

Respiratory Management in RyR1 Myopathy

Oscar Henry Mayer, MD
Medical Director, Pulmonary Function Testing Laboratory
Division of Pediatric Pulmonology
The Children's Hospital of Philadelphia

Sunday, June 24, 2017



Outline

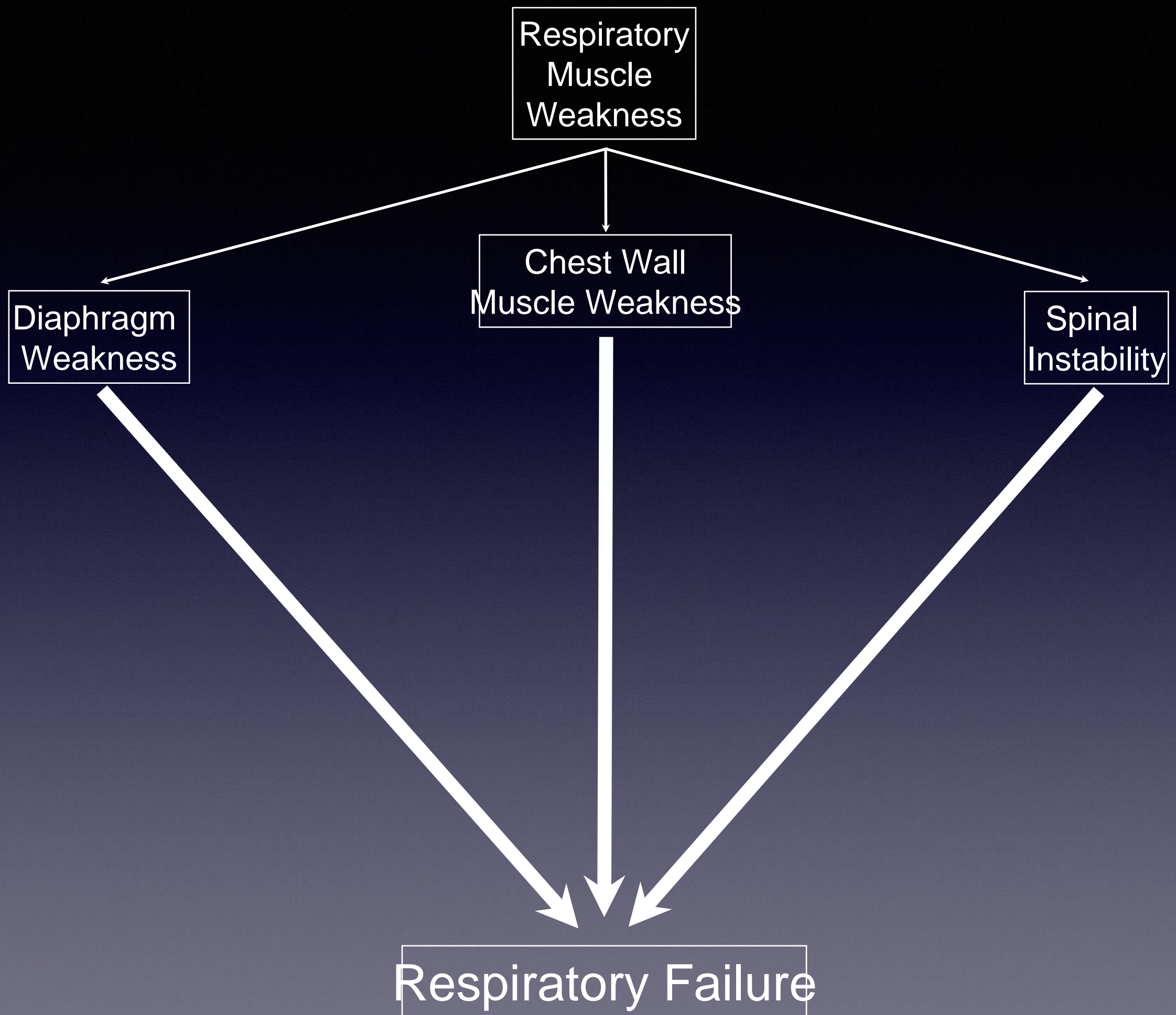
- Progression of Respiratory Disease
- “Timeline” of progression
- Treatment Options

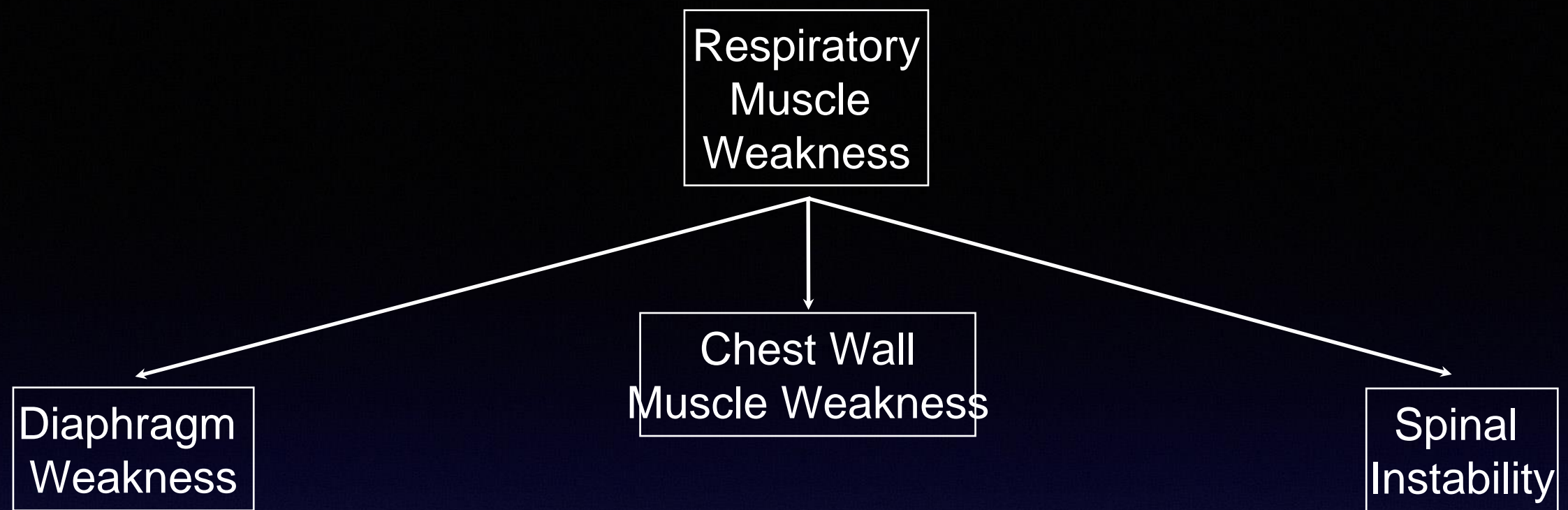
Progression of Disease

Respiratory
Muscle
Weakness

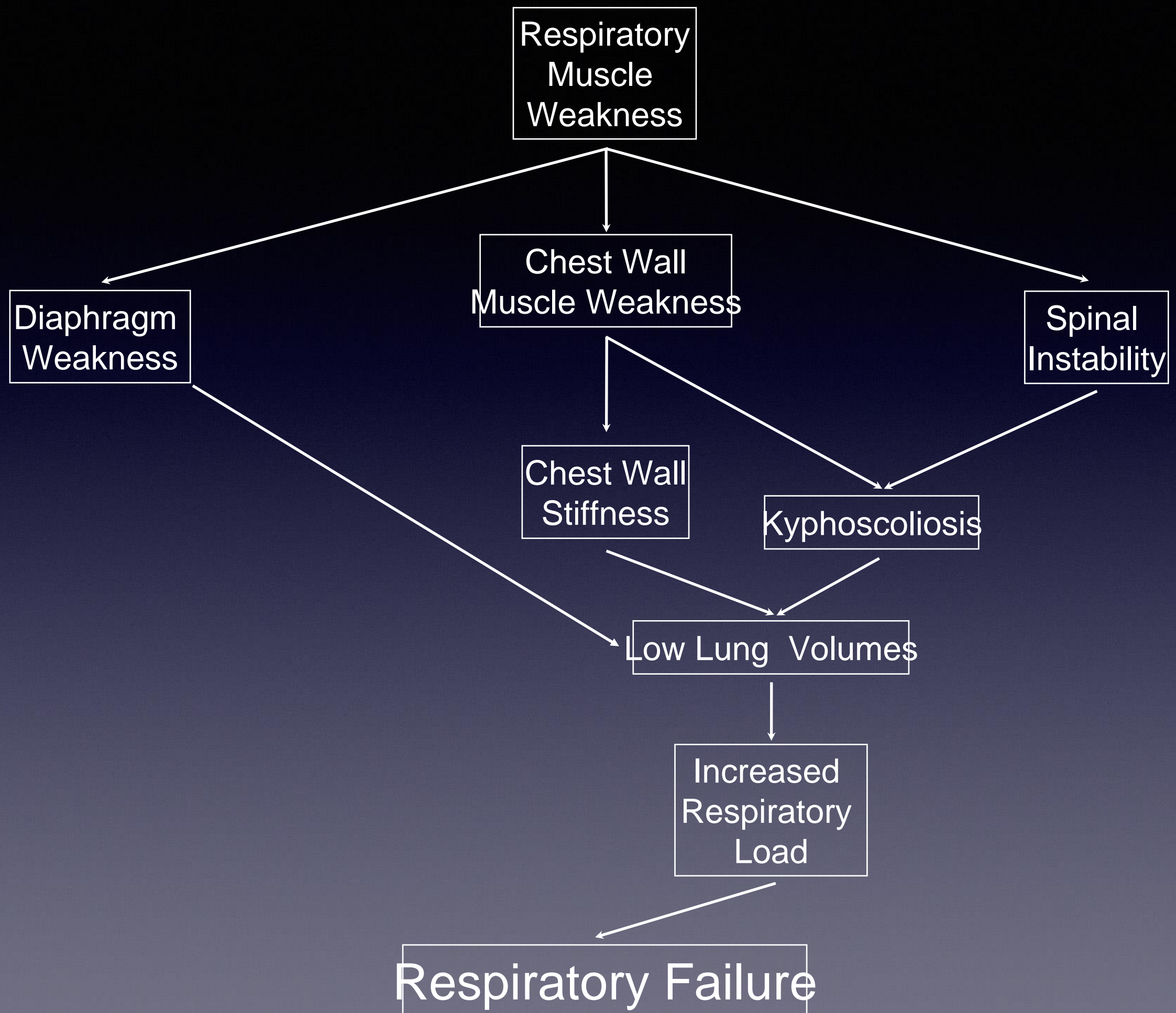


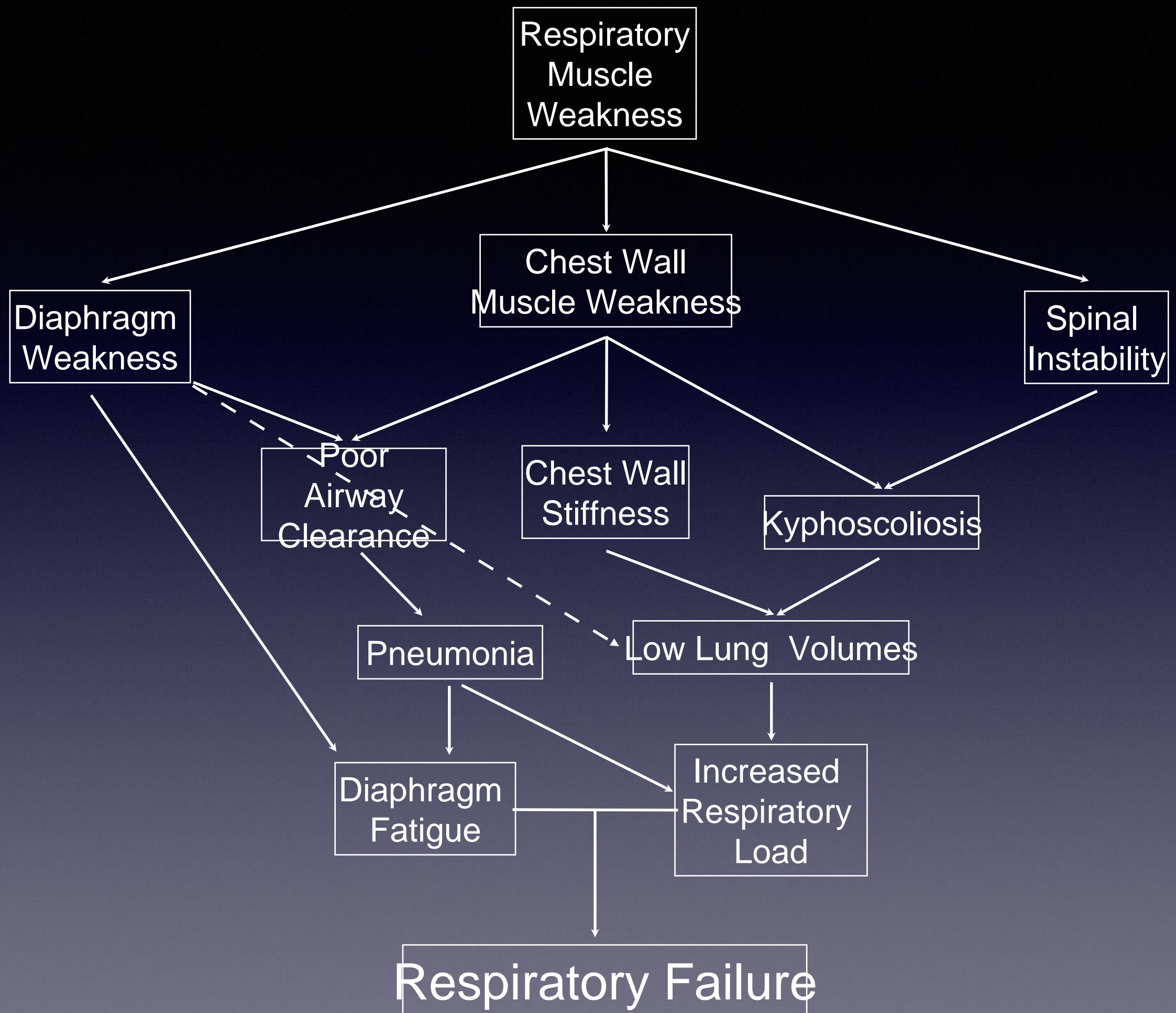
Respiratory Failure



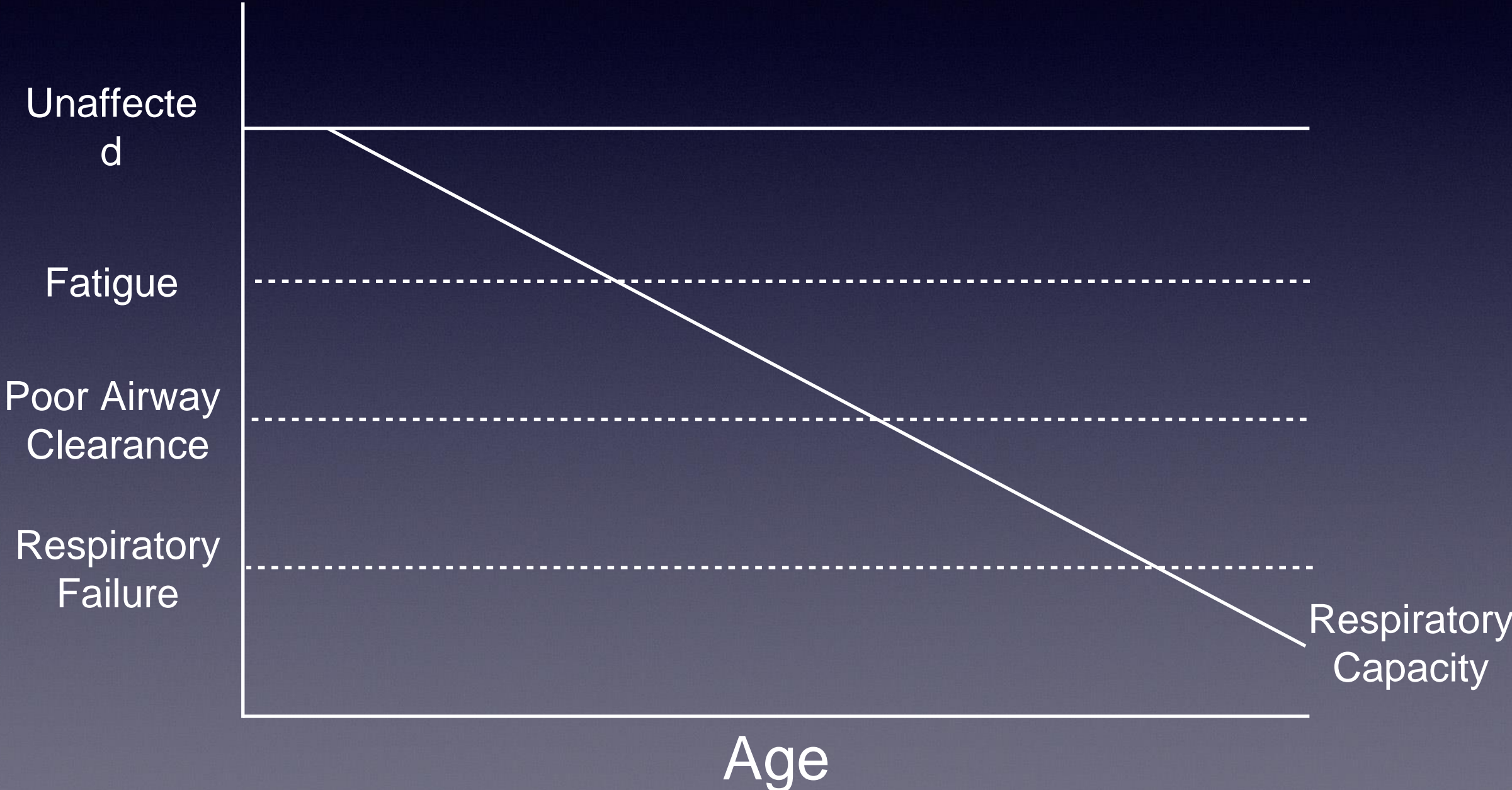


Respiratory Failure

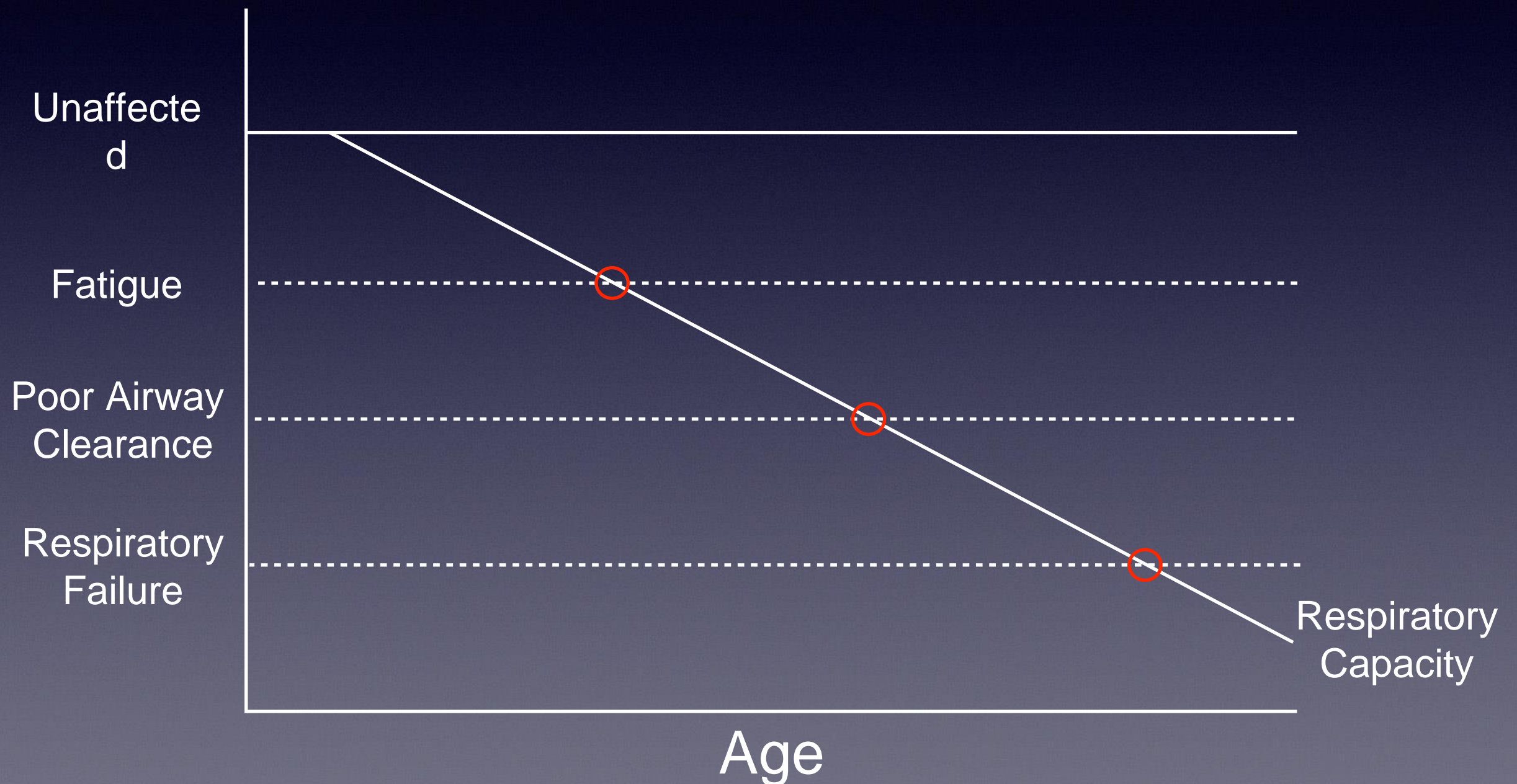




Progression of Disease



Progression of Disease



Assisted Airway Clearance

Coughing

- Inspiratory
 - Deep breath to get air beyond secretions
 - Stretch expiratory muscles
- Compressive - increased pressure
 - Exhalation against closed glottis
- Expulsive - mobilization
 - Rapid expiratory flow (> 270 L/m)

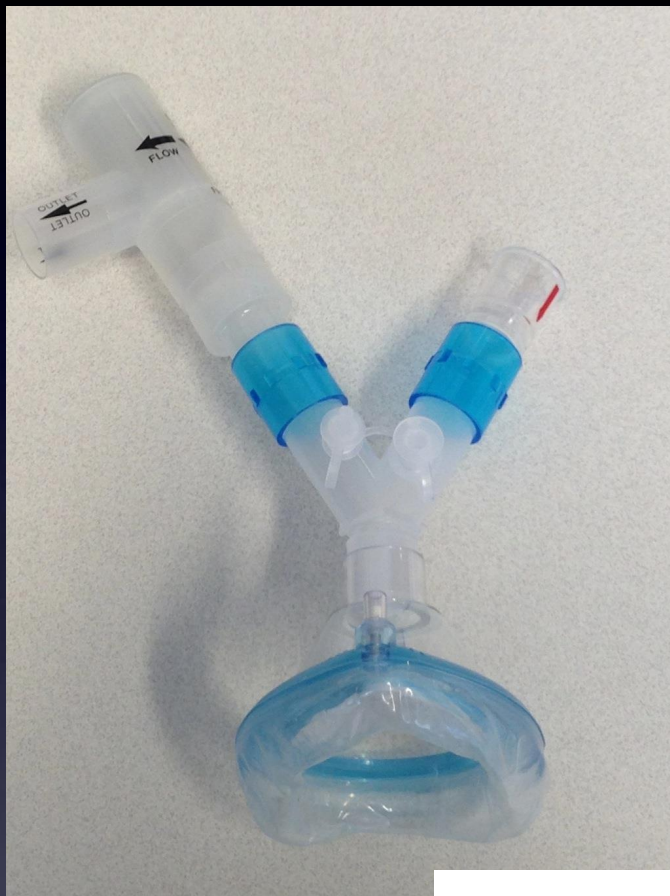
Support Weak Cough

- Inspiratory Assistance
- Expiratory Assistance
- Inspiratory / Expiratory Assistance

Inspiratory Assistance

- Breath Stacking
 - Oronasal Mask / One Way Valve
 - Intact inspiratory muscle strength
 - Resuscitation Circuit - Bag and Mask
 - Requires pharyngeal function
- Intermittent Positive Pressure Breaths

Inspiratory Assistance



Expiratory Assistance

- Chest Wall Compression
- Abdominal Compression
- Chest Wall and Abdominal Compression

Expiratory Assistance

Manually Assisted Cough

Rest



Exhalation



Fig. 1. Manually assisted cough via thoracic compression.

Fig. 2. Manually assisted cough via abdominal-thoracic compression.

Inspiratory & Expiratory Assistance

- Breath stacking / Manually Assisted Cough
- Mechanical In-Exsufflator (Cough Assist®)

Inspiratory & Expiratory Assistance

- Cough Assist
- Cycle
 - P_i 15-50 cm H₂O
 - Apply P_i for 2-3 seconds
 - P_e 15-50 cm H₂O 1-2 sec
- 5 cycles - Suction - 5 sets



Inspiratory

Expiratory

Cough Assist

Table 2—Peak Expiratory Flow Rates During Assisted and Unassisted Coughing

Case	Unassisted, L/s	Stack, L/s	Assisted, L/s‡	Exsufflator, L/s§
1	0.00	4.53*	5.39	6.10
2	2.97	4.40*	7.90	6.21
3	3.28	3.54*	3.28	7.81
4	1.83	3.12†	4.72	8.17
5	2.24	5.00†	4.03	6.48
6	0.00	2.93*	3.92	7.46
7	1.38	3.57*	3.18	7.46
8	2.07	3.03†	4.80	7.28
9	2.28	3.62*	4.58	6.75
10	2.10	2.44†	2.60	6.20
11	0.97	1.70†	4.22	7.46
12	1.66	3.14†	4.62	8.14
13	4.02	4.44†	4.77	7.46
14	2.33	4.50†	4.37	7.48
15	3.34	4.70†	4.92	7.78
16	0.97	1.78†	2.58	8.17
17	1.02	1.48†	3.32	6.42
18	1.00	2.25†	2.25	9.23
19	1.50	2.40†	4.40	7.80
20	1.51	4.33*	6.33	9.11
21	1.58	3.88*	3.68	7.81
Mean ± SD	1.81 ± 1.03	3.37 ± 1.07	4.27 ± 1.29	7.47 ± 1.02

Should be
above 4.5 L/s

Ventilation

What is Ventilation?

- Bring oxygen into the blood stream
- Remove carbon dioxide produced
 - Maintain acid-base balance
- Cyclic aeration of the lung to remove secretions

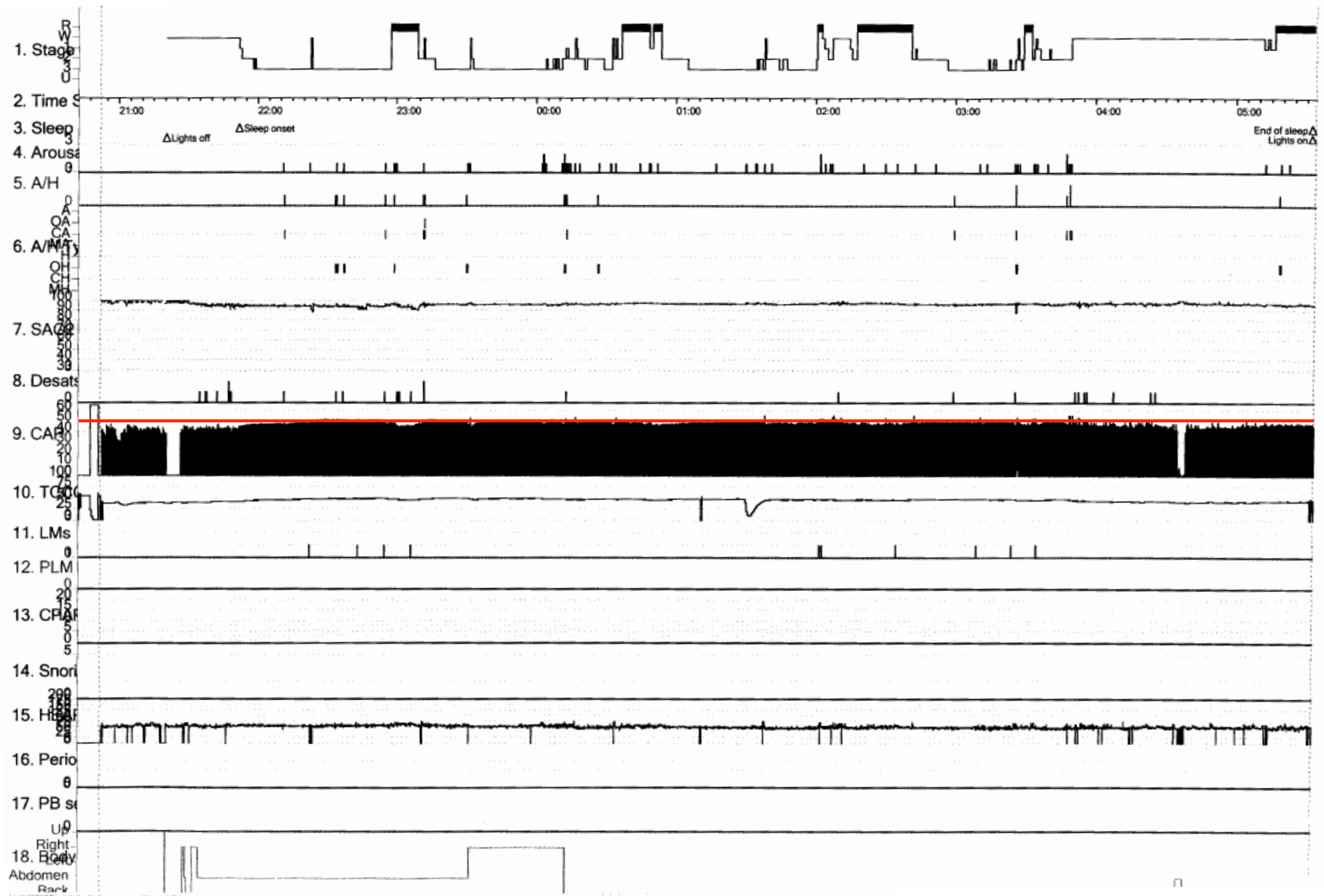
Clinical Symptoms of Respiratory Failure

- Morning headaches
- Inadequate Rest
 - Daytime fatigue
 - Failure to thrive
- More rapid loss of function

How to Evaluate Ventilation

- Hypoventilation
 - High Carbon Dioxide
- Night time hypoventilation before daytime
 - First occurs in REM sleep
- Full Sleep Study / 16-Channel Polysomnogram

Sleep Study



Sleep Study

ETCO2 Intervals	>60	50-60	45-50	35-45	<35
Sleep Time (%)	0.0	17.2	81.1	1.7	0.0

ETCO2 & TCCO2 Summary

	Maximum (Torr)		Mean (Torr)	
	ETCO2	TCCO2	ETCO2	TCCO2
Awake	52	50	44	44
REM	50	49	47	47
NREM	53	54	49	48
Total Sleep	53	54	48	48

Oxygenation Summary

SpO2 %	>= 95%	< 95%	< 92%	< 90%	< 88%	< 85%	< 80%	< 70%	< 60%
Sleep Time(minutes)	300.8	60.1	3.6	0.2	0.0	0.0	0.0	0.0	0.0
Sleep Time (%)	82.6	16.5	1.0	0.1	0.0	0.0	0.0	0.0	0.0

	SpO2 Min. (%)	SpO2 Max (%)	SpO2 Mean (%)
REM	92	99	97
NREM	88	99	97
Total Sleep	88	99	97

Respiratory Event Summary

		Obstructive			OAHl	Central		CAHI	Total
		Apnea	Hypop	Mixed		Apnea	Hypop		
Total	Count	1	10	0	11	7	0	7	18
	Index	0.2	1.6	0.0	1.8	1.2	0.0	1.2	3.0
REM	Count	0	2	0	2	0	0	0	2
	Index	0.0	1.7	0.0	1.7	0.0	0.0	0.0	1.7
Position (all stages)	Supine	Count	0	3	0	3	6	0	9
		Index	0.0	0.8	0.0	0.8	1.6	0.0	2.4
	Prone	Count	1	5	0	6	1	0	7
		Index	0.6	3.0	0.0	3.7	0.6	0.0	4.3
	Side	Count	0	2	0	2	0	0	2
		Index	0.0	2.9	0.0	2.9	0.0	0.0	2.9

Sleep Study

ETCO2 Intervals	>60	50-60	45-50	35-45	<35
Sleep Time (%)	0.0	17.2	81.1	1.7	0.0

ETCO2 & TCCO2 Summary

	Maximum (Torr)		Mean (Torr)	
	ETCO2	TCCO2	ETCO2	TCCO2
Awake	52	50	44	44
REM	50	49	47	47
NREM	53	51	49	48
Total Sleep	53	51	48	48

Oxygenation Summary

SpO2 %	>= 95%	< 95%	< 92%	< 90%	< 88%	< 85%	< 80%	< 70%	< 60%
Sleep Time(minutes)	300.8	60.1	3.6	0.2	0.0	0.0	0.0	0.0	0.0
Sleep Time (%)	82.6	16.5	1.0	0.1	0.0	0.0	0.0	0.0	0.0

	SpO2 Min. (%)	SpO2 Max (%)	SpO2 Mean (%)
REM	92	99	97
NREM	88	99	97
Total Sleep	88	99	97

**Nocturnal Pulse Oximetry
is Not a Viable Alternative**

Caution in Diagnosis

- Significant vs. Non-Significant hypercarbia
 - Is $\text{EtCO}_2 > 50$ for $< 20\%$ sleep time Normal?
- Patients are typically studied when well
 - What about during illness?
- Distinguish hypoventilation from obstructive sleep apnea

How to Support

How not to support

- Supplemental Oxygen
- High-Flow Nasal Cannula Air or Oxygen
- Continuous Positive Airway Pressure (CPAP)

What is Required for Ventilation?

- Interface
 - Nasal
 - Oronasal / Facemask
 - Oral
 - Chest - Negative Pressure Ventilation
- Bi-Level Pressure Generator

Interface



Mouthpiece Ventilation



Tracheostomy Tube



Interface

- Fit mask to patient's face
 - Experienced Nurse / Therapist
- Assess for comfort / pressure points
- Desensitization

How to Initiate Ventilation

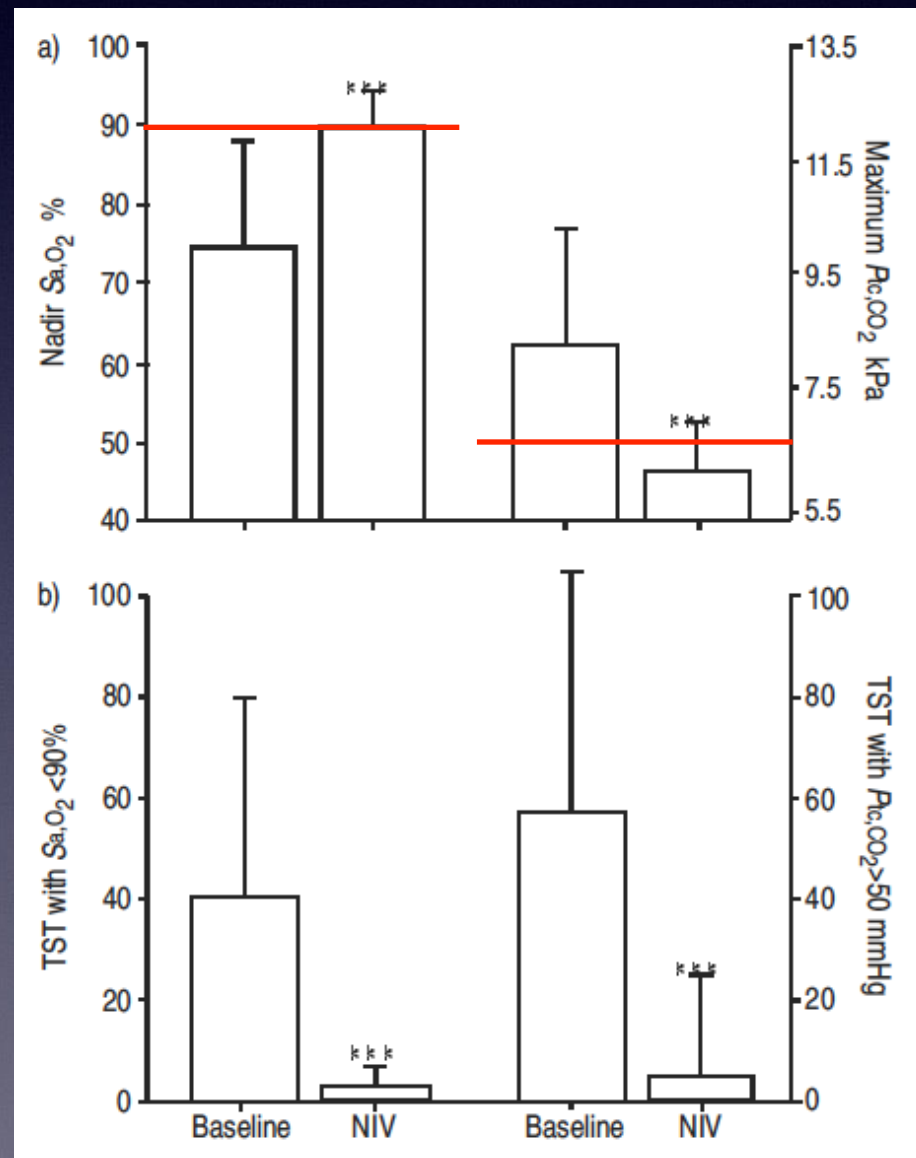
- Equipment
 - Interface - Nasal / Oronasal
 - Ventilator
- Titration - ideally with patient's equipment
 - Clinical
 - Sleep Study

Successful Ventilation Initiation

- Patient tolerance
 - Immediate
 - Ongoing
- Parent / Caregiver Training & Competence
- Follow-up to insure adequacy of support
 - May change with clinical status

Ventilation Outcome

Gas Exchange



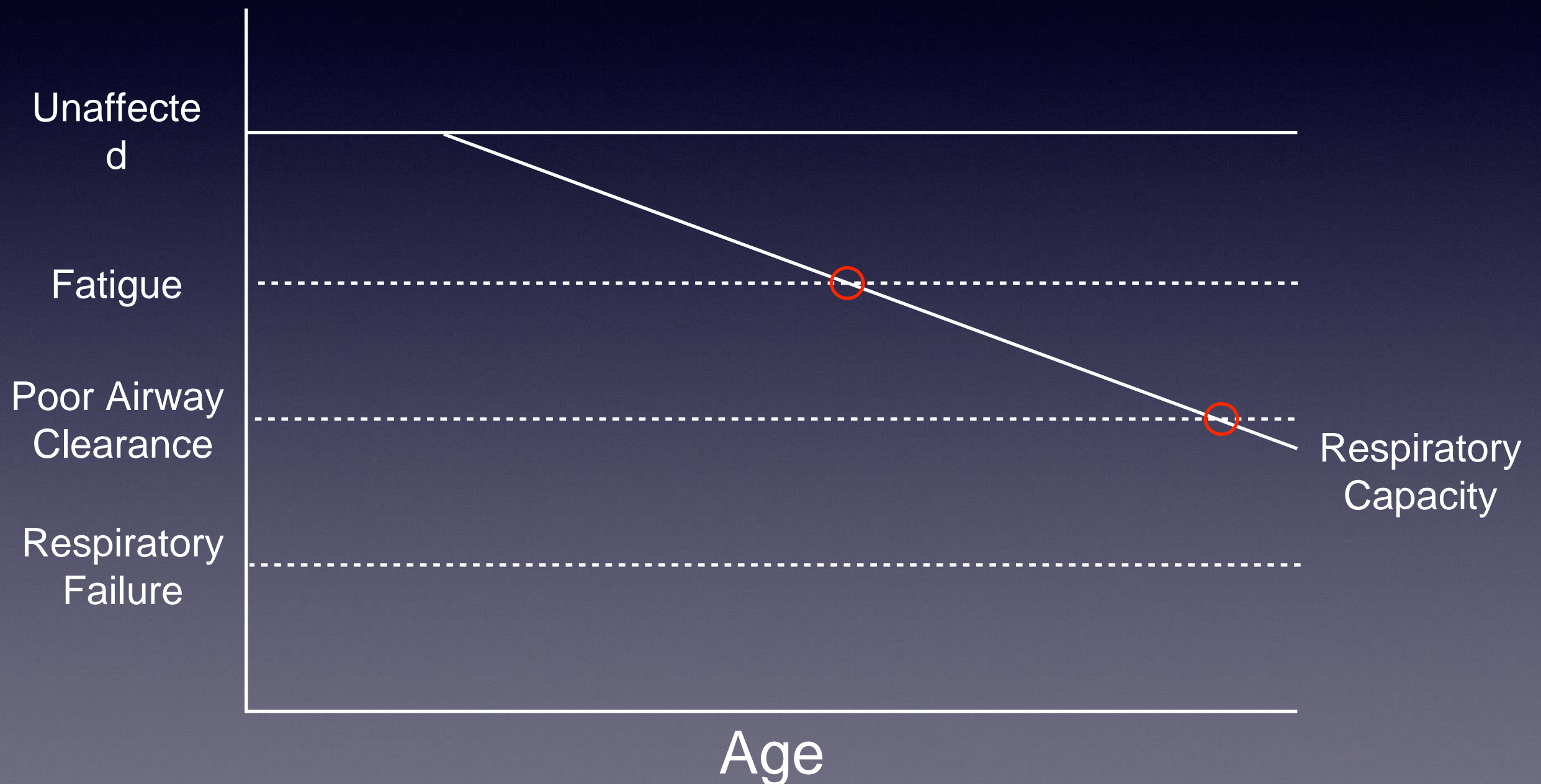
Use of a Tracheostomy Tube

- Absolute Indication
 - Incompetent upper airway / inability to be extubated
- Relative indications for tracheostomy tube
 - Interface problems - skin integrity
 - Facial interface refusal / intolerance
- Duration of NIPPV is not an absolute indication
 - Alter interfaces

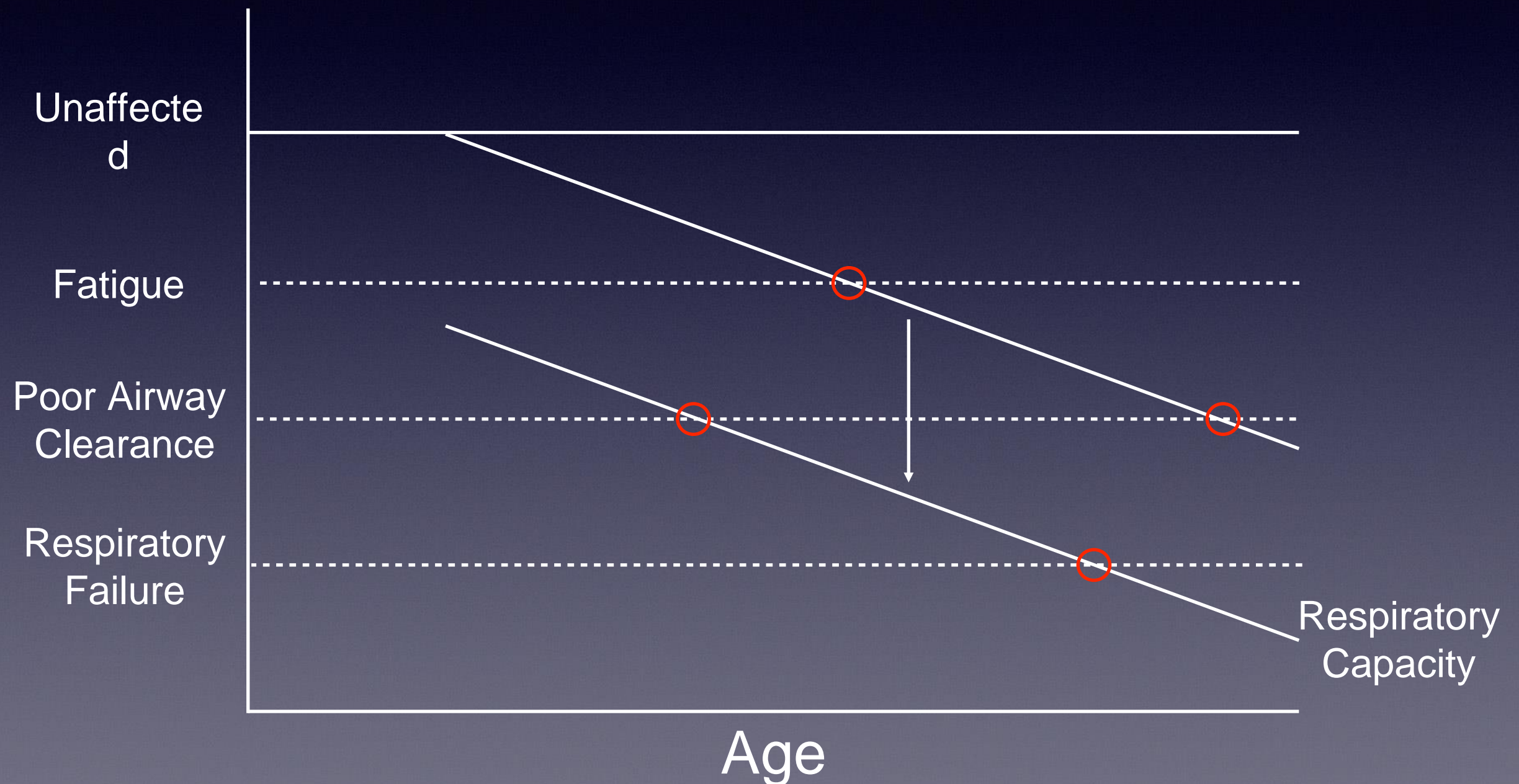
Progression of Disease

- Adjust level and amount of NIPPV support based on patient's need
- No advantage to more NIPPV support (duration or pressure) than is needed
- Be aware that normal ventilation when well does not insure normal ventilation when acutely ill

Progression of Disease



Acute Illness



Conclusion

- The onset of respiratory symptoms can be subtle
- Because the first onset can occur during an acute illness it is important to be prepared and proactive
- There are a variety of effective options to support airway clearance and ventilation
- Treatment needs to be fit to the patient not the patient fit to the treatment

mayero@email.chop.edu

Clinical Titration

- Normalize CO₂
 - Continuous EtCO₂ / TcCO₂ at night
- Chest Wall Motion - Maximize excursion
- Symptom Improvement
 - Quality of Sleep
 - Morning Headaches

Sleep Study Titration

- Titrate P_i and P_e to
 - Improve hypercapnea / oxygenation
 - Improve work of breathing
 - Thoracoabdominal asynchrony
- Diagnosis & titration may not be feasible together

Physiologic Titration

- Reduce EtCO₂ by 5% with maximal Pi and Pe
- Reduce work of breathing using Pi and Pe

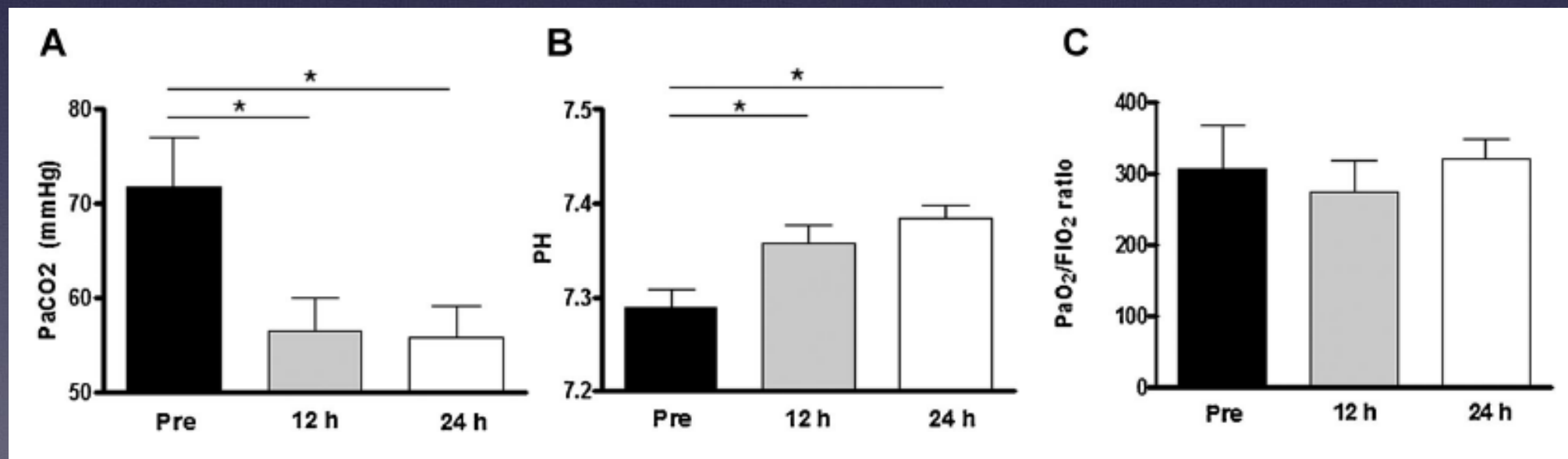
TABLE 3. SLEEP DATA DURING MECHANICAL VENTILATION WITH THE TWO SETTINGS

	US	PHYS	p Value
TST, min	281.1 ± 41.6	346.4 ± 99.9	n.s.
SE, % of TST	66.5 ± 22.4	80.7 ± 9.6	0.01
SWS, % of TST	17.7 ± 9.81	25.1 ± 10.8	n.s.
REM, % of TST	8.9 ± 7.4	17.3 ± 5.4	< 0.05
Arousal index, events/h	29.9 ± 17.2	16 ± 12.6	0.01
ODI, events/h	27.5 ± 25.2	8.2 ± 8.5	< 0.05
Sa _{O₂} nadir, %	67.8 ± 14.3	85.5 ± 4.5	0.0009
TST ₉₀ , %	31.3 ± 29.8	7.2 ± 9	< 0.05
NREM ineffective efforts, events/h	62.5 ± 75.1	15 ± 20	< 0.05

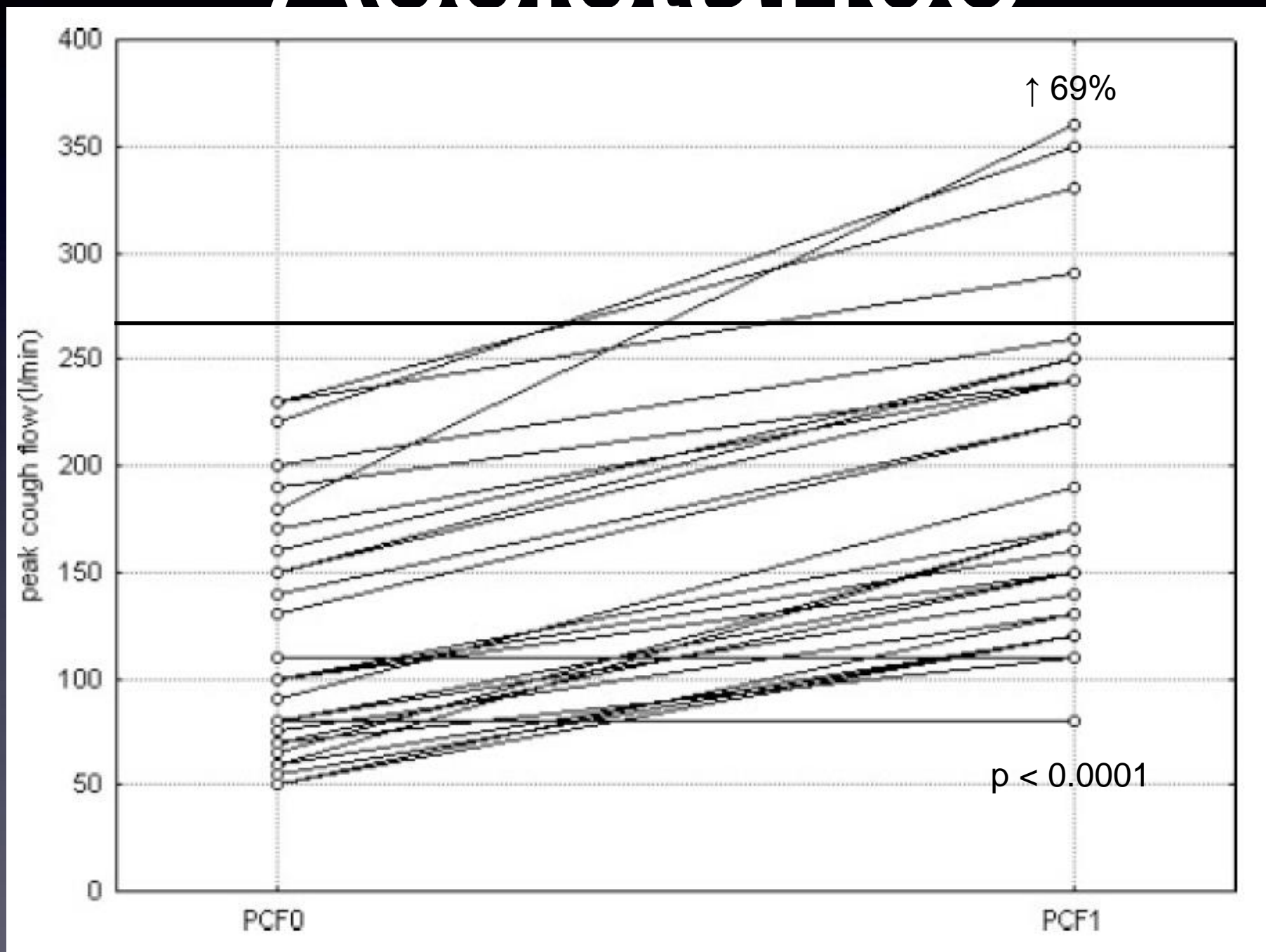
Definition of abbreviations: NREM = non-REM sleep; ODI = oxygen desaturation index (number of desaturation episodes · h of sleep or time in bed); PHYS = physiological setting; SE = sleep efficiency; SWS = slow wave sleep; TST = total sleep time; TST₉₀ = time spent with Sa_{O₂} < 90% (% of total sleep time or time in bed); US = usual setting.

NIPPV Outcomes

- Acute Care
 - Successful support in 12 of 16 cases
 - NIPPV and aggressive Cough Assist treatment



Inspiratory Assistance



270 L/m

Preventative Management

Preventative Management

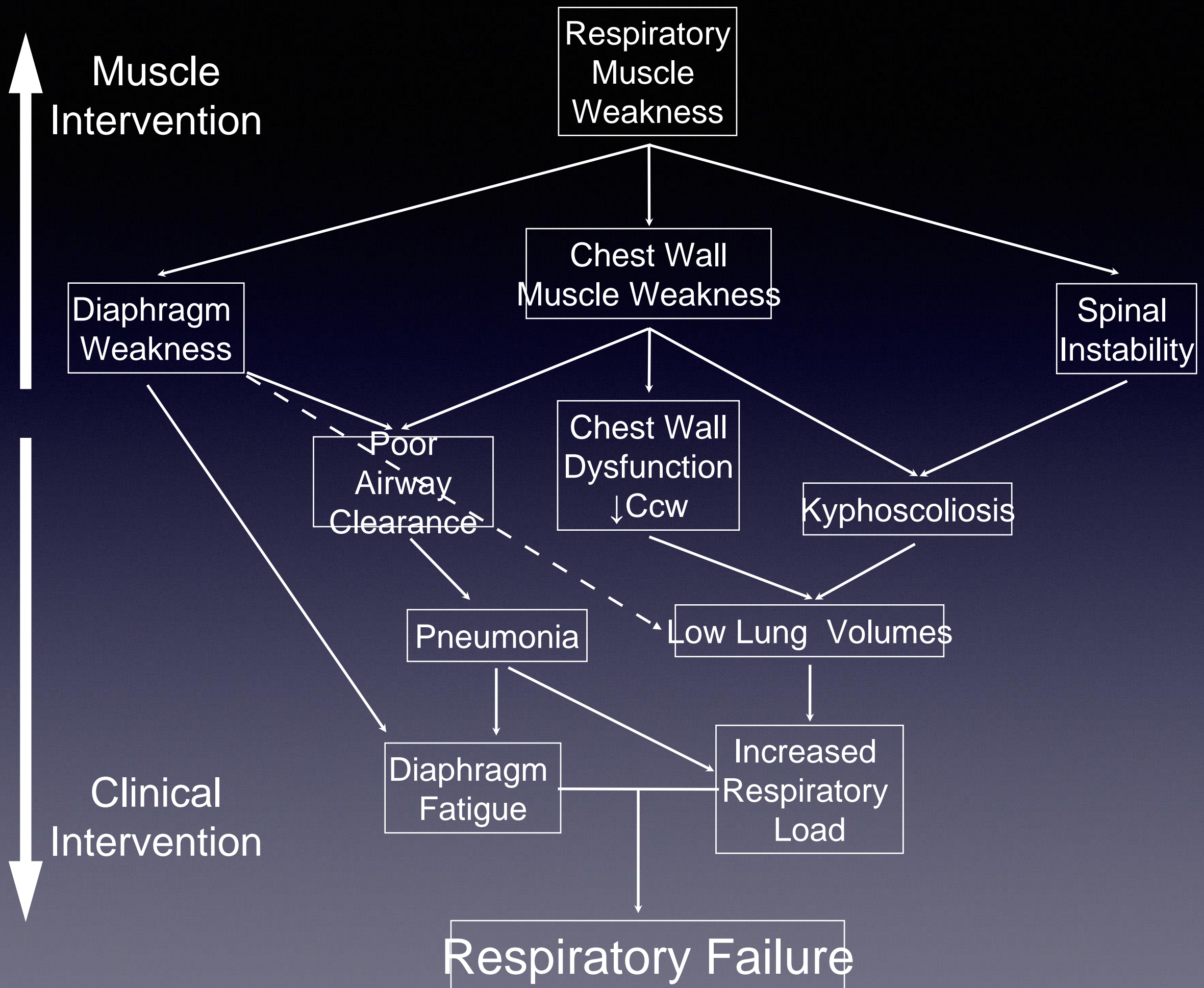
- Immunizations
 - Keep up to date with standard schedule
 - Seasonal Influenza Vaccination
 - No evidence for Palivizumab (RSV vaccine)
- Respiratory Range of Motion

Range of Motion

- Extend motion around joint to maximal
 - All directions
- Hold at point of maximal extension/flexion
 - Duration
- Repetition

Hyperinsufflation

Major Diagnoses	No. of Patients	Mean Age	Mean VCsit	Mean MIC	Mean LIC
DMD	53	26 (14–44) \pm 7	622 (1–2710) \pm 595	1252 (220–3280) \pm 670	1696 (840–3400) \pm 548
Myotonic	6	47 (36–53) \pm 7	2038 (1190–3580) \pm 864	2280 (1190–3720) \pm 874	2447 (1380–3850) \pm 851
Other myopathies	55	39 (11–85) \pm 18	1195 (270–2770) \pm 642	1741 (420–3360) \pm 825	2026 (500–3600) \pm 791
SMA	31	19 (7–56) \pm 14	861 (30–2160) \pm 554	1254 (30–2780) \pm 748	1544 (320–3100) \pm 670
Total	282	42 (7–85) \pm 20	1131 (0–3580) \pm 744	1712 (30–5100) \pm 926	2069 (320–5400) \pm 867

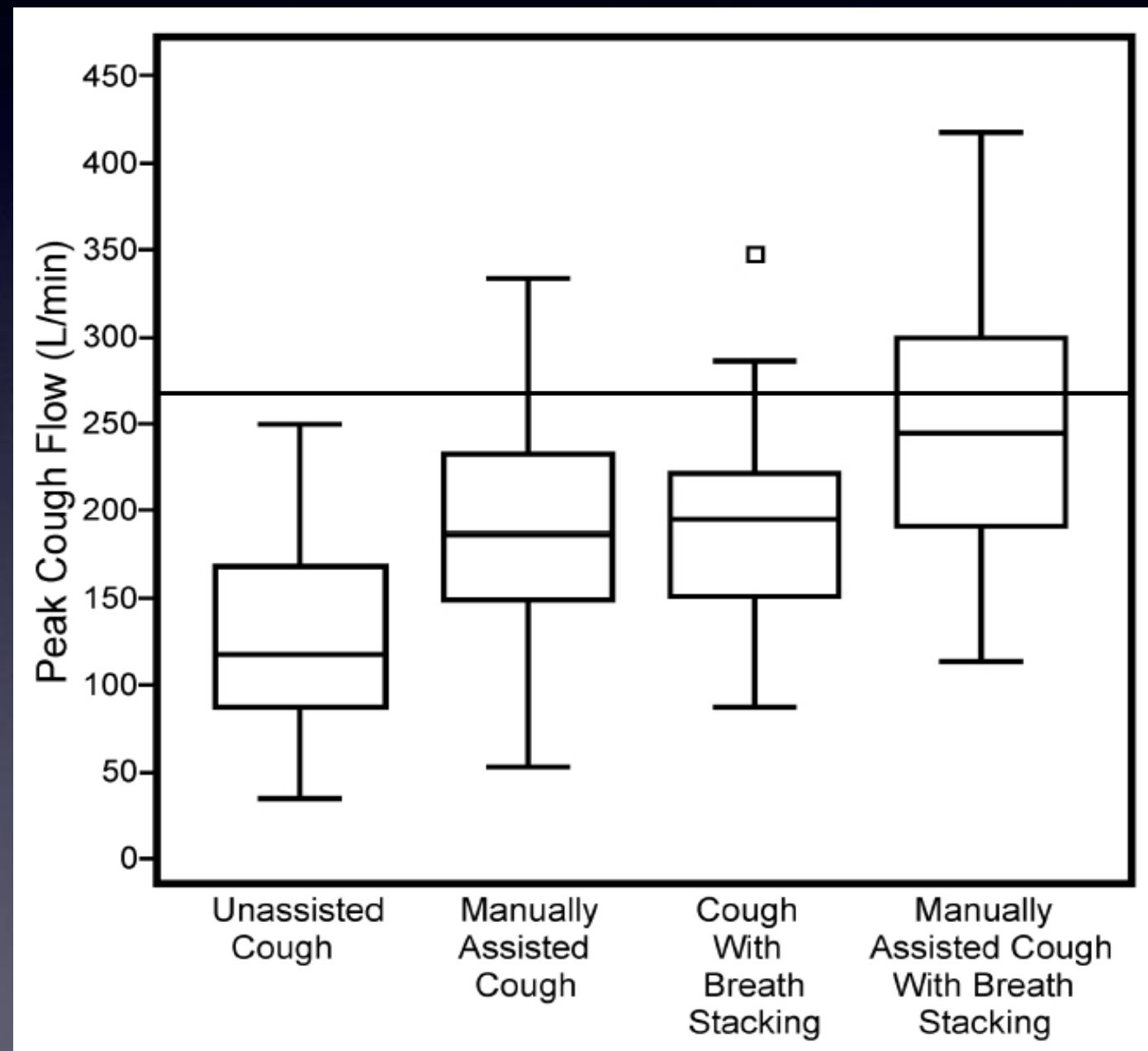


Inspiratory & Expiratory Assistance

Table 2—Peak Expiratory Flow Rates During Assisted and Unassisted Coughing

Case	Unassisted, L/s	Stack, L/s	Assisted, L/s‡	Exsufflator, L/s§
1	0.00	4.53*	5.39	6.10
2	2.97	4.40*	7.90	6.21
3	3.28	3.54*	3.28	7.81
4	1.83	3.12†	4.72	8.17
5	2.24	5.00†	4.03	6.48
6	0.00	2.93*	3.92	7.46
7	1.38	3.57*	3.18	7.46
8	2.07	3.03†	4.80	7.28
9	2.28	3.62*	4.58	6.75
10	2.10	2.44†	2.60	6.20
11	0.97	1.70†	4.22	7.46
12	1.66	3.14†	4.62	8.14
13	4.02	4.44†	4.77	7.46
14	2.33	4.50†	4.37	7.48
15	3.34	4.70†	4.92	7.78
16	0.97	1.78†	2.58	8.17
17	1.02	1.48†	3.32	6.42
18	1.00	2.25†	2.25	9.23
19	1.50	2.40†	4.40	7.80
20	1.51	4.33*	6.33	9.11
21	1.58	3.88*	3.68	7.81
Mean ± SD	1.81 ± 1.03	3.37 ± 1.07	4.27 ± 1.29	7.47 ± 1.02

Inspiratory & Expiratory Assistance



270 L/min

Inspiratory Assistance

- Intermittent Positive Pressure Breathing
- Pressure with maximal inspiratory volume
- Hold volume for 1-2 Seconds

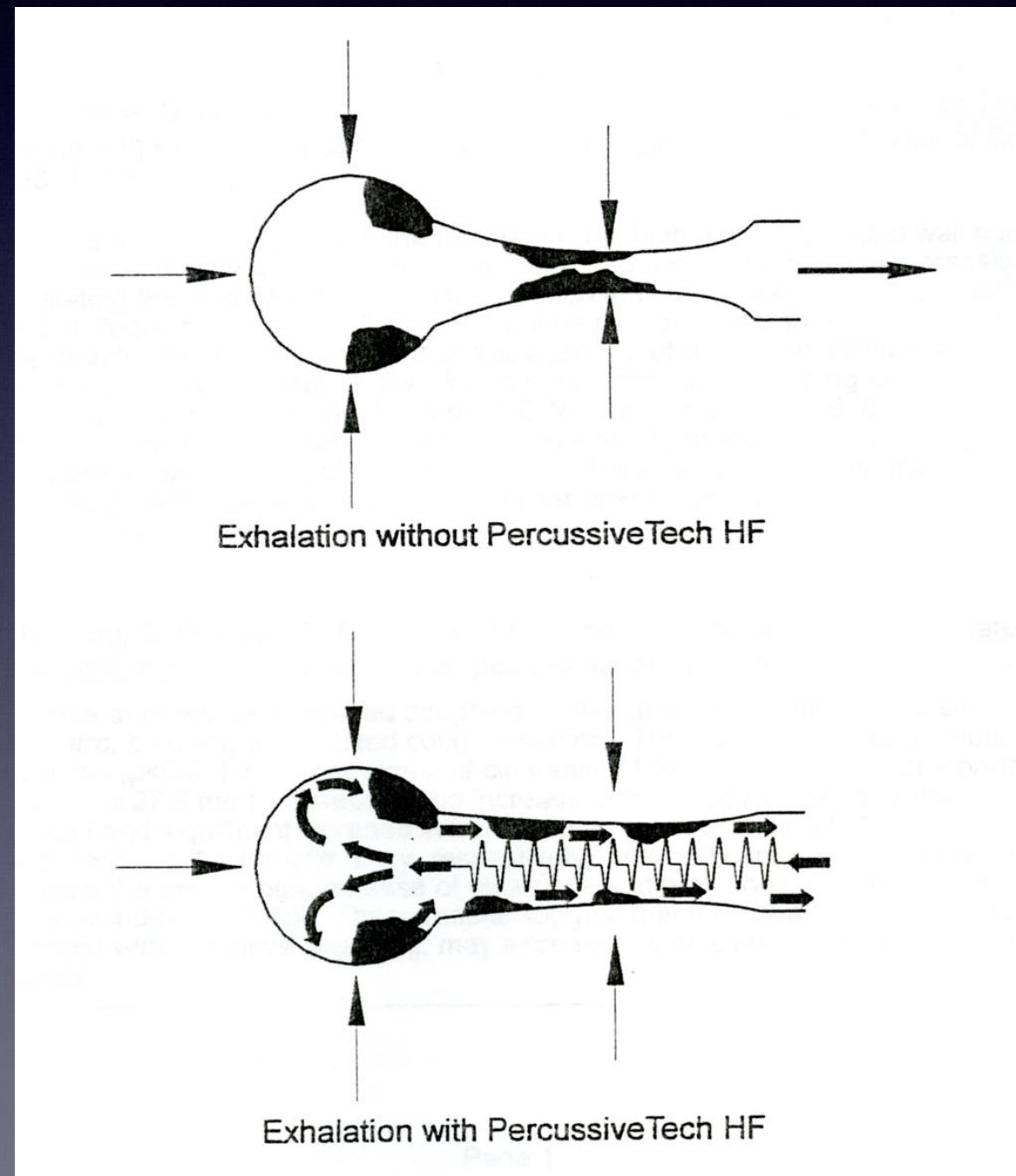


Intrapulmonary Percussive Ventilation

- High frequency oscillation under pressure
- Nebulization during treatment
- Performed during tidal breathing

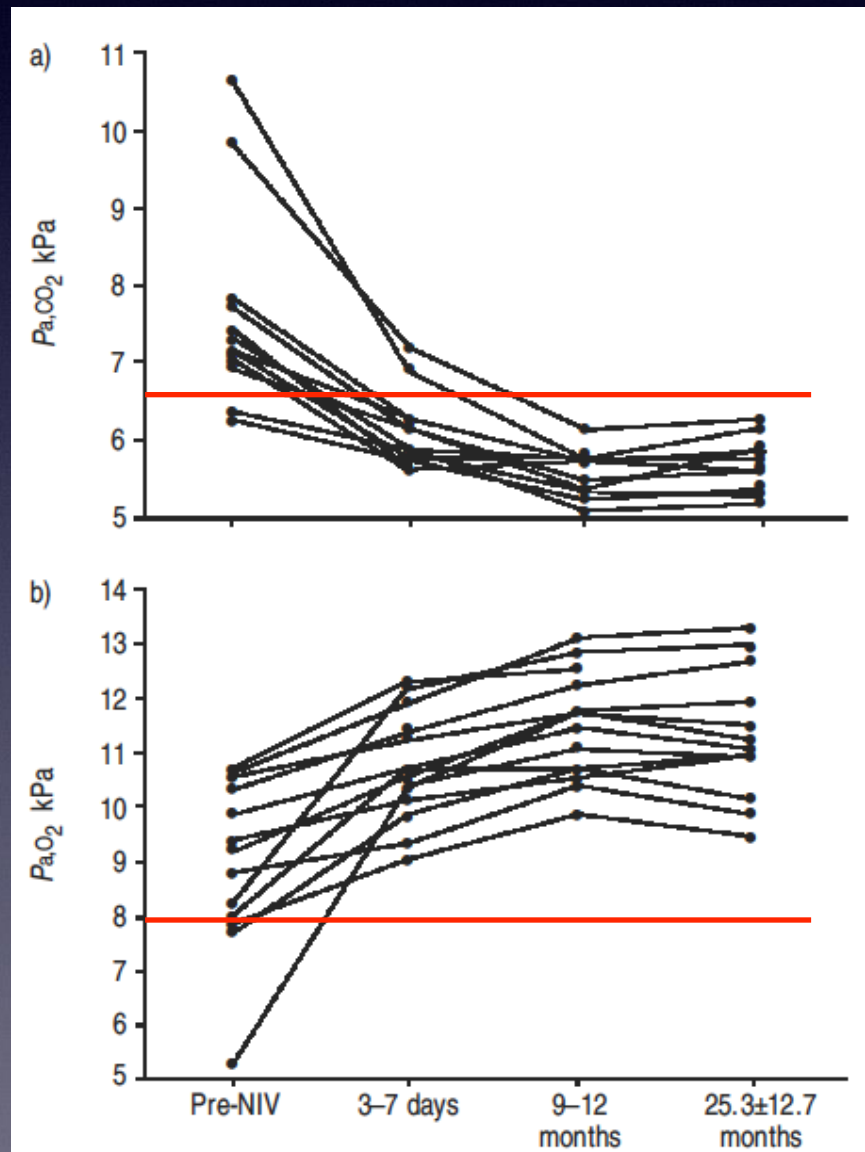


Intrapulmonary Percussive Ventilation



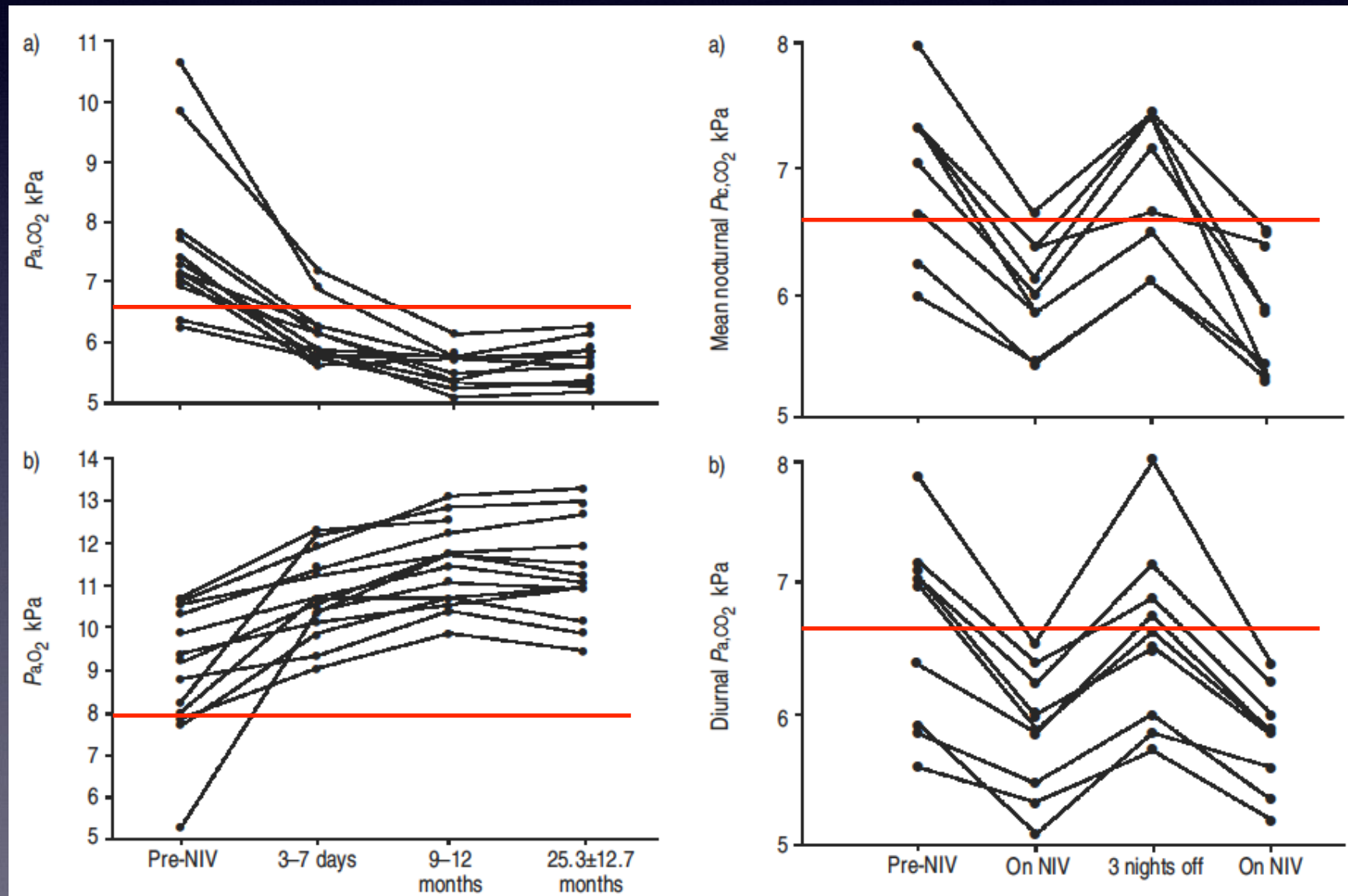
NIPPV Outcome

Gas Exchange



NIPPV Outcome

Gas Exchange



NIPPV Outcomes

Sleep Quality

Table 2. – Influence of noninvasive ventilation (NIV) on sleep-disordered breathing and sleep

	Before NIV	During NIV	p-value
RDI·h ⁻¹	10.5±13.1	3.1±3.5	<0.001
REM-RDI·h ⁻¹	20.5±21.1	3.0±5.3	<0.001
Arousal index·h ⁻¹	20.6±14.3	10.2±3.8	<0.001
Light-sleep %	55±12	44±13	<0.05
Slow-wave-sleep %	24±9	34±9	<0.05
REM-sleep %	18±6	20±6	0.18

Two Approaches To Treatment

Two Approaches

- Reactive
 - Treat symptoms after they have occurred and are established
- Proactive / Preventative
 - Treat symptoms as early as possible as they are starting
 - Prevent symptoms from occurring at all


Reactive - Unaffected

- Cold symptoms start
- Nasal congestion
- Fever
- Cough
- Medication
- Resolution

Reactive - DMD

- Cold symptoms start
- Nasal congestion
- Fever
- Cough
- Medication
- Resolution

Reactive - DMD

- Cold symptoms start
 - Nasal congestion
 - Fever
 - Cough
 - Medication
 - Resolution
- 
- Poor cough
 - Prolonged illness
 - +/- Pneumonia

Proactive Approach

- Cold symptoms start
- Nasal congestion

Assisted Airway
Clearance



Proactive Approach

- Cold symptoms start
- Nasal congestion
- Fever
- Cough
- Medication
- Resolution

Assisted Airway
Clearance



Preventative Management

- Immunizations
 - Keep up to date with standard schedule
 - Seasonal Influenza Vaccination
 - No evidence for Palivizumab (RSV vaccine)
- Respiratory Range of Motion - Dr. Sawnani

Proactive Management

- Cough a lot and cough early
- Insuring an effective cough
- Supporting an ineffective cough

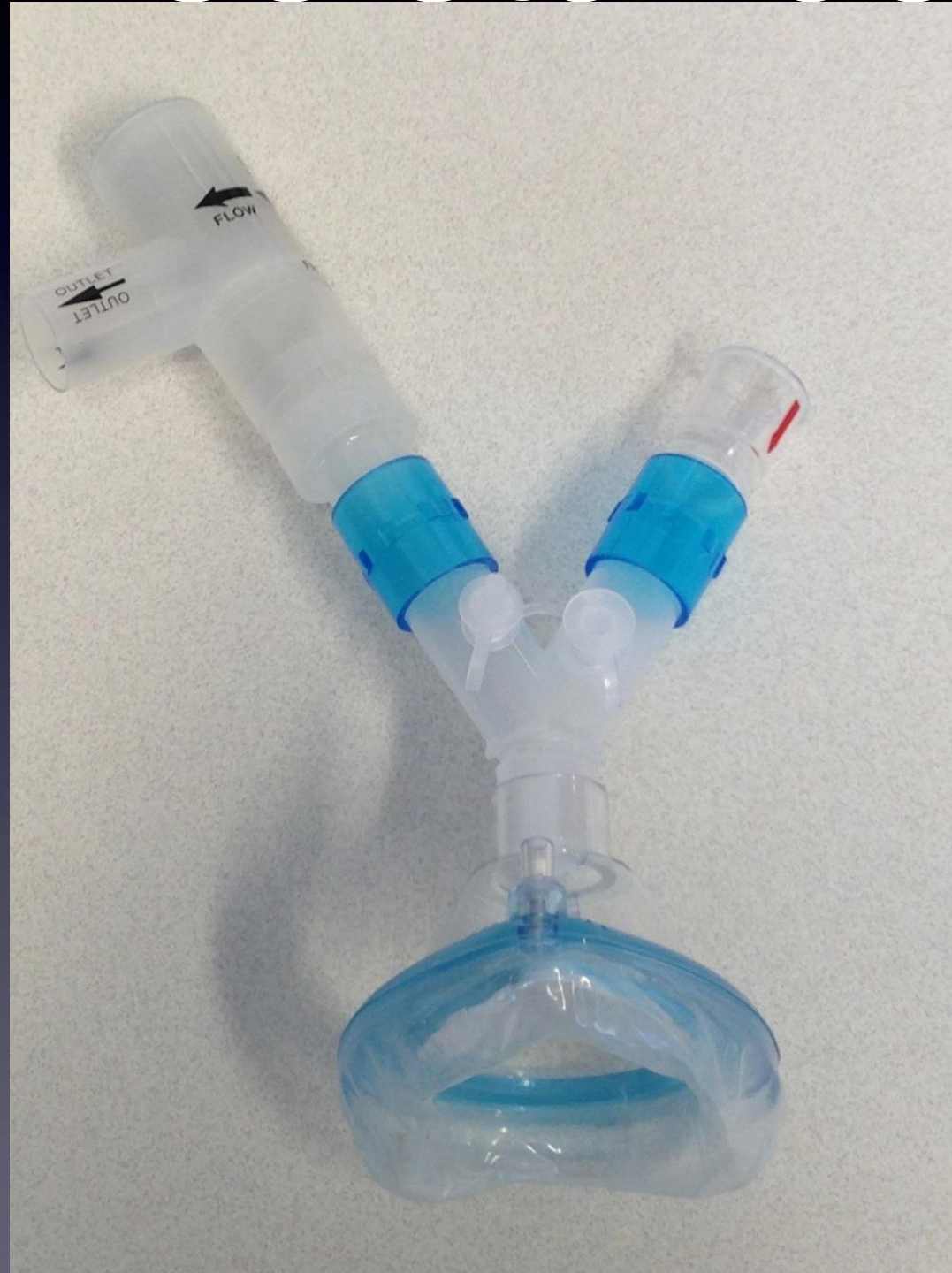
Coughing

- Inspiratory
 - Deep breath to get air beyond secretions
 - Optimize length tension relationship of expiratory muscles
- Compressive - increased pressure
 - Exhalation against closed glottis
- Expulsive - mobilization
 - Rapid expiratory flow ($> 160-180$ L/m)

Augment Weak Cough

- Inspiratory Assistance
- Expiratory Assistance
- Inspiratory / Expiratory Assistance
- Other

Inspiratory Assistance

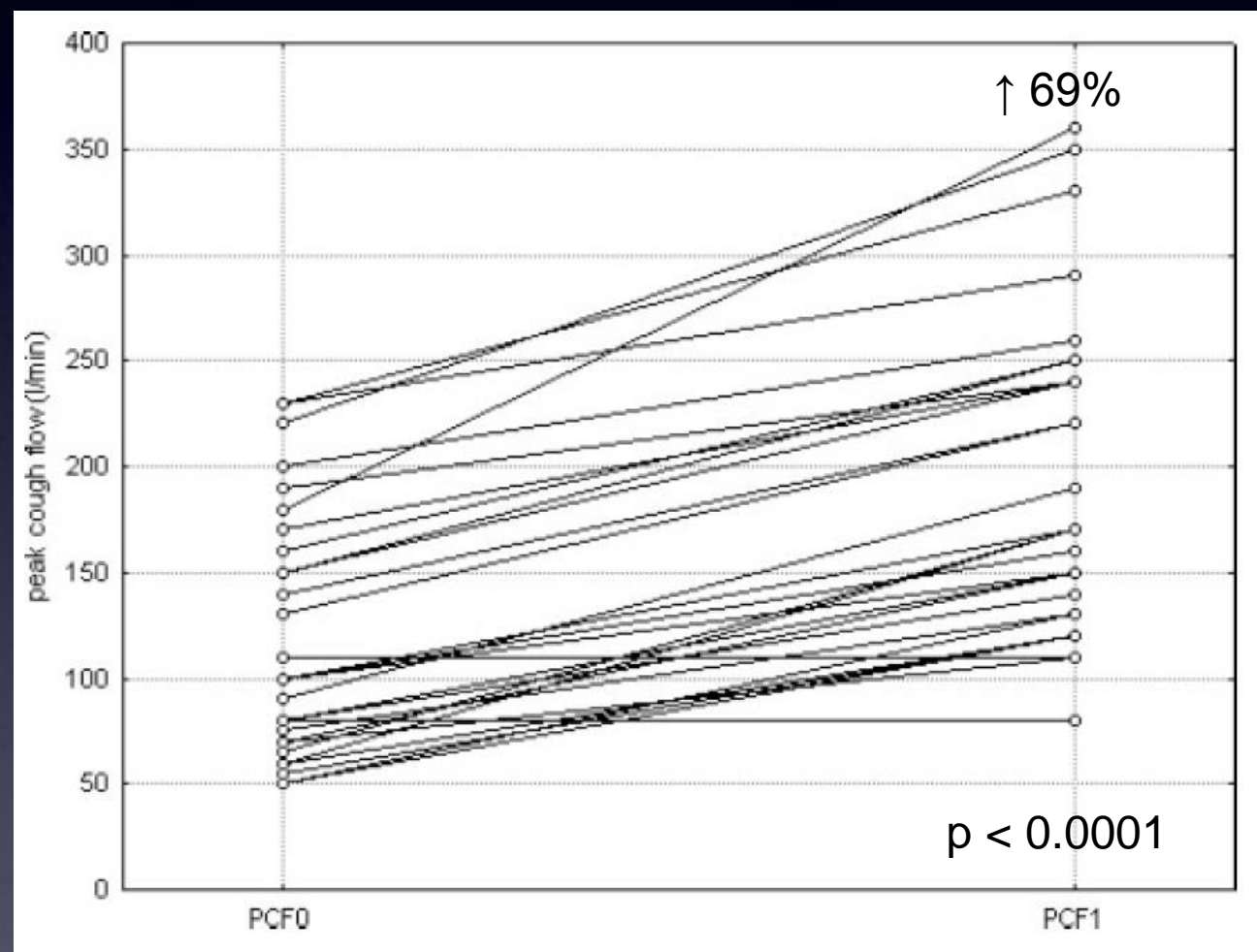


Inspiratory Assistance

- Intermittent Positive Pressure Breathing
 - Pressure with maximal inspiratory volume
 - Hold volume for 1-2 Seconds
 - Exhalation patient capacity of



Inspiratory Assistance



Inspiratory Assistance

- Breath Stacking
 - Oronasal Mask / One Way Valve
 - Intact Inspiratory Muscle Strength
- Intermittent Positive Pressure Breaths

Inspiratory Assistance

- Chest Wall Compression
- Abdominal Compression
- Chest Wall and Abdominal Compression

Expiratory Assistance

Manually Assisted Cough

Rest



Exhalation



Fig. 1. Manually assisted cough via thoracic compression.

Fig. 2. Manually assisted cough via abdominal-thoracic compression.

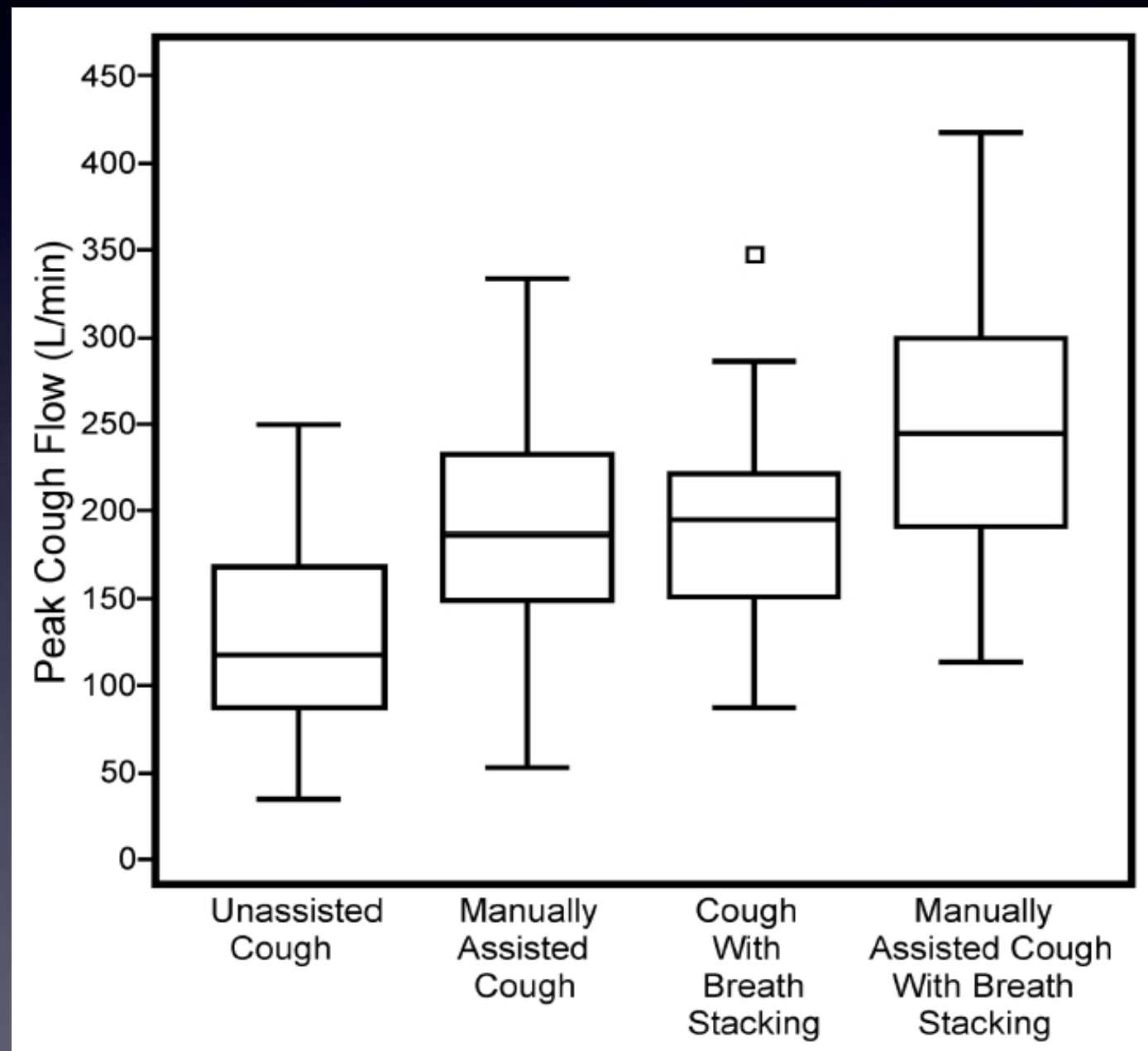
Inspiratory & Expiratory Assistance

- Breath stacking / Manually Assisted Cough
- Mechanical In-Exsufflator (Cough Assist®)

Inspiratory & Expiratory Assistance

Major Diagnoses	No. of Patients	Mean Age	Mean CPF	Mean ACPF
DMD	53	26 (14–44) \pm 7	1.58 (0.1–5.7) \pm 1.7	3.76 (0–6.2) \pm 1.4
Myotonic	6	47 (36–53) \pm 7	4.03 (2.7–4.7) \pm 0.8	5.10 (4.4–5.9) \pm 0.6
Other myopathies	55	39 (11–85) \pm 18	3.11 (0.1–7.5) \pm 1.8	4.64 (1.6–7.5) \pm 1.4
SMA	31	19 (7–56) \pm 14	1.76 (0.1–4.6) \pm 1.5	3.54 (1.7–5.5) \pm 1.1
Total	282	42 (7–85) \pm 20	2.52 (0.1–9.7) \pm 2.0	4.28 (0–9.7) \pm 2.2

Inspiratory & Expiratory Assistance



Toussaint, *et. al. Respir Care.* 2009.

Cough Assist



Inspiratory & Expiratory Assistance

Cough Assist
Cycle

Pi 15-50 cm H₂O

Hold at Target Pi for 1-2 seconds

Pe 15-50 cm H₂O 1-2 sec

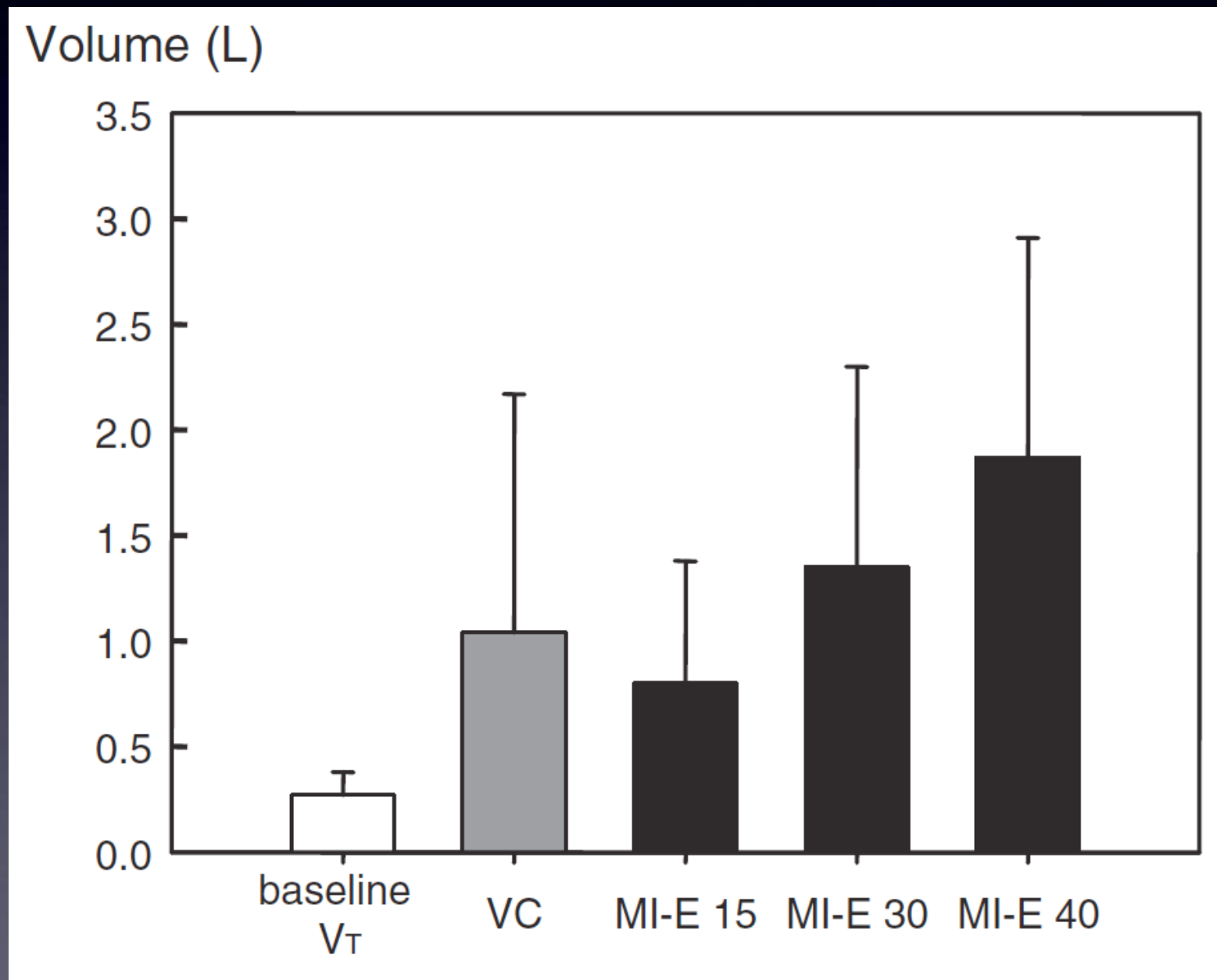
5 cycles

Suction

5 sets



Inspiratory & Expiratory Assistance

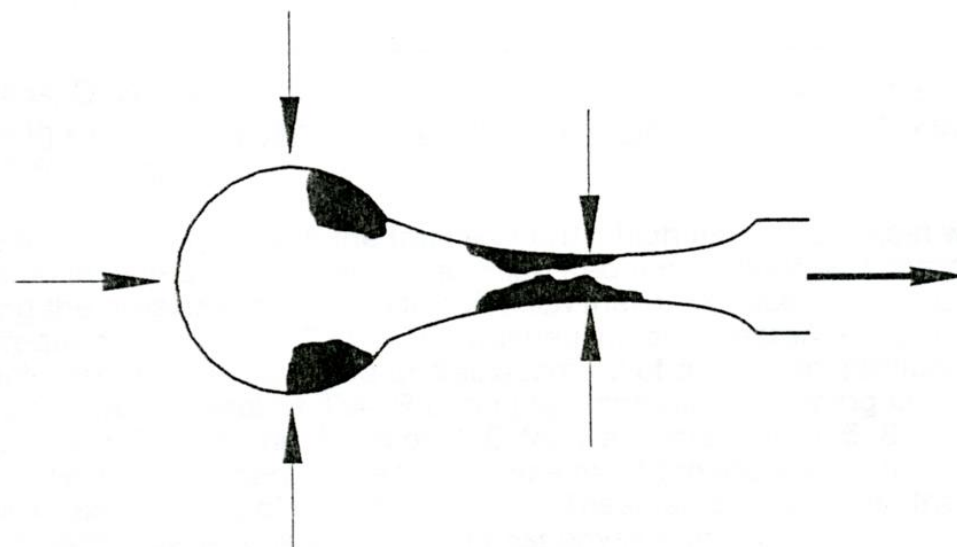


Intrapulmonary Percussive Ventilation

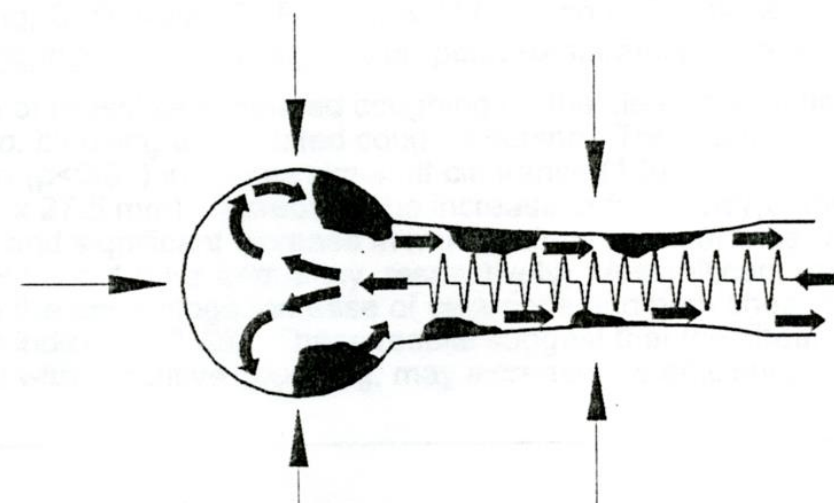
- High frequency oscillation under pressure
- Nebulization during treatment
- Performed by a respiratory therapist



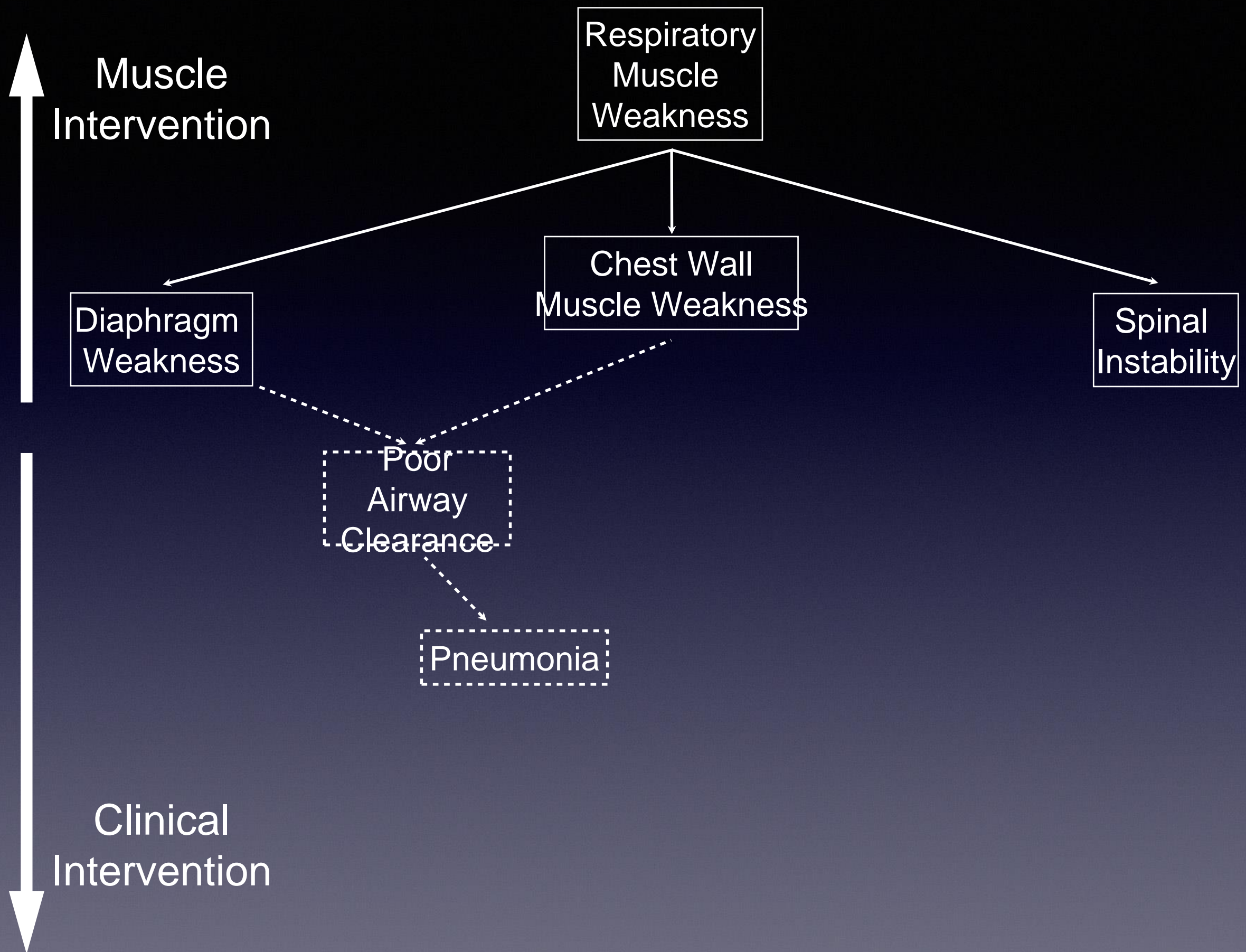
Intrapulmonary Percussive Ventilation



Exhalation without PercussiveTech HF



Exhalation with PercussiveTech HF



Intermittent Positive Pressure Breaths (IPPB)

- Apply inspiratory pressure
- Hyperinflate lungs
- Increase airway caliber
- Passive recoil
- Can be used with nebulization



