

Amato

53 patients ADRS

Conventional ventilation : lowest P_{ip}, V_t : 12 ml/kg, normal PCO₂

Protective : P_{ip} above the lower inflection point, V_t : less than 6 ml/kg, driving pressure less than 20 cm H₂O, permissive hypercapnia

Conv 17/24 (71%) had died on D28

Protect 11/29 (38%) had died on D28

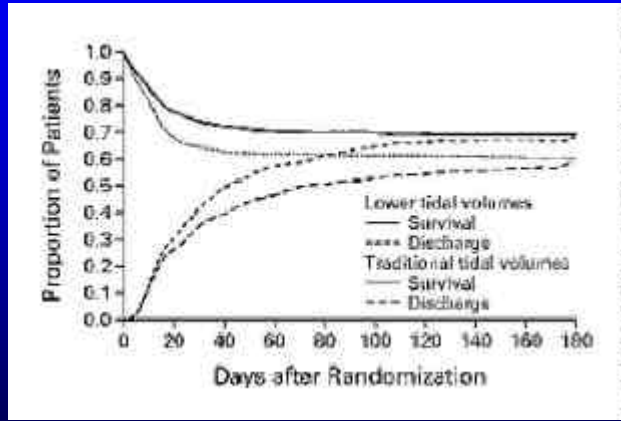
Stewart

120 patients

Limited-ventilation group : P_{IP} less than 30 cmH₂O, V_t : 8 ml/kg or less

Conventional ventilation group : P_{IP} allowed to rise as high as 50 cmH₂O, V_t : 10-15 ml/kg. All other ventilatory variables were similar in the 2 groups.

No change in mortality



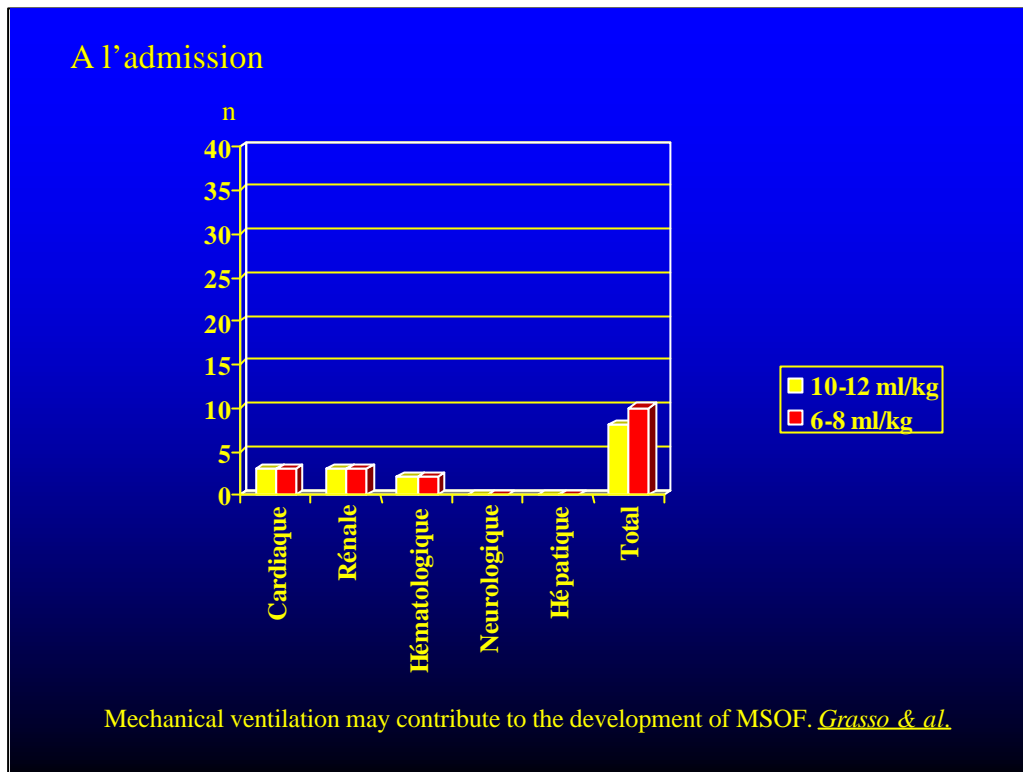
The Acute Respiratory Distress Syndrome Network, NEJM 2000

TABLE 4. MAIN OUTCOME VARIABLES.*

VARIABLE	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	P VALUE
Death before discharge home and breathing without assistance (%)	31.0	39.8	0.007
Breathing without assistance by day 28 (%)	65.7	55.0	<0.001
No. of ventilator-free days, days 1 to 28	12±11	10±11	0.007
Barotrauma, days 1 to 28 (%)	10	11	0.43
No. of days without failure of nonpulmonary organs or systems, days 1 to 28	15±11	12±11	0.006

* Plus-minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.

The Acute Respiratory Distress Syndrome Network, NEJM 2000



A83 - Mechanical ventilation may contribute to the development of MSOF. *Grasso & all.*

La mortalité de la plupart des patients ayant un ARDS est liée non pas à une insuffisance respiratoire aiguë mais à une défaillance multiviscérale. Une des hypothèses est que la ventilation mécanique pourrait exacerber l'augmentation de la perméabilité alvéolo capillaire et augmenter la réponse inflammatoire pulmonaire, conduisant à l'augmentation de la production de cytokines qui vont passer dans la circulation systémique et conduire à des dysfonctions d'organe à distance.

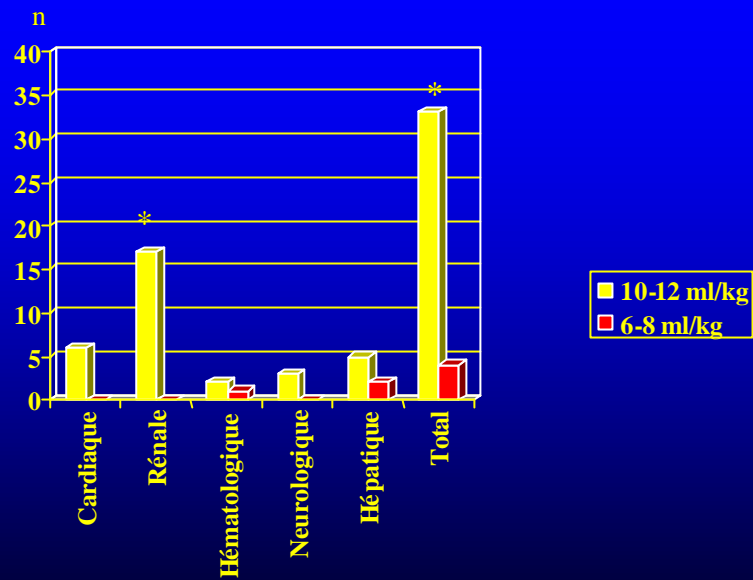
Méthode

les défaillances d'organes ont été examinées à l'entrée et à 72 h chez 37 patients randomisés pour recevoir une ventilation mécanique conventionnelle (Vt 10-12ml/kg Peep 5-6 cmH2O) ou une stratégie de ventilation protectrice (Vt 6-8 ml/kg Peep 14-18 cmH2O)

Résultats

On observe une corrélation entre les défaillances d'organe et les changements de concentration plasmique de l'Il6, TNF, IL1 et IL8 en fonction de la stratégie ventilatoire

A J3



Mechanical ventilation may contribute to the development of MSOF. *Grasso & al.*

Mechanical ventilation may contribute to the development of MSOF. Grasso & all. (suite)

Conclusion

Ces données démontrent que la stratégie de ventilation peut augmenter les taux sériques des médiateurs inflammatoires et que ces changements de concentrations plasmatiques sont corrélées avec la survenue d'une défaillance d'organe

- **Notion de volotraumatisme**
- Notion de Stress failure
- Interrelation alvéole-vaisseaux
- Stretch et matrice
- Stretch et Inflammation
- Stretch et Translocation
- Stretch et lésion pré-existante

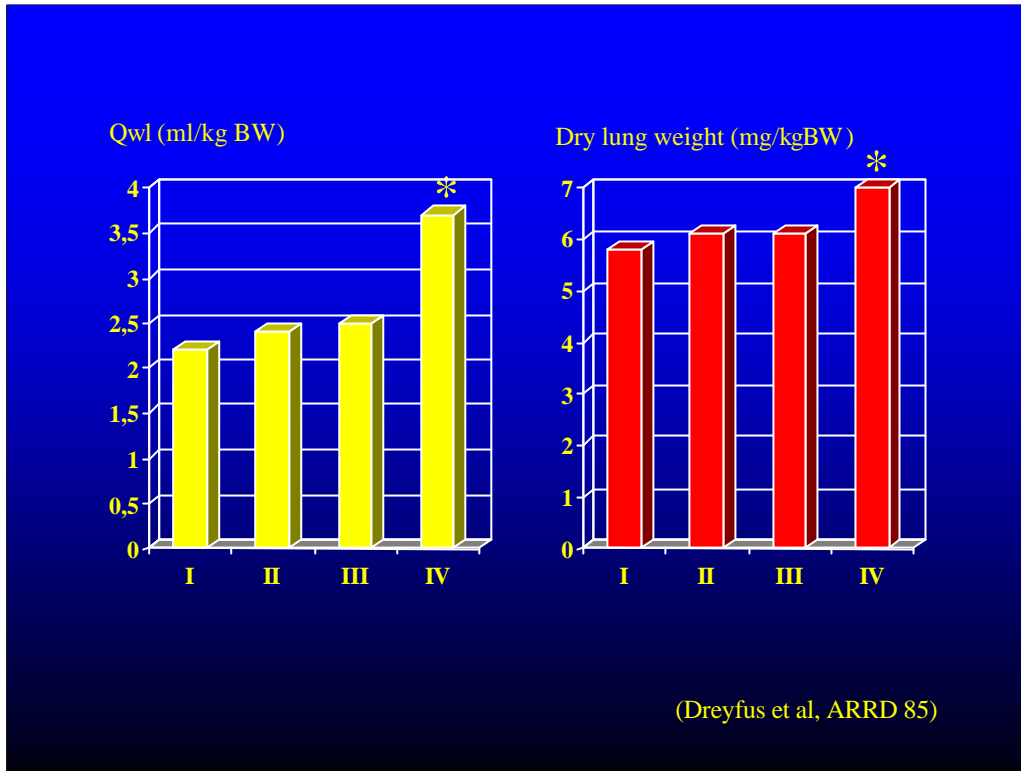
Poumon et Pression

● Volo-Barotraumatisme

- Webb et al ARRD 74
- Dreyfus et al ARRD 85
- Parker et al ARRD 90
- Corbridge et al ARRD 90
- Fu et al JAP 92
- Dreyfuss et al ARRD 93
- Dreyfuss et al AJRCCM 95

● Stress failure

- Rippe et al JAP 84
- Tsukimoto et al JAP 91
- West et al JAP 91
- Elliott et al JAP 92
- West Lancet 92
- West et al JAP 93
- Namba et al JAP 95

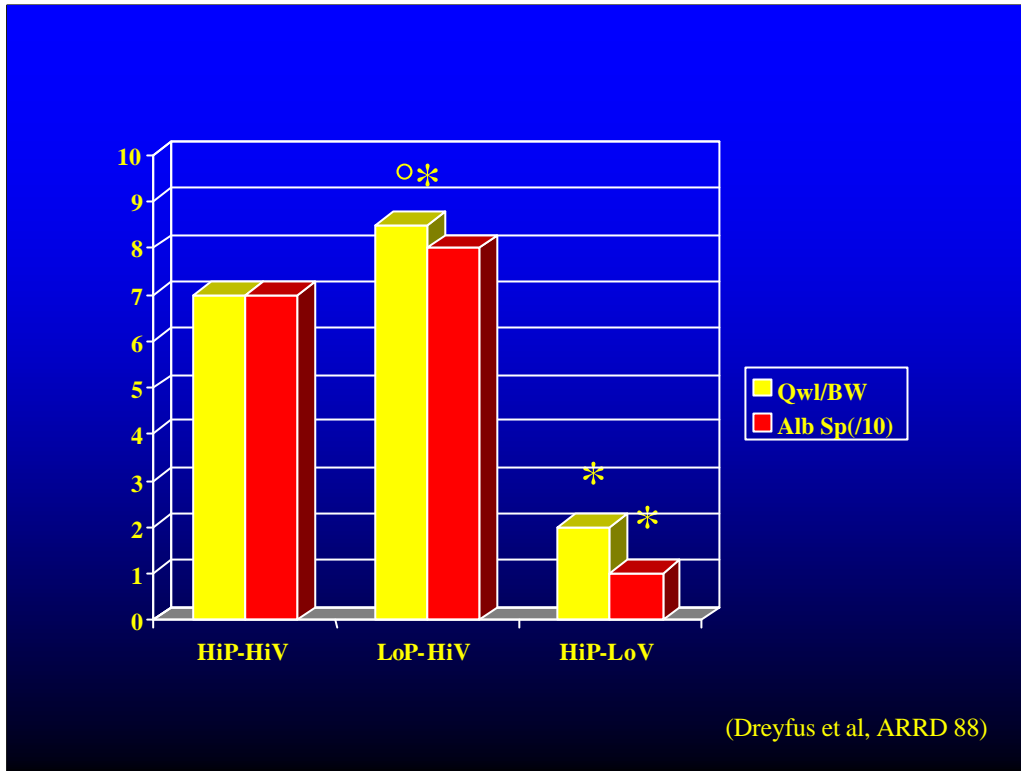


I : MV with 7 cm H₂O for 30 min

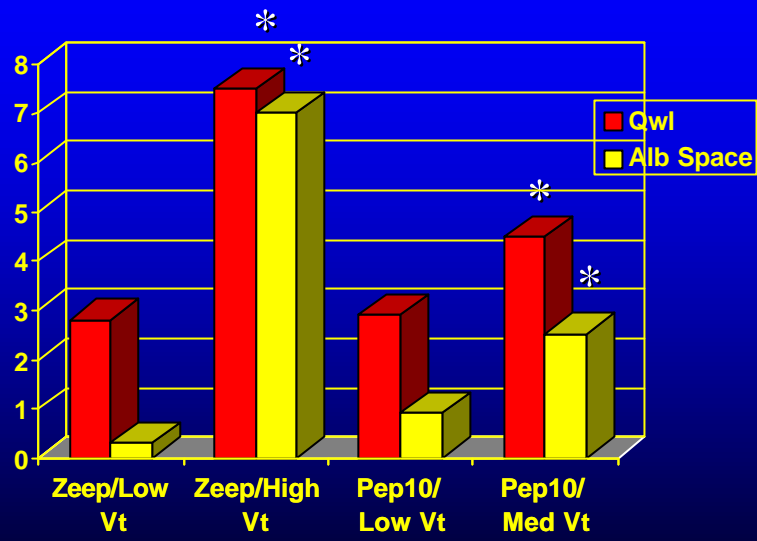
II : 5min with 45 cmH₂O and 25 min at 7cmH₂O

III : 10 min with 45 and 20 min with 7

IV : 20 min with 45 and 10 min with 7

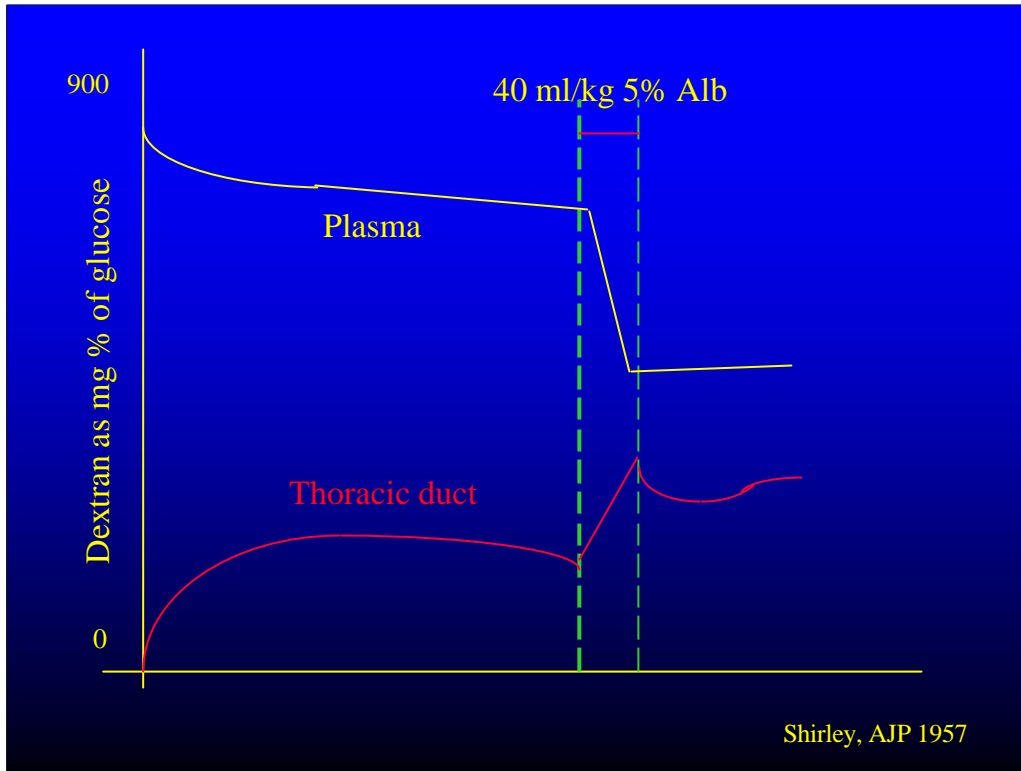


The respective roles of high pressure and high tidal volume to promote high airway pressure pulmonary edema are unclear. Positive end-expiratory pressure (PEEP) was shown to reduce lung water content in this type of edema, but its possible effects on cellular lesions were not documented. We compared the consequences of normal tidal volume ventilation in mechanically ventilated rats at a high airway pressure (HiP-LoV) with those of high tidal volume ventilation at a high (HiP-HiV) or low (LoP-HiV) airway pressure and the effects of PEEP (10 cm H₂O) on both edema and lung ultrastructure. Pulmonary edema was assessed by extravascular lung water content and microvascular permeability by the drug lung weight and the distribution space of ¹²⁵I-labeled albumin. HiP-LoV rat lungs were not different from those of controls (7 cm H₂O peak pressure ventilation). By contrast, the lungs from the groups submitted to high volume ventilation had significant permeability type edema. This edema was more pronounced in LoP-HiV rats. It was markedly reduced by PEEP, which, in addition, preserved the normal ultrastructural aspect of the alveolar epithelium. This was in striking contrast to the diffuse alveolar damage usually encountered in this type of edema. To our knowledge, this constitutes the first example of a protective effect of PEEP during permeability edema.

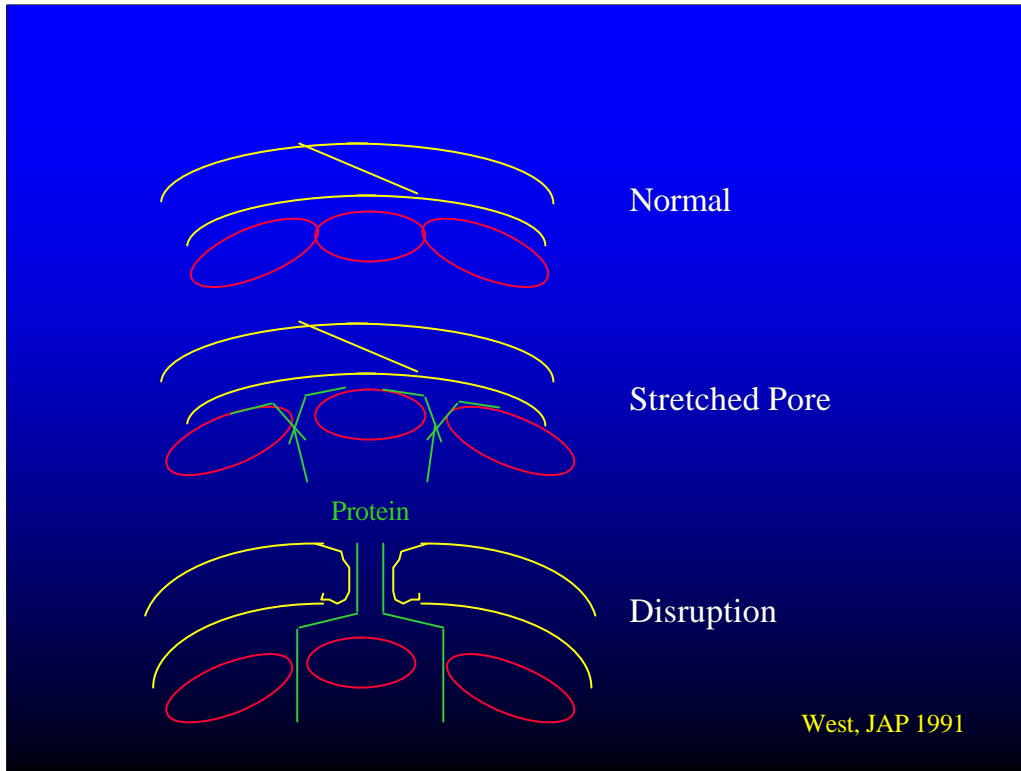


Dreyfus, ARRD 1993

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Dextran fraction of 255000 MW are injected in nembutalized dogs, concentration changes are followed in plasma, thoracic duct. The plasma volume is increased by the infusion of 40 ml/kg of 5% SAB in 0,9% saline. Plasma volume expansion decrease the resistance of the capillary wall to the passage of macromolecules.
 Stretched pore phenomenon



Normal morphology

Pore stretching with increased permeability of endothelium and leakage of protein into the interstitium, epithelium remains intact

Endoth and epith disruption caused by stress failure and consequent movement of protein into the alveolar space

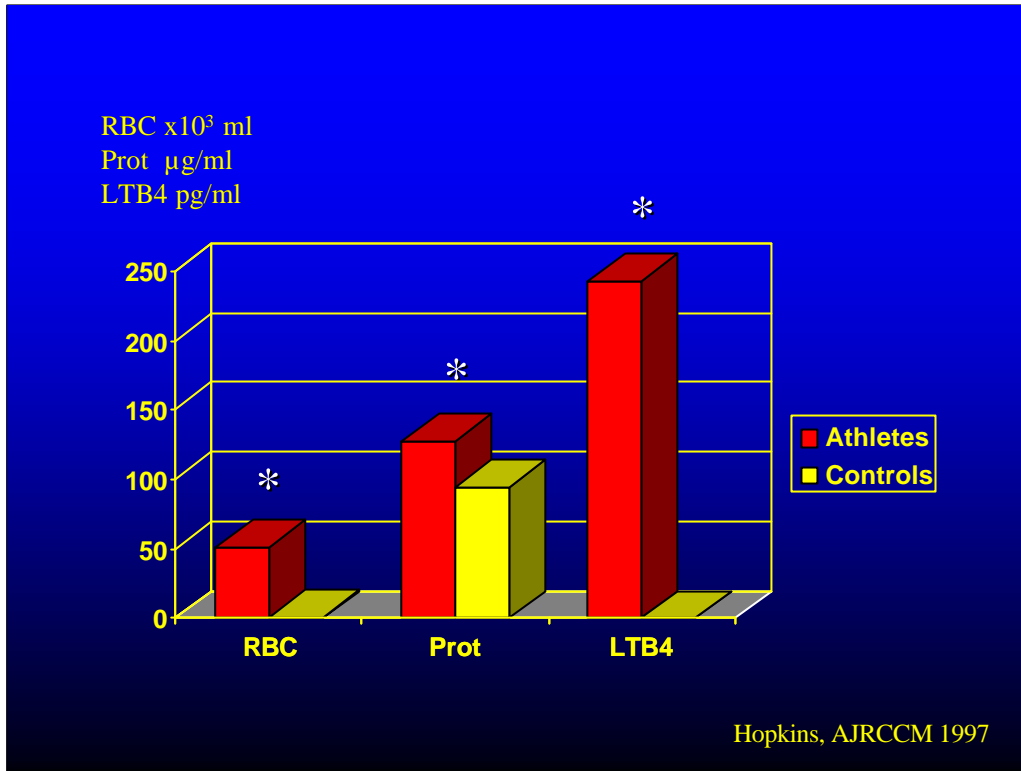
- Chevaux de course

- 5 min de marche
- 9 min de trot
- 3 min de galop

- Poumons fixés pour ME

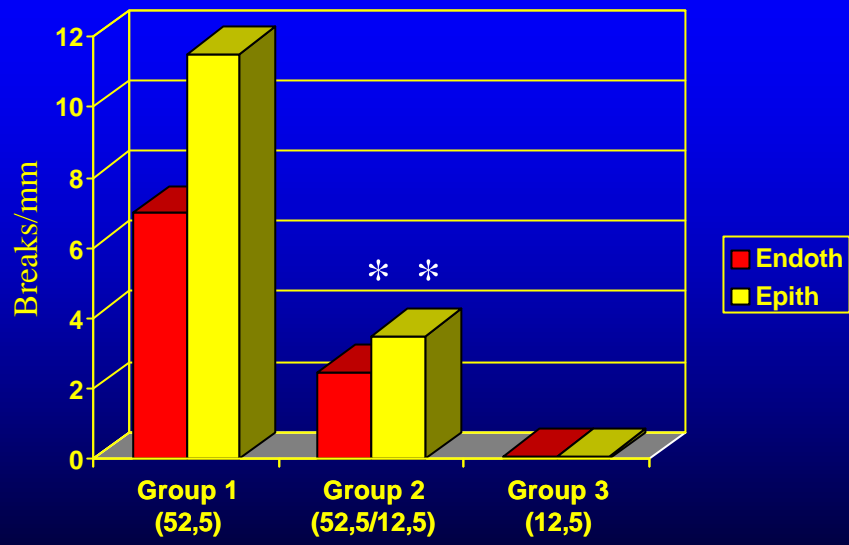
- Rupture de l'endothélium et de l'épithélium
- GR dans les espaces alvéolaires
- Oedème interstitiel
- Protrusion de l'endothélium dans la lumière capillaire

(West et al, J Appl Physiol 93)

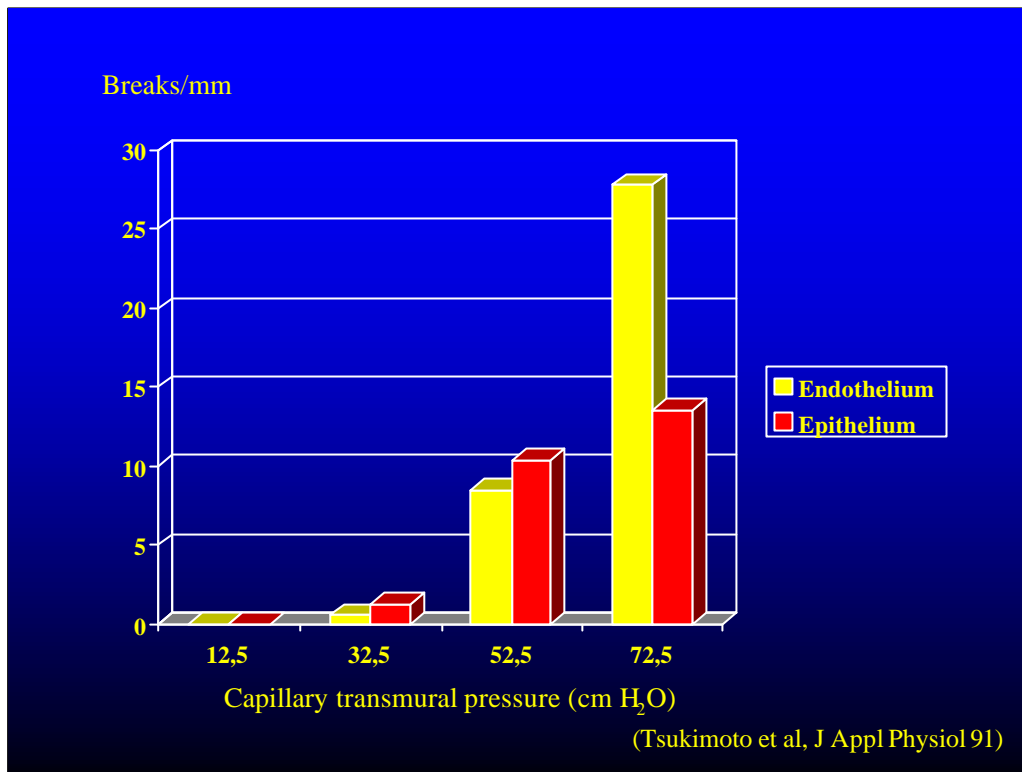


BAL in 6 healthy athletes with a history of lung bleeding and 4 normal sedentary controls.

4 km cycle hill climb as steep as 12% grade which took around 7 min to complete. Fibroscopy within 55 to 92 min after the exercise. NO diff between the 2 groups for TNF activity, LPS and IL8. Mechanism is not inflammatory but mechanical stress.



(Elliott, JAP 1992)



In situ rabbit perfused lungs

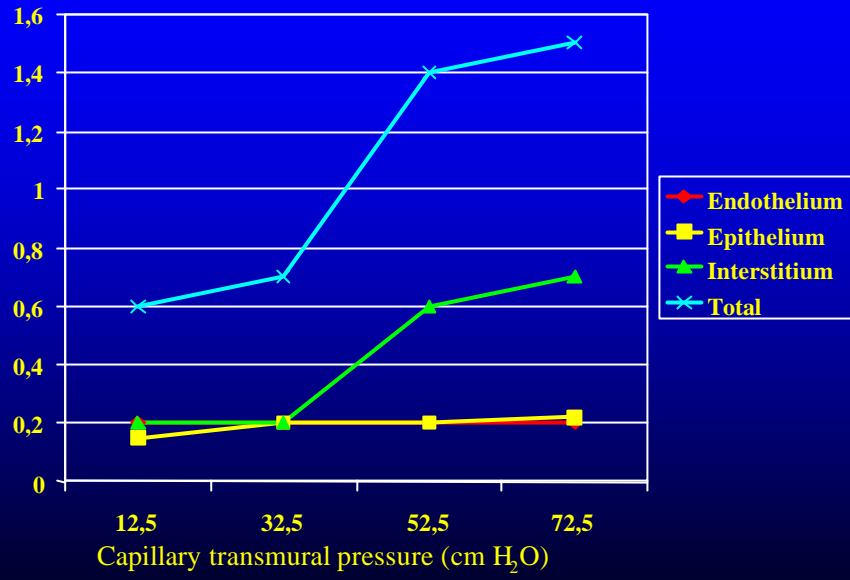
Alveolar pressure maintained at 5 cmH₂O

PAP : 20, 40, 60 & 80 cmH₂O

PVP : 15,35,55,&75 cmH₂O giving the preset cap transm pressure

The cause of the disrptions is believed to be stress failure

Thickness (μm)

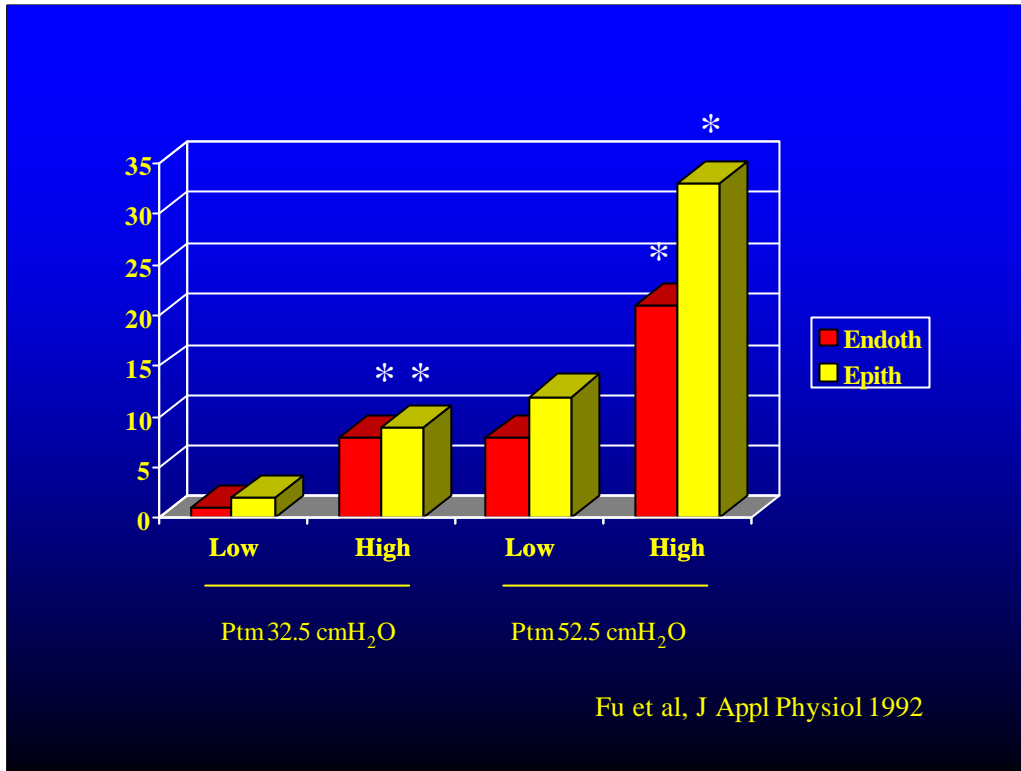


(Tsukimoto et al, J Appl Physiol 91)

	Ptm at failure (cm H ₂ O)
Rabbit	52,5
Dog	92,5
Horse	130,0

(Birks, Respir Physiol 1994)

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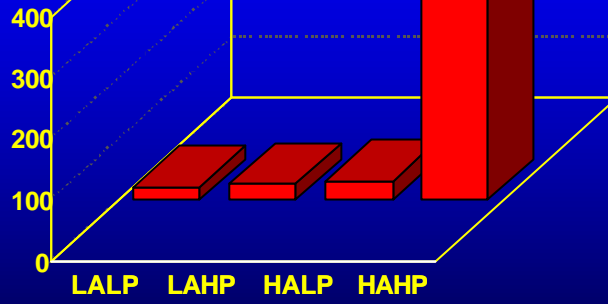


Rabbits

Comparaison du nombre de ruptures endothéliales et épithéliales en microscopie électronique à 2 pressions transmuraux différentes et 2 niveaux de distension pulmonaire : High 20 cmH₂O et low 5 cmH₂O

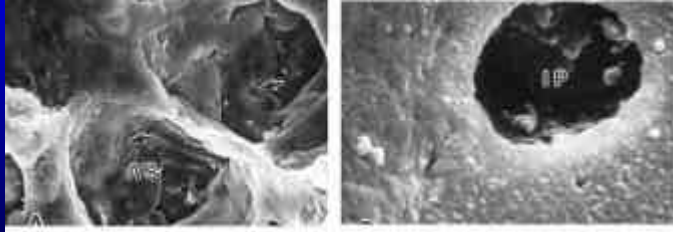
CONCL : A haut volume, augmentation du nombre de ruptures endo et épithéliales, argument pouvant expliquer l'apparition d'un trouble de perméabilité.

FITC-Dextran dans le LBA
(x E-5 mg/l)



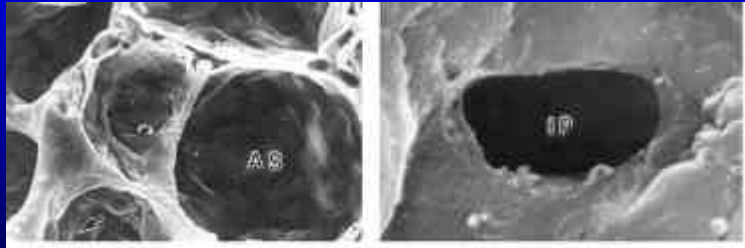
Guery et al, J Crit Care 1998

Pas de ventilation



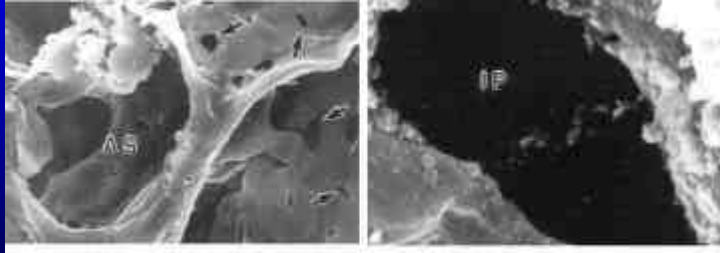
Guery et al, J Crit Care 1998

LALP



Guery et al, J Crit Care 1998

HAHP

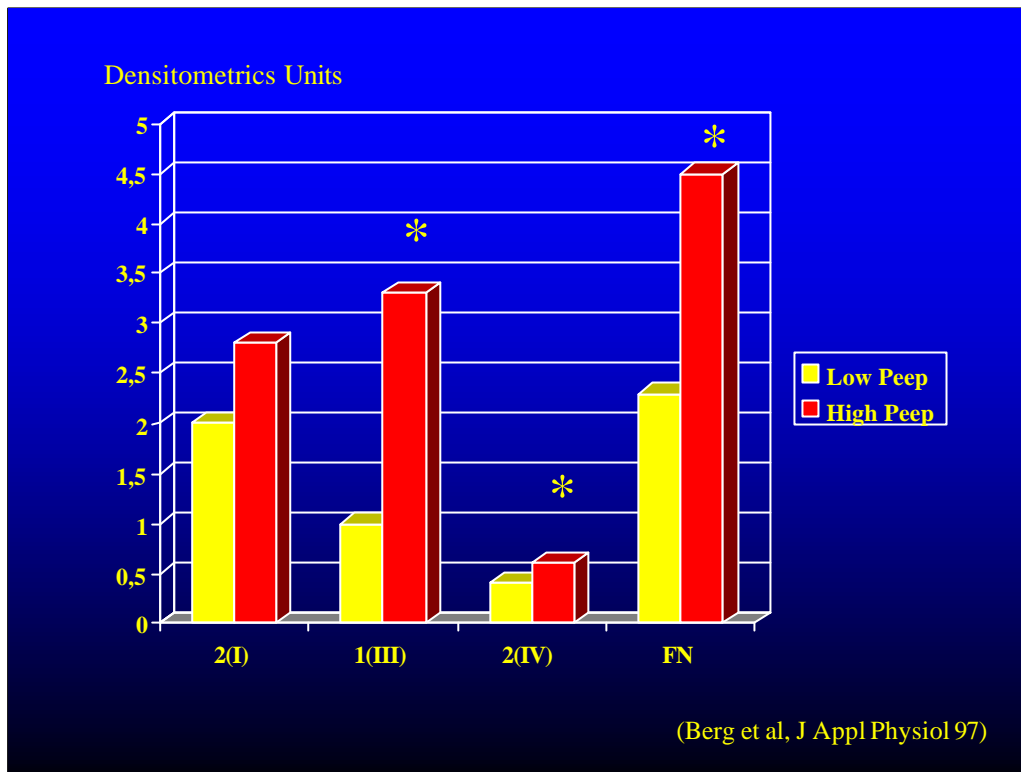


Guery et al, J Crit Care 1998

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- Cellules épithéliales exposées à un stretch (30 cm d'H₂O pendant 8h)
 - Libération d'endothéline, TGF-β2 et PDGF
- Exposition de fibroblastes au surnageant de culture
 - Augmentation de l'incorporation de proline de façon dose dépendante
- Favorise un environnement pro-fibrotique

(Tschumperlin et al, AJRCCM 2003)



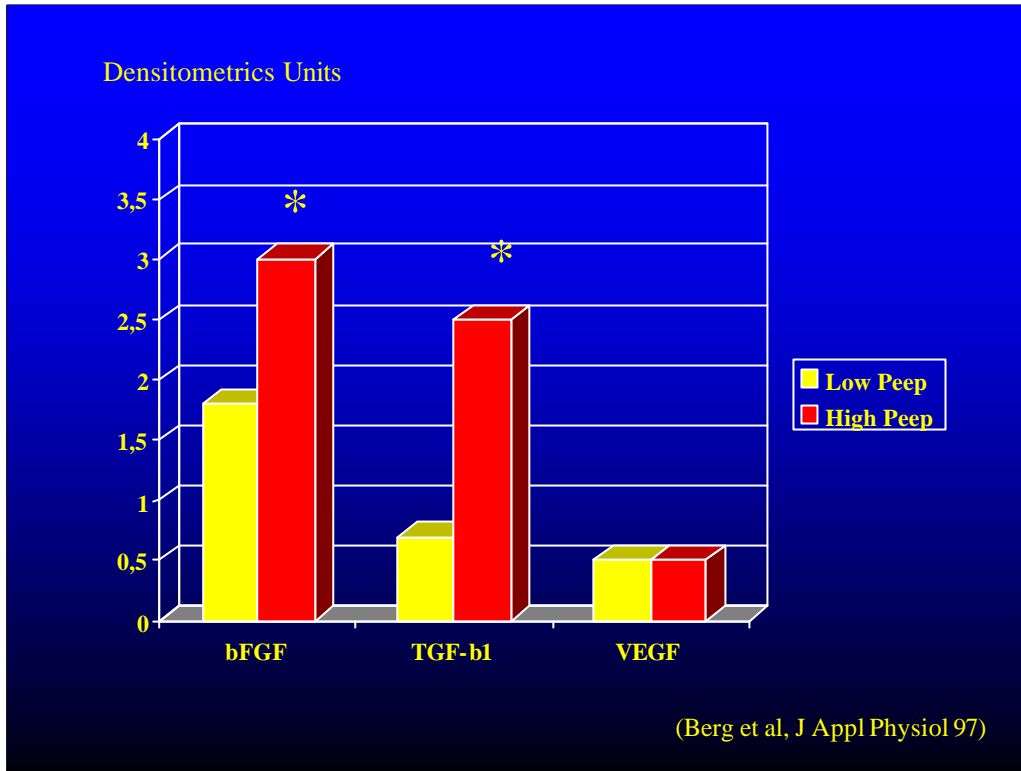
Rabbits

Gene expression quantified at the mRNA level by northern analysis of ECM components

High Peep : ventilation for 4 hours with 9 cm H₂O on one lung and 1 cm on the other one. No differences between the 2 lungs left and right they were therefore pooled and compared to the low peep level.

Low Peep : 2 cmH₂O

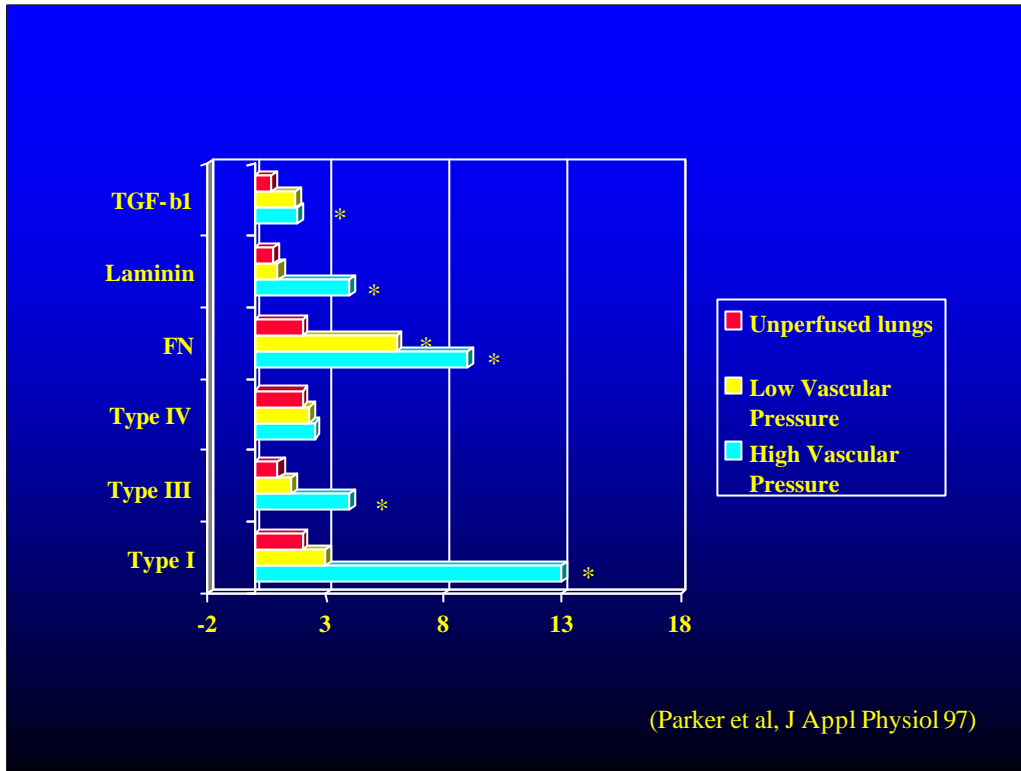
Conclusion : high lung inflation for 4 hours increases mRNA levels of ECM components and growth factors in lung parenchyma



Gene expression of growth factors

mRNA levels of growth factors that participate in vascular remodeling

Densitometric analysis of Northern blots hybridized to ³²P oligolabeled cDNA specific for bFGF,..... in parenchymal lung tissues.



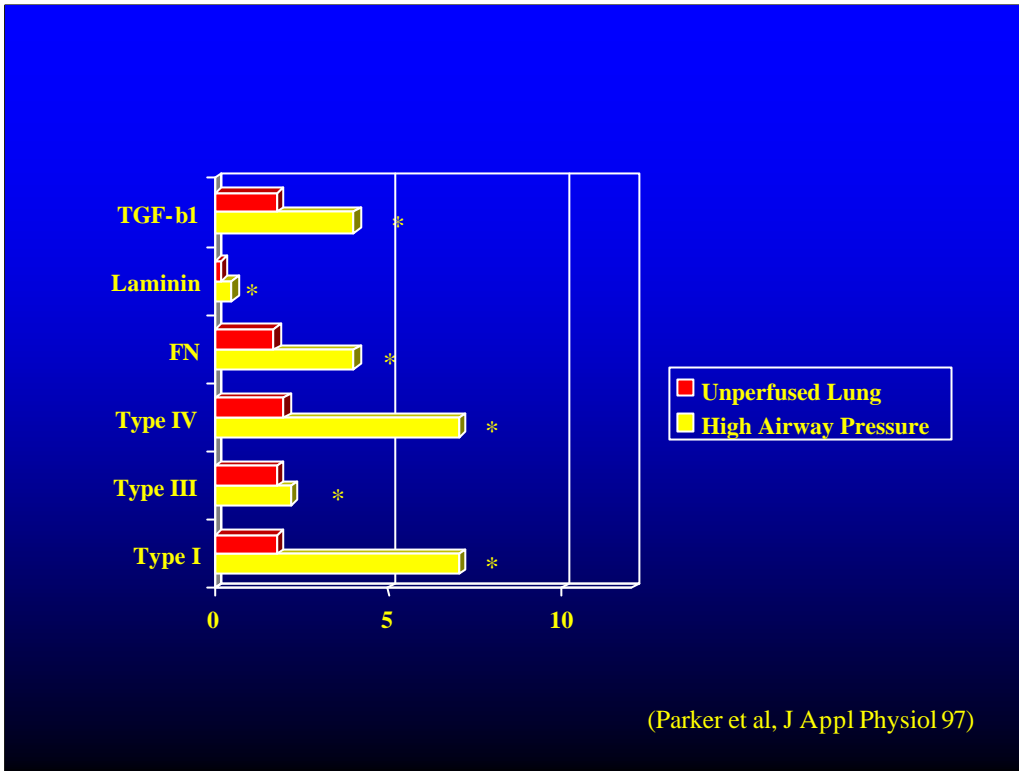
Isolated perfused rat lungs

Low pressure perfusion : 6ml/min perfusion - Vt 2,5ml, Pp 3 cm

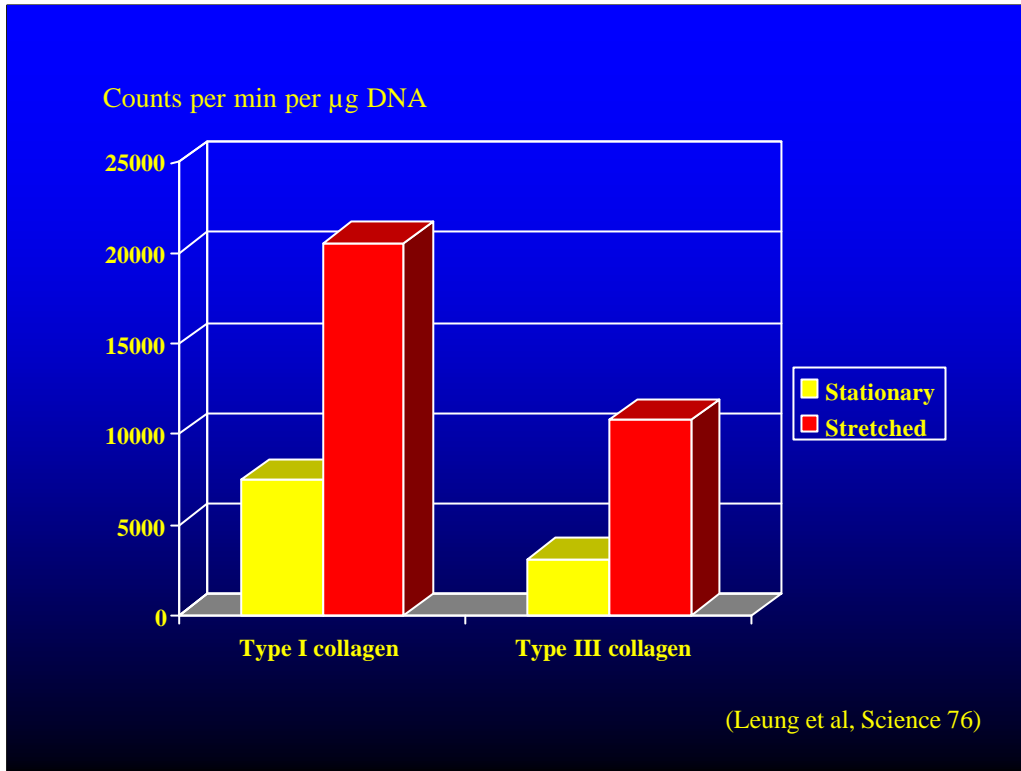
High vasc press : Ppv 28-30 cm

Duration 4 hours

RNA isolation and Northern blot analysis



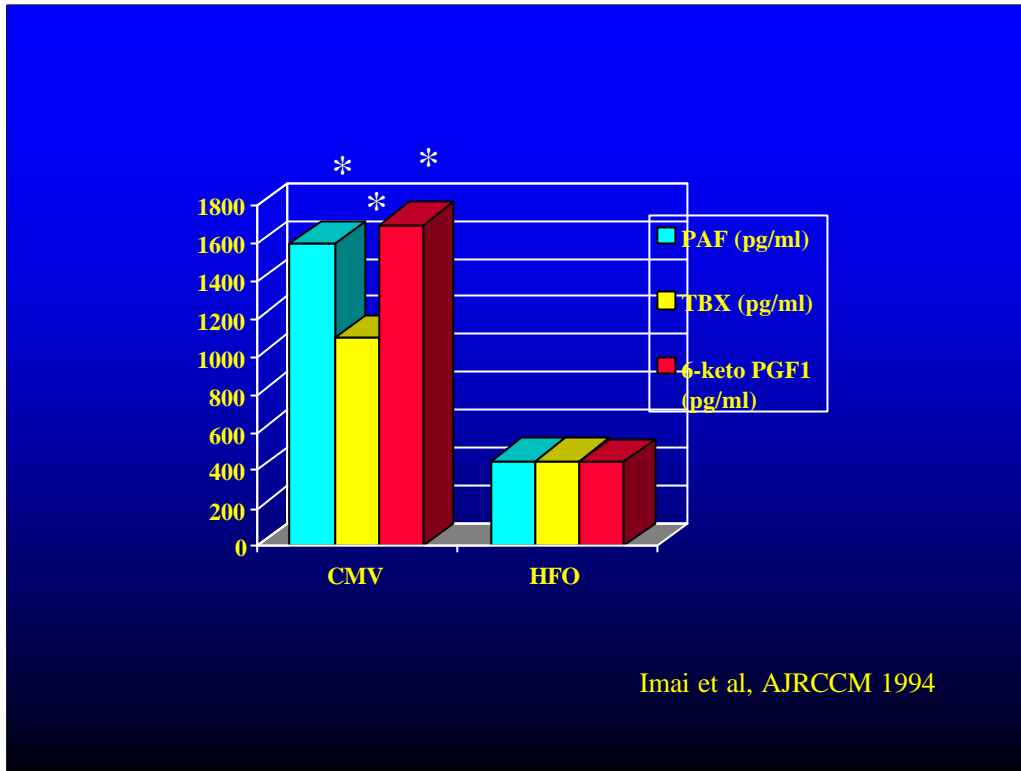
High airway pressure : Pep was increased to 10 cm and Vt to obtain a PIP of 35 cm



Rabbit aortic medial cells grown to confluence on purified elastin membranes subjected to repeated elongation and relaxation. This resulted in an increase in rates of collagen synthesis.

Measure : Incorporation of ^{14}C -proline into collagen. Stretch was applied for 2 days and radioactive precursor incorporated 8 hours prior harvesting.

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Rabbits

Dépletion en surfactant induite par lavage au SSI

ventilés soit en

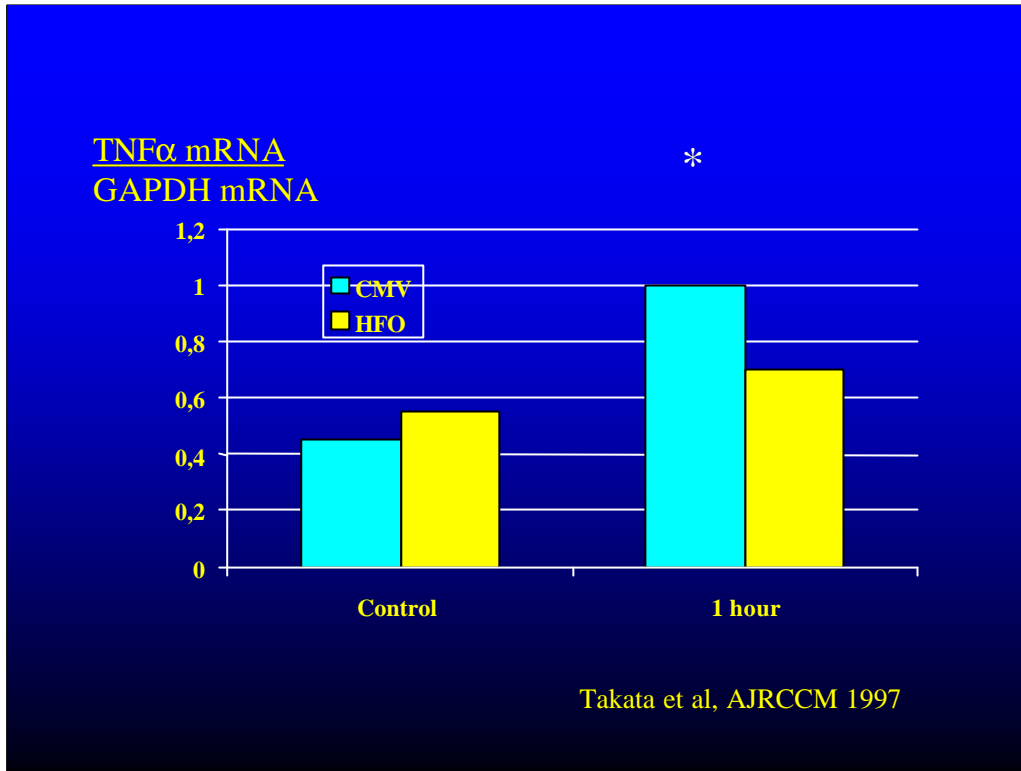
CMV : Ventilation contrôlée conventionnelle avec FiO₂ 1, MAP 15 cmH₂O

HFO : 15Hz, FiO₂ 1

Durée de 4 heures

Mesure de PAF, Thromboxane et 6 keto prostaglandine dans le LBA

Diminution importante lors de la ventilation en HFO



Rabbits

Effets de la ventilation conv versus la ventilation HFO sur l'expression intraalvéolaire du gène du TNF chez des lapins déplétés en surfactant

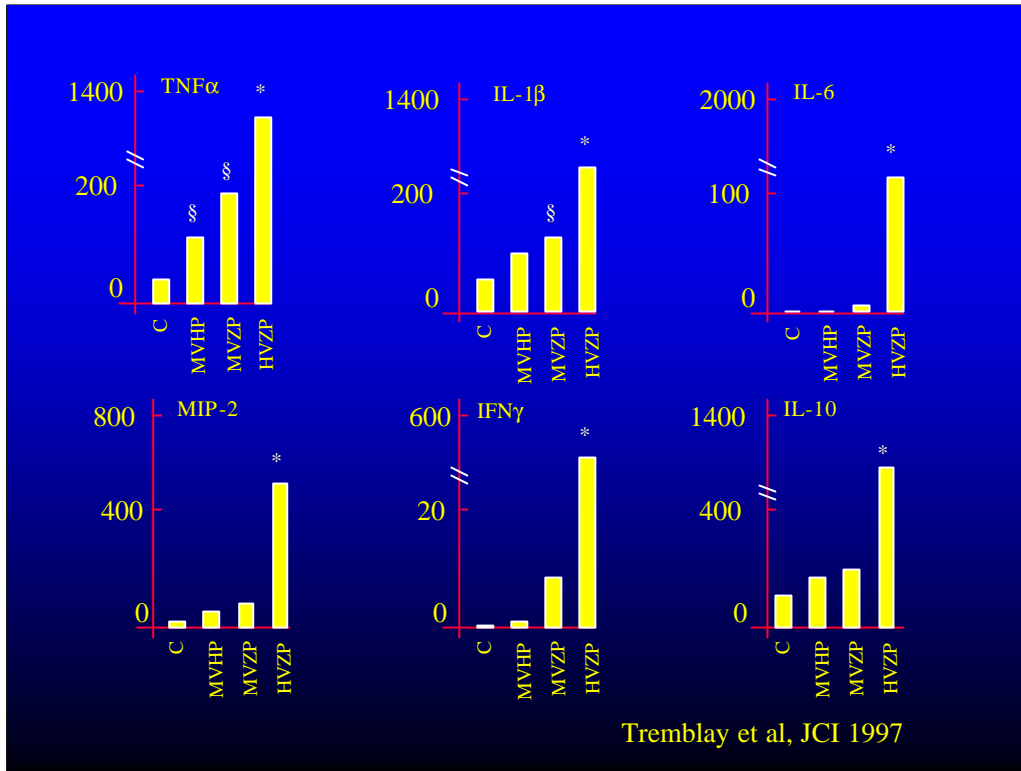
CMV : PIP28, PEP5 cmH₂O

HFO : 15Hz

Lors de la CMV, hypoxémie progressive, baisse de la compliance, augmentation des neutrophiles dans le LBA, formation de mb hyalines

La Quantité de TNF mRNA augmente avec la CMV

CONCL : l'activation du macrophage alv et la production de CK proinflammatoires joue un rôle majeur dans la phase précoce de l'agression pulm liée à la ventilation



Rats Sprague Dawley soumis à 2 heures de ventilation selon 4 protocoles différents

C : 7ml/kg,PEP3

MVHP : 15ml/kg, PEP10

MVZP : 15 ml/kg,PEP0

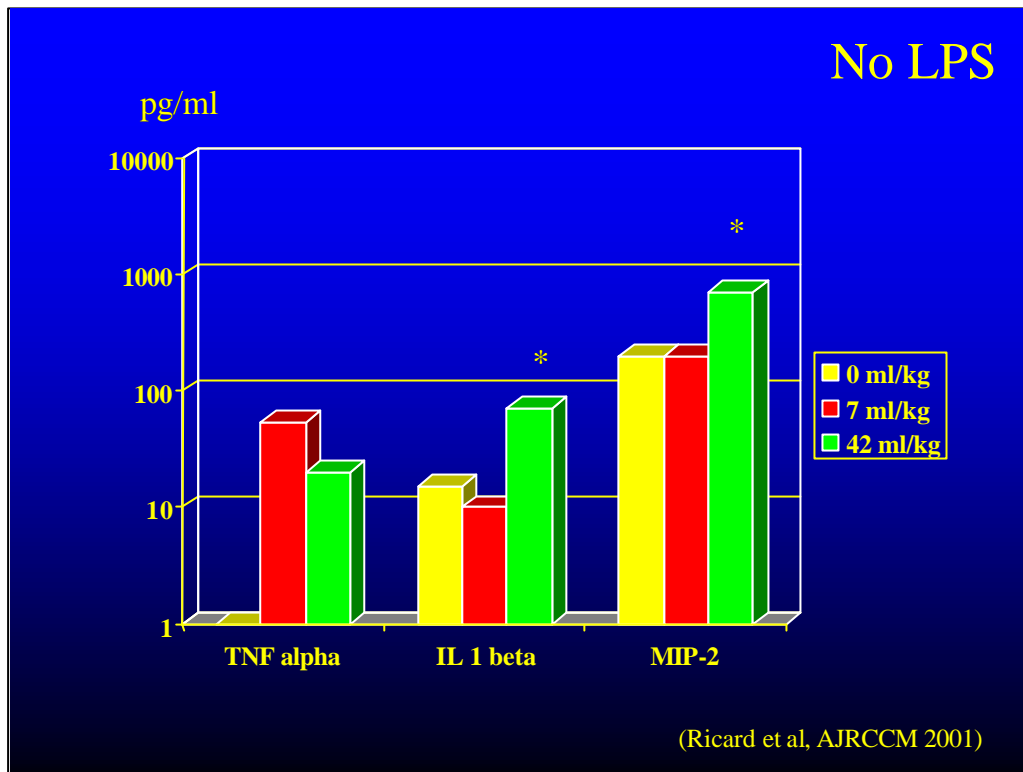
HVZP : 40 ml/kg,PEP0

Mesure des taux de cytokines au sein du liquide de LBA

CONCL : La ventilation mécanique est en mesure d'influencer la réponse inflammatoire anti inflammatoire du poumon et pourrait ainsi jouer un rôle dans l'initiation de la réponse inflamm systémique.

Problems

- Ischemia resulting from the absence of perfusion
- Boosting effect of endotoxin
- Most anti-inflammatory mediators non considered (sTNFR, IL1ra,..)



A 83 - Release of the chemokine MIP-2 but not the cytokines TNF-alpha and IL 1 beta during high volume mechanical ventilation of ex vivo rat. Ricard & al.

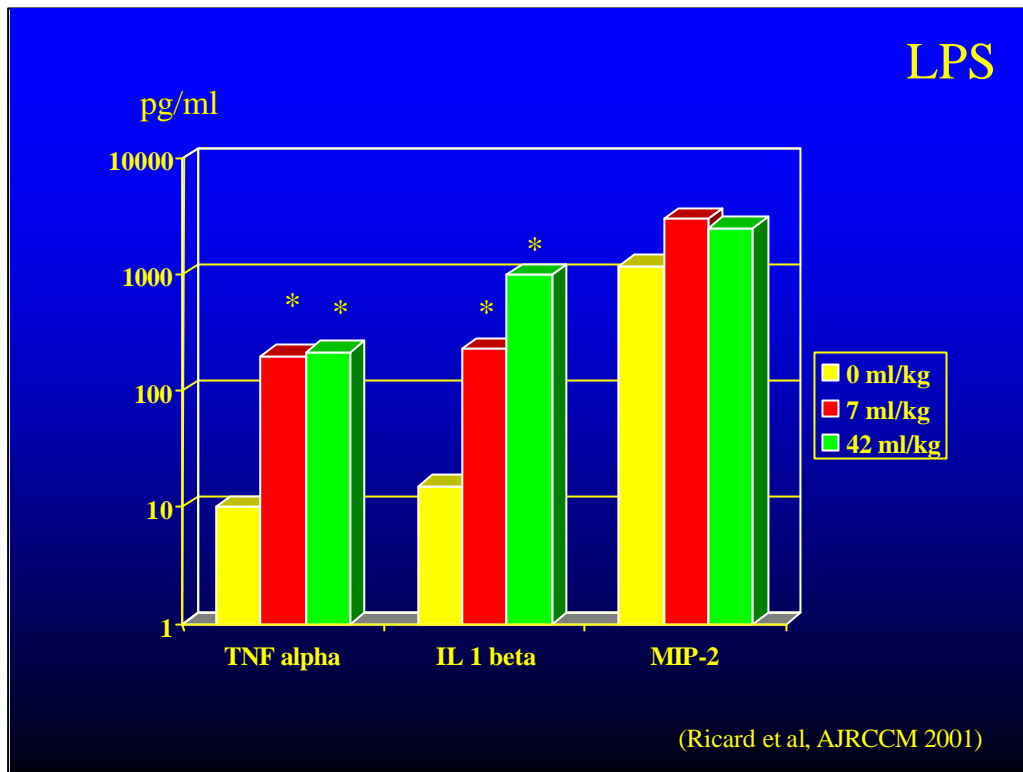
Stretch **in vitro** : production d' IL 8 et TNF alpha par les cellules pulmonaires

Question : existe-t-il **ex vivo** un relargage de MIP-2 ("famille" de l'IL8), TNF alpha et IL1 beta lors de la ventilation chez le rat à 7 ou 42 ml/kg ?

Résultats : la ventilation à haut volume entraine une production significative de MIP-2 mais pas de TNF ni d'IL1 beta au sein du liquide de lavage broncho alvéolaire

Conclusion :

- confirmation des résultats in vitro du relargage d'IL8 par les cellules pulmonaires soumises à un stretch
- question du TNF alpha : non retrouvé par cette équipe => controverse avec équipes Nord Américaines



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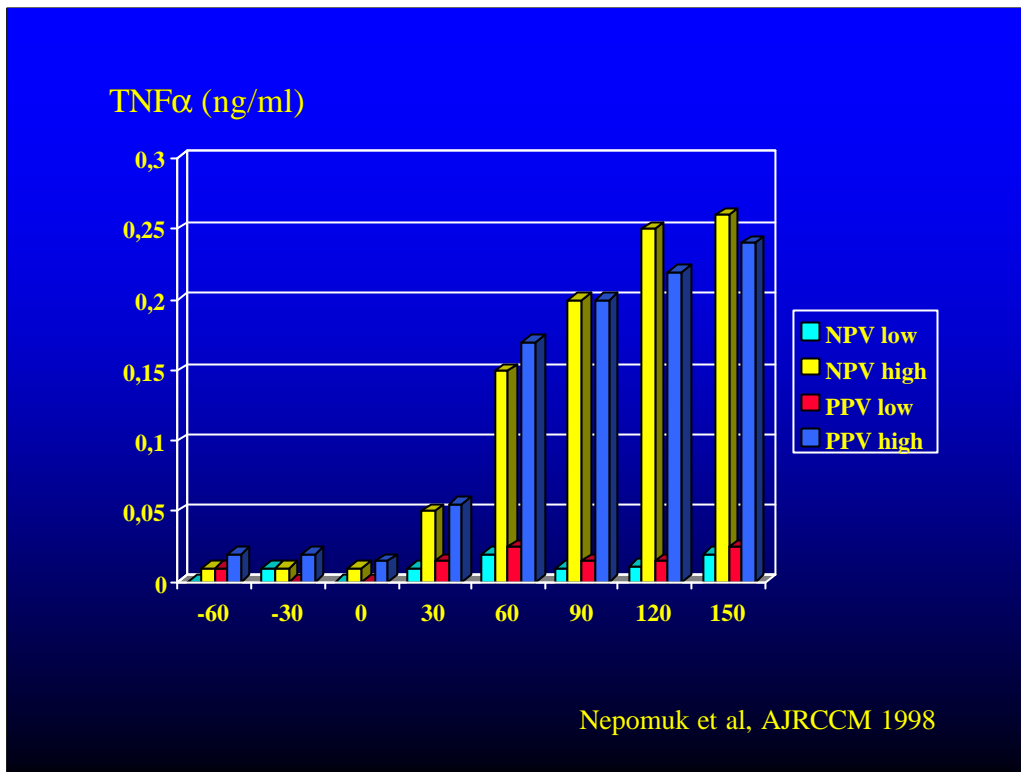
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Poumon isolé ventilé de souris

Mesure des taux de cytokines au sein du **perfusé** pendant une période de ventilation de 150 minutes

NPV low : Vt 200 μ l

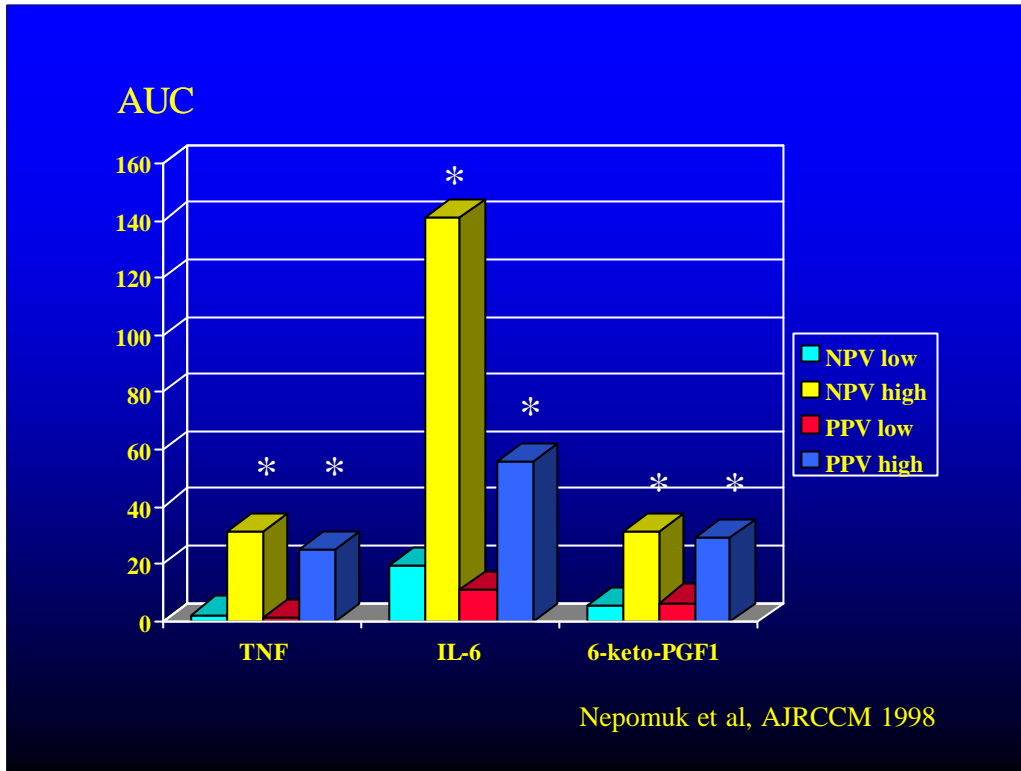
PPV low : 10 cm H₂O peak transpulmonary pressure

NPV high : 25 cmH₂O peak transpulmonary inspiratory pressure

PPV high : 25 cm H₂O peak transpulmonary pressure

Les deux modes d'hyperventilation induisent une augmentation de 1.75 fois de l'expression de TNF alpha et de l'IL6

CONCL : La ventilation artificielle cause un relargage de médiateurs dans le poumon et surtout en systémique



Mesure de la quantité« totale de médiateurs relargues au cours des 150 minutes de ventilation par Aires sous les courbes

● Van Bethman et al, AJRCCM 1998

- Isolated perfused mouse lung
- High Vt for 150 min
 - Considerable amount of TNF (200 pg/ml)
 - IL6 (1000 pg/ml)

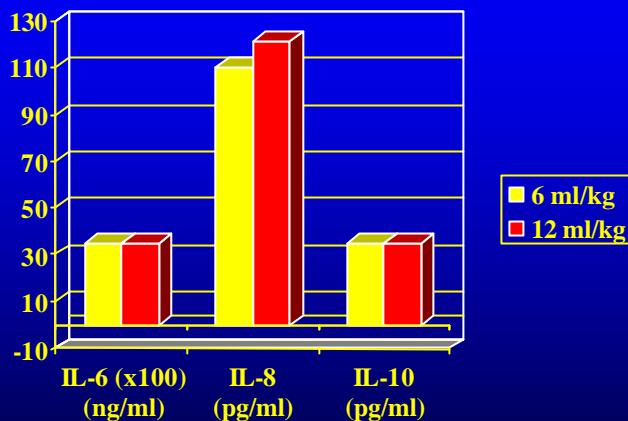
● Held et al, AJRCCM 2001

- Mediated by NFκB
- IL8, MIP1, IL6 increased in the control group....

● Non injurious ventilation inflammatory?

- Severe hypocapnia

A l'admission



Low tidal volume ventilation reduces plasma cytokines in human acute lung injury.
Wheeler & al.

A83 - Low tidal volume ventilation reduces plasma cytokines in human acute lung injury. *Wheeler & al.*

Sur les modèles animaux, la ventilation avec un haut volume courant entraîne le relargage de cytokines dans le liquide de lavage pulmonaire et dans le sang. Récemment, il a été observé que les patients porteurs d'un ARDS présentaient une diminution plus rapide de leur taux de cytokine en cas de stratégie ventilatoire protectrice, utilisant un faible volume courant et une Peep élevée ajustée sur les données de la courbe P/V.

Cependant, on ne sait pas si cette stratégie ventilatoire avec bas volume courant et Peep ajustée sur des critères d'oxygénation diminue le taux de cytokine.

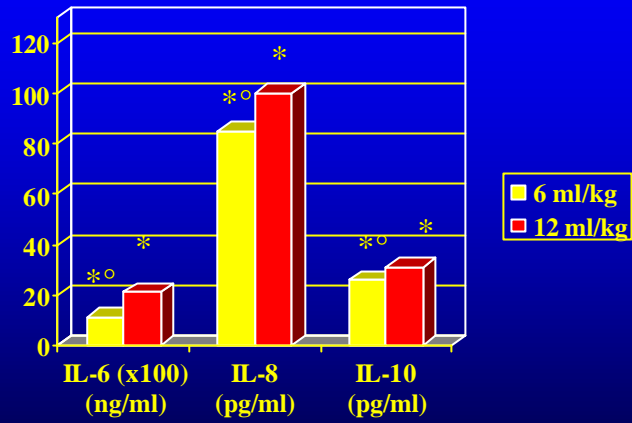
Méthode

234 patients de l'ARDS network

étude randomisée avec V_t de 6 versus 12 ml/kg

mesures plasmatiques des taux d'IL6, d'IL8 et d'IL10 à l'entrée et après 3 jours de ventilation

A J3



Low tidal volume ventilation reduces plasma cytokines in human acute lung injury.
Wheeler & al.

Low tidal volume ventilation reduces plasma cytokines in human acute lung injury. Wheeler & al. (suite)

Résultats

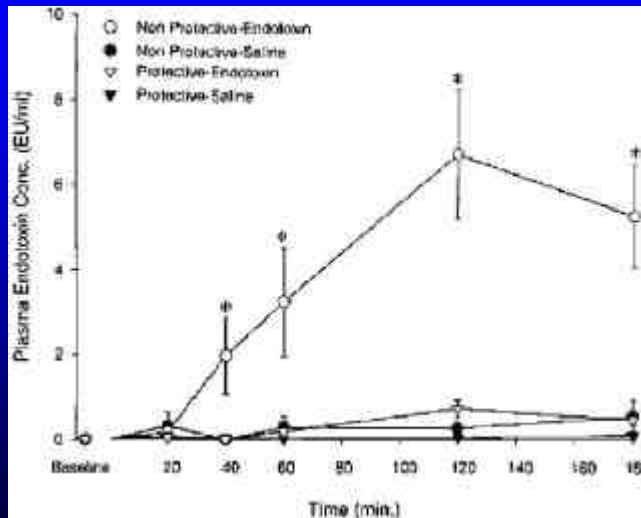
le groupe ventilé à 6ml/kg est associé à une plus grande diminution des taux plasmatiques d'IL6, IL8 et IL10

- HV for 30 min, gene array
 - No discernable lung injury
 - Upregulation of 10 genes
 - Transcription factors
 - Stress proteins
 - Inflammatory mediators
 - Suppression of 12 genes
 - Metabolic regulatory genes

Specific patterns of gene activation and suppression precede lung injury

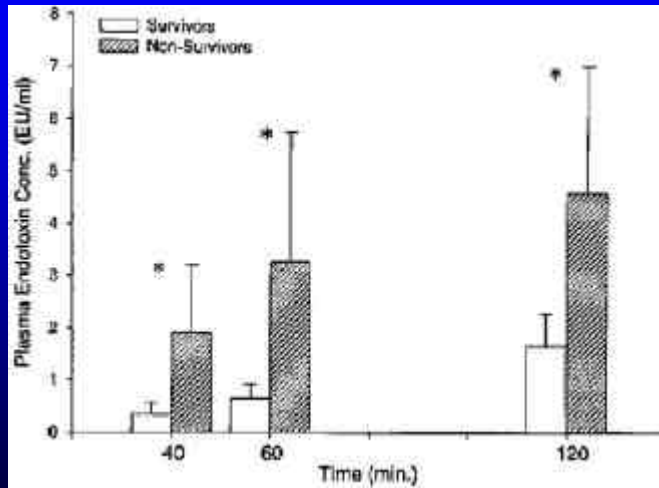
(Copland et al, AJRCCM 2003)

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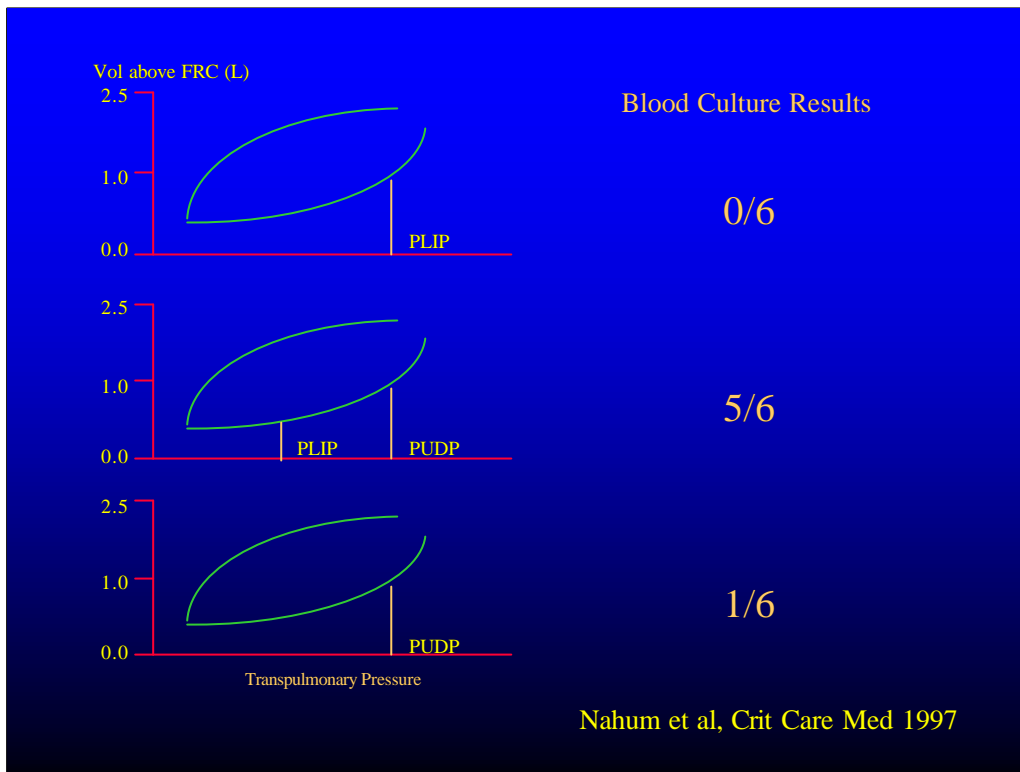


(Murphy et al, AJRCCM 2000)

Accumulating evidence strongly suggests that ventilatory strategy has an important impact on development of lung injury and patient outcome. Adverse ventilatory strategies have been shown to cause release of pulmonary-derived cytokines and may permit bacterial translocation from the lung to the systemic circulation. Because endotoxin is a potent and clinically important stimulant of cytokine-mediated systemic inflammatory responses that can lead to multiorgan failure, we investigated the effects of ventilatory strategy on lung-to-systemic translocation of endotoxin. We studied the effects of protective (tidal volume [VT] 5 ml · kg⁻¹, positive end-expiratory pressure [PEEP] 10 to 12.5 cm H₂O) versus nonprotective (VT 12 ml · kg⁻¹, PEEP zero) ventilatory strategy on translocation of endotracheally instilled endotoxin. Anesthetized New Zealand White rabbits were subjected to saline lung lavage, and 32 were randomized to one of four groups: PS (protective ventilation + instilled saline); PE (protective ventilation + instilled endotoxin); NS (nonprotective ventilation + instilled saline); NE (nonprotective ventilation + instilled endotoxin), and ventilated for 3 h. Plasma endotoxin levels increased significantly in the NE group, and remained low and unchanged in the other groups. Peak levels of plasma tumor necrosis factor- α (TNF- α) were higher in NE versus other groups. PaO₂ and mean arterial pressure (MAP) were lowest, and requirement for pressor and bicarbonate support greatest, in the NE group. Finally, plasma endotoxin levels were significantly greater in eventual nonsurvivors than survivors. These data provide convincing evidence for pulmonary translocation of lung-derived endotoxin. This translocation depends on ventilatory strategy, and suggests a pathophysiologic link between ventilatory strategy and outcome.



(Murphy et al, AJRCCM 2000)



Dogs

10⁸/8 CFU d'E coli dans la trachée puis ventilation pendant 6 heures

3 régimes ventilatoires

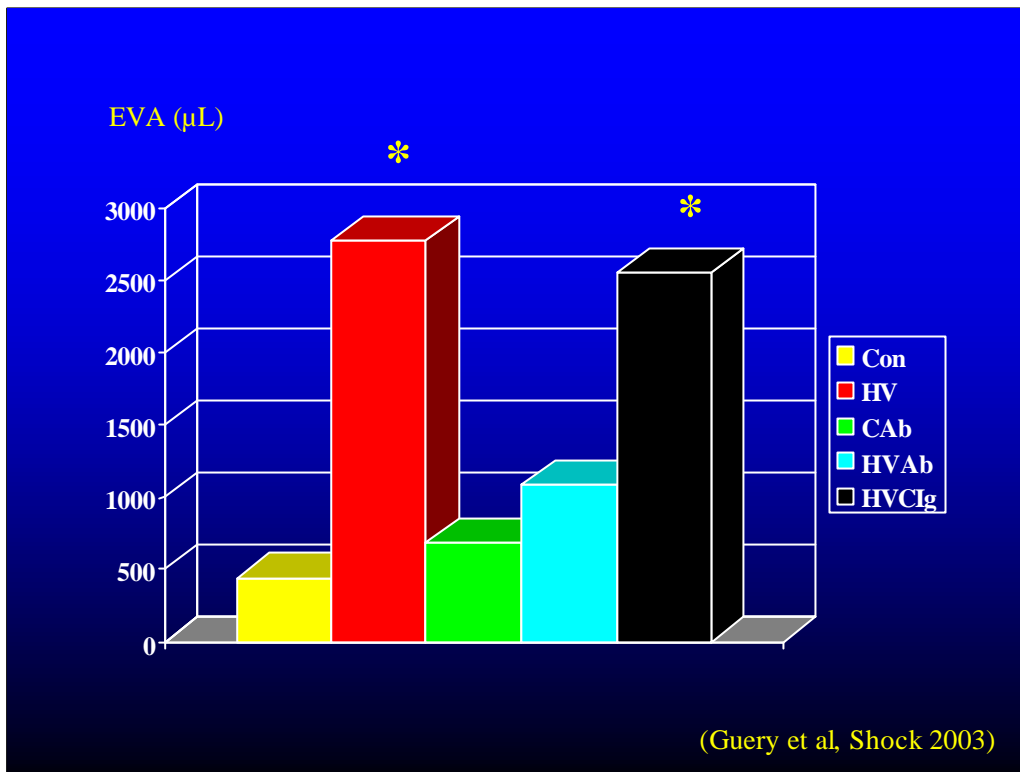
Groupe 1 : ventilation en dessous du point d'inflexion inférieur de la courbe pression vol, pression transpulmonaires basses avec ventilation des régions aérées mais pas des zones atelectatiques (PEP 3)

Groupe 2 : en dessous du point d'inflexion inf et au dessus du point d'inflexion sup, donc distension et closure reopening (PEP 3)

Groupe 3 : surdistension (Gpe 2 +PEP 10)

Groupe 2 most lung injury (gravimetric and histologic indices), plus de translocation bactérienne (Blood cultures)

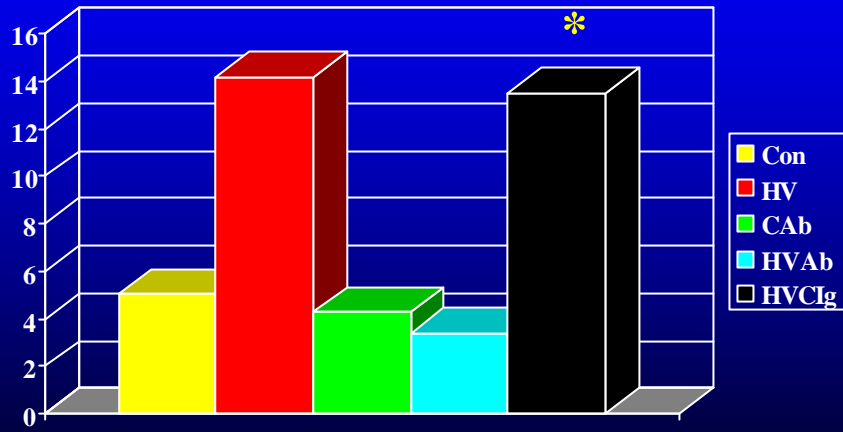
CONCL : Les régimes ventilatoires favorisant distension et ouverture/fermeture facilitent la translocation bactérienne



Mechanical ventilation is associated with several harmful effects mainly related to high tidal volumes (V_t). Ventilator-induced lung injury (VILI) can be responsible for an increased production of inflammatory mediators. We evaluated remote consequences, on the gut, of lung triggered inflammatory response, neutralizing anti-TNF antibody was administered to assess the role of TNF in lung and gut permeability changes.

Rats were anesthetized and ventilated for 2 hours. A control group (Con : $V_t = 10$ cc/kg) was compared to a high V_t group (HV : $V_t = 30$ cc/kg). One μCi of I125 labeled human serum albumin (HSA) was injected to measure extravascular albumin space (EVA). Gut permeability was evaluated by plasma-to-lumen ratio leakage of I125 HSA. EVA increased in the HV group from 446 ± 50 μL to 2783 ± 887 μL . Gut index of permeability increased from 5.1 ± 1.2 to 14.2 ± 4.9 . Anti-TNF antibody prevented both lung and gut increase in permeability. High tidal volume ventilation resulted in an increase in lung edema and gut permeability, antagonism of TNF with neutralizing antibodies abrogated the increase in gut permeability as well as lung edema.

Gut permeability index *



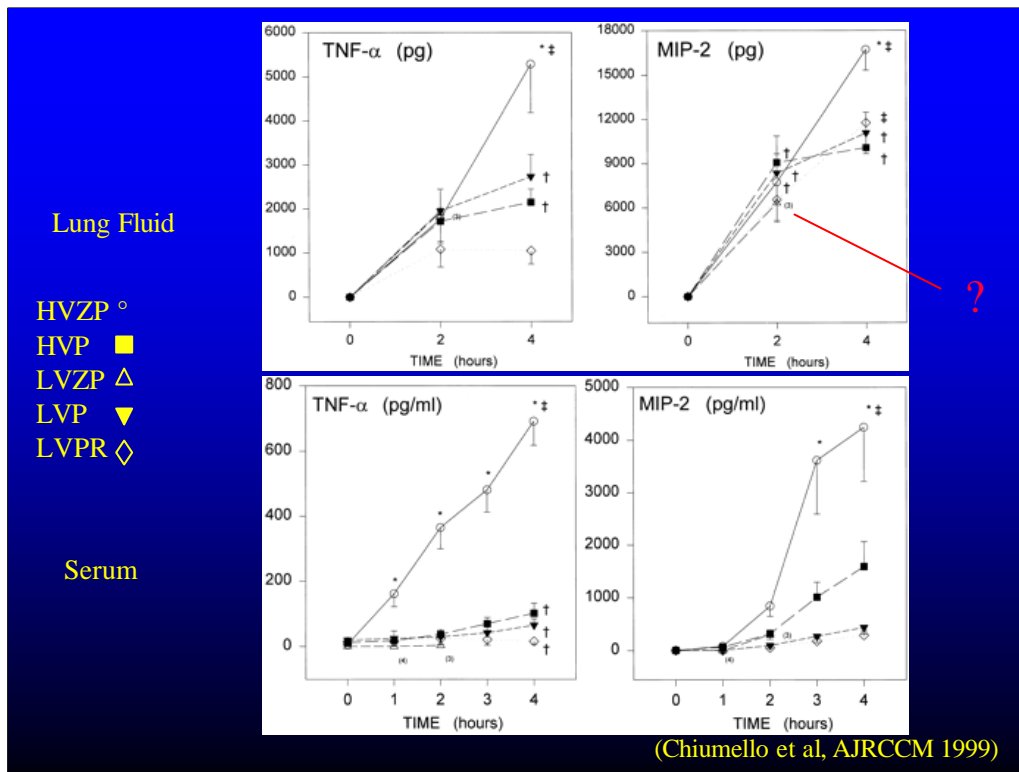
(Guery et al, Shock 2003)

● Systemic microvascular leak in vivo

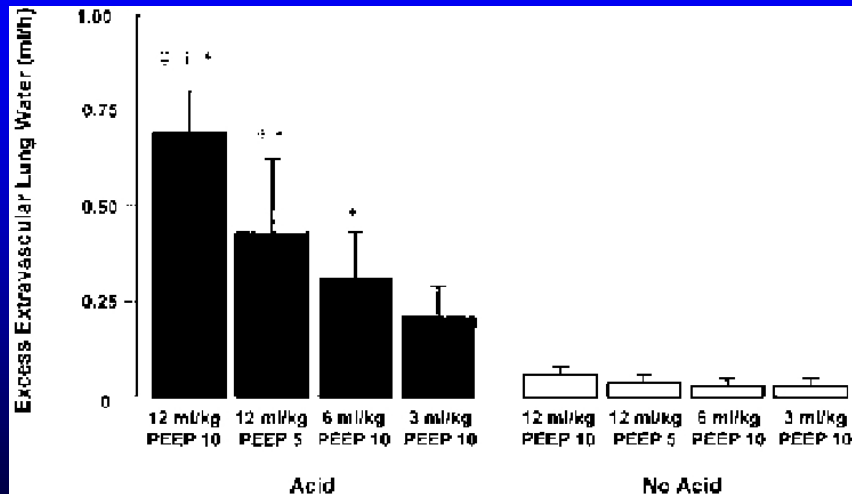
- Rats
- Ventilation with room air, 7 or 20 ml/kg for 2h
- Kidney vascular leak (Evans blue dye)
- Large V_t associated with a leak even after correction of the hypotension
- Endothelial NOS expression increased (not iNOS)
- NOS inhibitors attenuated the leak

(Choi et al, AJRCCM 2003)

- Notion de volotraumatisme
- Notion de Stress failure
- Interrelation alvéole-vaisseaux
- Stretch et matrice
- Stretch et Inflammation
- Stretch et Translocation
- **Stretch et lésion pré-existante**

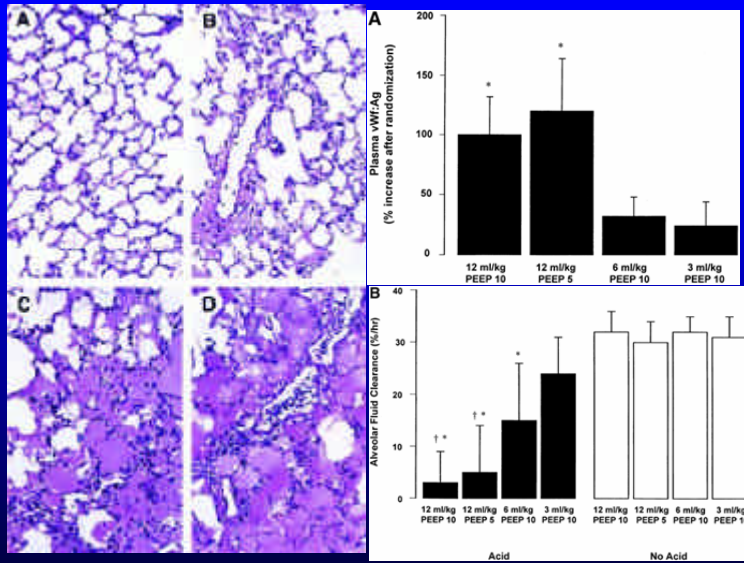


We examined the hypothesis that injurious ventilatory strategies (large tidal volume [VT] and/or low positive end-expiratory pressure [PEEP]) would increase release of inflammatory mediators into the lung and into the systemic circulation in a lung injury model. Lung injury was induced in 40 anesthetized paralyzed Sprague-Dawley rats (350 ± 2 g) by hydrochloric acid instillation (pH 1.5, 2.5 ml/kg). Rats were then randomized into five groups (n = 8): (1) high-volume zero PEEP (HVZP): VT, 16 ml/kg; (2) high-volume PEEP (HVP): VT, 16 ml/kg, PEEP, 5 cm H₂O; (3) low-volume zero PEEP (LVZP): VT, 9 ml/kg; (4) low-volume PEEP (LVP): VT, 9 ml/kg, PEEP, 5 cm H₂O; (5) same settings as (4) plus a recruitment maneuver performed every hour (LVPR). Respiratory rate was adjusted to maintain normocapnia and fraction of inspired oxygen (FIO₂) was 1. Cytokine concentrations (tumor necrosis factor-alpha [TNF- α] and macrophage inflammatory protein-2 [MIP-2]) were measured by ELISA. All animals in the LVZP group died before the end of the experiment. After 4 h of ventilation, the HVZP group had similar lung fluid TNF- α concentrations compared with the HVP group: $1,861 \pm 333$ pg/ml versus $1,259 \pm 189$ pg/ml; and much higher serum concentrations: 692 ± 74 pg/ml versus 102 ± 31 pg/ml ($p < 0.05$). An identical pattern was found for MIP-2. These results suggest that the particular ventilatory strategy can affect the release of cytokines into the systemic circulation, a finding that may have relevance for the development of multisystem organ failure.

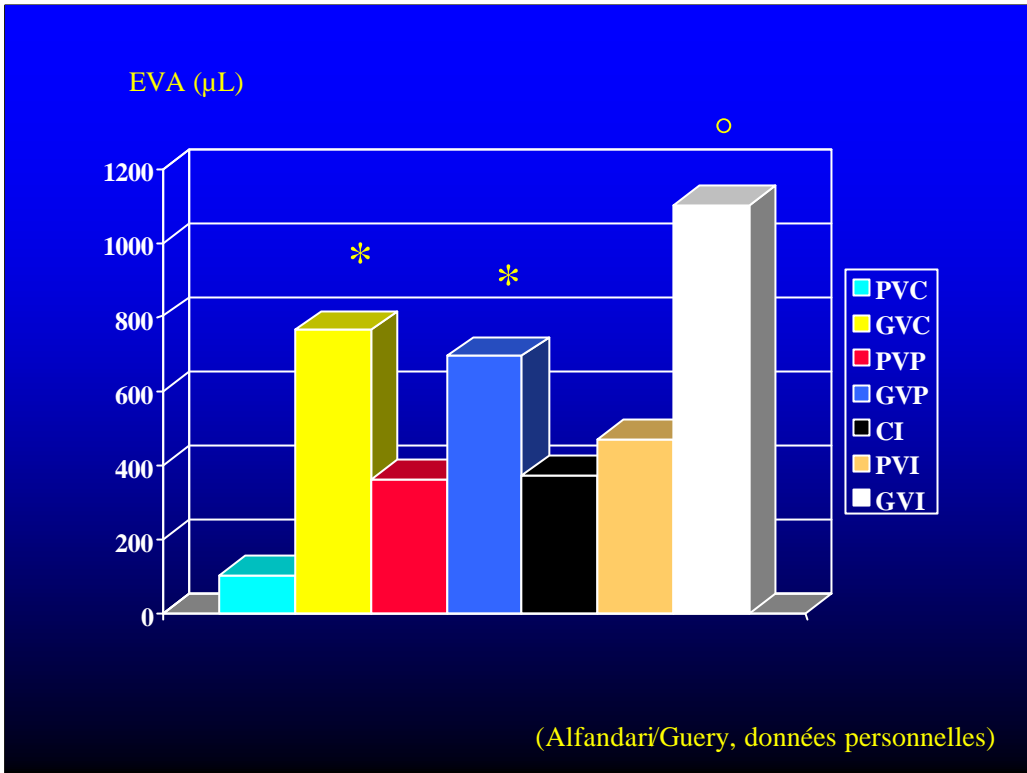


(Frank et al, AJRCCM 2002)

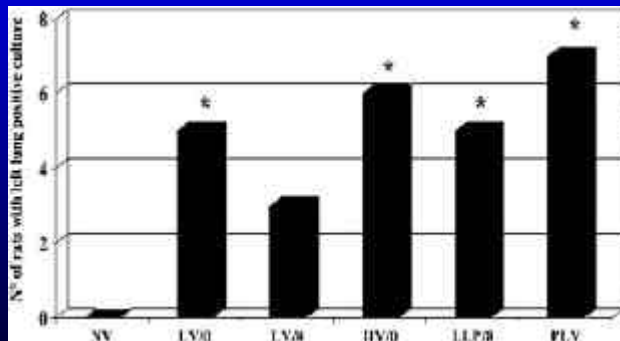
Using a rat model of acid-induced lung injury, we tested the hypothesis that tidal volume reduction at the same level of PEEP (10 cm H₂O) would diminish the degree of pulmonary edema by attenuating injury to the alveolar epithelial and endothelial barriers. Tidal volume reduction from 12 to 6 to 3 ml/kg significantly reduced the rate of lung water accumulation from 690 μ l/h to 310 μ l/h to 210 μ l/h. Ventilation with either 6 or 3 ml/kg reduced endothelial injury equally as measured by plasma vWf:Ag and permeability to albumin. Plasma RTI40, a marker of type I epithelial cell injury, decreased 46% when tidal volume was reduced from 12 to 6 ml/kg and decreased an additional 33% with 3 ml/kg ($p < 0.05$). The rate of alveolar epithelial fluid clearance was significantly faster in the 3-ml/kg group ($24 \pm 7\%/h$) compared with 6 ml/kg ($15 \pm 11\%/h$) and 12 ml/kg ($3 \pm 6\%/h$). We conclude that low tidal volume ventilation protects both the alveolar epithelium and the endothelium in this model of acute lung injury. The additional decrease in pulmonary edema with a tidal volume of 3 ml/kg is partly accounted for by greater protection of the alveolar epithelium.



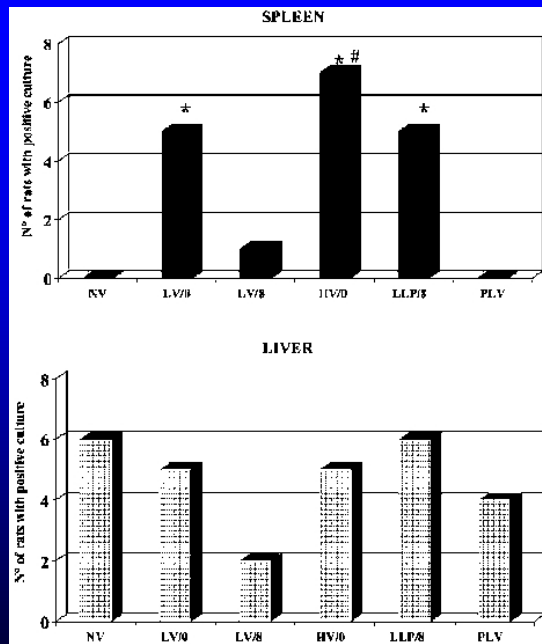
(Frank et al, AJRCCM 2002)



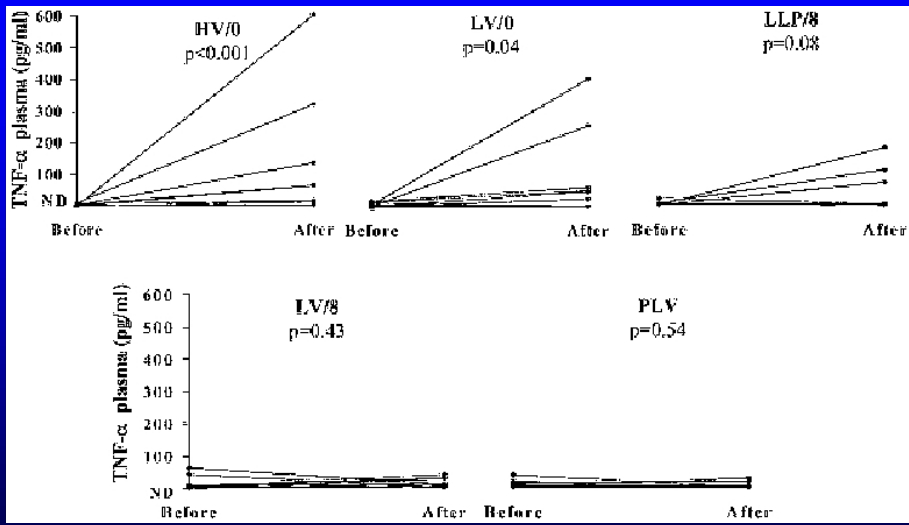
- Male Wistar rats, 1.4×10^7 *P.aeruginosa* right lung
- Left unventilated or ventilated 2h, Vt 6 ml/kg
 - No Peep, 8 cm Peep, 8 cm in LLP, 3 cm with partial liquid ventilation



(Shortgen et al, Int Care Med 2004)



(Shortgen et al, Int Care Med 2004)



(Shortgen et al, Int Care Med 2004)

- PA 103 instilled in the left lung
- Vt 6 vs 12 ml/kg with 3 or 12 of Peep
- Results
 - Injury to non involved region decreased with low Vt (W/D)
 - High Peep did not yield a protective effect but caused overdistension of the non involved lung
 - Higher TNF level in the non involved lung with high Vt
- Conclusion
 - Low Vt is protective in the non involved lung
 - High Peep attenuates this effect

(Kurahashi et al, Am J Physiol 2004)