Examples of Respiratory Compromise

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Introduction

- Describe clinical presentation of common subsets of respiratory compromise
- Discuss pathophysiology
- Discuss epidemiology and risk factors for poor outcomes
- Offer examples of predictive models / tools
- Propose gaps on knowledge

Control of breathing and airway protection

- 33 yo male presents to the emergency department with severe lower back pain after an MVA. His evaluation includes normal vitals & basic blood work. His toxicology reveals only benzodiazepine which he is prescribed. There is no evidence of fracture on radiography or CT.
- He is given fentanyl in the ER and the trauma service is called
- He is admitted to the general medical ward for pain control and an MRI
- He is prescribed ATC morphine and prn doses IV for severe / breakthrough pain in addition to NSAIDs.
- Four hours later he is found apneic and pulseless.
- ACLS is performed and he is intubated. The CXR shows a new infiltrate.

Control of breathing and airway protection

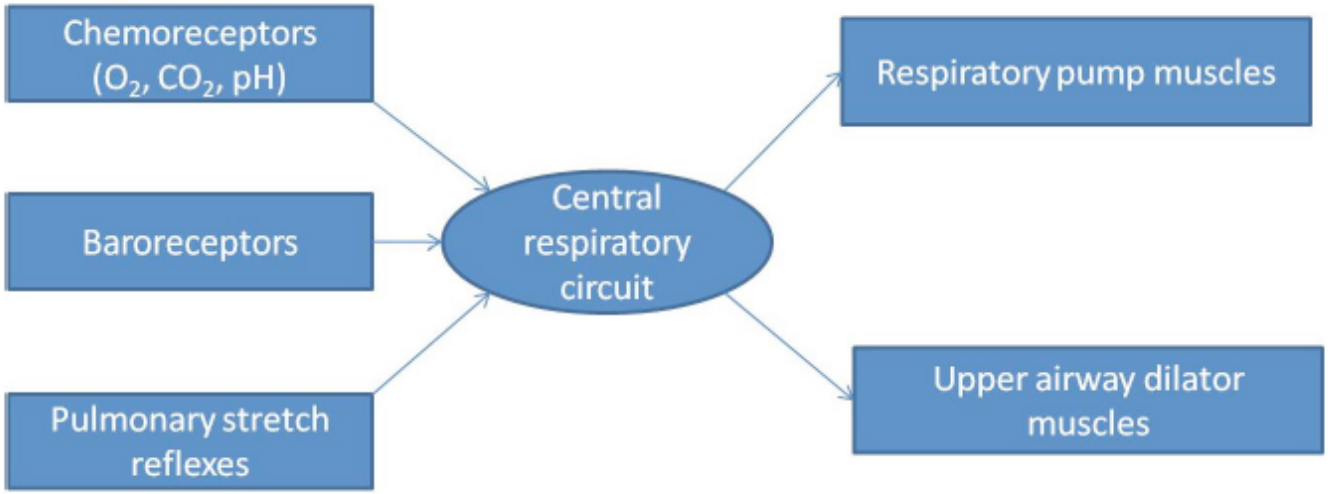
- Hallmarks
  - Central depression of respiratory drive
  - Loss of tone in upper airway
  - Blunting of airway clearance mechanisms
- Results
  - Impaired gas exchange (hypercapnia and hypoxemia)
  - Aspiration of upper pharyngeal contents into lower airways
  - Inability to clear lower airways of debris

→ Respiratory failure → cardiopulmonary arrest → death

Central respiratory depression – Opiates as paradigm

- 1.3 % risk of developing critical respiratory event post-op
- 1 % of those receiving fentanyl experienced adverse event including respiratory depression in ED
- Use of PCA with lock-outs lowers risks to 0.2 – 0.5 %
- Fatal events occur in the setting of inadequate and adequate monitoring

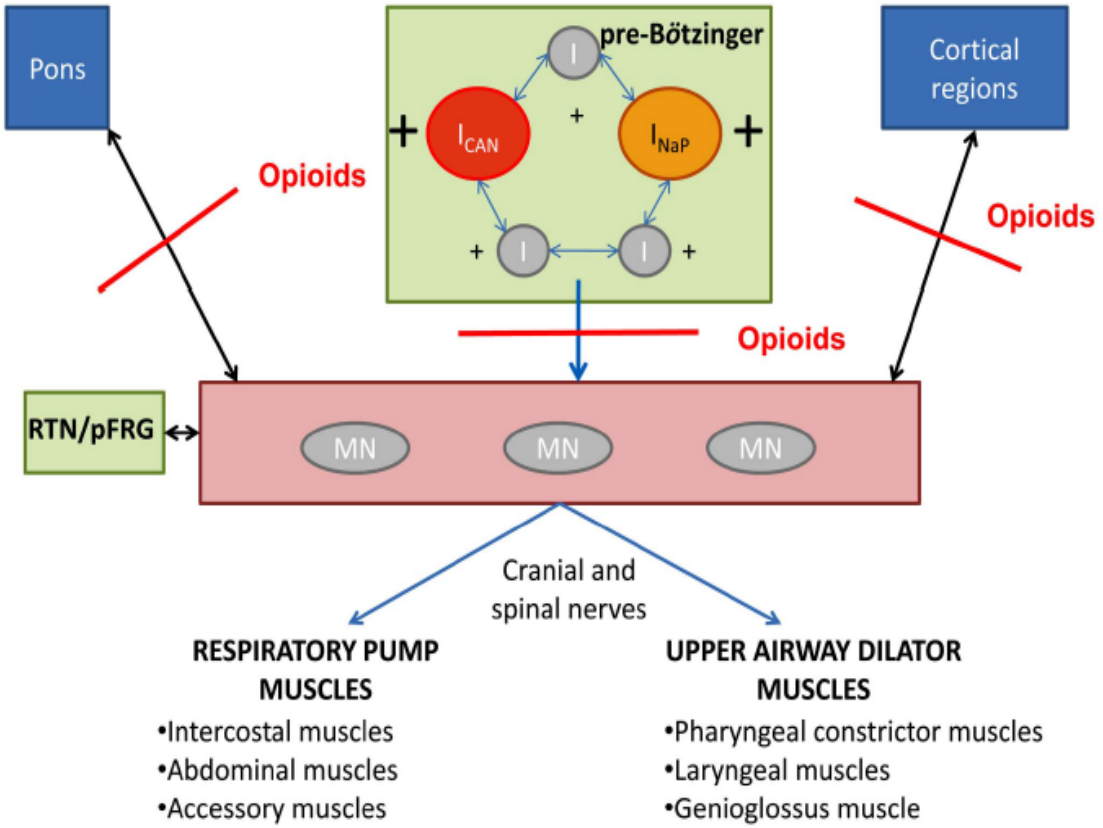
Overview of control of respiration



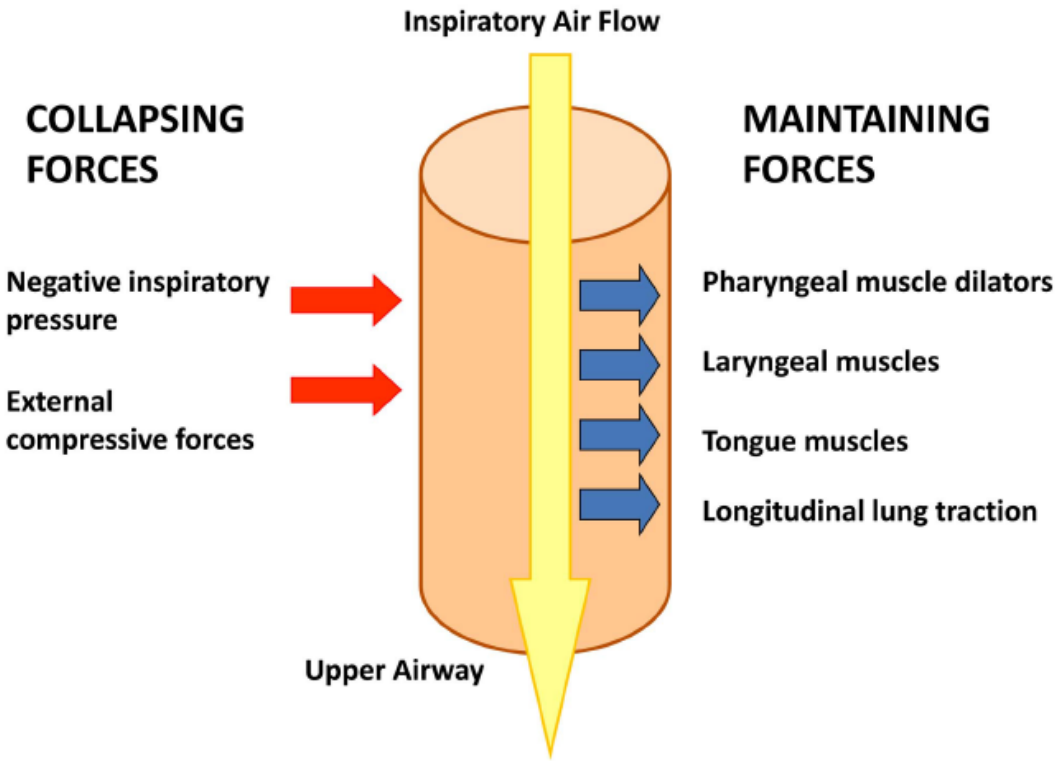
Mechanism of CNS opiate respiratory depression

- MEDULLA: Neurokinin 1 receptors (NK-1 R) expressing neurons in pre-Botinger complex mediate inspiration, inhibited by opiates
- CORTEX: Reduced sensitivity of chemoreceptors to changes in pCO_2 are well described among opiate addicted patients
- PONS: Suppression of acetyl-choline release in medial pontine reticular formation → "sleep-like" state

Mechanisms of central depression



Forces controlling patency of upper airway



Other effects

- Opioid receptors on bronchioles
  - Bronchoconstriction → increase in Raw
- Abdominal and chest wall rigidity
  - Especially at high doses (e.g. Stiff chest in fentanyl boluses)
  - Reduced phrenic nerve and diaphragm activity

  → Reduced Vt

Central depression by opiates: Biological factors

- Age – lower rates of clearance
- Gender – females - up to 25 % higher levels of oxycodone
- Ethnicity – some groups have enhanced clearance (allelic variants in CYP2D6); rapid metabolizers run greater risk of respiratory depression than poor metabolizers
- Co-morbidities – Hepatorenal impairments affect clearance (fentanyl and methadone minimally effected by liver or renal impairment)
- Drug interactions
  - Potentiation: Buprenorphine and opiates or benzos and opiates
  - Opiates and cardiac meds

Opiate induced resp failure: patient characteristics / profile

- Sleep disordered breathing
- Morbid obesity
- Snoring
- Older age
- Opioid naïve
- Post-surgical (esp. upper abdominal, chest wall or upper airway)
- Increased opioid dose need
- Prolonged anesthesia
- Use of additional sedating drugs
- Prior cardio-pulmonary disease, other major organ dysfunction (liver, renal)
- Smoker

Risk factors for respiratory failure / death

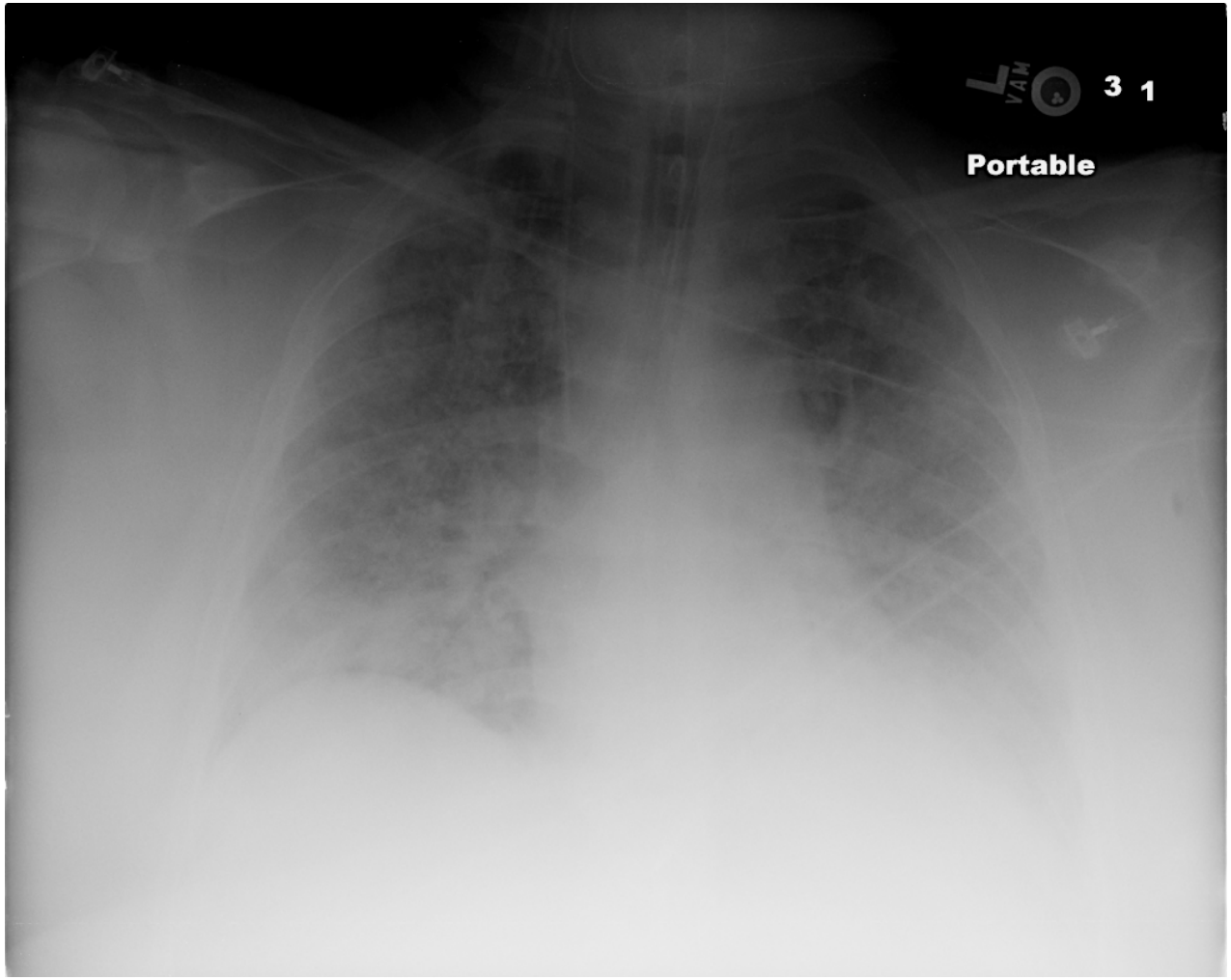
- Upper airway obstruction
- Chronic use of opioids (chronic blunting of chemoreceptors)
- Abnormal metabolism (e.g. mutation in CYP2D6 causing rapid metabolism of codeine to active metabolite)
- Joint Commission (Sentinel event alert, August 2012)
  - 11% Excessive dosing (esp. opioid naïve), drug-drug interactions, adverse reactions
  - 47% medication errors
  - 29% inadequate monitoring

Monitoring for central depression

- High frequency of nursing assessments at outset
  - Level of conscientiousness
  - Vitals
  - Pain scores
- Sudden death can occur despite monitoring
  - Can we identify susceptible individuals up front?
  - Is this more related to aspiration which is more difficult to detect and more common than we believe?
  - How do we monitor outside of ICU / recovery room?
  - Do we need more objective methods of monitoring outside of ICU / PACU?

Acute lung injury / ARDS

- Berlin Definition – JAMA 2012
  - Onset with 1 week
  - Bilateral opacities
  - Not explained by cardiac failure (objective assessment – TTE for example)
  - Poor oxygenation
    - Mild – P/F 200 – 300 on >= PEEP 5
    - Moderate – P/F 100 - 200 on > = PEEP 5
    - Severe – P/F < 100 on > = PEEP 5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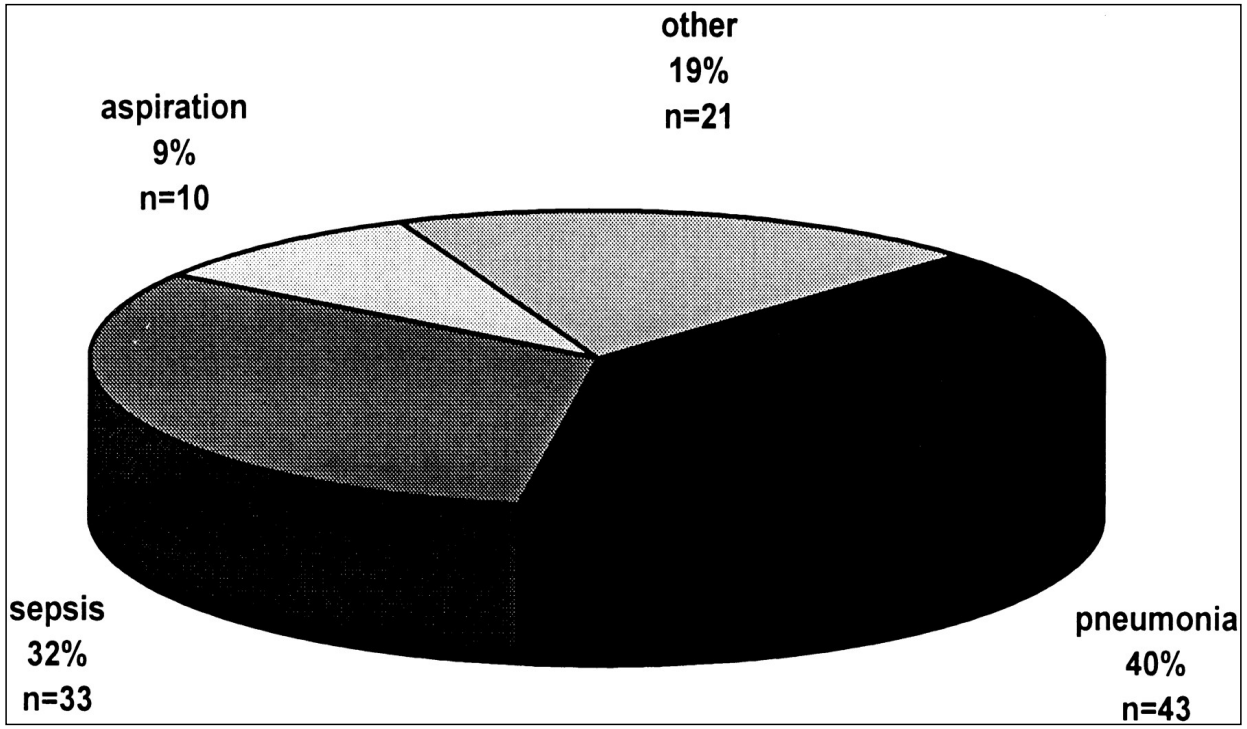
Portable


other
19%
n=21
aspiration
9%
n=10
sepsis
32%
n=33
pneumonia
40%
n=43

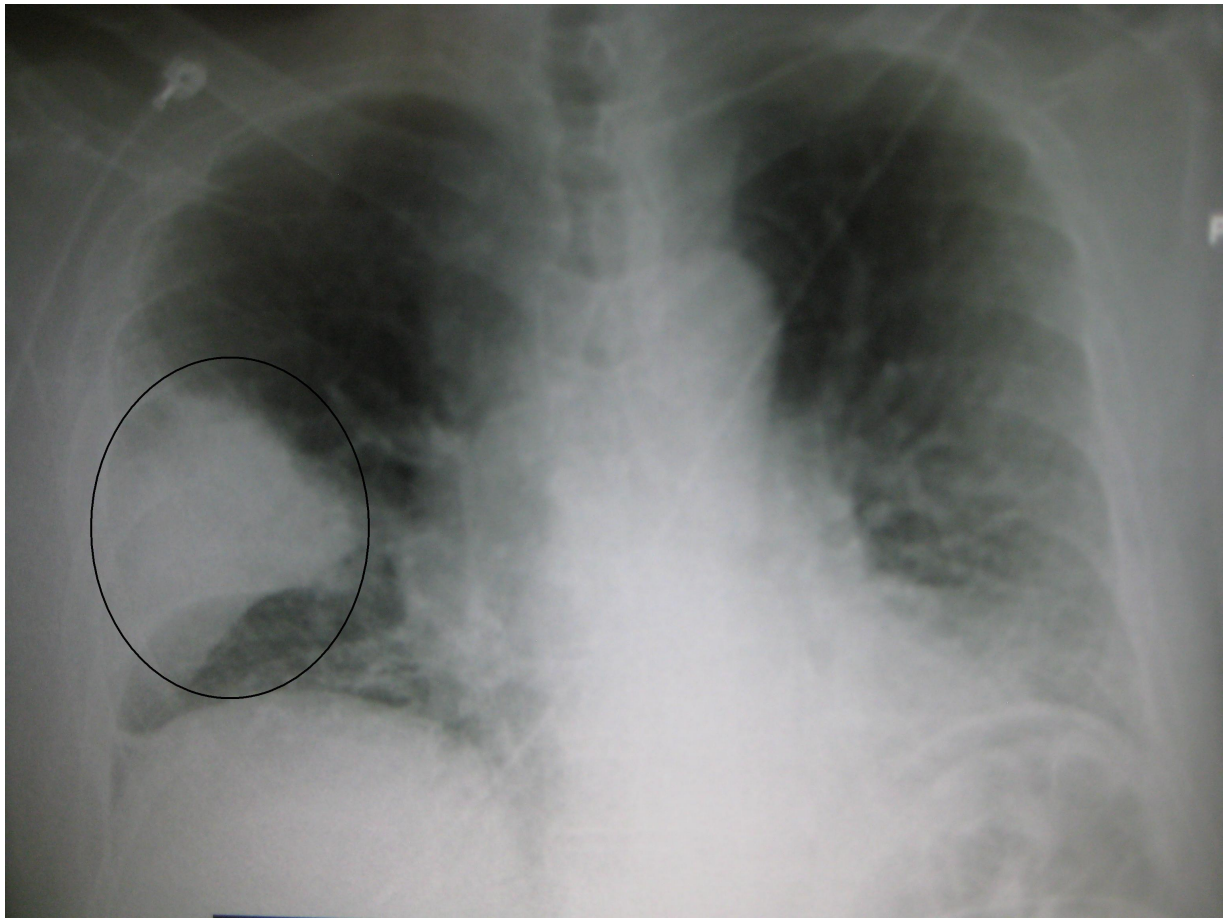
Risks Factors for Mortality in ARDS/ALI

Risk	Coefficient
Age >65	1.98
Cirrhosis	1.75
HIV	2.75
Malignancy	1.76
Transplant	3.67
Sepsis	1.02

Zilberberg, M.D. and Epstein, S.K. Am J Respir Crit Care Med; 1999; 157:1159

Pneumonia as model for Acute lung injury

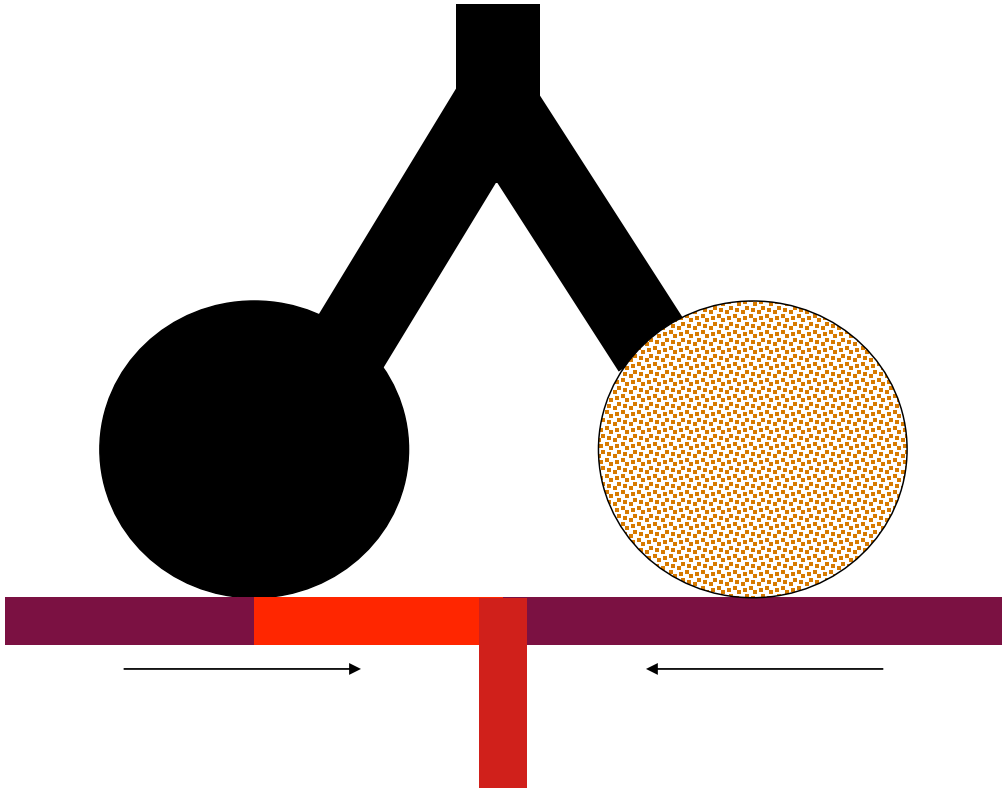
- Comprise large fraction of patients with ARDS
- Some are admitted and progress to insufficiency and failure
- Many tools to predict progression – not perfect



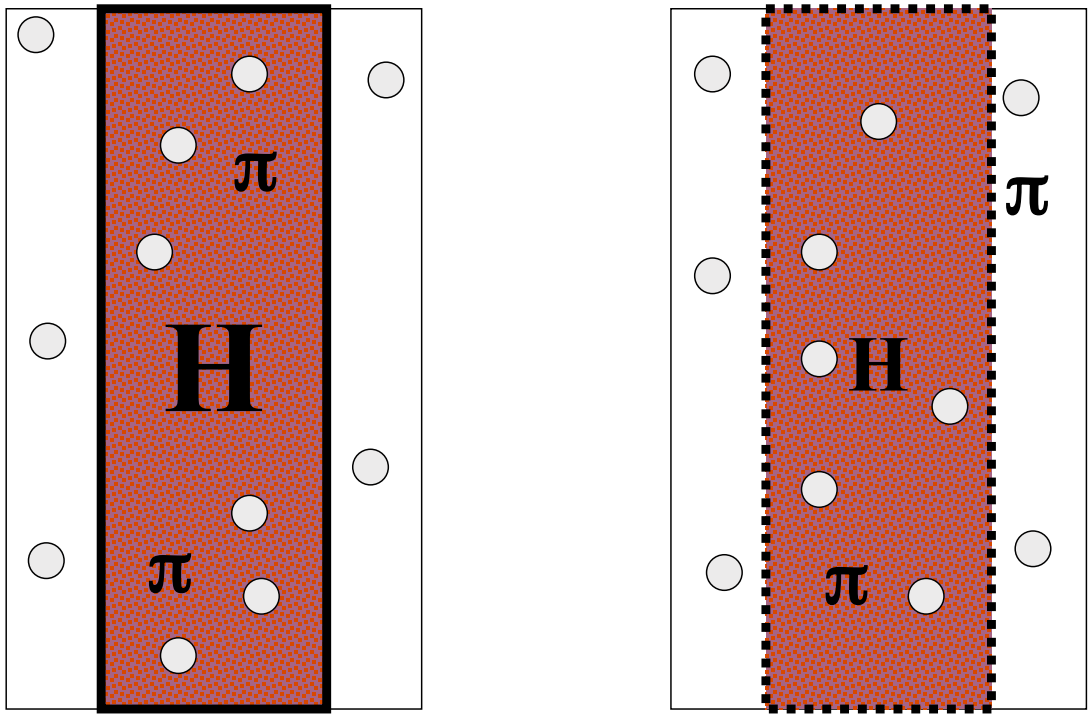
PNA - pathophysiology

- V/Q mismatch
- Airway obstruction – secretions, bronchospasm
  - Increased resistive W.O.B.
- Restrictive physiology – consolidation, effusion, atelectasis
  - Increased elastic W.O.B.
- Diffusion impairment
- Severe multi-lobar PNA –>ARDS
    - Physiological shunt (severe hypoxemia)
    - Severe restrictive physiology / reduced lung compliance (markedly increased WOB)
    - Increased dead-space ventilation (hypercapnia)

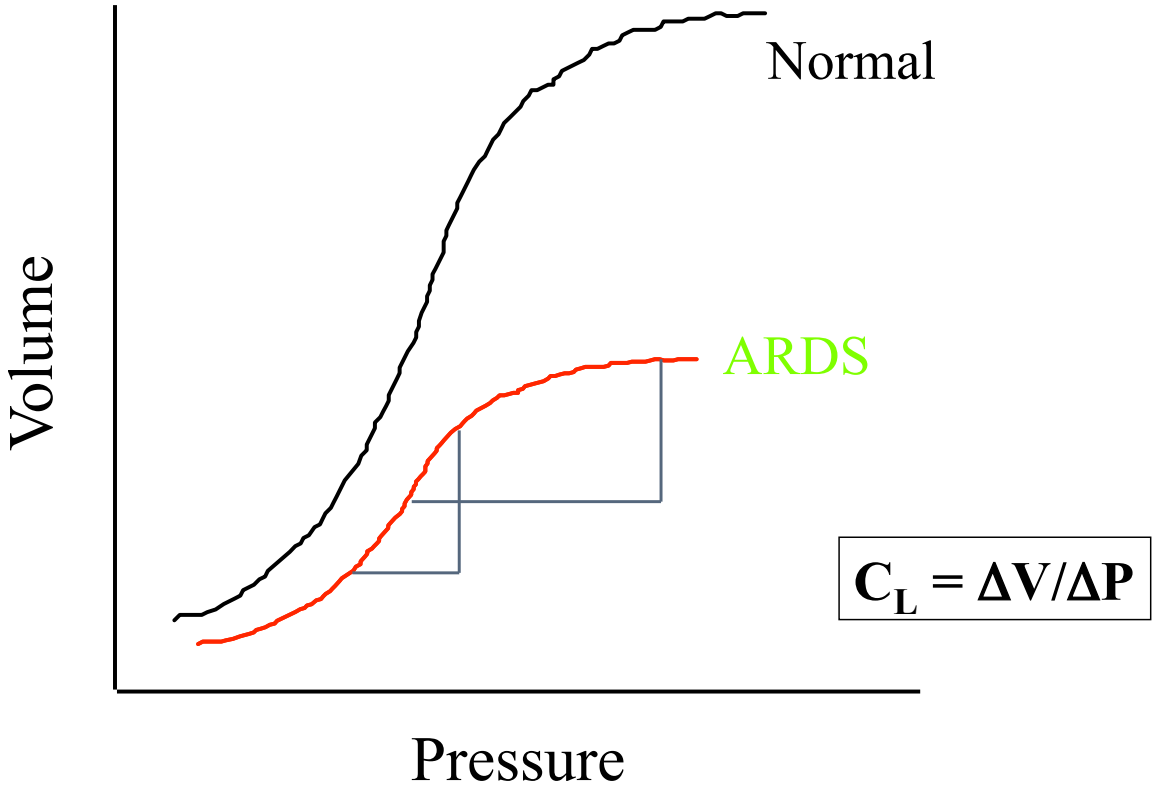
Shunt Physiology in ARDS



Hydrostatic & Non-hydrostatic Pulmonary Edema



Lung Compliance in ARDS



PNA – Progression / stages

- Clinical signs and symptoms
  - Cough
  - Dyspnea
  - Pleuritic chest pain
  - Fever / chills / sweats / hypothermia
  - Headache
  - Malaise
- Progression
  - Systemic Illness
    - Sepsis
    - Severe sepsis / septic shock / ARDS
  - Pulmonary
    - Respiratory insufficiency
    - Respiratory failure
    - Complications: ARDS, empyema, necrotizing pna, abscess, BP fistula, fibrosis, bronchiectasis

CRIT CARE 2012	PSI	CURB 65	CRB-65	CURB	CORB	ATS/IDSA	SMART-COP	SCAP	REA-ICU
MV						X			
Shock	X					X			
Age	X	X	X					X	X
Gender	X								X
Co-morbid	X								X
Mental status	X	X	X	X	X	X	X	X	
HR	X					X	X		X
T	X					X			
RR	X	X	X	X	X	X	X	X	X
BP	X	X	X	X	X	X	X	X	
P / F	X				X	X	X	X	X
pH	X							X	X
infiltrate	X					X		X	X
Na	X								X
Gluc	X								
Urea / Albumin		X (U)		X (U)		X (U)	X (ALB)	X (U)	X (U)
WBC / PLT						X			X (WBC)

Pooled discriminative performance

- Newer rules (ATS/IDSA 2007, SCAP and SMART-COP) better at predicting ICU admission
- High NPV is hallmark, however

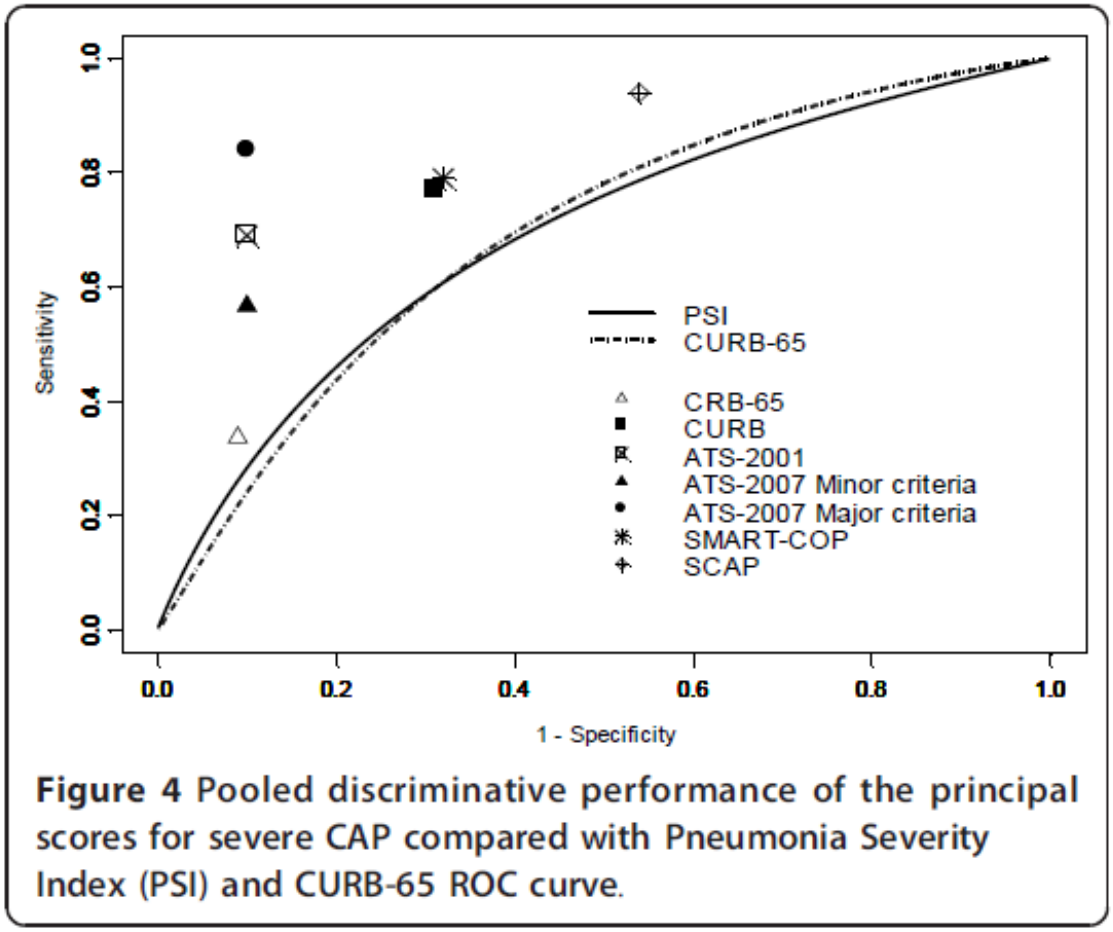


Figure 4 Pooled discriminative performance of the principal scores for severe CAP compared with Pneumonia Severity Index (PSI) and CURB-65 ROC curve.

Marti et al Crit Care 2012

PNA - Summary

- Many prediction rules exist – likely under-utilized?
- Often designed to predict 30 day mortality
  - Prediction of shorter term progression is more useful
  - Newer models focus on shorter term escalation of care as end-point
- Lack PPV needed to confidently identify those for closer monitoring
- High NPV - can identify those with low risk of progression to respiratory insufficiency, respiratory failure, ARDS, severe sepsis, shock
  - Helpful with triage
- Do we need to incorporate biomarkers or more physiologic data?
- Do these rules apply to non-bacterial forms of pna?

Bronchospasm – COPD and Asthma admissions

For Asthma admissions:

- Approximately 500,000 admissions annually
- 1.7 – 2.0 % of all ICU admissions
  - Approximately 30 % require intubation
  - Mortality rate once intubated ranges between 6 and 42%
  - Mortality much higher in intubated patients (to be avoided)
- 5000 deaths annually

Mortality risk factors for patients with SA

- Prior intubation
- Frequent hospitalizations
- Prior ICU admission

- Predicting mortality
  - **Less than 50 %** of asthma mortalities possess these features

  →Risk stratification difficult

  →Few formal tools exist that predict in-hospital deterioration

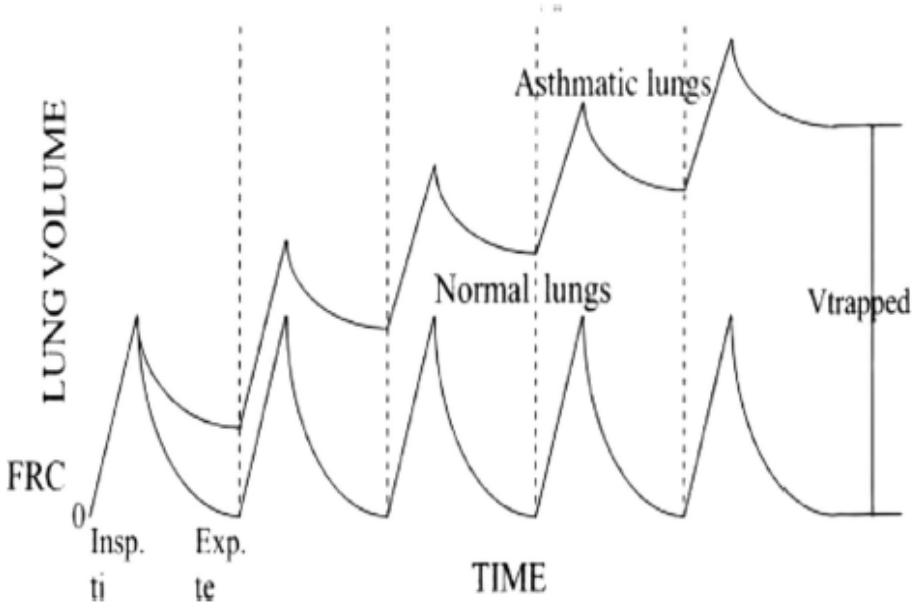
Pathophysiology of acute severe asthma

- Three hallmarks
  - Inflammation
  - Bronchoconstriction
  - Mucus production
- Results in:
  - Increased airway resistance
    → Increased resistive WOB
  - Air trapping (unable to empty to baseline FRC)
    → Dynamic hyperinflation
    → Increased elastic recoil
    → Increased elastic WOB
    Reduced Vt
    →Increased dead-space → hypercapnia
  - Mucus plugging of small airways
    → V/Q mismatch → hypoxemia

Dynamic hyperinflation

With each respiratory effort:

- More air is trapped and there is increased end exp volume
- Vt is smaller → increased dead-space ventilation
- The elastic recoil of the lung is increased
- *Also increase in intra-thoracic pressures =* ***Auto-PEEP***



Extra-pulmonary consequences

- Lactic acidosis
  - Increased WOB (resistive and elastic)
  - Anaerobic metabolism in the setting of hypoxemia
  - Side-effect of high doses of SABA
- Reduced Cardiac output, hypotension

  Dynamic hyperinflation → auto-PEEP (increased intra-thoracic pressures)
  - Reduce venous return to RV
  - Rapid RV filling during exaggerated inspiratory efforts → septal displacement into LV, impaired LV filling / reduced SV
  - Increased RV afterload due to auto-PEEP → worsening of IV septal displacement
  - Clinical manifestation = Pulsus pardoxus
    - Exaggerated reduction in SBP during inspiration (> 12 – 15 mmHg)
- Myocardial ischemia
  - Increased WOB
  - Rapid HR due to SABA, reduced SV, anxiety
  - Hypotension

TABLE 3. Classifying Severity of Asthma Exacerbations

Variable	Severe Exacerbation*	Imminent Respiratory Arrest
Symptom		
Dyspnea	At rest	Unable to speak
Speech	Single words, no phrases	Lethargic, confused,
Alertness	Agitated	Obtunded
Signs		
Respiratory rate	>30/min	<10 breaths/min
Heart rate	>120/min	<60/min
Pulsus paradoxus	>25 mm Hg	Normal/low
Use of accessory muscles	Evident	Paradoxical
Wheeze	Present–loud	"Silent chest"
Functional assessment		
PEF	<40% predicted	<25% predicted
paO_2	<60 mm Hg	N/A
$paCO_2$	>42–45 mm Hg	N/A
SaO_2	<91%	N/A

NHBLI, Guidelines for the diagnosis and management of asthma

TABLE 2. Risk Factors for Death From Asthma

Asthma History
Previous severe exacerbation (intubation or ICU admission)
Two or more hospitalizations in last year
Three or more emergency department visits in last year
Hospitalization or emergency department visit within past month
Greater than 2 canisters of short-acting beta agonist per month
Difficulty perceiving asthma symptoms or severity of exacerbations
Other risk factors: lack of action plan, sensitivity to alternaria
Previous severe exacerbation (intubation or ICU admission)
Two or more hospitalizations in last year
Social History
Low socioeconomic status
Illicit drug use
Major psychosocial problems
Inner-city residence
Comorbidities
Cardiovascular disease
Other chronic lung disease
Chronic psychiatric disease

NHBLI, Guidelines for the diagnosis and management of asthma

Evaluation

- History
- HR, RR, Pulse
- Peak flow, FEV1
- Pulsus paradoxus
- Oxygen saturation
- ABG
- Assessment of breathing pattern
- Assessment of volume status
- Assessment of mental status
- Response to initial therapy

Asthma exacerbations - Summary

- Risk factors for poor outcomes exist but are inconsistently present in those who deteriorate / die
- Extra-pulmonary manifestations suggest poor outcomes
- Deterioration can be sudden / rapid
- Mechanical ventilation of patients with asthma adds to their risk
- Should a formal tool for be developed to predict decline?
- Could enhanced monitoring of these patients impact mortality / outcomes?

Pulmonary embolus

- Cardiovascular and respiratory deterioration possible
- In those without overt hemodynamic instability in can be difficult to know who is “sick”
- Management / monitoring of the hemodynamically stable patient is not straightforward

The PE story we all have heard

- 70 yo male with a h/o HTN and COPD presents to the ED with pleuritic chest pain and dyspnea for two days.
- P105, BP 110/65, RR 22 O2 sat 92% r/a, Afebrile
- No adventitious sounds on lung exam, heart exam tachy, extremities cool with no edema
- Trop-I 0.5 → ?, EKG – sinus tach, inv T-waves across precordium
- CTA – RUL lobar embolus; IV flattening
- He is admitted to a monitored bed
- TTE – mild RV HK with RA and RV enlargement; IV septal flattening
  - A second TTE on HD # 2 is unchanged
- He is placed on LMWH immediately and given Coumadin on HD #2
- Discharged with 4 days of LMWH on HD #2
- Within 12 hours he is brought back to the hospital by EMS after a PEA arrest and expires in the ED

Epidemiology

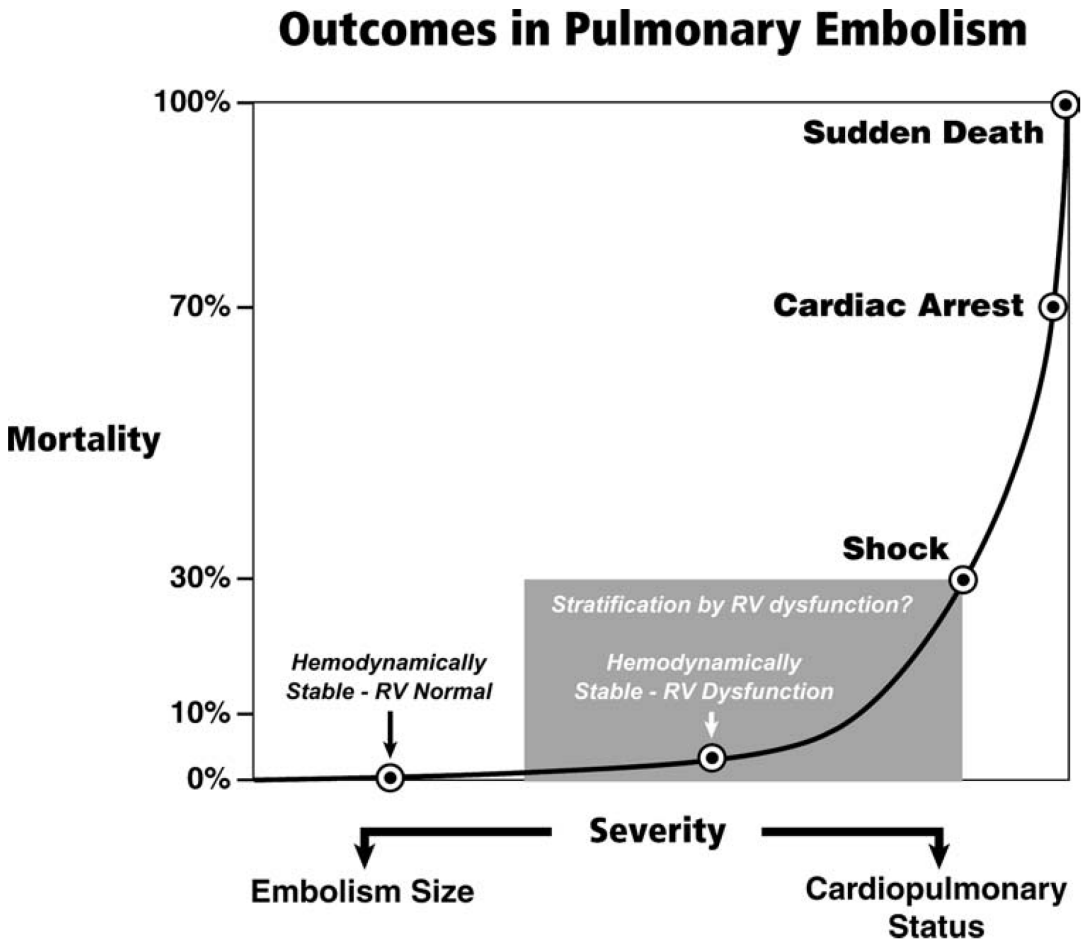
- 600,000 PE's per year in the US
- Accounts for 100,000 to 200,000 deaths
- Mortality rates:
  - 13.0 - 17.5 % at 3 months across all severities
- Most deaths within 60-90 minutes

Recognized Groups by Risk

- High risk (Massive) - hemodynamic compromise: 22%
  - In **past**,
    - Massive used to describe angiographic score for occlusion
    - V/Q obstruction score (Miller Index)
  - 35 – 75% mortality
- Intermediate risk (Sub-massive) = RV dysfunction, no hemodynamic compromise: 31%
  - 5 – 25% mortality
  - Difficult to distinguish clinically from Low risk
- Low risk PE: 47%
  - Often asymptomatic
  - Incidental finding; small clots in distal vessels
  - 1 – 4 % short term mortality

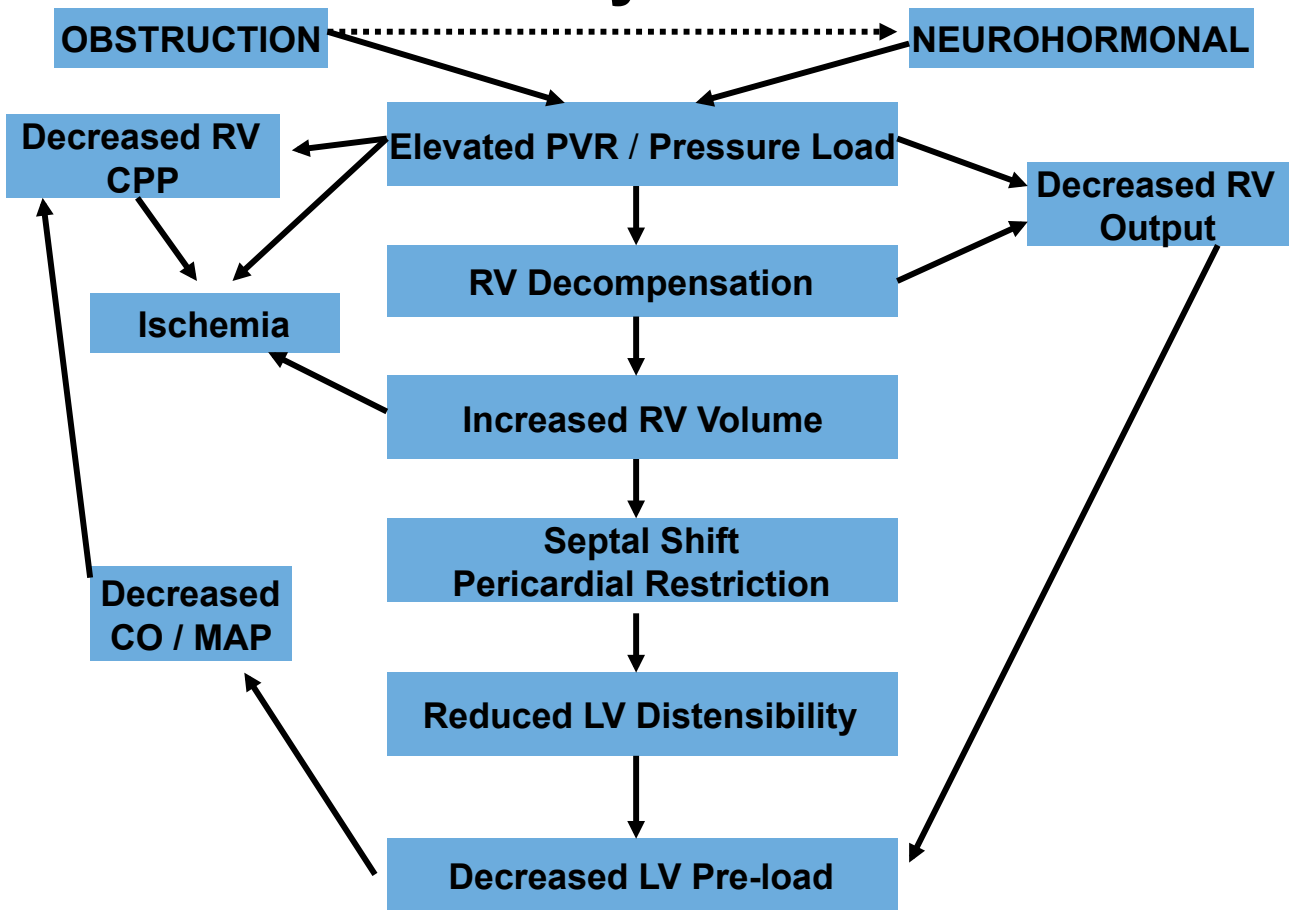
- Major PE = Intermediate and High risk PE

Grifoni et al; Circulation, vol 101, 2000; ICOPER, Lancet 1999; Circulation 2011 v123



Wood, Chest 121(3), 2002

Hemodynamics



Wood, Chest 121(3), 2002

IMPAIRED GAS EXCHANGE

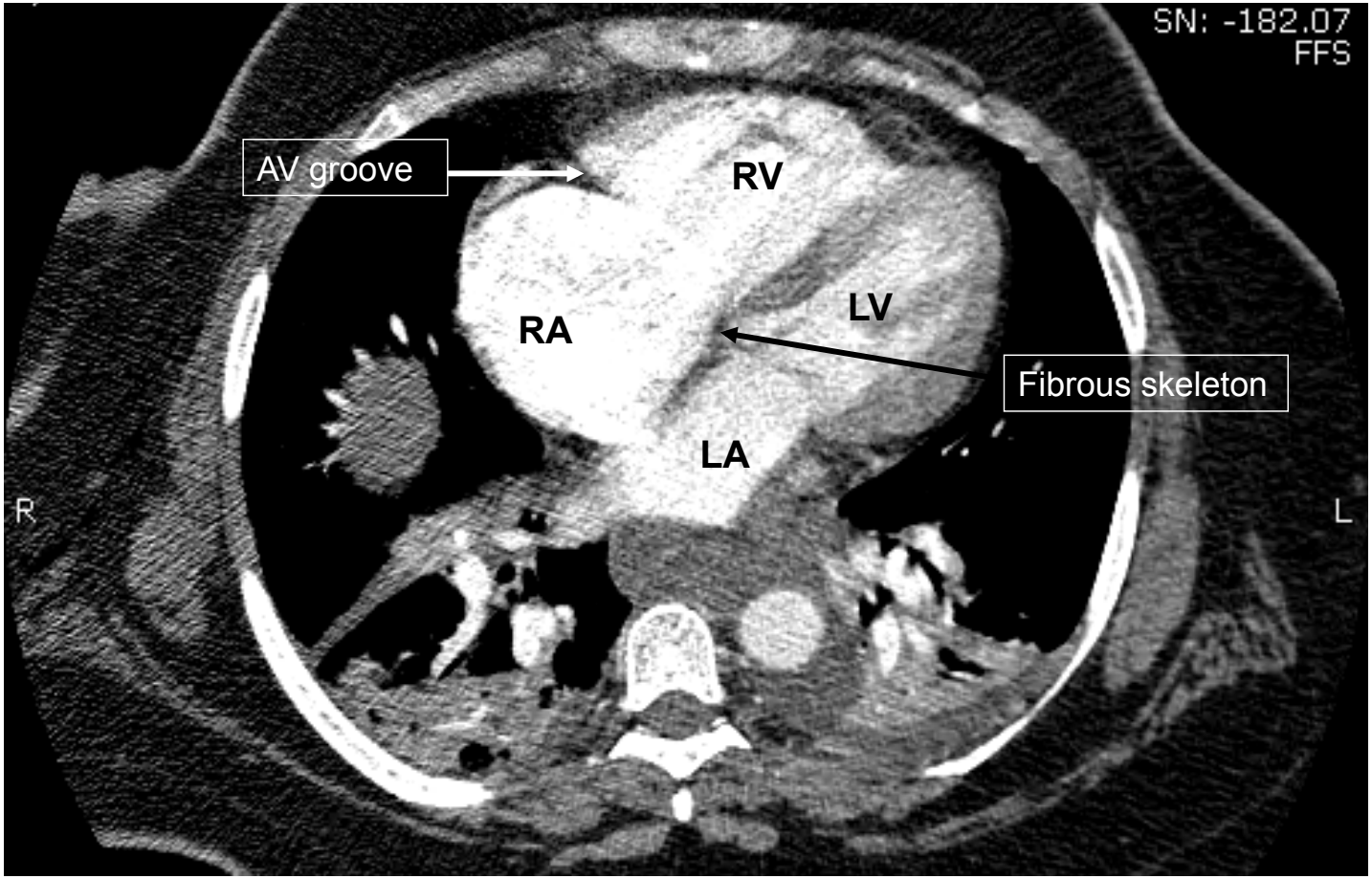
- **V / Q mismatch**
- **Reduced mixed-venous saturation**
- **Impaired diffusion**
- Right – to – left shunt
- Dead space ventilation → hypercapnia?

- Hypoxia adds to increases in PVR

Markers used to assess severity

- **Vital signs:** BP, HR, (RR)
- **Troponin** released in response to low CPP & myocardial injury
  - CPP = MAP – RV intra-cavitary pressure
  - Others = HFABP
- **Oxygen saturation**
- **Co-morbidities**
- **Clot burden:** Especially co-existing DVT
- RV strain:
  - **BNP** released in response to RV pressure load / dilation
  - **TTE**
  - **EKG**
  - **CTA**

--> Ideally we want to detect deterioration prior to drop in BP


SN: -182.07
FFS
AV groove
RV
LV
RA
Fibrous skeleton
LA
R
L

PE Severity Index (PESI)

- Weighted variables (11)
- Easy to obtain

PESI Classes & Mortality

Class	Points	Mortality (30 day)
I	0 - 65	0 – 1.6
II	66 - 85	1.7 – 3.5
III	86 - 105	3.2 – 7.1
IV	106 - 125	4.0 – 11.4
V	> 125	10 – 24.5

→ Prospectively validated
→ Elevated risk possible w/out hemodynamic compromise
→ Most helpful for triage decisions (Low risk = I & II; High risk = III, IV and V)

Table 1. Original and Simplified Pulmonary Embolism Severity Index (PESI)

Variable	Score: Original PESI[a]	Score: Simplified PESI[b]
Age >80 y	Age in years	1
Male sex	+10	
History of cancer	+30	1
History of heart failure	+10	1[c]
History of chronic lung disease	+10	
Pulse ≥110 beats/min	+20	1
Systolic blood pressure <100 mm Hg	+30	1
Respiratory rate ≥30 breaths/min	+20	
Temperature <36°C	+20	
Altered mental status	+60	
Arterial oxyhemoglobin saturation level <90%	+20	1

Simplified PESI (SPESI)

- Predicts 30 Day Mortality
- 11 variables to 6

SPESI
Score of 0 = Low risk → 1.1%
Score 1 or greater = High risk → 8.9%

PESI
Low risk → 2.1%
High risk → 14%

Jimenez et al, Arch Int Med 2010

ROC curves of SPESI and PESI (30 day mortality)

- SPESI has greater sensitivity (96 v. 88)
- PESI and SPESI have similar NPV (97 v. 99)
- PESI and SPESI have similar PPV (10.9 v. 10.9)

- SPESI has similar operating characteristics yet is easier to use

- Does not tell us about in-hospital decline

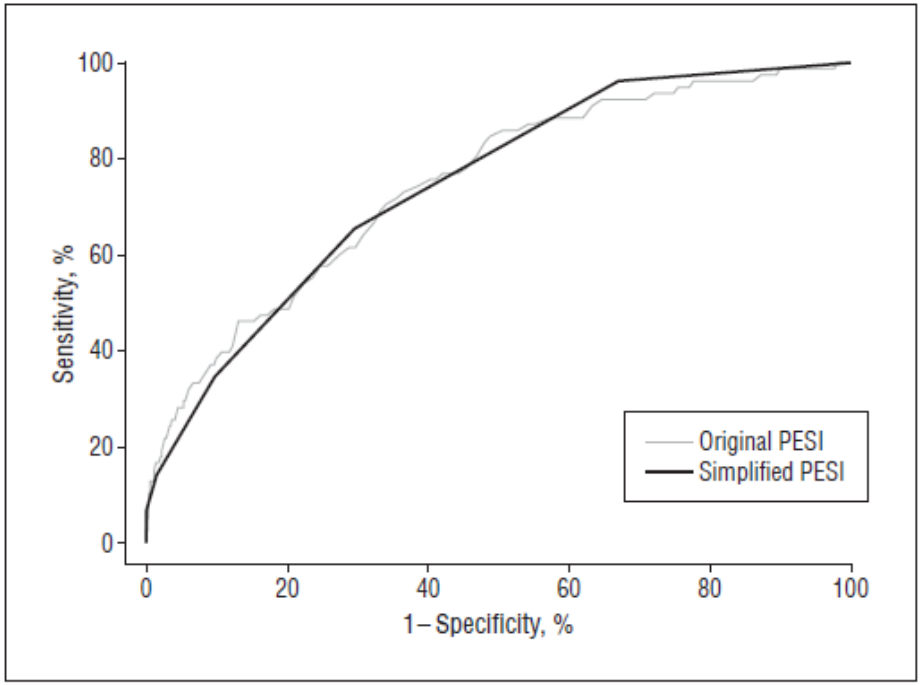


Figure. Receiver operating characteristic curves for 30-day mortality for the original and the simplified Pulmonary Embolism Severity Index (PESI) in this study's derivation cohort.

Jimenez et al, Arch Int Med 2010

PE Risk Score: Identification of Intermediate-risk patients with acute symptomatic PE

Goal: Identify normotensive patients at higher risk for complications (consideration of aggressive therapy?)

Predictor	Points
SBP 90 – 100	2
Elevated Troponin	2
RVD (TTE or CTA*)	2
HR > 110	1

Stage	Points	30 day**
I	0 - 2	4.2 %
II	3 - 4	10.8 %
III	> 4	29.2 %

*PROTECT criteria for CTA

**Cumulative incidence of 30 Day PE related complications (PE related death, recurrent PE, hemodynamic collapse, mechanical ventilation)

Bova et al Eur Resp J v44 2014

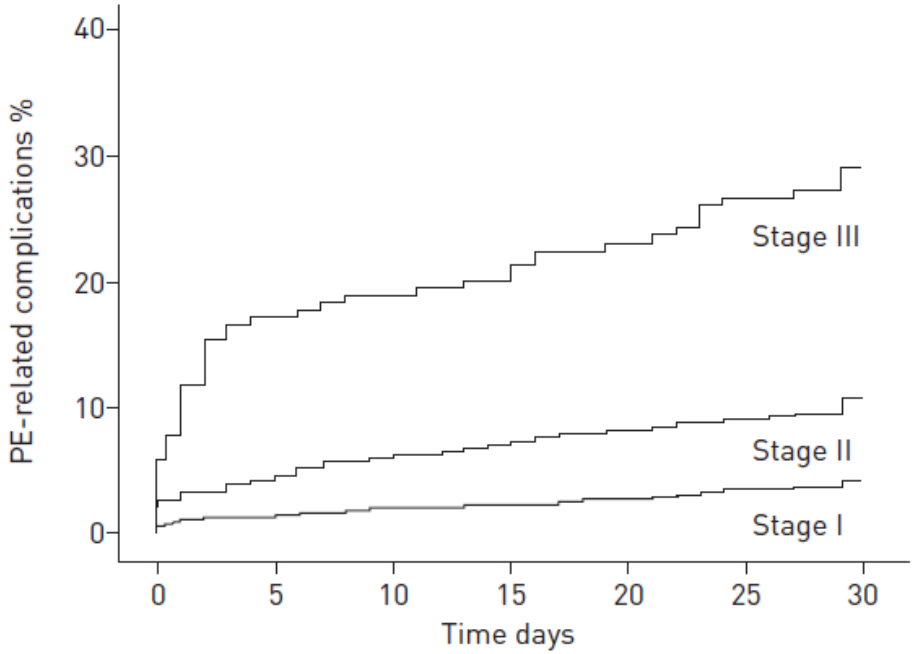
PE Risk Score: Identification of Intermediate-risk patients with acute symptomatic PE

30 day cumulative complication rate for symptomatic PE stratified by stage

Stage	In Hosp	30 day**	30 day mortality
I	**3.6**	4.2	1.7
II	**9.7**	10.8	5.0
III	**28.0**	29.2	15.5

In-hospital events contribute greatly to events at 30 days

Bova et al Eur Resp J v44 2014



Did not account for bleeding risk or for thrombotic burden (i.e. presence of DVT)

PE predictors of poor outcome / clinical deterioration

- Validated models / scoring systems exist
- Models have good NPV but poor PPV so, by themselves, can not efficiently inform decisions about aggressive therapy or enhanced monitoring
- Models allow us to classify patients as low risk with reasonable certainty
  - Allows outpatient management of PE
- Models often not applicable to the in-hospital setting (outcomes at 30 days)
- PE risk score (Bova et al, Eur Resp J 2014) alludes to in-hospital events but requires prospective validation for this end-point

Afferent inputs from chemo receptors, stretch receptors and baroreceptors

NTS – nucleus tractus solitarus – relays info on pO2 from carotid sinus
RTN – retrotrapezoid nucleus – main site of cerebral chemoreception
MRN – Medullary raphe nucleus – senses changes in pH and pCO2