Or, the “twins catastrophe” of the lungs !!

ARDS

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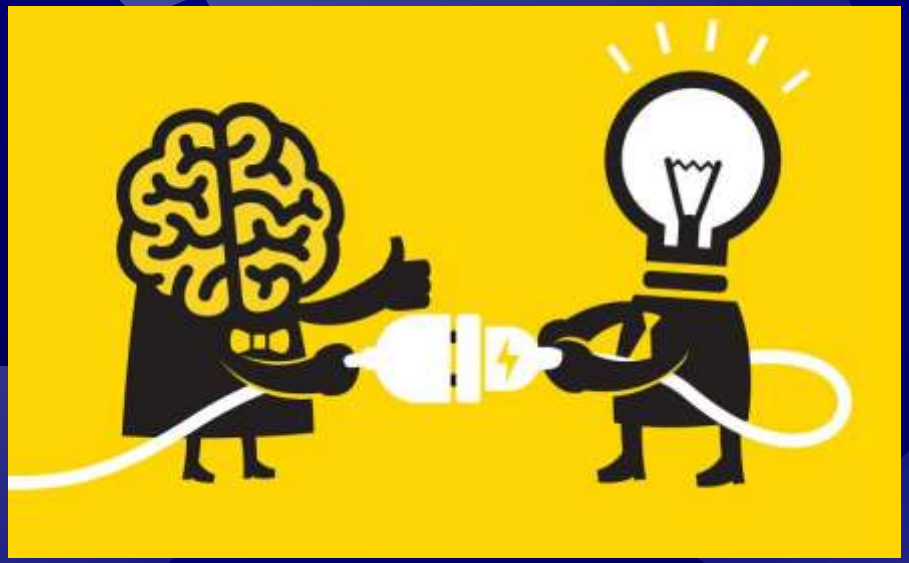
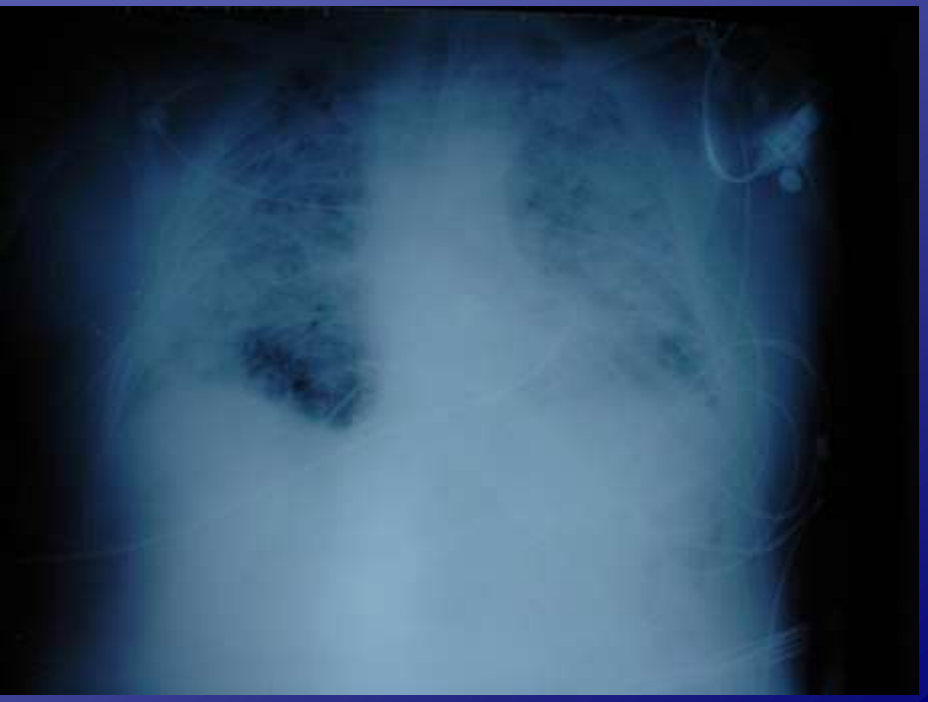


Or,
everything you wanted to know about this dreadful entity and you did not dare to ask!!!!



ARDS= Adult Respiratory Distress Syndrome (coming from IRDS= Infant Respiratory Distress Syndrome)

SYNONIMS

Shock lung

Non-cardiac pulmonary edema

Da Nang lung

Stiff lung

Wet lung

Oxygen pneumonitis

Post-traumatic pulmonary insufficiency

Do you know how (and when) did it start?

- Ashbaugh, Bigellow and Petty- 1967
- 12 patients with tachypnea, refractory hypoxia and diffuse opacities on chest X ray
- After infection or trauma

Vă rog să vă gândiți: ați mai văzut un asemenea caz?

- 58-yr old male, after an open fracture of tibia and fibula
- Operated-external fixation, in the next hours after accident
- Four days later : dyspnea, 32 resp/minute obtunded, warm, BP 105/70, pulse 115
- Diffuse wheezes to auscultation, use of accessory respiratory muscles, breathes with open mouth

First ABG:

PaO2 42 (FiO2 mask 0.4)-

PaO2/FiO2 105

PaCO2 31

pH 7.35

First X ray: diffuse, bilateral interstitial congestion with some areas of alveolar infiltrates

ARDS- The definition, once upon a time…….

An acute scenario of acute respiratory failure, which MUST INCLUDE the following :

- History compatible with ARDS etiol
- Clinical signs of respiratory dis es
- A chest X-ray showing di pacities **yes**
- Acute hypoxia, PaO im Hg at FiO2 of > 40% **yes**
- No sign of cardiac failure or exacerbation of chro onary disease (such as COPD) **yes**

This is exactly our case!!!!!

But in 2012, in Berlin
(Ferguson ND Intensive Care Med)

- Onset within 7 days after a clinical insult
- Bilateral opacities "consistent with pulmonary edema" on chest Rx or CT

	PaO2/FiO2	Death
Mild	201-300	27%
Moderate	101-200	32%
Severe	<100	45%

So, our case is very close to the severe form!

How frequent it is?

- **First question:**

How often is ARDS in ICU (of all patients)?

***5%**

10%

25%

- **Percentage of ventilated patients with ARDS?**

- **23%**
- **50%**
- **60%**

Answers:

10%

23%

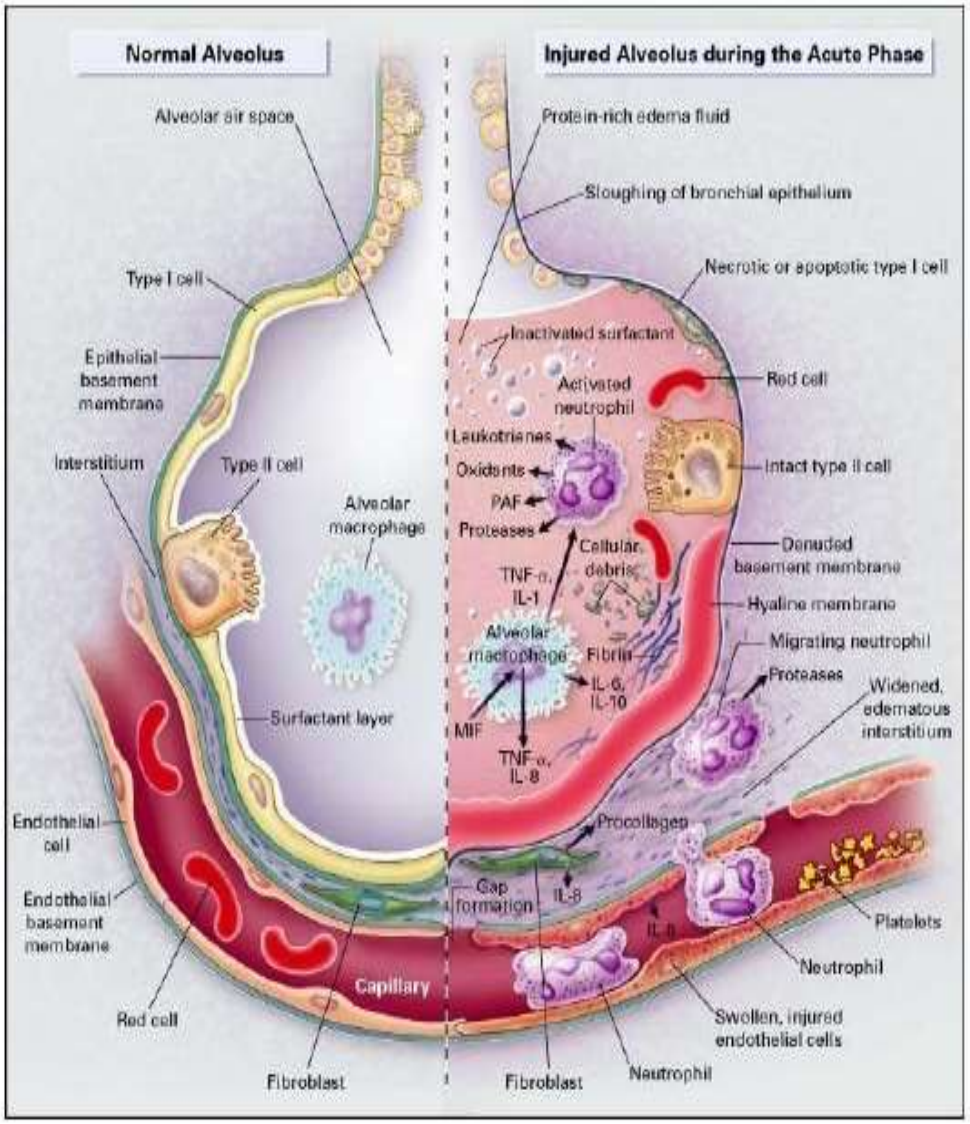
How frequent it is (2)?

- 10-86 cases per 100,000 population
- Interesting enough, highest numbers in Australia and USA
- Underreported in less-income countries, but not only…..
- Causes of underestimation:

  *paucity of diagnosis means

  *misinterpretation of X ray

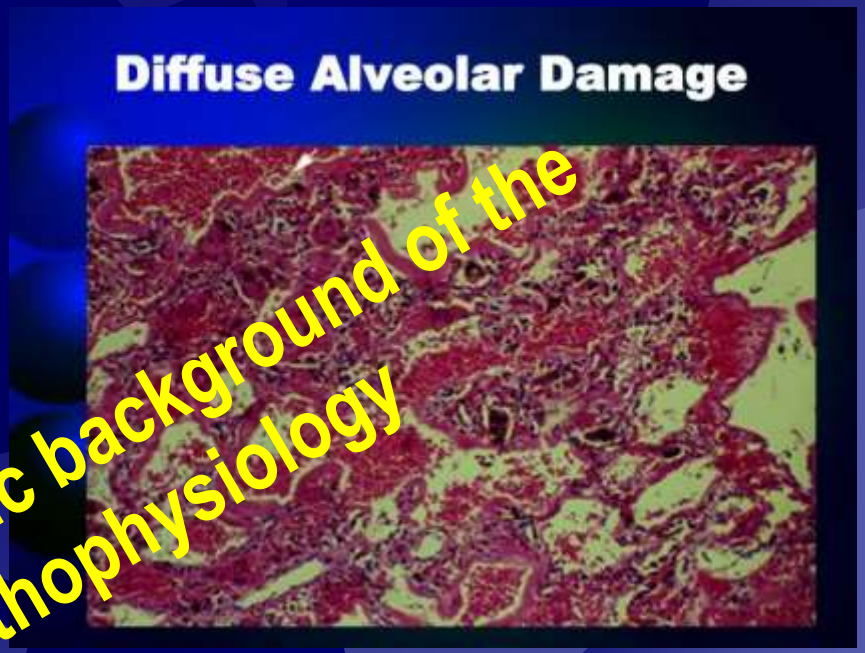
ARDS:Pathogenesis



Do not worry, I do not intend to mention every single detail !!!!

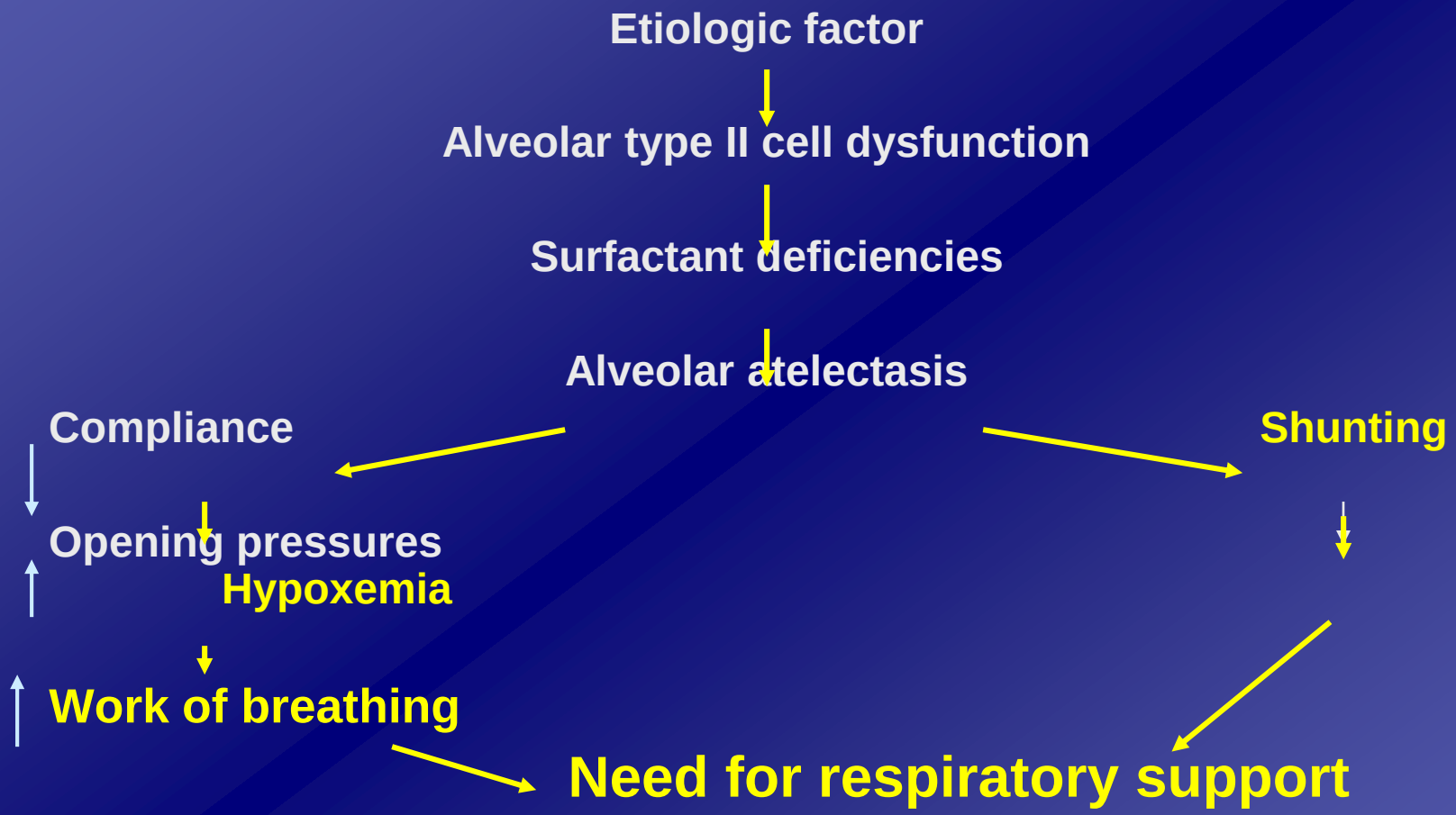
Thompson T et al 2017

"Diffuse alveolar damage is best thought of as a common histologic finding in patients with ARDS"



This is the anatomic background of the ARDS pathophysiology

How the things start ?



And the continuation ?

- **Diffuse injury of the alveolo-capillary membrane**

↓

Increase permeability

↓

Pulmonary edema

↓

Decrease in pulmonary compliance

And more…..

Small airways edema

↓

Reduction in the caliber of the bronchioles

↓

Bronchospasm

↓

Increase in ariway resistance

Injury of the alveolo-capillary membrane

↓

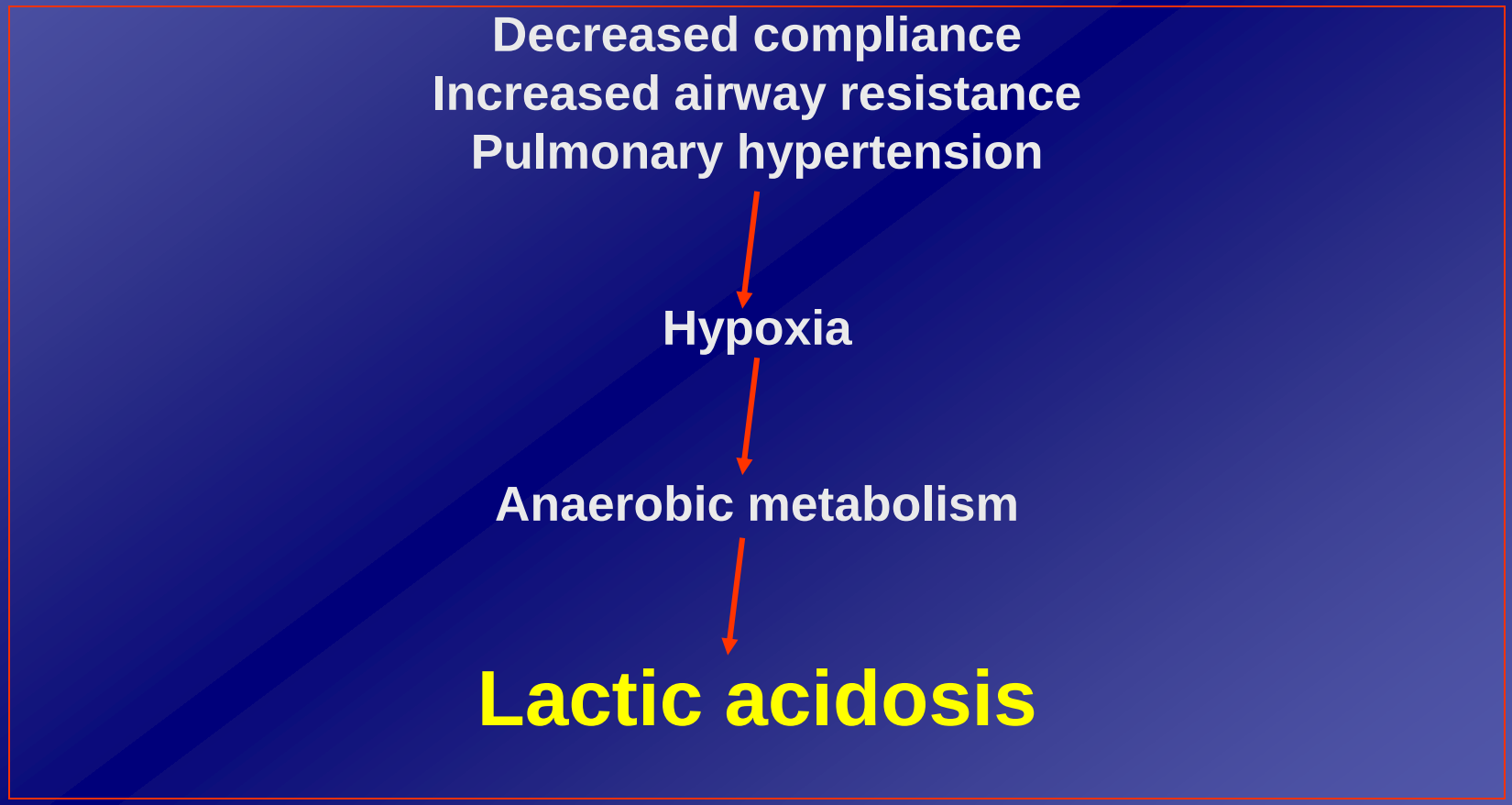
Injury of the pulmonary capillary circulation

↓

Pulmonary → ***pulmonary hypertension*** ← *thromboxan*

Emboli → ***pulmonary hypertension*** ← *serotonin*

And what about the tissue participation to the ARDS “cascade” ?



To summarize:

- Shunting
- Increased work of breathing
- Decreased pulmonary compliance
- Pulmonary hypertension
- Lactic acidosis

And this is the end…..

ARDS

↓

Refractory hypoxia

↓

Oxygen delivery failure

↓

MULTIPLE ORGAN FAILURE

Something rather new and also interesting……

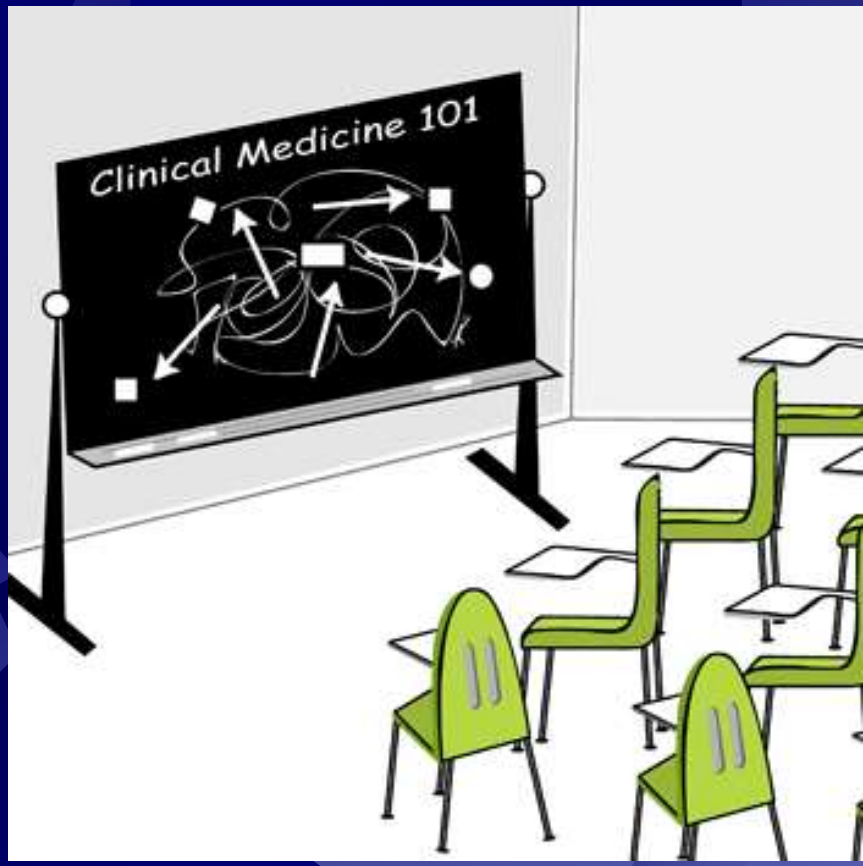
The genetic susceptibility to ARDS!!

- More than 40 candidate genes have been identified as being associated with the development and/or outcome of ARDS!!

It means that some persons may have multiple variants that modify the risk of ARDS

(Meyer NJ, Calfee CS, 2017)

And now about the clinical aspects of ARDS



The first clinical question : is that ARDS or a transitory stage, called acute lung injury (ALI) ?

same signs and symptoms but with a better prognosis and a shorter clinical course

DIAGNOSTIC CRITERIA

ARDS

- Acute
- Very severe hypoxia
- Bilateral interstitial or alveolar infiltrates
- Needs mechanical support

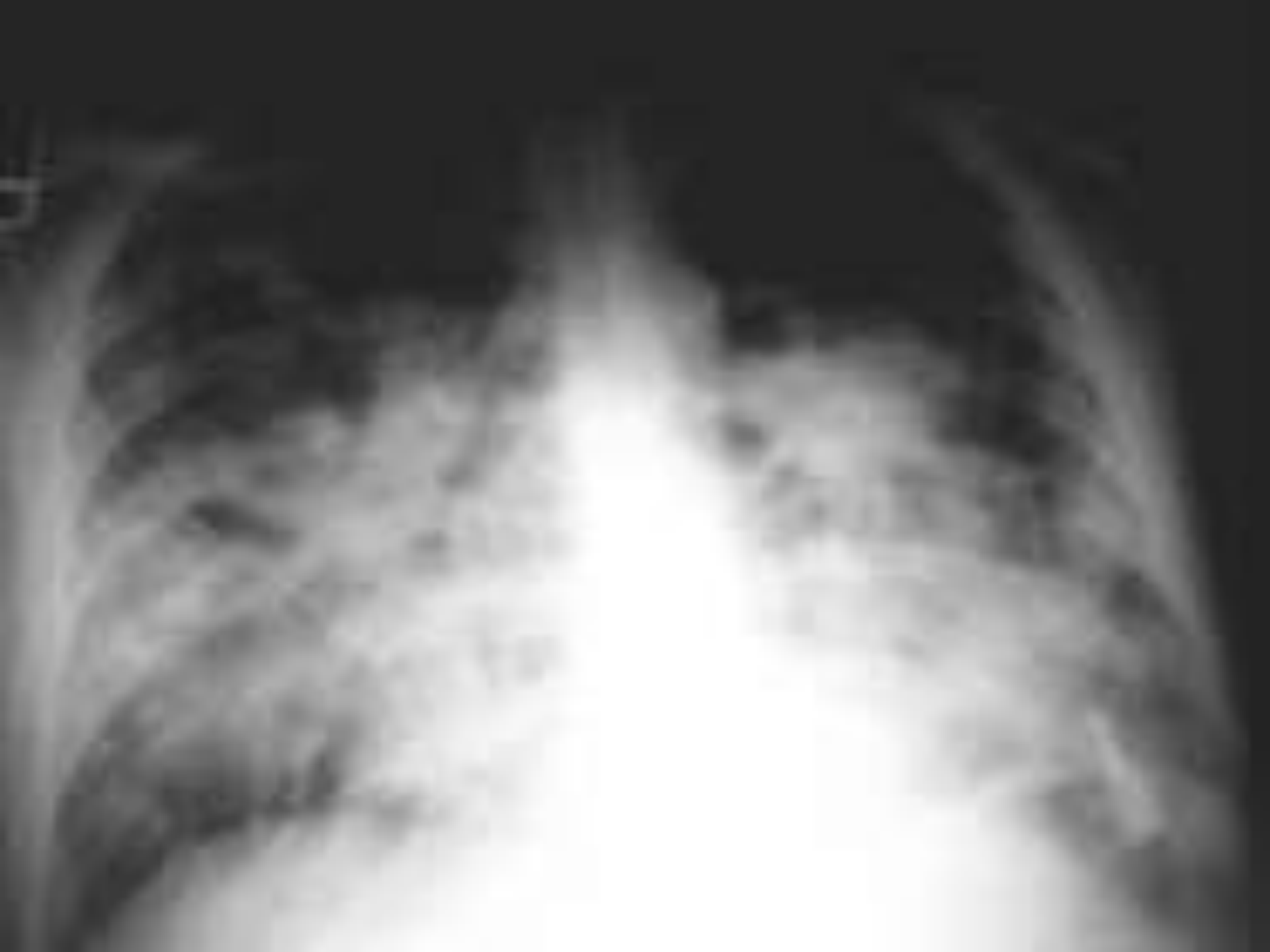
ALI (Acute lung injury, or pre-ARDS?)

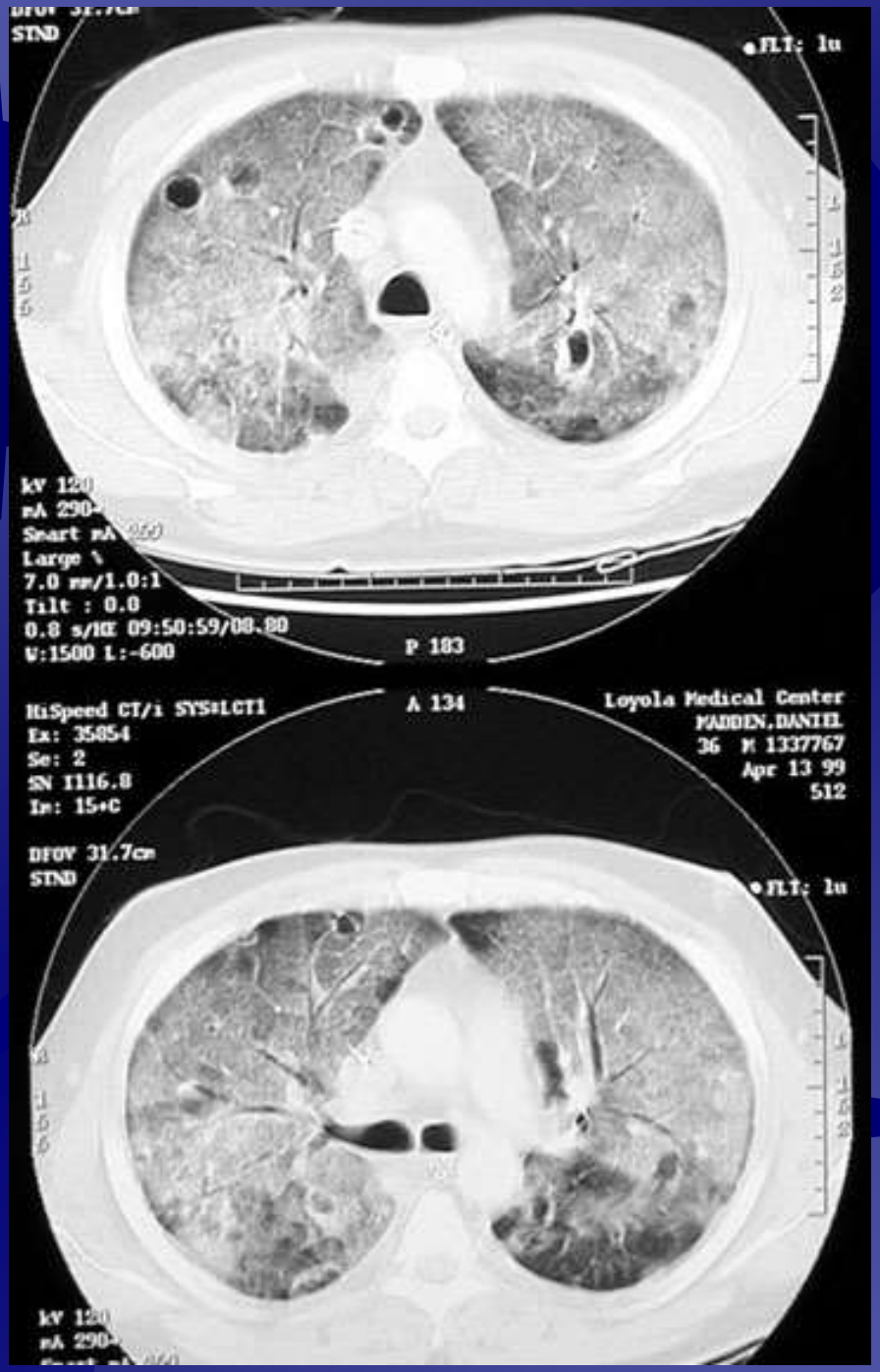
- Acute
- Moderate hypoxia
- Same
- Usually solved by oxygenotherapy

QUESTION: is ALI similar to moderate form of ARDS (see Berlin definition)?

ARDS Clinical course

- Rapid
- Within 12 to 48 hr of the predisposing event
- Awake patients become anxious,agitated & dyspnoeic, **breathes with the mouth open**
- Use of accessory respiratory muscles
- Alae nasi evident
- Dyspnoea on exertion proceeding to severe when hypoxemia intervenes
- Stiffening of lung leads to increase work of breathing,small tidal volumes,rapid respiratory rate




STND
FLT: lu
kV 120
mA 290
Smart mA
Large \
7.0 mm/1.0:1
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0.8 s/IOE 09:50:59/08.80
W:1500 L:-600
P 183
A 134
HiSpeed CT/i SYS#LCT1
Ex: 35854
Se: 2
SN I116.8
Im: 15#C
Loyola Medical Center
MADDEN,DANIEL
36 M 1337767
Apr 13 99
512
DFOV 31.7cm
STND
FLT: lu
kV 120
mA 290

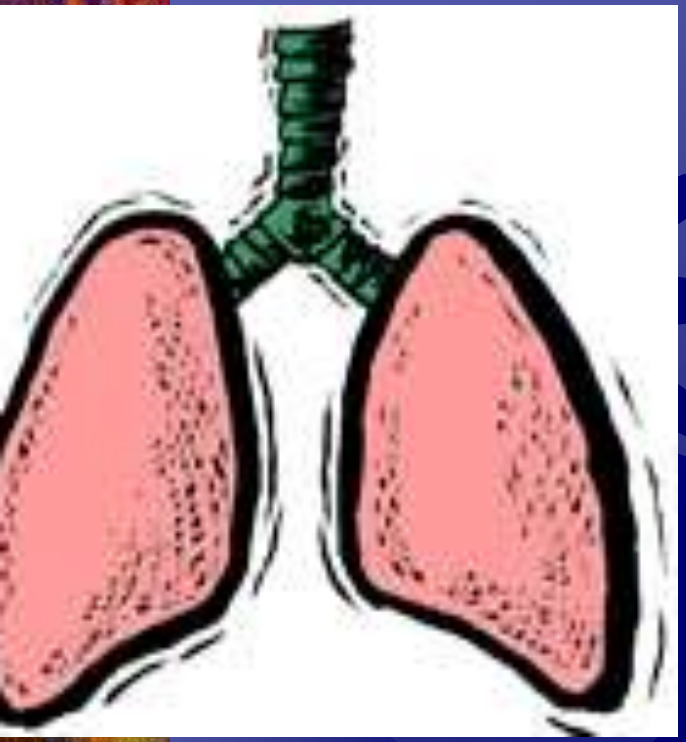
ARDS is not one single clinical entity

When the etiologic factor belongs to the pulmonary parenchima

We call it DIRECT ARDS

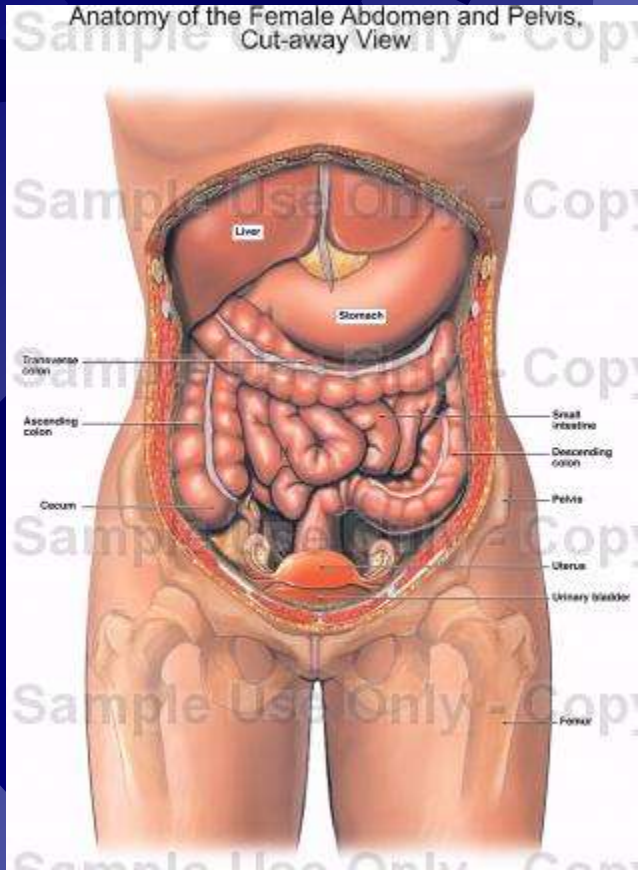
And when the cause of the syndrome comes from outside the respiratory system , we call it

INDIRECT ARDS

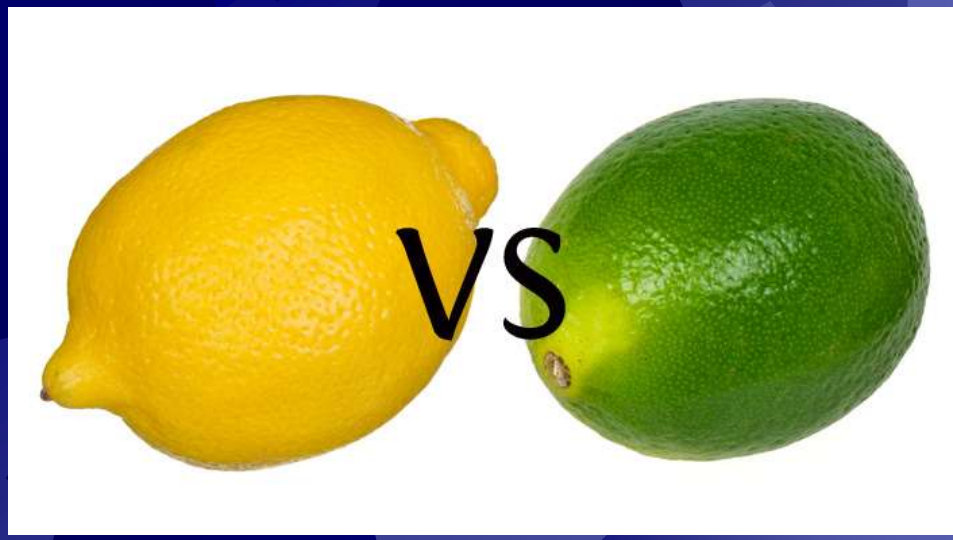


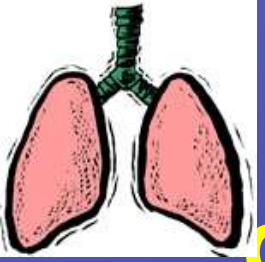
INDIRECT=Extra-pulmonary

DIRECT= Pulmonary



Of course, the etiology is different!





Clinical disorders associated with ARDS

Direct lung injury

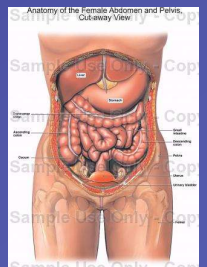
("Pulmonary ARDS")

- Aspiration of gastric contents
- Pulmonary contusion
- Toxic gas inhalation
- Near drowning
- Diffuse pulmonary infection
- Fat emboli
- Oxygen toxicity (?)

Indirect lung injury

("Extra-pulmonary ARDS")

- Severe sepsis
- Major trauma
- Overtransfusion
- Acute pancreatitis
- Drug overdose
- Shock
- Post cardiac bypass/lung transplants



Clinical disorders associated with ARDS (2)

- **FREQUENT CAUSES**

SEPSIS	
BACTEREMIA WITHOUT SEPSIS SYNDROME	**4%**
SEVERE SEPSIS/SEPSIS SYNDROME	**35-45%**
MAJOR TRAUMA	**20-25%**
MULTIPLE BONE FRACTURES	**5-10%**
PULMONARY CONTUSION	**17-22%**
HYPERTRANSFUSION	**5-36%**
ASPIRATION OF GASTRIC CONTENTS	**22-36%**

What can frequently mimic the radiological aspects of ARDS ?

Congestive heart failure

Aspiration pneumonia

Diffuse pneumonia

Lung contusion

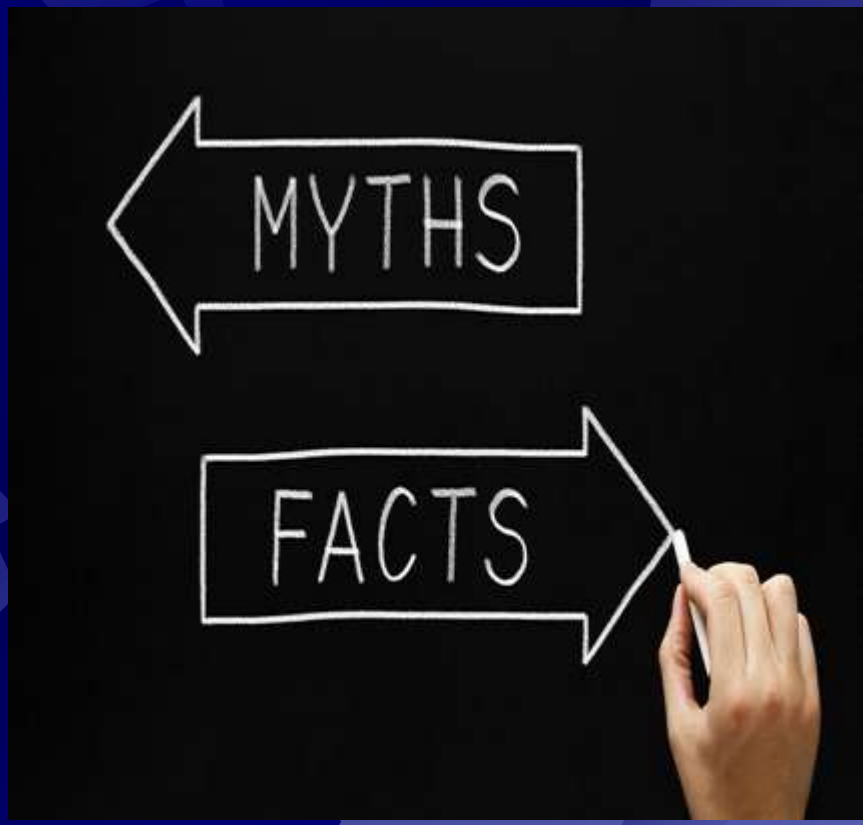
Pulmonary emboli

But do not forget !! All the above can easily progress into a ARDS clinical picture !!

Are you tired?! Better keep your energy for the second part!!!!!!

And now, the second part:

TREATMENT



Rhodes A et al 2017

“The first priority in the care of patients with ARDS is identification and treatment of the underlying cause or causes”

Therapy -goals

- Treatment of the underlying precipitating event
- Cardio-respiratory support
- Specific therapies targeted at the lung injury
- Supportive therapies

Respiratory Support

There are many ways to assist an inefficient respiratory pattern

1. There would be a place for **spontaneous respiration**? We shall see
2. **Mechanical ventilation-** the classical vs modern approach
3. **PEEP**- the old panacea !
4. **Protecting ventilation**
5. **Prone position-** it does help !
6. **Recruitment** maneuvers – le dernier cri !!

But let’s start with the end!!!

The last recommendations of three major scientific organizations:

American Thoracic Society

European Society of Intensive Care

Society of Critical Care

Am J Resp Crit Care Med 2017;195:1253

Here they are:

Positive indications:

- Mechanical ventilation, using lower tidal volumes (4-8 cc/Kg)
- Low inspiratory pressure < 30 cm H2O
- Prone position for more than 12 hours/day in severe ARDS

NEGATIVE indications:

- Routine use of high frequency oscillatory ventilation

CONDITIONAL indications:

- Higher PEEP in severe ARDS
- Recruitment maneuvers in moderate or severe ARDS
- Big question mark : ECMO

And now, let's discuss some specific points of treatment

Spontaneously Breathing Patient

- In the early stages of ARDS the hypoxia may be corrected by FiO2 0.4-0.6 with CPAP 5 cm water
- Peak inspiratory flow rates of >= 70l/ min require a tight-fitting face mask with a large reservoir bag
- If the patient is well oxygenated on FiO2 < 0.6 and apparently stable without CO_2 retention, then **ward** monitoring may be feasible but close observation (every15 to 30 min), continuous oximetry, and regular blood gases are required

BUT,

Brochard, Slutsky and Pesenti

Am J Resp Crit Care Med 2017

Spontaneous ventilation SUPERIMPOSED on mechanical ventilation may worsen the lung injury

Contd..

Any problems with spontaneous respiration?

*high/low volumes (the patient “settles” this!!!)

*high respiratory rate

*ventilating the dead space

- The risk of increased lung injury
- Difficulty in sedating the patient

What about noninvasive ventilation?

Thompson T et al NEJM 2010

- **may increase the risk of death when used for patients with severe hypoxemia**
- **An alternative: oxygen through high-flow nasal cannulae + noninvasive ventilation provided with a helmet**

It may reduce ventilation-induced lung injury (VILI, see later)

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But the main danger is……

The trap: postponing the treatment is looking for trouble !

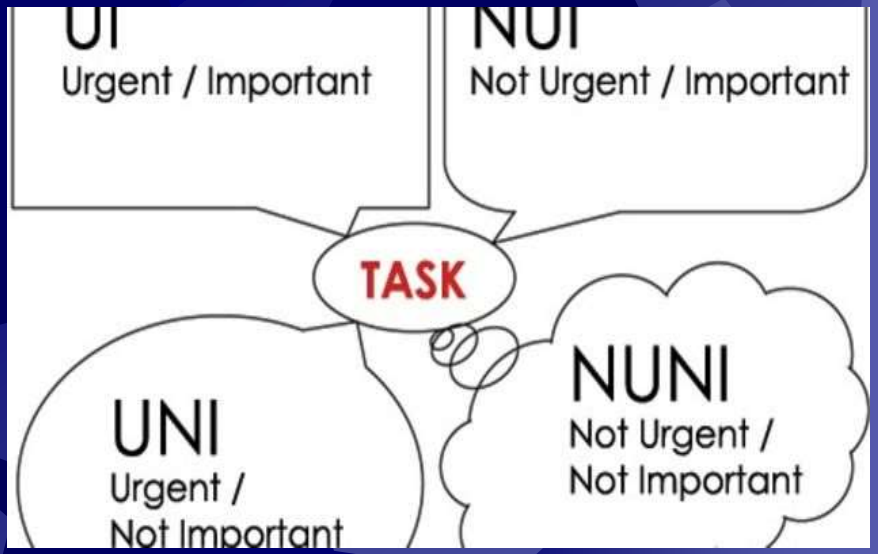
To wait until the late manifestations of ARDS (compliance, increase in respiratory work , or increased $PaCO_2$)

IS TO FLIRT WITH THE DISASTER

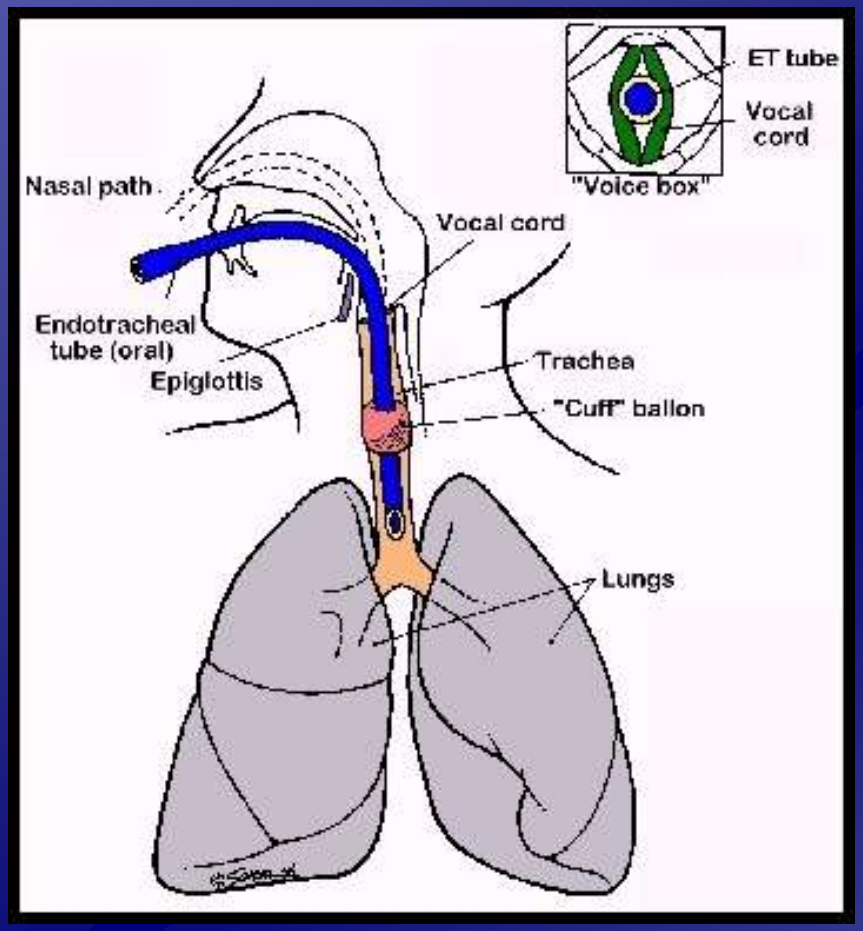
Since cardiorespiratory arrest is not uncommon under these circumstances

JH Siegel, Handbook of Critical Care, 1982

And now, let's go to the real thing



Mechanical Ventilation



The aim is to increase PaO_2 while minimizing the risk of further lung injury (Oxygen toxicity, Volu-barotrauma).

Contd..

Indications for mechanical ventilation

- Inadequate Oxygenation($PaO_2 < 70$ on $FiO_2 >= 0.6$)
- Rising or elevated $PaCO_2$(> 45) OR a decrease $PaCO_2$ → exhaustation !!
- Clinical signs of incipient respiratory failure

Ventilate and……

- Be sure that the gas exchange process is as normal as possible
- Control secretions
- Sedate and comfort the patient
- Check the absence of leak around the tube cuff, but avoid the cuff overdistention

Lung protective strategy in ARDS

Slutsky AS, NEJM 2001;345:610-611

- Ventilator- induced lung injury (VILI), and not hypoxia, may be the primary cause of death of many patients with ARDS
- This is why some authors decided to **LIMIT** the peak inspiratory pressure (pressure-controlled ventilation) **EVEN** if it could produce CO_2 retention

So, let's speak about VILI

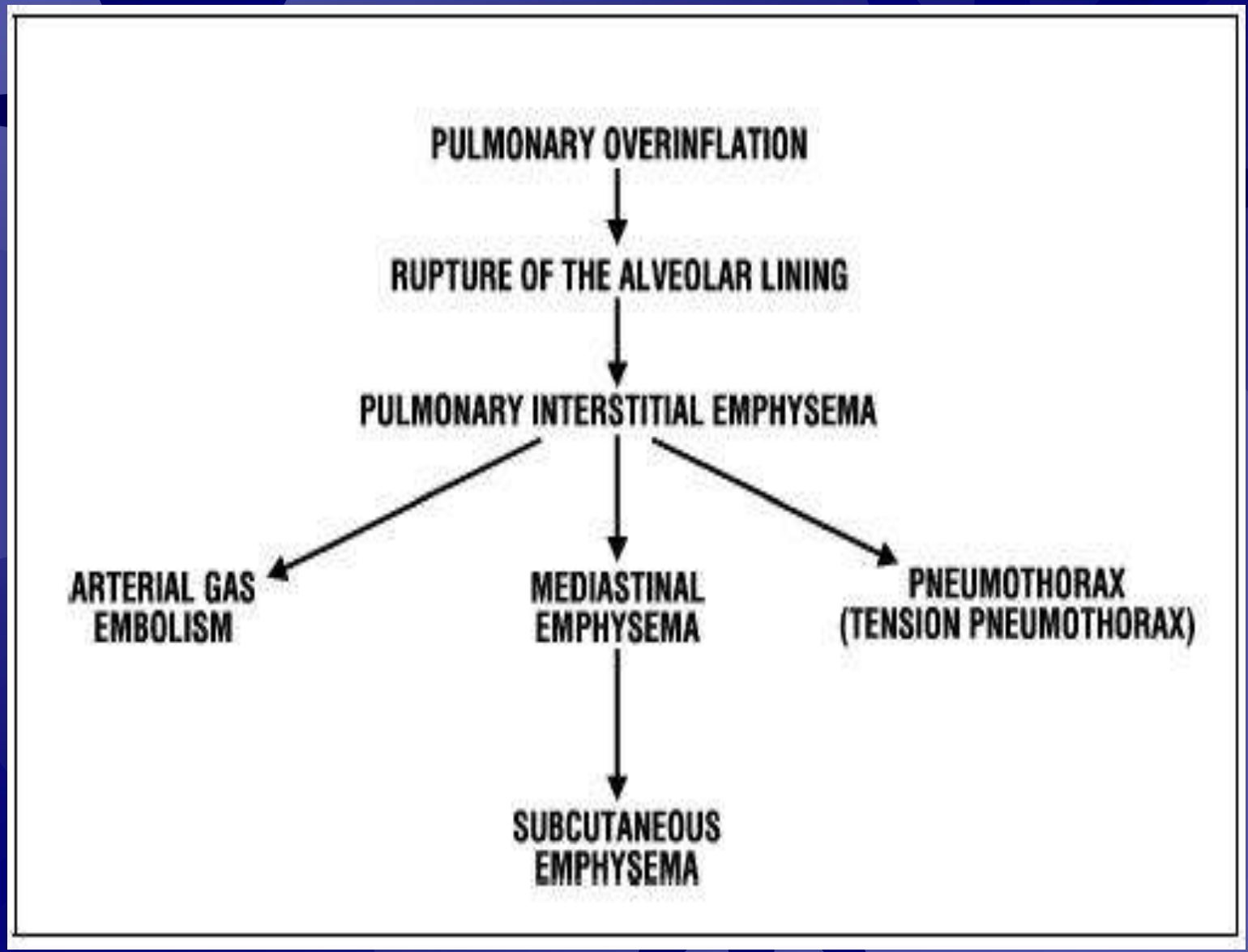
- *New Engl J Med 2000;342:1301*

"Protective ventilation-low tidal volumes and low inspiratory pressure- can reduce VILI and improve prognosis"

- *Slutsky, Ranieri NEJM 2013*

"VILI can occur because of ventilation at high lung volumes leading to:

- alveolar rupture
- air leak
- barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema)"


PULMONARY OVERINFLATION
RUPTURE OF THE ALVEOLAR LINING
PULMONARY INTERSTITIAL EMPHYSEMA
ARTERIAL GAS EMBOLISM
MEDIASTINAL EMPHYSEMA
PNEUMOTHORAX (TENSION PNEUMOTHORAX)
SUBCUTANEOUS EMPHYSEMA

NEJM 342:1301-1308 May 4, 2000 Number 18

Next

Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome

The Acute Respiratory Distress Syndrome Network

TABLE 1. SUMMARY OF VENTILATOR PROCEDURES.*

VARIABLE	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	GROUP RECEIVING LOWER TIDAL VOLUMES
Ventilator mode	Volume assist–control	Volume assist–control
Initial tidal volume (ml/kg of predicted body weight)†	12	6
Plateau pressure (cm of water)	≤50	≤30
Ventilator rate setting needed to achieve a pH goal of 7.3 to 7.45 (breaths/min)	6–35	6–35
Ratio of the duration of inspiration to the duration of expiration	1:1–1:3	1:1–1:3
Oxygenation goal	PaO_2, 55–80 mm Hg, or SpO_2, 88–95%	PaO_2, 55–80 mm Hg, or SpO_2, 88–95%
Allowable combinations of FiO_2 and PEEP (cm of water)‡	0.3 and 5 0.4 and 5 0.4 and 8 0.5 and 8 0.5 and 10 0.6 and 10 0.7 and 10 0.7 and 12 0.7 and 14 0.8 and 14 0.9 and 14 0.9 and 16 0.9 and 18 1.0 and 18 1.0 and 20 1.0 and 22 1.0 and 24	0.3 and 5 0.4 and 5 0.4 and 8 0.5 and 8 0.5 and 10 0.6 and 10 0.7 and 10 0.7 and 12 0.7 and 14 0.8 and 14 0.9 and 14 0.9 and 16 0.9 and 18 1.0 and 18 1.0 and 20 1.0 and 22 1.0 and 24
Weaning	By pressure support; required by protocol when $FiO_2 \leq 0.4$	By pressure support; required by protocol when $FiO_2 \leq 0.4$

*PaO_2 denotes partial pressure of arterial oxygen, SpO_2 oxyhemoglobin saturation measured by pulse oximetry, FiO_2 fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

†Subsequent adjustments in tidal volume were made to maintain a plateau pressure of ≤50 cm of water in the group receiving traditional tidal volumes and ≤30 cm of water in the group receiving lower tidal volumes.

‡Further increases in PEEP, to 34 cm of water, were allowed but were not required.

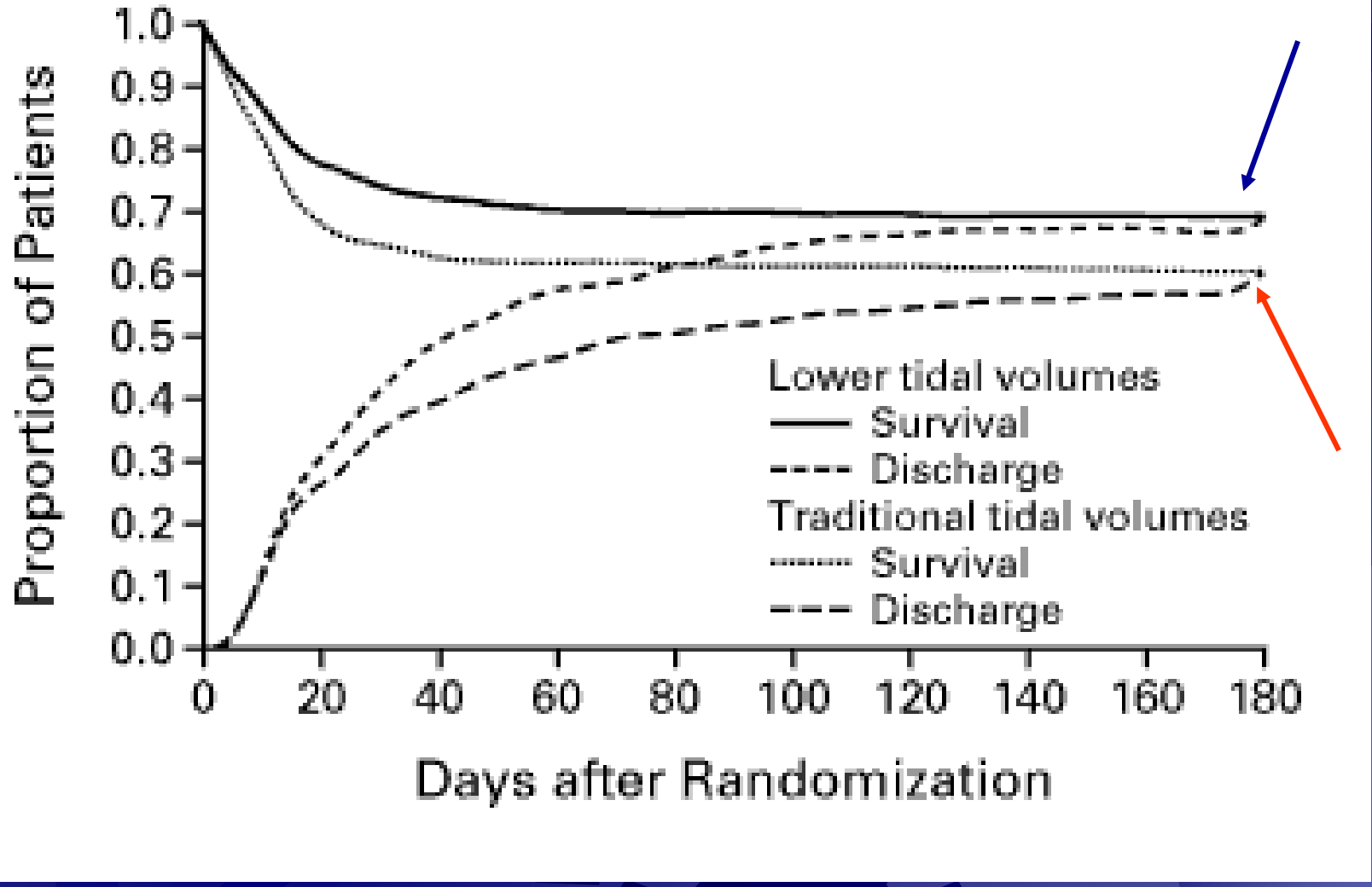


Figure 1. Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.
The status at 180 days or at the end of the study was known for all but nine patients. Data on these 9 patients and on 22 additional patients who were hospitalized at the time of the fourth interim analysis were censored.

P E E P

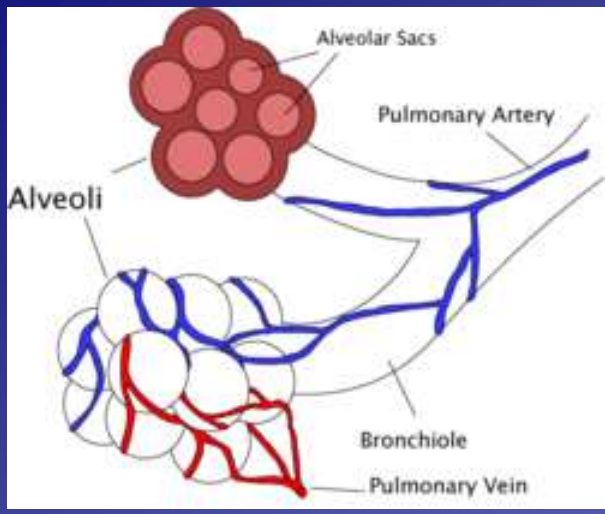
THE GOAL: to establish the **“optimal PEEP”**:

The PEEP level which limits overdistension during inspiration and prevent alveolar collapse during expiration

(Ranieri, Am J Resp Crit Care Med 1997;156:1082)

An optimal PEEP will keep the oxygenation close to normal without affecting the cardiac output

It would keep the alveoli not too distended, preventing baro-volutrauma



PRONE POSITION

(the first description : Brian, Am Rev Resp Dis 1974;110:143-supplement)

- **30 years ago we had a problem:**

!! no large studies

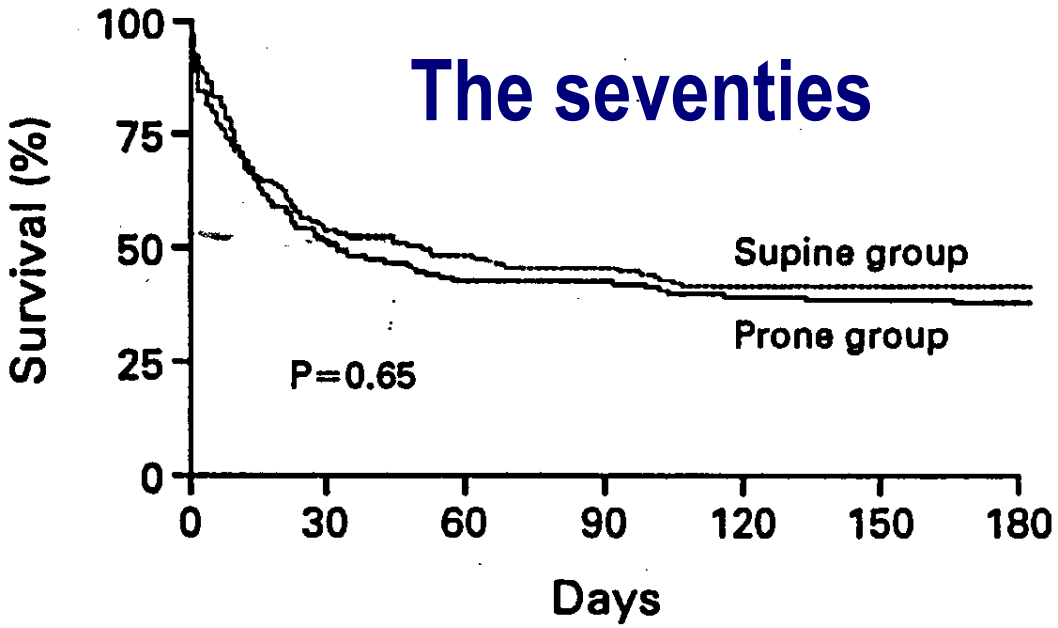
!! no idea how long it has to be in use for each patient

But, we understood that

The possible working hypothesis :

RECRUITMENT OF PREVIOUS ATELECTATIC UNITS

The seventies



No. at Risk							
Supine group	152	82	72	68	62	62	62
Prone group	152	78	63	63	58	57	56

Figure 1. Kaplan–Meier Estimates of Survival at Six Months.

The status at 183 days was known for all but seven patients (four in the prone group and three in the supine group). The difference between groups was not significant (P=0.65 by the log-rank test).

Prone position(2)

PROBLEMS

1.LOGISTICS (“proning team”)

2.SECONDARY EFFECTS:

a.displacement of vascular devices

(cardiovascular instability ?)

b.inadvertent extubation

c.facial injury (decubitus, edema)

d.pressure ulcers

Prone position(PP): where are we today? *(Slutsky and Ranieri 2013)*

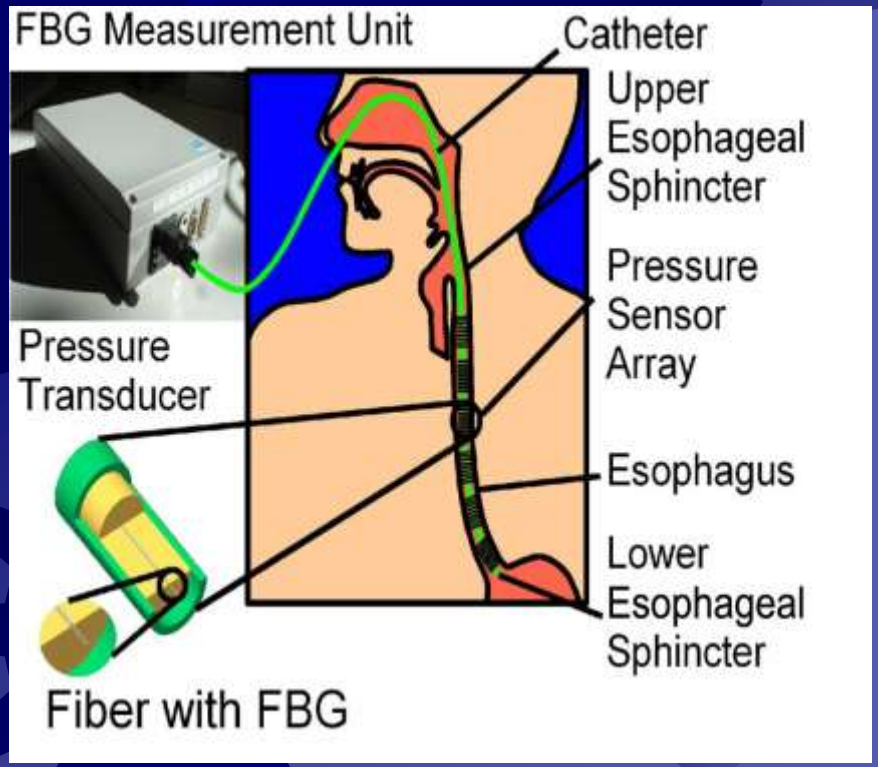
- About 70% of patients improve the pulmonary situation in prone position
- PP minimizes VILI and increase homogeneity of ventilation
- Guerin et al NEJM 2013:

*466 patients, PaO2/FiO2 ratio <150

*mortality at 28 days : non PP=33%, PP=16%

Another proposal: high PEEP and recruitment maneuvers

- Indicated in case of pulmonary edema or severe alveolar collapse
- The problem: possible barotrauma
- The possible solution: adjustment of PEEP by measuring the transpulmonary pressure (e.g. esophageal pressure)



Did you get enough regarding the respiratory support ?!

If yes……

ADJUVANT THERAPY

*Treatment of the most probably etiology : sepsis

*Neuromuscular blocking agents

*Antiinflammatory agents

*Cardiovascular support

*ECMO

*Nitric oxide

Treatment of Sepsis

Preventing and treating sepsis

- Perfect sterility and aseptic techniques
- Blood and secretions cultures when necessary
- No preventive antibiotherapy
- Prevention of ventilator-associated pneumonia (a subject of an one-hour story!!!!)
- Only specific antibiotics for specific germs

Use of neuromuscular blocking agents

Papazian L, NEJM 2010

- 348 ARDS patients, randomized to receive or not cisatracurium, with the onset of ARDS
- Reduction of the number of ventilator-free days
- Decrease in the percentage of barotrauma
- Mortality:

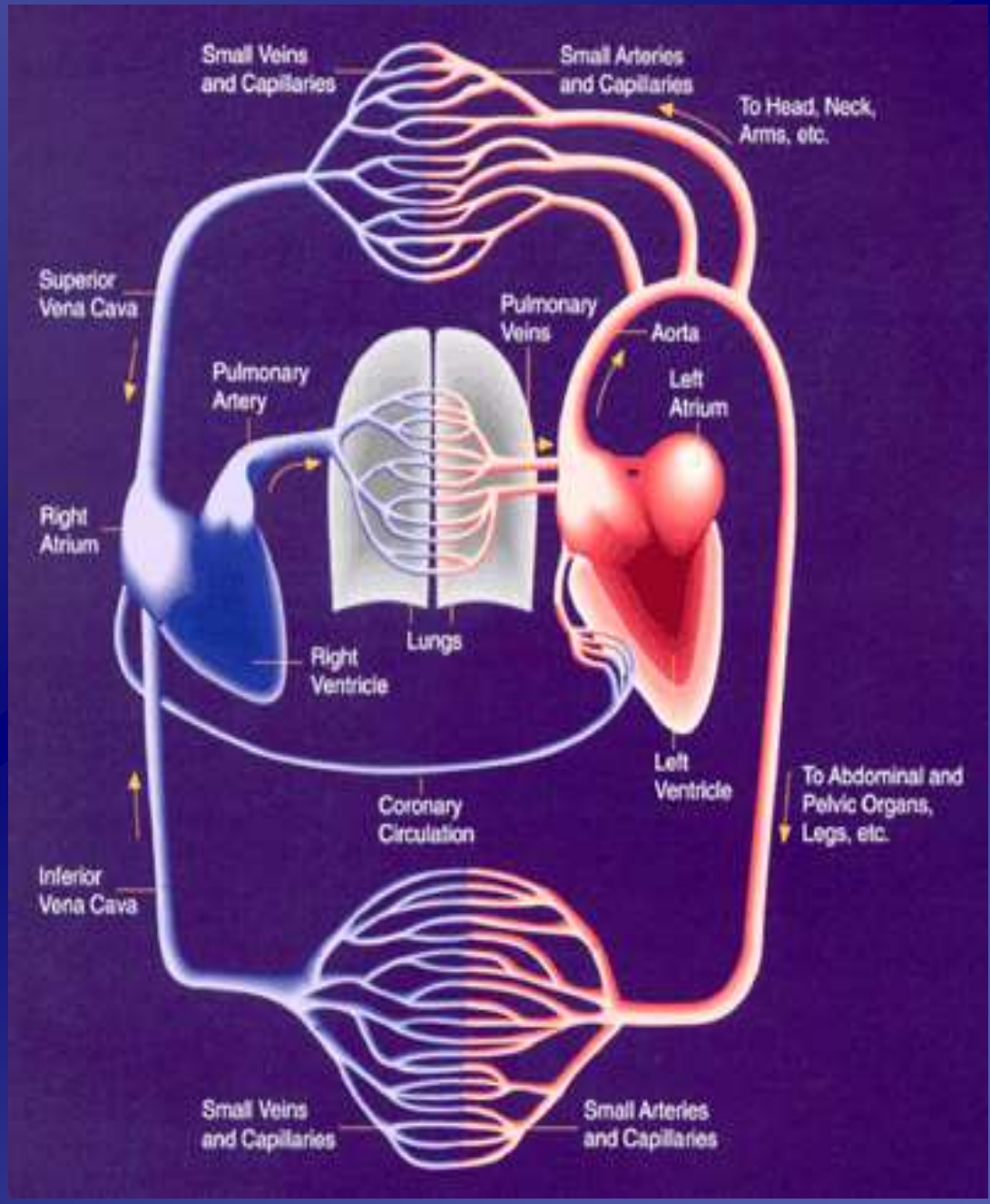
  at 28 days: 24% vs 33%

  at 90 days: 31% vs 40%
- Explanation: improves the patient-ventilator synchrony!!

What about the antiinflammatory agents?

- GLUCOCORTICOIDS
- May improve oxygenation and airway pressures
- In patients with pneumonia may hasten radiological recovery
- No survival benefit
- Harmful if the treatment started 14 days or more after ARDS have been diagnosed

Cardio-vascular Support



- **Invasive monitoring is very often indicated (Arterial line, PA catheter (Swan-Ganz) to measure cardiac outputs and if available, continuous mixed venous oxygen saturation)**

Big question mark today!!!!

- **In order to minimize pulmonary oedema, aim to keep PCWP low (8 to 10 mm Hg) and support the circulation with inotropes if necessary**

- **The role of colloids and albumin is relatively minor: the increased capillary permeability allows these molecules to equilibrate with the alveolar fluid with little increase in net plasma oncotic pressure**

Contd..

What's new with nitric oxide?

Monsalve-Nharro JA Farmacia Hospitalaria, 2016

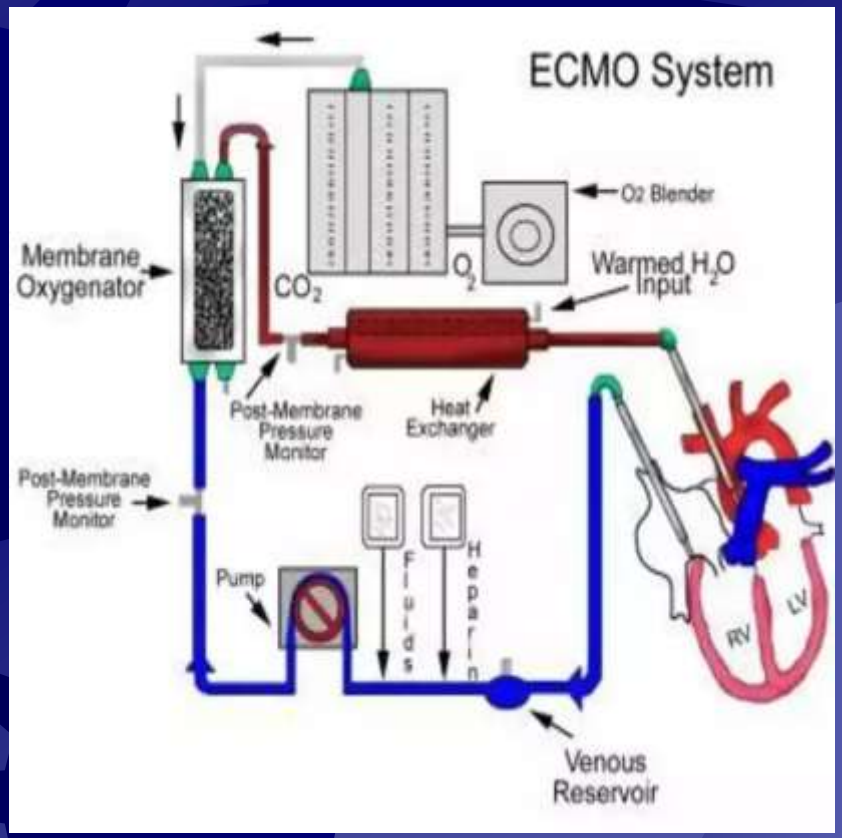
- Only patients with severe ARDS (Pao2/FiO2 < 100) and only all the other "classical" measures have been taken
- Together with invasive mechanical ventilation
- Be aware of methemoglobinemia and high NO2

Adhikari a et al Crit Care Med 2014

- *329 ARDS with very severe forms*
- No effect on mortality

And finally: ECMO

- Reserved only for patients with very severe forms of ARDS (PaO2/FiO2 <60)
- Only after all lung-protective measures and correction of fluid overload have failed to improve oxygenation
- *Noah MA (JAMA2011):*suggests that treatment could be beneficial only in specialized centers!



Do you still remember our patient?!

Here it is!!!

- 58-yr old male, after an open fracture of tibia and fibula
- Operated-external fixation, in the next hours after accident
- Four days later : dyspnea, 32 resp/minute obtunded, warm, BP 105/70, pulse 115
- Diffuse wheezes to auscultation, use of accessory respiratory muscles, breathes with open mouth

First ABG:

PaO2 42 (FiO2 mask 0.4)

PaCO2 31

pH 7.35

First X ray: diffuse, bilateral interstitial congestion with some areas of alveolar infiltrates

He is already on garamicin and cefuroxime

What can happen ?!

The patients is transferred to the ICU

- **Tracheal intubation, mechanical ventilation,**
- **RR 14 VT 550 PEEP 7**

FiO2 1

- **Sedation to a stage of "sleepy but arousable"**

And now…..?

Four hours later……

Improvement in ABG, PaO2 245 at FiO2 1, PaCO2 31 but….

Peak inspiratory pressure (PIP) 44 cm

BP 90/50, Urinary output 20 ml/hr

24 hours later

- Patient still intubated and ventilated
- Some purulent secretion around the pins
- High fever and leucoytosis

What has to be done :

***take the patient to OR**

***review the wound**

take cultures

Then:

- **Change antibiotics**
- **Assist circulation**
- **Give nutrition**

What do you change, what do you add ?

Decrease FiO2, VT and then (may be) PEEP to 5

Add fluids and decide upon hemodynamic monitoring if no improvement

Improvement in urinary output, but PaCO2 55, pH 7.28

Now you have a problem !

Possible further scenarios

Patient slowly recovers

***intubated and ventilated wirh small volumes and pressures**

***7th day: tracheostomy**

***14th day : IMV**

***17th day : spontaneous respiration**

20th day: removal of tracheostomy cannula

Things go worse!!

***VAP**

***change of antibiotics**

***still hypoxic**

***worsening of the pulmonary X ray image**

***ECMO – no improvement**

So, what can happen to this specific patient ?

- In most situations he will be cured
- In some 20% of cases he would develop a multi-vital organ failure and die after weeks
- In some cases he will go on with chronic osteomyelitis

  *multiple surgery

- *readmission to hospital

  *antibiotics

- There is a slight chance that chronic pulmonary parenchimal changes will affect his life

Causes of sudden deterioration in ARDS

Respiratory

- Pneumothorax
- Bronchial plugging
- Displaced ET tube
- Pleural effusion (Haemothorax)
- Aspiration(Eg NG feed)

Cardiovascular

- Arrhythmia
- Cardiac tamponade
- Myocardial infarction
- GI bleed(Stress Ulcer)
- Septicaemia

Just a couple of words about ARDS outcome

The main question is :why ARDS patients die ??!!

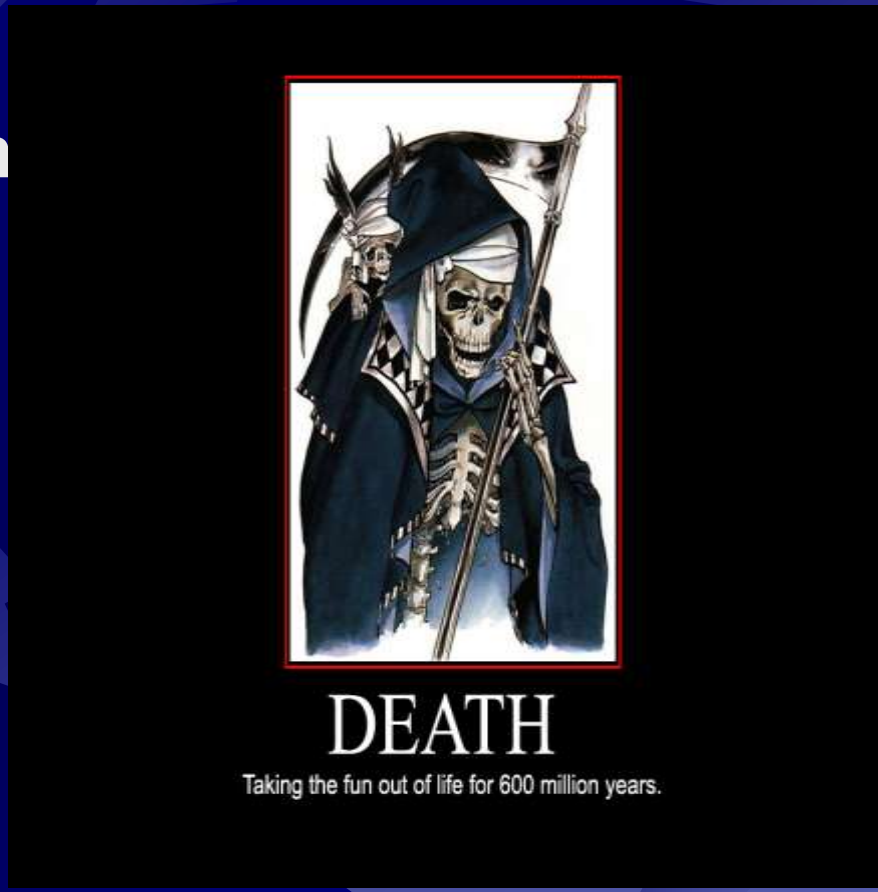
- Mostly because of multiple vital organ failure:

  *renal

  *hepatic

  *coagulation

  *septic shock
- Very few because of refractory hypoxia



Bellani G et al JAMA 2016

- 29,144 patients admitted to ICUs
- 10% of all ICU admittances
- All fulfilled the ARDS criteria
- Categories:

*mild ARDS- mortality 35%

* moderate ARDS-mortality 40%

*severe ARDS-mortality 46%

- Without saying: the highest mortality among those patients who have been underrecognized and undertreated!!!

And if they even do not die….

"Full recovery after ARDS happens very slowly, if at all!!"

"At one year after discharge:

****vital capacity is reduced***

****6-minute walk distance is diminished***

****less than 50% of patients returned to work"***

(G.Bernard, NEJM 2017)

Herridge MS, NEJM 2003

- 109 ARDS survivors evaluated 3, 6 and 12 months after discharge from ICU
- The survivors were :

*younger

*longer stay in ICU

*non steroid treatment

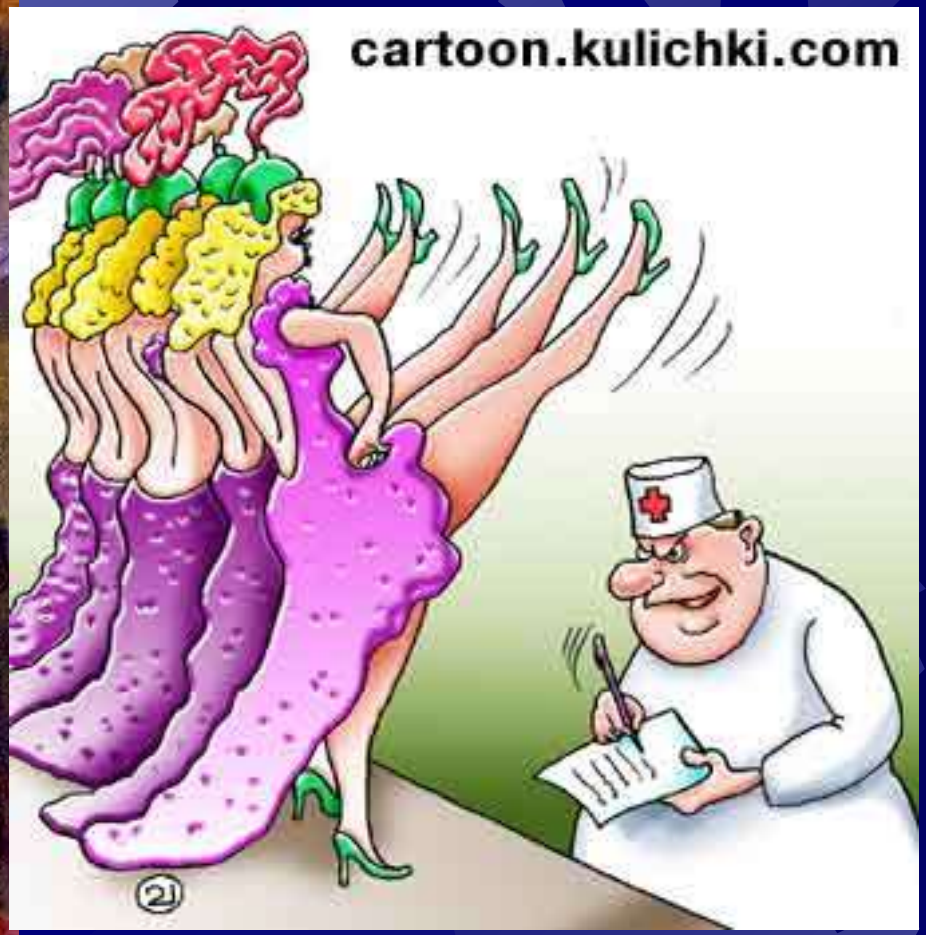
*rapid resolution of lung injury

- Lost on average 18% of their weight at ICU discharge, which explains fatigue and functional limitations
- 6% had a SaO2 <88 at exercise at 12 months
- Average distance walked : 281 m at 3 months and 422 m at 12 months

And a last but not least important question:

If this is the situation, how come that so few medical centers all over the world have a post-ICU outpatient clinic?!!

In conclusion: definition of medicine –for ARDS….



This is a profession in which the physician's task is to offer the best he/she has and wait for nature and/or G-d to help!!!!