Pulmonary & Extra-pulmonary ARDS: FIZZ or FUSS?

Dr. Rajagopala Srinivas

Senior Resident,

Dept. Pulmonary Medicine,

PGIMER, Chandigarh.

The beginning..

"The etiology of this respiratory distress syndrome remains obscure. Despite a variety of physical and possibly biochemical insults, the response of the lung was similar in all 12 patients. In view of the similar response of the lung to a variety of stimuli, a common mechanism of injury may be postulated"

Ashbaugh et al. Lancet 1967; 2: 319–323.

The AECC (American European conference) later defined two subsets in their consensus conference

“a direct ("primary" or "pulmonary") insult, that directly affects lung parenchyma, and an indirect ("secondary" or "extra-pulmonary") insult, that results from an acute systemic inflammatory response”

Bernard GR, Artigas A, Brigham KL, et al
Am J Respir Crit Care Med 1994; 149: 818–824.

Useful concept or distinctive sub-groups?

Acute Respiratory Distress Syndrome Caused by Pulmonary and Extrapulmonary Disease

Different Syndromes?

LUCIANO GATTINONI, PAOLO PELOSI, PETER M. SUTER, ALESSIA PEDOTO, PAOLA VERCESI, and ALFREDO LISSONI

Istituto di Anestesia e Rianimazione, Universita' di Milano and Servizio di Anestesia e Rianimazione, Ospedale Maggiore IRCCS, Milano, Italy; and Division of Surgical Intensive Care, University Hospital of Geneva, Geneva, Switzerland

Am J Respir Crit Care Med Vol 158. pp 3–11, 1998

12 patients with ARDSp and 9 patients of ARDSexp

Est (L) more in ARDSp and Est (w) more in ARDSexp

IAP more in ARDSexp and co-related with Est

Increase in PEEP lead to rise of Est in ARDSp and fall of Est in ARDSexp (more recruitment in ARDSexp)

Different respiratory mechanics and response to PEEP observed consistent with a prevalence of consolidation in ARDSp Vs prevalent edema and alveolar collapse in ARDSexp

Am J Respir Crit Care Med Vol 158. pp 3–11, 1998

Lump or split?

SPLIT?

- Etiological events are distinct
- Pathogenetically different
- Morphology differs
- Physiologically distinguishable
- Varied responses to Rx
  - PEEP
  - Prone pressure ventilation
- Response to inhaled vasodilators different

Lump?

•Etiological case mix common

•Practical difficulties in case assignment

•Current clinical management similar

•Not related to outcomes

Are ARDSp and ARDSexp different?

1) Epidemiology
2) Pathophysiology
3) Morphological aspects
4) Respiratory mechanics
5) Ventilatory strategies
6) Response to pharmacological agents and
7) Long-term recovery

1.Epidemiology: Is ARDSp more common than ARDSexp?

In most studies, ARDSp more common than ARDSexp

Varies from 47-75% of total

Study from our centre

N=180

ARDSp (pneumonia most common)=123

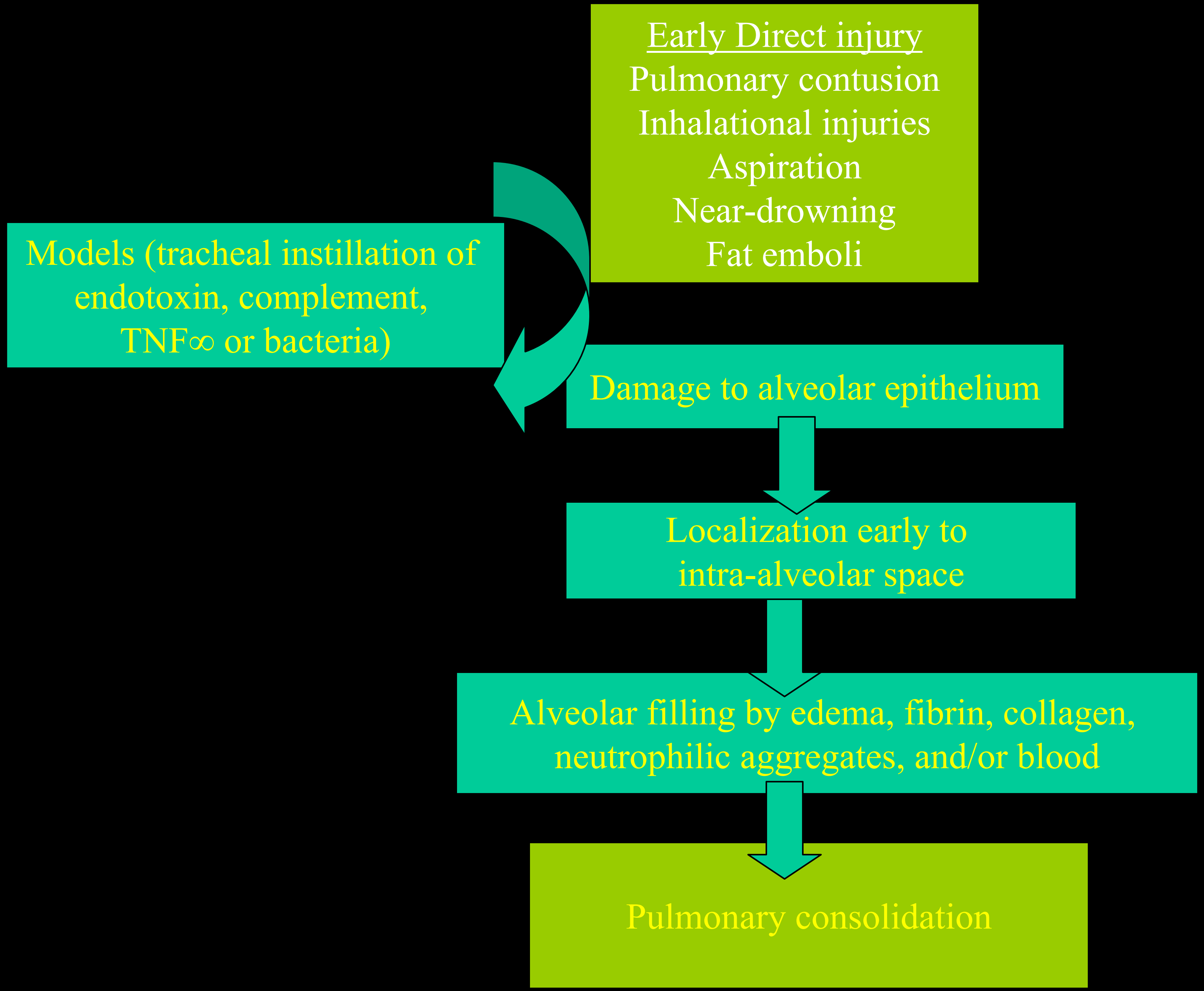
ARDSexp (sepsis most common)=57

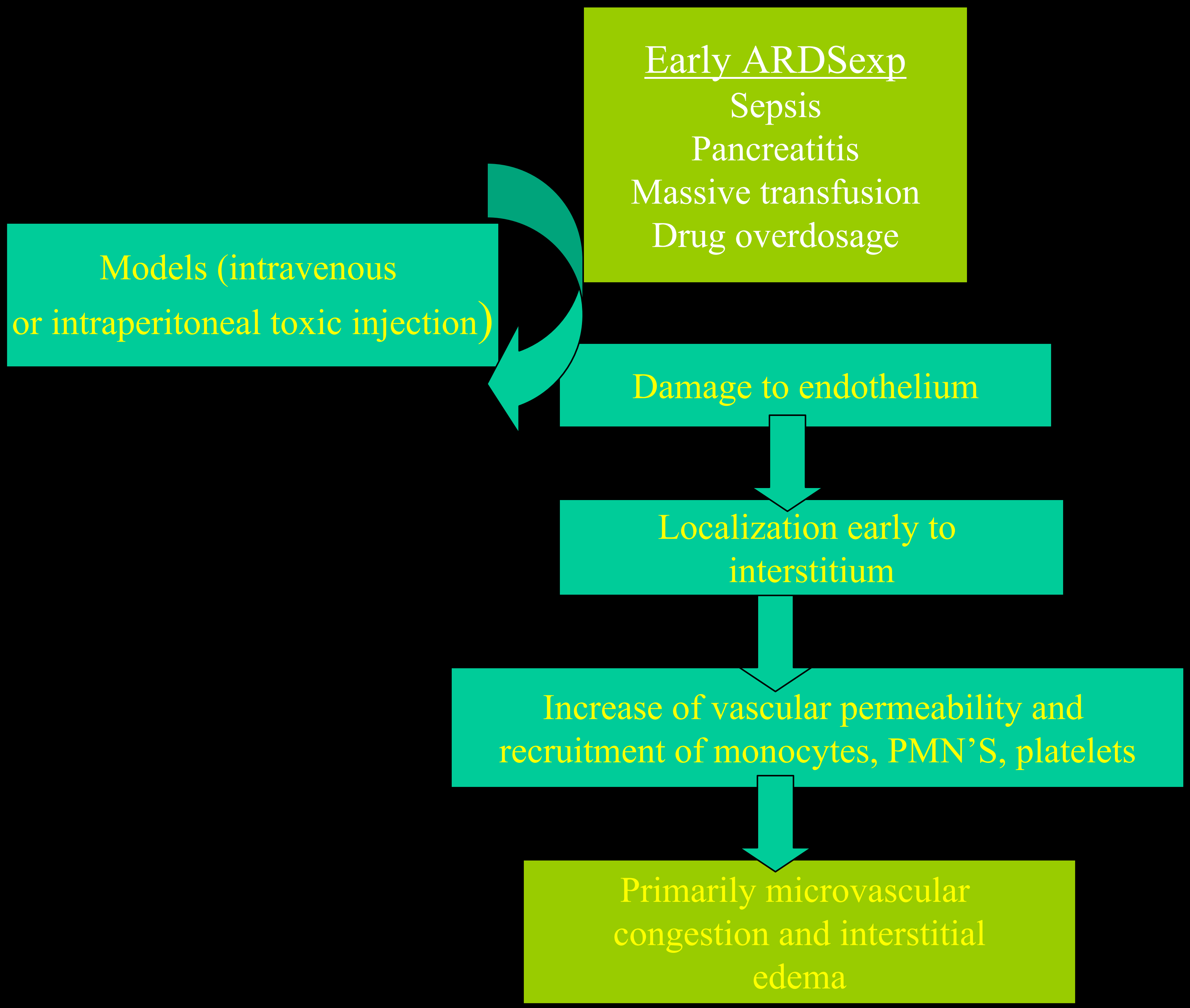
In the largest study (n=902), the incidence of both were equal

Why the discrepancy?

The lack of agreement among various studies because

1. Baseline status differ
2. Prevalence of the disease precipitating ARDS in each center
3. Impact of therapy and
4. Overall distribution of these factors in the studied population.


Early Direct injury
Pulmonary contusion
Inhalational injuries
Aspiration
Near-drowning
Fat emboli
Models (tracheal instillation of endotoxin, complement, TNF∞ or bacteria)
Damage to alveolar epithelium
Localization early to intra-alveolar space
Alveolar filling by edema, fibrin, collagen, neutrophilic aggregates, and/or blood
Pulmonary consolidation


Early ARDSexp
Sepsis
Pancreatitis
Massive transfusion
Drug overdosage
Models (intravenous or intraperitoneal toxic injection)
Damage to endothelium
Localization early to interstitium
Increase of vascular permeability and recruitment of monocytes, PMN'S, platelets
Primarily microvascular congestion and interstitial edema

1. In late stages, however it is homogenous
2. Both might be simultaneously operative.

3.Morphology

	ARDSp	ARDSexp
Alveoli		
Alveolar epithelium	++Damage	Damage
Alterated type I and II cell	++Damage	Normal
Alveolar neutrophils	Prevalent	Rare
Apoptotic neutrophils	Prevalent	Rare
Fibrinous exudates	Present	Rare
Alveolar collapse	++Increased	Increased
Local interleukin	Prevalent	Rare
Interstitial space		
Interstitial oedema	Absent	High
Collagen fibres	++Increased	Increased
Elastic fibres	Normal	Normal
Capillary endothelium	Normal	++Damage
Blood		
Interleukin	Increased	++Increased
TNF-∞	Increased	++Increased

Are ARDSp and ARDSexp morphologically distinct?

Cannot be reliably distinguished from each other

Predominance of alveolar collapse, fibrinous exudate and alveolar wall oedema in ARDSp

Hoelz C, Negri EM, Lichtenfels AJ, et al.
Pathol Res Pract 2001; 197: 521–530.

Collagen content in ARDSp > ARDSexp in the early phase, while no differences in elastin content.

Negri EM, Hoelz C, Barbas CSV et al
Pathol Res Pract 2002; 198:355–361.

4.Radiology: ARDSp vs. ARDSexp

Initial CT evaluation from Gattinoni's group

N=33, ARDSp (22) and ARDSexp (11)

Consolidation and GGO equally present in ARDSp; asymmetric consolidation characteristic.

Predominant GGO in ARDSexp; more symmetric.

Pleural effusions in half; Kerley B and pneumatocoeles uncommon.

Goodman LR, Fumagalli R, Tagliabue P, et al.
Radiology 1999, 213:545–552.

One other evaluated this as a primary goal

N=41; ARDSp (16) and ARDSexp (25)

Significantly higher incidence of intense parenchymal opacification demonstrated in nondependent areas with direct insults

Inversely related to the time from intubation to CT

No single feature is predictive of either.

Desai SR, Wells AU, Suntharalingam G, et al.
Radiology 2001, 218:689–693.

What can we conclude?

1. Increase in the lung densities most prominent in dependent lung regions in supine position

2) ARDSp due to CAP two prevalent patterns described:

   Dependent extensive consolidation and air bronchograms with GGO

   Homogeneous diffuse interstitial and alveolar infiltration, without evidence of atelectasis

3) In ARDSp, due to VAP, densities in the dependent part of the lung (likely atelectasis) are prevalent with the remaining nondependent lung substantially normal

4) ARDSexp has predominant GGO

5. Respiratory mechanics: ARDSp vs. ARDSexp

Seminal observations included “a stiff respiratory system” or loss of compliance

Traditionally, this was assumed to be due to altered lung compliance

When the abnormal compliance was partitioned,

ARDSp-high lung elastance → consolidated lung

ARDSexp- chest wall elastance → raised intra-abdominal pressure and gut edema.

Gattinoni et al. Am J Respir Crit Care Med Vol 158, 1998

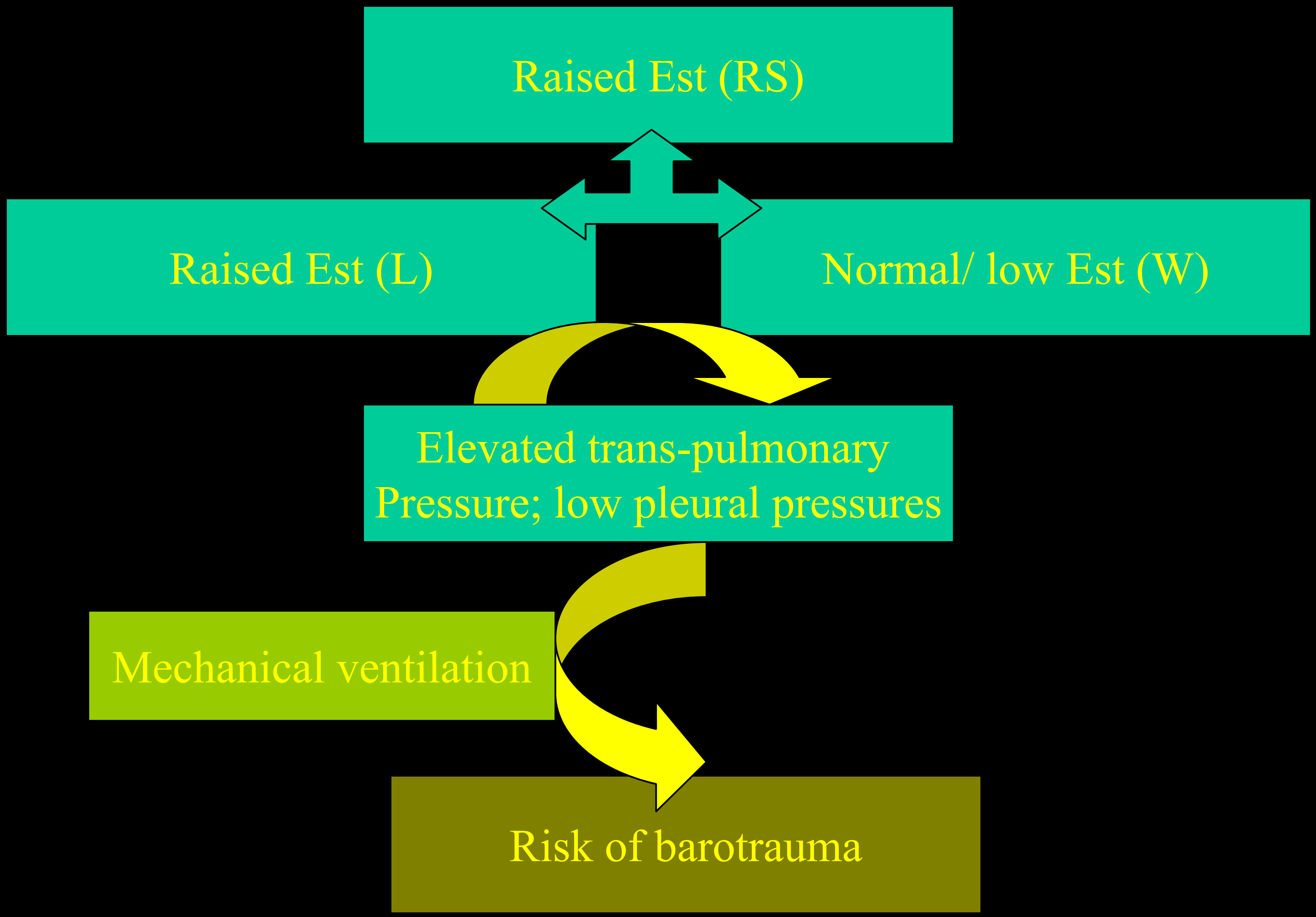
Respiratory system resistance is similar in ARDSp and ARDSexp

However chest wall resistance is greater in ARDSexp

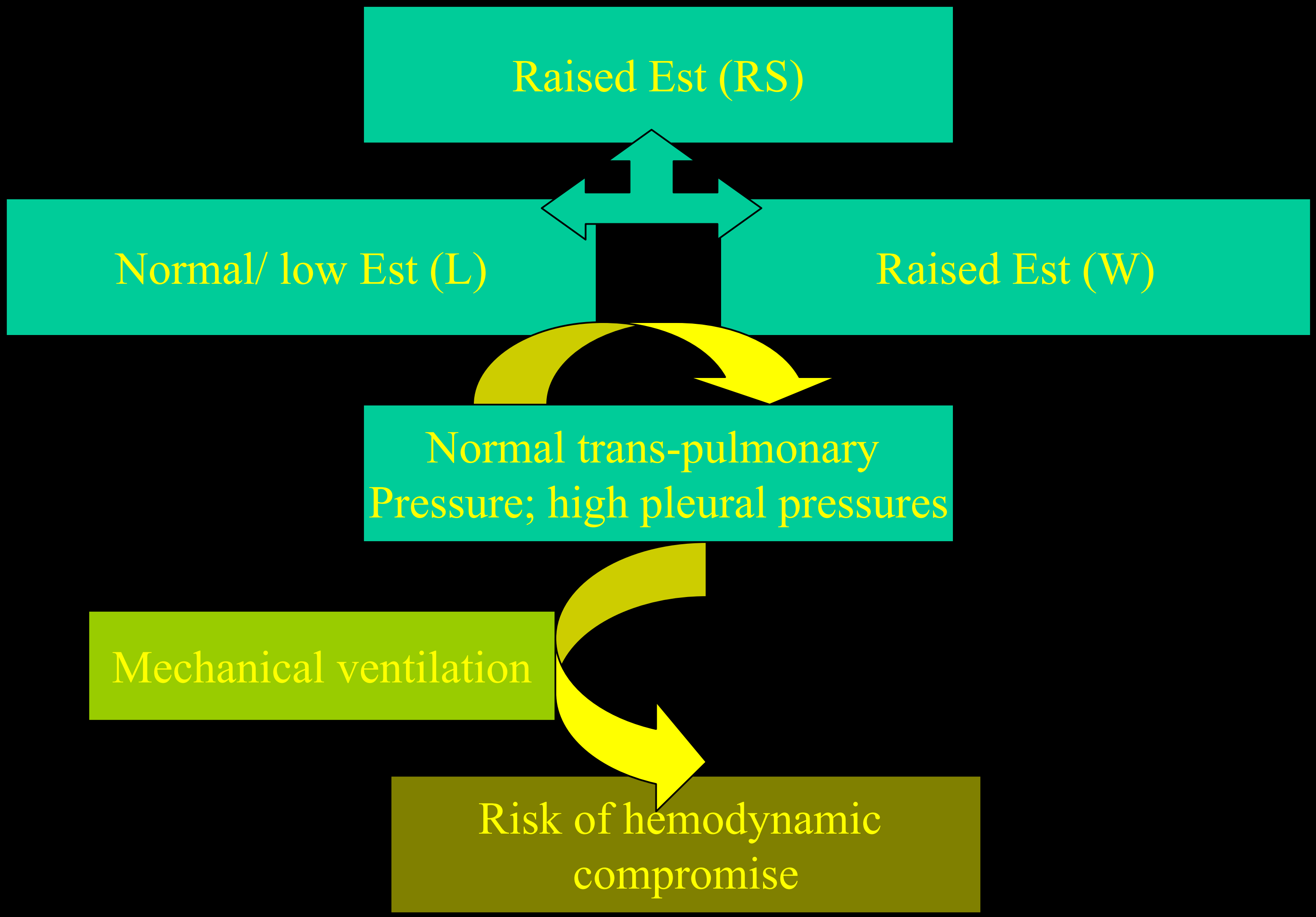
So, at a given airway pressure, higher trans-pulmonary pressures are seen in ARDSp

So, what is the significance of this divergent respiratory mechanics?

ARDSp


Raised Est (RS)
Raised Est (L)
Normal/ low Est (W)
Elevated trans-pulmonary
Pressure; low pleural pressures
Mechanical ventilation
Risk of barotrauma

ARDSexp


Raised Est (RS)
Normal/ low Est (L)
Raised Est (W)
Normal trans-pulmonary Pressure; high pleural pressures
Mechanical ventilation
Risk of hemodynamic compromise

Ventilatory strategies: ARDSp vs. ARDSexp

1. Efficacy of low tidal volume ventilation

Efficacy of Low Tidal Volume Ventilation in Patients with Different Clinical Risk Factors for Acute Lung Injury and the Acute Respiratory Distress Syndrome

MARK D. EISNER, TAYLOR THOMPSON, LEONARD D. HUDSON, JOHN M. LUCE, DOUGLAS HAYDEN, DAVID SCHOENFELD, MICHAEL A. MATTHAY, and the Acute Respiratory Distress Syndrome Network

Division of Pulmonary and Critical Care Medicine, and Division of Occupational and Environmental Medicine, Department of Medicine, University of California, San Francisco; Pulmonary and Critical Care Medicine, and ARDS Network Clinical Coordinating Center, Massachusetts General Hospital, Harvard University; Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington; Department of Biostatistics, Harvard School of Public Health; Department of Anesthesia and Cardiovascular Research Institute, University of California, San Francisco

Am J Respir Crit Care Med Vol 164. pp 231–236, 2001

Retrospective analysis of 902 patients; NO difference in efficacy.

6. Ventilatory strategies: ARDSp vs. ARDSexp
1. Application of PEEP.

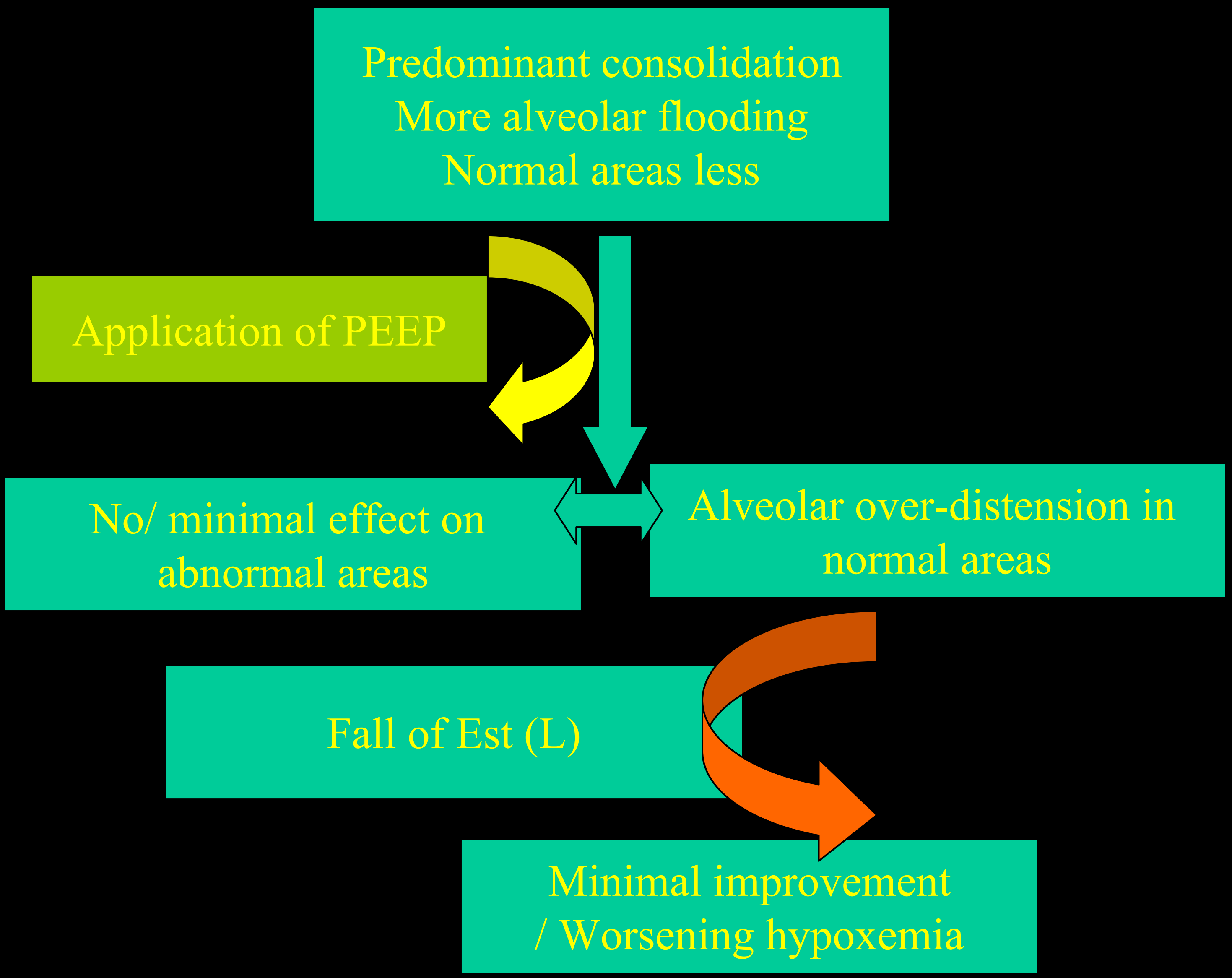
Potential for recruitment more in atelectasis than in consolidation

Applied airway pressure may partition differently, leading to varying recruitment

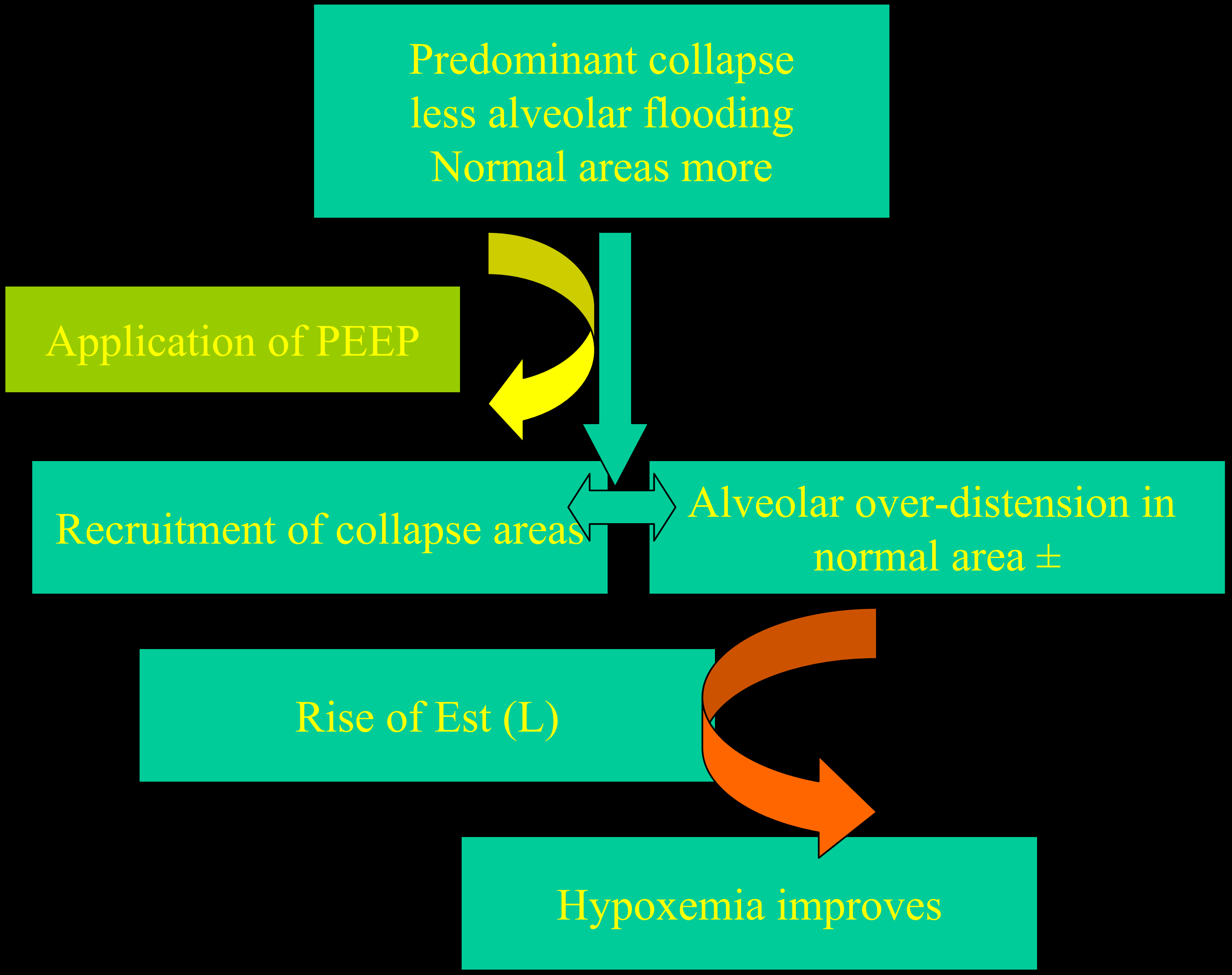
Use of higher PEEP and higher Pl ($Cstat_{res}$) may be safer in ARDSexp since $Cstat_W > Cstat_L$

Time course to oxygenation may be different in ARDSp

ARDSp


Predominant consolidation
More alveolar flooding
Normal areas less
Application of PEEP
No/ minimal effect on abnormal areas
Alveolar over-distension in normal areas
Fall of Est (L)
Minimal improvement / Worsening hypoxemia

ARDSexp


Predominant collapse
less alveolar flooding
Normal areas more
Application of PEEP
Recruitment of collapse areas
Alveolar over-distension in
normal area ±
Rise of Est (L)
Hypoxemia improves

Does this translate into management differences?

In clinical practice, PEEP useful in ARDS irrespective of etiology

Clinically, it is possible that both ARDSp and ARDSexp have a mix of consolidation and collapse

Preponderance of one does not negate benefit of PEEP in ARDSp.

Other mechanisms of benefit might have a role

- Regional diversion of ventilation
- Regional diversion of perfusion

ARDS Net strategy did not use different strategy for both sub-groups.

Low tidal ventilation efficacy same in both groups

Am J Respir Crit Care Med Vol 164. pp 231–236, 2001

Potentially,

1. Levels of PEEP can higher in ARDSexp (chest wall partitioning) before compliance falls
2. Volutrauma with higher PEEP less likely with ARDSexp

Ventilatory strategies: ARDSp vs. ARDSexp
1. Prone position ventilation

Mechanisms by which prone position acts:

1. Increase in FRC
2. Changes in diaphragm position/ movement
3. Secretions drainage
4. Gravity directed blood flow to less injured areas
5. Reduction of heart/ mediastinum compression
6. Changes in chest wall compliance

Raised intra abdominal pressure

Collapse vs consolidation

7. Whither data….?

2-hour physiological study (n=47);31 ARDSp and 16 ARDSexp

In prone position

(1) the response in oxygenation more marked in ARDSexp compared with ARDSp (3 FOLD)

(2) Rate of increase in oxygenation slower in ARDSp

(3) the densities, determined that in prone position decreased to a greater degree in ARDSexp

Lim CM, Kim EK, Lee JS, et al Intensive Care Med 2001;27:477–485

Large prospective trial in 73 patients

51 ARDSp and 22 ARDSexp

Prone position for 6 h for 10 days

The improvement in oxygenation was greater in ARDSexp compared with ARDSp

Mortality was not different between the two groups

Pelosi P, Brazzi L, Gattinoni L Eur Respir J 2002; 20:1017–1028.

Response to pharmacological agents

Data on iNO and prostacyclin are non-conclusive

Response to iNO greater in ARDSp

Attributed to greater shunting

Rialp G, Betbese AJ Am J Respir Crit Care Med 2001; 15: 243–249

However, response to prostacyclin greater in ARDSexp

Domenighetti G Crit Care Med 2001; 29: 57–62.

Are long term outcomes different in ARDSp and ARDSexp?

Influence of direct and indirect etiology on acute outcome and 6-month functional recovery in acute respiratory distress syndrome

Ganesh Suntharalingam, FRCA; Kate Regan, MRCP; Brian F. Keogh, FRCA; Clifford J. Morgan, FRCA; Timothy W. Evans, MD, PhD

Crit Care Med 2001; 29: 562-7

No difference in FVC and DLco between the two groups

8. Mortality: ARDSp vs. ARDSexp

TABLE 3. MORTALITY AMONG PATIENTS WITH PULMONARY VERSUS NONPULMONARY RISK FACTORS FOR ALI/ARDS: EFFICACY OF THE LOW V_T VENTILATION STRATEGY

Clinical Risk Factor*	Low V_T Ventilation[†] 6 ml/kg (*n* = 473)	Traditional V_T Ventilation 12 ml/kg (*n* = 429)	All Patients[‡] (*n* = 902)
Pulmonary	32% 76/234	40% 89/220	36% 165/454
Nonpulmonary	29% 70/239	40% 84/209	34% 154/448

* Pulmonary conditions = pneumonia or aspiration; nonpulmonary = trauma, sepsis, or other.

[†] p = 0.61 for interaction between clinical risk factor and ventilator treatment strategy, after controlling for covariates.

[‡] p = 0.57 for comparison of case fatality rate among pulmonary versus nonpulmonary conditions.

Also non-pulmonary organ failure and time to liberation from mechanical ventilation similar.

Am J Respir Crit Care Med Vol 164. pp 231–236, 2001

OR

I have been doomed to such a dreadful shipwreck

that man is not truly one, but truly two.

I say two, because the state of my own knowledge does not pass beyond that point.

Others will follow, others will outstrip me on the same lines; and I hazard the guess that man will be ultimately known for a mere polity of multifarious, incongruous, and independent denizens

The Strange Case of Dr. Jekyll and Mr. Hyde

Robert Louis Stevenson

Two-face or multi-faced??

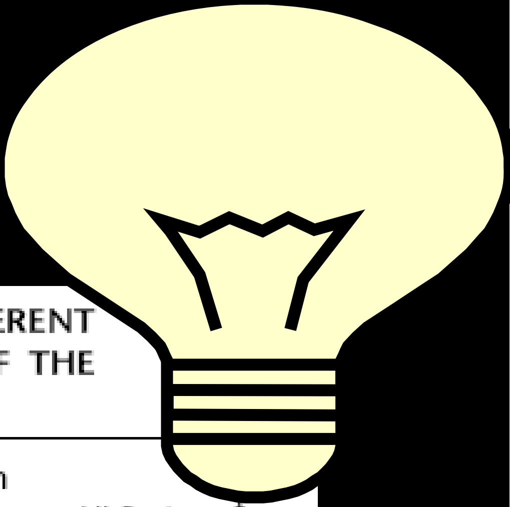


TABLE 2. MORTALITY AMONG PATIENTS WITH DIFFERENT CLINICAL RISK FACTORS FOR ALI/ARDS: EFFICACY OF THE LOW V_T VENTILATION STRATEGY

Clinical Risk Factor	Low V_T Ventilation* 6 ml/kg (*n* = 473)	Traditional V_T Ventilation 12 ml/kg (*n* = 429)	All Patients† (*n* = 902)
Sepsis	38%	50%	43%
	47/125	55/111	102/236
Pneumonia	31%	42%	36%
	50/162	66/158	116/320
Aspiration	36%	37%	37%
	26/72	23/62	49/134
Trauma	12%	11%	11%
	7/59	4/37	11/96
Other	29%	40%	35%
	16/55	25/61	41/116
Total‡	31%	40%	35%
	146/473	173/429	319/902

Am J Respir Crit Care Med Vol 164. pp 231–236, 2001

Summary

1. Prevalent damage in early stages of a direct insult is intra-alveolar whereas in indirect injury is interstitial edema
2. Radiological pattern in ARDSp is prominent consolidation and ARDSexp is GGO
3. Primary abnormalities are raised lung and chest wall elastance in ARDSp and ARDSexp respectively
4. PEEP, inspiratory recruitment and prone position more effective in ARDSexp.
5. Further studies are warranted to better define if the distinction between ARDS of different origins can improve clinical management and survival.