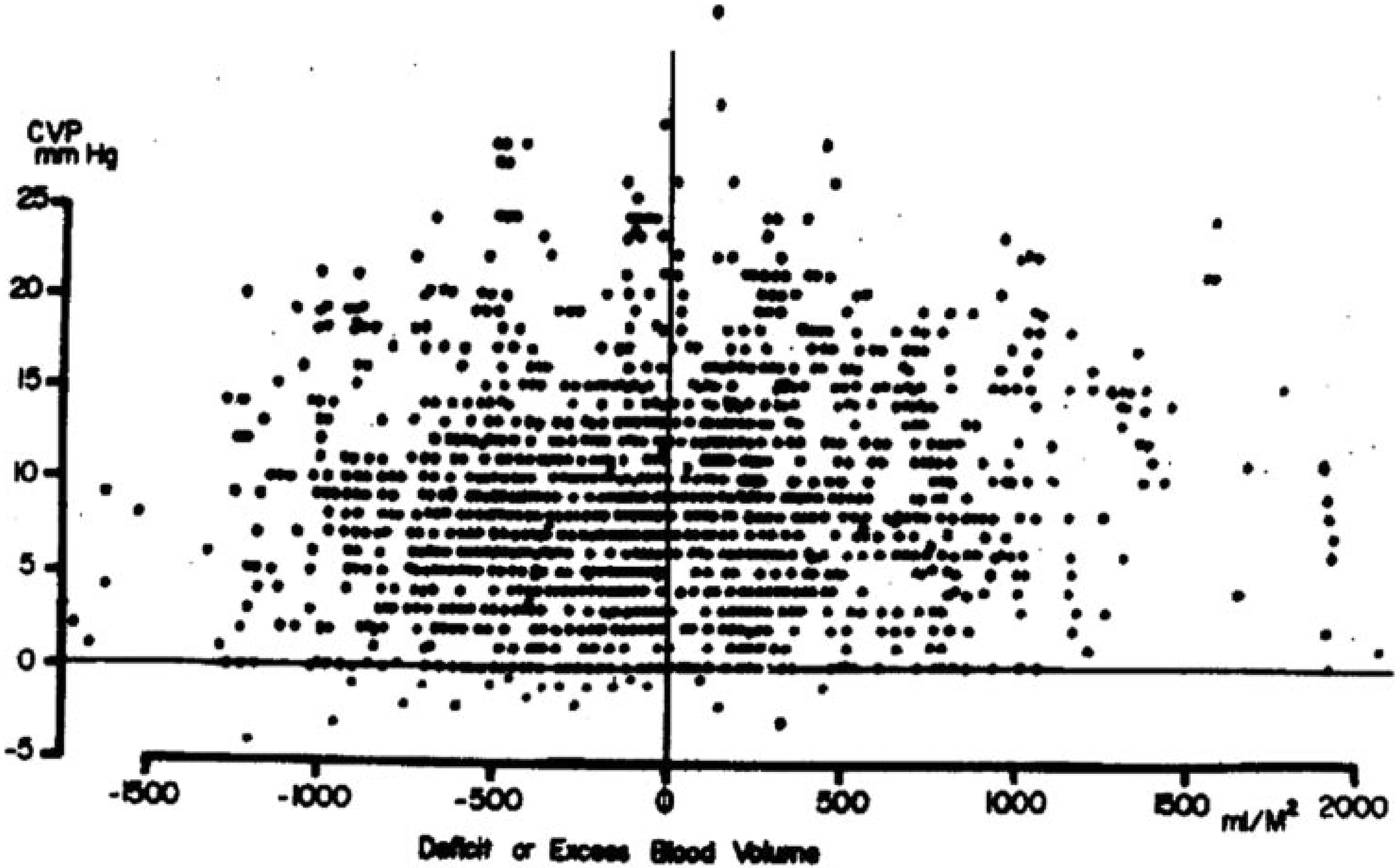


Predicting fluid responsiveness in ICU patients

	Responders/Non-responders	% Responders
Calvin (Surgery 81)	20/8	71%
Schneider (Am Heart J 88)	13/5	72%
Reuse (Chest 90)	26/15	63%
Magder (J Crit Care 92)	17/16	52%
Diebel (Arch Surg 92)	13/9	59%
Diebel (J Trauma 94)	26/39	40%
Wagner (Chest 98)	20/16	56%
Tavernier (Anesthesiology 98)	21/14	60%
Magder (J Crit Care 99)	13/16	45%
Tousignant (A Analg 00)	16/24	40%
Michard (AJRCCM 00)	16/24	40%
Feissel (Chest 01)	10/9	53%
Mean	211/195	52%

Michard & Teboul. Chest 121:2000-8, 2002

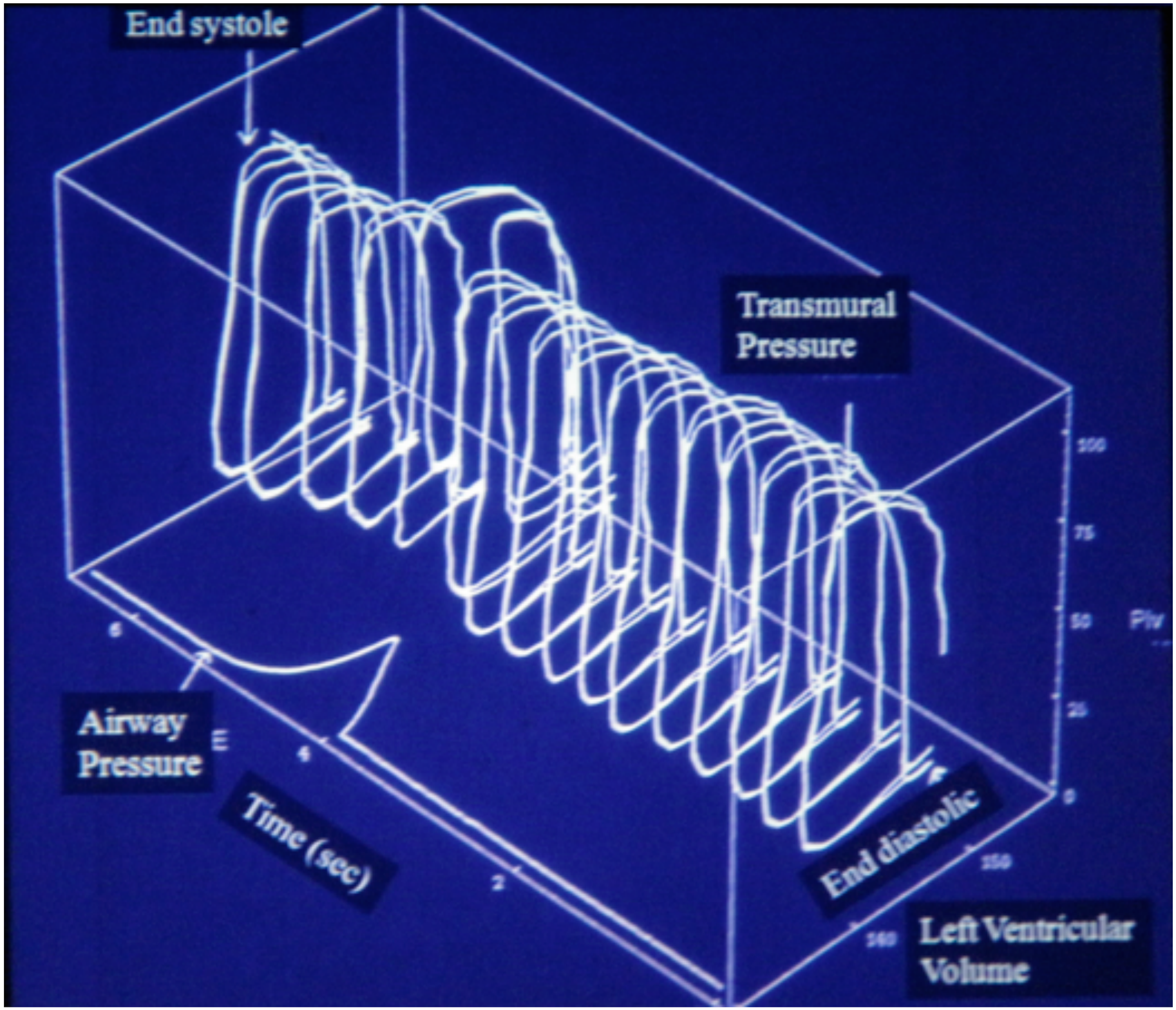
1500 simultaneous measurements of blood volume and CVP in a cohort of 188 ICU patients demonstrating <u>no association</u>



(r=0.27)

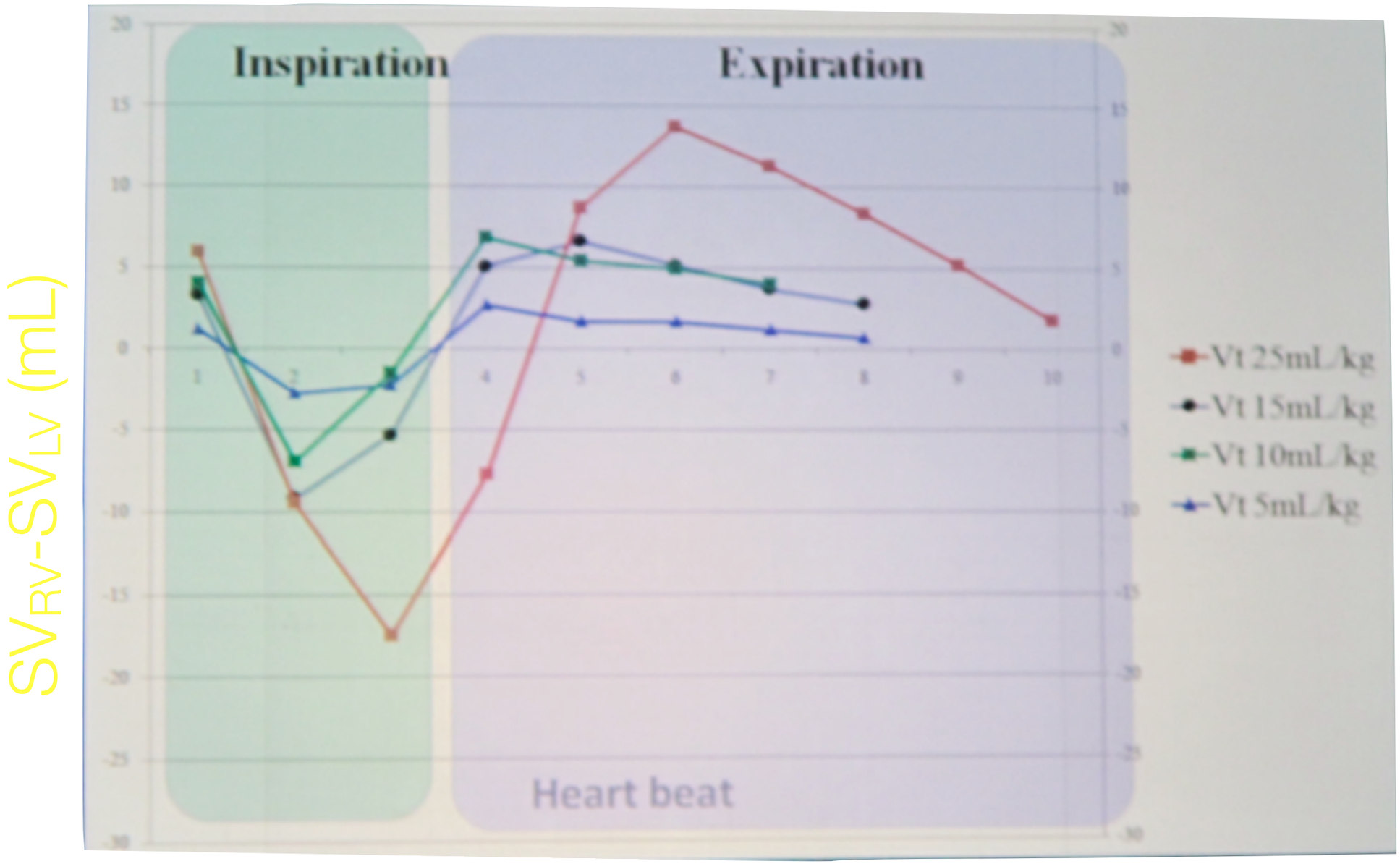
Marik et al. Chest 134:172-178, 2008

Pressure-volume loops during positive pressure ventilation



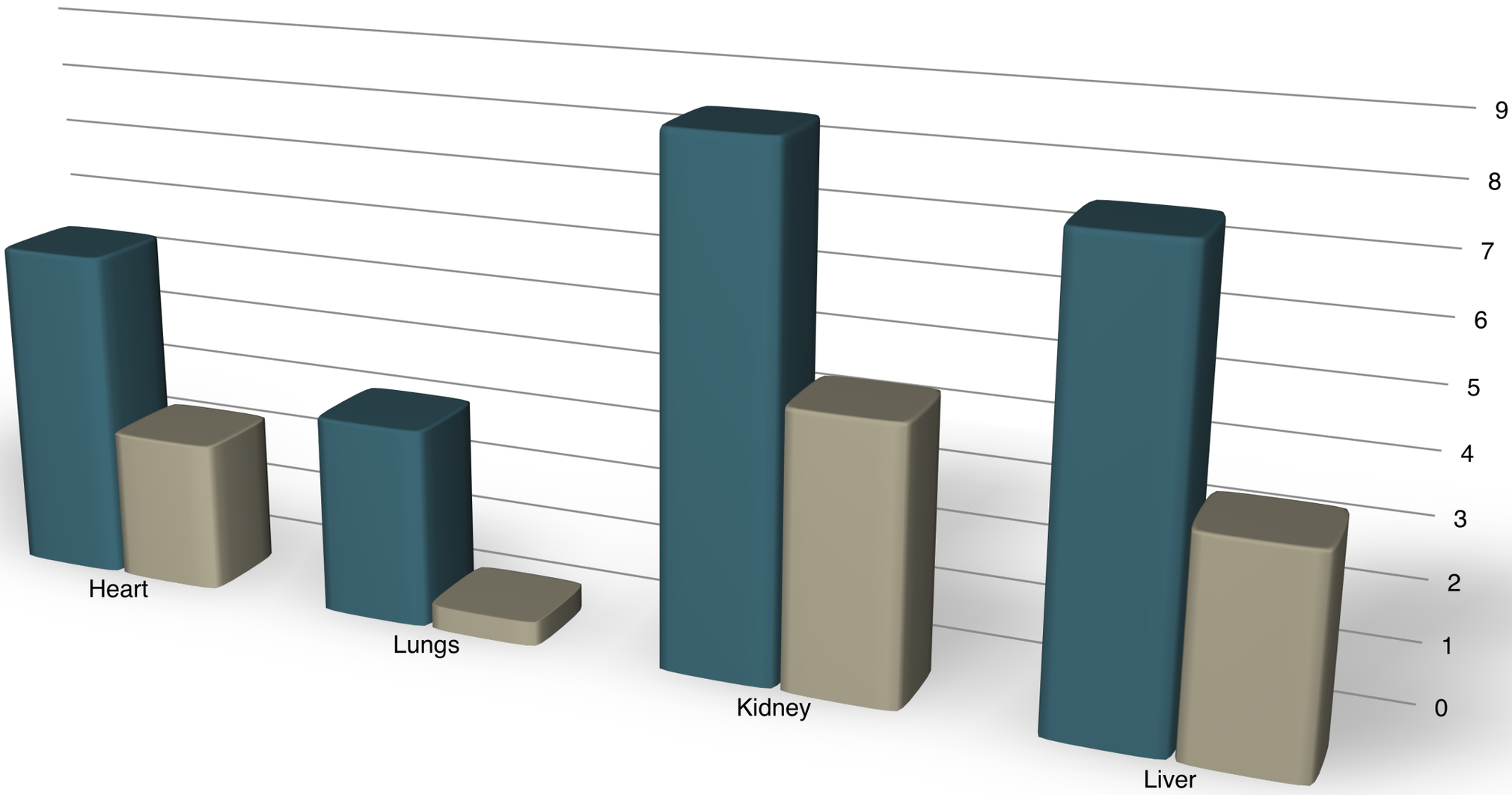
Denault et al. J Appl Physiol 91:298-308, 2001

Effect of tidal volume on the dynamic intrathoracic blood volume shifts



Pinsky et al. J Appl Physiol 56:765-71, 1984
Mesquida, Kim, Pinsky preliminary data

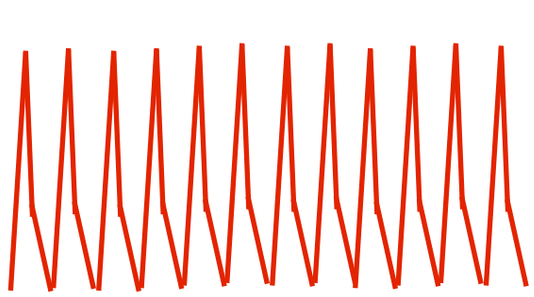
Preload responsiveness is associated with lower organ yield from brain-dead donors



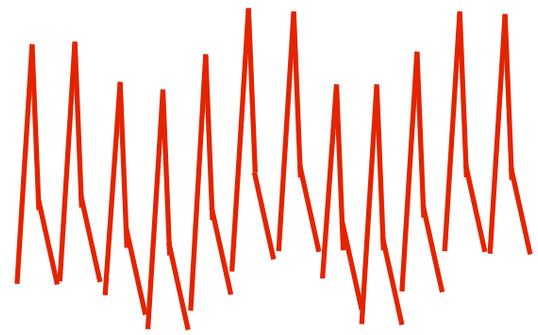
Murugan et al. Crit Care Med 2009

Cardiopulmonary interactions

"The more sensitive a ventricle is to preload, the more the stroke volume will be impacted by changes in preload due to positive pressure ventilation"



Preload independant

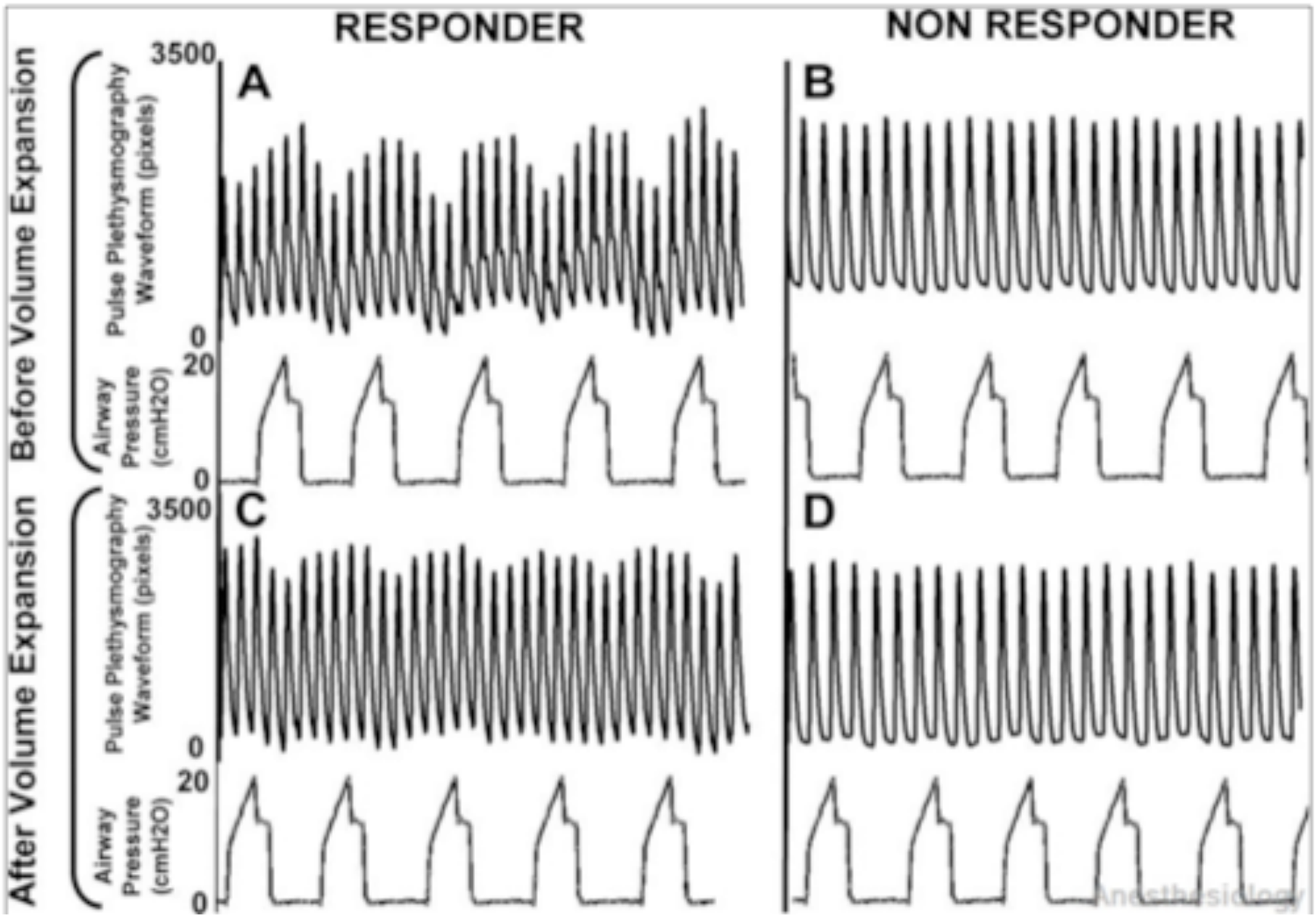


Preload dependant

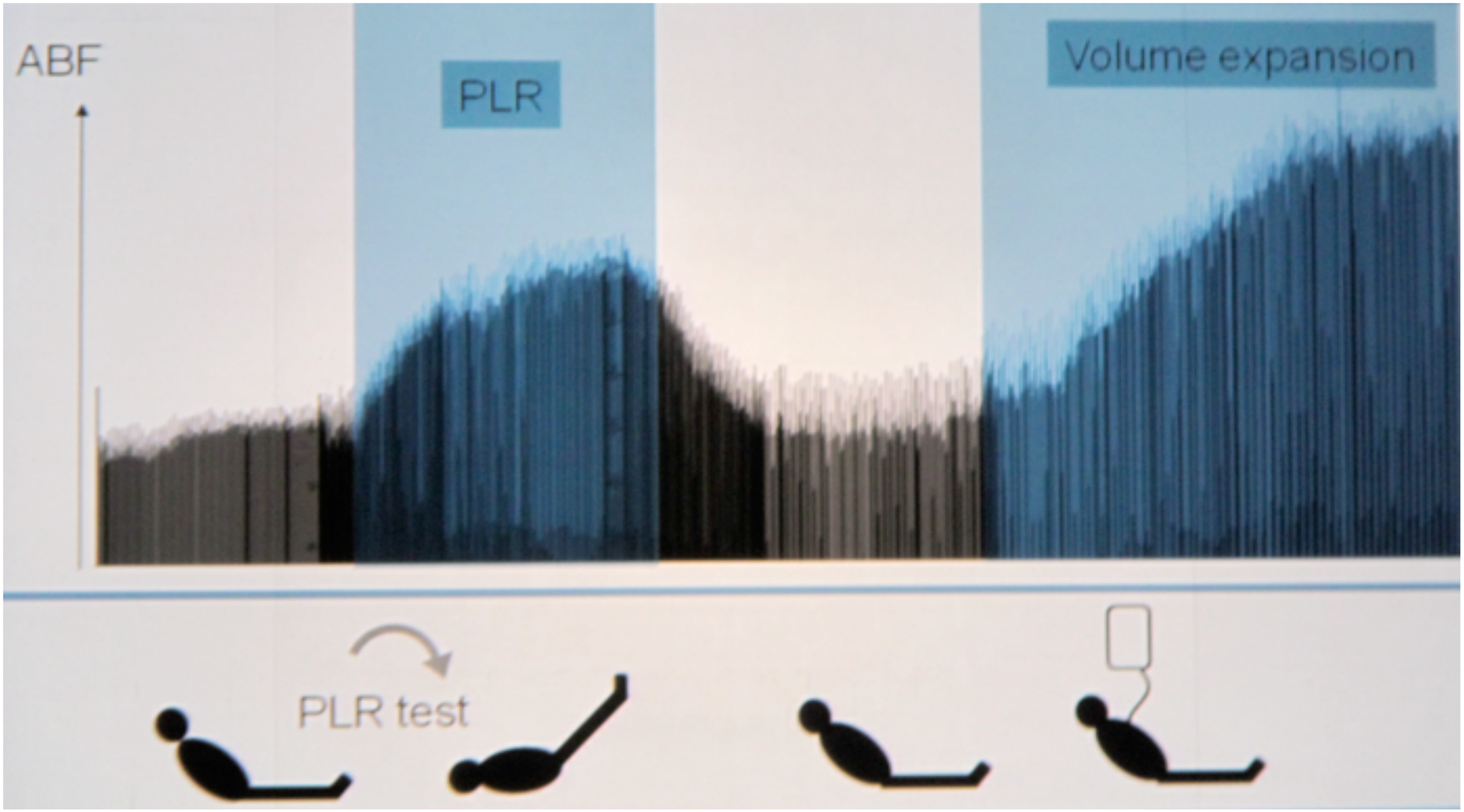
$$\Delta SV = \frac{SVmax - SVmin}{(SVmax + SVmin)/2}$$

Murugan et al. Crit Care Med 2009

Respiratory Variations in Pulse Oximetry Plethysmographic Waveform Amplitude to Predict Fluid Responsiveness in the Operating Room



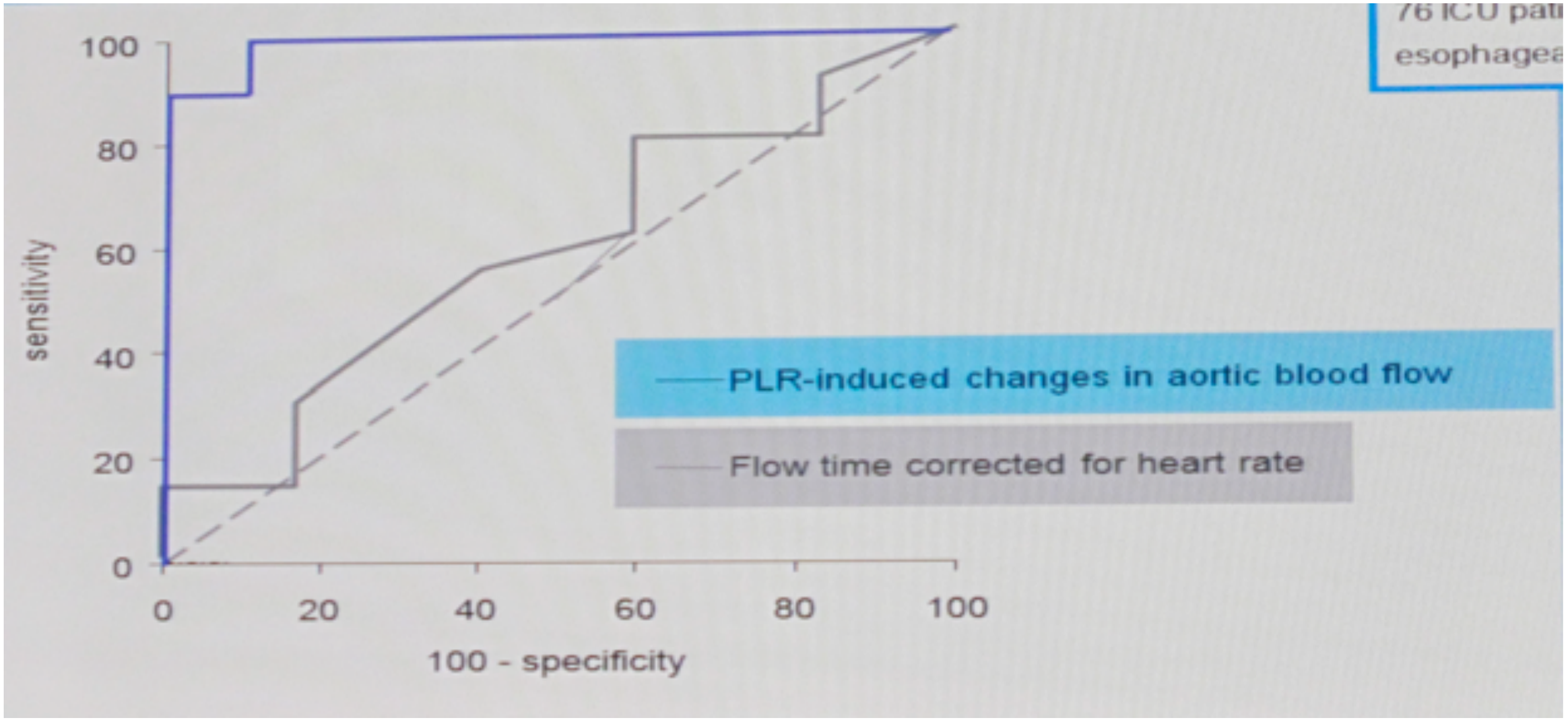
Passive leg raising - an alternative for predicting fluid responsiveness



Fluid therapy in Resuscitated Sepsis
Less is more

- When given additional fluid, some patients will respond... other patients will not: hemodynamics fail to improve and the fluid bolus is ineffective, at best.
- Moreover, ineffective fluid challenges often lead to additional boluses, culminating in a grossly edematous patient (still hypotensive and oliguric)
- When patient has indications for a fluid bolus (and)...if there is reasonable potential for harm, a dynamic predictor should be used to limit fluid infusion only to patients who will benefit.

Passive leg raising vs. oesophageal doppler



Monnet et al. CCM 2006

Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: A systematic review of the literature*

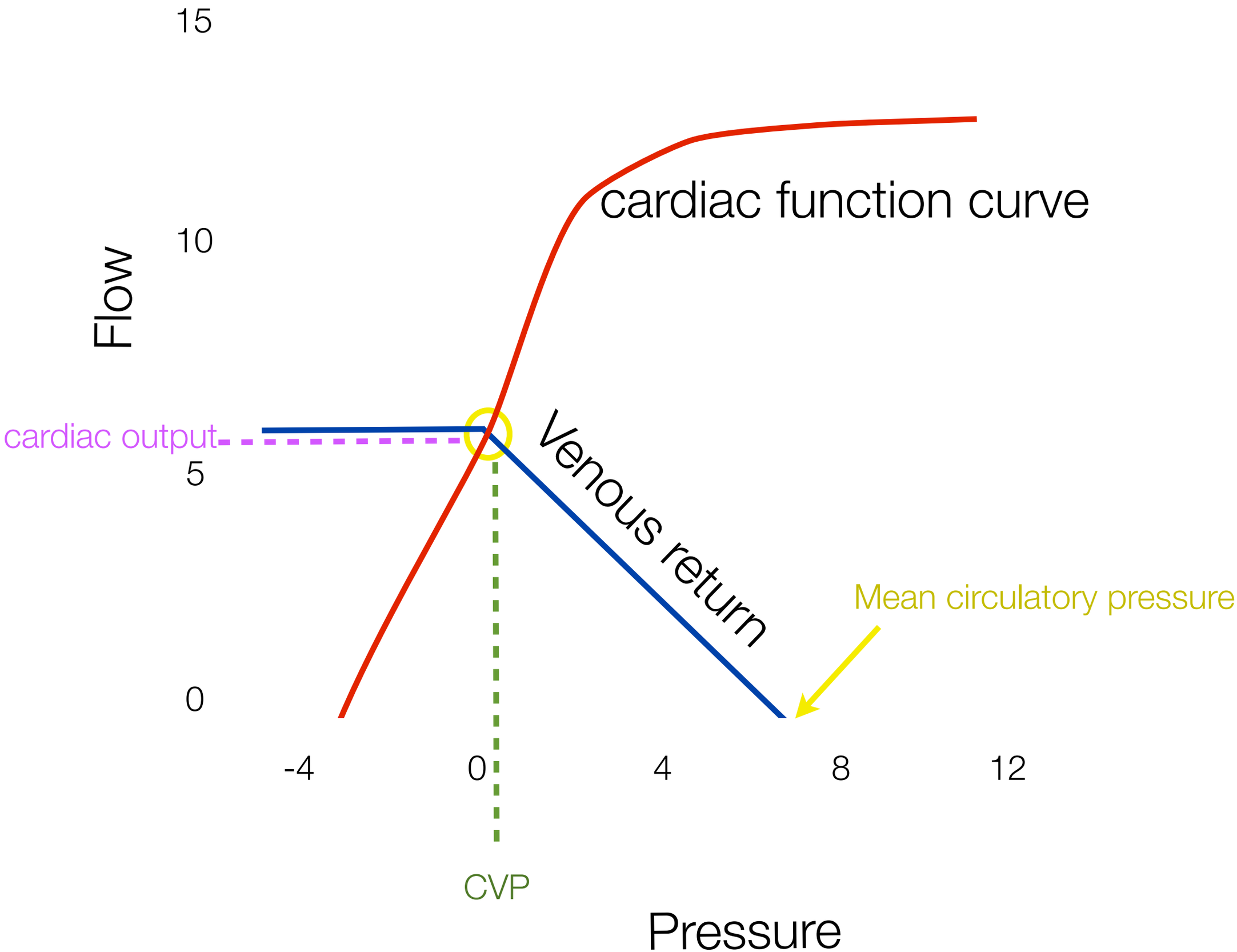
Paul E. Marik, MD, FCCM; Rodrigo Cavallazzi, MD; Tajender Vasu, MD; Amyn Hirani, MD

				Dynamic Variable		
Author	Year	n	Patient	SPV	PPV	SVV
Tavernier (31)	1998	15	ICU-sepsis	Y	N	N
Michard (32)	1999	14	ICU-ARDS	N	Y	N
Michard (33)	2000	40	ICU-sepsis	Y	Y	N
Berkenstadt (34)	2001	15	Neurosurg[a]	N	N	Y
Reuter (35)	2002	20	Post C.Surg	Y	N	Y
Reuter (36)	2002	20	Post C.Surg	N	N	Y
Reuter (37)	2003	12	Post C.Surg-a	N	N	Y
		14	Post C.Surg-b			
Bendjelid (38)	2004	16	Post C.Surg	Y	Y	N
Rex (39)	2004	14	Post C.Surg	N	N	Y
Kramer (40)	2004	21	Post C.Surg	Y	Y	N
Marx (41)	2004	10	ICU-sepsis	N	N	Y
Hofer (42)	2005	35	Post C.Surg	N	Y	Y
Preisman (43)	2005	18	Post C.Surg	Y	Y	Y
De Backer (44)[d]	2005	27	ICU-mixed	N	Y	N
Wiesenack (45)	2005	20	C.Surg[a]	N	Y	Y
Feissel (46)	2005	20	ICU-sepsis	N	Y	N
Solus-Biguenet (47)	2006	8	Hepatic surgery	N	Y	N
Charron (48)	2006	21	ICU-mixed	N	Y	N
Natalini (49)	2006	22	ICU-mixed	Y	Y	N
Wyffels (50)	2007	32	Post C.Surg	N	Y	N
Feissel (51)	2007	23	ICU-sepsis	N	Y	N
Lee (52)	2007	20	Neurosurg[a]	N	Y	N
Cannesson (53)	2007	25	C.Surg[a]	N	Y	N
Cannesson (54)	2008	25	C.Surg[a]	N	Y	N
Auler (55)	2008	59	Post C.Surg	N	Y	N
Belloni (56)	2008	19	C.Surg[a]	Y	Y	Y
Cannesson (57)	2008	25	C.Surg[a]	N	Y	N
Hofer (58)	2008	40	Post CABG	N	Y	Y
Biasis (59)	2008	35	Liver transplant	N	Y	Y

→ High level of evidence

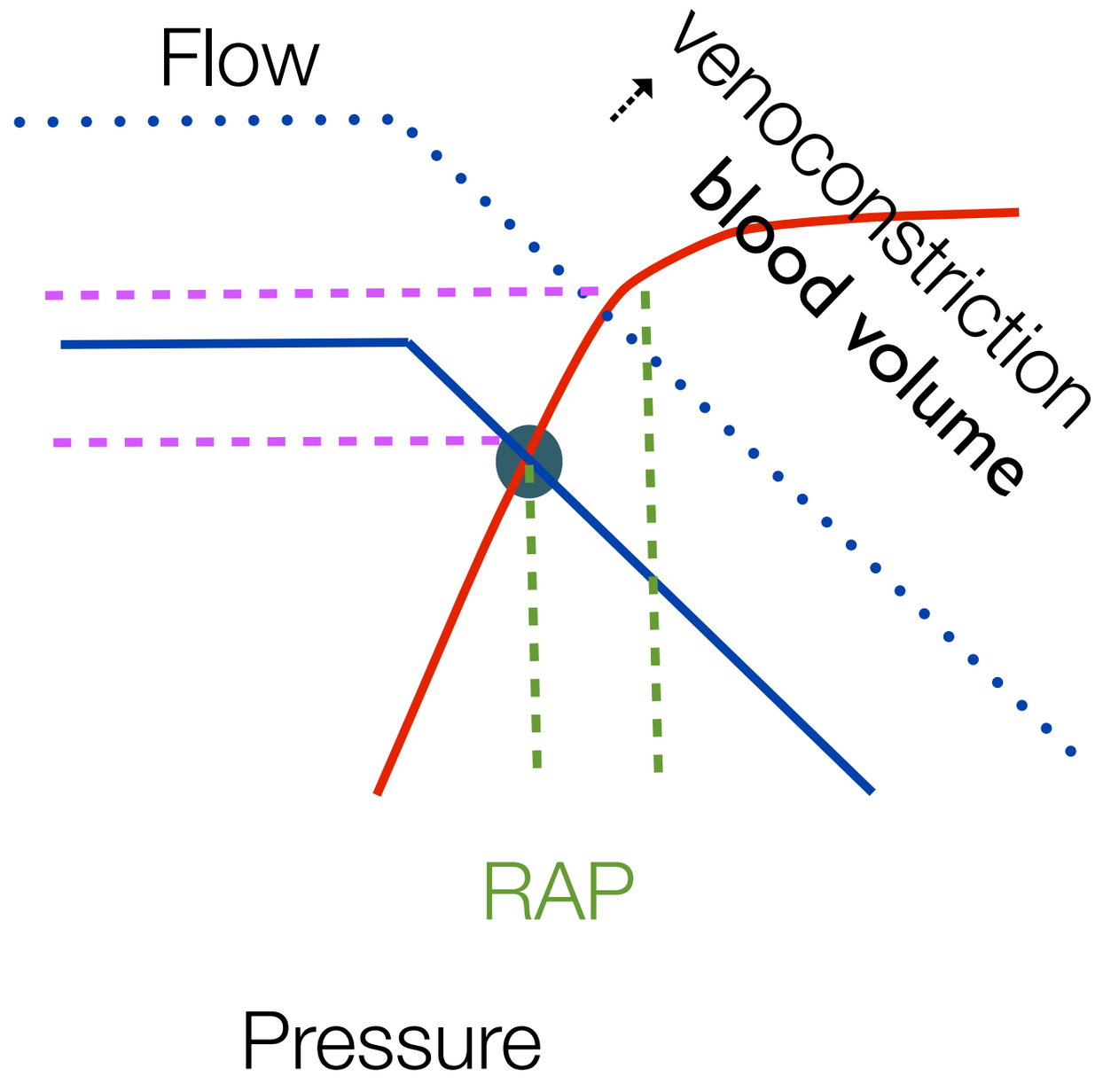
Meta-analysis of 29 studies, 685 patients

Starling meets Guyton



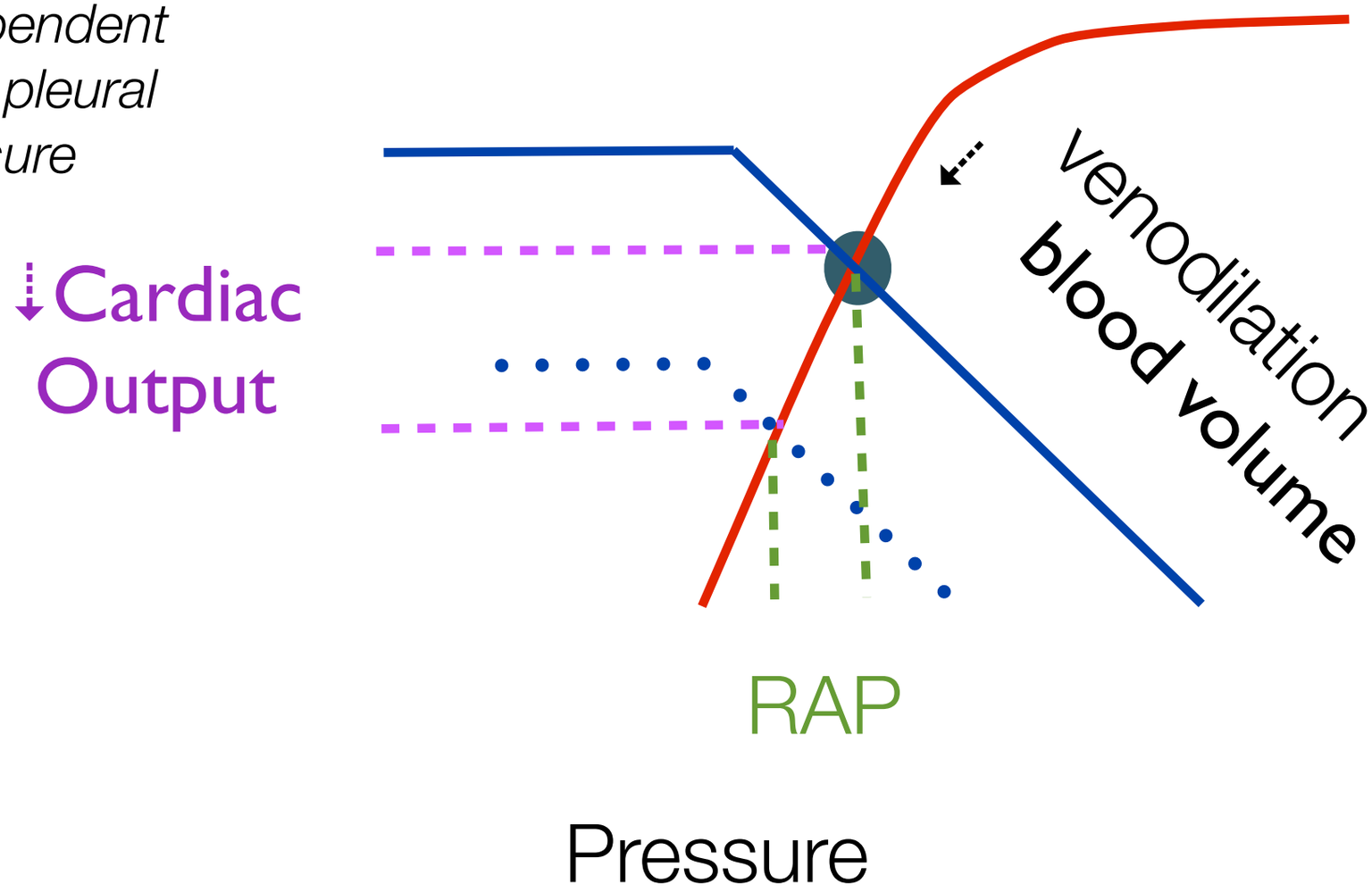
Increase in cardiac output by venoconstriction or increased blood volume

Is dependent on intracavity pressure, (which "opposes" blood flowing from the extra-thoracic capillaries and veins). It is independent from the pleural pressure



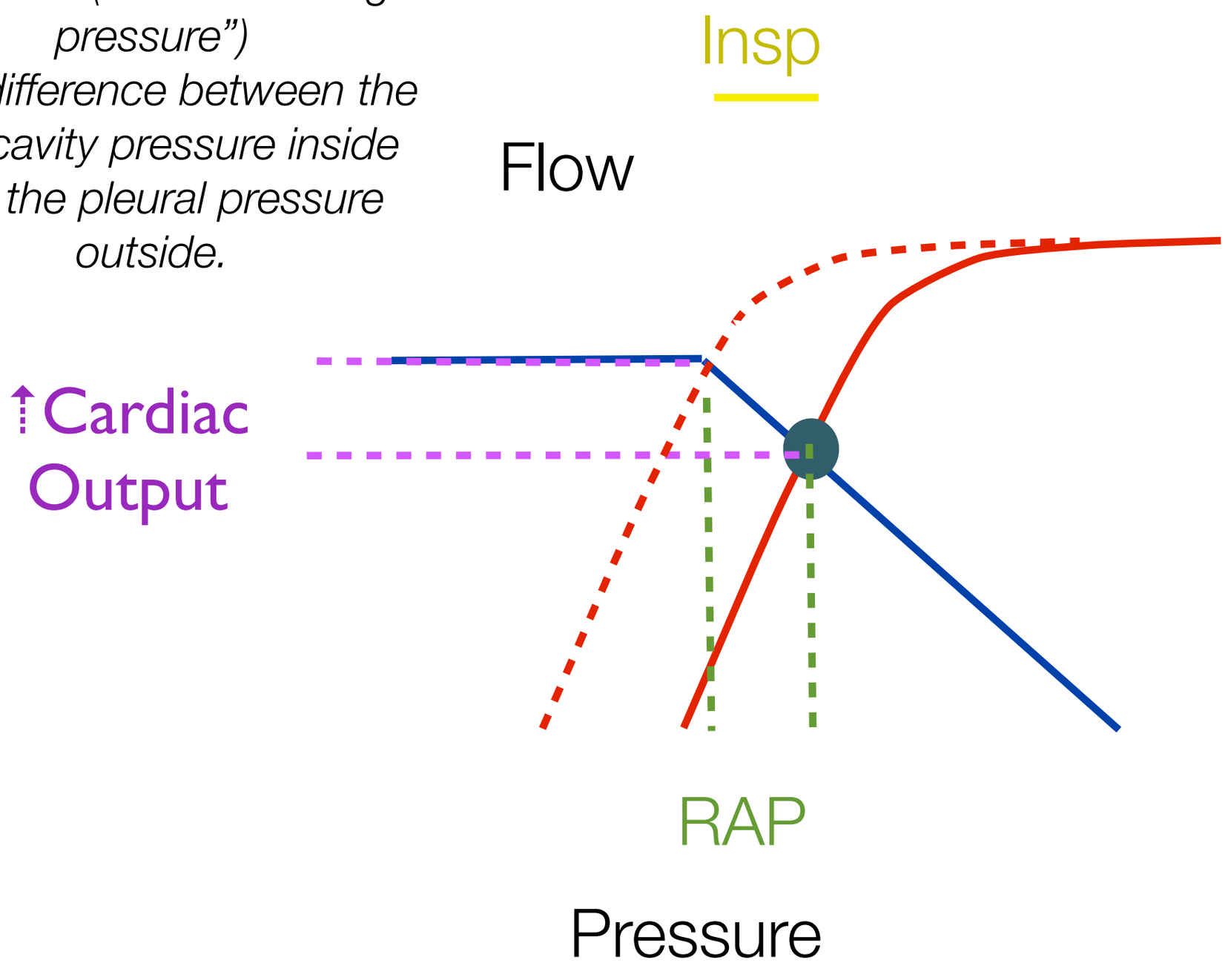
<u>Decrease</u> in cardiac output by venodilation or decreased blood volume

Is dependent on intracavity pressure, (which "opposes" blood flowing from the extra-thoracic capillaries and veins). It is independent from the pleural pressure



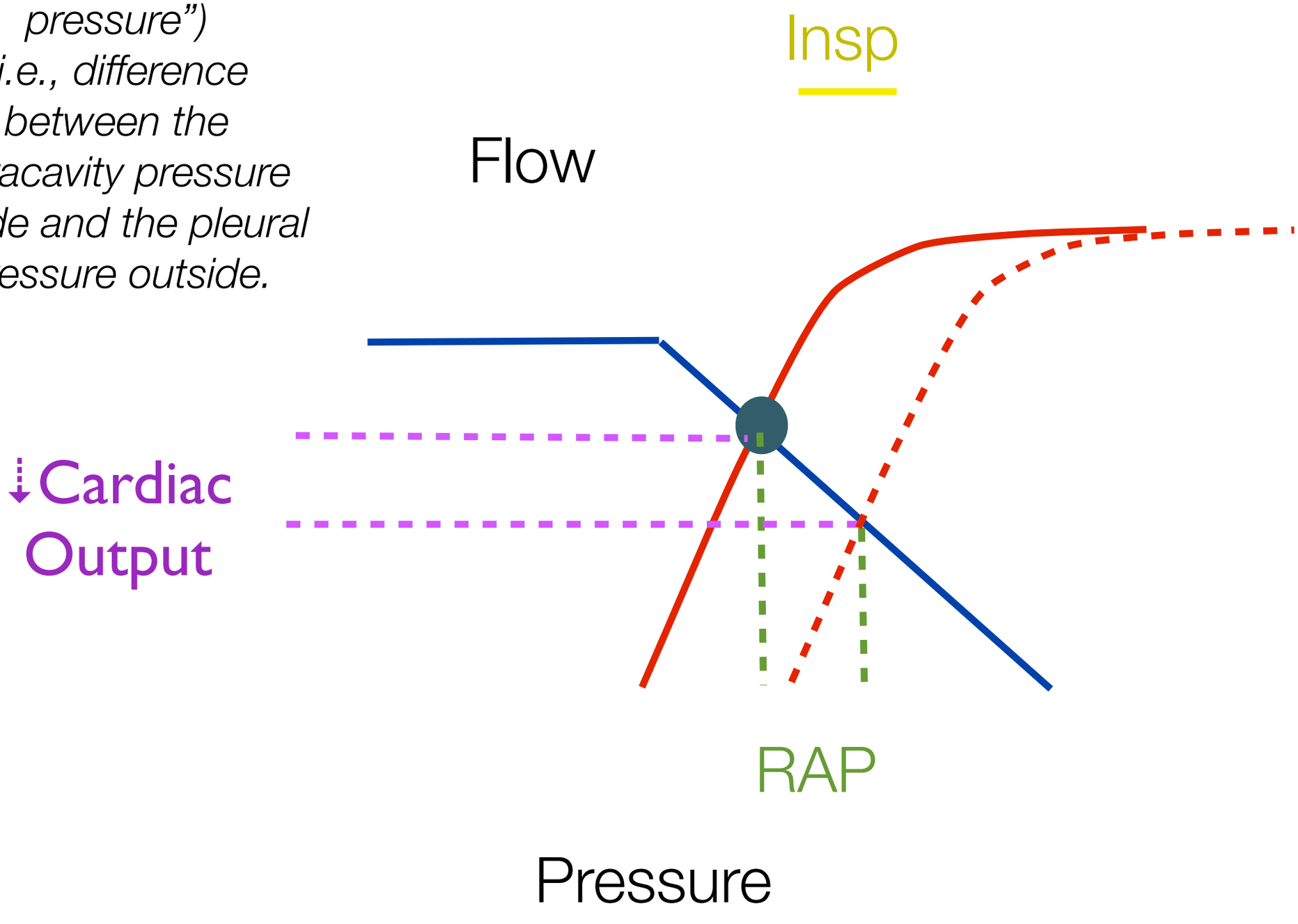
Shift in Starling curve with <u>negative</u> inspiratory pleural pressure

Is dependent on <u>transmural</u> pressure (the "distending pressure")
i.e., difference between the intracavity pressure inside and the pleural pressure outside.

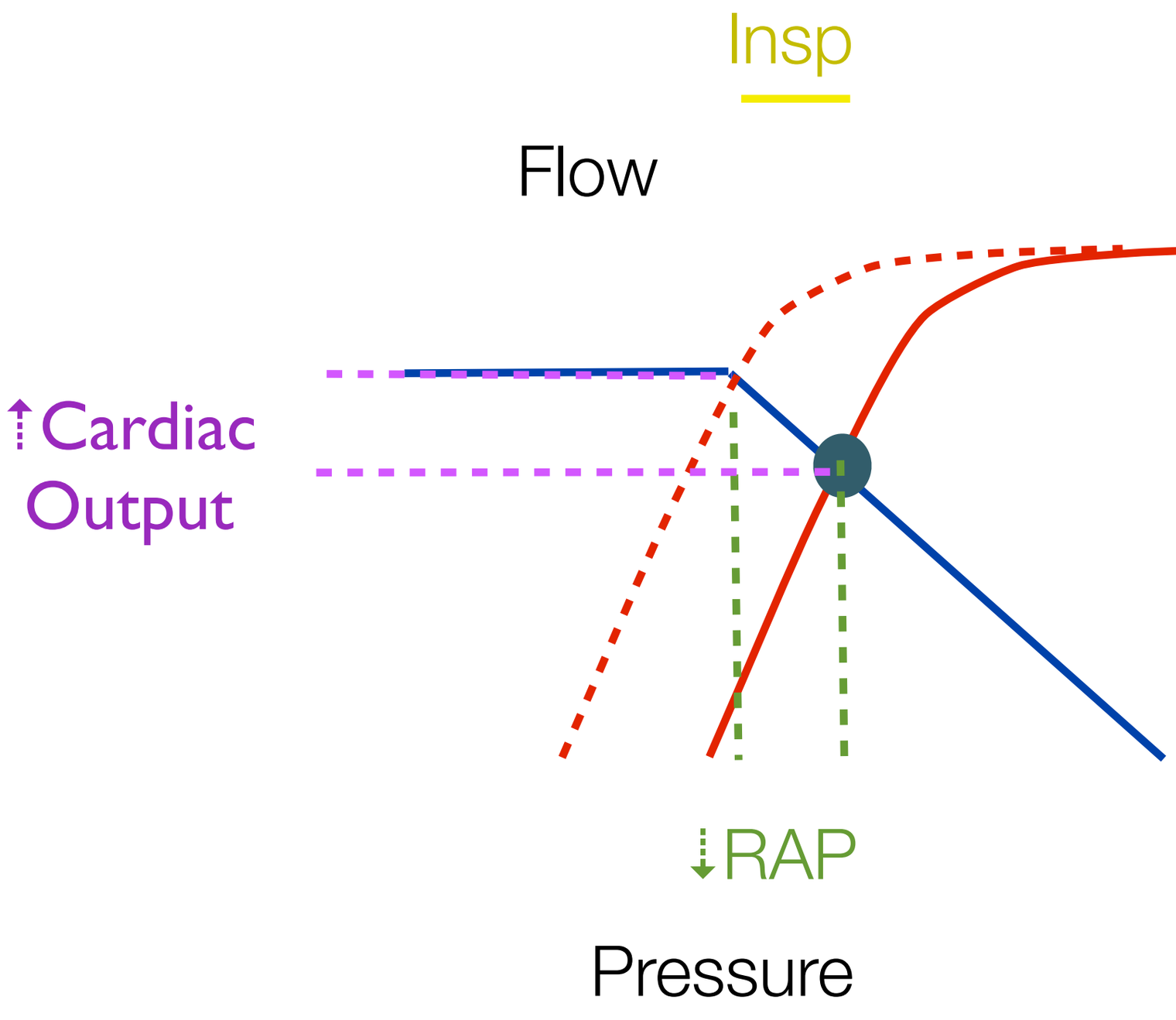


Shift in Starling curve with <u>positive</u> inspiratory pleural pressure

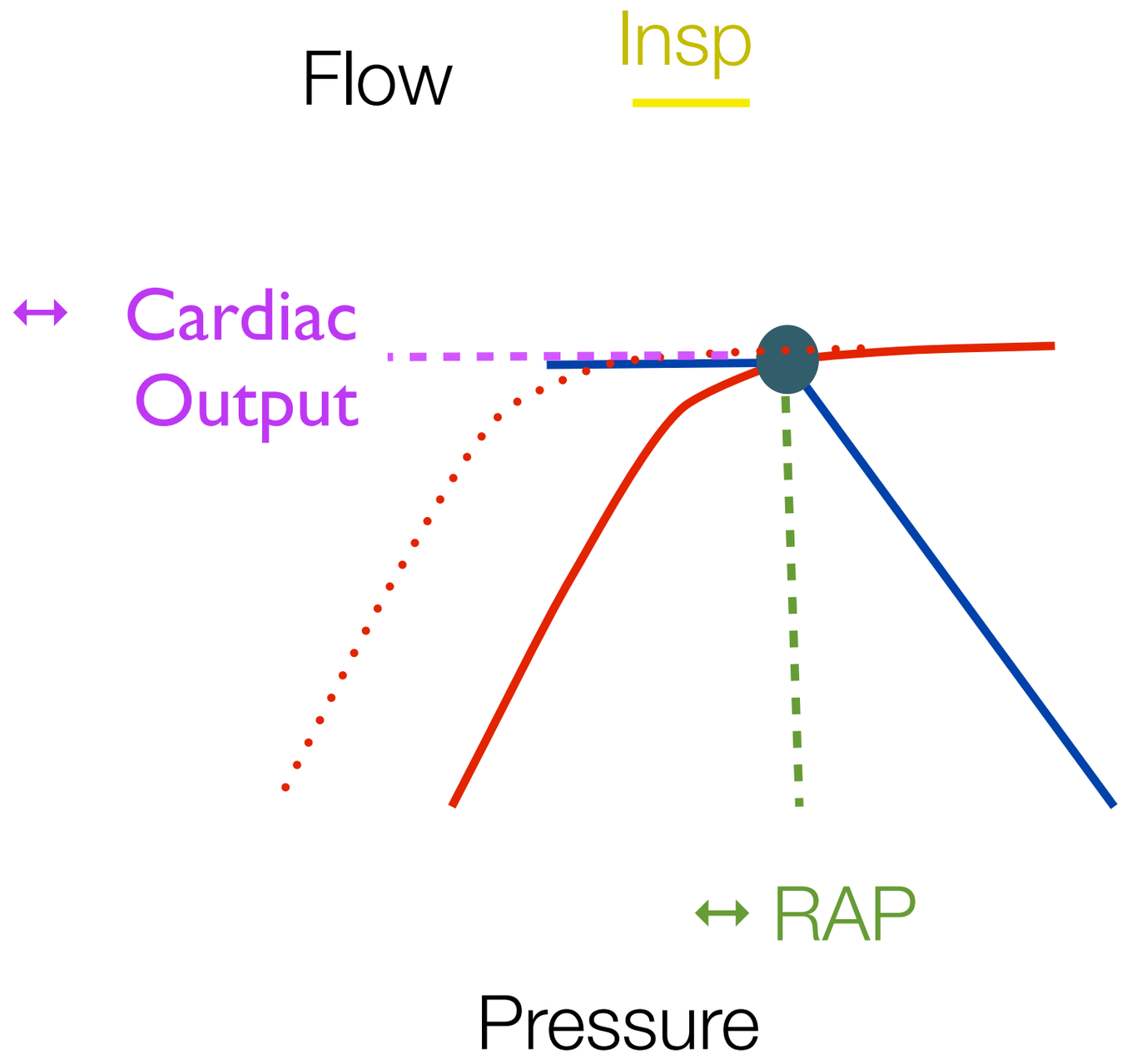
Is dependent on <u>transmural</u> pressure (the "distending pressure") i.e., difference between the intracavity pressure inside and the pleural pressure outside.



CVP and spontaneous ventilation - Fluid responsive



CVP and spontaneous ventilation - Fluid unresponsive



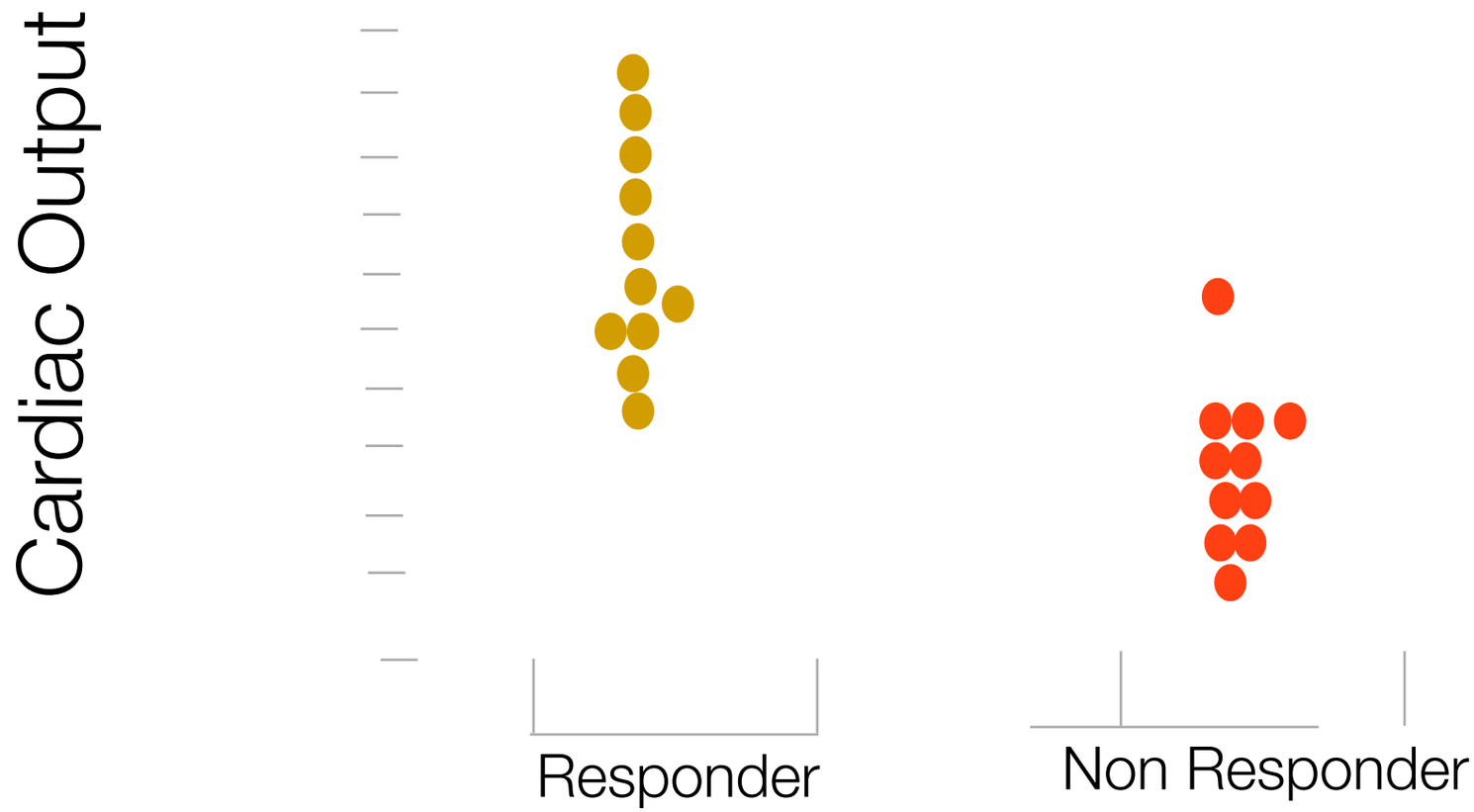
Respiratory variations in CVP predict response to fluid challenge in spontaneous breathing patients

Inspiratory fall in CVP

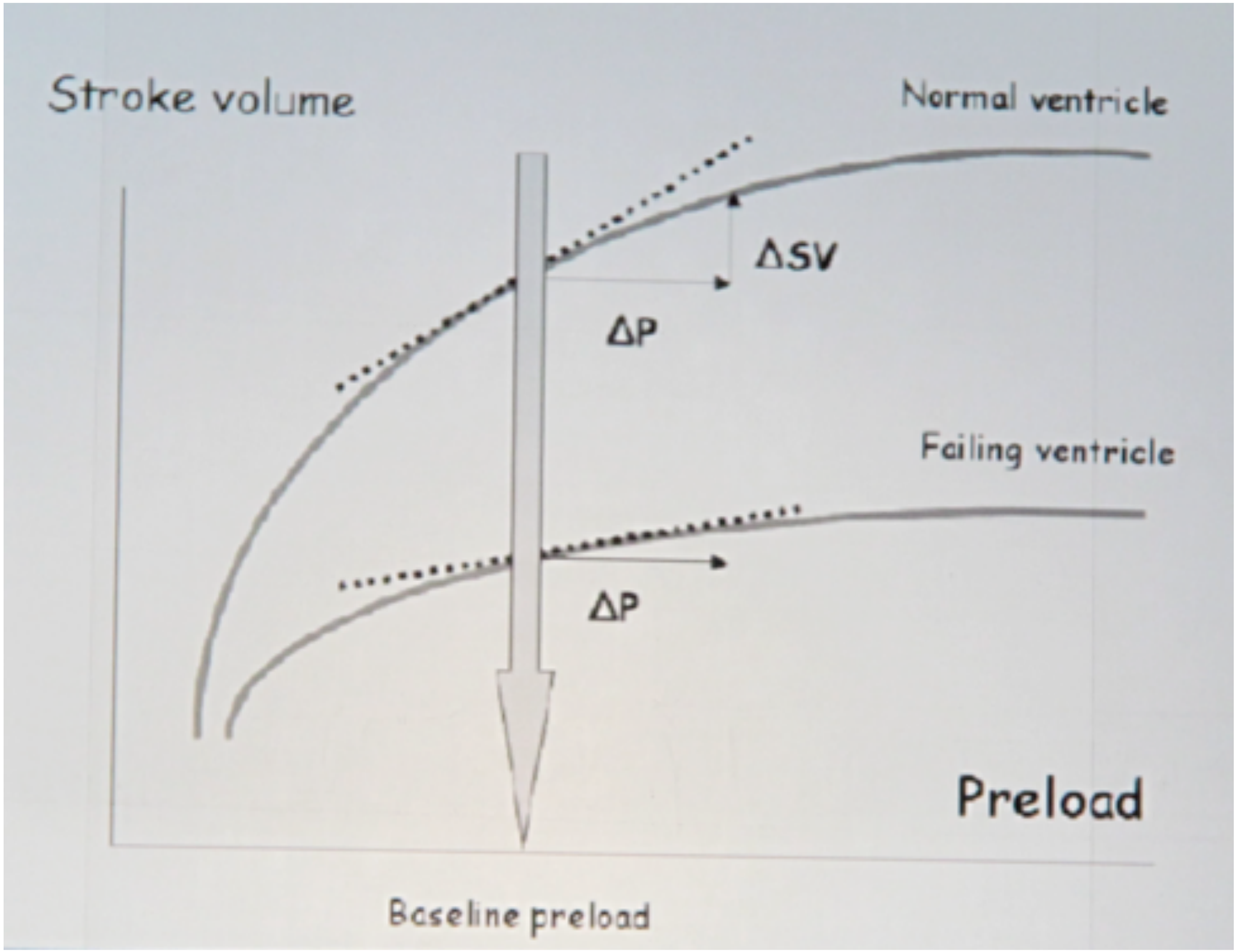
CO increased in 16/19 pts

No inspiratory fall in CVP

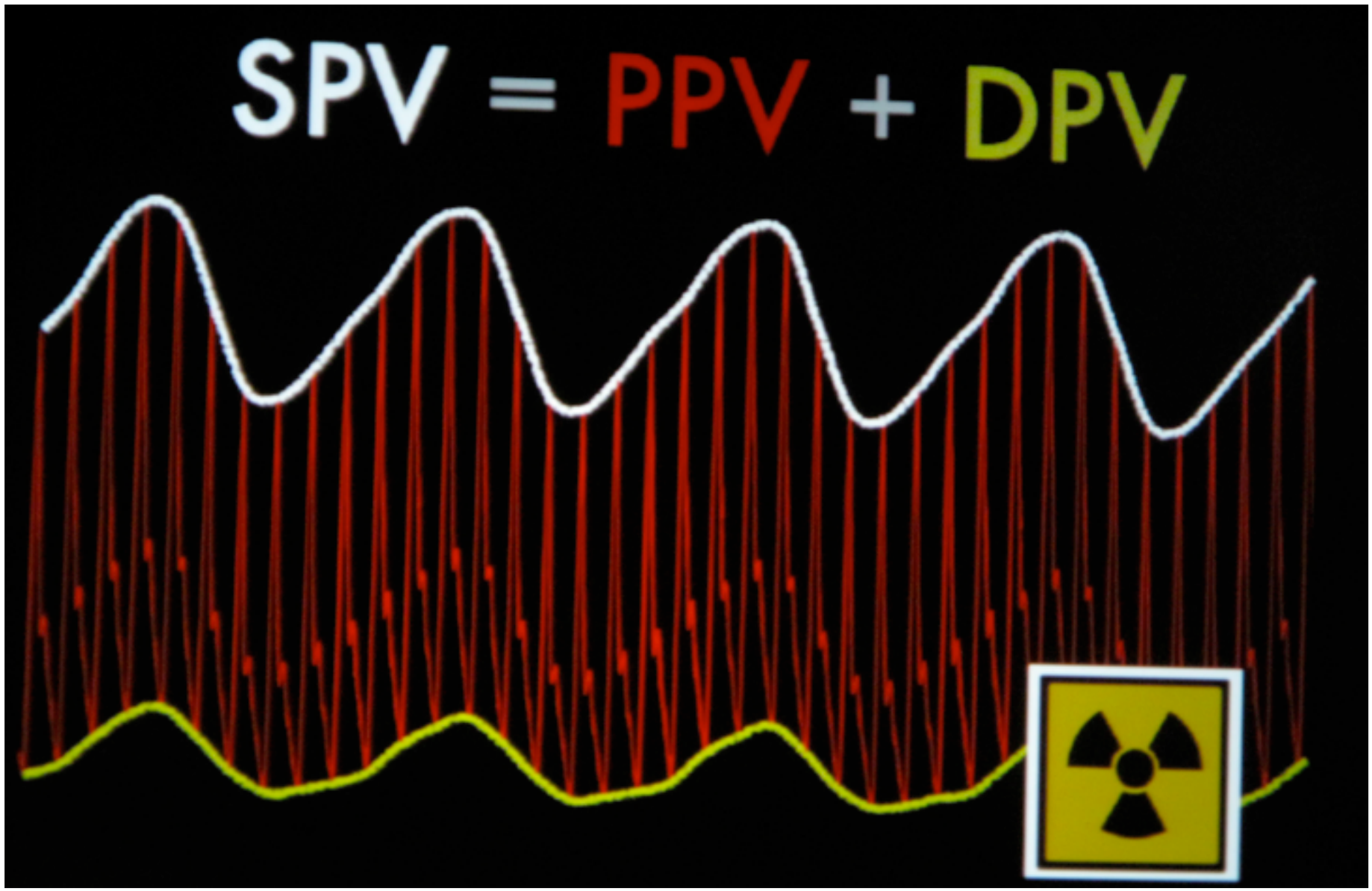
CO increased in 1/14 pts



Assessing cardiac preload or fluid responsiveness?
It depends on the question we want to answer



SPV is not PPV. DPV accounts for ~ 1/3rd of SPV



Micro-circulation

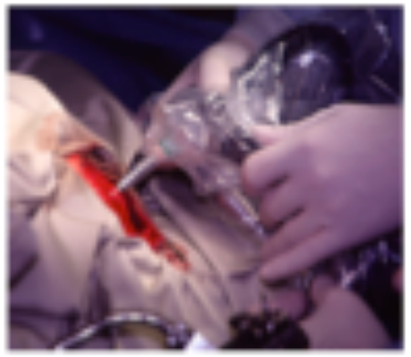
The Physiology of the Microcirculation

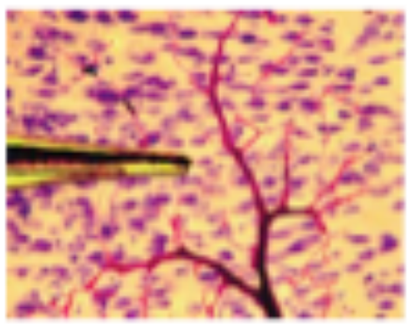
- The **microcirculation** describes the smallest vessels in the vasculature (< 100 μm) within organs responsible for the distribution of blood and its nutrients to the tissues of the organs.

- The vessels on the arterial side of the microcirculation are called the arterioles, which are well innervated, are surrounded by smooth muscle cells, and are 10–100 μm in diameter.

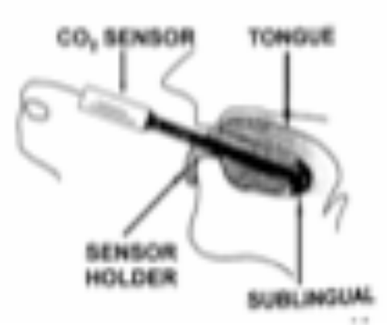
Monitoring the Microcirculation

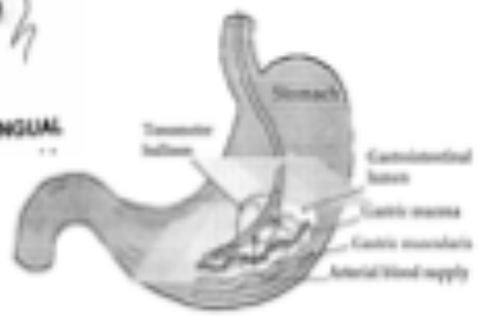
Methods to monitor the microcirculation and tissue oxygenation





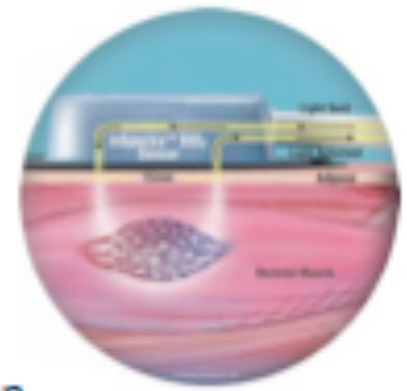
Microcirculatory perfusion	Parameter
• Gastric tonometry	• Tissue CO_2
• Laser doppler	• Velocity
• OPS/SDF imaging	• FCD, Flow, Heterogeneity





Tissue oxygenation

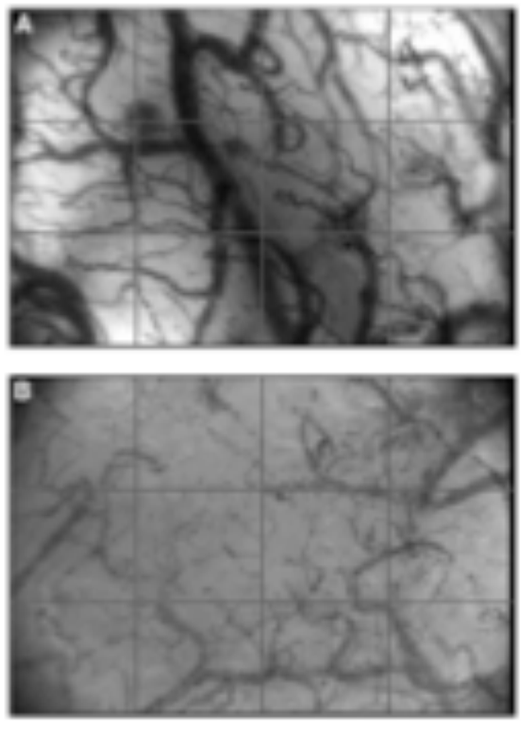
• Oxygen electrodes	• Tissue oxygen pressures
• Spectrophotometry	• Microcirculatory Hb saturation
• NIRS	• Hb saturation/Oxygen consumption



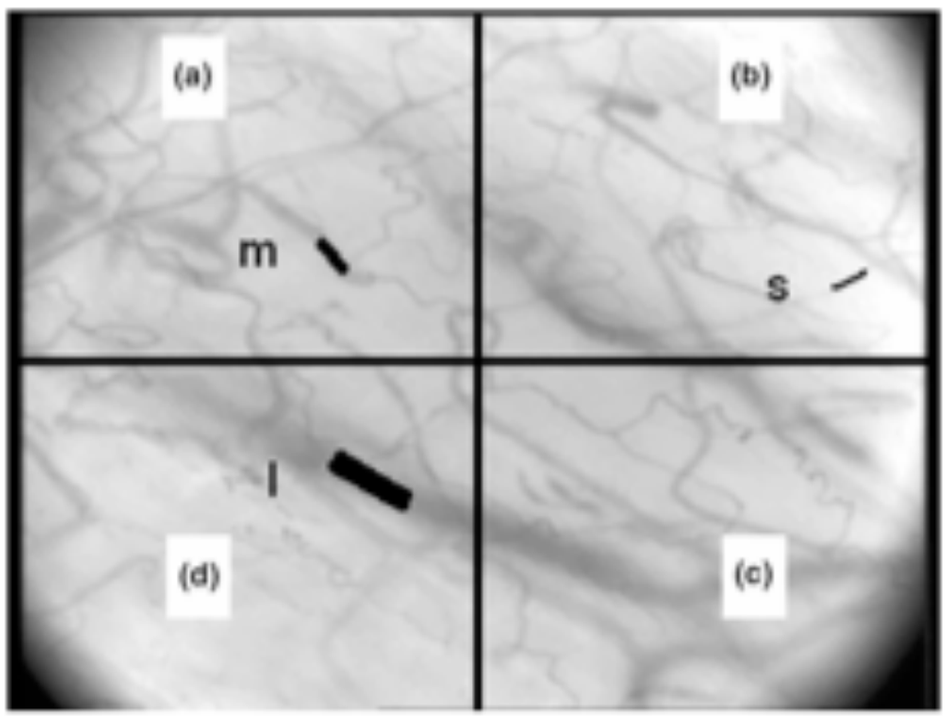
Monitoring the Microcirculation

Scoring sub-lingual microcirculatory abnormalities in septic patients

Diffusion
Functional Capillary Density



Convection
Microcirculatory Flow Index

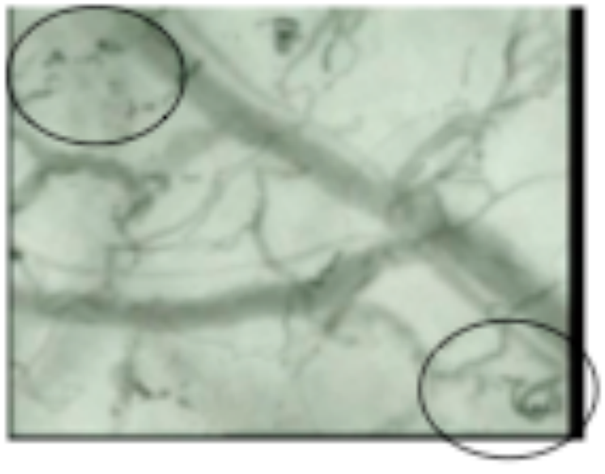


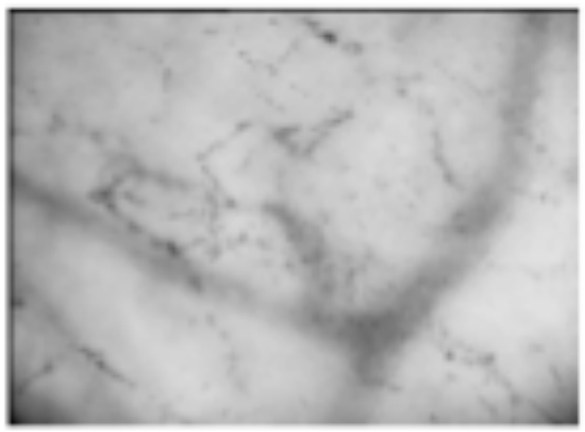
Heterogeneity index

De Backer D et al., Am J Respir Crit Care Med, 2002,166:98–104.;
Boerma EC et al., Critical Care, 2005, 9:R601–R606

Microcirculatory Dysfunction

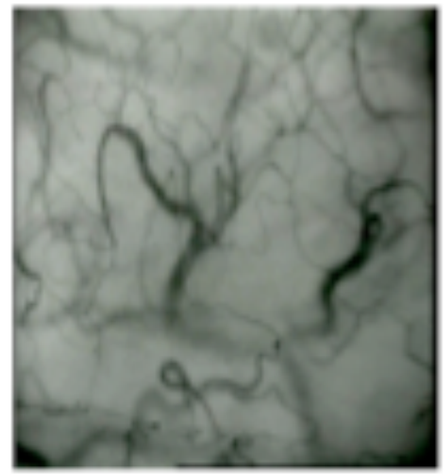
Microcirculatory dysfunction in states of disease leading to a reduction in tissue oxygenation

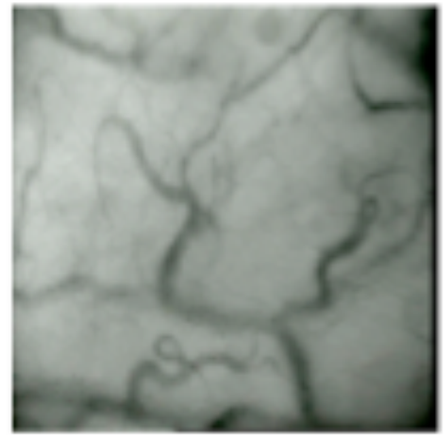




Sepsis

- In congestive heart failure there is a defect in **convection**
- In severe hemodilution there is a defect in **diffusion**
- In sepsis there is a defect in **diffusion and convection**





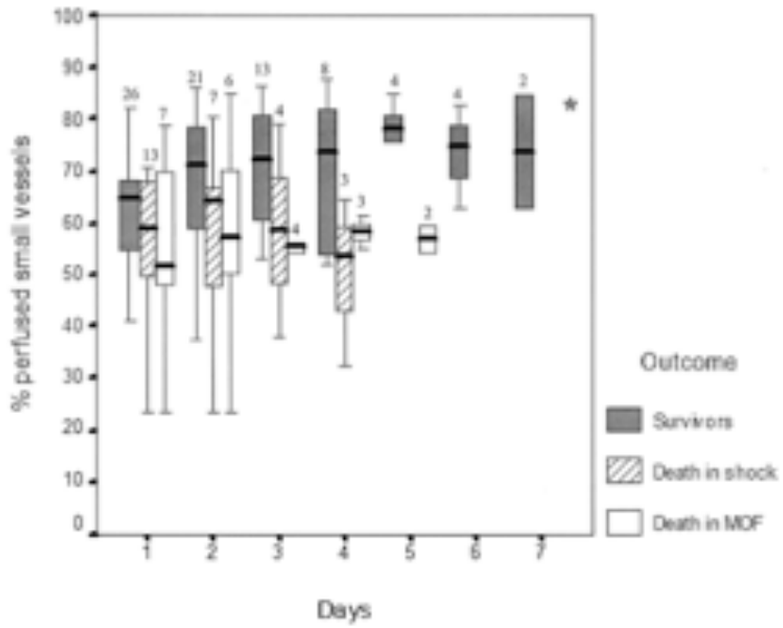
Hemodilution (CABG)

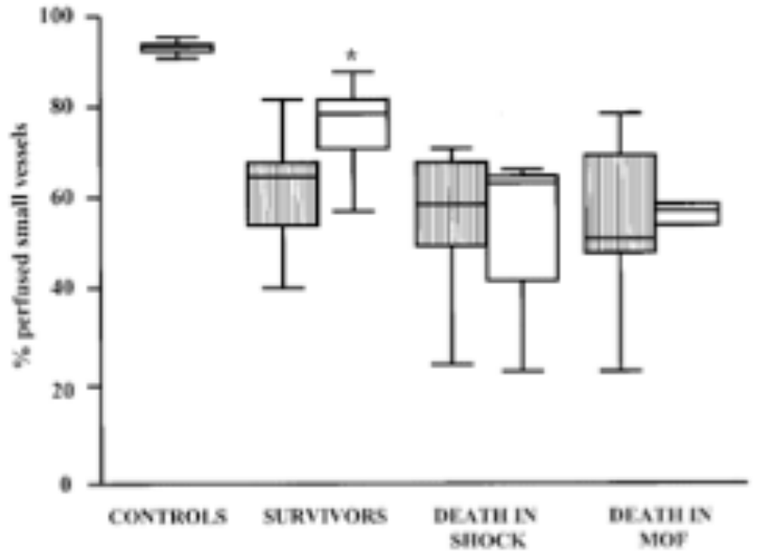
Microcirculatory Dysfunction

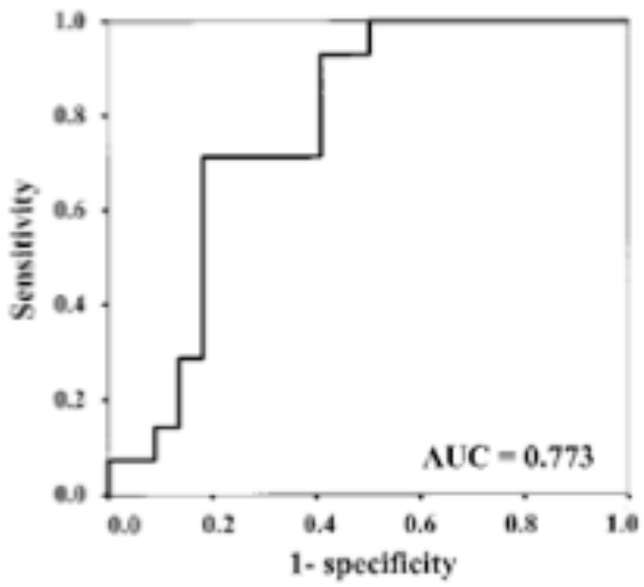
Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock

Yasser Sakr, MB, BCh, MSc; Marc-Jacques Dubois, MD; Daniel De Backer, MD, PhD;
Jacques Creteur, MD, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Microcirculatory alterations improve rapidly in septic shock survivors but not in patients dying with multiple organ failure, regardless of whether shock has resolved.



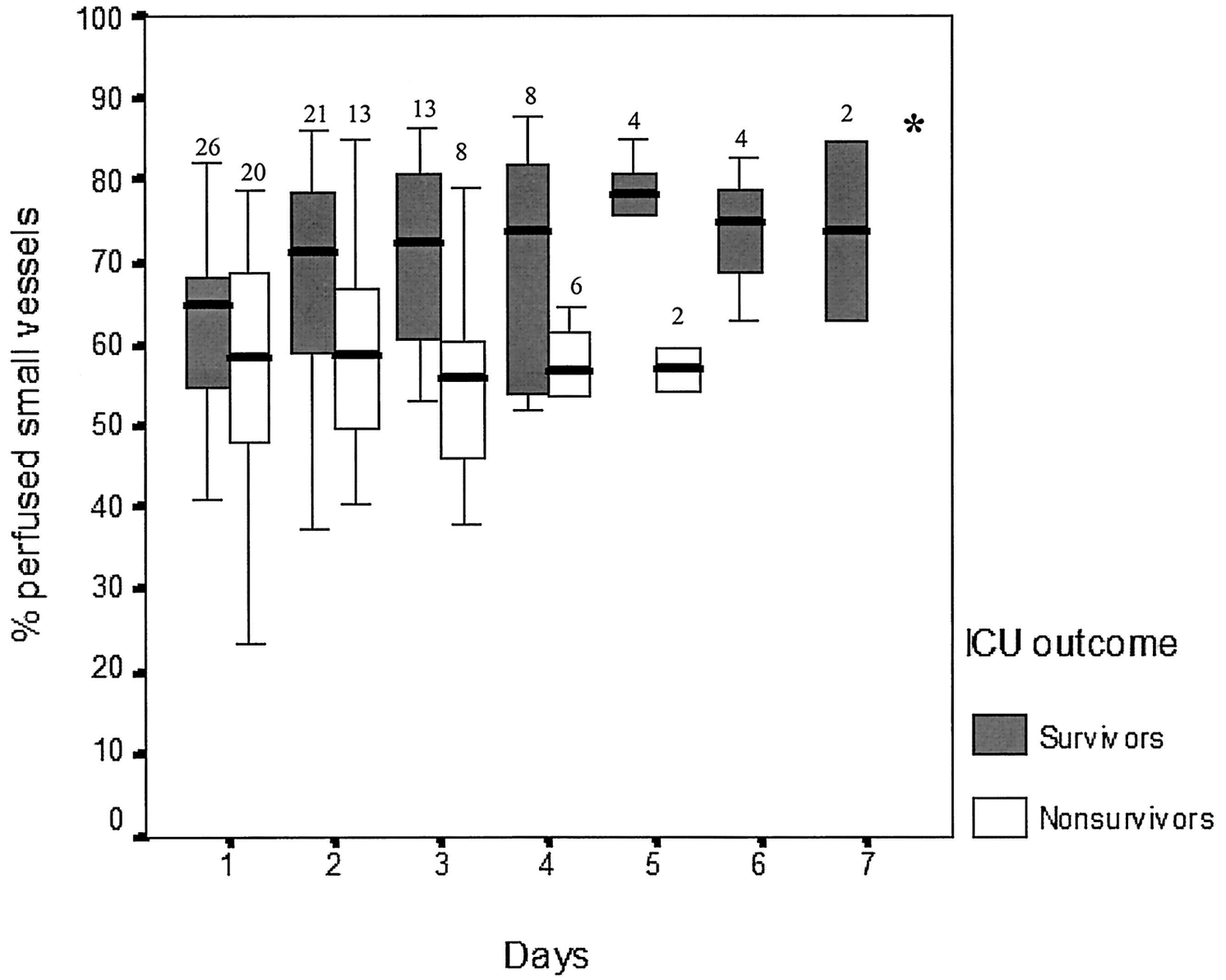




Despite similar hemodynamic and oxygenation profiles and use of vasopressors at the end of shock, patients dying after the resolution of shock in multiple organ failure had a lower percentage of perfused small vessels than survivors.

Crit Care Med, 2004, 32:1825–1831

Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock



Despite similar hemodynamic and oxygenation profiles and use of vasopressors at the end of shock, patients dying after the resolution of shock in multiple organ failure had a lower percentage of perfused small vessels than survivors.

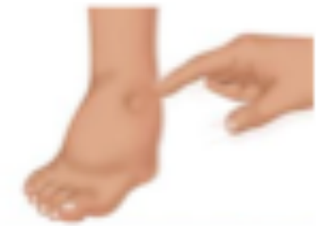
CCM 2004, 32:1825-1831

Microcirculation: The Good & The Bad

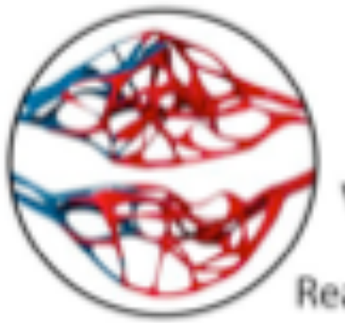
SHOCK

Hypovolemia

Fluid Therapy



The Microcirculation



The Good
Stroke volume
Tissue oxygenation
Perfusion
Viscosity

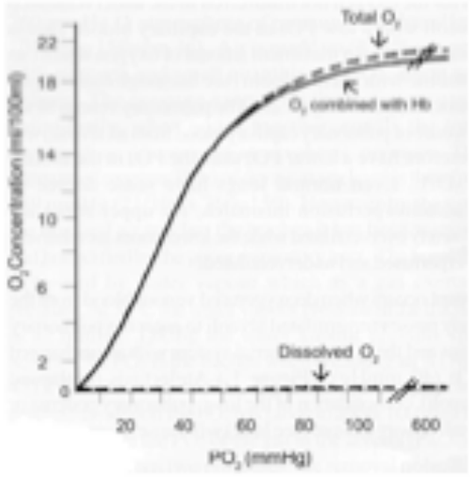
The Bad
Venous congestion
Edema
Reactive oxygen species
Coagulation
Anemia-hypoxemia
Glycocalyx-endothelium
Acidosis

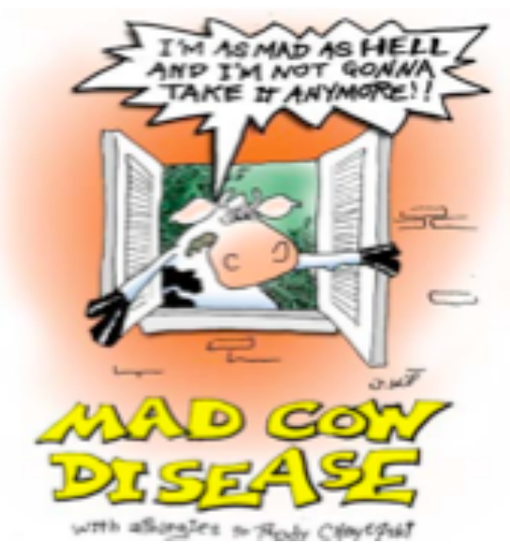
Fluids do a whole lot of things!

Do plasma substitutes have additional properties beyond correcting volume deficits?

Effects

- Blood flow (distribution)
- pO_2
- Hb
- Volume
- Blood sheer stress
- (auto) regulation
- Hct
- Viscosity (hypotension)
- Metabolic inflammation





Colloids

- Hydroxyethyl Starch Solutions (HES)
- Gelatins
- Dextrans
- Albumin

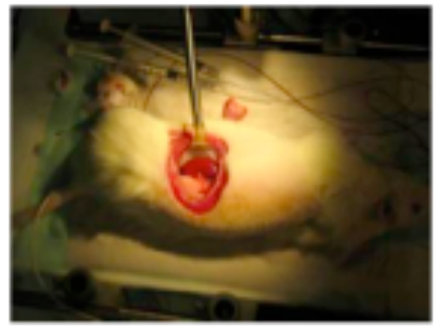
Crystalloids

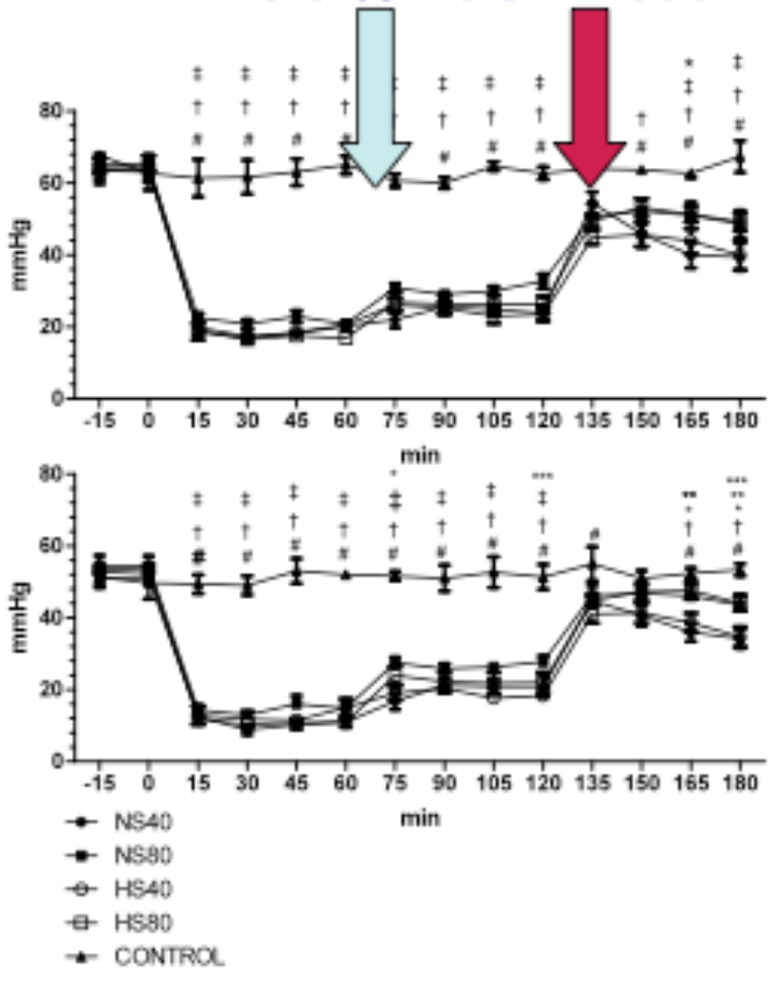
- Balanced (e. g. Ringer's Lactate)
- Un-balanced (e. g. 0.9 % NaCl)

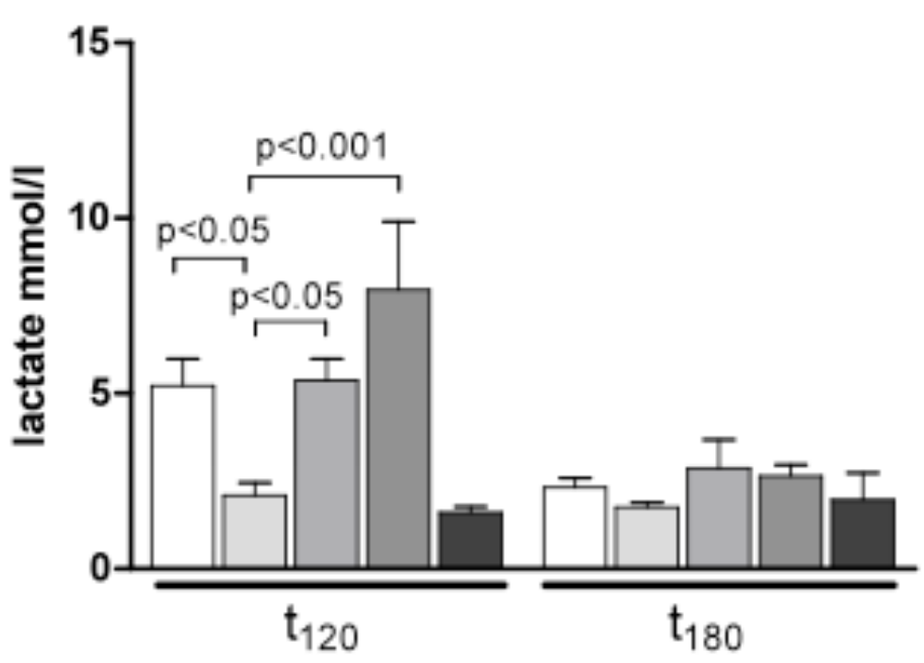
Joachim Boldt, SHOCK, 2006, Vol. 25, No. 2, pp. 103–116

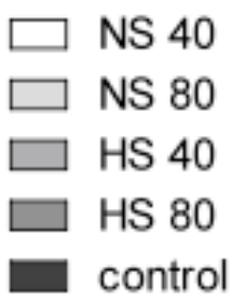
Improvement of Microcirculation with HES 130/0.4

0.9% NaCl resuscitation does not improve renal oxygenation during hemorrhagic shock in rats







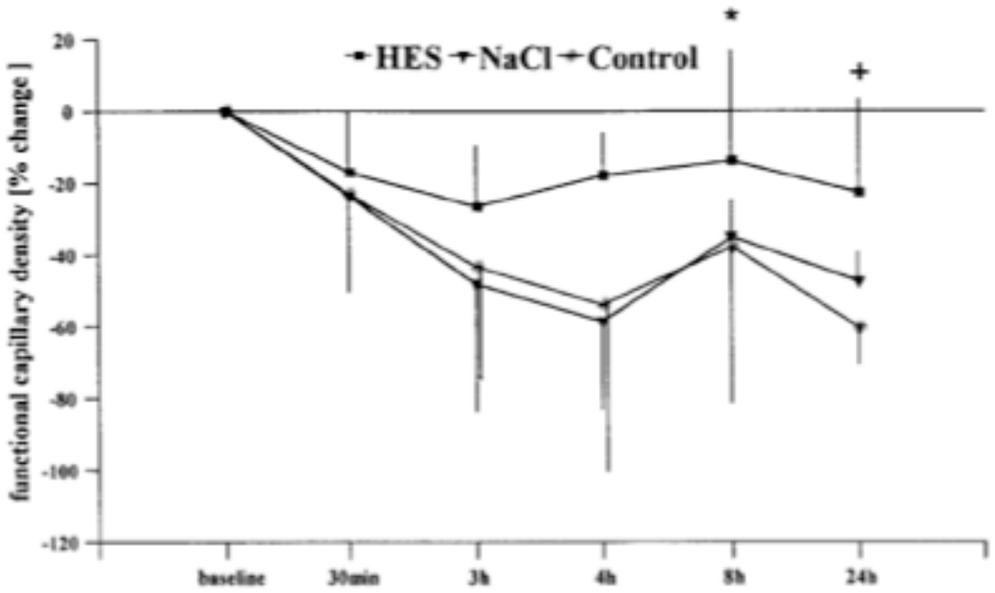


0.9 % NaCl 24.8 ml
Voluven® 5.9 ml

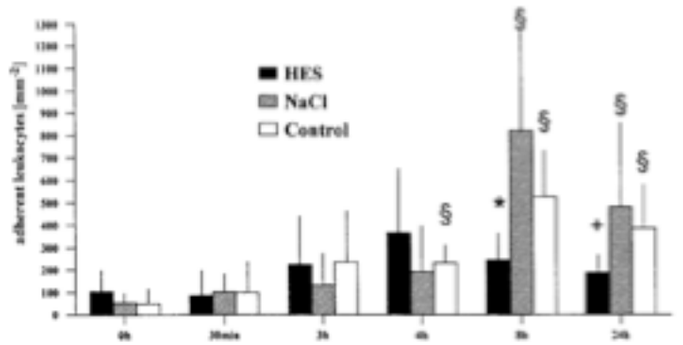
Legrand M, Mik EG, Ballestra G, Lutter R, Pirracchio R, Payen D, Ince C, Anesthesiology, 2010, 112(1):119–27

Improvement of Microcirculation with HES 130/0.4

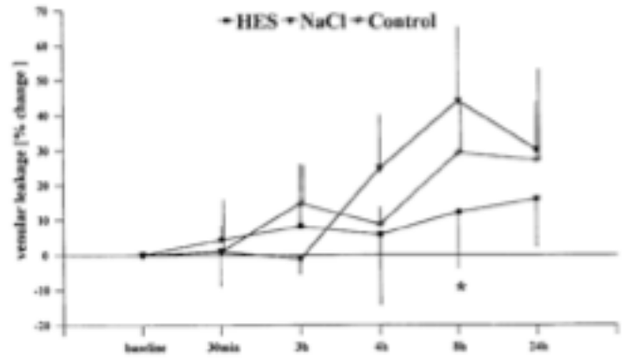
Hydroxyethyl Starch (130 kD), but Not Crystalloid Volume Support, Improves Microcirculation during Normotensive Endotoxemia



Functional capillary density



Adherent leucocytes

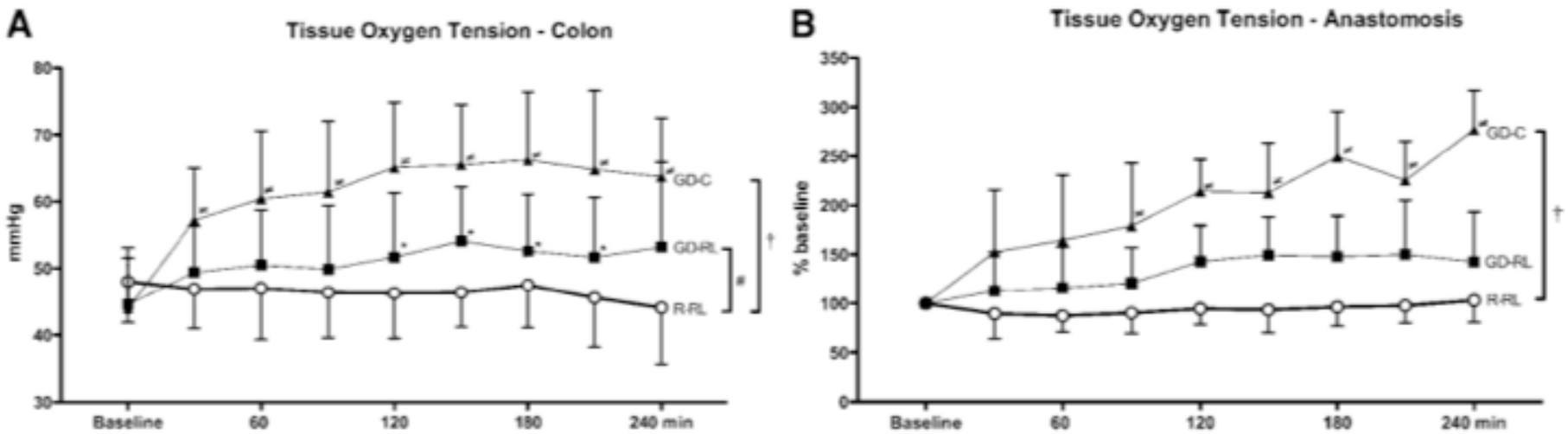


Venular leakage of FITC

Hoffmann JN, Vollmar B, Laschke MW, Inthorn D, Schildberg FW, Menger MD, Anesthesiology, 2002, 97:460–470

Improvement of Microcirculation with HES 130/0.4

Goal-directed Colloid Administration Improves the Microcirculation of Healthy and Perianastomotic Colon (colonic anastomosis pig model for abdominal surgery)

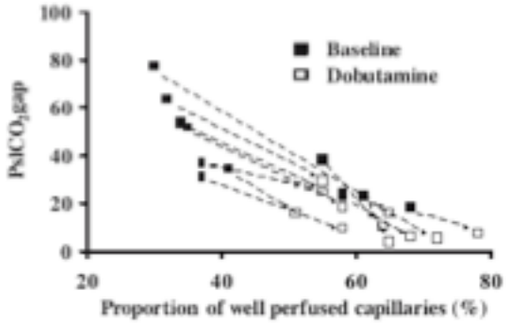


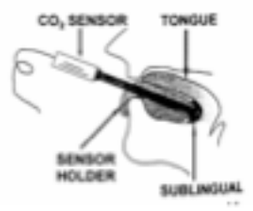
Study: Restricted vs. goal-directed Ringer's lactate (R-RL vs. GD-RL) or GD-colloid (HES 130/0.4). GDT guided by mixed venous oxygen saturation (SvO_2). Assessment of tissue oxygen tension; healthy vs. perianastomotic colon tissue. **Results:** Restricted crystalloid group received 924± 44 ml of RL. GD-crystalloid received 943± 68 ml of RL plus 1794± 211 ml of RL as boluses. GD-colloid group received 917±41 ml of RL plus 831± 267 ml as boluses of HES during the study.

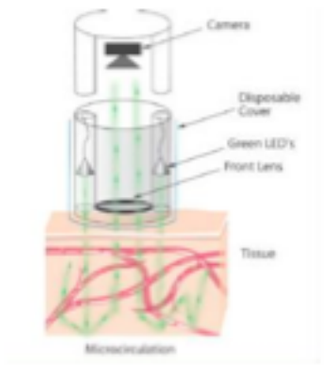
Kimberger O, Arnberge M, Brandt S, Plock J, Sigurdsson G, Kurz A, Hiltebrand L, Anesthesiology, 2009, 110:496–504

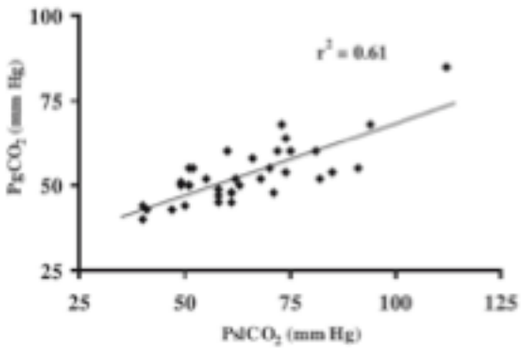
Improvement of Microcirculation with HES 130/0.4

Sublingual capnometry tracks micro-circulatory changes in septic patients

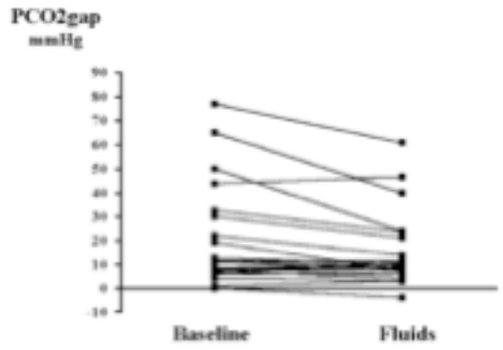


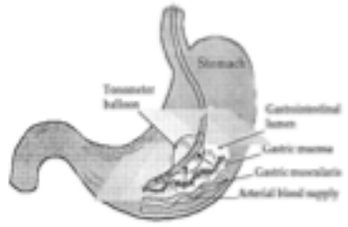




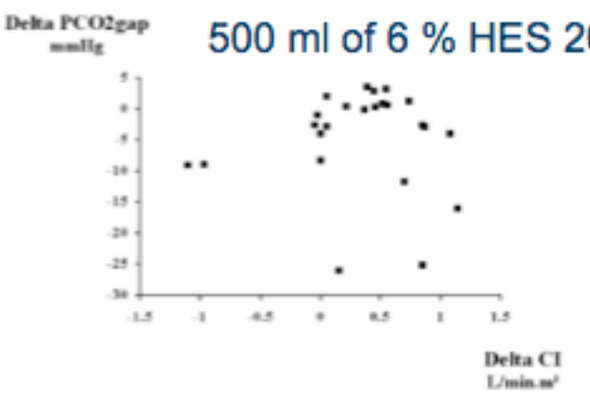


Effects of fluid challenge on gastric mucosal PCO_2 in septic patients





500 ml of 6 % HES 200/0.6



Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL, Intensive Care Med, 2006, 32:516–523;
Silva E, De Backer D, Creteur J, Vincent JL, Intensive Care Med, 2004, 30:423–429

Improvement of Microcirculation with HES 130/0.4

Colloids Versus Crystalloids and Tissue Oxygen Tension in Patients Undergoing Major Abdominal Surgery

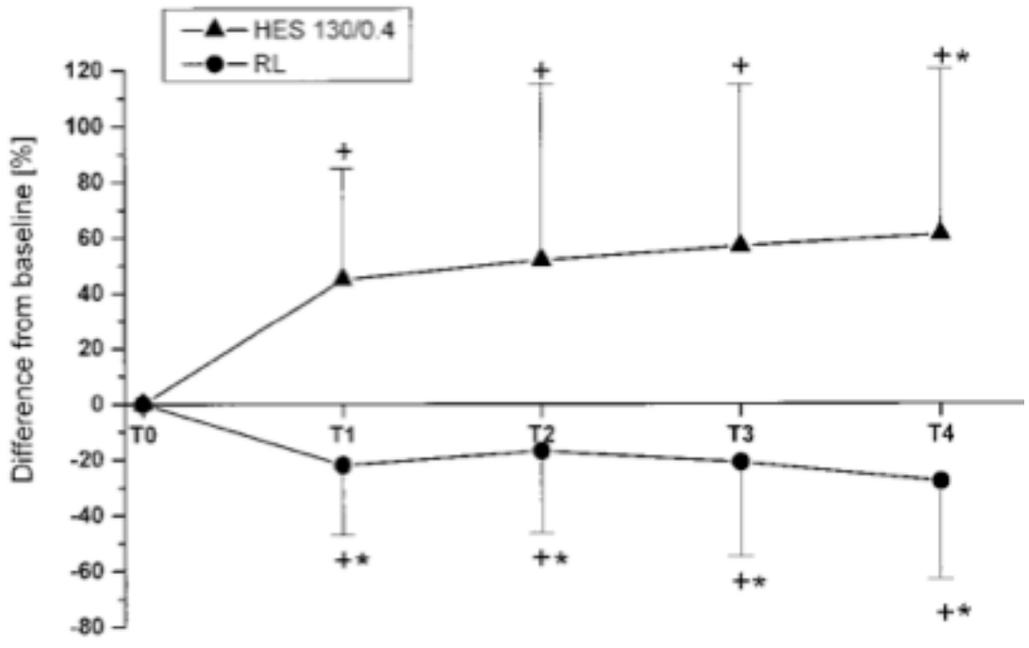
Table 3. Volume Input and Output (Cumulative)

Variable	End of surgery (T3)	First POD (T4)
RL (mL)		
HES 130/0.4	2070 ± 870	3050 ± 440
RL group	5940 ± 1910*	11740 ± 2630*
Colloids (mL)		
HES 130/0.4	1850 ± 380	2920 ± 360
RL group	—	—
PRBC (units per group)		
HES 130/0.4	8	10
RL group	8	11
FFP (units per group)		
HES 130/0.4	—	—
RL group	—	2
Urine (mL)		
HES 130/0.4	640 ± 230	2620 ± 370
RL group	1980 ± 250*	5960 ± 420*
Drainage blood loss (mL)		
HES 130/0.4		770 ± 180
RL group		690 ± 170

POD = postoperative day; RL = lactated Ringer's solution; PRBC = packed red blood cells; FFP = fresh frozen plasma; HES = hydroxyethyl starch.

Data are presented as mean ± SD unless otherwise noted.

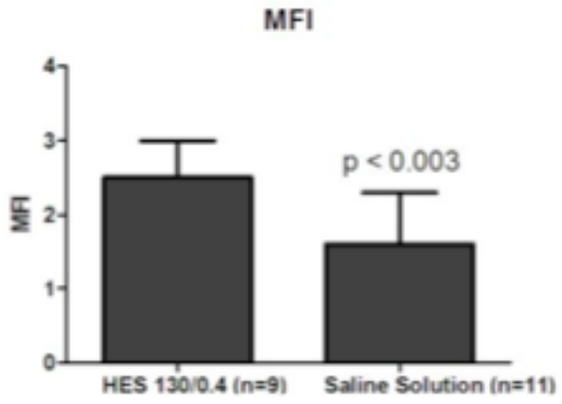
* $P < 0.05$ compared with the other group.

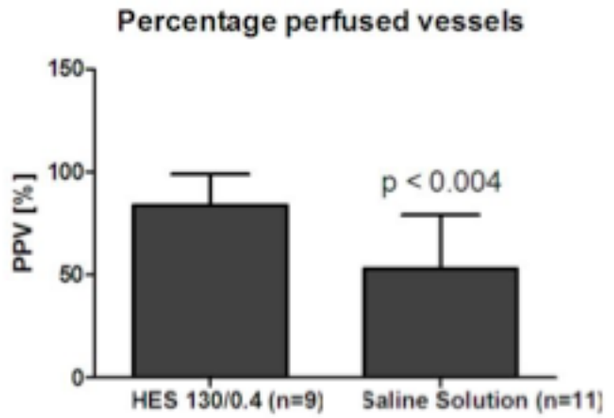


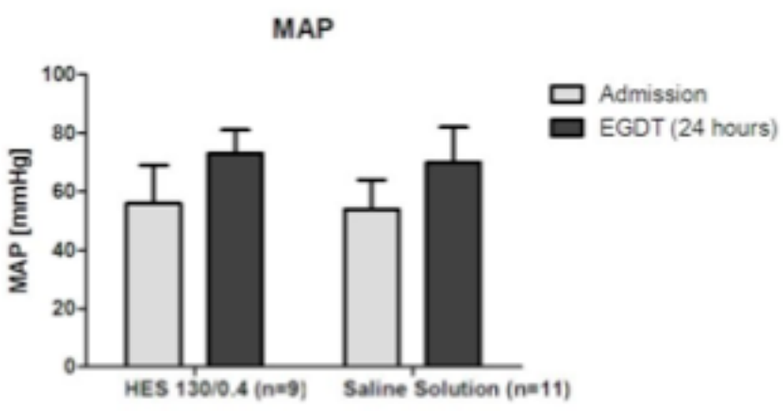
Lang K, Boldt J, Suttner S, Haisch G, Anesth Analg, 2001, 93:405–409

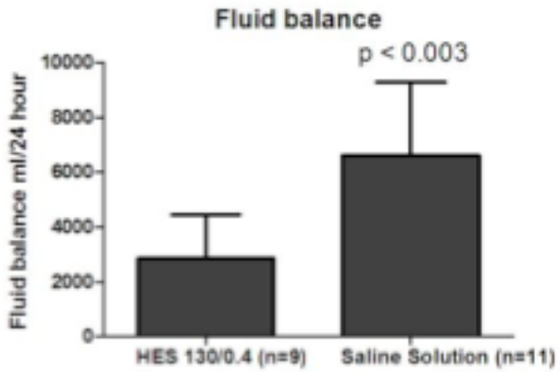
Improvement of Microcirculation with HES 130/0.4

Hydroxyethyl starch 130/0.4 is superior to saline solution for resuscitation of the microcirculation



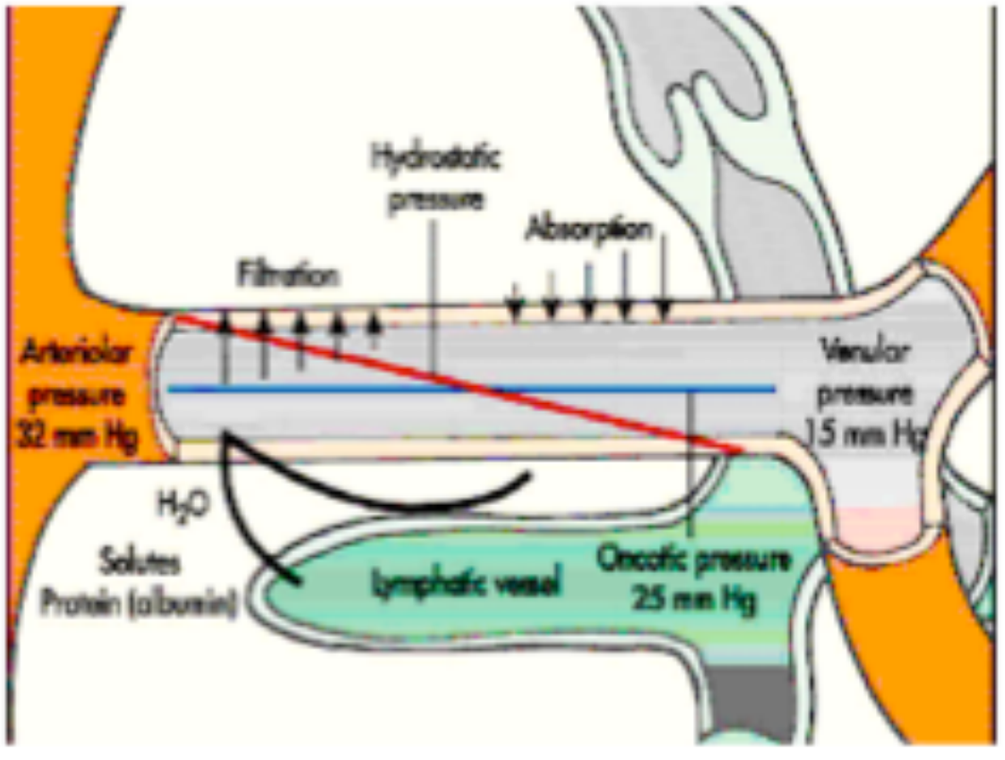






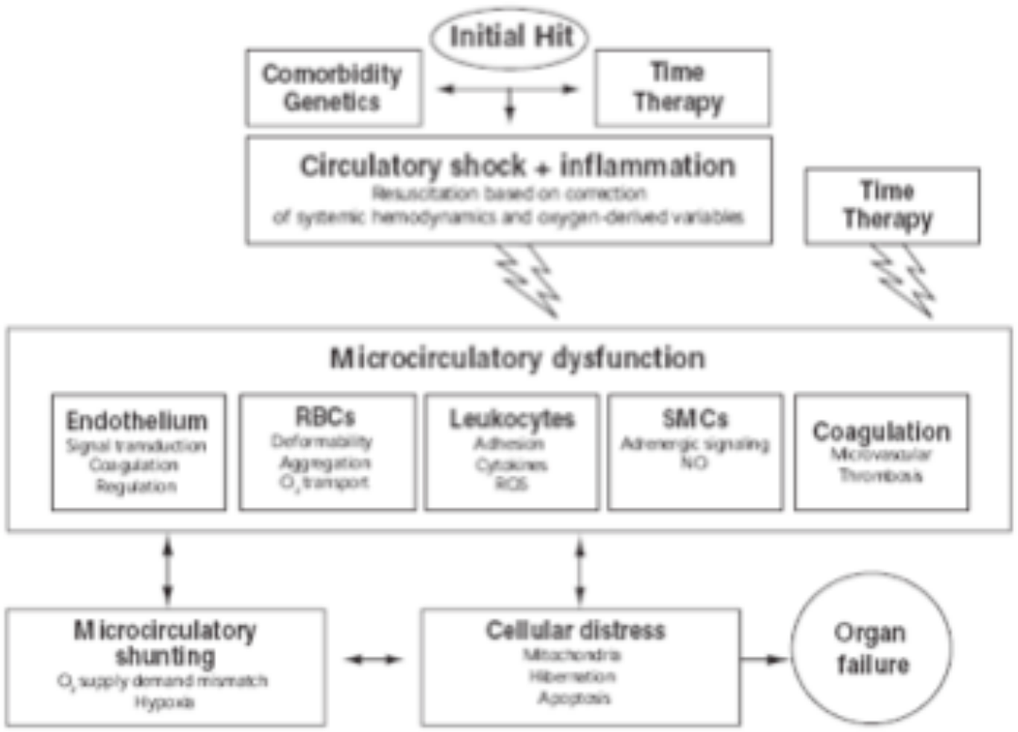
Dubin A, Pozo MO, Casabello CA, Murias G, Palizas F, Moseinco M, Palizas F, Kanoore Edul VS, Ince C, Minerva Anesthesiologica, 2009, 75:2–8

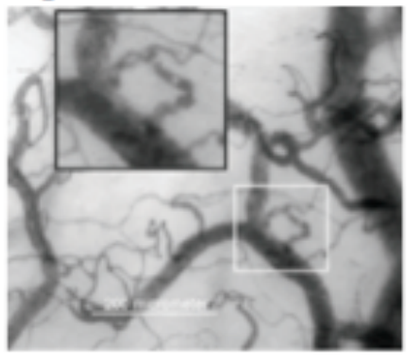
The microcirculation - physiology

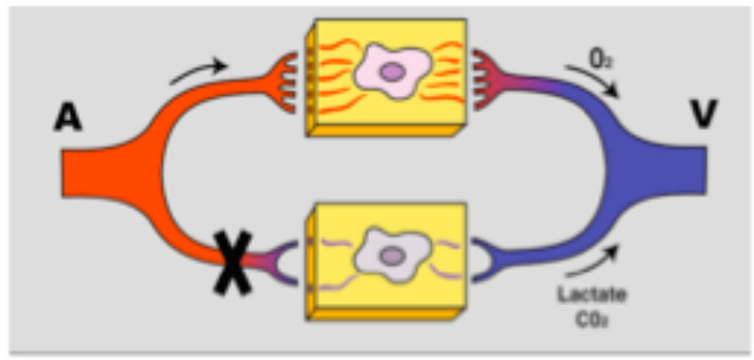


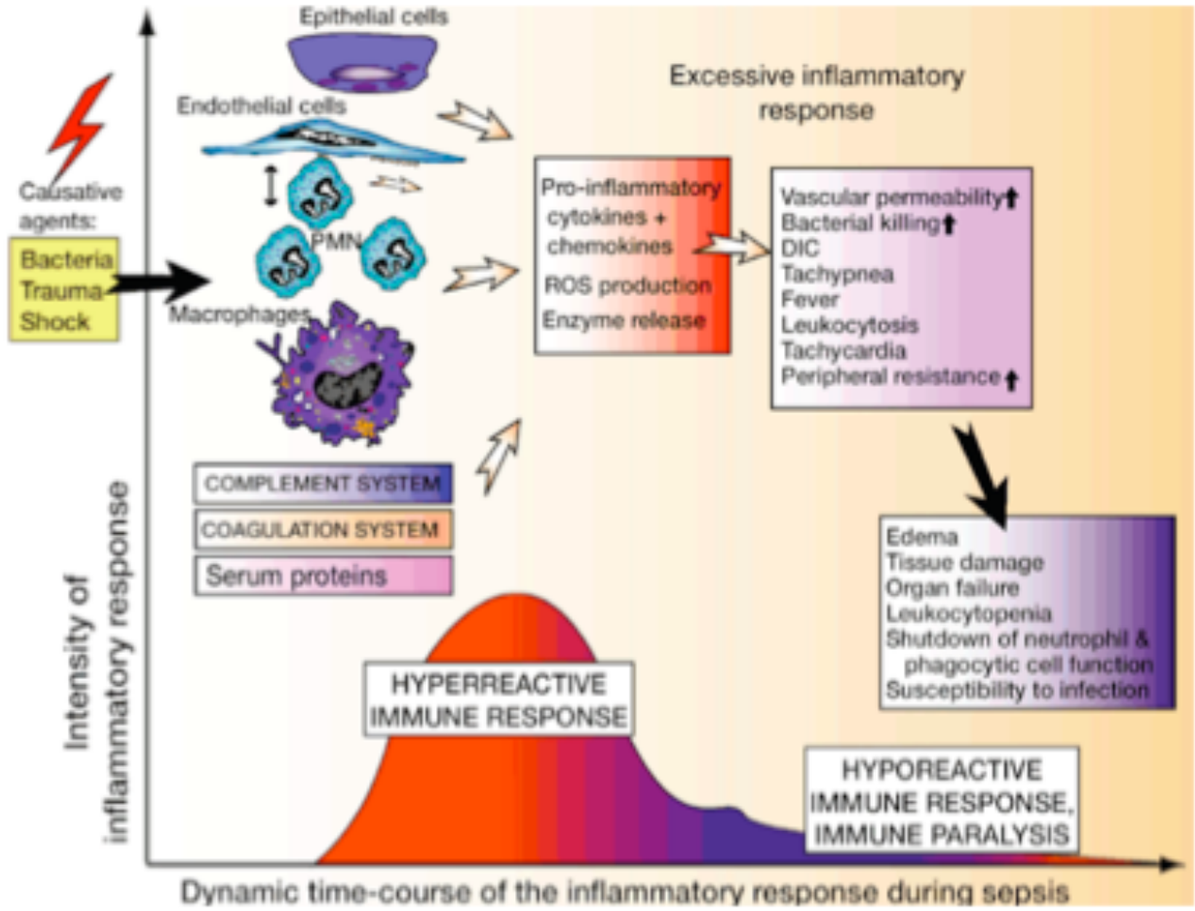
The microcirculation and sepsis

The microcirculation is the motor of sepsis







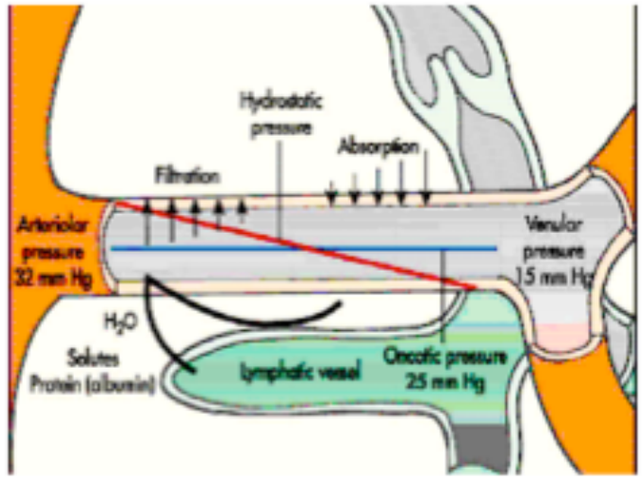


- Coagulatory/RBC dysfunction
- Endothelial barrier dysfunction
- Capillary fall out
- Inflammatory activation
- Weak microcirculatory units are shunted
- Hypoxia, apoptosis, organ dysfunction
- ***Not detected by systemic variables***
- ***Not responsive to therapy per se***

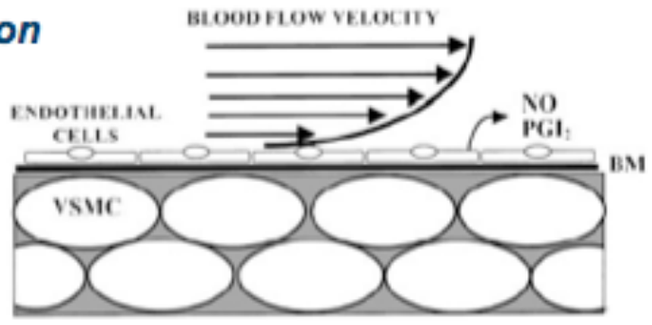
Ince C, Critical Care, 2005, 9:S13–S19

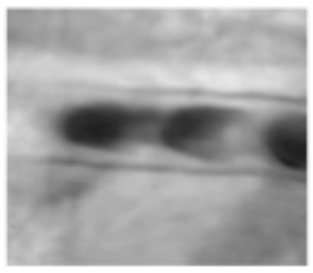
The microcirculation -physiology

- Arterioles carry the blood to the capillaries, measuring 5-10 µm in diameter, which are in direct contact to the tissue cells. They are only 1 cell thick.
- These microvessels, connect arterioles and venules, and enable the exchange of water, oxygen, carbon dioxide, as well as many other nutrient and waste chemical substances between blood and surrounding tissues.
- The microcirculation also forms an important immunological function.

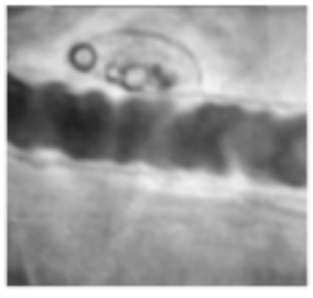


regulation

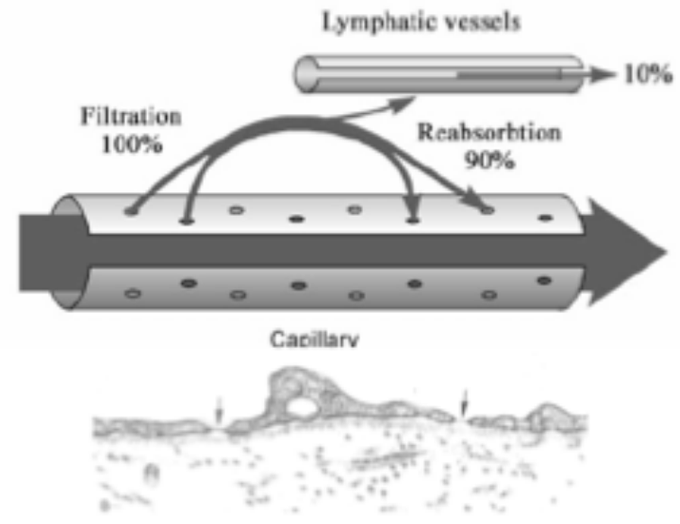


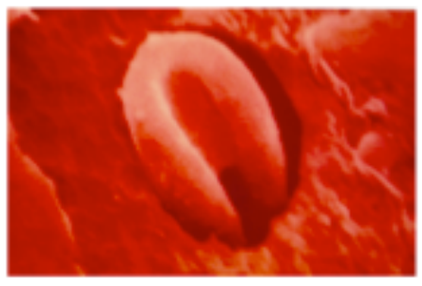


glycocalyx

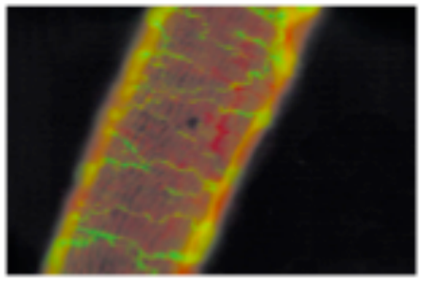


starling equation



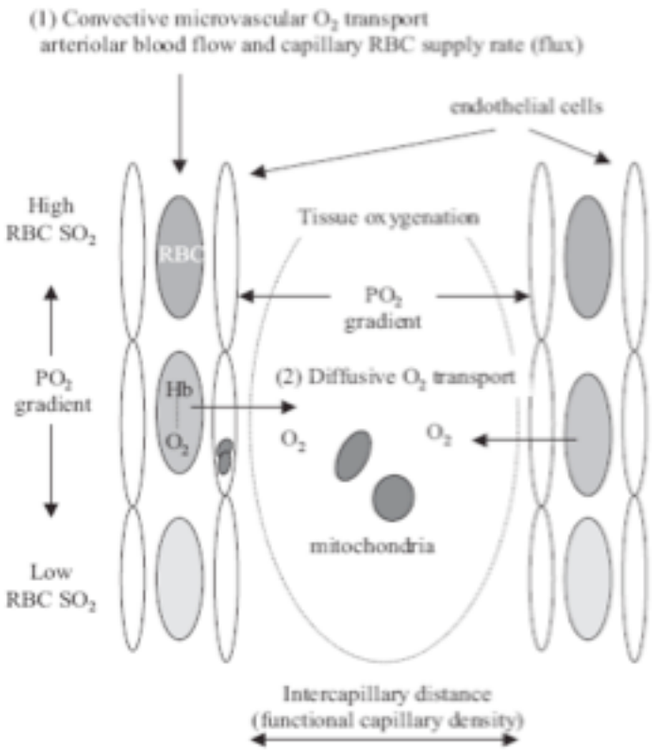


deformability

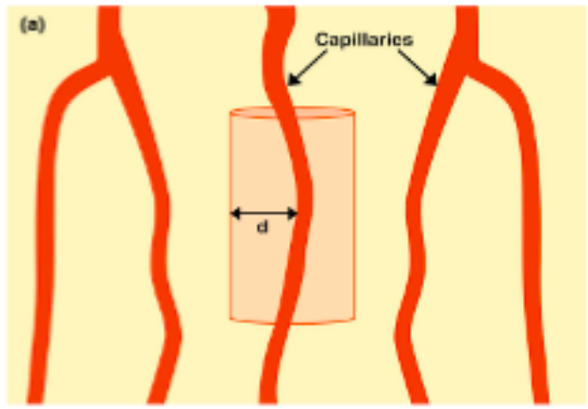


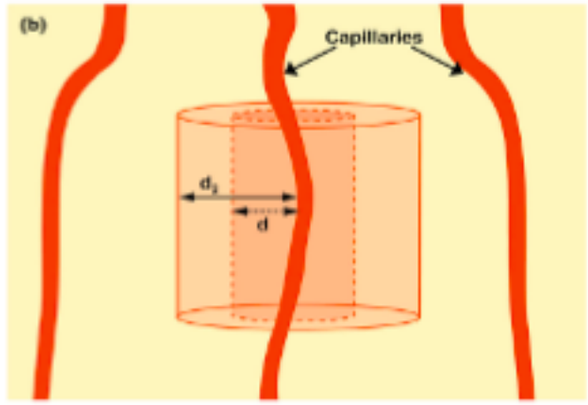
The microcirculation and oxygenation

Diffusion of oxygen in the tissues is the true rate limiting process



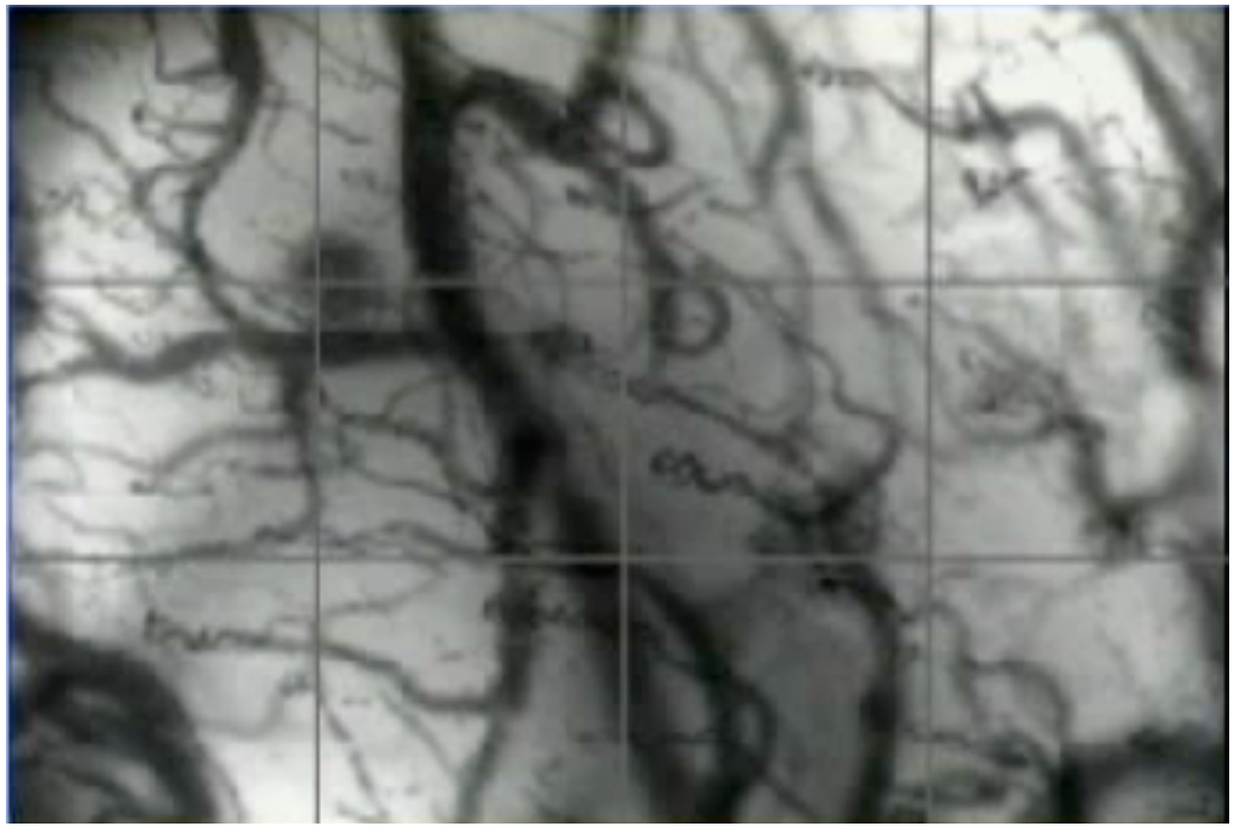
$$VO_2 = \frac{D \times A\,(\,capO_2 - mitO_2)}{L^2}$$



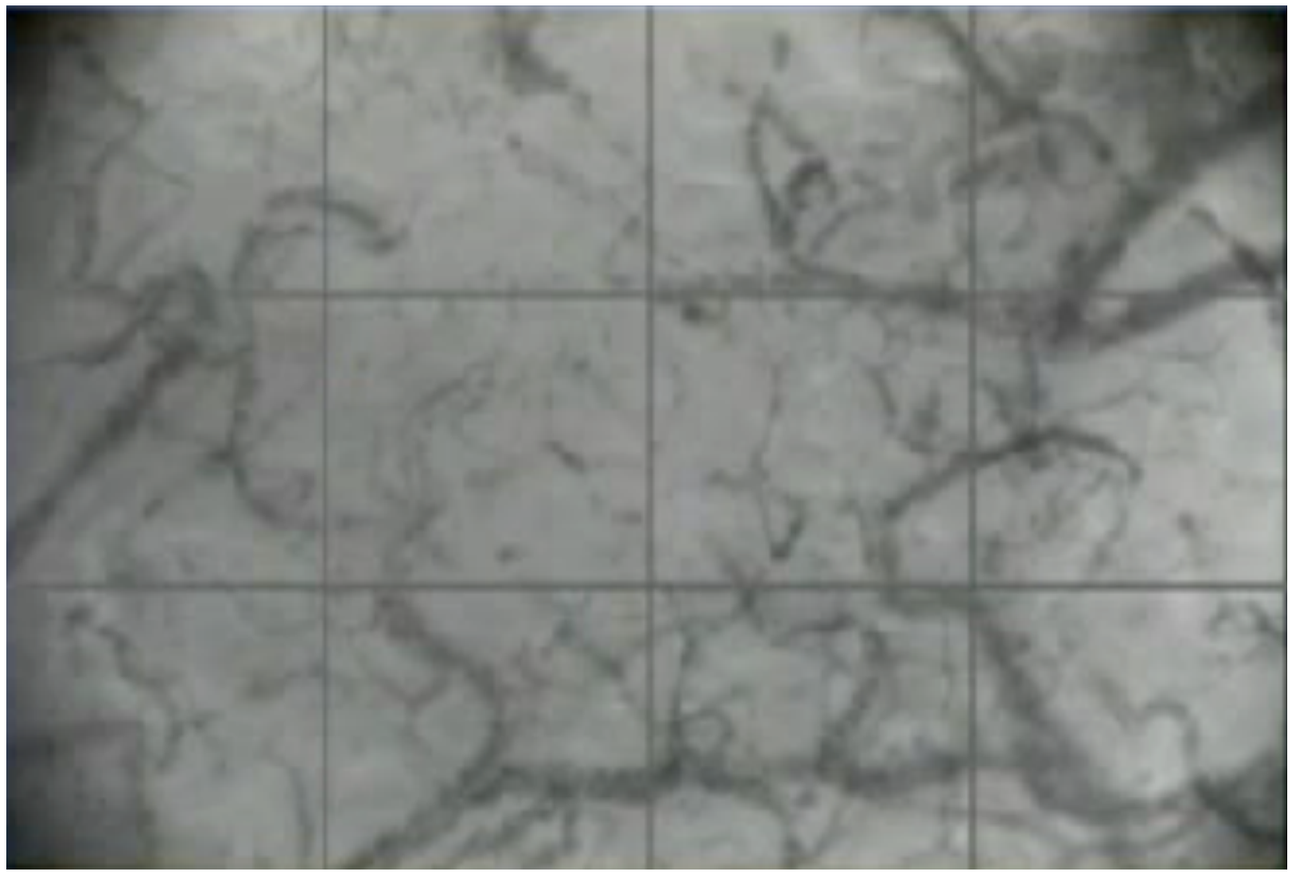


VO_2	volume of O_2 transported by diffusion
D	diffusion constant
A	systemic capillary surface area
$capO_2$	capillary pO_2
$mitO_2$	mitochondrial pO_2

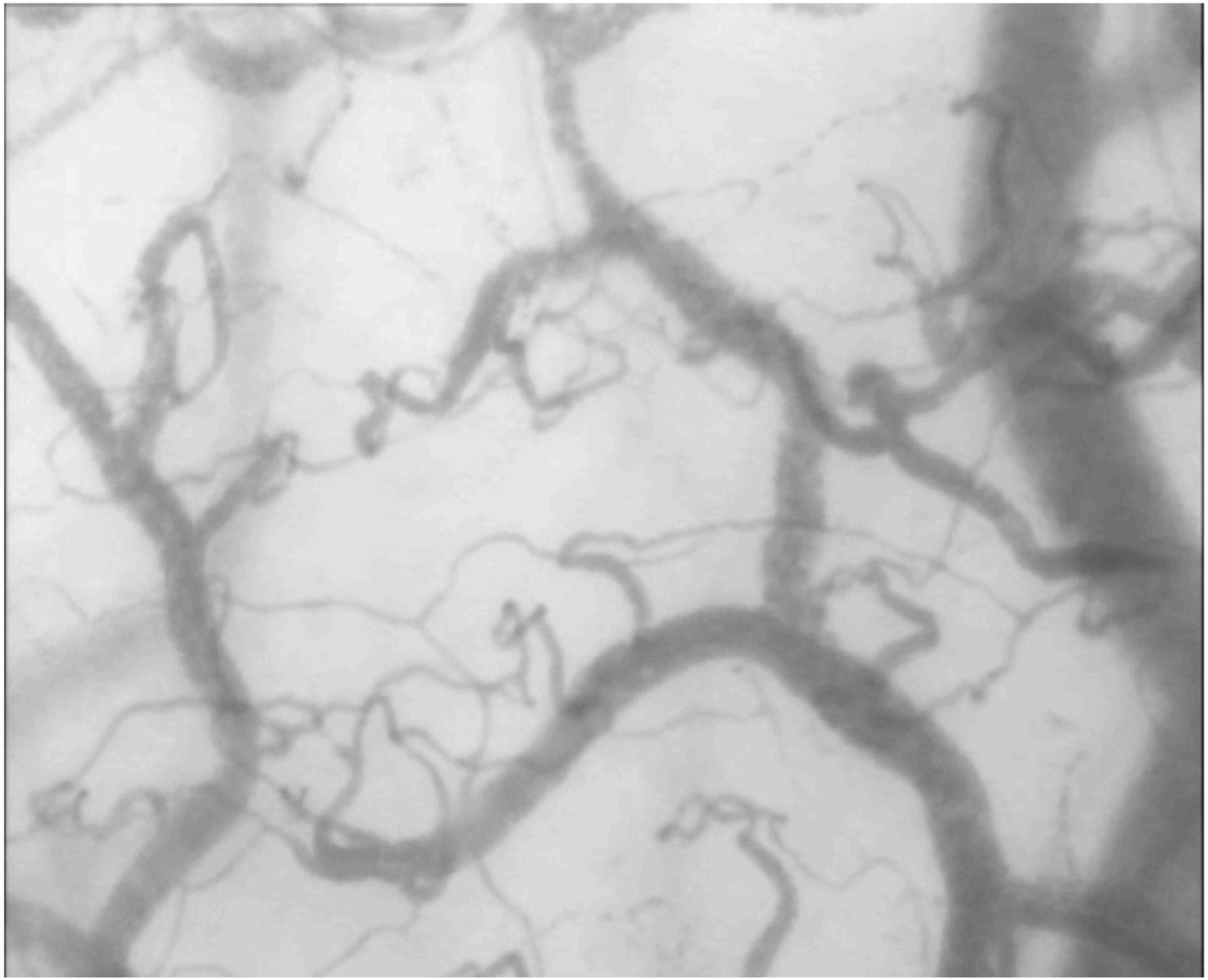
Normal microcirculation



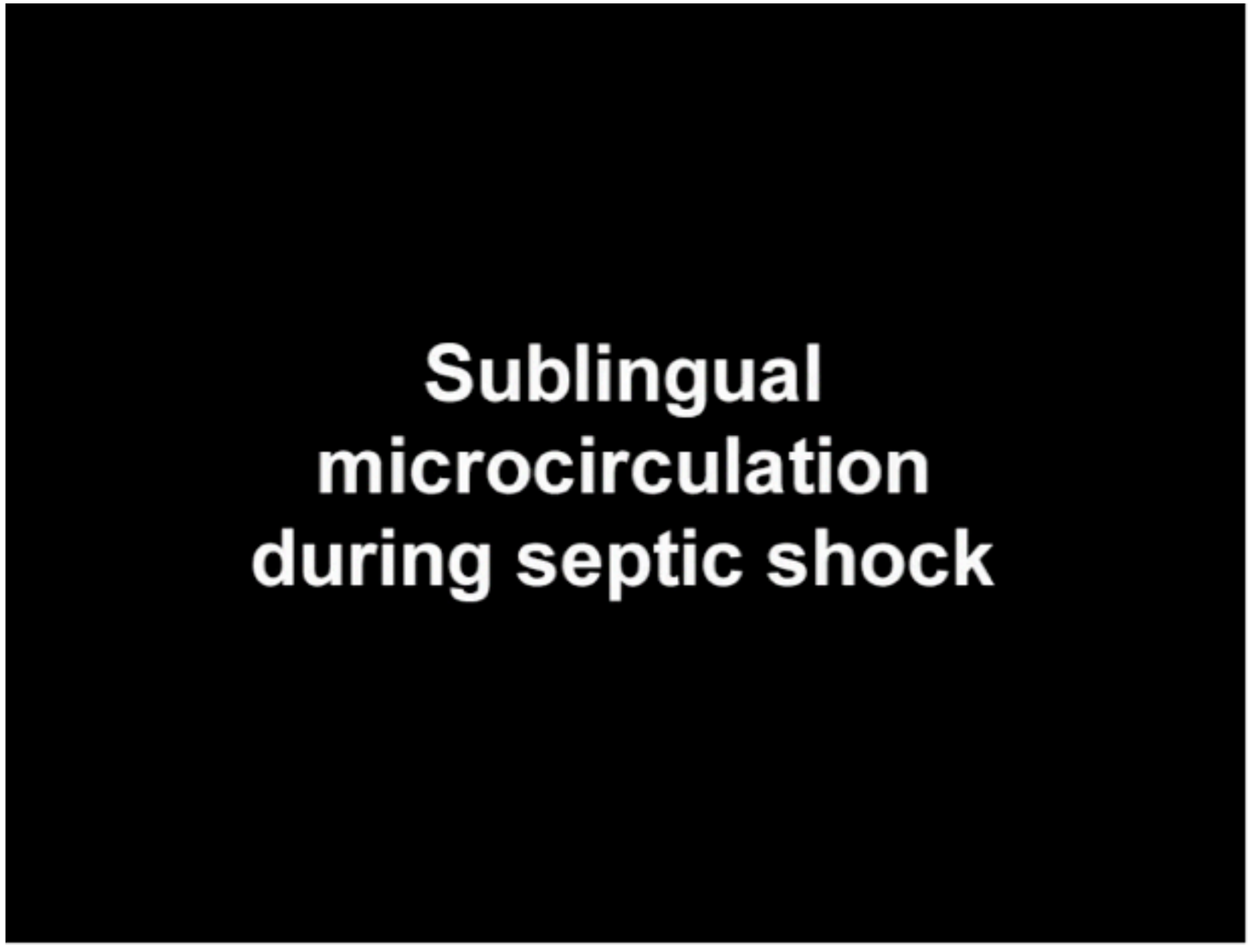
Abnormal microcirculation
Septic shock



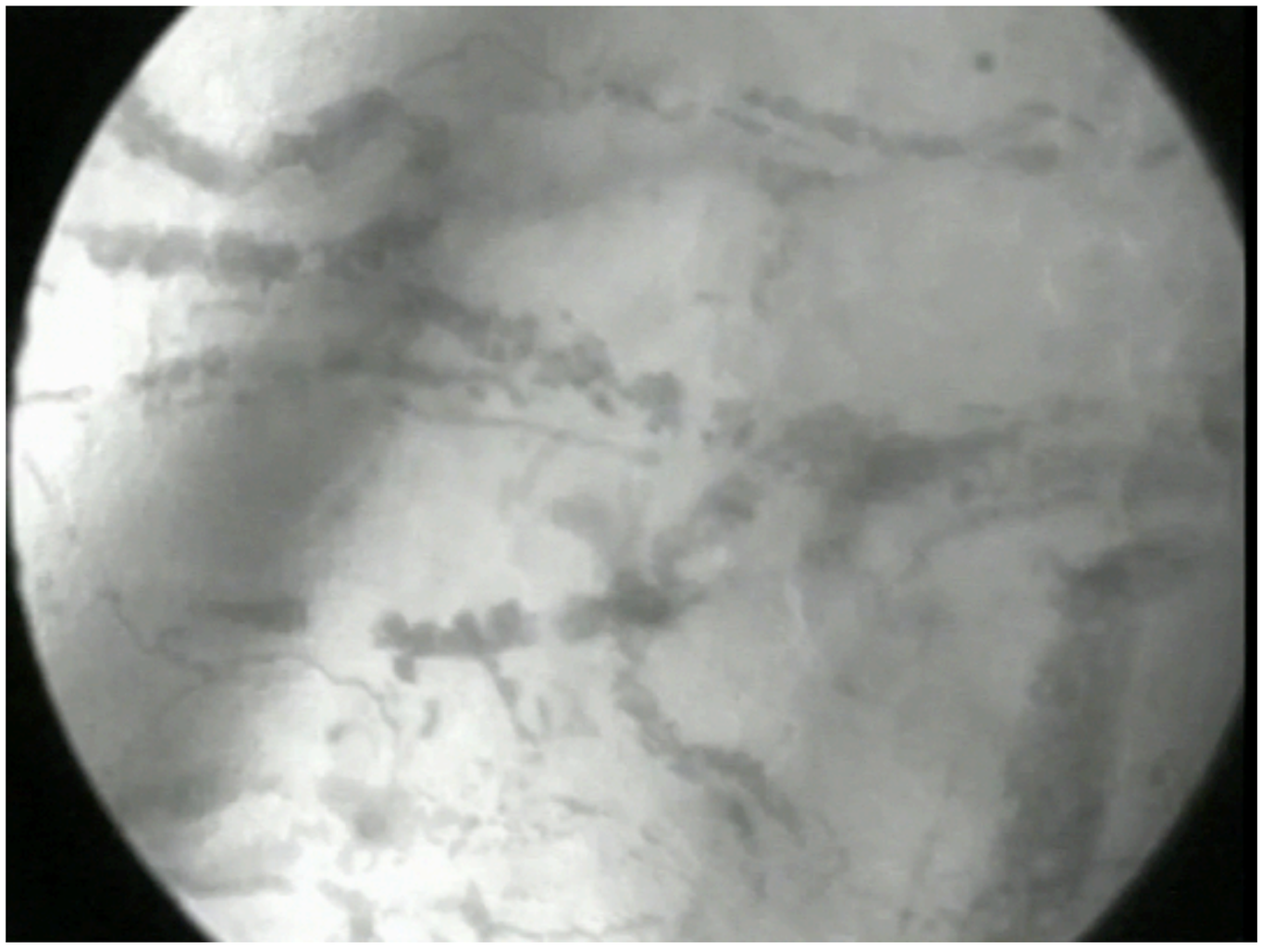
Normal microcirculation



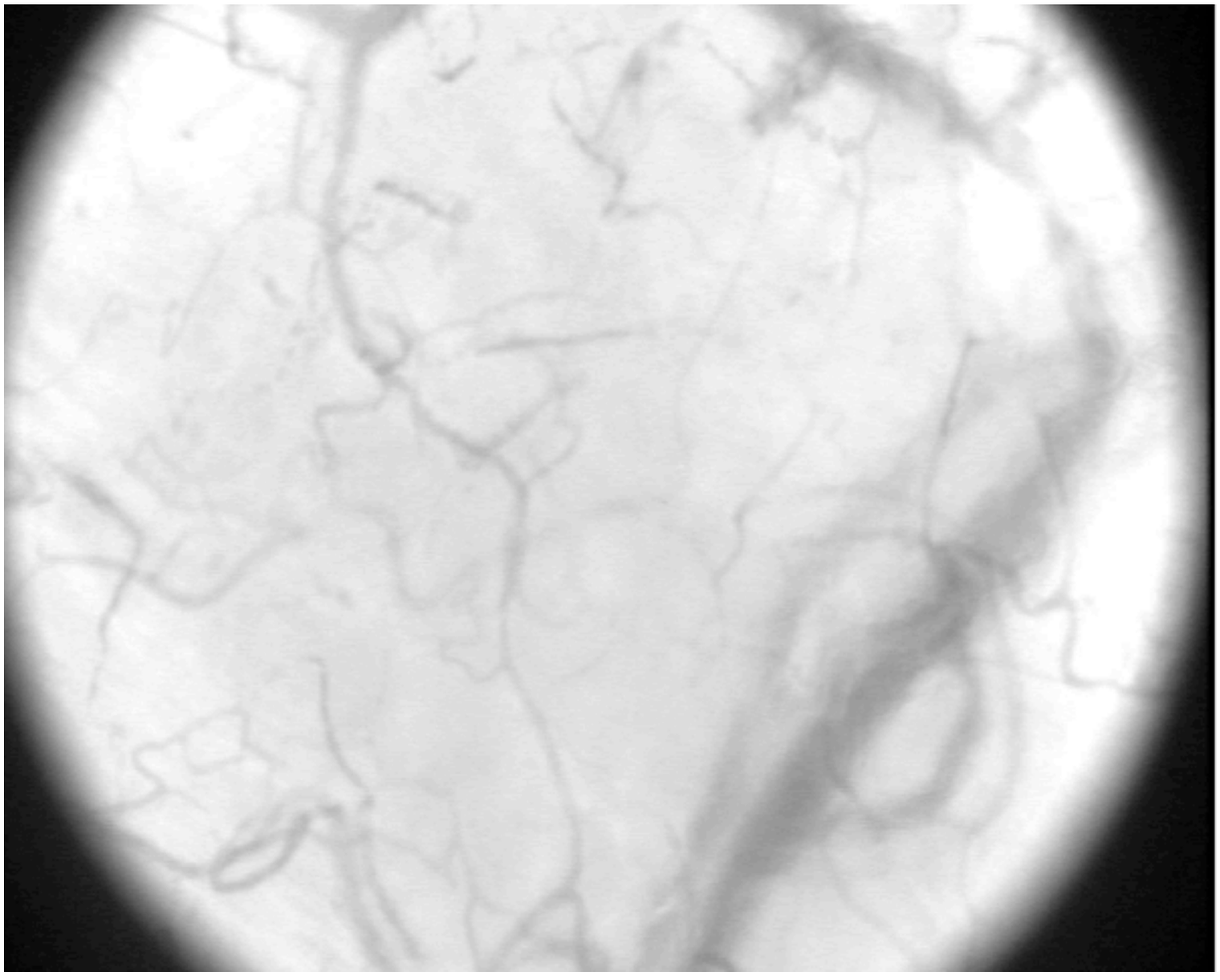
Microcirculation in Sepsis



Microcirculation in cardiogenic shock

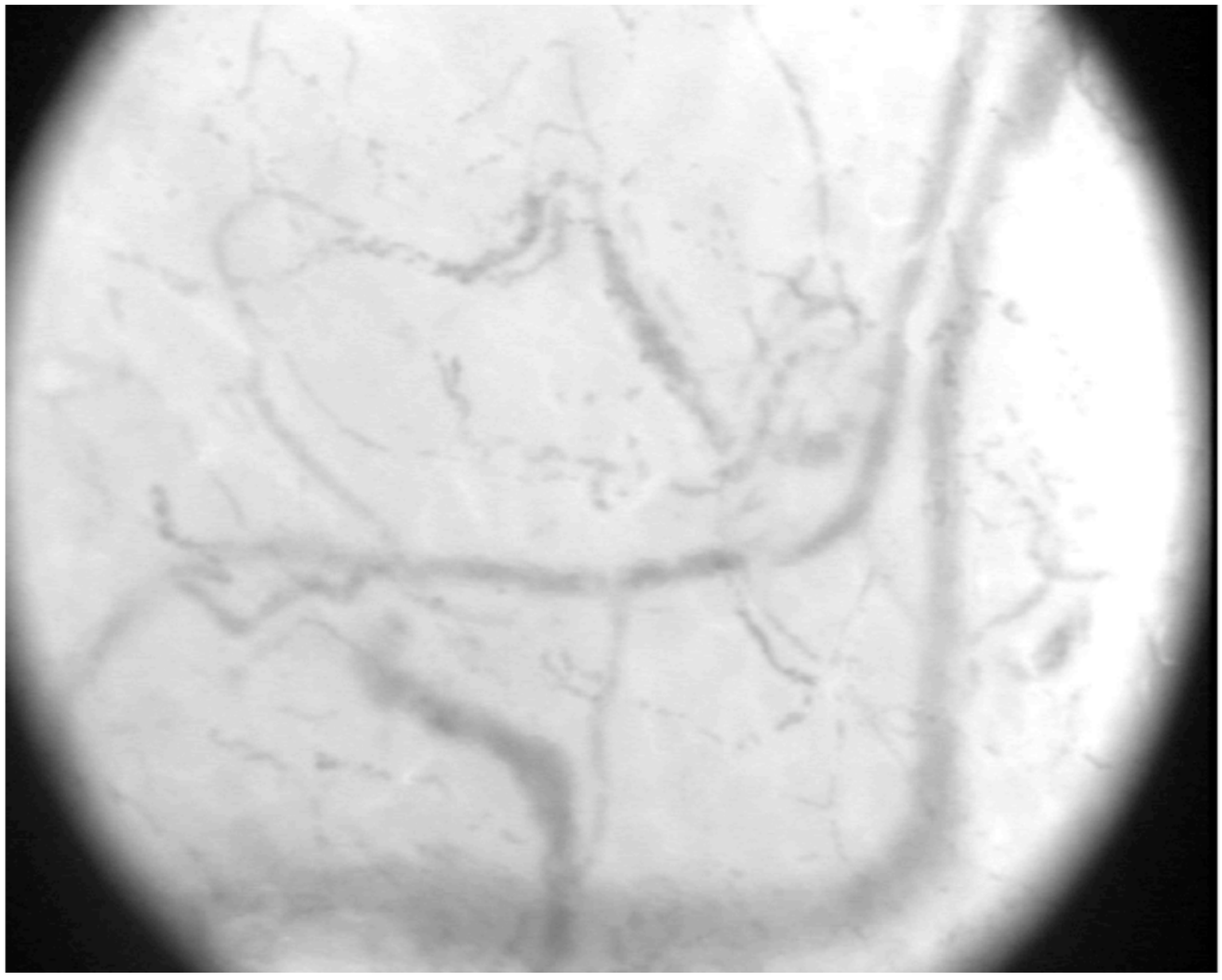


Microcirculation before terlipressin



MAP 58
HR 98
CVP 13
UO 20 ml/hr

Microcirculation after terlipressin

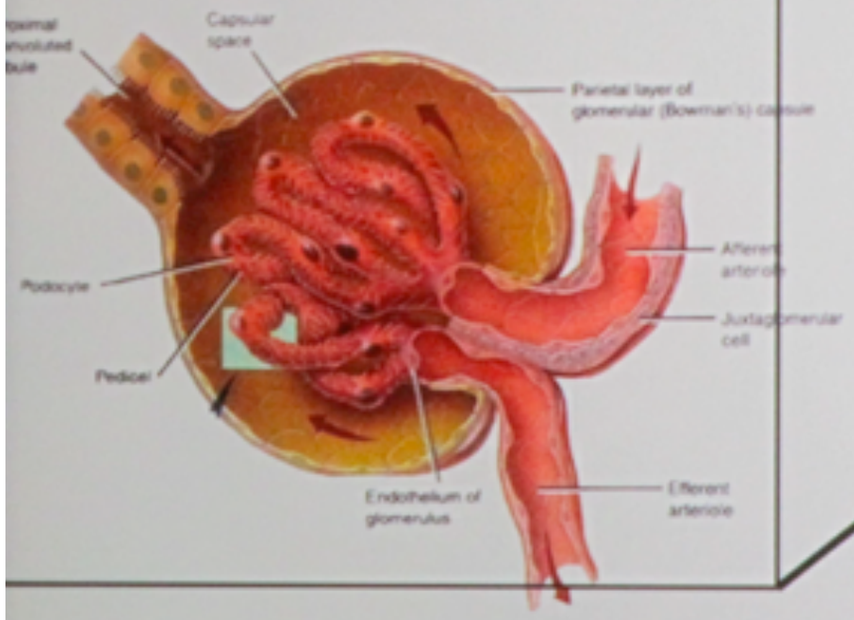


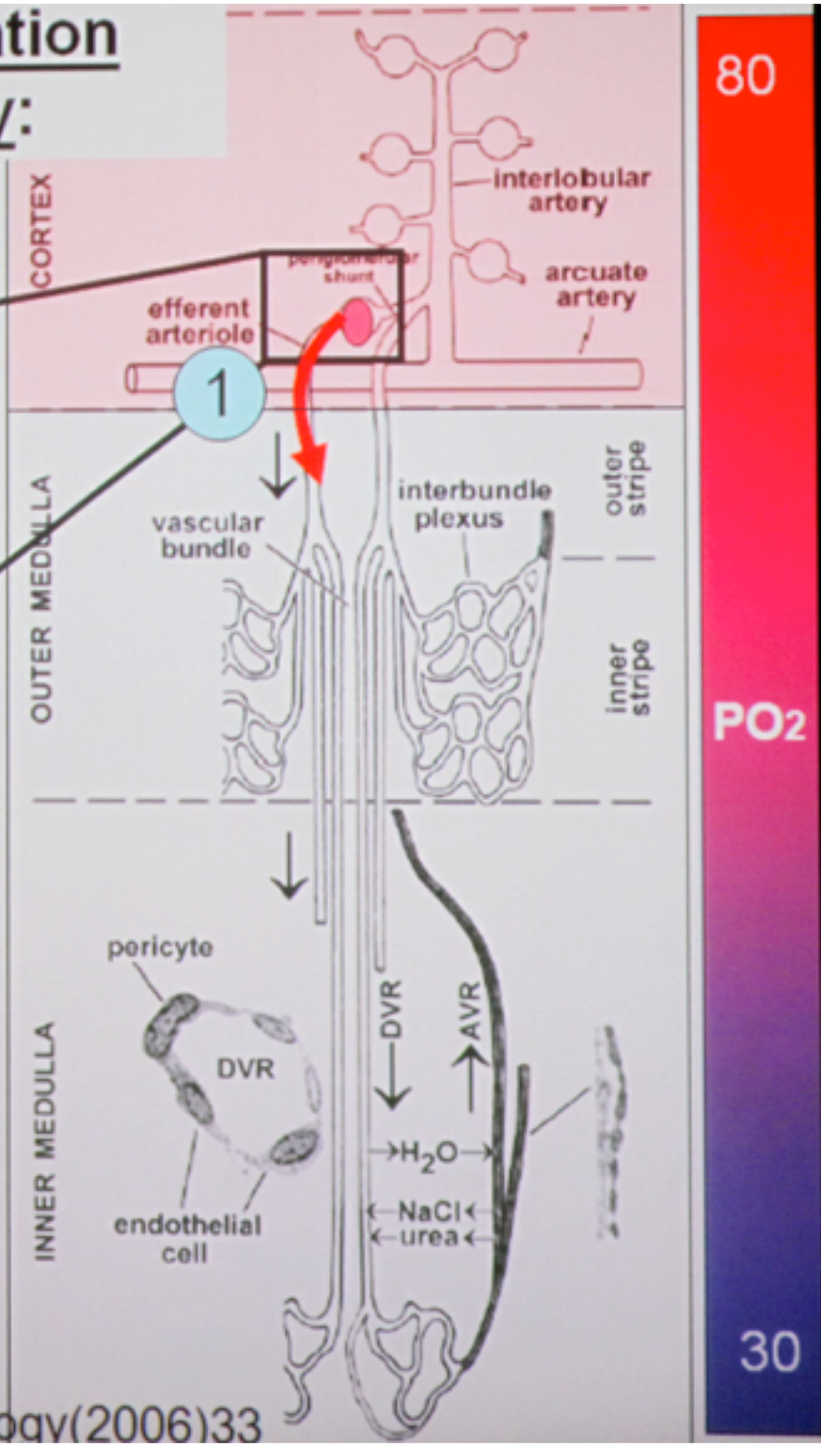
MAP 80
HR 98
CVP 12
UO 110 ml/hr

Renal

The renal microvasculature organization compromises tissue oxygen delivery:

1 Low medullary blood flow



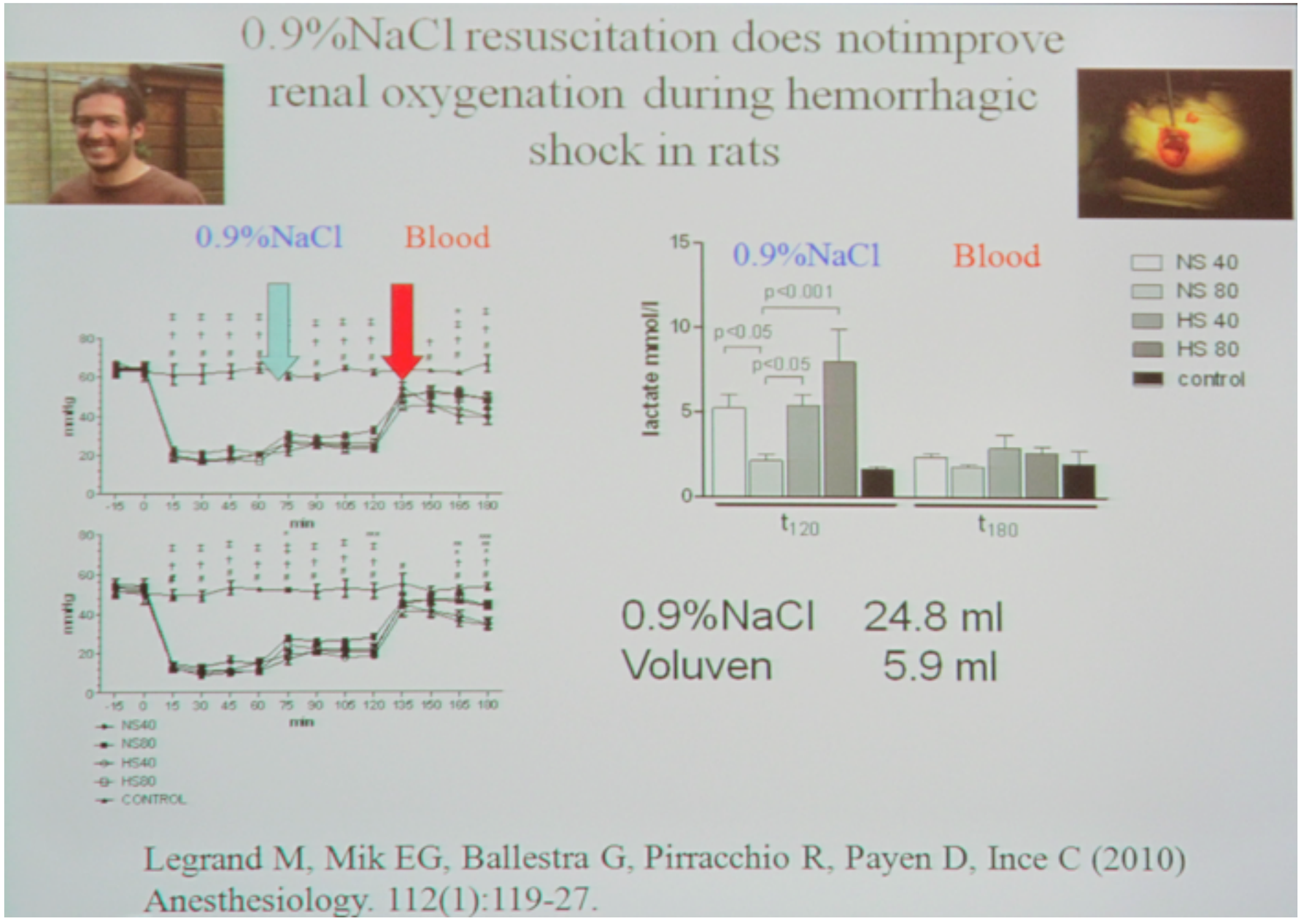


O'Connor et al. Clin Exp Pharmacology and Physiology(2006)33

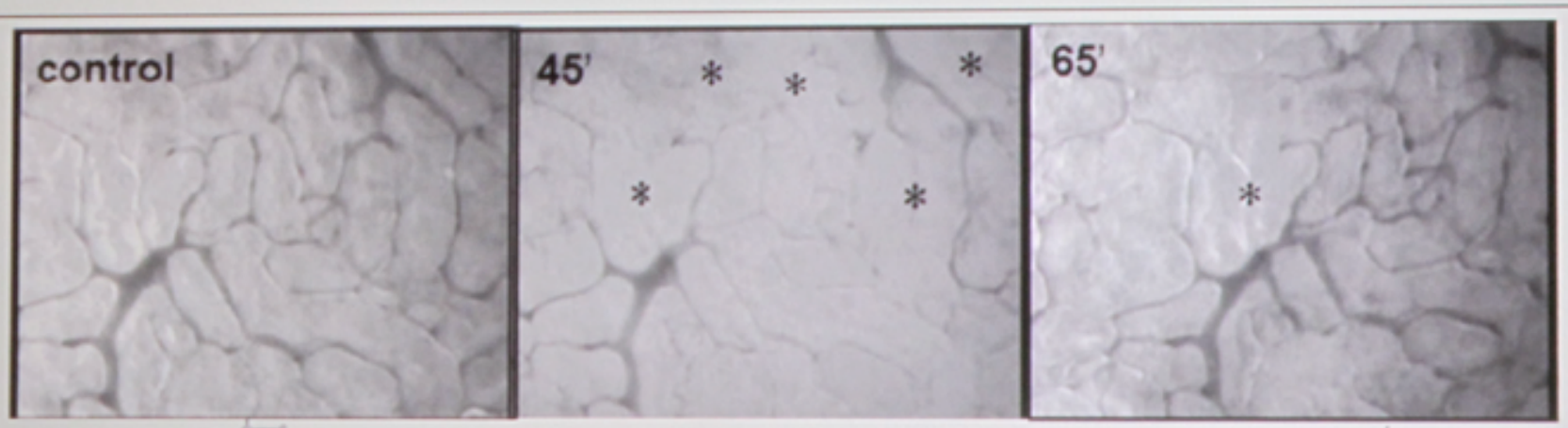
Comparisons of fluid management capability

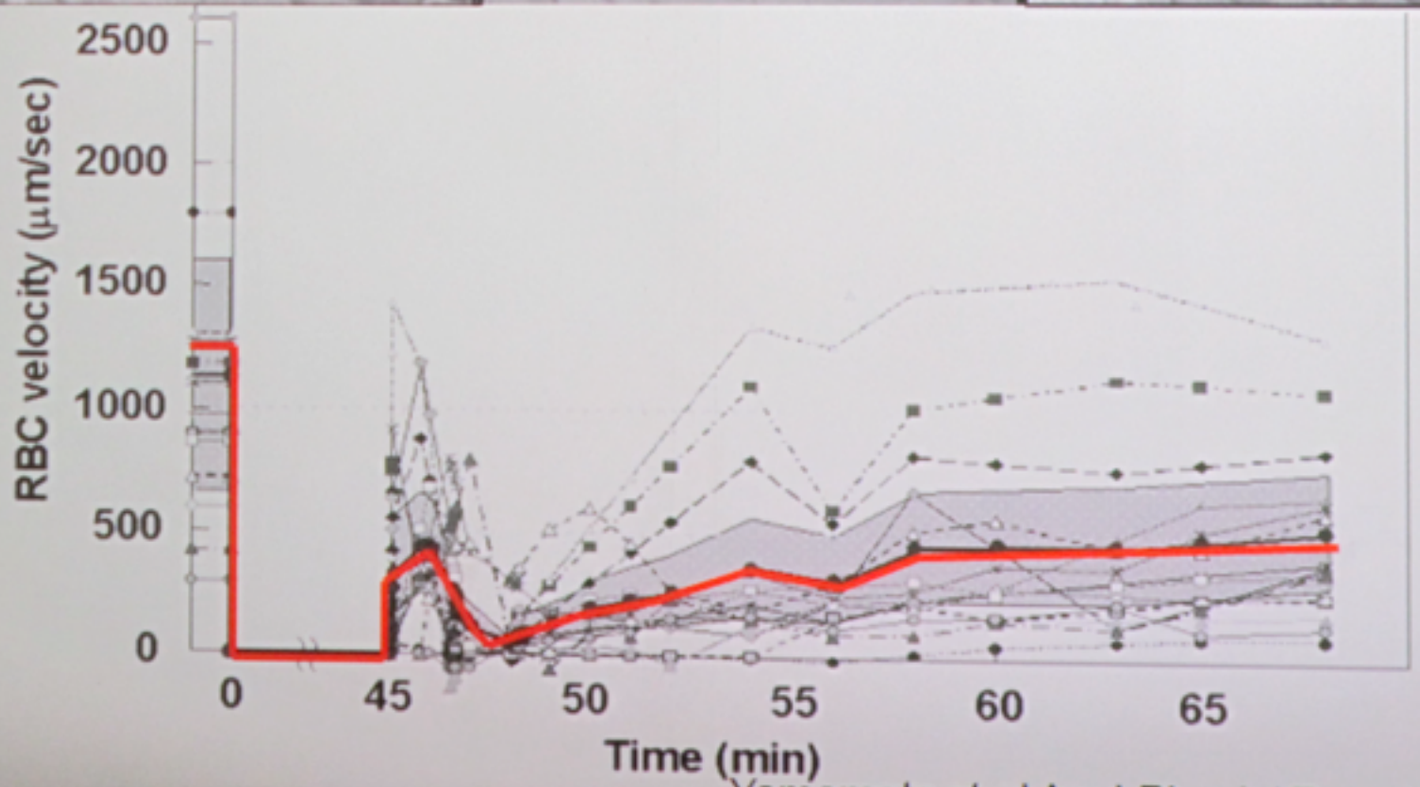
	Normal Kidney	Intermittent HD	Peritoneal Dialysis	CRRT
Ultrafiltration (ml/min)	120	34	14	100
Vol. of filtrate (L)	173	8	14	144
Vol. removed/day (L)	0.1-1.5	0-8	0-14	0-100
Regulatory mechanism	GFR control	UFR control	UFR control	UFR control
	Reabsorption			Replacement fluid
Sensing mechanism	Hemodynamic			? hemodynamic status
	Volume status			? vol. status

Look this up in anesthesiology



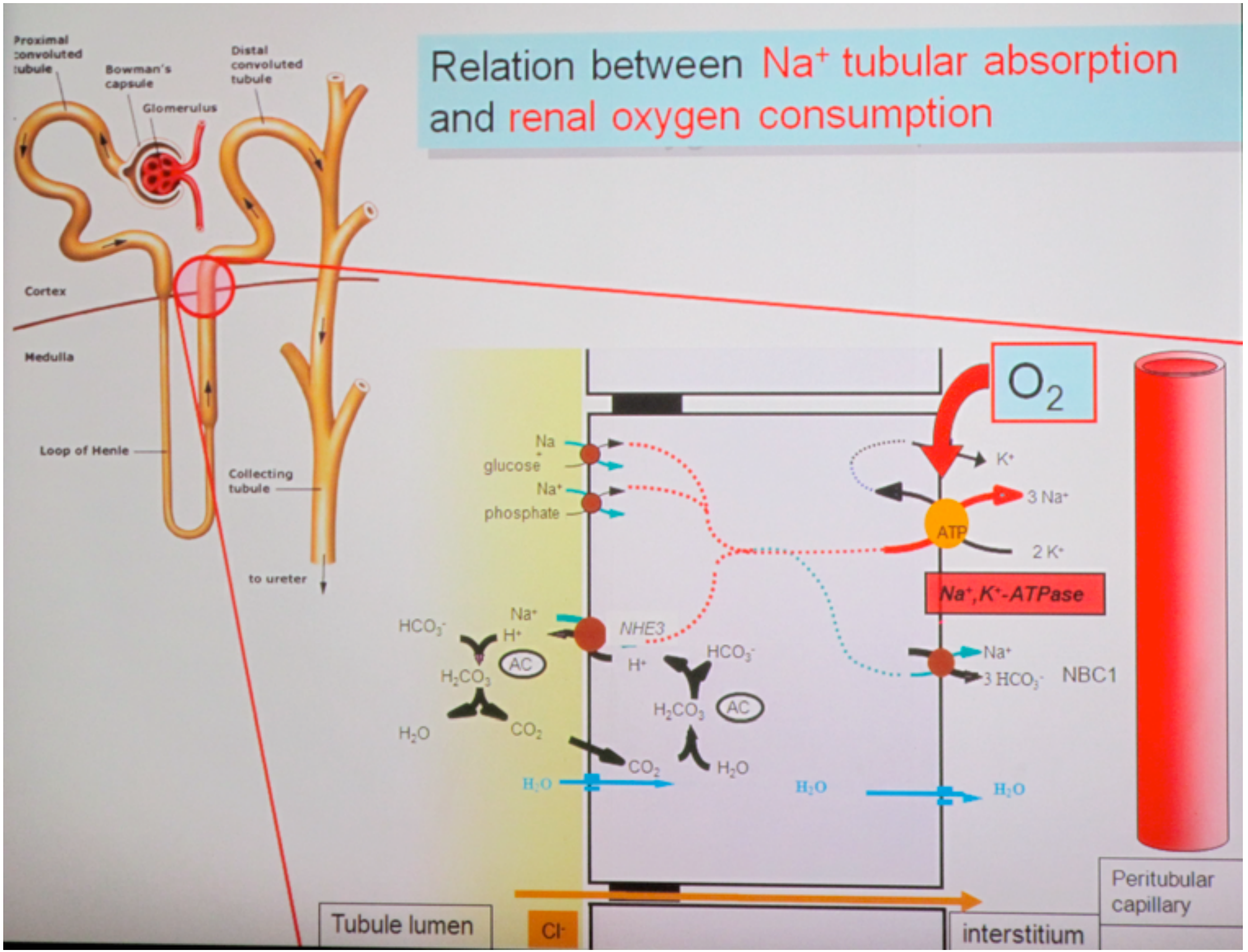
Ischemia-reperfusion hits the MICRO-circulation of the kidney

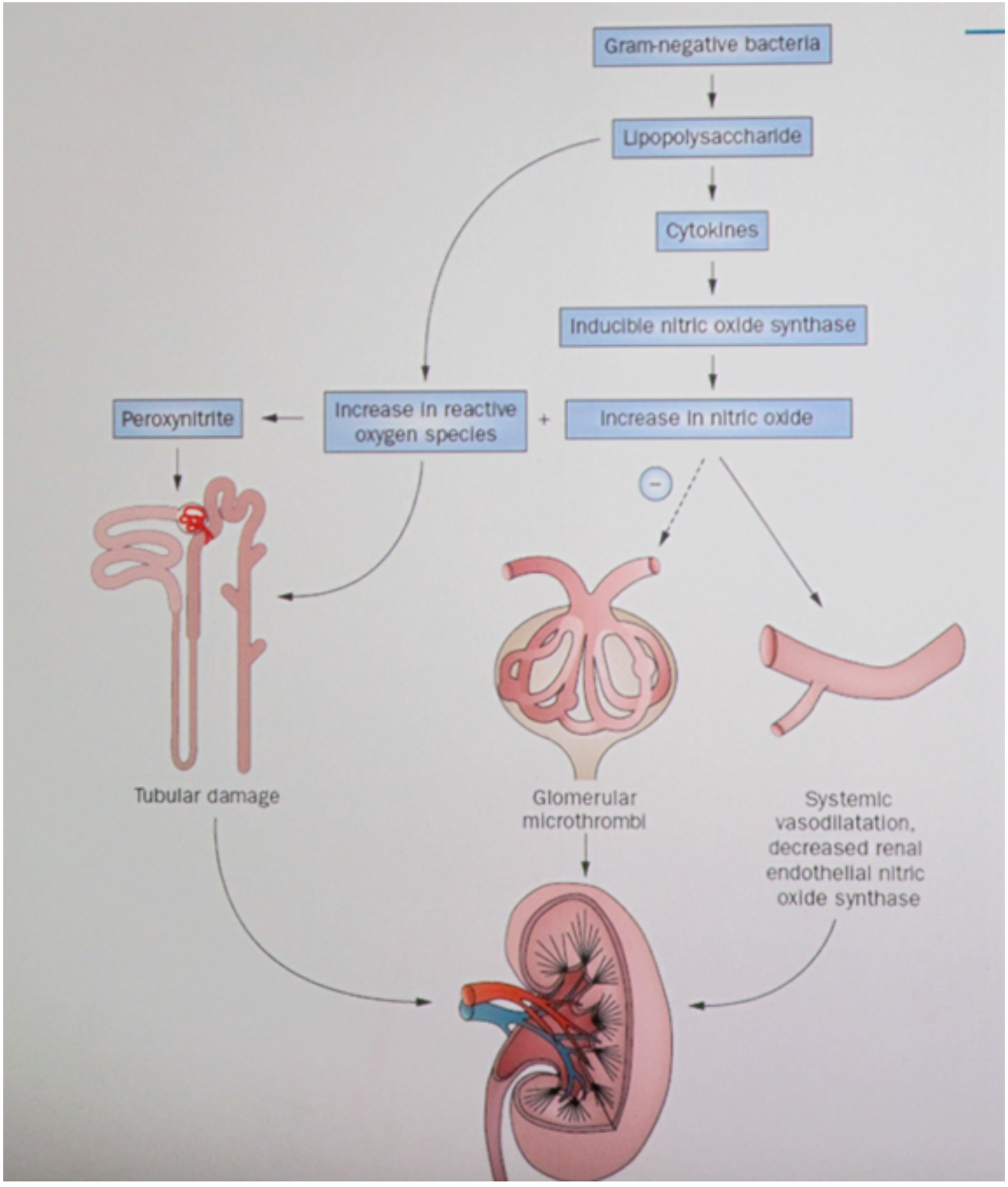




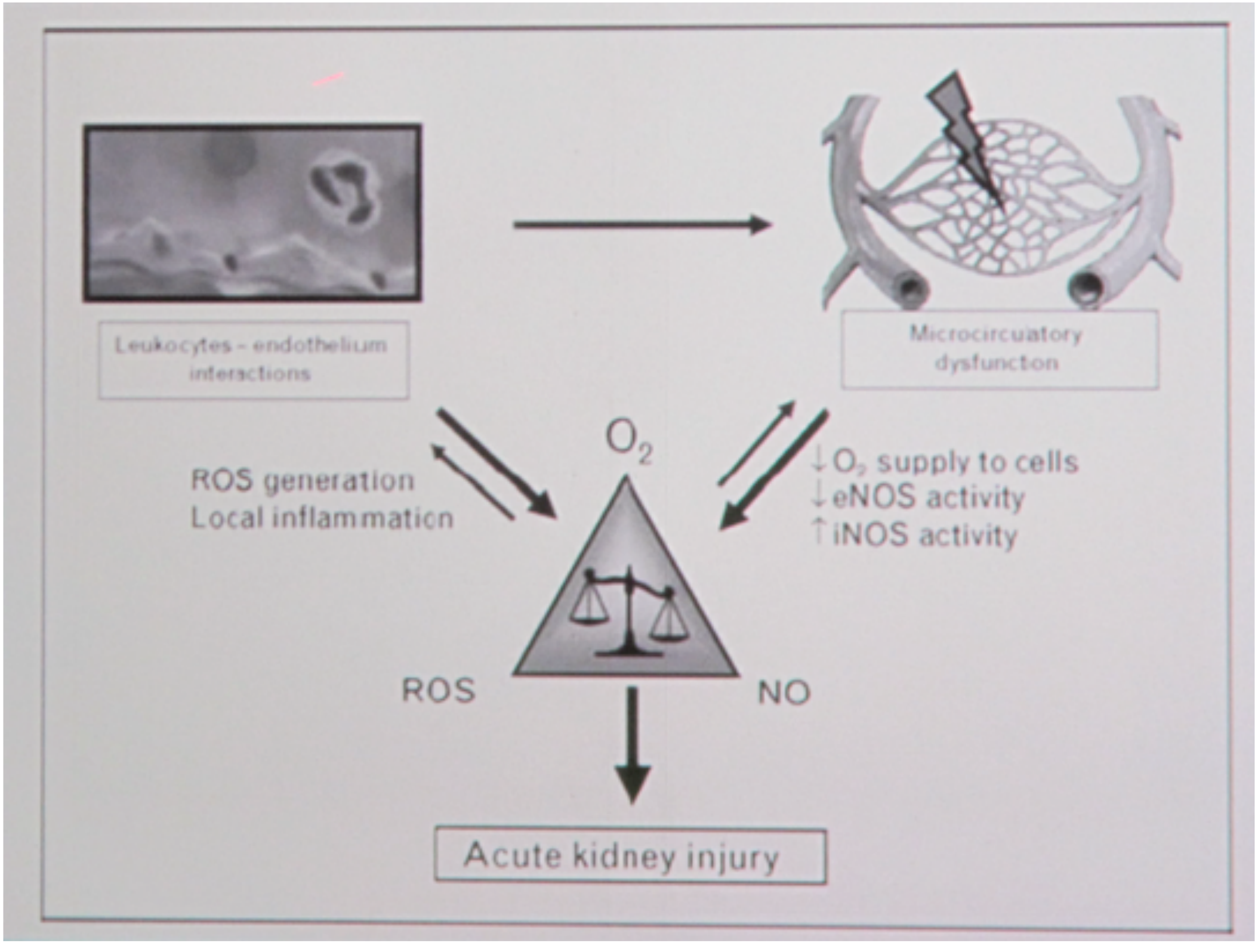
Yamamoto et al AmJ Physiol Renal Physiol 2002

Relation between Na^+ tubular absorption and renal oxygen consumption

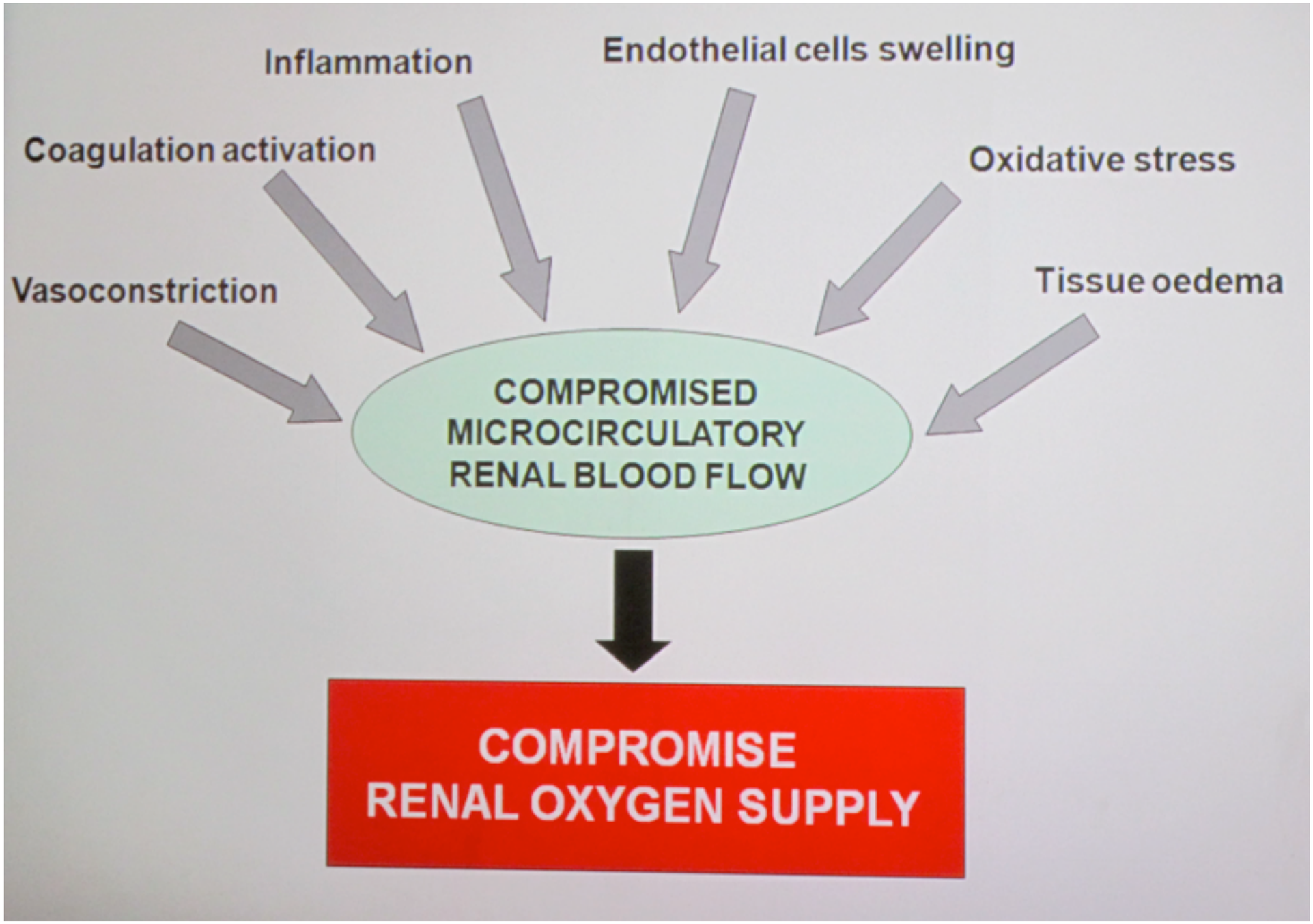



Gram-negative bacteria
Lipopolysaccharide
Cytokines
Inducible nitric oxide synthase
Peroxynitrite
Increase in reactive oxygen species
+
Increase in nitric oxide
−
Tubular damage
Glomerular microthrombi
Systemic vasodilatation, decreased renal endothelial nitric oxide synthase

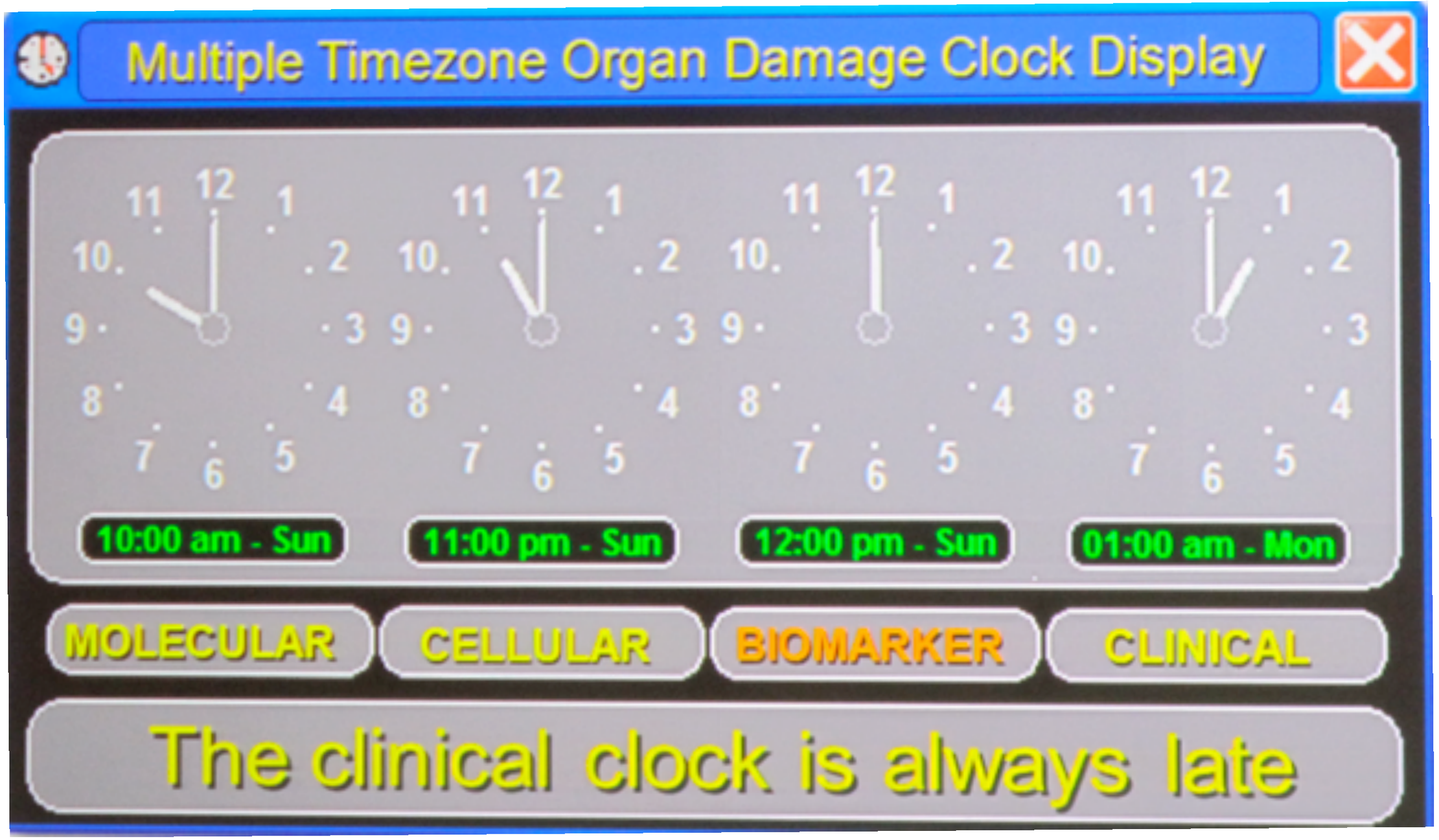
Role of the microcirculation in acute kidney injury



Curr Opin Crit Care 15:503-508



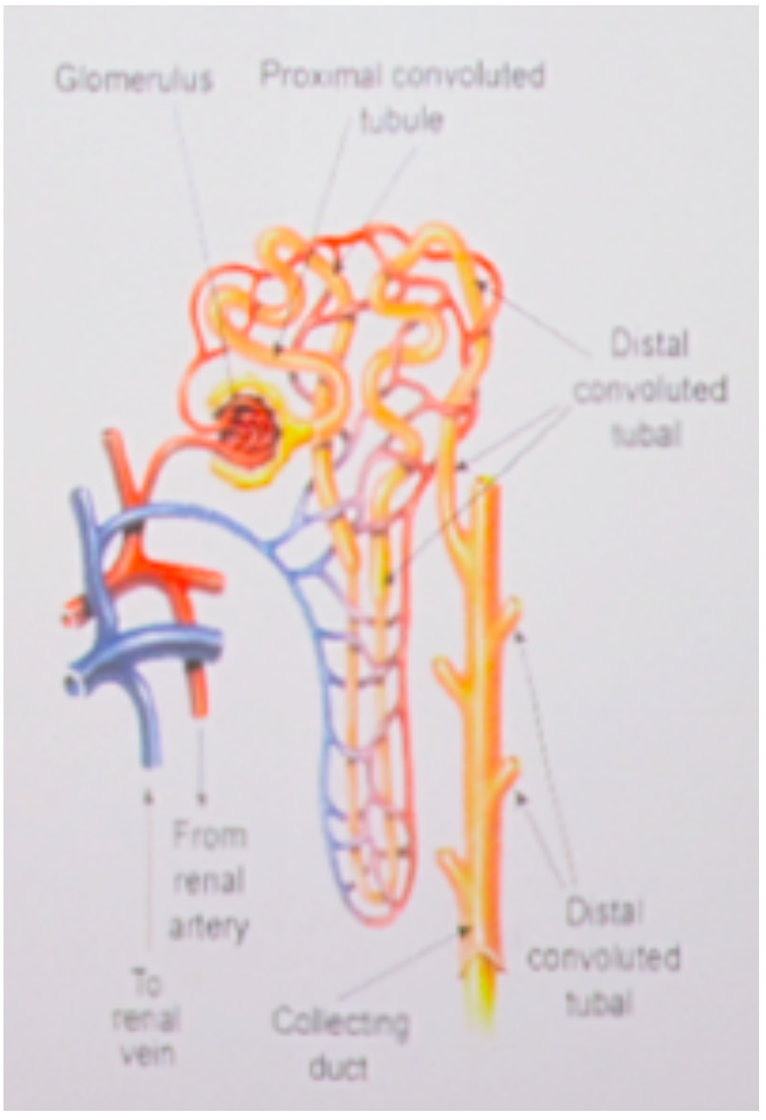
Legrand et al. Mol Med 2008



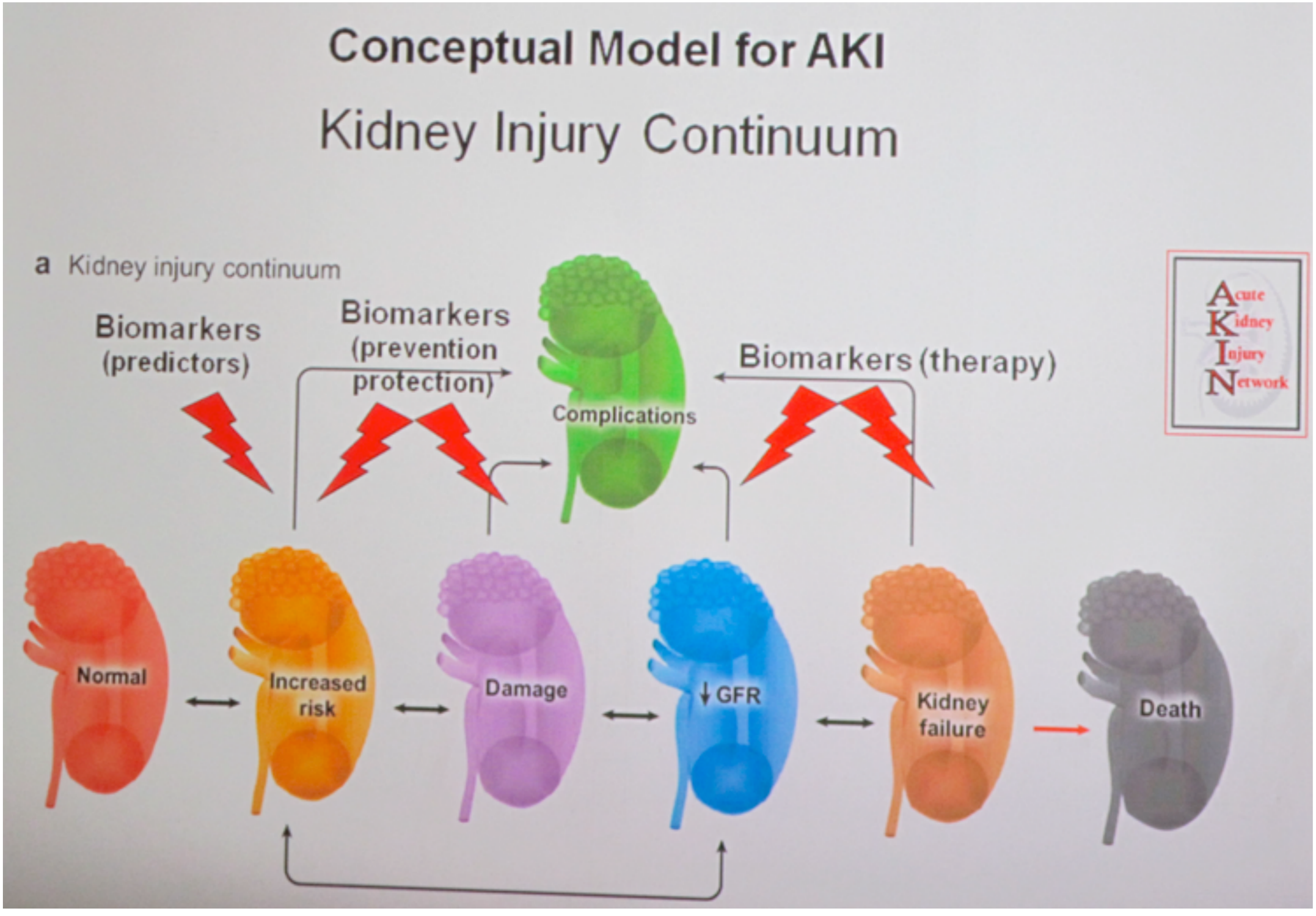
Injury begins inducing molecular modifications subsequently evolving into cellular damage. Cells start to produce biomarkers of injury well before the clinical syndrome develops.

Neutrophil gelatinase-associated lipocalin (NGAL)

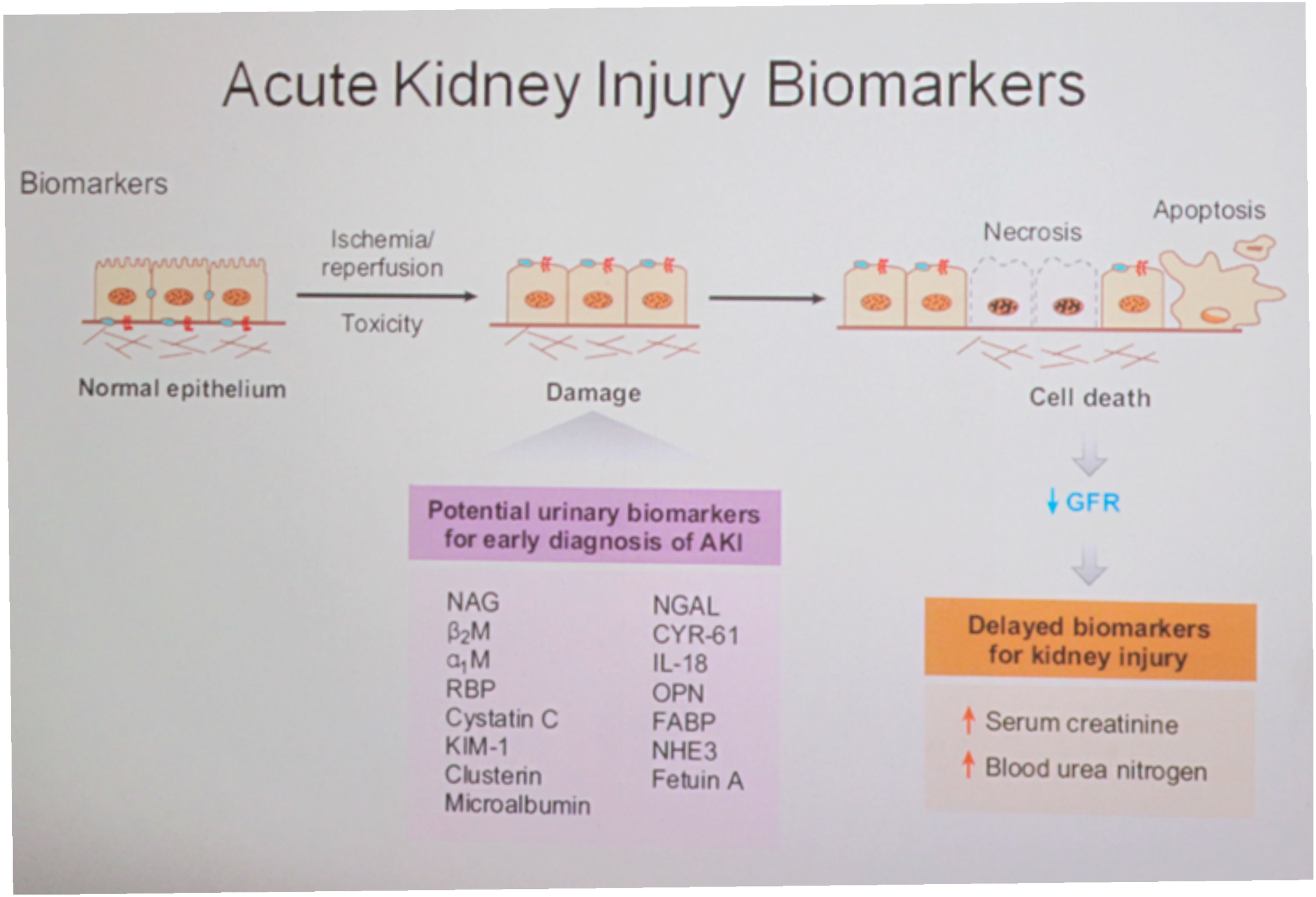
- 25-kDA protein
- Bound to gelatinase of neutrophils
- Expression in injured epithelia of trachea, lungs, stomach, colon, and kidney
- Upregulation proximal tubules
- May induce re-epithelialization and reduce apopotosis



Conceptual model for AKI- Kidney Injury Continuum



Acute Kidney Injury Biomarkers



Cystatin C

- Cystatin C is a cysteine protease inhibitor released into the blood by all nucleated cells. > 99% is cleared by the GFR and tubular reabsorption. The urine content is negligible under physiological conditions.
- Cystatin C levels are not affected by age, gender nor muscle mass. It is a better predictor of glomerular function than creatinine.
- In the ICU, a 50% increase predicts AKI 1-2 days before the rise in serum creatinine.
- During CVVH there is no change in serum concentration of cystain C. This suggests that it can be used to monitor renal function.

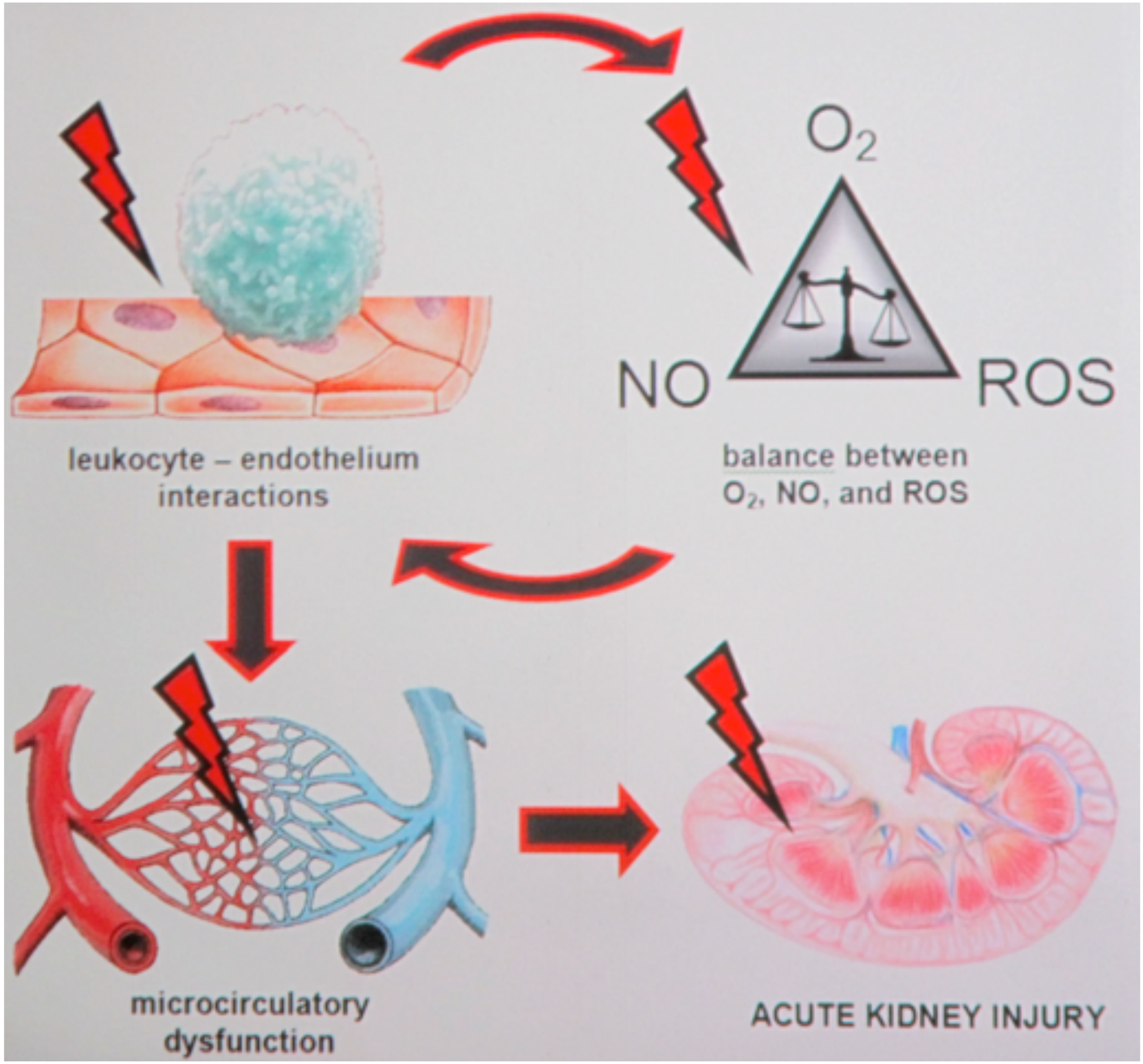
Biomarkers

CONCLUSIONS

- Serum cystatin C, plasma and urine NGAL and urine IL-18 perform best for early diagnosis of AKI.
- Serum cystatin C, urine interleukin-18 (IL-18), and urine kidney injury molecule-1 (KIM-1) perform best for the differential diagnosis of established AKI.
- Urine *NAG*, KIM-1, and IL-18 perform best for mortality risk prediction after AKI.

This brings new hope for a timely diagnosis of AKI and a timely institution of measures for prevention, protection and RRT. These biomarkers represent a unique possibility for a timely diagnosis of AKI, and protection of the kidney from further insults.
Large studies are needed to define their applicability to different types of AKI and the incremental prognostic value over traditional clinical variables.

Pathogenesis of acute kidney injury



Hepatic

SBP-induced circulatory dysfunction defined mechanisms

Spontaneous bacterial peritonitis

Albumin

Arterial vasodilation
Cardiac dysfunction
Cytokines, NO, CO

Impairment of effective arterial blood volume

Activation of vasoconstrictor systems

Reduced renal perfusion

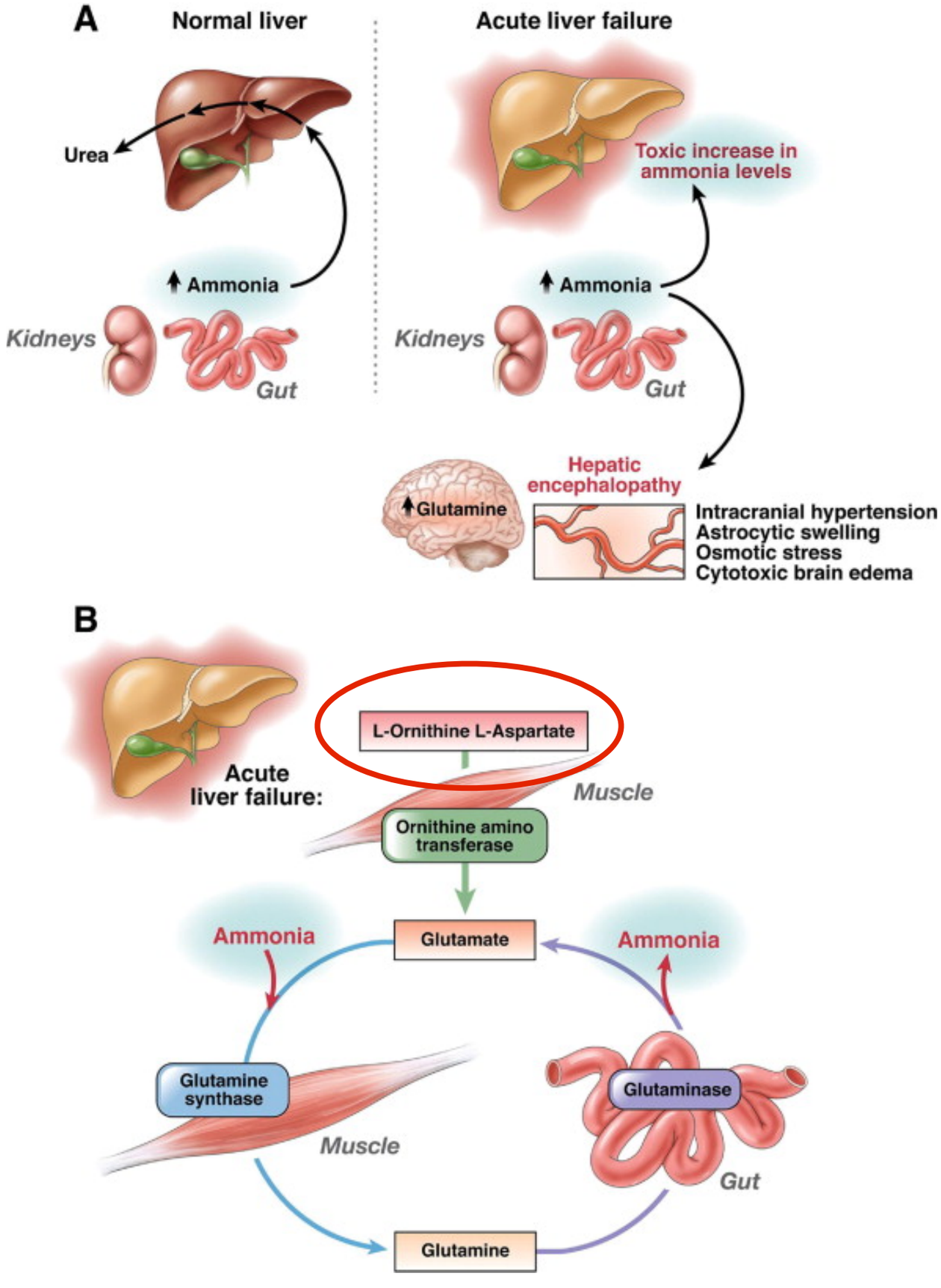
Hepatorenal syndrome

Acute variceal bleeding

- Best practice - elective intubation within ICU environment
- Meta-analysis of 40 yrs reduction in mortality 65 -> 40% (2001)
- Recent study 12% in hospital mortality (2006)
- Survival related to:
    - Child’s score
    - Renal dysfunction

Advanced liver disease/aetiology

- Increased severity correlate with outcome
  - CP>=12-85%
  - MELD 30-9 - 77%
- ICU scoring systems
  - SOFA (includes liver) best - 3 organ failure >90% mortality



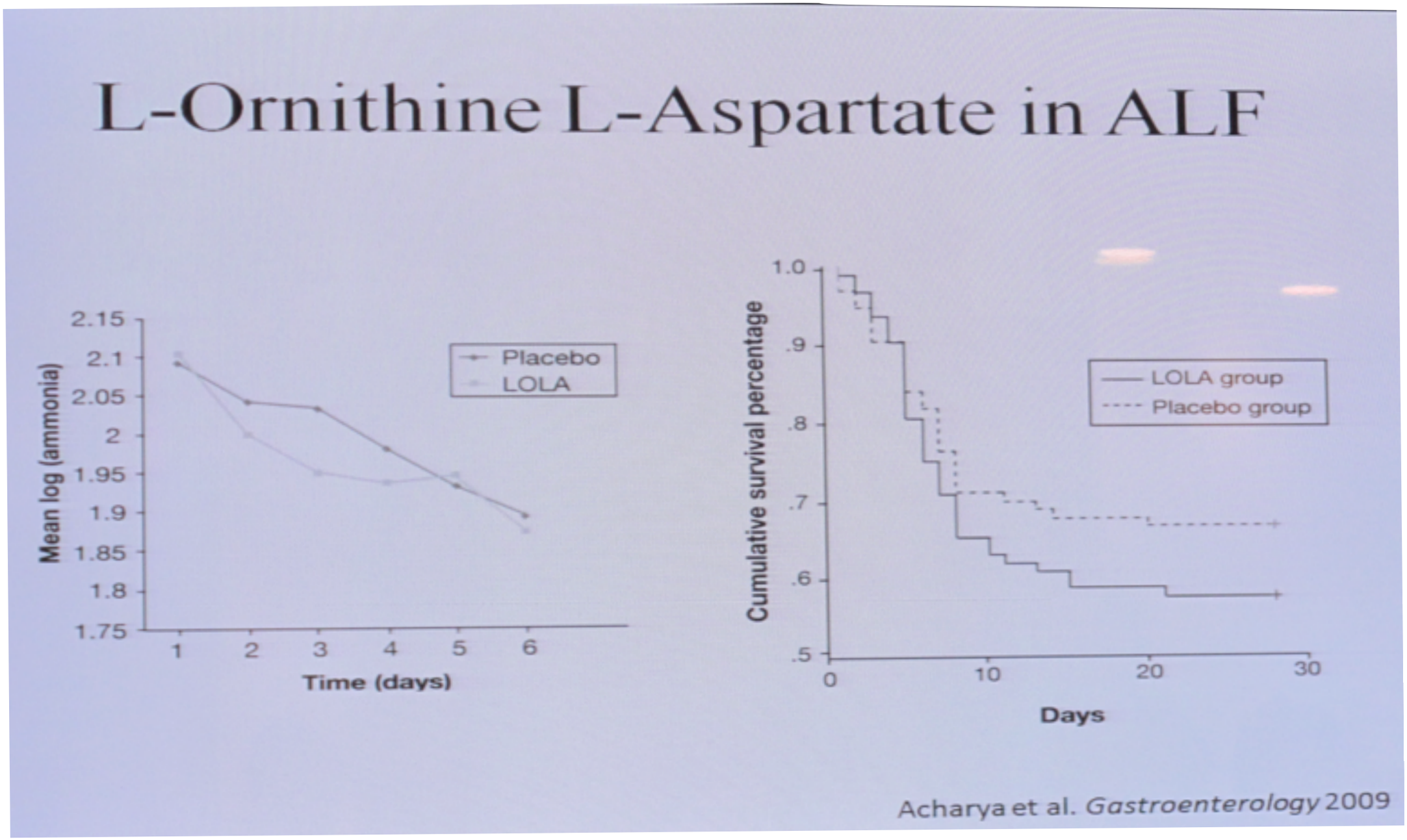
Severe liver dysfunction--> impaired urea synthesis.

Ammonia + glutamate --> glutamine (major **alternative** ammonia de-tox pathway)

If it occurs in **astrocytes** --> brain swelling.

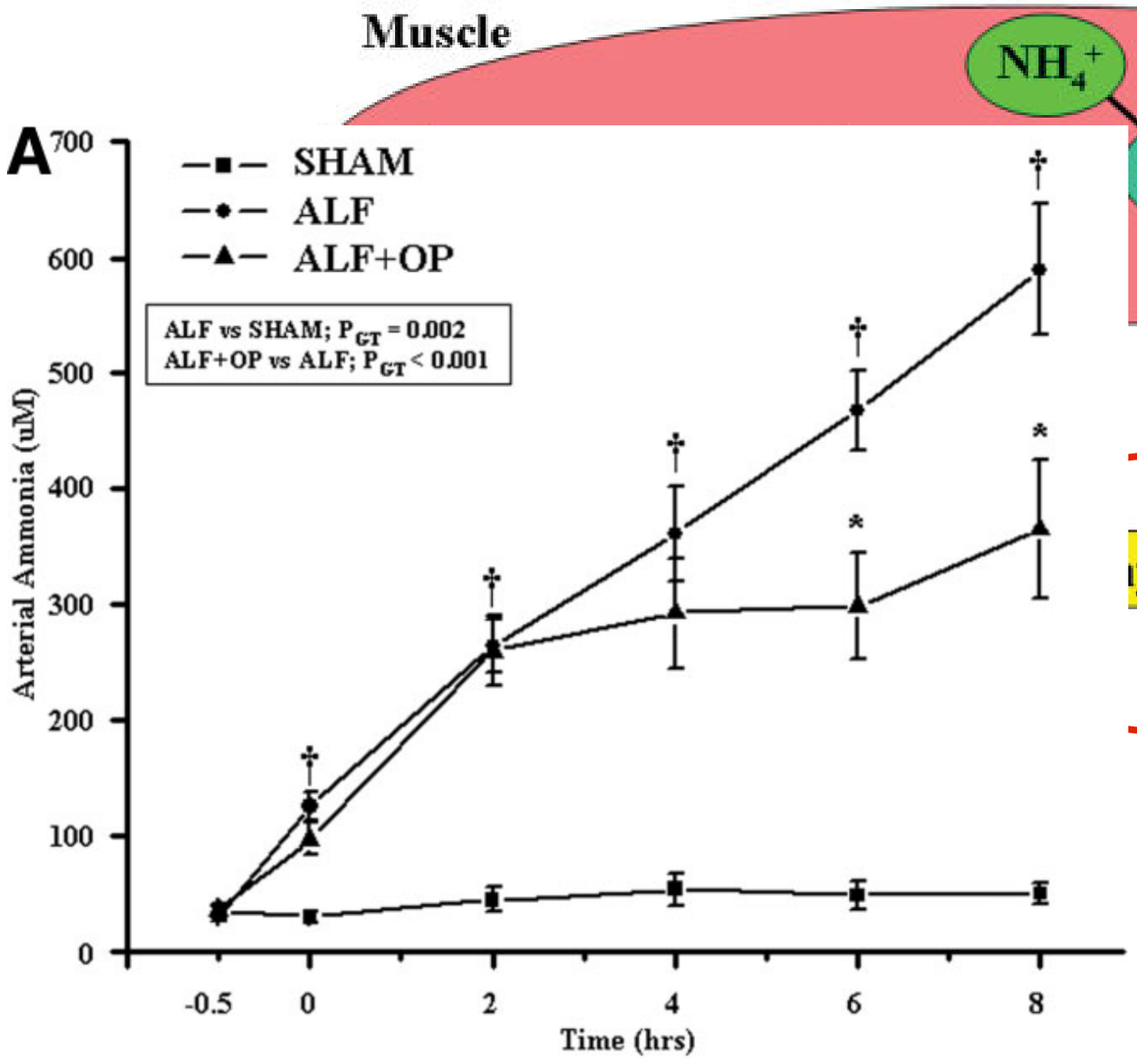
LOLA acts to stimulate glutamine synthesis in **muscle** --> ammonia detoxification.

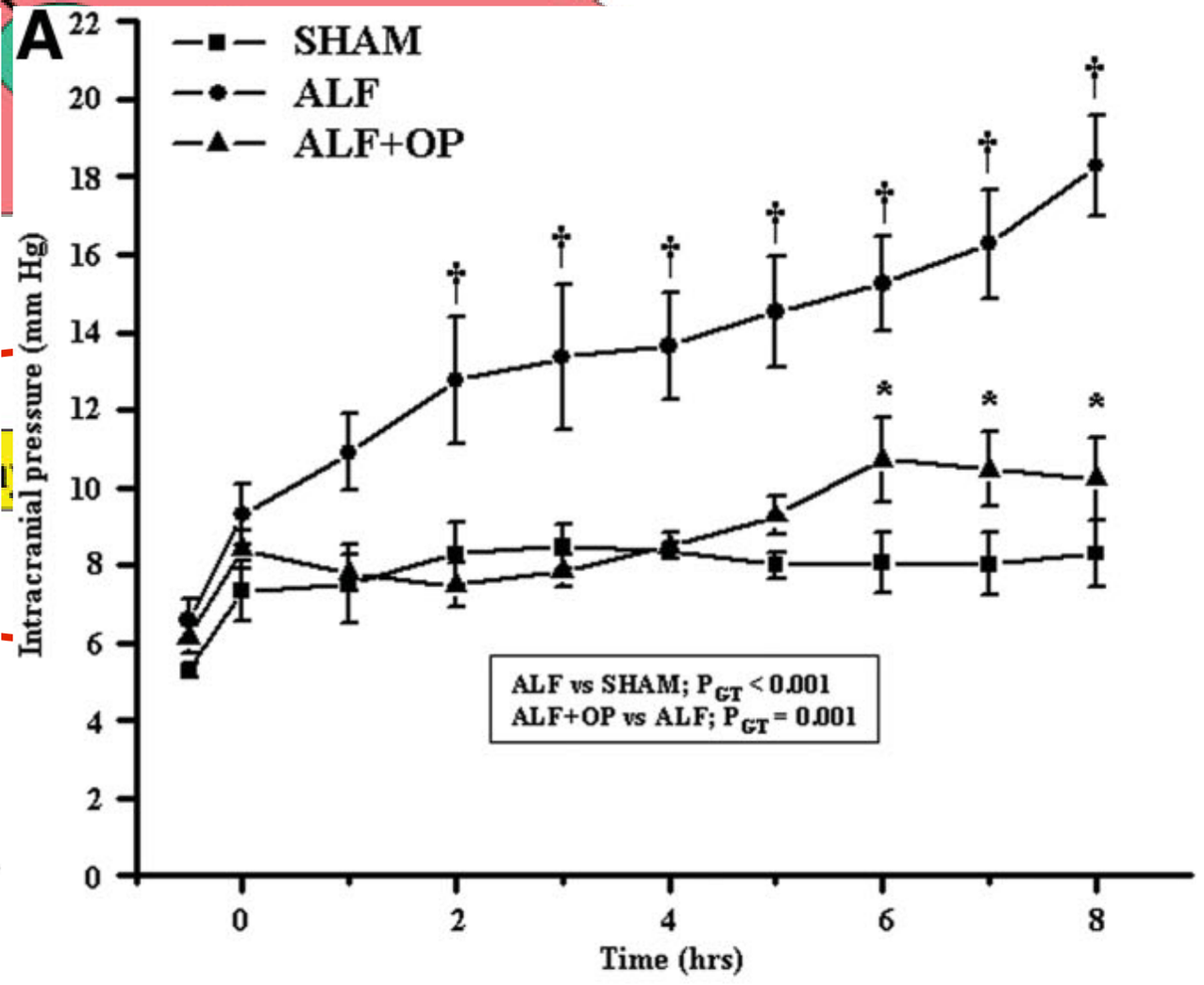
“LOLA”



But is only part of the story.....as ammonia rebound may occur, as the glutamine formed is metabolized in the gut to ammonia !

“LOPA” - L-Ornithine Phenylacetate

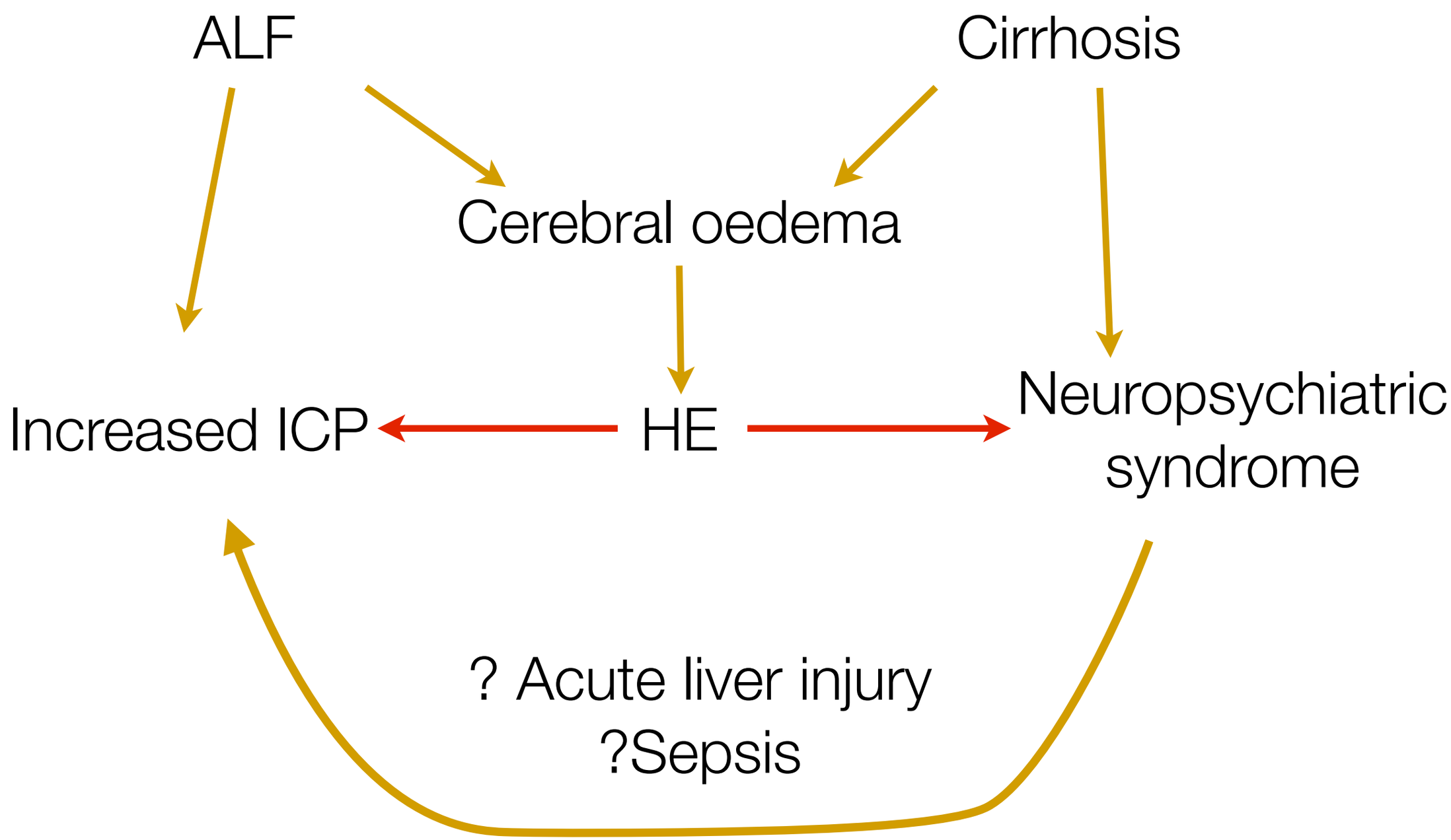




Excreted in the urine

Giving LOPA with LOLA may **stop ammonia rebound** by stopping from glutamine being metabolized in the gut to ammonia. Phenylacetate lowers ammonia by binding glutamine to form phenylacetylglutamine instead of ammonia.

Pathophysiological basis of hepatic encephalopathy in acute on chronic liver failure



Jalan et al. Int J Biochem Mol Biol 2003

How does cirrhosis predispose to ACLF

Cirrhosis → Altered gut permeability → Endotoxaemia → Priming → ACLF

Insult

Increased expression of TLR's 2 and 4 Liver, kidneys, brain

Shah et al. AASLD 2009

Prevalence of infections in liver failure

Acute liver failure	
Bacterial infections	26-80%
Fungal infections	19-30%
Cirrhosis	25-46%

Rolando et al. Sem Liv Dis 2003, Fernandez et al. Hepatology 2002

Pathogenesis of bacterial infections

Enteric bacteria

Non-enteric bacteria

Impaired hepatic RES function
Reduced systemic clearance
Portosystemic shunts

Bacterial translocation to lymphatics

Impaired mucocutaneous barriers.Instrumentation

Hemorrhage

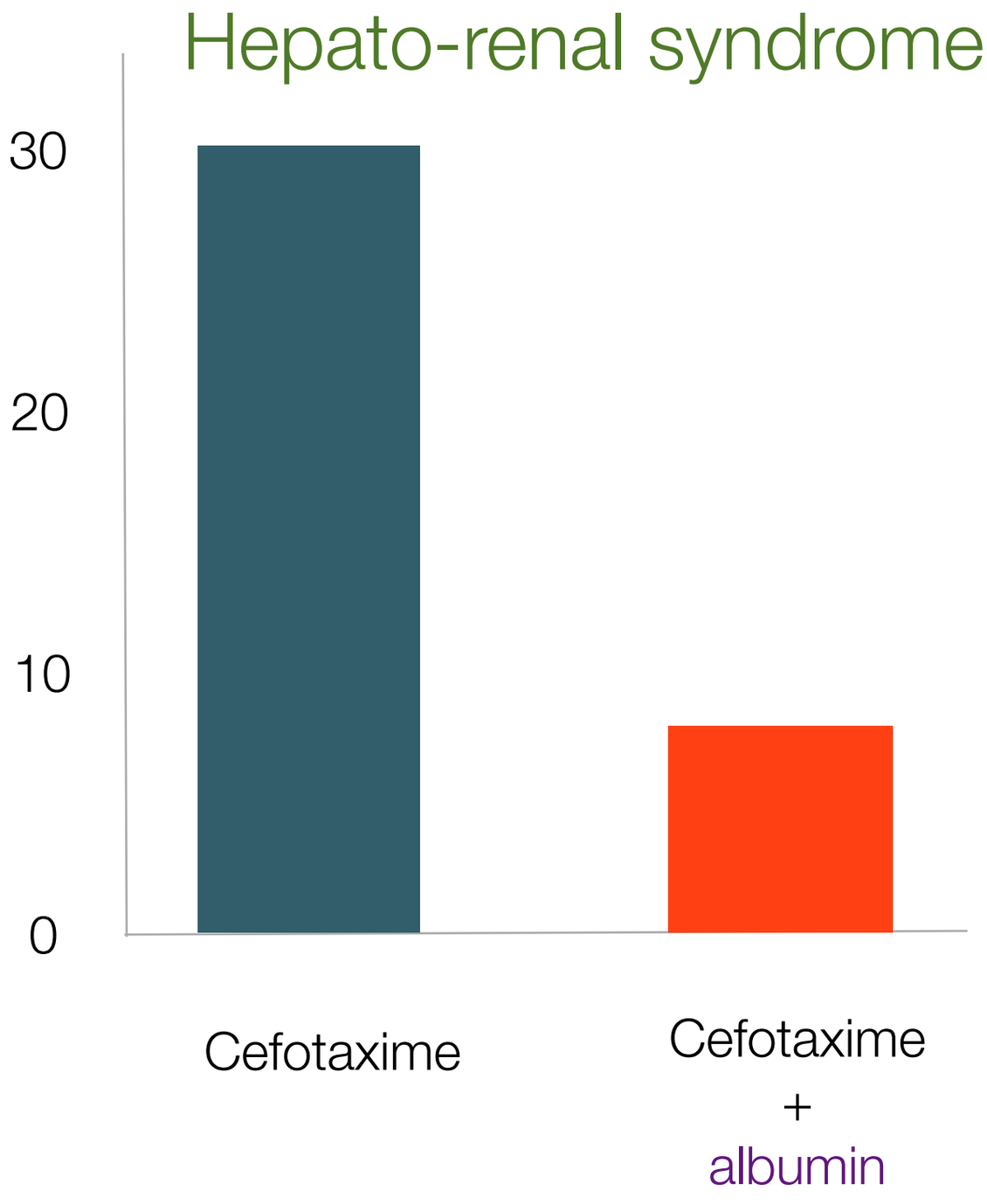
Spontaneous bacteremia

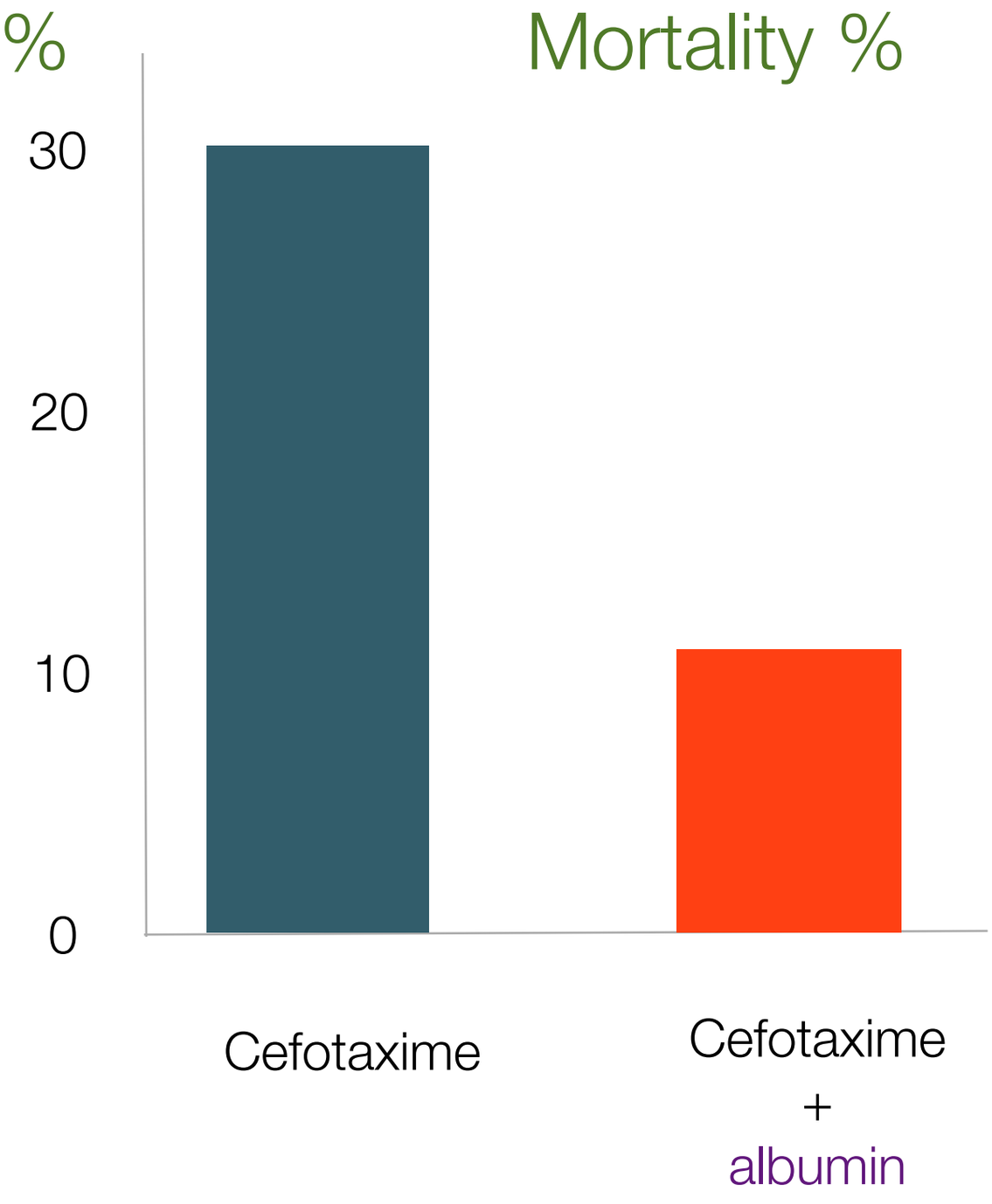
Reduced antimicrobial activity of ascitic fluid

Spontaneous bacterial peritonitis

Pneumonia, secondary bacteremia, urinary infections

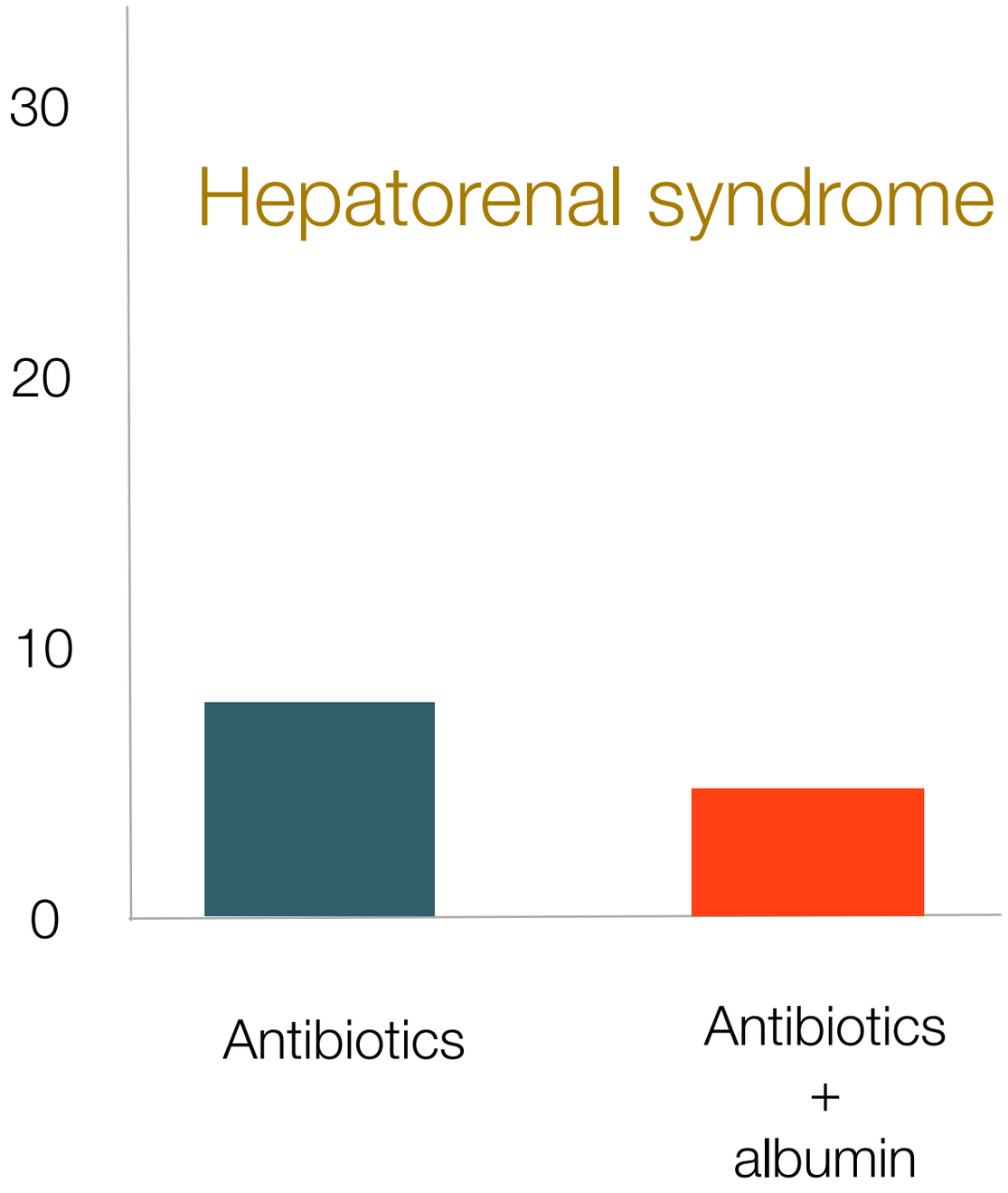
Effects of plasma volume expansion with albumin in SBP

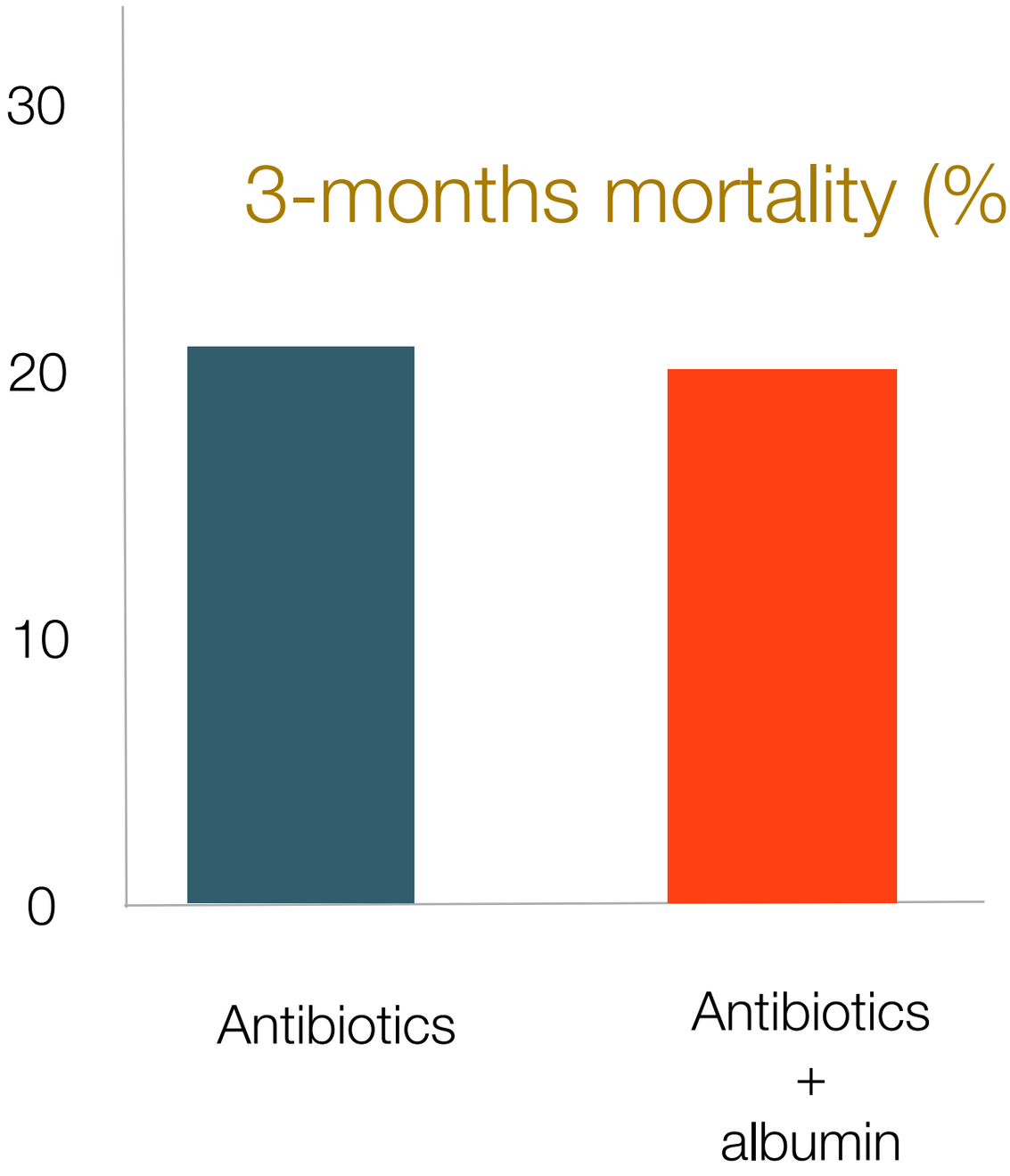




Sort et al. NEJM 1999

Effects of plasma volume expansion with albumin in non-SBP





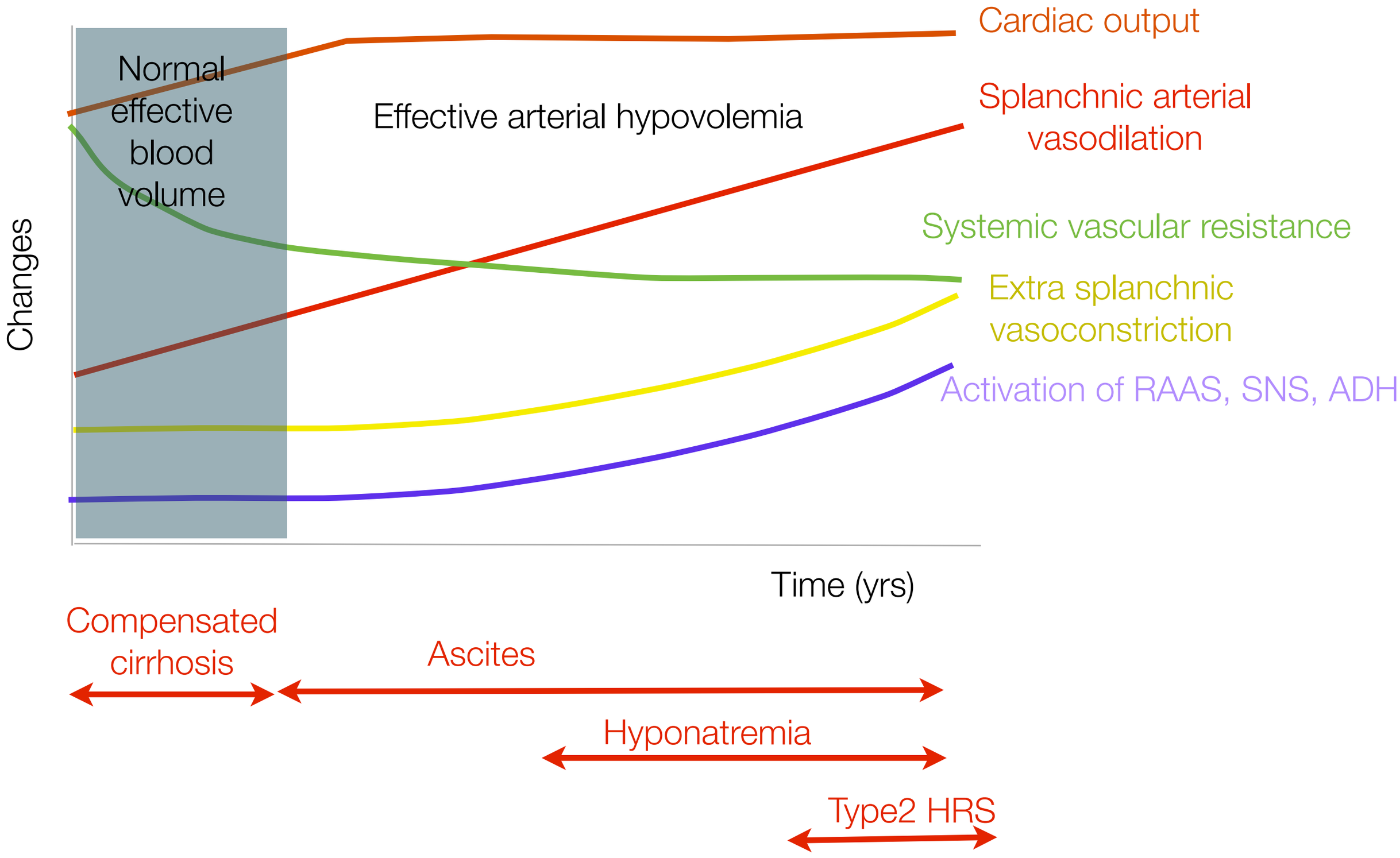
Nazar et al. J Hepatol 2009

Antibiotic prophylaxis - Current indications in liver failure

- In ALF : oral or systemic antibiotics
- In cirrhosis
  - Upper GI bleeding : oral norfloxacine 400 mg/12h during 7 days. Ceftriaxone 1g/d IV if advanced cirrhosis
  - Secondary prophylaxis of SBP : norfloxacin 400 mg/day.
  - Primary prophylaxis : Low protein ascites and poor liver or renal function

Rimois et al. J Hepatol 2003

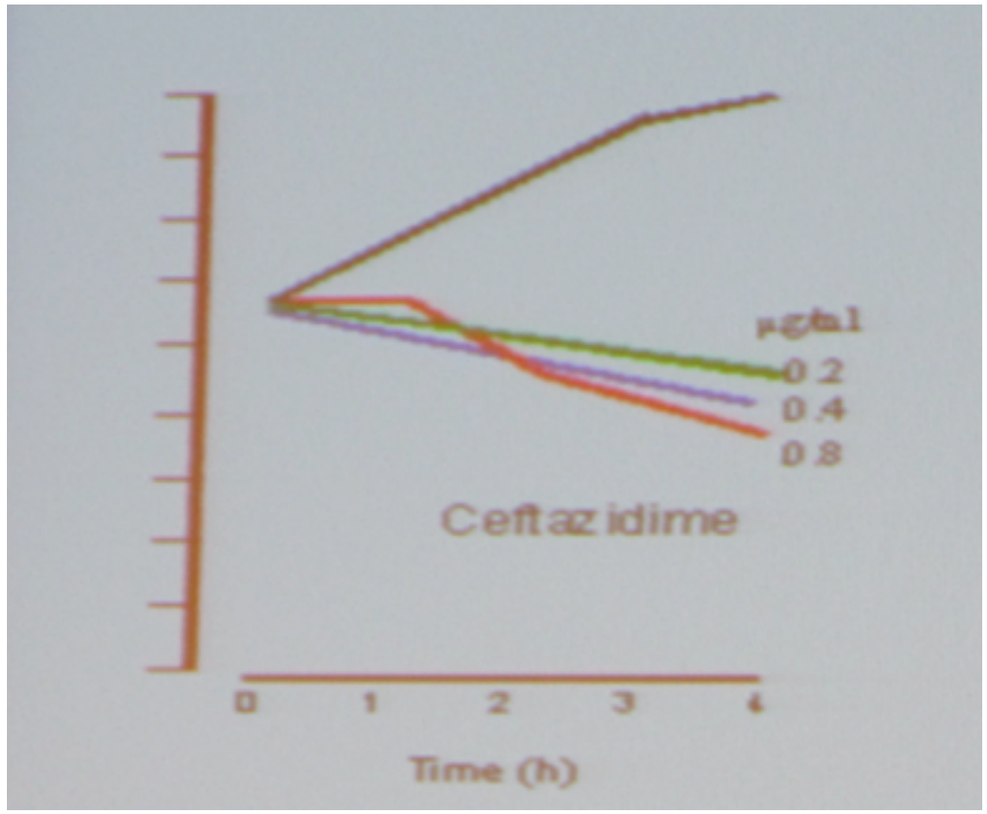
Peripheral arterial vasodilation hypothesis



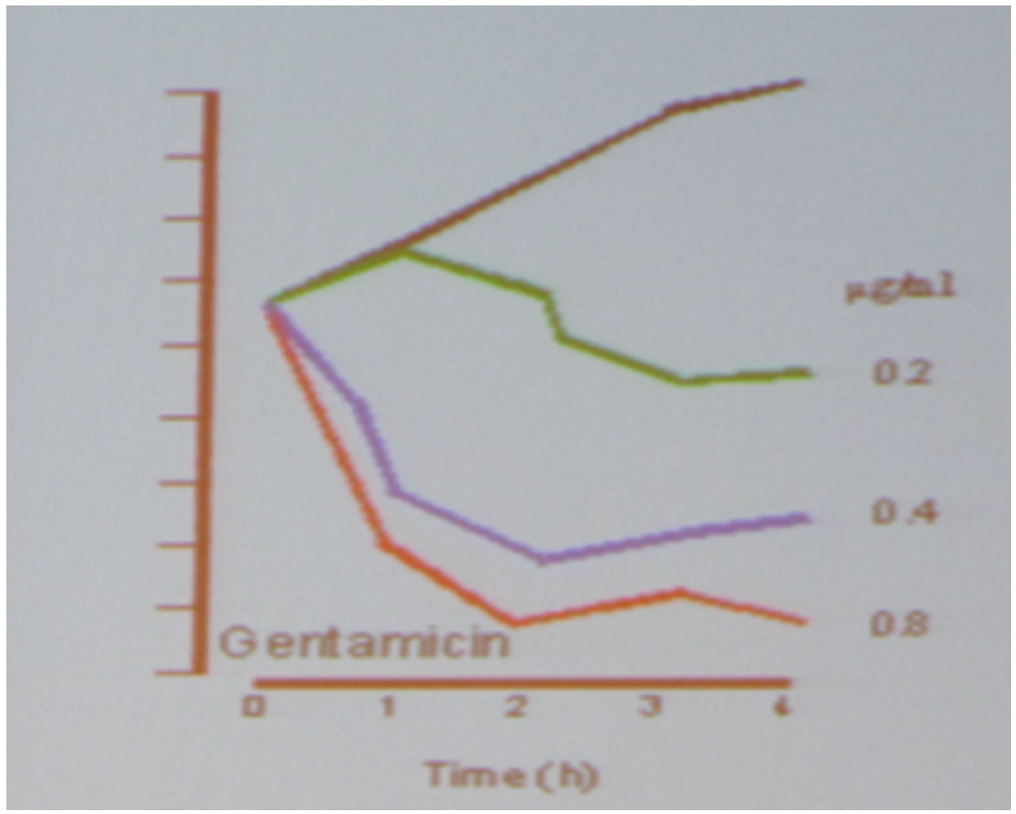
Infection

Kill characteristics

Time dependent



Concentration dependent



ß-lactams

Time>MIC

Aminoglycosides

dose dependent

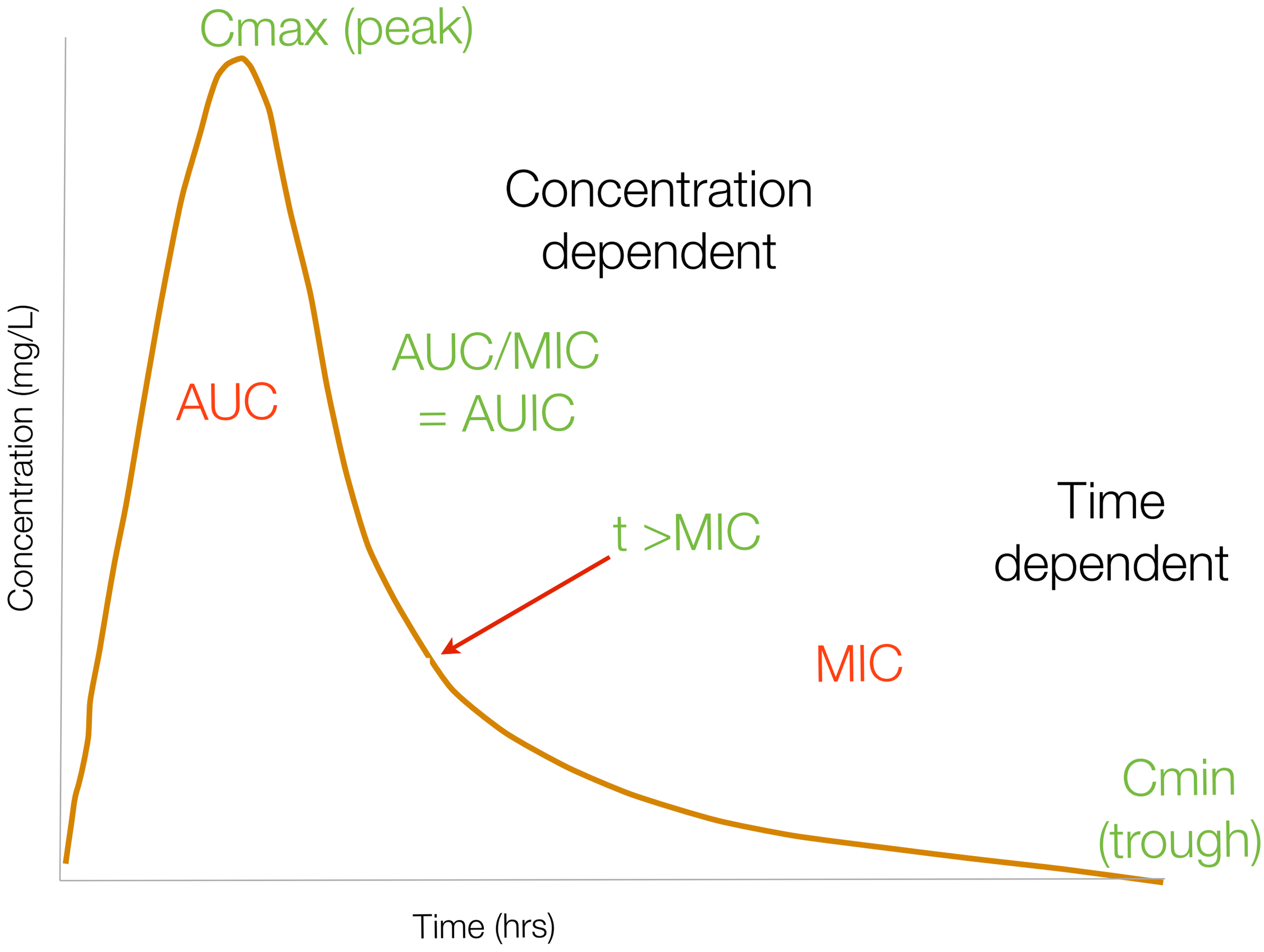
Vancomycin

?Time>MIC

Fluoroquinolones

Peak/MIC AUC/MIC

Serum antibiotic levels over a dosing interval



Sepsis

Increased cardiac output → Increased clearance

Leaky capillaries/ decreased albumin → Increased Vd

Increased clearance + Increased Vd → Low plasma concentrations

Normal organ function → Unchanged Vd → Normal plasma concentrations

End organ dyfunction → Decreased clearance → High plasma concentrations

Up to 30% of ICU patients had high Cr clearance

Low levels of antibiotics lead to increased resistance

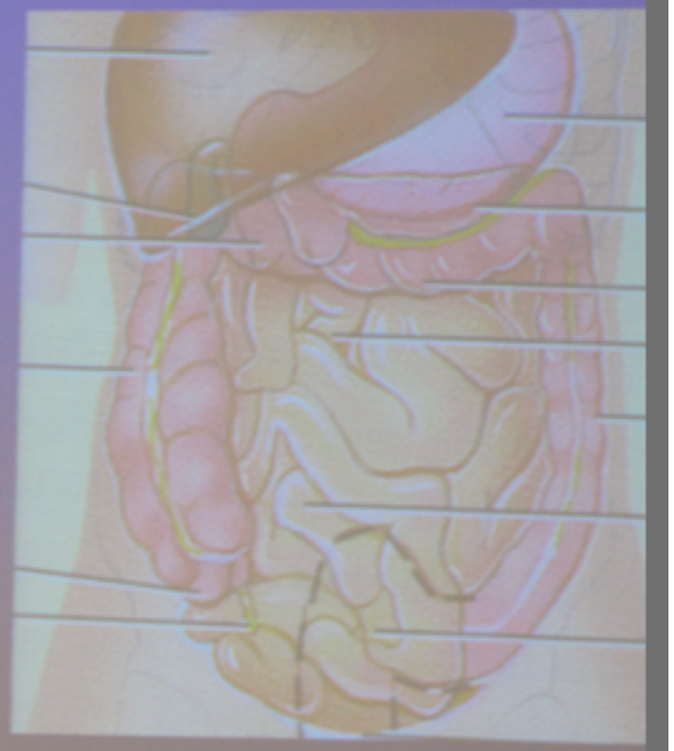
Roberts and Lippman Crit Care Medicine 2009: 37; 840-851

BOWEL BACTERIAL LOAD

MORE BACTERIA IN/ON OUR BODY THAN CELLS

10 quadrillion cells

100 quadrillion bacterial cells



ANTIBIOTICS KILL BACTERIA, BUT NOT ALL

Physiology

Sydney Ringer's solution

- Clinician and pharmacologist
- The effect of electrolytes on cardiac and involuntary muscle.
- Accidentally mixed a cardiac bath with **(London) tap water**

Ringer S. "Concerning the influence exerted by each of the constituents of the blood on the contraction of the ventricle. Journal of Physiology 1882:3:380-393

"The salts of sodium, potassium, calcium and chloride in definite concentrations and in precise proportion is necessary for protoplasmic activity"

Hartmanns solution

- Alexis Frank Hartmann (1898-1964)
- Paediatrician and biochemist
- 1932 added sodium lactate to Ringer's solution
- "Normal" saline rehydration of children with diabetic ketoacidosis increased acidosis and worsened the prognosis
- "Need proportionally more sodium than chloride in parenteral solutions to avoid the development of an acidosis in children"
- Hyperchloraemic metabolic acidosis

Albumin pharmacokinetics

Normal

Synthesis
12gm/day

Plasma
3 litres
40 g/L
120 g

Catabolism
12gm/day

Leakage

5% hr

Lymph

Interstitium
11 L
15 g/L
165 g

Critical illness

Synthesis
???gm/day

Plasma
3 litres
15 g/L
45 g

Catabolism
??gm/day

Urinary
/gut/
haemorrhage

Leakage

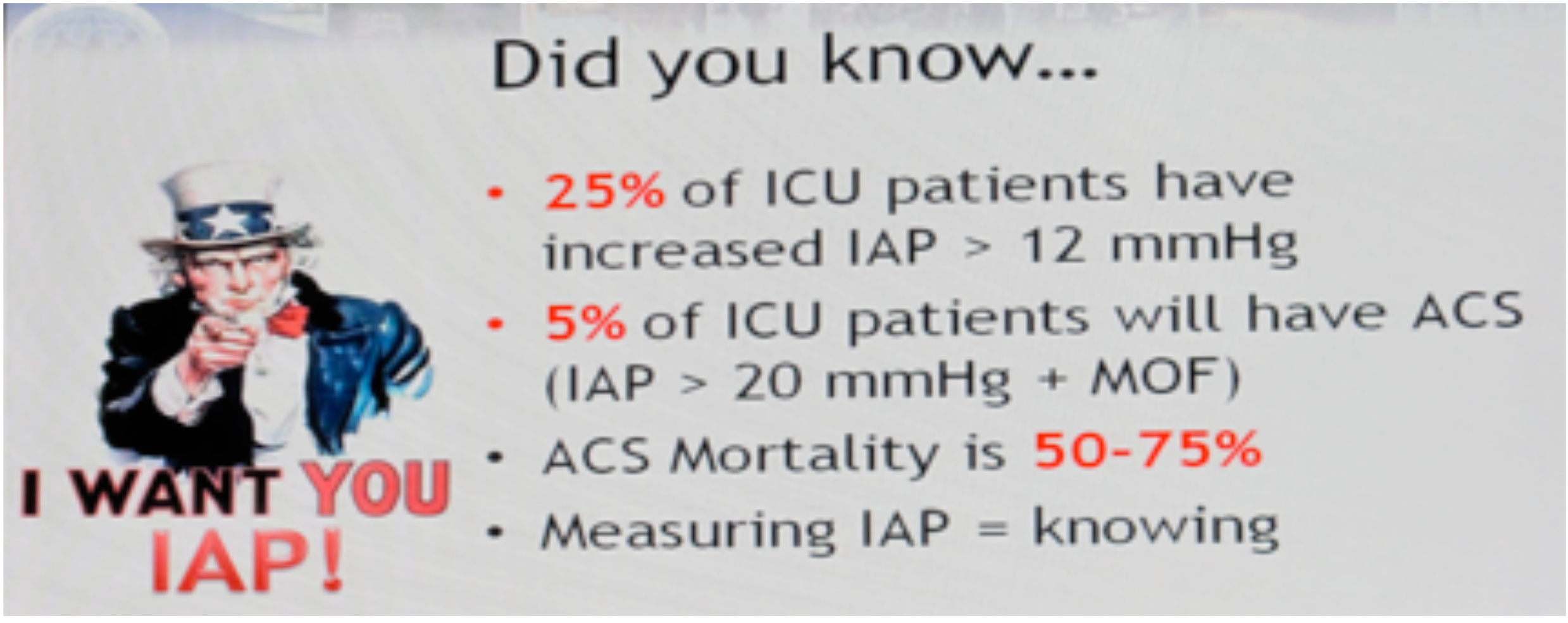
20% hr

Lymph

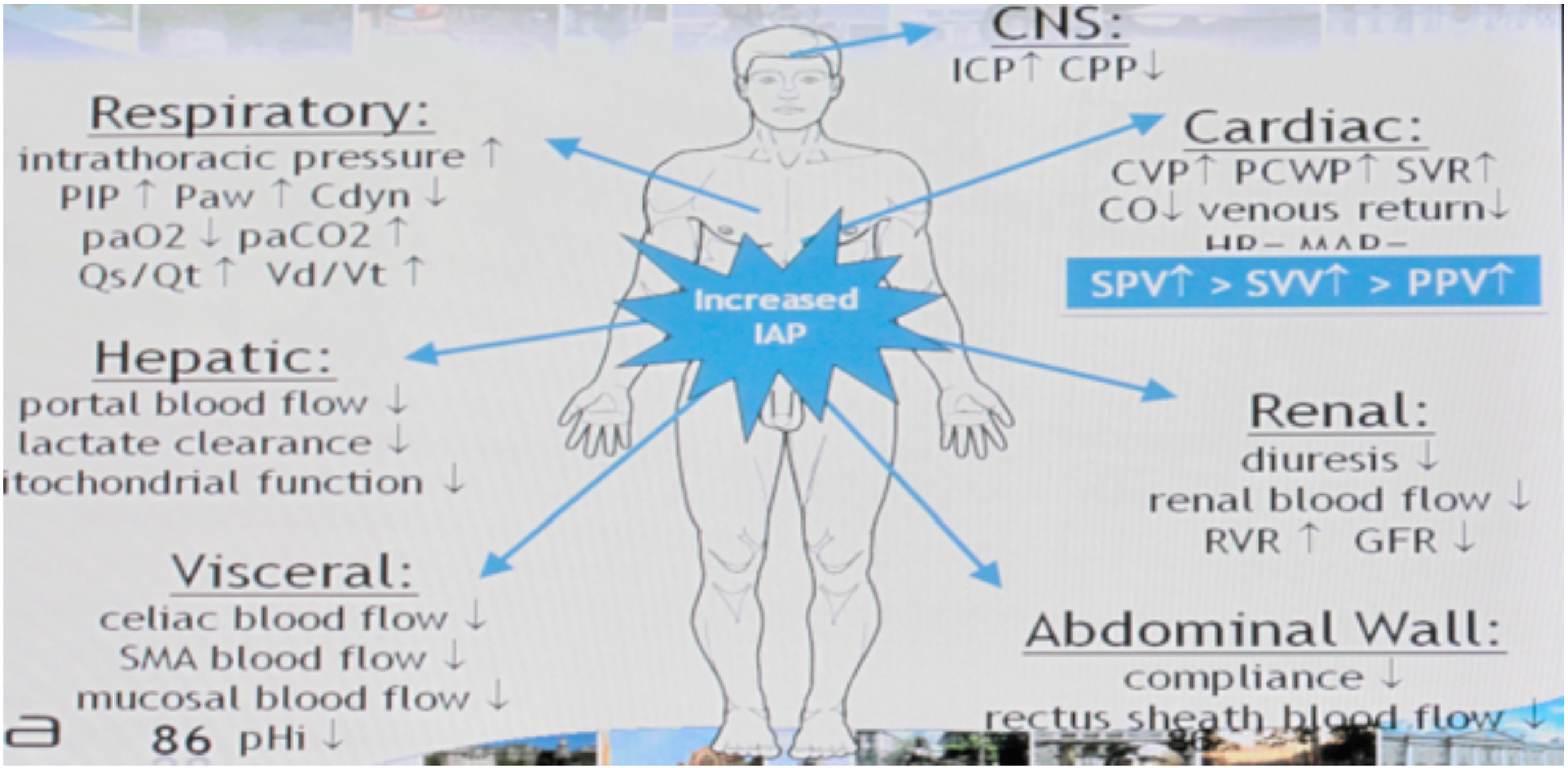
Interstitium
20 L
8 g/L
160 g

Intra abdominal hypertension

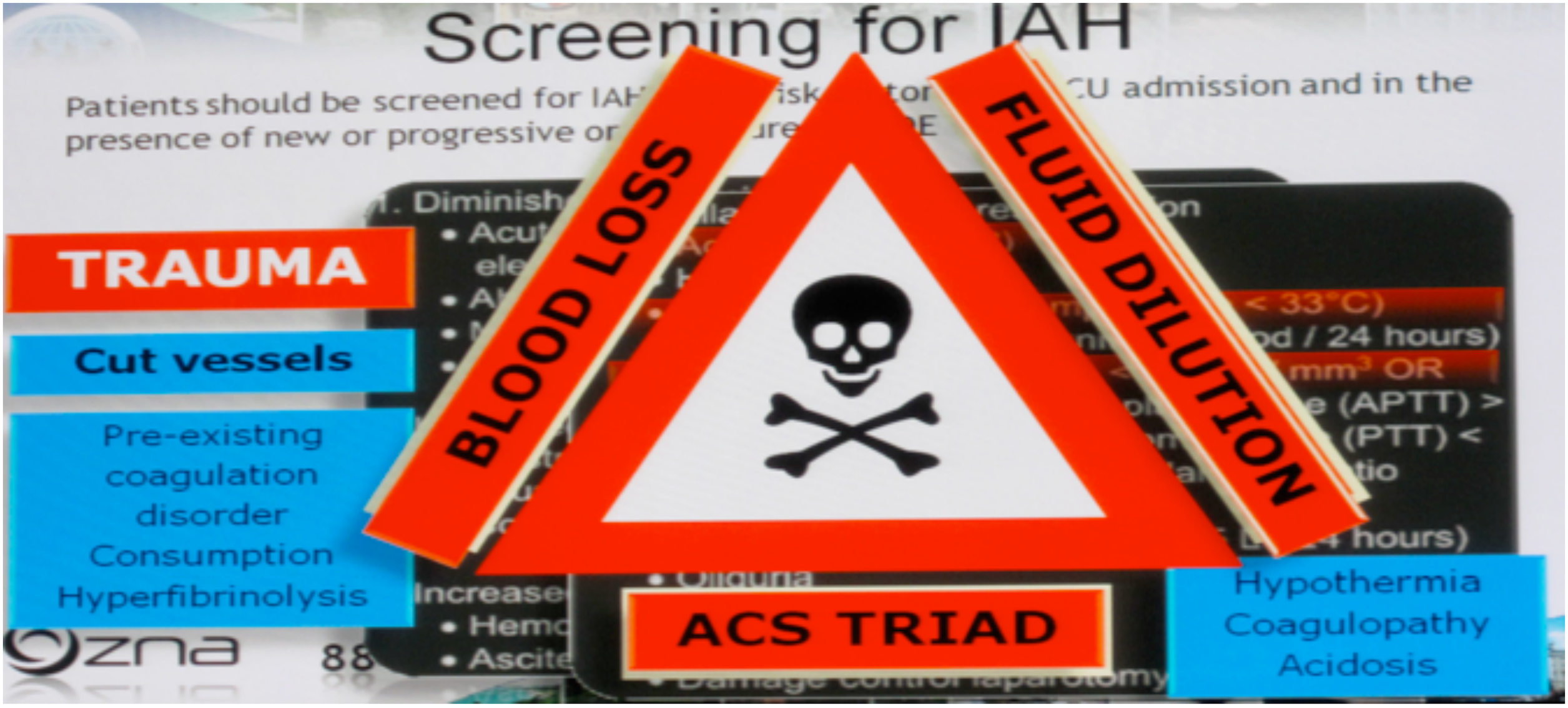
Intra abdominal hypertension



Intra abdominal hypertension

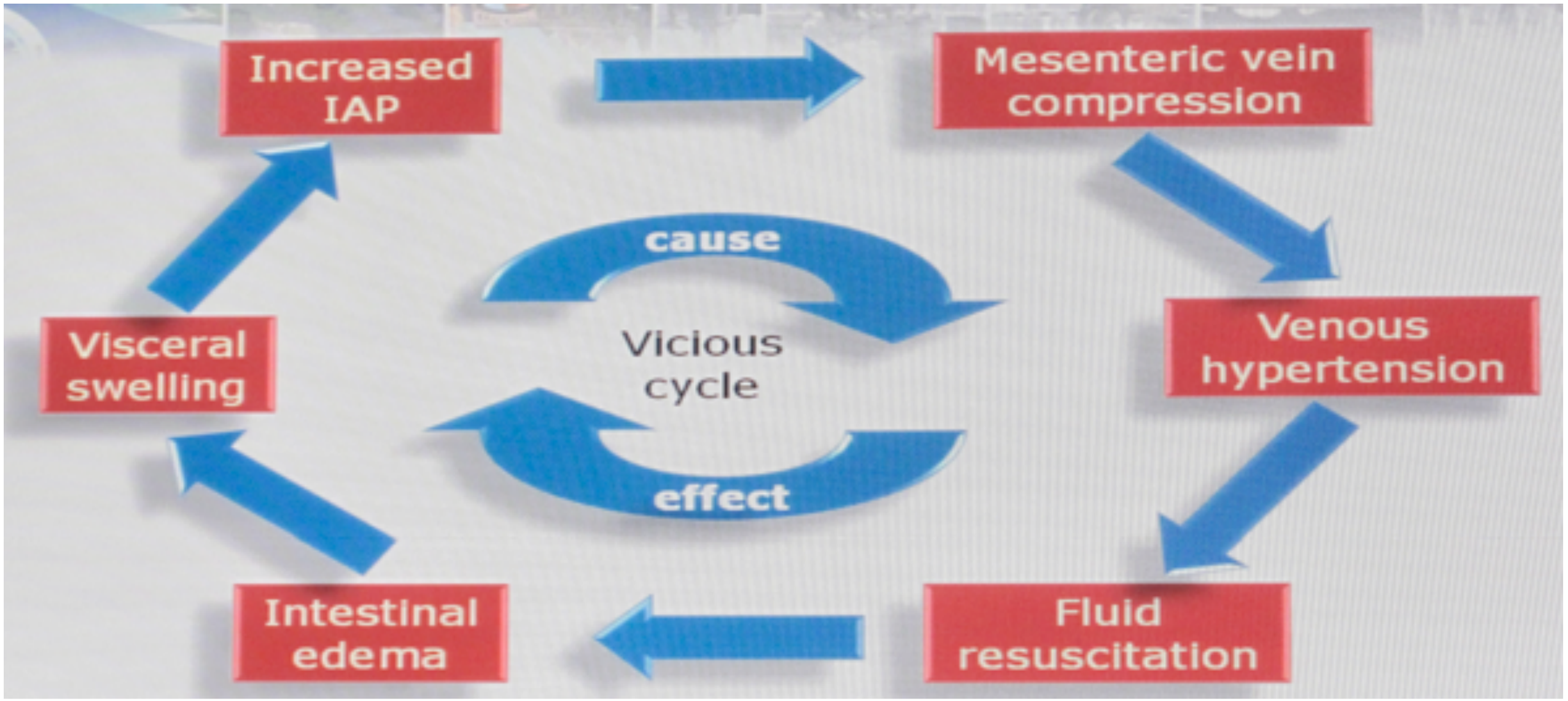


Intra abdominal hypertension



Cheatham et al. ICM 2007; 33:951

Intra abdominal hypertension



Pulmonary embolism

Pulmonary embolism-Thrombolysis?

Pro

- Mortality almost never occurs in patients with initial normal RV function
- Right ventricular dysfunction is bad
- Thrombolysis improves RVD
- Risk of delayed shock

Pulmonary embolism-Thrombolysis?

Con

- Risk of dying correlates best with shock
- Rt ventricular dysfunction is very common
- Patients with RVD usually survive
- No clear evidence of a mortality benefit
- Resolution of PE at 7 days is equivalent
- **Risk of intracranial bleed**

Pulmonary embolism-Thrombolysis

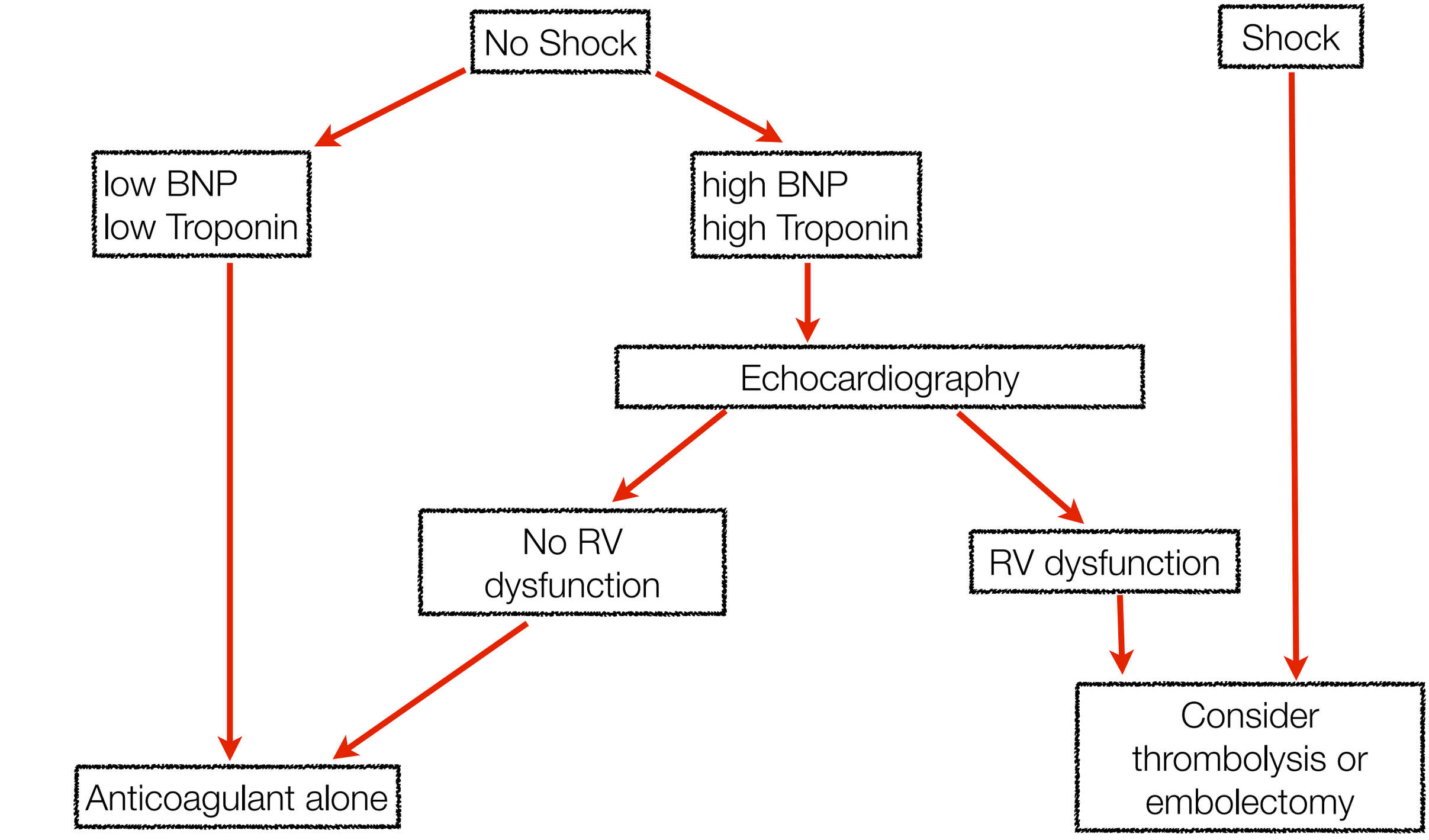
Indications

- Persistent hypotension-typical use
- Persistent severe hypoxaemia despite maximization of 02 therapy - rare

Pulmonary embolism - conclusions

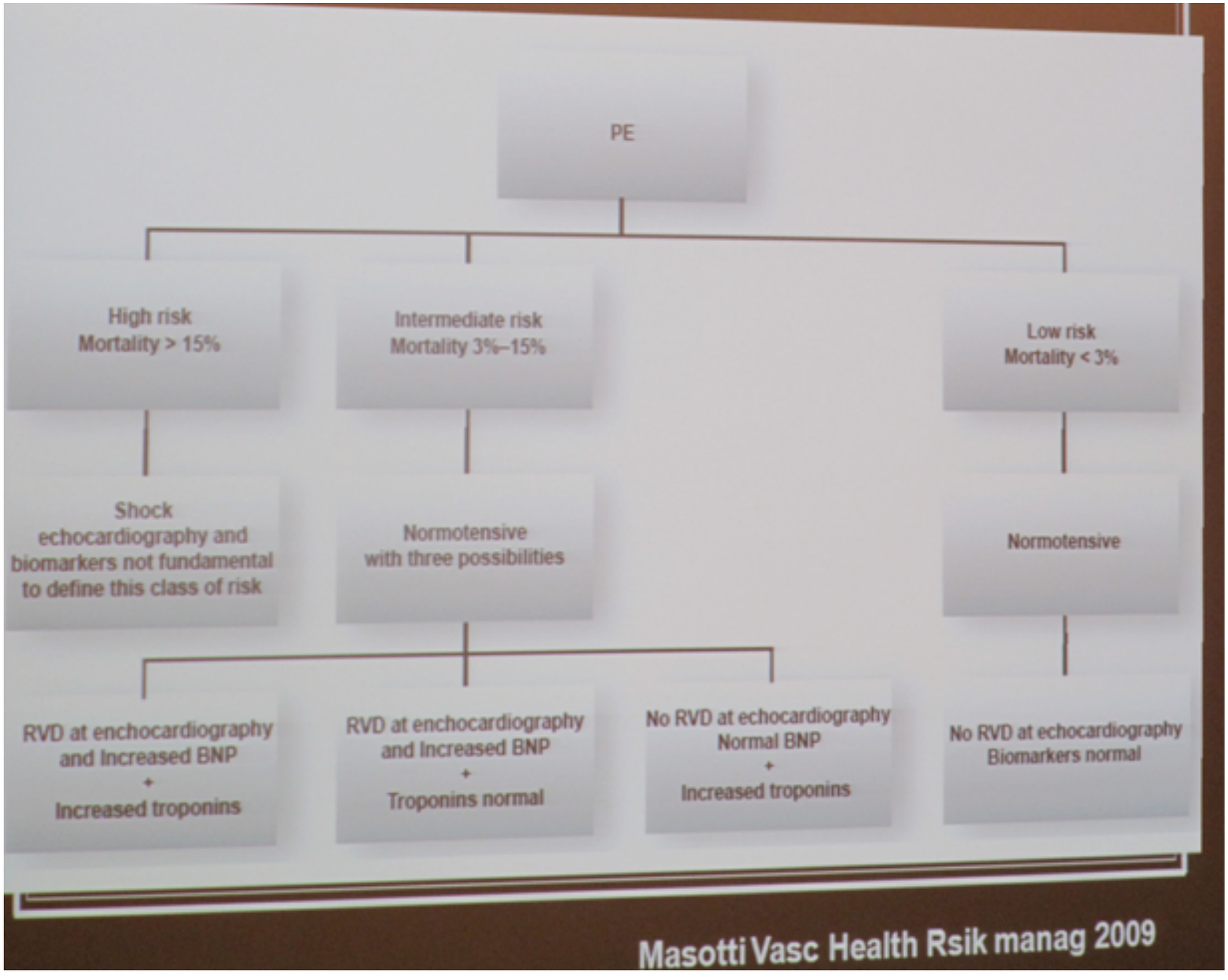
- Echocardiography is highly specific and has a low sensitivity in the diagnosis of PE
- In patients with RV dilation TEE has a good sensitivity and high specificity in PE diagnosis
- Presence of central thrombus, PFO and RVD are associated with poor prognosis
- Then echo examination with contrast should be performed in patients with suspected and confirmed PE.

Pulmonary embolism - biomarkers and echocardiography diagnostic strategy and treatment



Kucher et Goldhaber Circulation 2003

Pulmonary embolism



Pulmonary embolism

Pronostic of patients with PE and SBP >90 mmHg (n=1035)

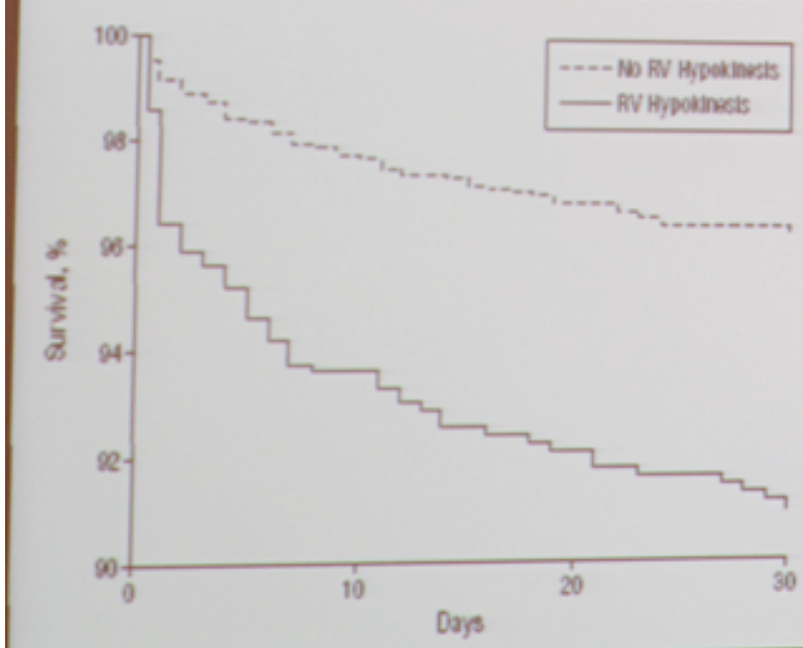
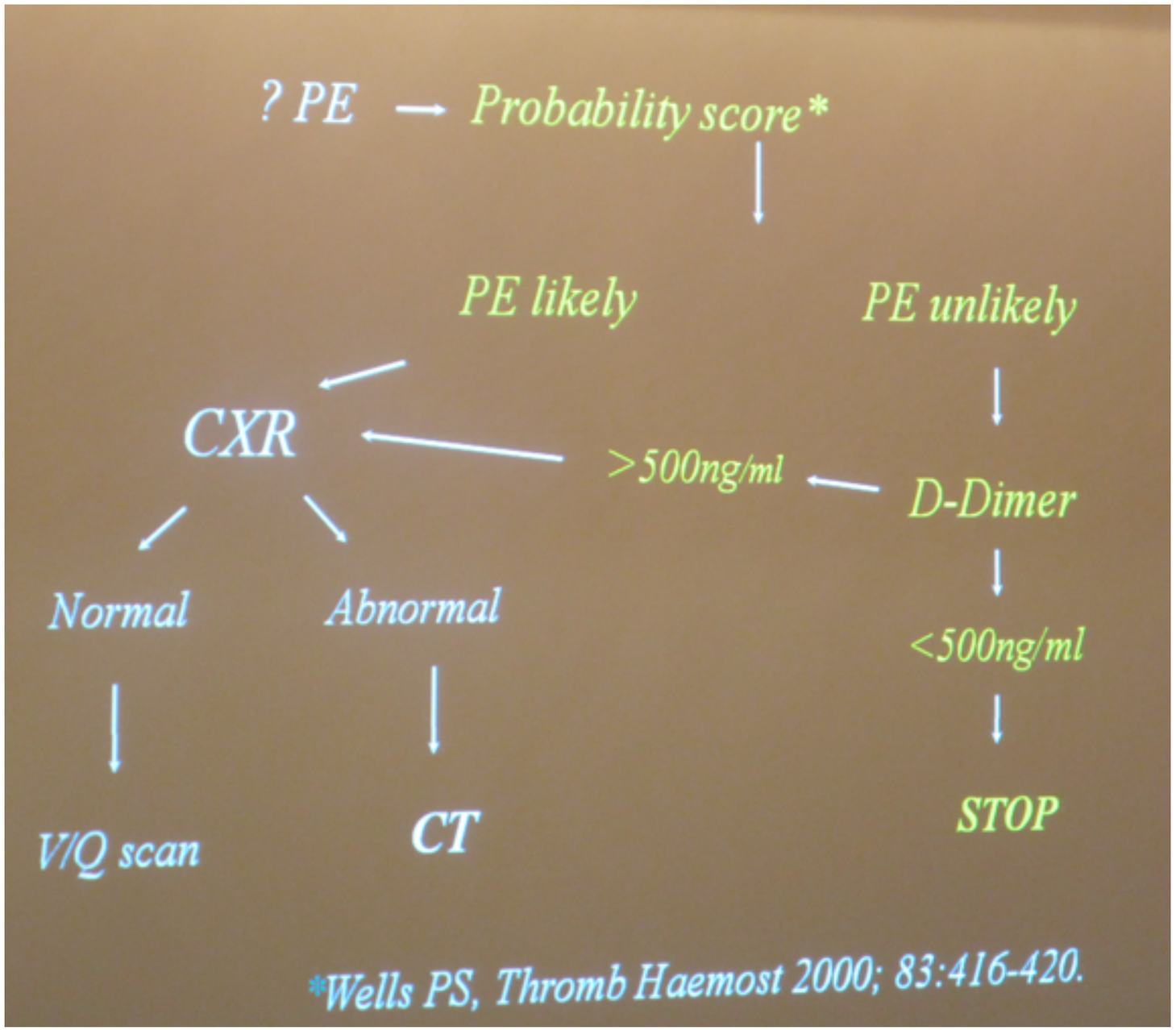


Table 3. Multivariable Analysis of Univariately Significant Variables for Predicting Mortality at 30 Days, Stratified by the International Cooperative Pulmonary Embolism Registry Institution

Variable	Adjusted Hazard Ratio (95% Confidence Interval)
Right ventricular hypokinesis	1.94 (1.23-3.06)
Cancer	2.31 (1.52-3.51)
Congestive heart failure	1.92 (1.18-3.11)
Chronic lung disease	1.77 (1.11-2.83)
Age >70 y	1.70 (1.15-2.52)
Systolic arterial pressure ≤100 mm Hg	1.58 (0.98-2.54)
Heart rate >100 beats per min	1.42 (0.95-2.12)
Right heart thrombus	1.11 (0.52-2.33)
Thrombolysis	1.33 (0.81-2.17)

Kucher Goldhaber Arch Intern med 2005

Pulmonary embolism



Pulmonary embolism