# Are Neuromuscular Blockers Helpful in ARDS?

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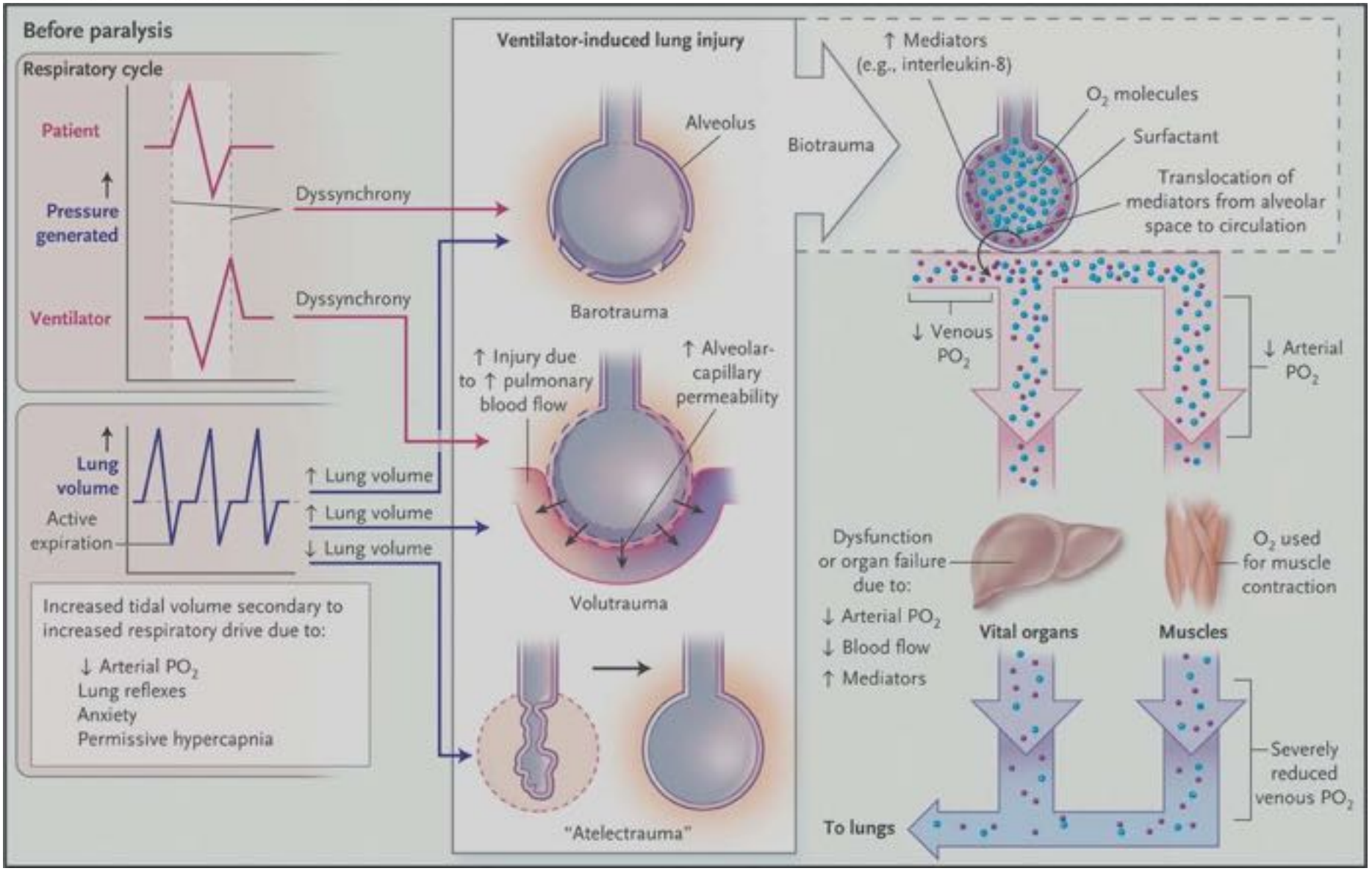
# Objectives

- Indications for using neuromuscular blockers to improve patient-ventilator interaction and perhaps outcome in ARDS
- Potential complications of sedation and neuromuscular blockade
- Guidelines and considerations for use of neuromuscular blockade

# What is the rationale for early paralysis in ARDS?

# Mechanisms by Which NMBAs Might Lead to Improved Survival in Patients with ARDS




Slutsky AS. *N Engl J Med* 2010;363:1176-80

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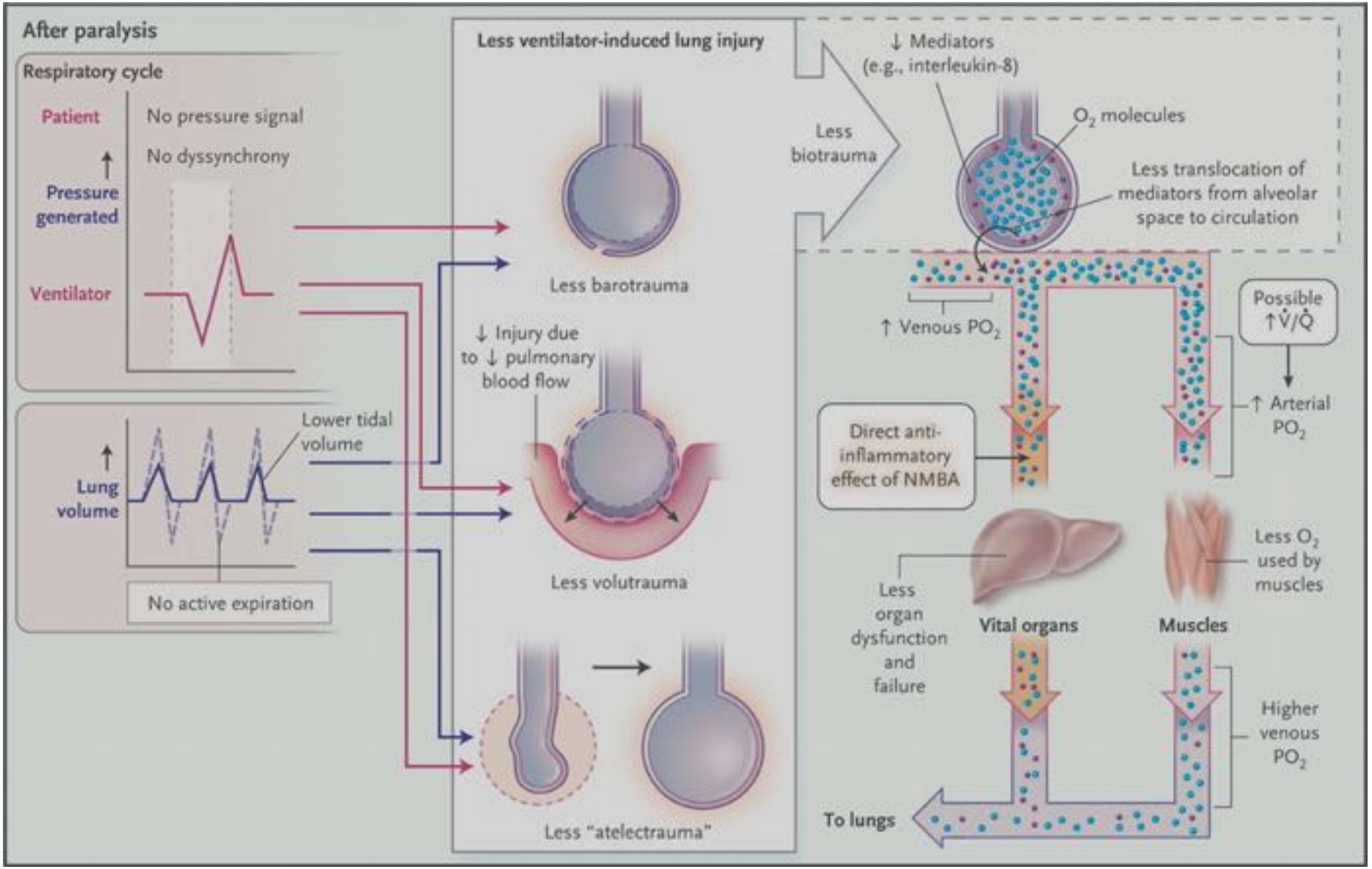


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# NMBAs improve oxygenation in ARDS

Gainnier M al. *Crit Care Med* 2004;32:113-9

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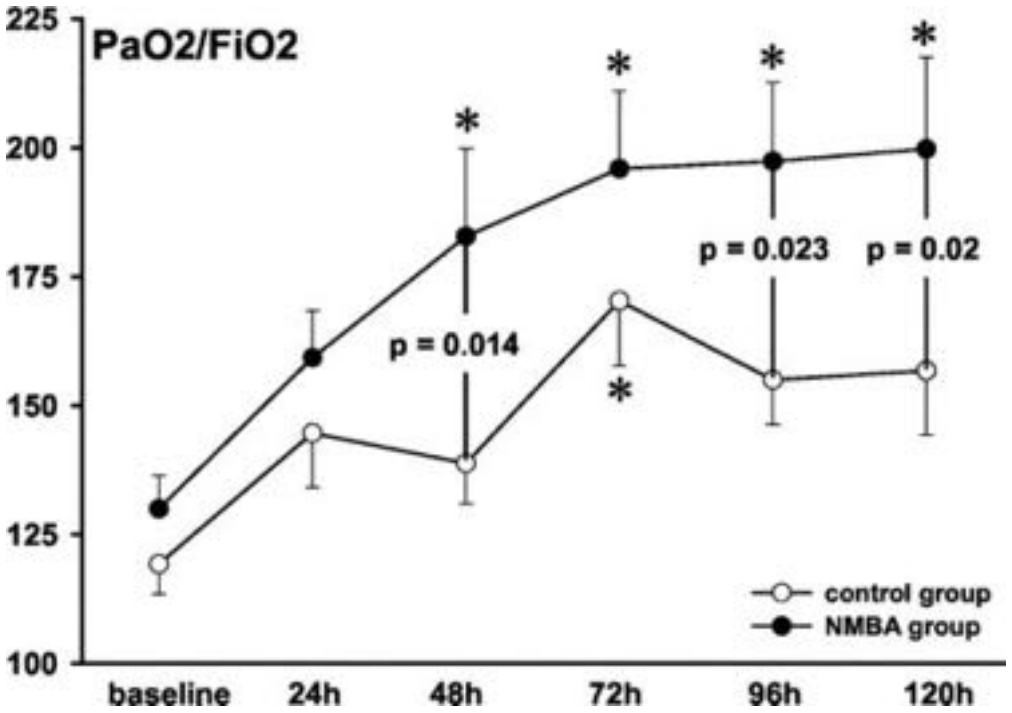
- Compared to controls:
  - PaO2/FiO2 improved
  - PEEP decreased
  - Peak & plateau airway pressure decreased



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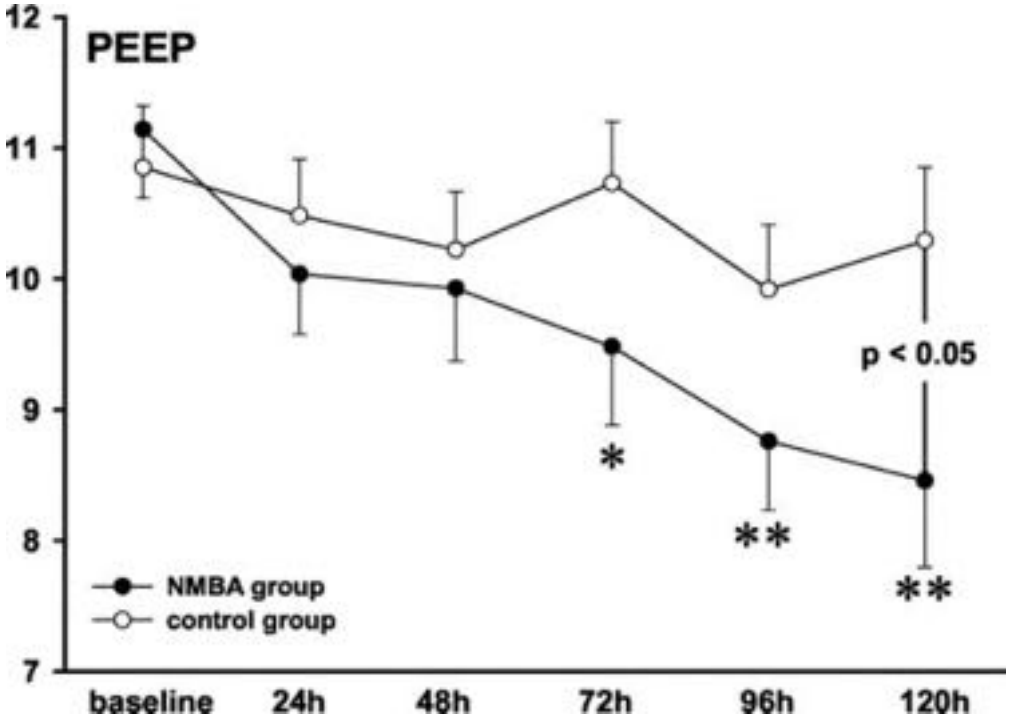

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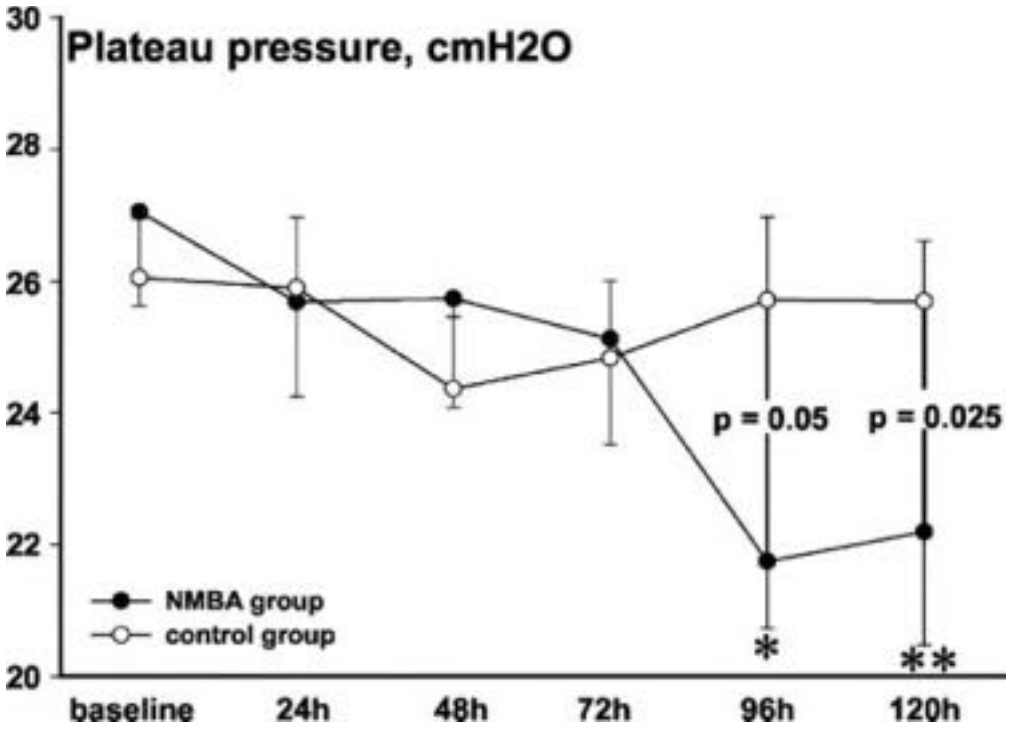
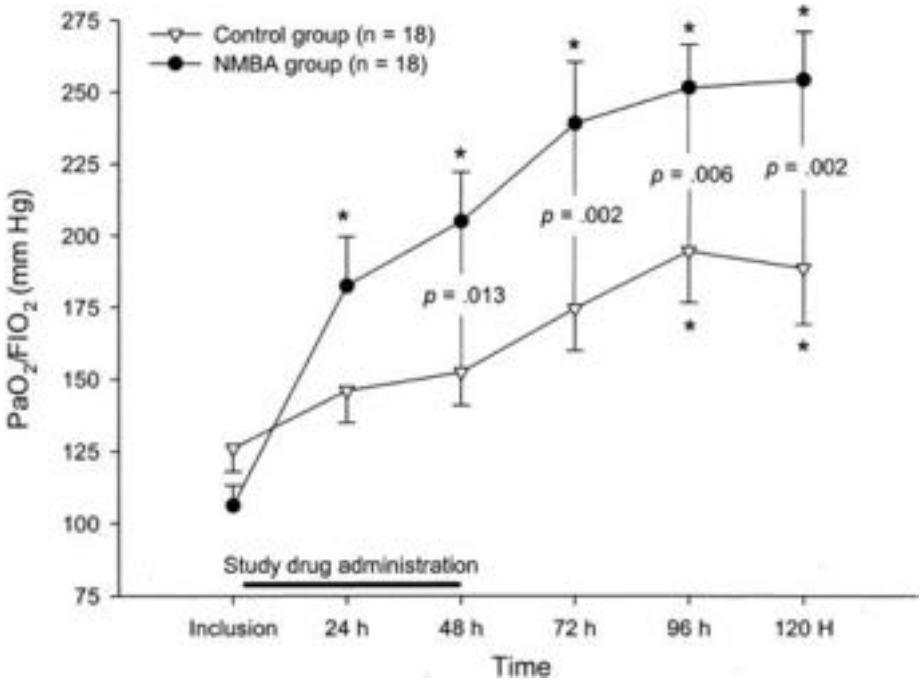


# NMBAs ↓ inflammatory response in ARDS

Forel JM al. *Crit Care Med* 2006;34:2749-57

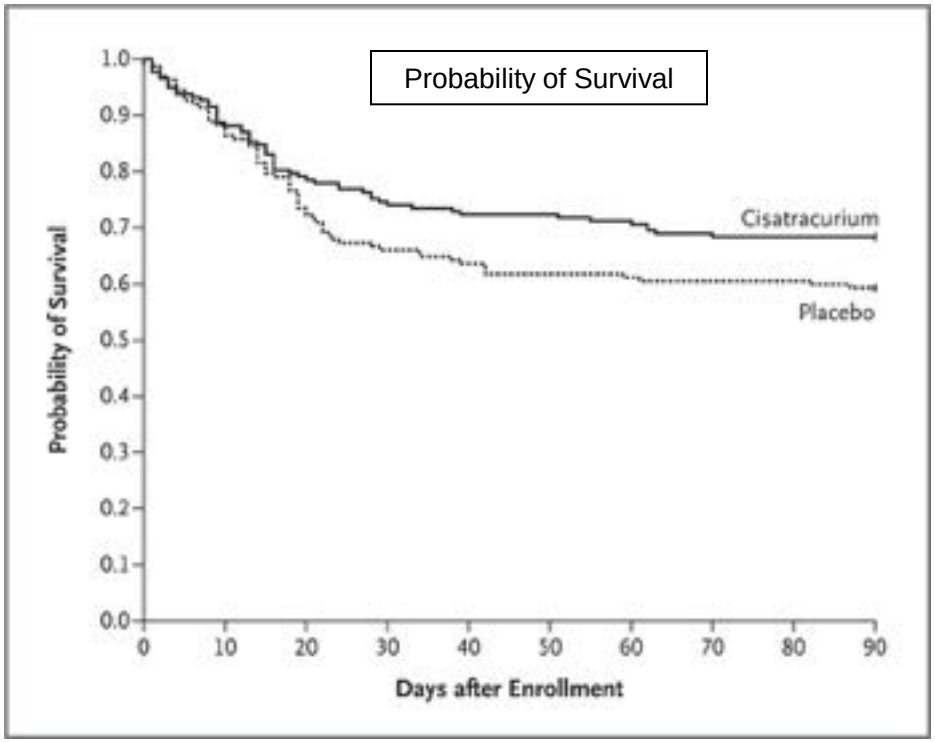
- 36 ARDS pts randomized to ± cisatracurium infusion for 48 h.
- $PaO_2/FiO_2$ improved in NMBA group
- BAL IL-8, IL-6 & IL-1β & serum IL-1β and IL6 lower in NMBA group at 48 h.
- BAL cell count and $TNF_\alpha$ no different
- Duration of MV, MV free days, and mortality not different
- Effect of the drug or pattern of ventilation?



# Neuromuscular Blockers in Early ARDS

Papazian L et al. *N Engl J Med* 363:1107-16,2010

- 340 ARDS pts ($PaO_2/FiO_2$ < 150 mmHg) in 20 French ICU's
- Randomized to ± cisatracurium infusion: 15 mg bolus, then 37.5 ml/hr for 48 h
- Reduced adjusted mortality at 28 days from 33.3 to 23.7%



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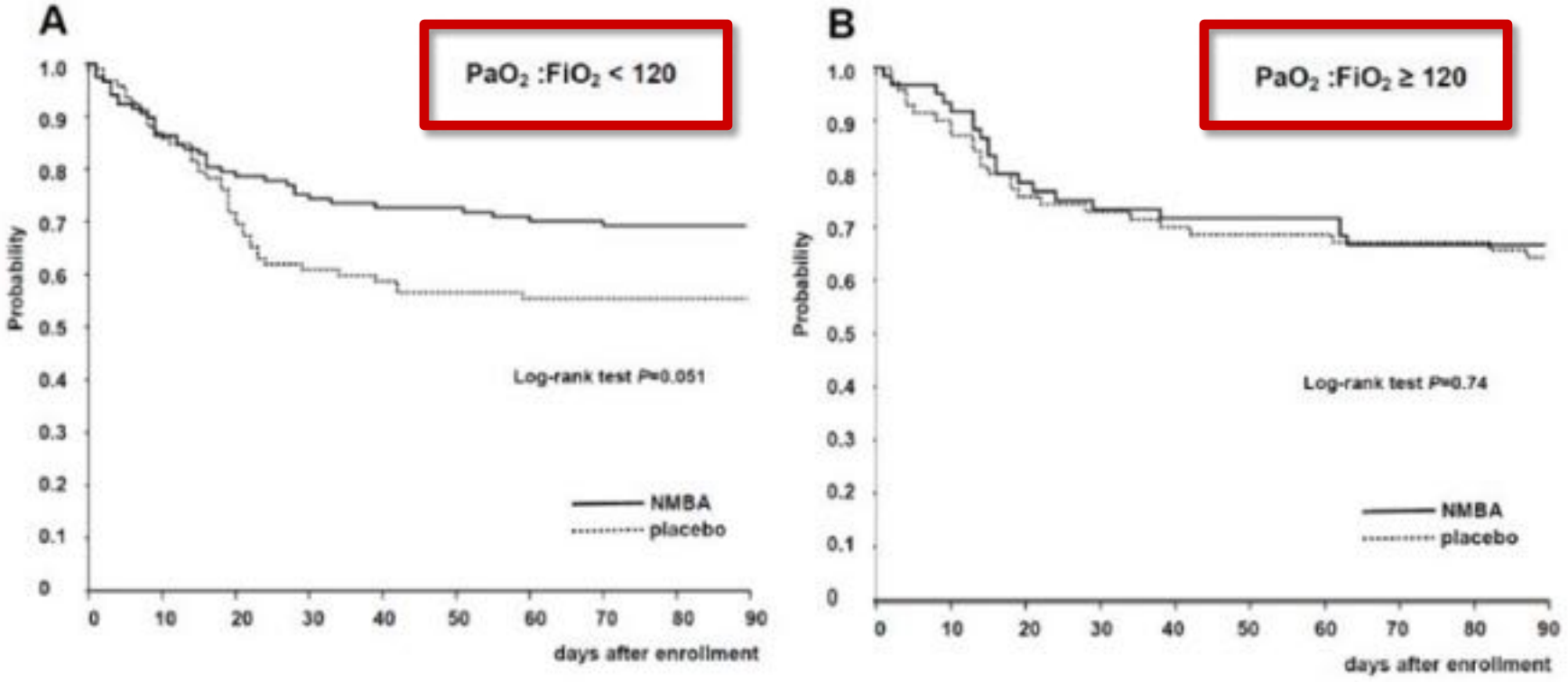
Probability of Survival




Beneficial effect limited to patients with $PaO_2/FiO_2 < 120$

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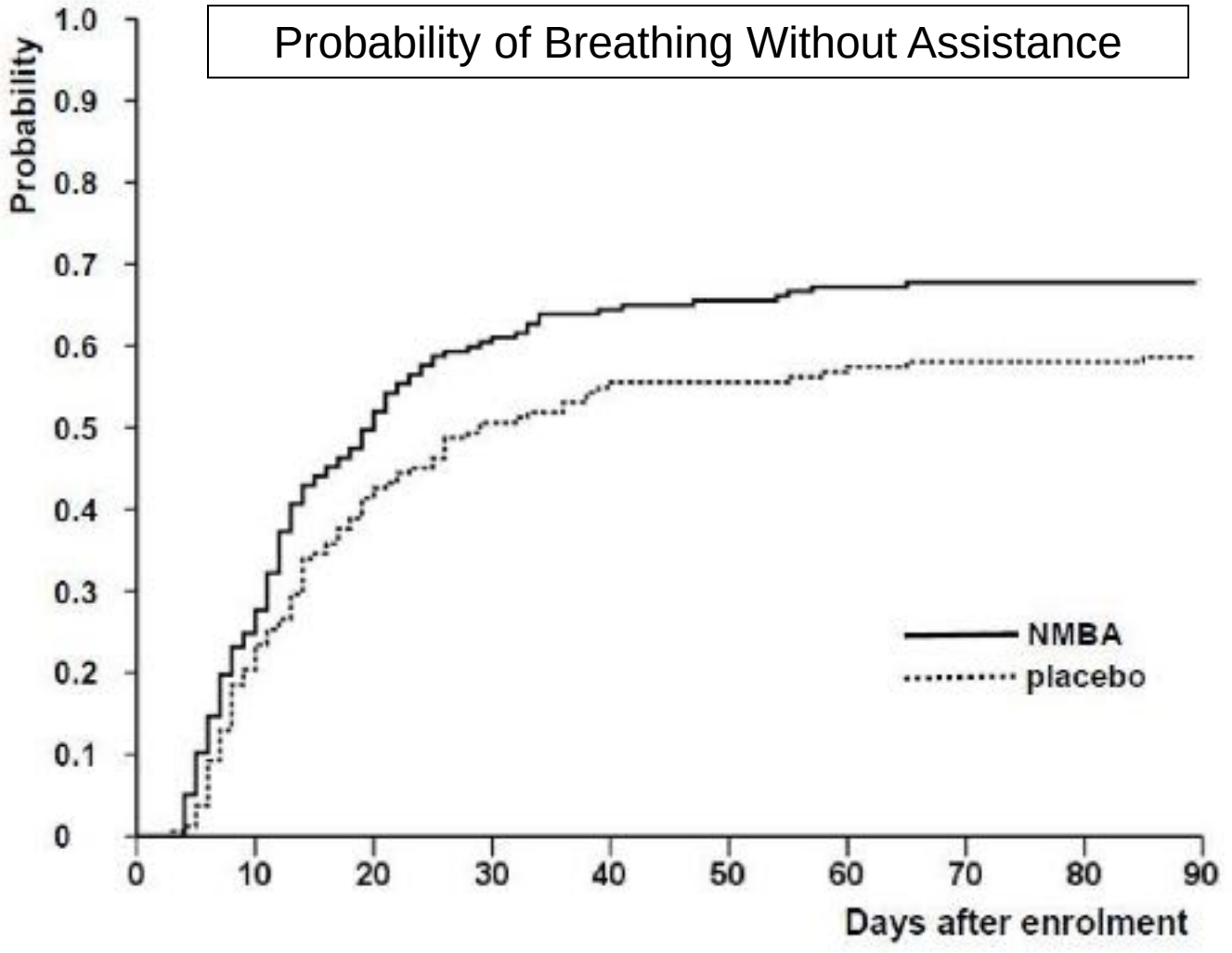

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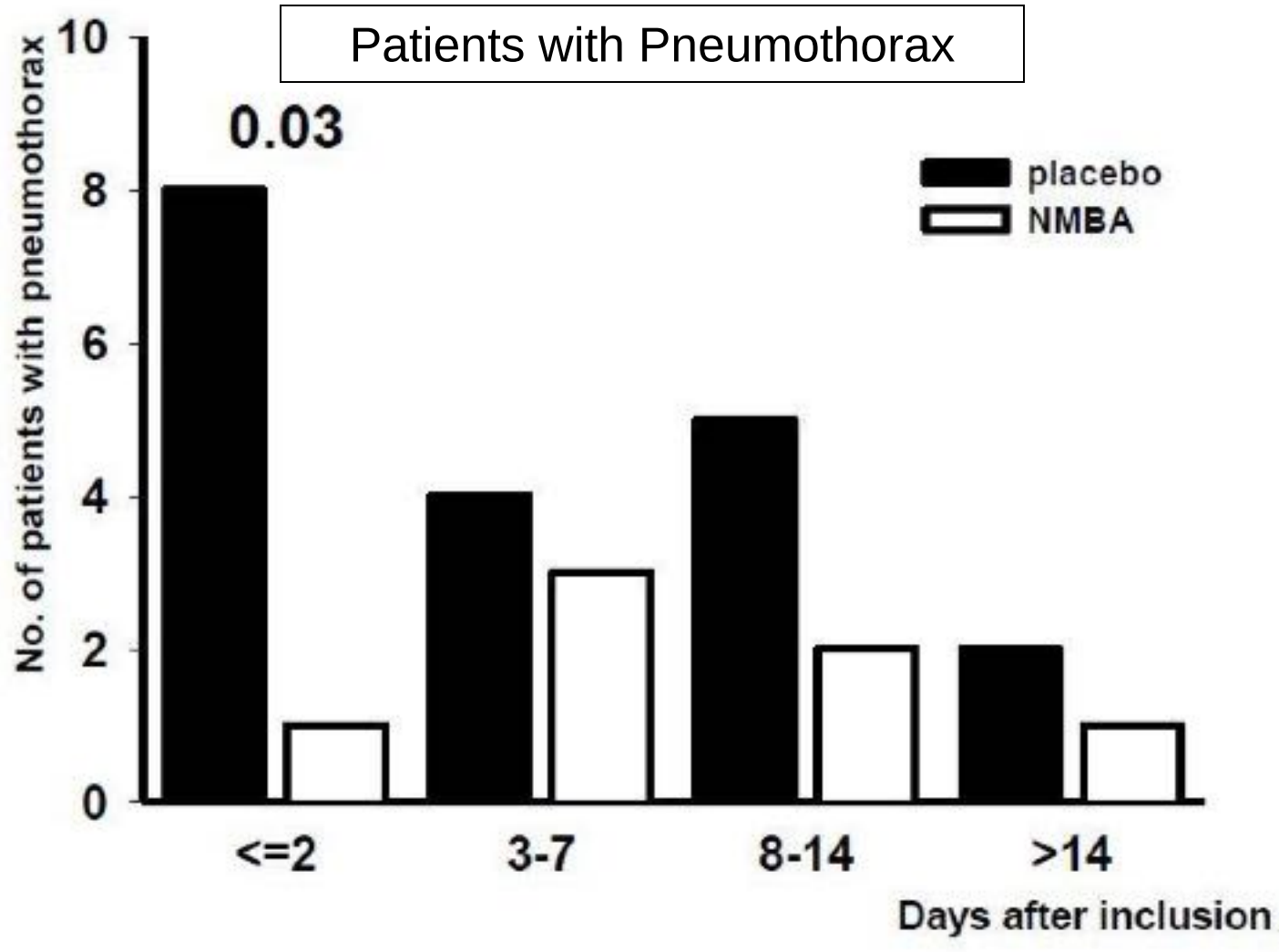


# What are the risks?

# Disadvantages of NMBAs

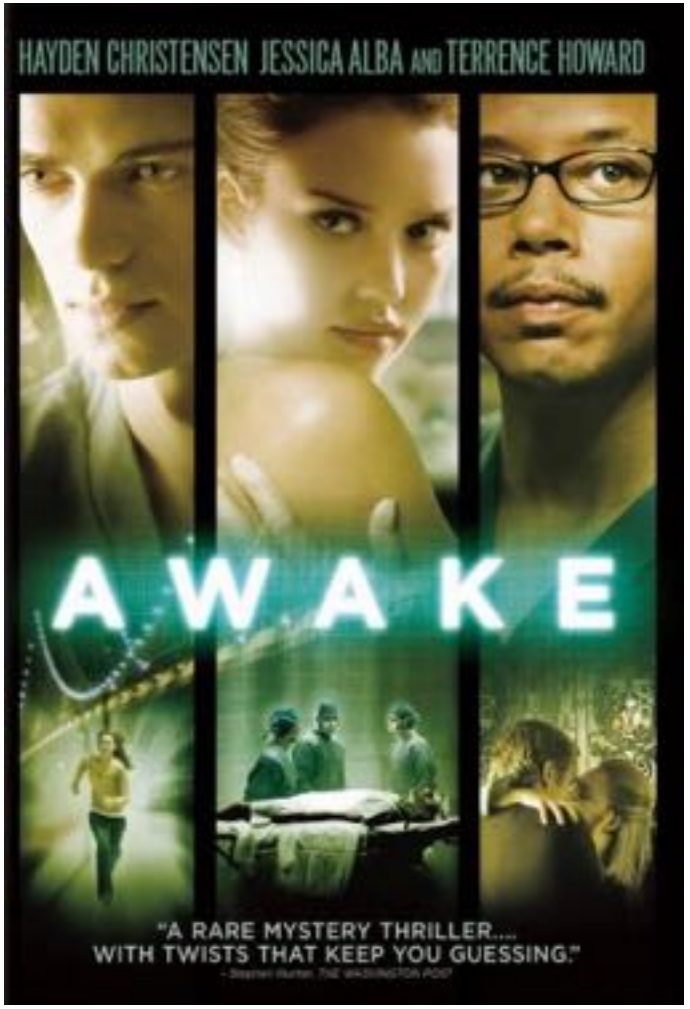
- Effect on $PaO_2$ variable
- Increased atelectasis
- Cephalad displacement of diaphragm
- Airway closure

# Problems with Muscle Relaxants

- Danger of disconnects
- Elimination of cough
- Hinder neurologic & psychologic evaluation
- Prolonged blockade
- Myopathy/Neuropathy

# Overdose of Muscle Relaxants

- An awake but paralyzed patient
  - “A mind entombed in a corpse”
- A paralyzed patient in pain
- Possible nerve & muscle damage
- Difficult and prolonged reversal



# What is the impact on muscle function?

# Prolonged Paralysis following Neuromuscular Blockade


- Op de Coul AA et al: Neuromuscular complications in patients given Pavulon (pancuronium bromide) during artificial ventilation. *Clin Neurol Neurosurg* 1985; 87:17-22
- Lagasse RS et al. Prolonged neuromuscular blockade following vecuronium infusion. *J Clinc Anesth* 1990;2:269-71
- Partridge BL et al. Prolonged neuromuscular blockade after long-term infusion of vecuronium bromide in the intensive care unit. *Crit Care Med* 1990;18:1177-9
- Margolis BD et al. Prolonged reversible quadriparesis in mechanically ventilated patients who received long-term infusions of vecuronium. *Chest* 1991;100:877-8
- Gooch JL, Suchyta MR, Balbierz JM, et al: Prolonged paralysis after treatment with neuromuscular junction blocking agents. *Crit Care Med* 1991; 19:1125-1131
- Segredo V et al. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med* 1992;327:524-8

# Prolonged Paralysis following Neuromuscular Blockade


- Vanderheyden BA et al: Prolonged paralysis after long-term vecuronium infusion. *Crit Care Med* 1992; 20:304-307
- Barohn RJ et al. Prolonged paralysis due to nondepolarizing neuromuscular blocking agents and corticosteroids. *Muscle Nerve* 1994;17:647-54
- Meyer KC et al: Prolonged weakness after infusion of atracurium in two intensive care unit patients. *Anesth Analg* 1994; 78:772-774
- Hoey LL et al. Prolonged neuromuscular blockade in two critically ill patients treated with atracurium. 1995;15:254-9
- Geller TJ et al. Vecuronium-associated axonal motor neuropathy: a variant of critical illness polyneuropathy? *Neuromusc Disord* 2001;11:579-82
- Tabarki B et al. Critical illness neuromuscular disease: clinical, electrophysiolgoical, and prognostic aspects. *Arch Dis Child* 2002;86:103-7

# Neuromuscular Weakness

Intensive Care Med (2001) 27: 1288–1296
DOI 10.1007/s001340101009

ORIGINAL

J. Garnacho-Montero
J. Madrazo-Osuna
J. L. García-Garmendia
C. Ortiz-Leyba
F. J. Jiménez-Jiménez
A. Barrero-Almodóvar
M. C. Garnacho-Montero
M. R. Moyano-Del-Estad

**Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients**

- Prospective controlled trial
- Examined 73 septic patients with multi-organ failure in the ICU
- 63% developed critical illness polyneuropathy (CIP) after 10 days of mechanical ventilation
  - As diagnosed by sensory and motor nerve conduction studies

# Neuromuscular Weakness

- Of the 50 patients that developed CIP…
  - 9 received NMB (6 vecuronium, 3 atracurium)
  - Only 1 patient in the non-CIP group received NMB
- Multivariant analysis found independent RFs for the development of CIP

| | Odds ratio | 95% CI | *p* value |
|---|---|---|---|
| Hyperosmolality | 4.8 | 1.05–24.38 | 0.046 |
| Parenteral nutrition | 5.11 | 1.14–22.88 | 0.02 |
| Use of NMBAs | 16.32 | 1.34–199 | 0.0008 |
| Neurologic failure[a] | 24.02 | 3.68–156.7 | 0.001 |
| Renal replacement therapy | 0.02 | 0.05–0.15 | 0.001 |

[a] GCS below 10

# Neuromuscular Weakness

- Other trials have NOT been able to demonstrate this association:
  - DeJonghe B, et al.  JAMA 2002;22:2859-67
  - Bednarik J, et al.  J Neurol 2005;252:343-51
  - De Letter MA, et al. Crit Care Med 2001, 29:2281-86
  - Berghe G, et al. Neurology 2005, 64:1348-53
  - Papazian L, et al.  NEJM 2010, 363:1107-16

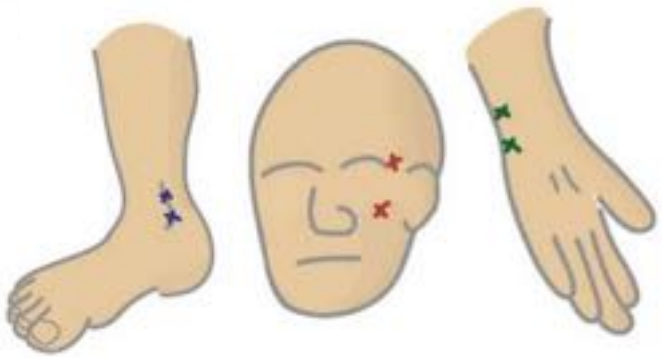
# Neuromuscular Weakness

- Risk factors implicated in the development of critical illness polyneuropathy and myopathy:
  - Severity of illness
  - Female gender
  - Duration of organ dysfunction and duration of ICU stay
  - Renal failure or RRT
  - Hyperosmolality
  - TPN
  - Vasopressor support
  - Central neurologic failure (GCS <10)
  - Hyperglycemia
  - Corticosteroids
  - Neuromuscular blockade

From: Hermans et al. Crit Care 2008;12:238

# Monitoring and Titrating

- Depth of neuromuscular blockade should be assessed by train-of-four (TOF) monitor
- Drug should be titrated to achieve 1-2 twitches in TOF



**Common Monitoring Sites**

**Ulnar nerve**

*Adductor pollicis*

- Adducts thumb

**Facial nerve (CN VII)**

*Orbicularis occuli*

- Closes eyelid

*Corrugator supercilii*

- Furrows brow

**Posterior tibial nerve**

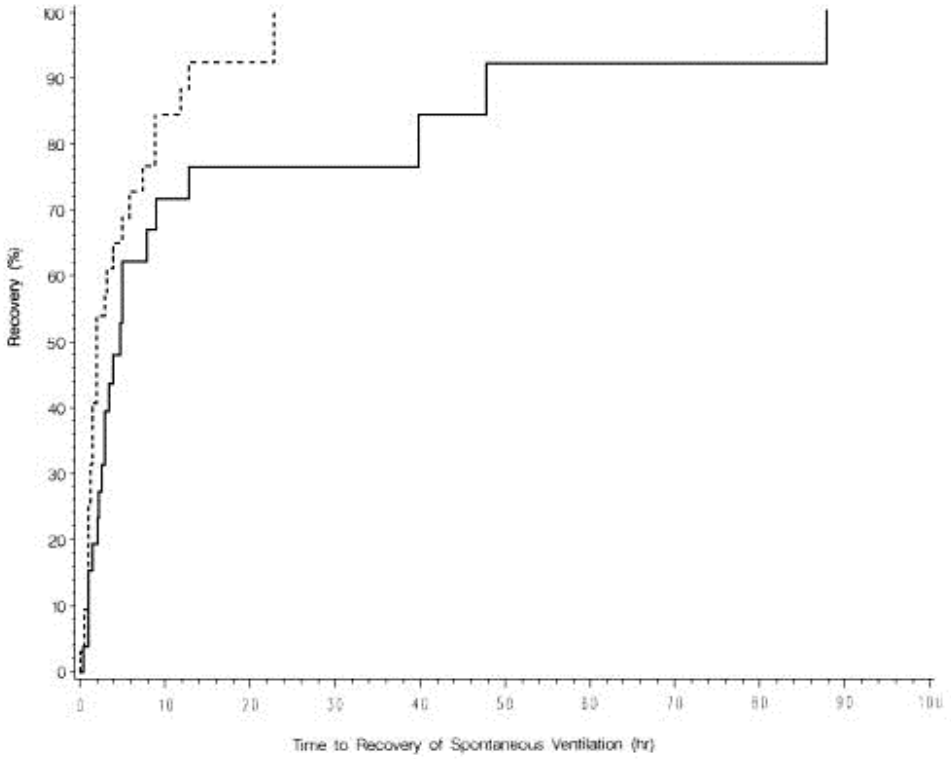
*Flexor hallucis brevis*

- Flexes big toe

# Peripheral nerve stimulation vs. standard clinical dosing of NMBAs in critically ill patients

Rudis MI et al. *Crit Care Med* 1997;25:575-83

- Prospective randomized single-blind trial in 77 pts of PNS monitoring (T4 1:4) vs. clinical response to vecuronium
- PNS group
  - Used less drug/hr
    (0.028 vs 0.07 mg/kg/hr)
  - Less total drug
    (286 vs. 106 mg)
  - Recovered neuromuscular function (RR 1.89) & spont ventilation faster (RR 2.27)



# Available NMB Agents

| Agent | Active Metabolite | Metabolism | Elimination | Side Effects |
|---|---|---|---|---|
| Pancuronium | Yes | Liver | Renal excretion | Vagolytic |
| Vecuronium | Yes | Liver | Renal Excretion | None |
| Rocuronium | No | Liver | Renal Excretion | None |
| Atracurium | No | No | Hofmann elimination* | Histamine release |
| Cisatracurium | No | No | Hofmann Elimination* | None |

* Hofmann elimination = spontaneous degradation in the plasma, independent of organ function

# Supportive Care

- Remember to…
  - Ensure adequate sedation and analgesia prior to neuromuscular blockade
  - Frequent turning and pressure point padding to avoid pressure ulcers
  - Elevate HOB to decrease aspiration and VAP
  - Suction based on secretions as patient will not have cough reflex
  - Very close supervision and avoidance of ventilator disconnections
  - Apply eye lubrication and/or cover eyelids to avoid corneal abrasions

# Use of NMBA's in ARDS

- Supportive evidence provided by 3 randomized studies – all from the same group
- No data to support use for other than severe ARDS
- Use of neuromuscular blockade should be rare
  - Should have little need beyond > 48 hr
- Avoid corticosteroids and steroidal NMBAs (e.g., vecuronium, pancuronium)
- Discontinue NMBAs As soon as practical