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"Matching the Mechanical Breath with Dynamic Alveolar Pathophysiology to Reduce VILI"

7th Biennial Midwest Mechanical Ventilation and Critical Care Conference September 29-30, 2017

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So what is the Magic Trick?

Science

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Nieman Disclosures

- None of the funding organizations or sponsors had any role in the design and conduct of any of our studies including: the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of any of our manuscripts.

- Consultant for Interxon Corporation
- Consultant for the DoD developing Mechanical Ventilators for Marine Mammals
- NIH R01 grant: Gene therapy to treat acute lung injury using
- Travel and honorarium funded by Dräger Medical
- Dräger Medical equipment used in our studies
- CDMRP DoD grant: A novel drug (TRB-N0224) to reduce ARDS incidence
- Established a APRV Network website
- Conduct an APRV Workshop Sponsored by Upstate Medical University
- Patent for: "Method of preventing acute lung injury"
- Patent for: "Novel method of assessing alveolar inflation in ARDS using sound"
- Patent for: "A device (MIST) to remove toxic ascites and prevent MODS and ARDS
- Patent for: "Apparatus, system and method of assessing alveolar inflation"

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How do we 'Trick' the ARDS Lung into Ventilating and Oxygenating without Exacerbating Tissue Injury?

- Understanding the *science* of ARDS pathophysiology
- Combine this understanding with the *science* of VILI in terms of applied stress and resultant strain on lung tissue

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"Physiology is the basis of medical reasoning, not statistics. Statistics are a tool"

Luciano Gattinoni

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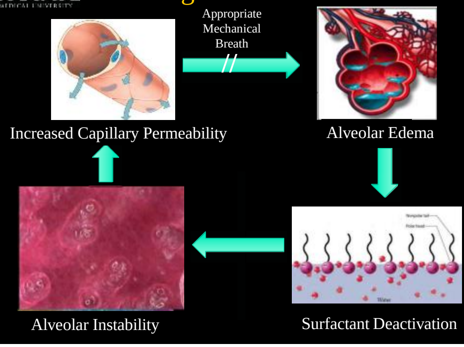
Pathologic Tetrad of ARDS



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Hypothesis

Properly adjusted Mechanical Ventilation can reduce the severity of all components that comprise the Pathologic Tetrad of ARDS

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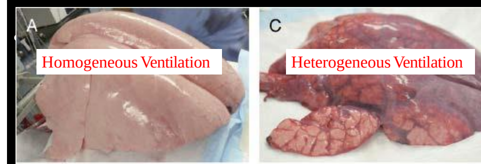
Why does the ARDS Tetrad Render the Lung so Vulnerable to VILI?



Roy S et al *Shock* 2013;39:28

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How do we 'Trick' the ARDS Lung into Ventilating and Oxygenating without Exacerbating Tissue Injury?

- Understanding the *science* of ARDS pathophysiology
- Combine this understanding with the *science* of VILI in terms of applied stress and resultant strain on lung tissue

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Mechanism of VILI at the Alveolar Level

- Dynamic alveolar strain (R/D)
  - Tetrad: Edema/Surfactant deactivation
- Stress-Concentration (S-C)
  - Tetrad: Edema/Surfactant deactivation
- Over-distension
  - In the presence of R/D or S-C adjacent alveoli and ducts can over-distend

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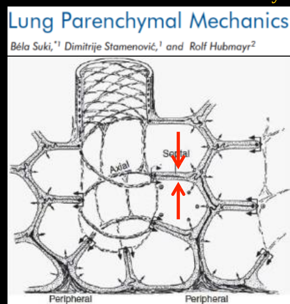
Normal Alveolar Micro-Anatomy



COMPREHENSIVE PHYSIOLOGY

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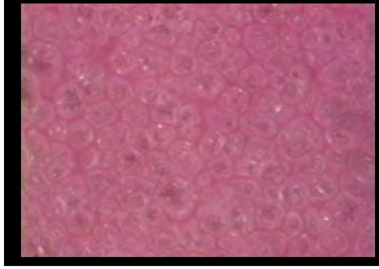
Normal Homogeneous Alveolar Minimizes Dynamic Strain and OD



~2% ! in Alveolar Area with each Breath

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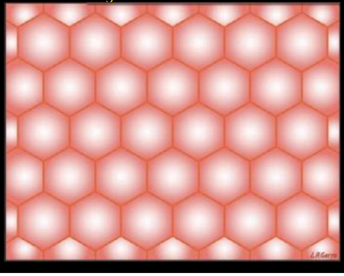
Normal Homogeneous Alveolar Minimizes Dynamic Strain and OD



~2% ! in Alveolar Area with each Breath

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What happens to this homogeneous ventilation when alveoli become unstable with Acute Lung Injury?

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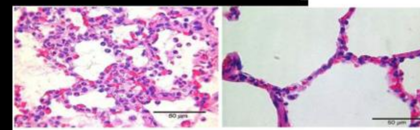
Research Open Access

Effect of positive end-expiratory pressure and tidal volume on lung injury induced by alveolar instability

Jeffrey M Halter[1], Jay M Steinberg[1], Louis A Gatto[2], Joseph D DiRocco[1], Lucio A Pavone[1], Henry J Schiller[3], Scott Albert[1], Hsi-Ming Lee[4], David Carney[5] and Gary F Nieman[1]

Critical Care 2007, 11:R20



	Alveolar Wall Thickening	Intra-alveolar Edema	Neutrophil Infiltration	Wet/Dry Ratio
High TV/Low PEEP	3.25±0.16	2.60±0.33	120.1±15.2	8.59±0.7
Low TV/High PEEP	2.60±0.31*	1.00±0.15*	61.8±6.5*	8.52±1.0

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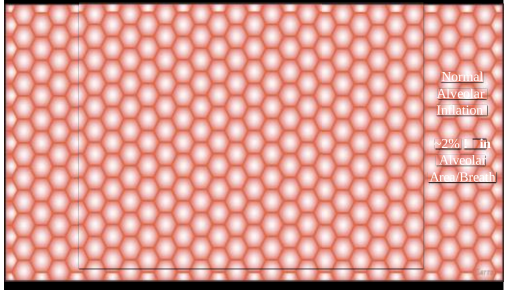
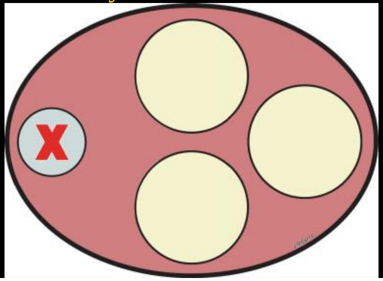
Dynamic Alveolar Strain (R/D)



Heterogeneous Ventilation: Large Dynamic Strain



Heterogeneous Alveolar Ventilation

Schiller, *Crit Care Med*. 2001;29(5):1049

Mechanism of VILI at the Alveolar Level

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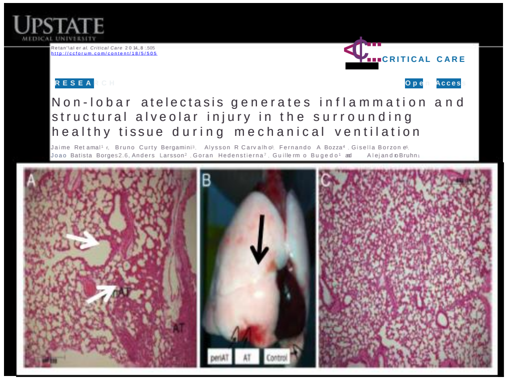
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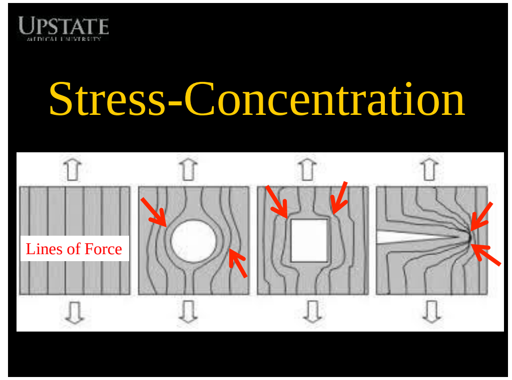
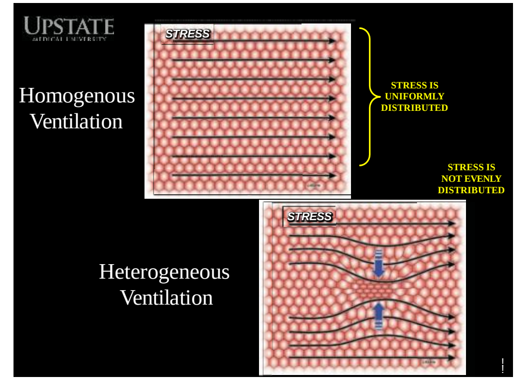
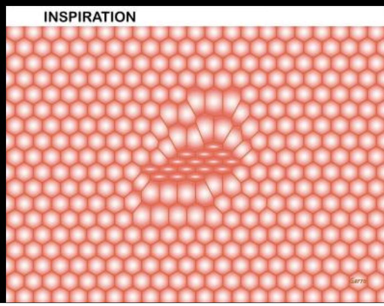
Retan'\al er al. Critical Care 2014,18:505
http://ccforum.com/content/18/5/505
CRITICAL CARE
RESEARCH
Open Access
Non-lobar atelectasis generates inflammation and structural alveolar injury in the surrounding healthy tissue during mechanical ventilation
Jaime Retamal, Bruno Curty Bergamini, Alysson R Carvalho, Fernando A Bozza, Gisella Borzone, Joao Batista Borges, Anders Larsson, Goran Hedenstierna, Guillermo Bugedo and Alejandro Bruhn
A
B
C
AT
periAT
AT
Control


UPSTATE
Stress-Concentration
Lines of Force


UPSTATE
Homogenous Ventilation
STRESS
STRESS IS UNIFORMLY DISTRIBUTED
STRESS IS NOT EVENLY DISTRIBUTED
Heterogeneous Ventilation
STRESS

Stress-Concentration (S-C)



Mechanism of VILI at the Alveolar Level

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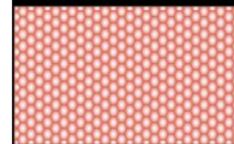
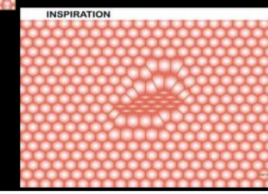
Over-Distension



Dynamic Alveolar Strain (R/D)

Stress-Concentrator (S-C)



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How must the Mechanical Breath be Adjusted to Minimize the Problems caused by ARDS Pathophysiology:

- Maintain homogeneous alveolar ventilation
  - (*Open the lung*: prevent stress-concentration)
- Prevent alveolar collapse at expiration
  - (*Keep the lung open*: prevent dynamic strain)

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"Open the Lung and Keep the Lung Open"

B. Lachmann

Intensive Care Med 1992

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We Create the Problem and then Attempt to Devise Solutions for the Problem that We have Created!

- Wouldn't it make more sense to prevent the problem in the first place?
- The problem is *Heterogeneous Loss of Lung Volume*
  - Causing high inspiratory drive with the potential of SB-induced VILI
  - Causing stress-risers and alveolar instability
  - Causing over-distension of 'Baby Lung'
  - If the lung is open, VILI disappears, no problem to fix!

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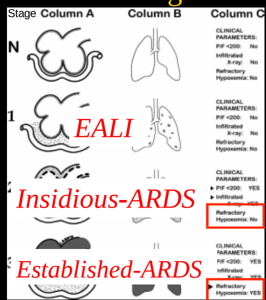
ARDS Pathogenesis



Roy et al *J Trauma Acute Care Surg*. 2012,73:391

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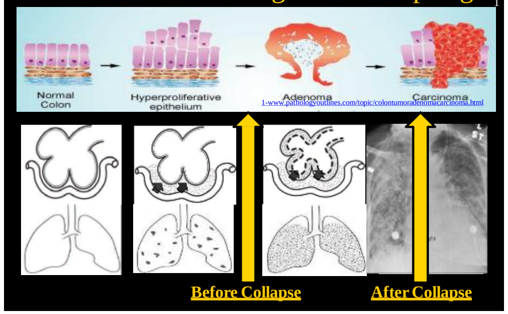
Prevent the Lung from Collapsing



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What is the Current Ventilation Strategy to Open the Lung and Keep it Open?

- Recruitment maneuvers
  - Open the lung
- PEEP
  - Keep the lung open
- Reduced Vt and Pplat
  - Minimize alveolar over-distension in the presence of dynamic strain and stress-concentrators

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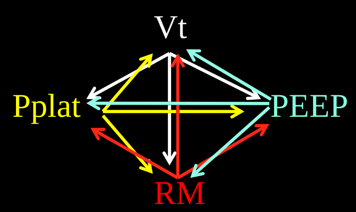
Current Protective Ventilation Strategies use the same 4-Parameters



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Villar J, Curr Opin Crit Care 2014;20:3-9

No Reduction in ARDS Mortality since 1998

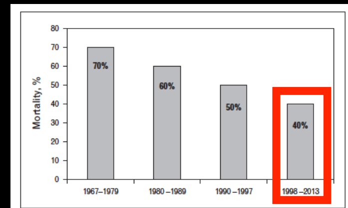

FIGURE 1. Schematic representation of average reported mortality in observational and randomized controlled trials in adult patients with acute respiratory distress syndrome since 1967. Data have been compiled from [6■■,11,12■,26,27■].

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Insanity: doing the same thing over and over again and expecting different results

Albert Einstein

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Why haven't these strategies worked?

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Understanding <u>Dynamic</u> Alveolar Physiology

- Alveoli are <u>*not*</u> elastic in nature
  - Do not inflate and deflate in a linear fashion like a balloon
- Rather, alveoli are a <u>*viscoelastic*</u> system
  - <u>*Time lag*</u> from when the force (i.e. Vt) is applied or removed and when the alveolus begins to change volume
  - Dynamic alveolar inflation and deflation can be modeled as a: *Spring and Dashpot*

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Spring and Dashpot Model

Time Lag between the time the stress is applied or released and the initiation of the strain

Force = Vt
Applies Stress to the Lung

Spring = Rapid Strain

Dashpot = Slow Strain

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How can we use this knowledge of dynamic alveolar physiology to design a better protective ventilation strategy?

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Protective Mechanical Ventilation: The Old and the New

- Old thinking: RM+PEEP+LVt
  - RM: Reduce stress-concentrators (S-C)
  - PEEP: Reduce dynamic alveolar strain (R/D)
  - LVt: Minimize OD of 'Baby Lung'
- New Thinking: Spring and Dashpot
  - Long I-time: Reduce stress-concentrators (S-C)
  - Short E-time: Reduce dynamic alveolar strain

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Extend the *Duration* at Inspiration

Continually recruit alveoli with each breath: Reduce S-C

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Extend Inspiratory <u>Duration</u> to Cause Full Alveolar Strain (i.e. Alveolar Recruitment)

Force = Vt

Applies Stress to the Lung

Spring = Rapid Strain

Dashpot = Slow Strain

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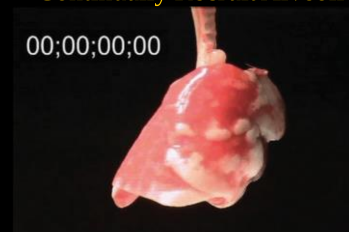
Extended *Inspiratory Duration* will Continually Recruit Alveoli



Minimizing Stress-Concentrators

Albert SP et al *J Appl Physiol*, 2009

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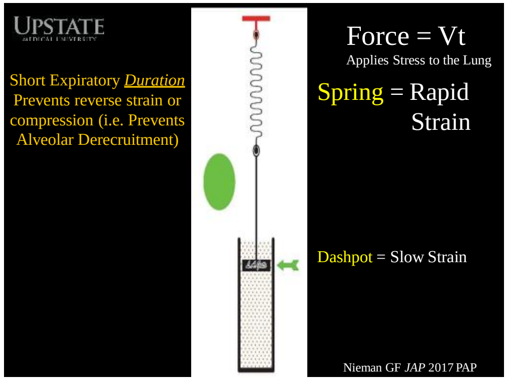
Reduce the <u>*Duration*</u> at Expiration

Minimize alveolar collapse and reopening: Reduce dynamic strain


UPSTATE
Short Expiratory Duration
Prevents reverse strain or compression (i.e. Prevents Alveolar Derecruitment)
Force = Vt
Applies Stress to the Lung
Spring = Rapid Strain
Dashpot = Slow Strain
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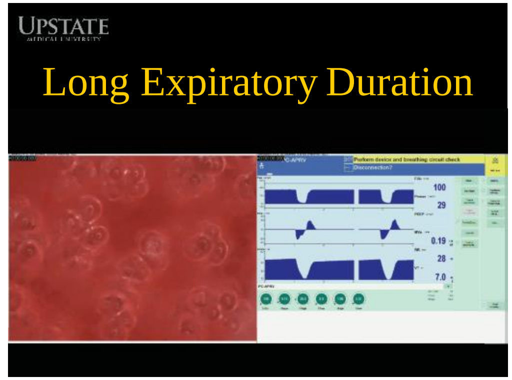
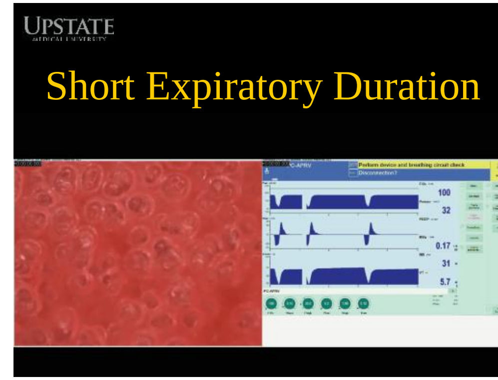

UPSTATE
Long Expiratory Duration


UPSTATE
Short Expiratory Duration

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What Mechanical Breath Strategies use Inspiratory and Expiratory Duration to Protect Alveoli?

- HFOV
- Inverse I:E
- APRV

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Jain et al. Intensive Care Medicine Experimental (2016) 4:11
DOI 10.1186/s40635-016-0085-2

Intensive Care Medicine Experimental

REVIEW

Open Access

he 30-year evolution of airway pressure **release ventilation (APRV)**

Sumeet V. Jain, Michaela Kollisch-Singule, Benjamin Sadowitz, Luke Dombert, Josh Satalin, Penny Andrews, Louis A. Gatto, Gary F. Nieman and Nader M. Habashi

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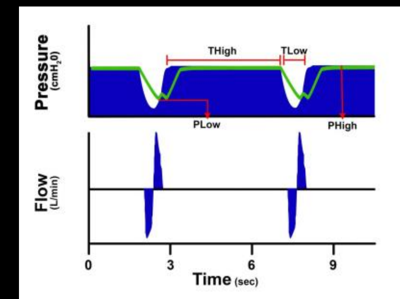
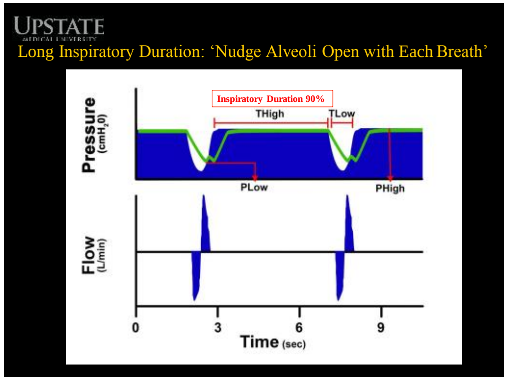
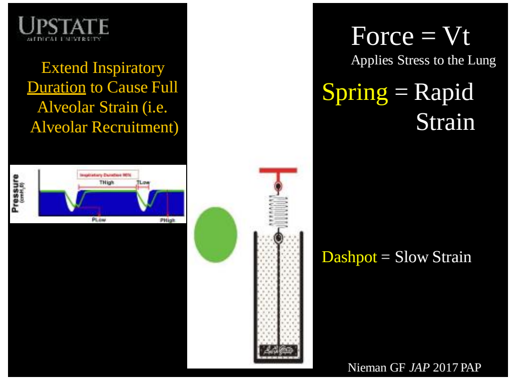
APRV Used as a Tool to Precisely Adjust Durations




UPSTATE
Long Inspiratory Duration: 'Nudge Alveoli Open with Each Breath'
Inspiratory Duration 90%
THigh
TLow
Pressure (cmH2O)
PLow
PHigh
Flow (L/min)
0
3
6
9
Time (sec)


UPSTATE
Extend Inspiratory Duration to Cause Full Alveolar Strain (i.e. Alveolar Recruitment)
Force = Vt
Applies Stress to the Lung
Spring = Rapid Strain
Dashpot = Slow Strain
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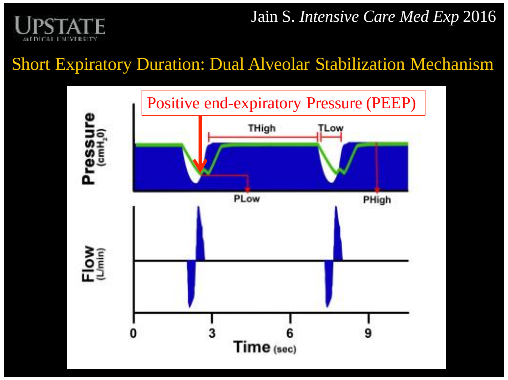
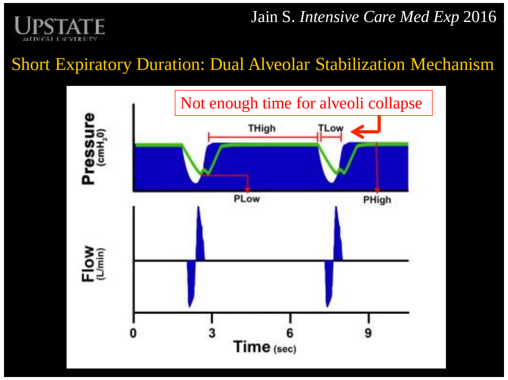
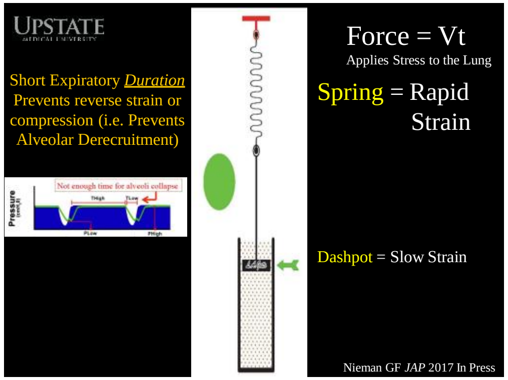
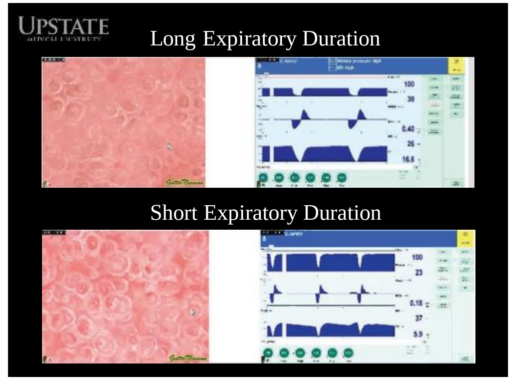
UPSTATE
Extended Inspiratory Duration will Continually Recruit Alveoli
00;00;00;00
00;00;00;00
Inspiratory Pressure Held: 1 sec
Inspiratory Pressure Held: 5 secs
Minimizing Stress-Concentrators
Albert SP et al J Appl Physiol, 2009

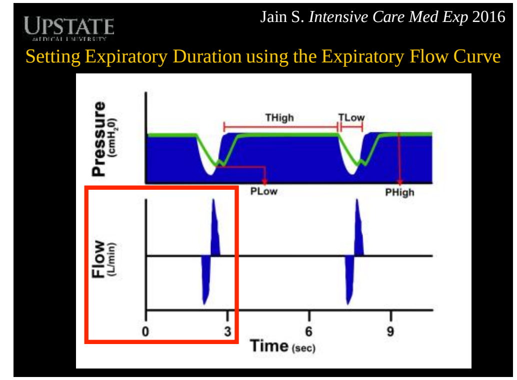

UPSTATE
Extended *Inspiratory Duration* will Continually Recruit Alveoli
00;00;00;00
00;00;00;00
Inspiratory Pressure Held: 1 sec
Inspiratory Pressure Held: 5 secs
Minimizing Stress-Concentrators
Albert SP et al *J Appl Physiol*, 2009

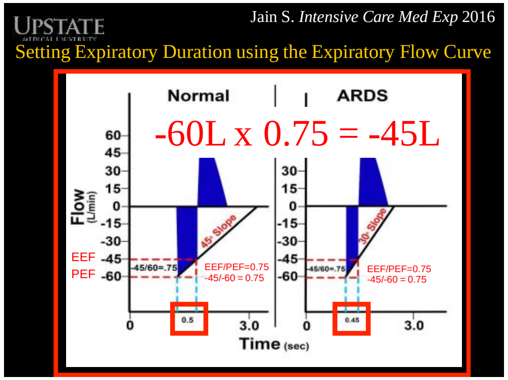

UPSTATE
Jain S. *Intensive Care Med Exp* 2016
Short Expiratory Duration: Dual Alveolar Stabilization Mechanism
Positive end-expiratory Pressure (PEEP)
Pressure (cmH2O)
THigh
TLow
PLow
PHigh
Flow (L/min)
0
3
6
9
Time (sec)

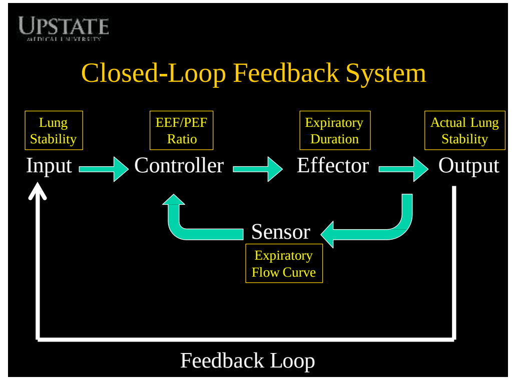

UPSTATE
Jain S. *Intensive Care Med Exp* 2016
Short Expiratory Duration: Dual Alveolar Stabilization Mechanism
Not enough time for alveoli collapse
Pressure (cmH2O)
THigh
TLow
PLow
PHigh
Flow (L/min)
0
3
6
9
Time (sec)

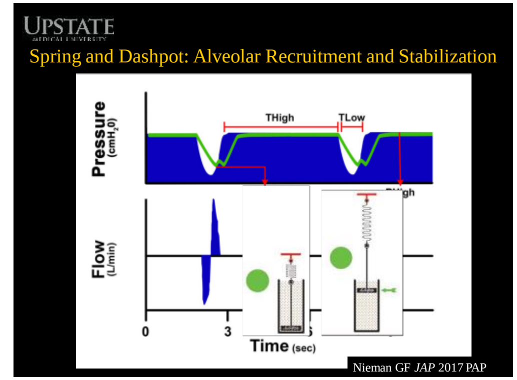

UPSTATE
Short Expiratory Duration Prevents reverse strain or compression (i.e. Prevents Alveolar Derecruitment)
Not enough time for alveoli collapse
Force = Vt
Applies Stress to the Lung
Spring = Rapid Strain
Dashpot = Slow Strain
Nieman GF JAP 2017 In Press

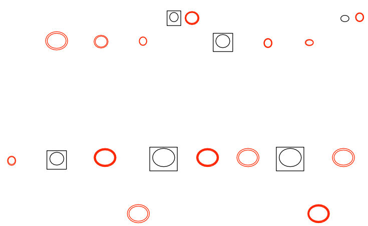

UPSTATE
Long Expiratory Duration
Short Expiratory Duration


UPSTATE
Jain S. Intensive Care Med Exp 2016
Setting Expiratory Duration using the Expiratory Flow Curve
Pressure
THigh
TLow
PLow
PHigh
Flow (L/min)
0
3
6
9
Time (sec)


UPSTATE
Jain S. *Intensive Care Med Exp* 2016
Setting Expiratory Duration using the Expiratory Flow Curve
Normal
ARDS
-60L x 0.75 = -45L
Flow (L/min)
EEF
PEF
45 Slope
30 Slope
EEF/PEF=0.75
-45/-60 = 0.75
Time (sec)


UPSTATE
Closed-Loop Feedback System
Lung Stability
EEF/PEF Ratio
Expiratory Duration
Actual Lung Stability
Input
Controller
Effector
Output
Sensor
Expiratory Flow Curve
Feedback Loop


UPSTATE
Spring and Dashpot: Alveolar Recruitment and Stabilization
Pressure
THigh
TLow
Flow (L/min)
Time (sec)
Nieman GF *JAP* 2017 PAP



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APRV

Personalized, Adaptive, Flow Directed, Duration Dependent, Ventilator Strategy

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Data Supporting our Hypothesis

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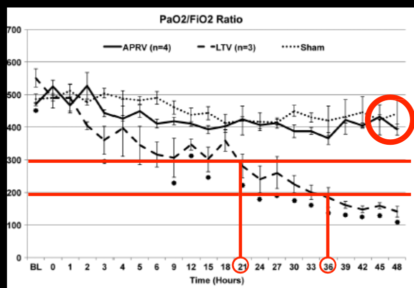
PaO_2/FiO_2 Ratio



Roy et al *Shock* 2013;39:28

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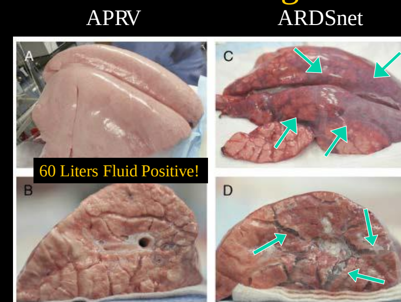
Gross Lung



Roy et al *Shock* 2013;39:28

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Early application of airway pressure release ventilation may reduce mortality in high-risk trauma patients: A systematic review of observational trauma ARDS literature

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Andrews et al, *J Trauma Acute Care Surg 2013;75:635*

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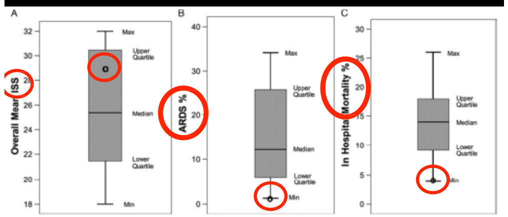
Preemptive APRV in Humans



Andrews et al, *J Trauma Acute Care Surg 2013;75:635*

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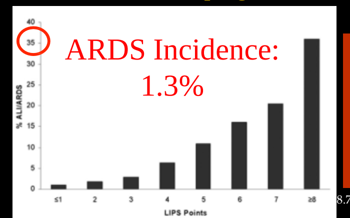
Odds of Developing ARDS



Cartin-Cebel R et al AJRCCM 2009

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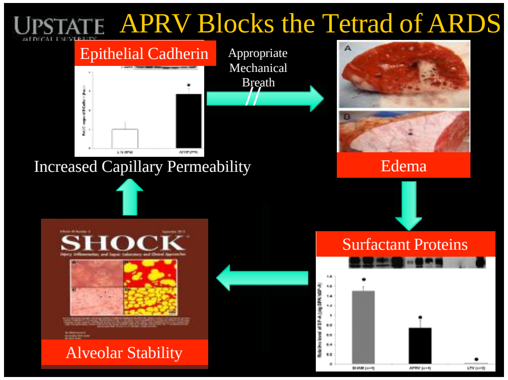
Hypothesis

Properly adjusted Mechanical Ventilation can reduce the severity of all components that comprise the Pathologic Tetrad of ARDS



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Conclusion

APRV can block all 4-components of the Pathologic Tetrad of ARDS

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Summary

- Mechanism of VILI in the Microenvironment
  - Alveolar stress-concentrators
  - Dynamic alveolar strain
  - Alveolar over-distension
    - Secondary to S-C and dynamic strain
- Dynamic Alveolar Physiology
  - Viscoelastic alveolar volume change
- Components of the Mechanical Breath that will Protect the Lung
  - Extended Inspiratory duration
  - Short Expiratory duration

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Conclusion

- Properly set APRV acts like a splint to protect the lung with altered physiology keeping it open until the lung has a chance to 'heal'.
- If we '*Open the Lung and Keep it Open*' or better yet, '*Never Give the Lung a Chance to Collapse*' all of the mechanisms associated with VILI will be significantly reduced or eliminated.

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Can Ventilator Settings be Adjusted to Minimize VILI?

Homogeneous Ventilation

Heterogeneous Ventilation

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"Matching the Mechanical Breath with Dynamic Alveolar Pathophysiology to Reduce VILI"

7th Biennial Midwest Mechanical Ventilation and Critical Care Conference September 29-30, 2017

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