Fenotypy/subfenotypy ARDS

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The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material

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Eddy Fan
Luigi Camporota
Massimo Antonelli
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Richard Beale

Intensive Care Med (2012) 38:1573–1582
DOI 10.1007/s00134-012-2682-1

The ARDS conceptual model

Face validity derives from an understanding of how clinicians recognize patients with the syndrome, therefore, considerable discussion focused on developing a conceptual model of ARDS. The panel agreed that ARDS is a type of acute diffuse lung injury associated with a predisposing risk factor, characterized by inflammation leading to increased pulmonary vascular permeability and loss of aerated lung tissue. The hallmarks of the clinical

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loss of aerated lung tissue. The hallmarks of the clinical syndrome are hypoxemia and bilateral radiographic opacities [23] (using standard chest X-ray or computed tomography [CT] scan), associated with several physiological derangements including: increased pulmonary venous admixture, increased physiological dead space, and decreased respiratory system compliance. The morphological hallmarks in the acute phase are lung edema, inflammation, hyaline membranes, and alveolar hemorrhage (i.e., diffuse alveolar damage) [24].

Direktní vs indirektní ARDS?

There are many common etiologic risk factors for ARDS, which the AECC definition classified into direct and indirect lung injury categories. Although some experimental and clinical studies show modest overall differences in the inflammatory responses and radiographic patterns as well as physiologic responses to ventilatory treatment, the direct and indirect categories overlap to such a large degree that the committee decided not to include direct and indirect ARDS as distinct entities in the Berlin definition (Table 2). Identification of the risk factor leading to ARDS in an individual patient, regardless of its direct or indirect nature, rather serves to guide therapy for the underlying disease leading to ARDS.

Risk factor
Pneumonia
Non-pulmonary sepsis
Aspiration of gastric contents
Major trauma
Pulmonary contusion
Pancreatitis
Inhalational injury
Severe burns
Non-cardiogenic shock
Drug overdose
Multiple transfusions or transfusion-associated acute lung injury (TRALI)
Pulmonary vasculitis
Drowning

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Fenotyp

Fenotyp je soubor všech pozorovatelných vlastností a znaků živého organismu. Představuje výsledek spolupůsobení genotypu, epigenetiky a prostředí čili to, jak organismus v daném znaku (znacích) nakonec skutečně vypadá.

Obecně rozlišujeme znaky kódované majorgeny, na jejichž projev ve fenotypu nemá prostředí žádný nebo téměř žádný vliv (barva očí, krevní skupiny, struktura bílkovin), a znaky kódované minorgeny, na jejichž projev má prostředí vliv velký (velikost rostliny, množství semen atp.).

Zhruba lze říci, že fenotyp = genotyp + epigenetika + prostředí.

subphenotype

English [edit]

Etymology [edit]

from *sub-* + *phenotype*

Noun [edit]

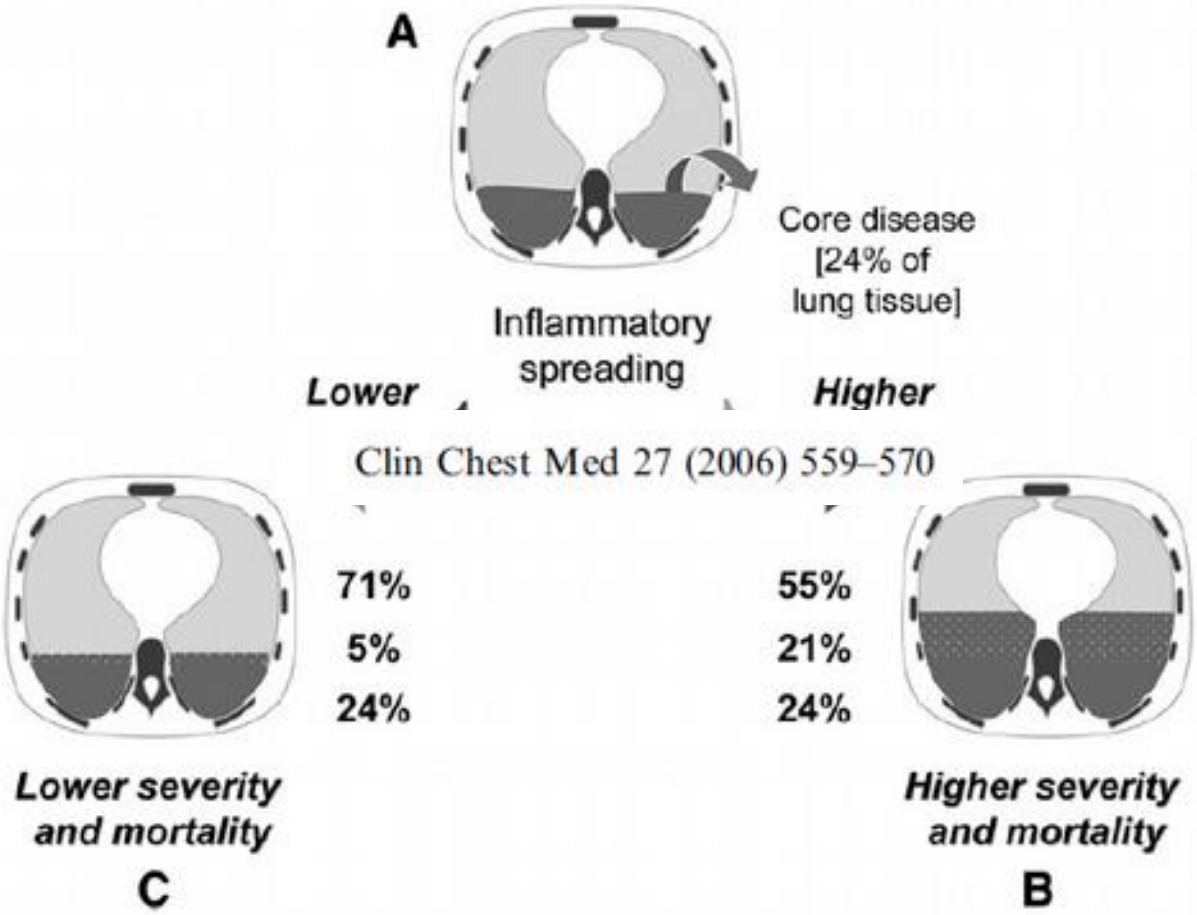
subphenotype (*plural* **subphenotypes**)

1. (*biology*, *pathology*) A subset of a phenotype that is characteristic of a subset of a population

Možné klasifikace subfenotypů

- Dle závažnosti
  - PaO_2/FiO_2
  - LISS
- Čas
- Extrapulmonary vs pulmonary ARDS
- Nízký vs vysoký transpulmonální tlak
- Dle CT scan ARDS study group
- *Recruitable/non-recruitable*
- *Hyper/hypo inflamatorní subfenotyp*

ARDS pathophysiology



Clin Chest Med 27 (2006) 559–570

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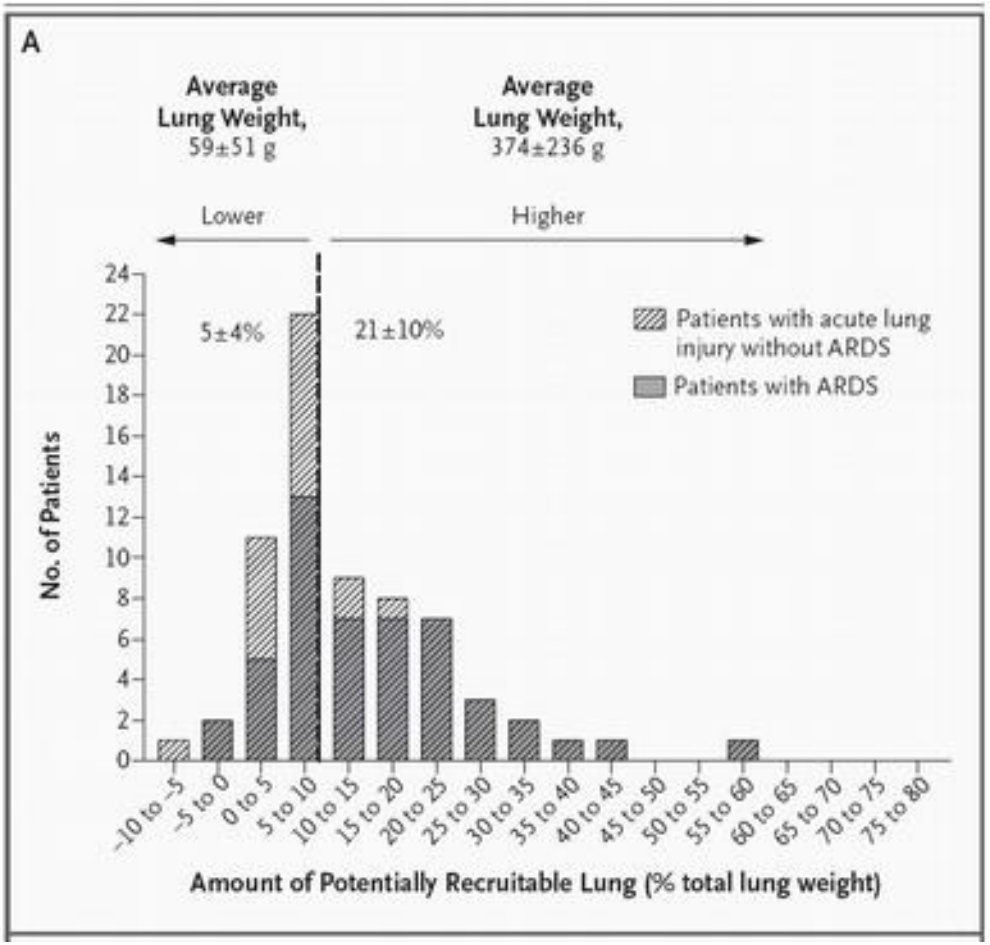
Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D., F.R.C.P., Pietro Caironi, M.D., Massimo Cressoni, M.D., Davide Chiumello, M.D., V. Marco Ranieri, M.D., Michael Quintel, M.D., Ph.D., Sebastiano Russo, M.D., Nicolò Patroniti, M.D., Rodrigo Cornejo, M.D., and Guillermo Bugedo, M.D.

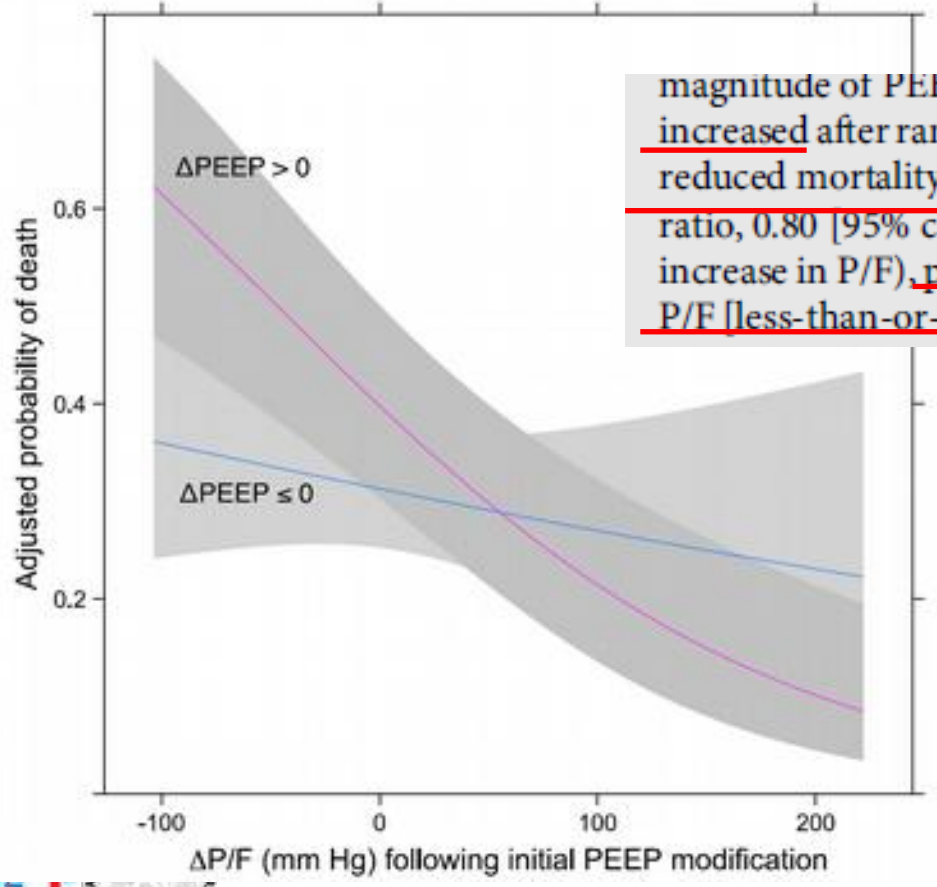


N Engl J Med 2006;354:1775-86.

Oxygenation Response to Positive End-Expiratory Pressure Predicts Mortality in Acute Respiratory Distress Syndrome

A Secondary Analysis of the LOVS and ExPress Trials

Ewan C. Goligher[1,2,3,4], Brian P. Kavanagh[1,5,6], Gordon D. Rubenfeld[1,2,7], Neill K. J. Adhikari[1,2,7], Ruxandra Pinto[7], Eddy Fan[1,2,4], Laurent J. Brochard[1,2,8], John T. Granton[1,2,4], Alain Mercat[9], Jean-Christophe Marie Richard[10], Jean-Marie Chretien[11], Graham L. Jones[12], Deborah J. Cook[12,13], Thomas E. Stewart[1,2,4], Arthur S. Slutsky[1,2,4], Maureen O. Meade[12,13], and Niall D. Ferguson[1,2,3,4]



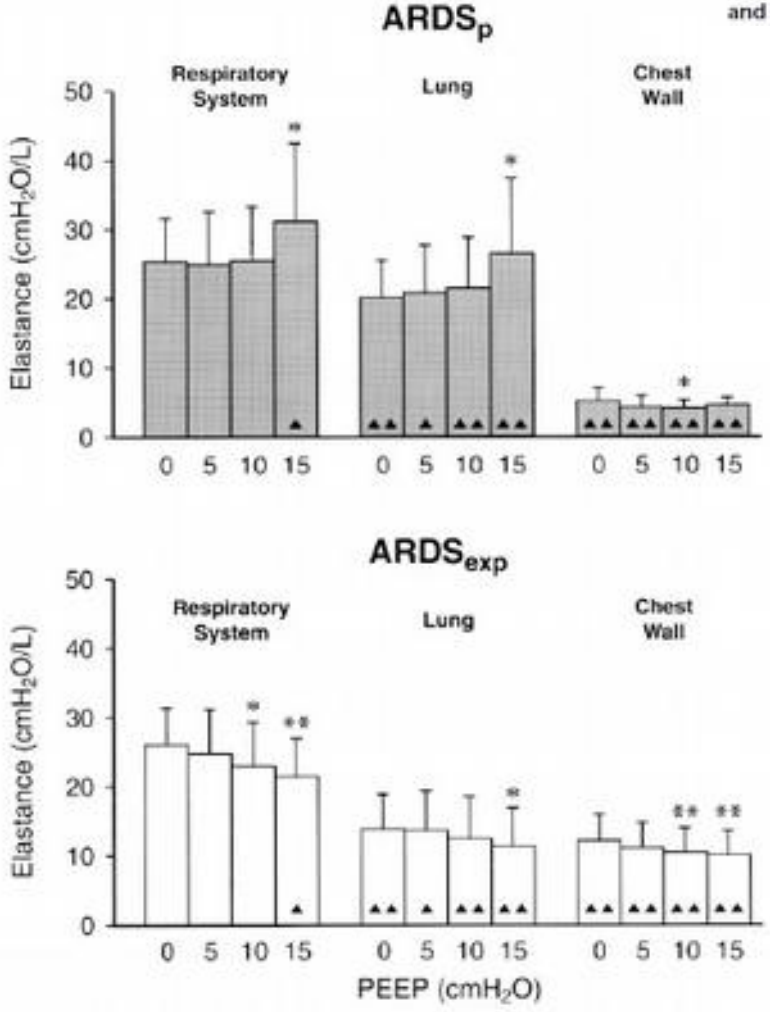
magnitude of PEEP change. Among patients in whom PEEP was increased after randomization, an increase in P/F was associated with reduced mortality (multivariable logistic regression; adjusted odds ratio, 0.80 [95% confidence interval, 0.72–0.89] per 25–mm Hg increase in P/F), particularly in patients with severe disease (baseline P/F [less-than-or-equal-to] 150 mm Hg). Changes in compliance and

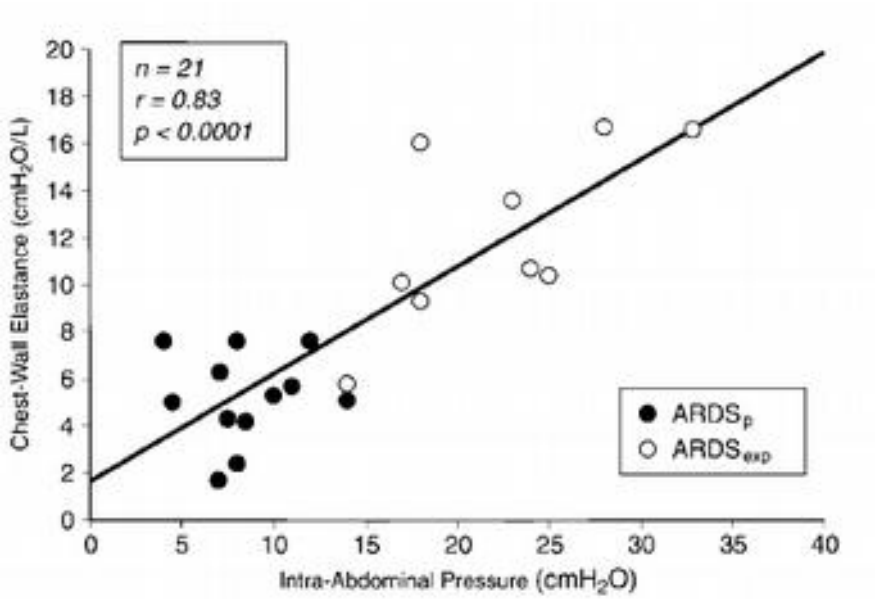
Am J Respir Crit Care Med Vol 190, Iss 1, pp 70–76, Jul 1, 2014

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

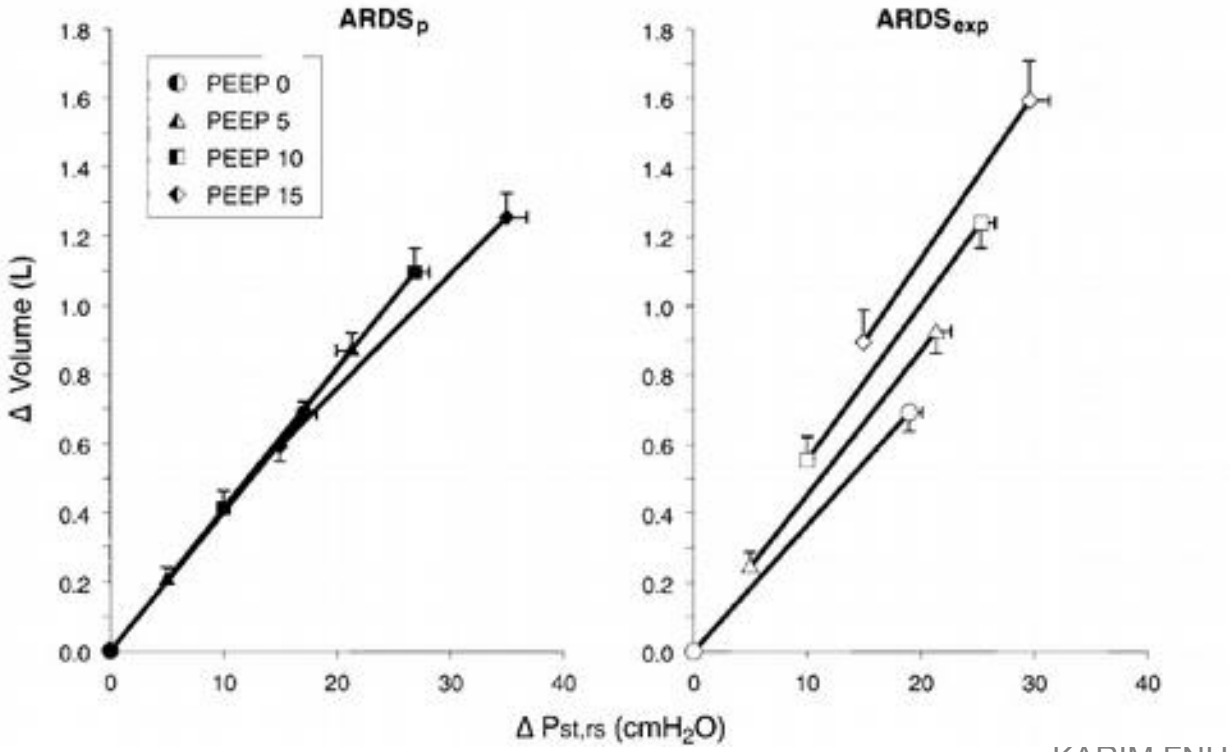




AM J RESPIR CRIT CARE MED 1998;158:3–11.

END-EXPIRATORY LUNG VOLUME AND ESTIMATED RECRUITMENT FOR ARDS CAUSED BY PULMONARY OR EXTRAPULMONARY DISEASE AT DIFFERENT PEEP LEVELS*

	PEEP ($cm\ H_2O$)			
	0	5	10	15
EELV, L				
$ARDS_p$	0.556 ± 0.254†	0.762 ± 0.319‡	0.970 ± 0.381‡	1.150 ± 0.356‡§
$ARDS_{exp}$	0.602 ± 0.291†	0.847 ± 0.338‡	1.155 ± 0.367‡	1.494 ± 0.340‡
Estimated recruitment, L				
$ARDS_p$		−0.002 ± 0.088	−0.003 ± 0.098§	−0.031 ± 0.092‖
$ARDS_{exp}$		0.043 ± 0.120†	0.153 ± 0.200**	0.293 ± 0.241††



AM J RESPIR CRIT CARE MED 1998;158:3–11.

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Acute Respiratory Distress Syndrome Caused by Pulmonary and Extrapulmonary Disease

Different Syndromes?

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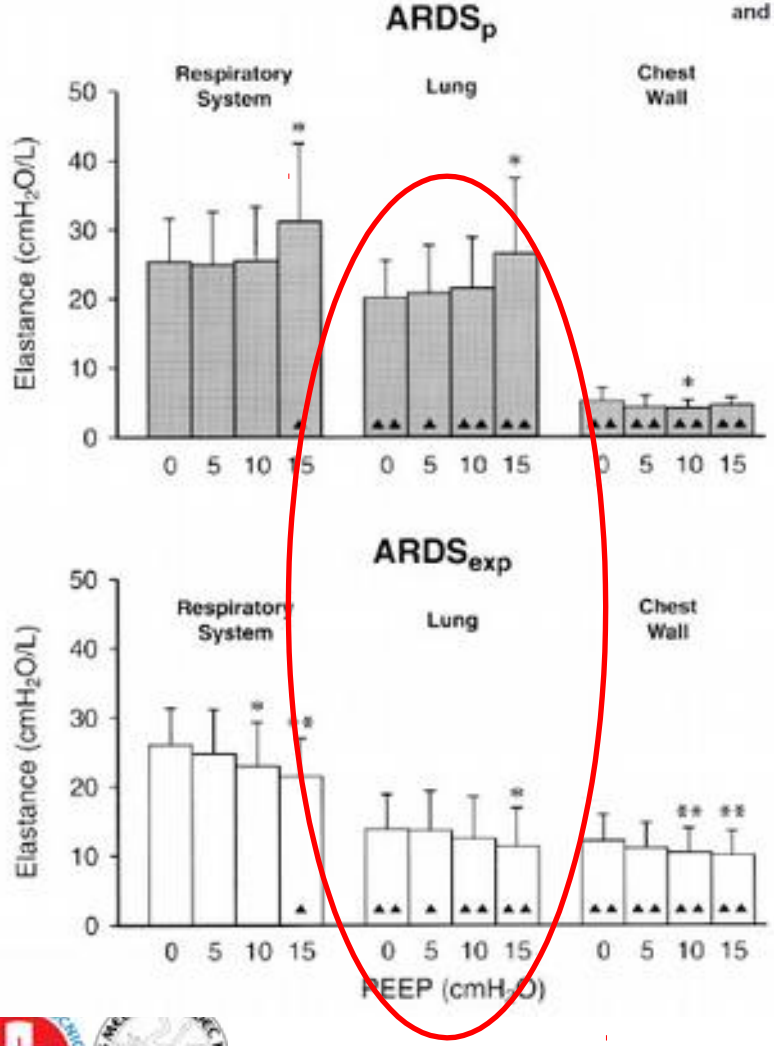

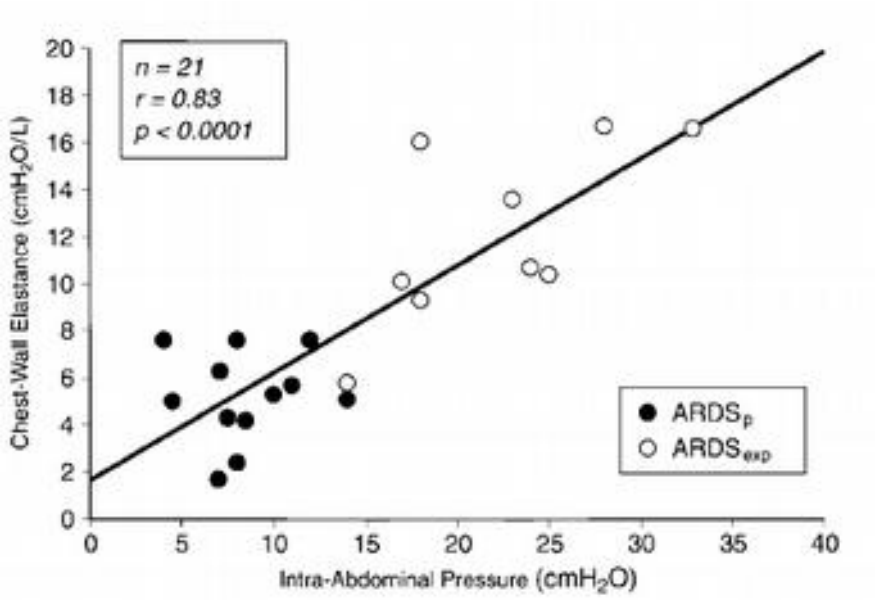

AM J RESPIR CRIT CARE MED 1998;158:3–11.

Transpulmonary Pressure Describes Lung Morphology During Decremental Positive End-Expiratory Pressure Trials in Obesity*

Iacopo Fumagalli, MD[1-3]; Lorenzo Berra, MD[2]; Changsheng Zhang, MD, PhD[2]; Massimiliano Pirrone, MD[1-3]; Roberta R. De Santis Santiago, MD, PhD[1-3]; Susimeire Gomes, MSc[3]; Federico Magni, MD[4]; Glaucia A. B. dos Santos, MSc[3]; Desmond Bennett, BA[5]; Vinicius Torsani, RRT, MSc[3]; Daniel Fisher, RRT[5]; Caio Morais, RRT[3]; Marcelo B. P. Amato, MD, PhD[3]; Robert M. Kacmarek, RRT, PhD[2]

TABLE 1. Patients' Respiratory Parameters

Respiratory Parameters, $n = 16$	Baseline	Optimal PEEP	p
PEEP (cm H_2O)	12.7 ± 2.9	21.7 ± 3.7	< 0.001
Plateau pressure (cm H_2O)	23.8 ± 3.4	28.3 ± 4.3	< 0.001
Peak pressure (cm H_2O)	33.3 ± 65.1	38.8 ± 4.9	< 0.001
End-inspiratory transpulmonary pressure (cm H_2O)	2.5 ± 5.1	6.1 ± 3.2	0.001
End-expiratory transpulmonary pressure (cm H_2O)	−4.4 ± 4.6	2.1 ± 2.0	< 0.001
End-expiratory lung volume (mL/kg ideal body weight)	19.6 ± 8.0	30.4 ± 9.1	< 0.001
Elastance of the respiratory system (cm H_2O/L)	23.9 ± 7.1	18.6 ± 6.1	< 0.001
Elastance of the lung (cm H_2O/L)	16.6 ± 5.1	10.8 ± 4.3	< 0.001
Elastance of the chest wall (cm H_2O/L)	7.2 ± 2.9	7.7 ± 3.5	0.547
Pao_2/Fio_2	163.4 ± 56.7	273.4 ± 72.1	< 0.001
$Paco_2$ (mm Hg)	47.9 ± 13.4	50.9 ± 11.6	0.140

PEEP = positive end-expiratory pressure.

During all the study procedures, patients were ventilated with a tidal volume of 6.6 ± 1.0 mL/kg ideal body weight, respiratory rate of 24.1 ± 6.2 breaths/min, and Fio_2 of 66% ± 21%. Data are expressed as mean ± so, paired Student t test.

DOI: 10.1097/CCM.0000000000002460

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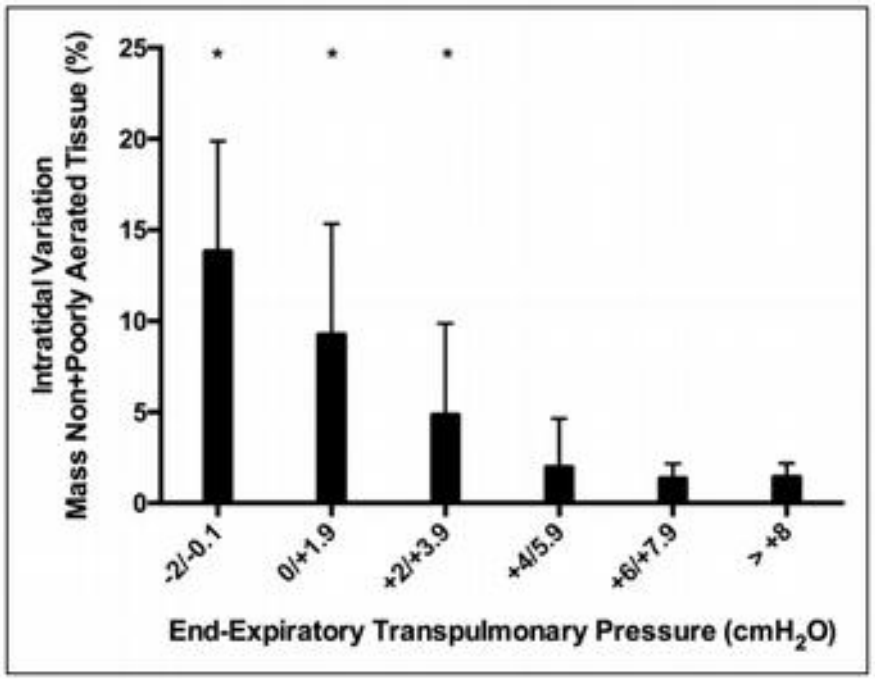
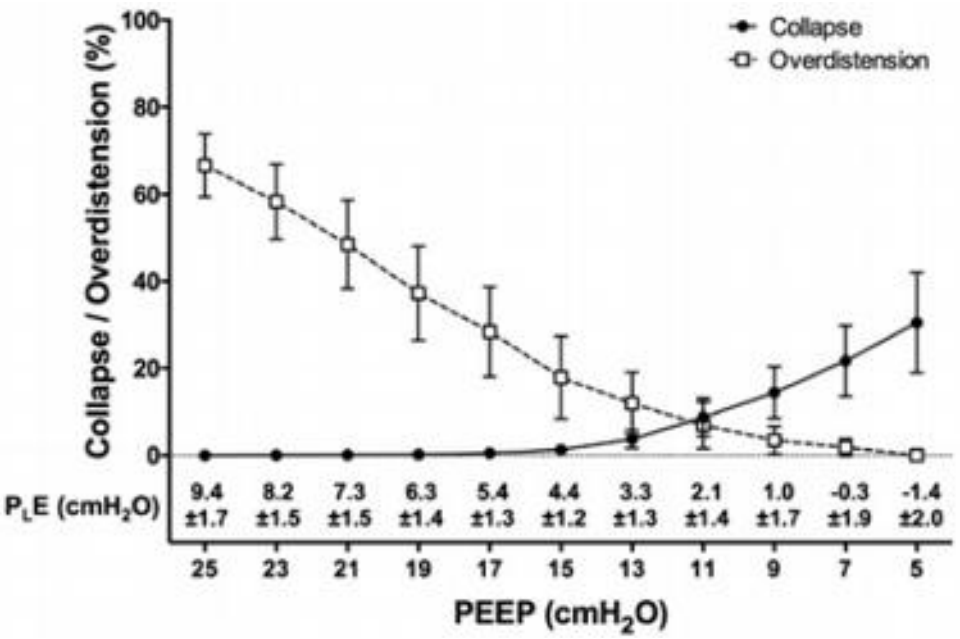
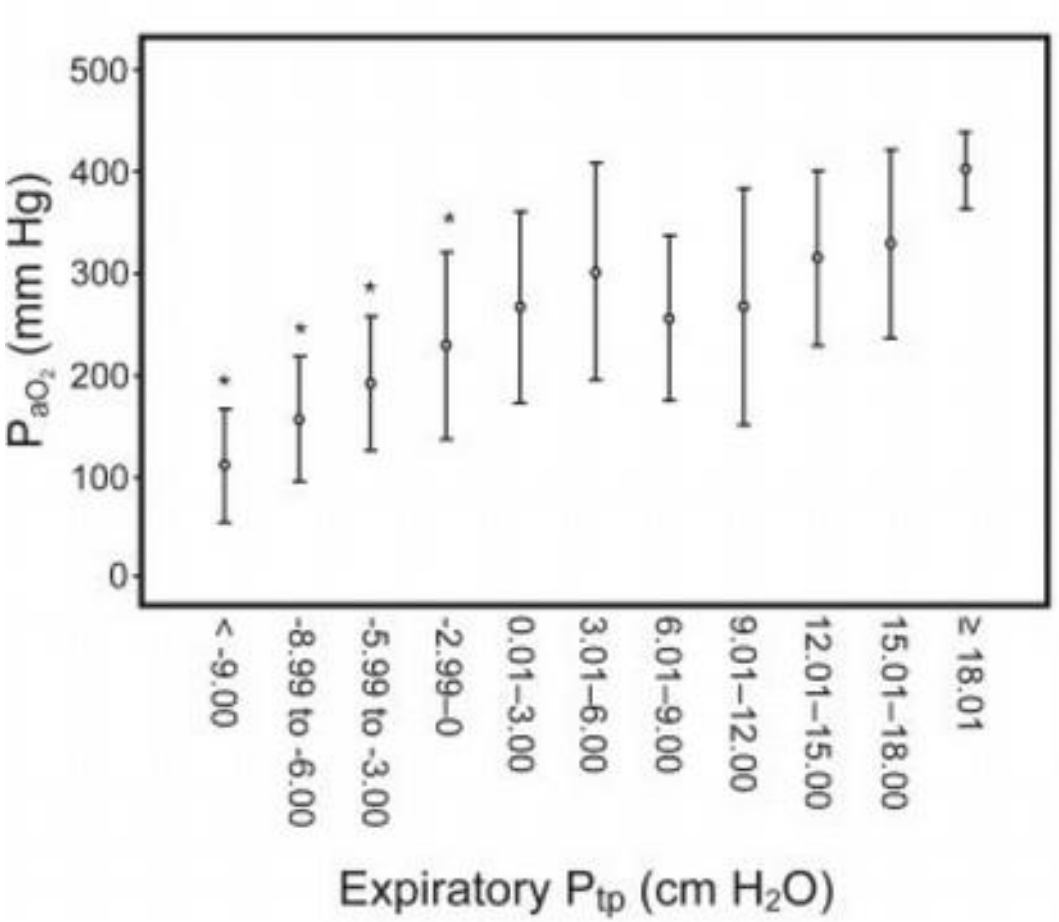




DOI: 10.1097/CCM.0000000000002460

KARIM FNHK a LFHK UK

Vliv výchozího transpulmonálního tlaku



Respir Care 2013;58(5):754–763.

Lobární charakter

Intensive Care Med (2000) 26: 857–869
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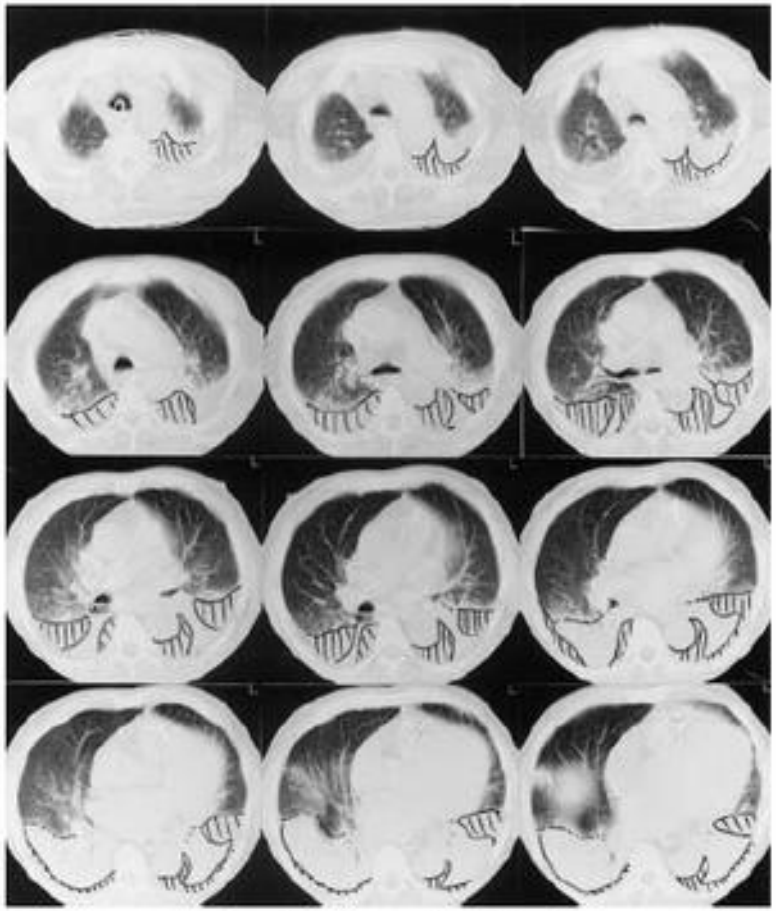
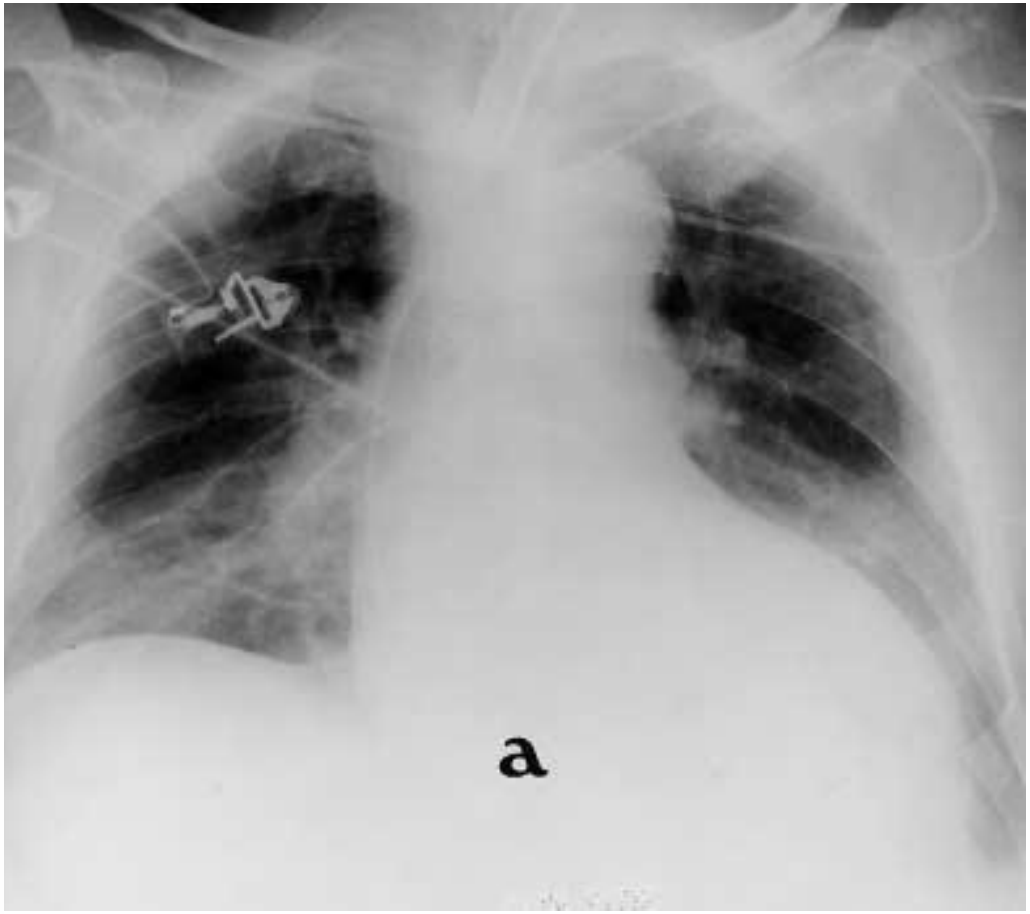
Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology





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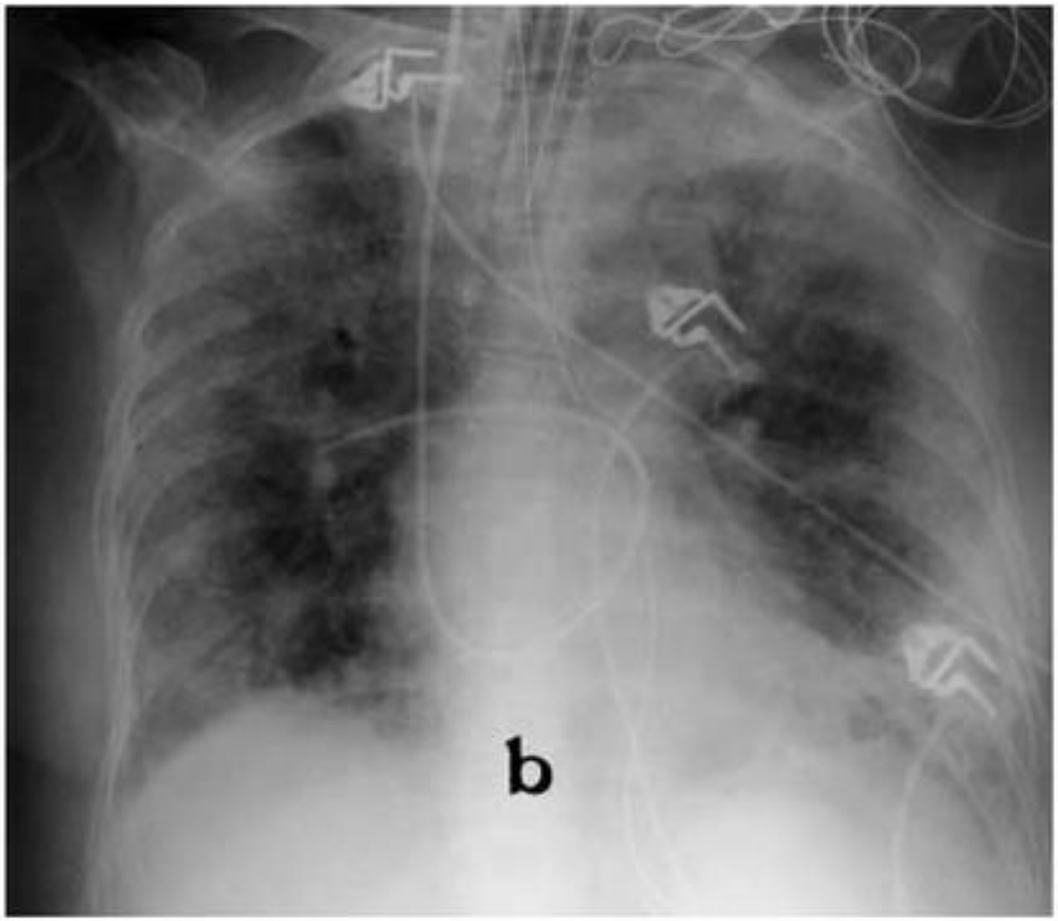
Difuzní charakter



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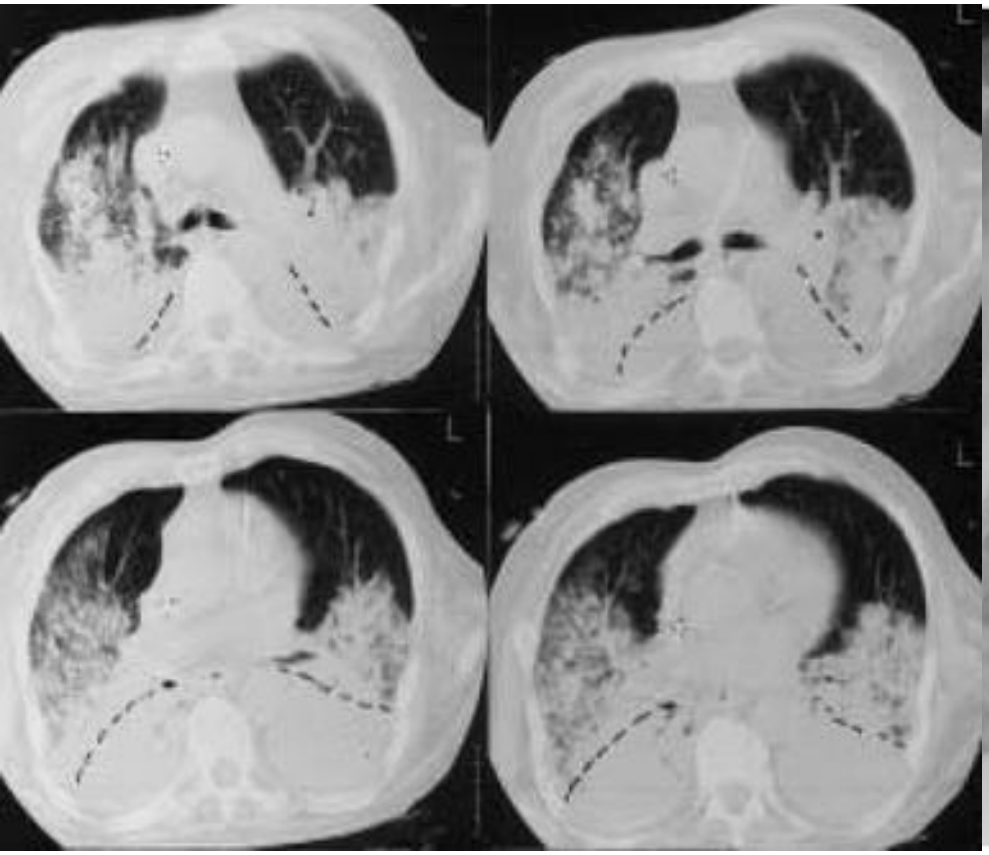
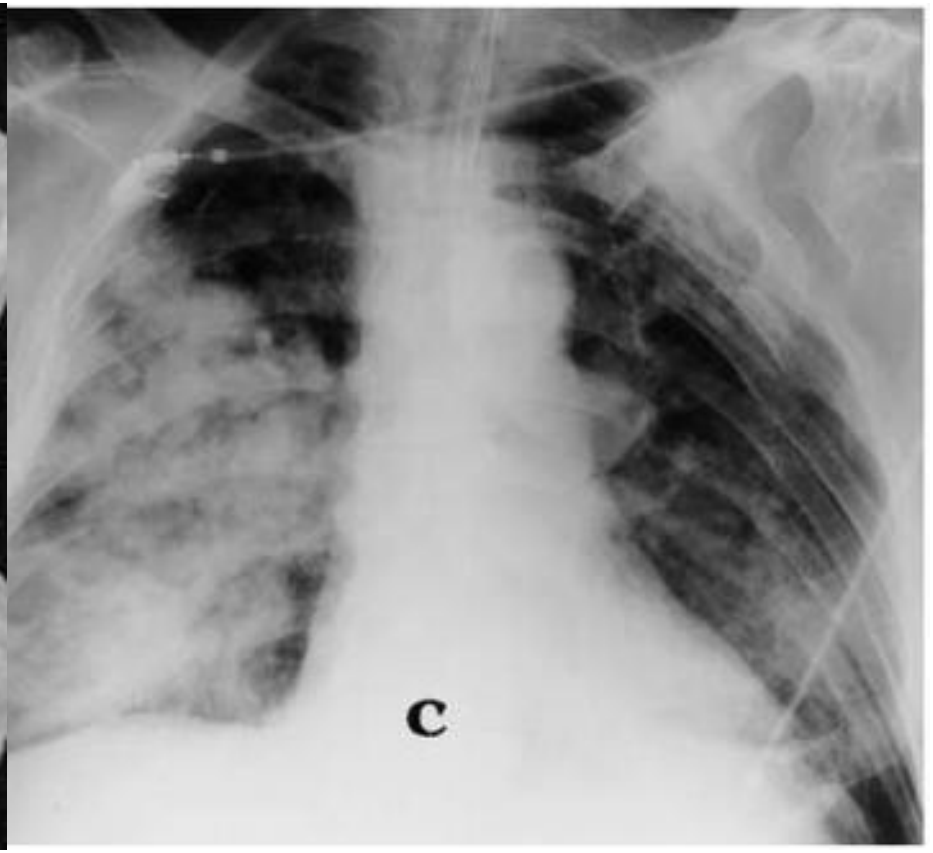
„Patchy“ charakter





Intensive Care Med (2000) 26: 1215–1227

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Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure

Table 4 PEEP-induced changes (Δ) in lung volumes in the three groups of patients (*LA* lobar CT attenuations, *DA* diffuse CT attenuations, *PA* patchy CT attenuations, *ΔFRC* change in functional residual capacity)

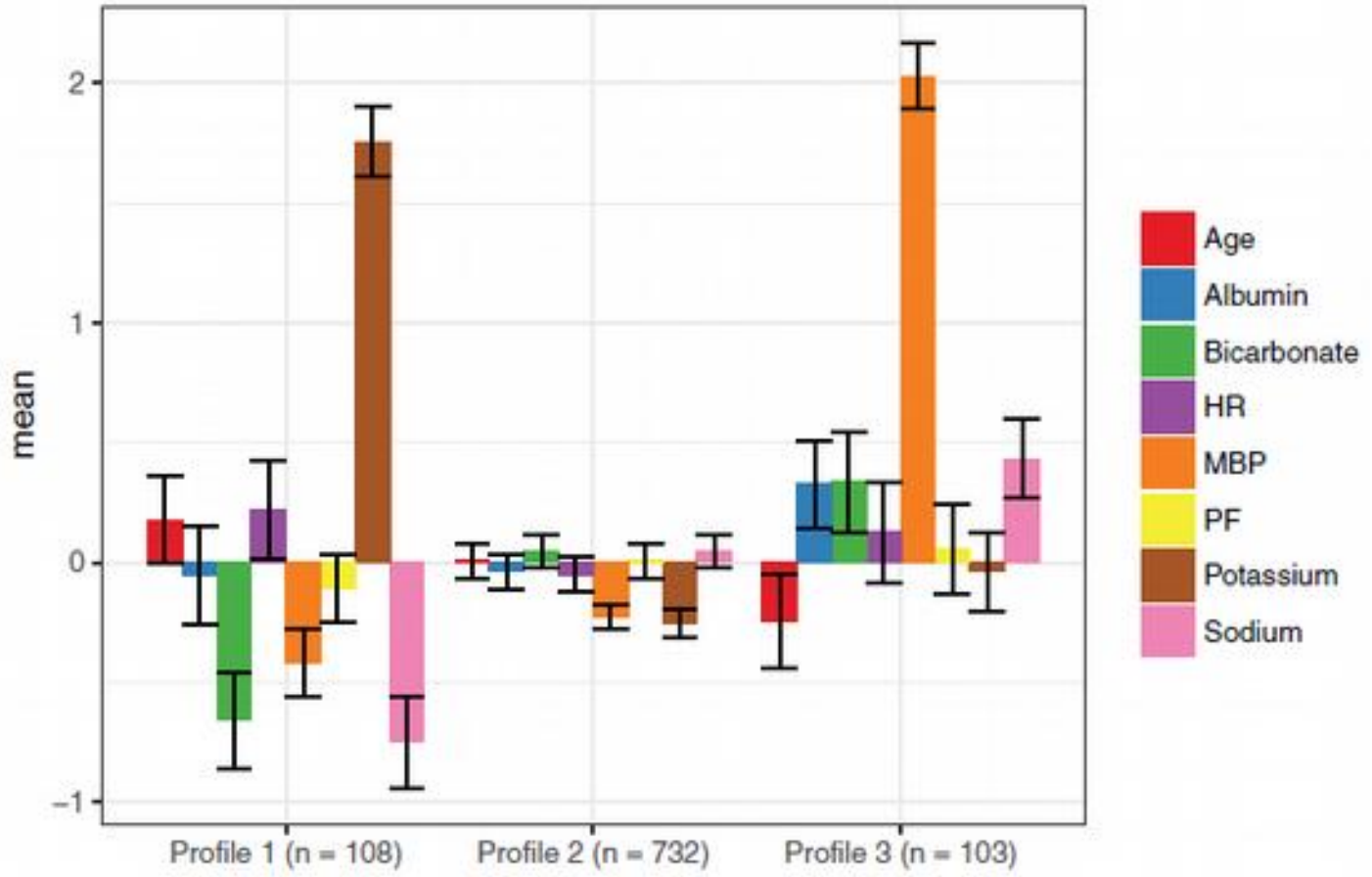
	LA ($n = 26$)	DA ($n = 16$)	PA ($n = 29$)	PEEP	p Value[a]
ΔTotal volume (ml)	674 ± 303*	510 ± 281*	666 ± 355*	0.0001	NS
ΔPleural fluid (ml^{-1})	19 ± 53	46 ± 48	11 ± 76	0.01	NS
ΔFRC (ml)	696 ± 286*	507 ± 282*	634 ± 271*	0.0001	NS
ΔVolume of tissue (ml)	−22 ± 149	3 ± 107	32 ± 165	NS	NS
ΔOverdistended lung areas (ml)	47 ± 97*	2 ± 4	18 ± 24*	0.008	0.048
ΔNormally aerated lung areas (ml)	820 ± 344*	601 ± 473*	815 ± 354*	0.0001	NS
ΔPoorly aerated lung areas (ml)	−111 ± 169	290 ± 298	−6 ± 187	NS	0.0001
ΔNonaerated lung areas (ml)	−82 ± 68*	−383 ± 164*	−161 ± 151*	0.0001	0.0001

*$p < 0.05$ vs. ZEEP
[a]p values refer to the repeated measures ZEEP-PEEP (PEEP) and to the interaction between the 3 groups using a two-way analysis of variance

Identification of three classes of acute respiratory distress syndrome using latent class analysis

Zhongheng Zhang

Department of Emergency Medicine, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Hangzhou, China



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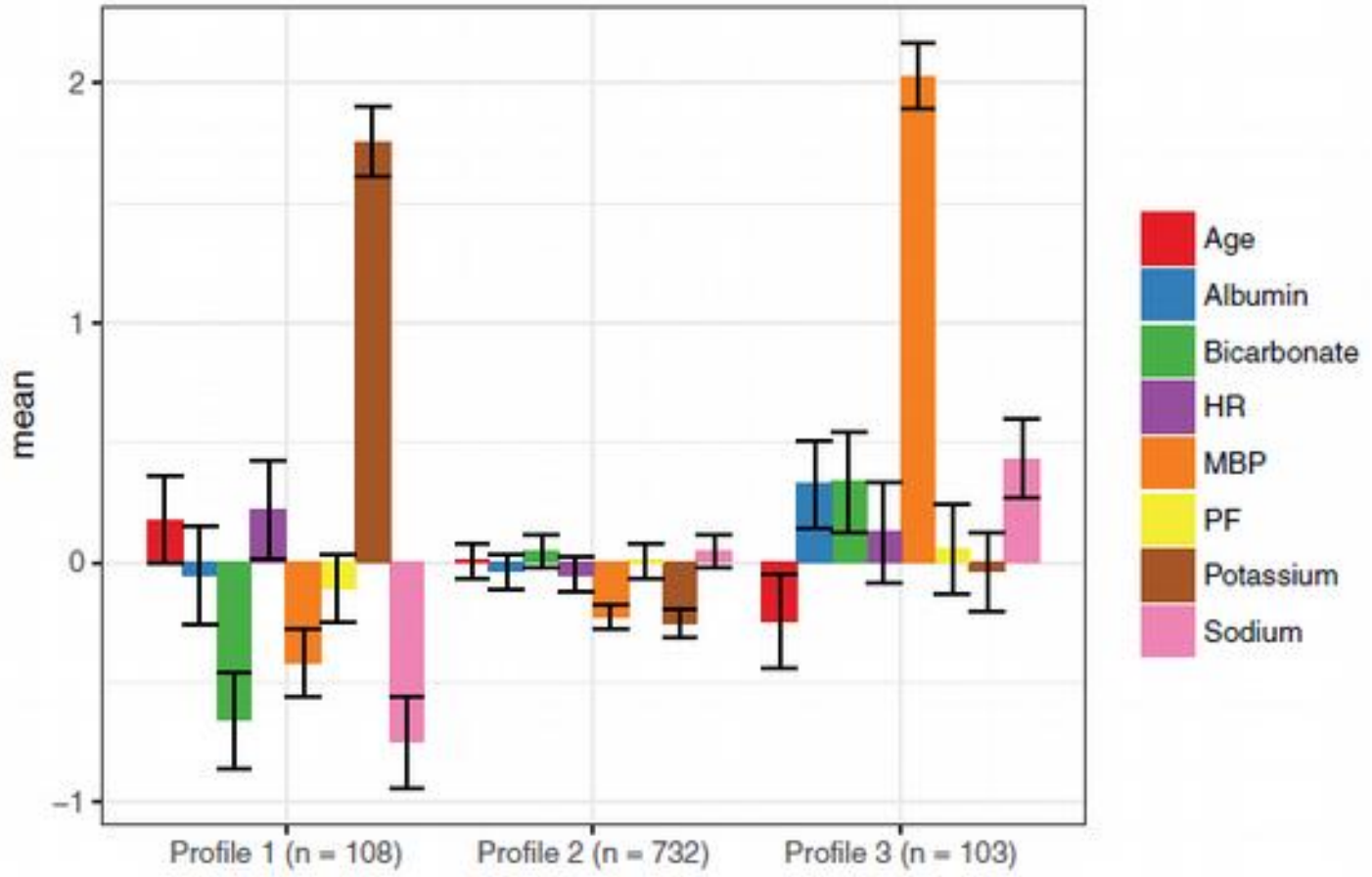

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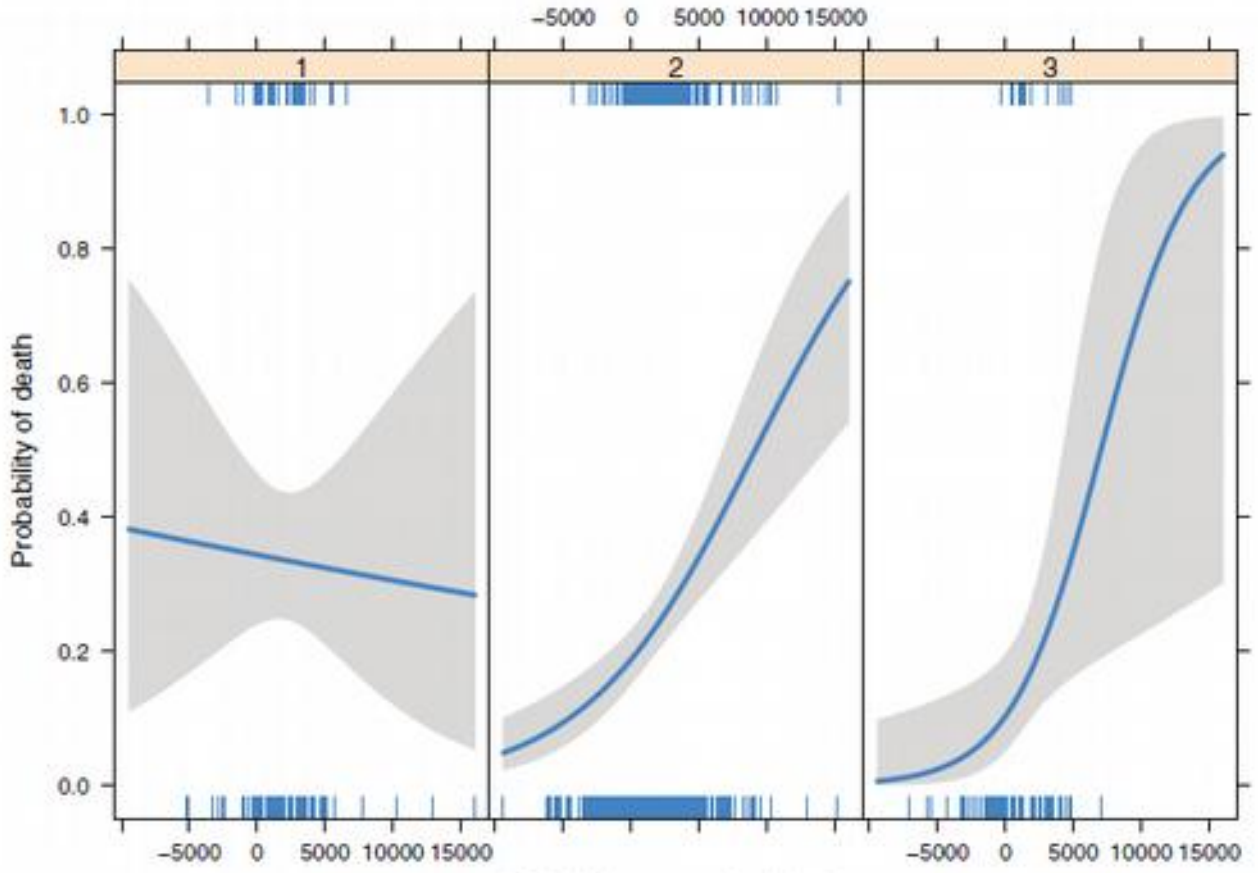
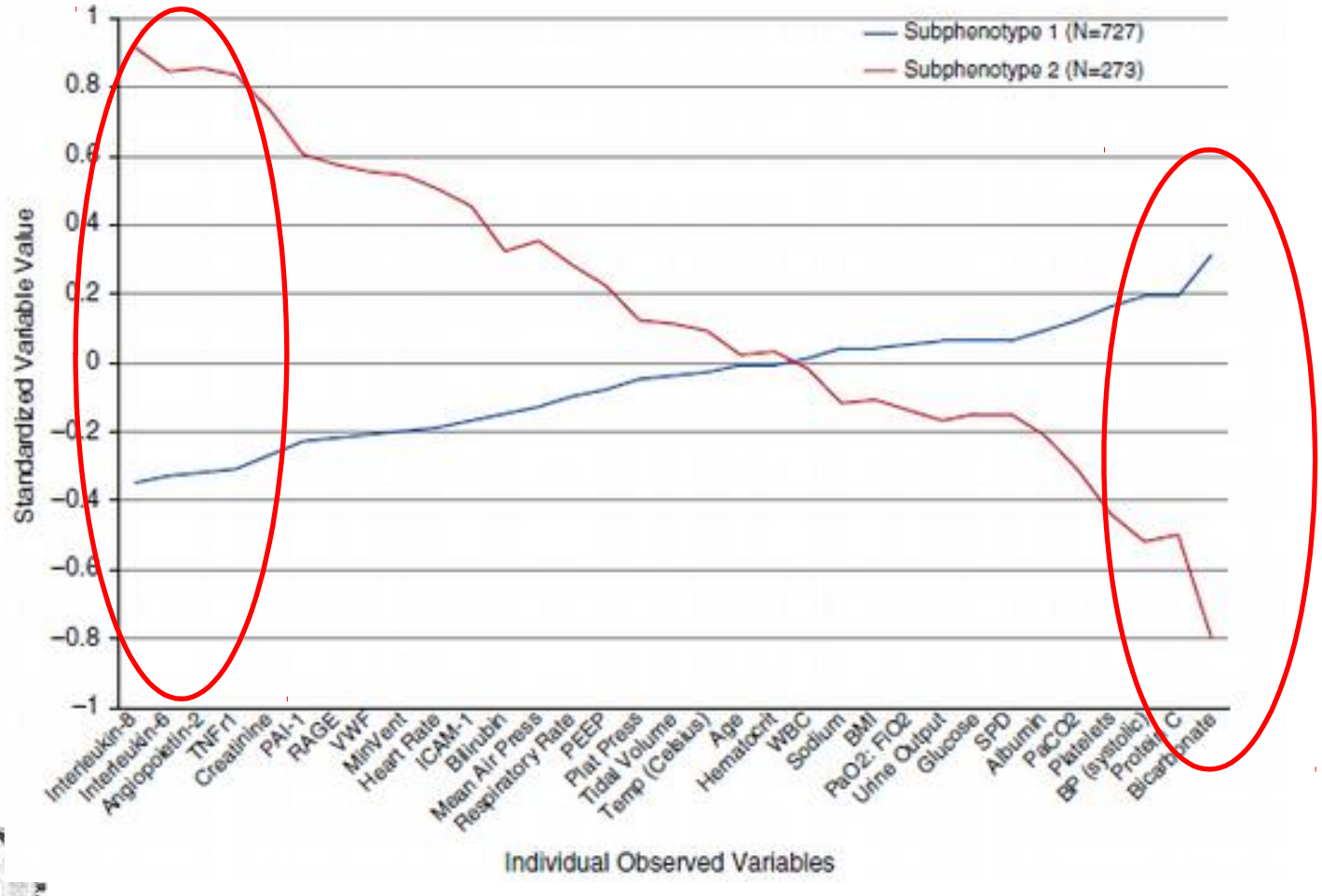


DOI 10.7717/peerj.4592

Acute Respiratory Distress Syndrome Subphenotypes Respond Differently to Randomized Fluid Management Strategy

Katie R. Famous[1], Kevin Delucchi[2], Lorraine B. Ware[3,4], Kirsten N. Kangelaris[5], Kathleen D. Liu[6,7], B. Taylor Thompson[8], and Carolyn S. Calfee[1,7]; for the ARDS Network



Am J Respir Crit Care Med Vol 195, Iss 3, pp 331–338, Feb 1, 2017

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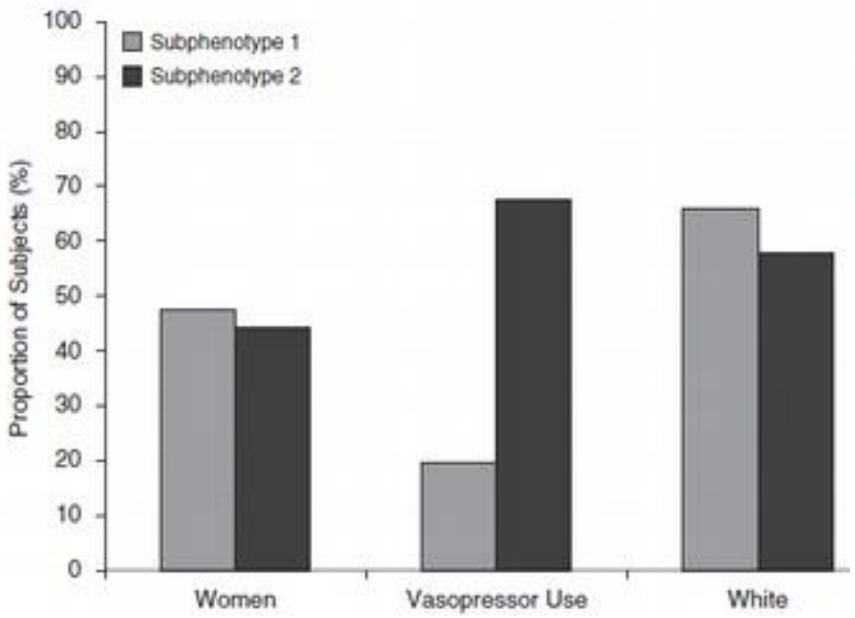

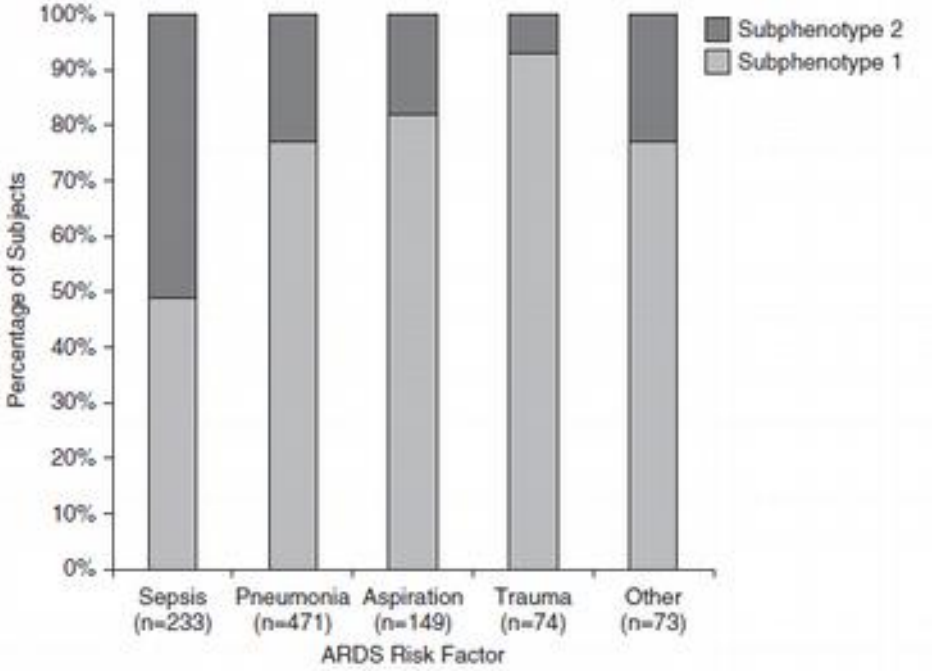

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Table 3. Clinical Outcomes by ARDS Subphenotype

	Subphenotype 1 (*n* = 727)	Subphenotype 2 (*n* = 273)	*P* Value
60-d mortality, %	21	44	<0.0001
90-d mortality, %	22	45	<0.0001
Ventilator-free days, median	19	3	<0.0001

	Subphenotype 1		Subphenotype 2		
Fluid-management strategy	Liberal (*n* = 355)	Conservative (*n* = 372)	Liberal (*n* = 142)	Conservative (*n* = 131)	*P* Value
60-d mortality, %	24	17	39	49	0.0093
90-d mortality, %	26	18	40	50	0.0039
Ventilator-free days, median	17	21	5	0	0.35

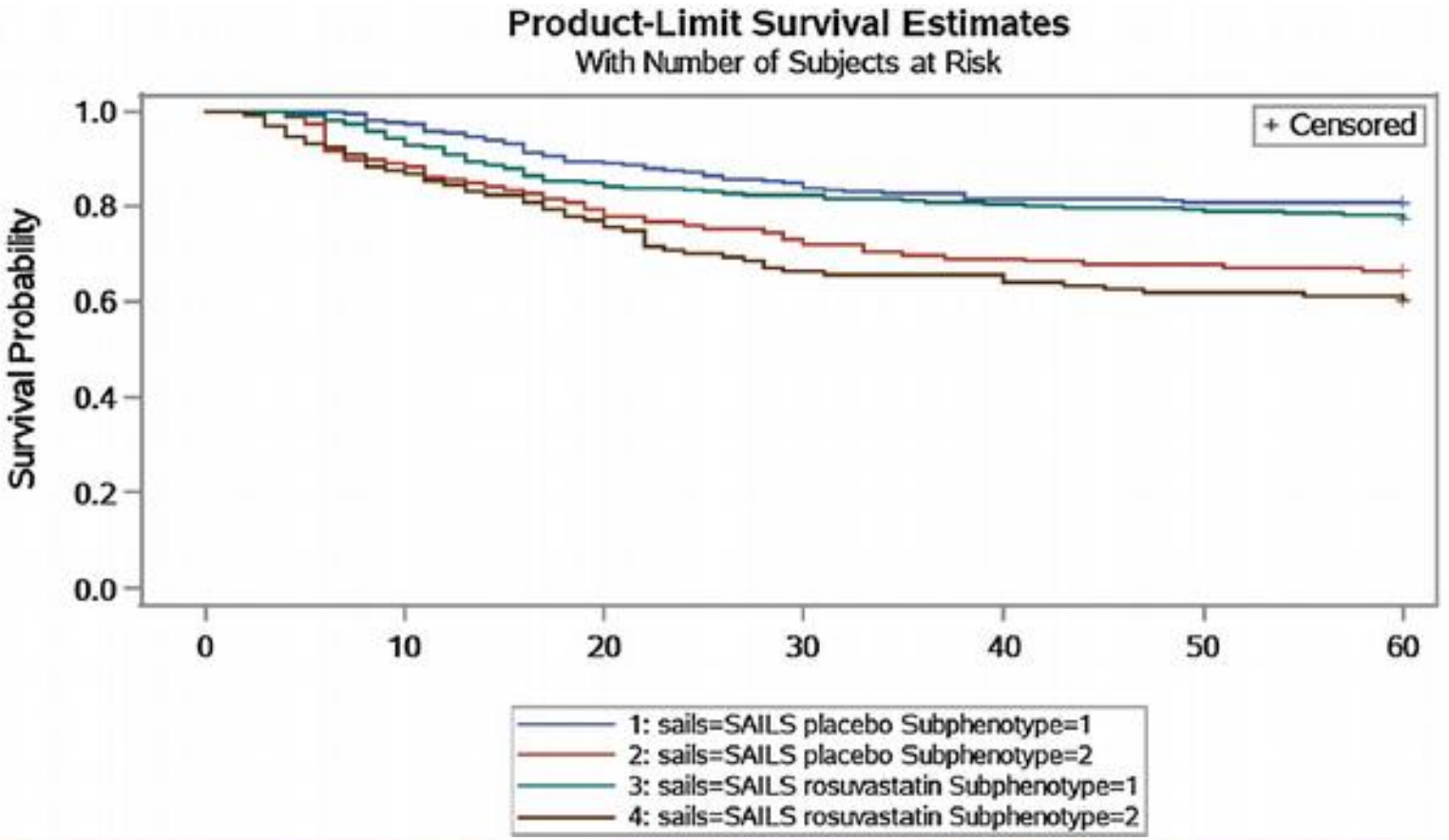
Am J Respir Crit Care Med Vol 195, Iss 3, pp 331–338, Feb 1, 2017

Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study

Pratik Sinha[1*], Kevin L. Delucchi[2], B. Taylor Thompson[3], Daniel F. McAuley[4,5], Michael A. Matthay[1,6,7], Carolyn S. Calfee[1,6,7] and for the NHLBI ARDS Network

Class-defining variables for initial LCA model	Total population	Hypo-inflammatory ($n = 468$)	Hyper-inflammatory ($n = 277$)	p value
Heart rate (beats min^{-1})	118.4 (± 22.7)	114.4 (± 21.7)	124.0 (± 21.7)	< 0.001
Systolic blood pressure (mmHg)	85.4 (± 15.62)	87.2 (± 15.7)	76.6 (± 12.3)	< 0.001
Respiratory rate (breaths min^{-1})	32 (27–38)	33.5 (26–39.75)	35 (29–40)	< 0.001†
Urine output (mL over previous 24 h)	1605 (± 1236)	1888 (± 1326)	1165 (± 967)	< 0.001
Vasopressor use at baseline	406 (54.6%)	180 (38.7%)	226 (81.6%)	< 0.001
Creatinine (mg/dL)	1.5 (± 1.2)	1.1 (± 0.73)	2.0 (± 1.16)	< 0.001
Bicarbonate (mmol/L)	21.8 (± 5.52)	22.9 (± 4.7)	18.6 (± 4.8)	< 0.001
Albumin (g/dL)	2.2 (± 0.64)	2.3 (± 0.6)	2.0 (± 0.6)	< 0.001
Bilirubin (mg/dL)	0.8 (0.5–1.4)	0.8 (± 0.8)	2.0 (± 1.9)	< 0.001
Interleukin-6 (pg/mL)	443.2 (173–1510)	281.7 (115.0–600.0)	1618.4 (517.2–3205.3)	< 0.001†

Intensive Care Med (2018) 44:1859–1869
https://doi.org/10.1007/s00134-018-5378-3



Outcome	Hypo-inflammatory		Hyper-inflammatory		p value
	Placebo ($n=220$)	Rosuvastatin ($n=248$)	Placebo ($n=146$)	Rosuvastatin ($n=131$)	
60-day mortality, *n* (%)	42 (19.1%)	56 (22.6%)	49 (33.6%)	52 (39.7%)	0.877
90-day mortality, *n* (%)	44 (20.0%)	56 (22.6%)	52 (35.6%)	52 (39.7%)	0.953
Ventilator-free days, median (IQR)	24 (4–26)	23 (9.5–26)	16.5 (1–23)	13 (1–23)	0.697

Intensive Care Med (2018) 44:1859–1869
https://doi.org/10.1007/s00134-018-5378-3

Acute respiratory distress syndrome (ARDS) phenotyping

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Intensive Care Med
https://doi.org/10.1007/s00134-018-5480-6

ARDS Sub-Phenotypes

All RCT reanalyses uses clinical variables and biomarkers

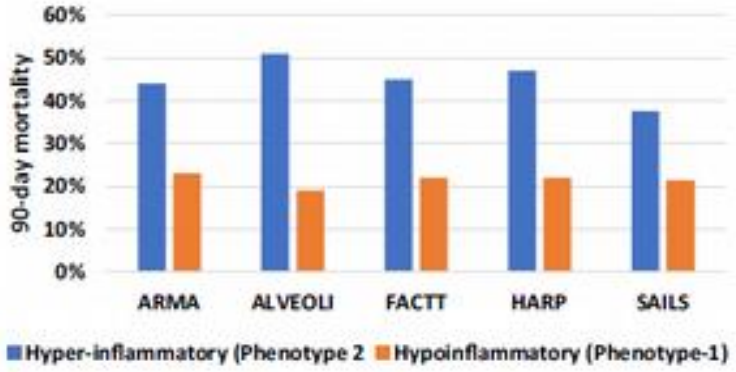
Clinical variables

- **Demographics:** *Age; gender; ethnicity; BMI*
- **ARDS aetiology:** *trauma; sepsis; aspiration; pneumonia or other*
- **Organ dysfunction:** *Respiratory[1]; CVS[1]; Bilirubin; Platelets; Renal[2]*
- **Other:** *Temperature; Sodium; Glucose; Albumin; bicarbonate*

Biomarkers

- **Lung epithelial:** *SP-D; sRAGE*
- **Endothelial:** *ANG2; ICAM-1; vWF;*
- **Coagulation:** *PAI-1; Protein-C*
- **Inflammation:** *IL-6; IL-8; sTNFR; CRP; WCC*

Latent class analysis



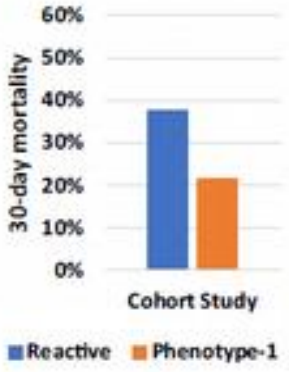
	ARMA N=473	ALVEOLI N=549	FACTT N=1000	HARP N=539	SAILS N=745
% Hyper-inflammatory	32.8%	26.5%	27.2%	34.5%	37.2%
Phenotype discriminant markers	sTNFR-1; IL-6; vasopressor use	sTNFR-1; IL-6; vasopressor use	sTNFR-1; IL-8; bicarbonate	sTNFR-1; IL-6; low platelets; vasopressor	sTNFR-1; IL-8; bicarbonate

Observational cohort analysis uses only biomarkers

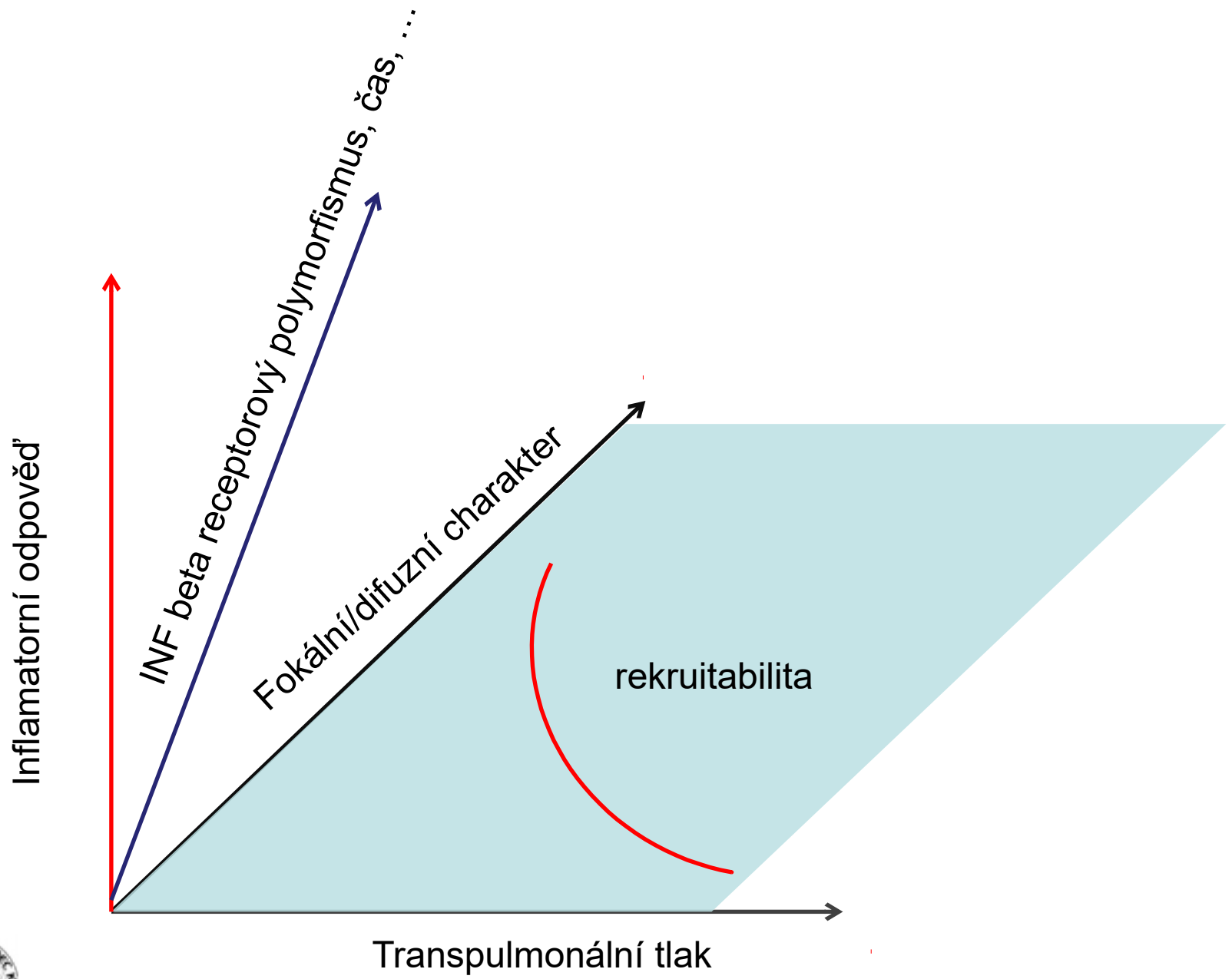
Biomarkers

- **Lung epithelial:** *None*
- **Endothelial:** *E-selectin; P-selectin; ANG1/2*
- **Coagulation:** *antithrombin; D-Dimer; tPA; PAI-1*
- **Inflammation:** *fractalkine; GM-CSF; ICAM-1; IFN-γ; IL-1ß; IL-6; IL-8; IL-10; IL-13; TNF-α; MMP-8; TIMP-1*

Cluster analysis



	Cohort Study N=700
% Reactive phenotype	51.9%
Phenotype discriminant markers	IL-6; IFN-γ; ANG1/2; PAI-1


Inflamatorní odpověď
INF beta receptorový polymorfismus, čas, …
Fokální/difuzní charakter
rekruitabilita
Transpulmonální tlak

Závěry

- Populace nemocných s ARDS je heterogenní z pohledu odpovědi na ventilační postupy, odpovědi a rizikovosti tekutin a potenciálně i efektu imunomodulačních intervenci
- Posouzení morfologického typu plicní patologie, recruitability/odpovědi na PEEP a inflamatorního typu jsou důležité pro taktiku orgánové podpory nemocných s ARDS

Děkuji za pozornost.