



Rational Management of Neuromuscular Blockers

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Why monitor?

- To determine onset of block and readiness for intubation or procedure start.
- To guarantee paralysis when patient movement would be deleterious
- To assess ability to reverse relaxants.
- To time recovery to coincide with end of surgery
- To ensure adequate recovery and readiness for extubation.



Why monitor?

The single most important aspect of neuromuscular monitoring centers around recovery issues.

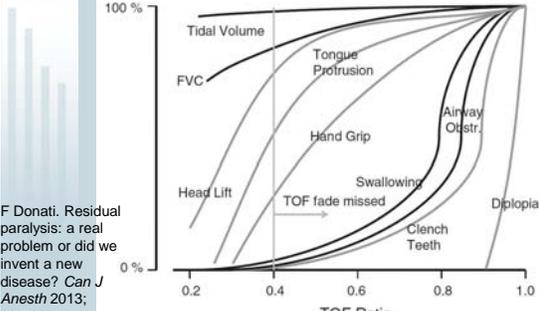


Extubation Criteria- Good reason to monitor

- Former standard was TOF ratio > .7
 - Associated with eye-opening, hand grasp, and acceptable recovery of spirometry parameters
- Recent studies have shown that at .7, pharyngeal dysfunction may persist
- Clinical tests show poor sensitivity (~12%) to detect residual blockade
- Have to "fail" 8 clinical tests just to achieve 50% sensitivity (Cammu, et. al, 2006)
- Clinical tests poorly specific. May be weak even if TOFR > 0.9
- TOFR of 0.9 is now accepted level of recovery/extubation



(Un)reliability of clinical indicators

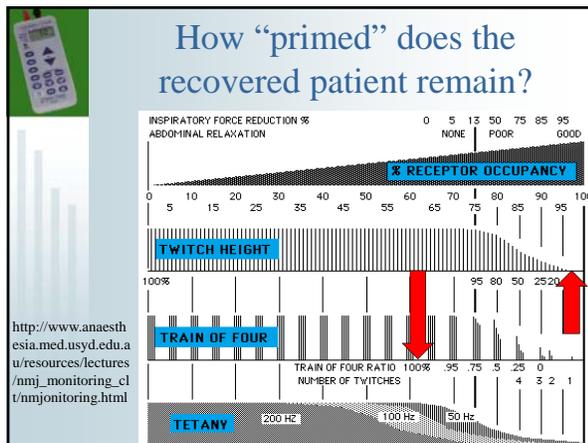
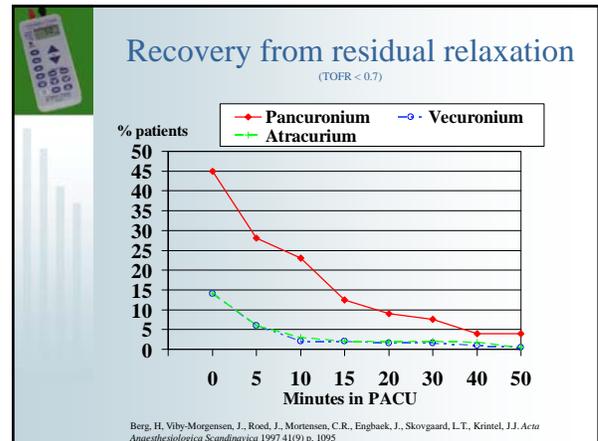


F Donati. Residual paralysis: a real problem or did we invent a new disease? *Can J Anesth* 2013; 60:714-29

Complications of Residual Relaxation

Patients with Postoperative Pulmonary Complications						
	Pancuronium			Vecuronium or Atracurium		
	Number	n	%	Number	n	%
TOFR > 0.7	167	8	4.8	426	23	5.4
TOFR < 0.7	59	10	16.9 *	24	1	4.2

Berg, H, Viby-Morgensen, J., Røed, J., Mortensen, C.R., Engbaek, J., Skovgaard, L.T., Krintel, J.J. *Acta Anaesthesiologica Scandinavica* 1997 41(9) p. 1095



- ### Older patients are at more risk
- Residual blockade 60% in elderly and 30.0% in younger patients.
 - Airway obstruction, hypoxemic events, symptomatic weakness, pulmonary complications, and prolonged PACU stay were more common in elderly.
 - Most adverse events were observed in patients with residual blockade (young and old)
- Murphy, et al. Residual Neuromuscular Block in the Elderly: Incidence and Clinical Implications. *Anesthesiology* 2015;123(6):1322-1336.

- ### Older patients are at more risk
- 1,444 patients retrospective review in Australia
 - Neostigmine reversal was associated with more pulmonary complications with increasing age and ASA status, and
 - Greater PONV overall
 - Sugammadex group: very low complications
- Ledowski, et al. Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade. *Eur J Anaesthesiol* 2014;31:423-429

- ### Duration of Drug May be Key
- PORC is lower in patients receiving intermediate-acting relaxants.
 - Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarization: a meta-analysis. *Br J Anaes.* 98(3):302-16, 2007 Mar.
 - Incidence of T4/T1 < .9 greater in vecuronium vs. cisatracurium.
 - Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. 2010. *Br J Anaes.* 105(3):304-9.



Implications of residual relaxation

- decrease of inspiratory retropalatal and retroglottal upper airway volume
- attenuation of the normal increase in anteroposterior upper airway diameter during forced inspiration
- decrease in genioglossus activity during maximum voluntary tongue protrusion
 - Eikermann, Matthias (2007). "The predisposition to inspiratory upper airway collapse during partial neuromuscular blockade.". *American journal of respiratory and critical care medicine* 175 (1), p. 9.



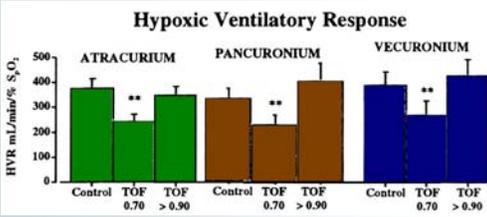
Complications of Residual Relaxation

- Posterior cricoarytenoid muscles return to function 5 minutes after lateral cricoarytenoid muscle.
- Hemmerling TM, Michaud G, Trager G, Donati F. Simultaneous determination of neuromuscular blockade at the adducting and abducting laryngeal muscles using phonomyography. *Anesthesia & Analgesia*. 2004;98(6):1729-33.



Complications of Residual Relaxation

Hypoxic Ventilatory Response

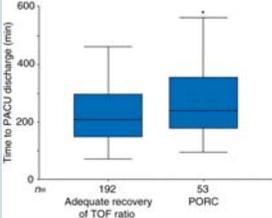


Drug	Condition	HYR (mL/min/% SpO ₂)
ATRACURIUM	Control	~380
	TOF 0.70	~240**
	TOF > 0.90	~350
PANCURONIUM	Control	~330
	TOF 0.70	~220**
	TOF > 0.90	~400
VECURONIUM	Control	~380
	TOF 0.70	~260**
	TOF > 0.90	~420

From: Eriksson, L.L. *Acta Anaesthesiol Scand*, (1996) Volume 40(5) 520-523.



Residual relaxation prolongs PACU stay



Group	n	Time to PACU discharge (min)
Adequate recovery of TOF ratio	192	~200
PORC	53	~280

- Butterly A, Bittner EA, George E, Sandberg WS, Eikermann M, Schmidt U. Postoperative residual curarization from intermediate-acting neuromuscular blocking agents delays recovery room discharge. 2010. *Br J Anaes*. 105(3):304-9.




Is reversal mandatory?



- Short-acting drugs make spontaneous recovery (without reversal) feasible.
- Advantages- cost, nausea?, side-effects



Complications of Residual Relaxation

- 57,000 cases
- 2,846 (5%) had SpO₂ < 90% after extubation or were re-intubated.
- Vecuronium, roc, and cis connected to increased risk for respiratory events
- Neither PNS monitoring nor reversal reduced the incidence of events.
- Vlessides, M. Neuromuscular Blockers Linked to Post-Op Breathing Problems *Anesthesiology News* (04/01/12) Vol. 38, No. 4

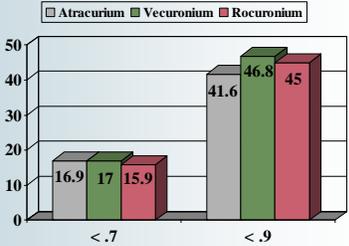



Is reversal mandatory?

- To challenge things further...
- PNS subjective measurement tests (tactile/visual) very specific, but not very sensitive
 - 95% of pts who demonstrate fade do have residual relaxation.
 - Complete recovery $>.9$ seen in only 50% of pts who appear to have no fade.
- Patients not reversed show up in PACU with residual blockade



Incidence of residual relaxation



TOF Ratio	Atracurium	Vecuronium	Rocuronium
<.7	16.9	17	15.9
<.9	41.6	46.8	45

TOF Ratios among 526 patients 2 hours after administration of relaxant without reversal.

Debuene, B, Plaud, B, Dilje, M, Donati, F. Residual Paralysis in the PACU after a Single Intubating Dose of Nondepolarizing Muscle Relaxant with an Intermediate Duration of Action. *Anesthesiology*, 2003;98(5): 1042-1048



So we need to reverse, right?

- 164 patients paralyzed using vecuronium, atracurium, or rocuronium
- Of those not reversed, 60% showed residual relaxation (TOFR < 0.8)

Hayes, A.H., Mirakhur, R.K., Breslin, D.S., Reid, J.E., McCourt, K.C. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. (2001) *Anaesthesia*. 56(4) 312-8.



So we need to reverse, right?

- 164 patients paralyzed using vecuronium, atracurium, or rocuronium
- Of those not reversed, 60% showed residual relaxation (TOFR < 0.8)
- Of those reversed, 49% showed residual relaxation (TOFR < 0.8)**

Hayes, AH, Mirakhur, RK, Breslin, DS, Reid, JE, McCourt, KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. *Anaesthesia*. 2001;56(4): 312-8.



So we need to reverse... right?

- 640 patients
- 40% did not exceed TOFR > 0.9 even after reversal
- 15% did not exceed TOFR > 0.7
- Cammu GG, et. al. Postoperative residual paralysis in outpatients versus inpatients. *Anes Analg*.2006;102:426-9.



Incidence of residual relaxation

- 1,571 patients from 32 hospitals in China.
- Routine practice
- 41% were < 0.7; and 17% were < 0.9
- Longer lead time with neostigmine and longer interval since last NMB dosing were associated with less PORC.

Yu, et. al. Incidence of postoperative residual neuromuscular blockade after general anesthesia: a prospective, multicenter, anesthetist-blind, observational study *Current Medical Research and Opinion* 2016;32(1)

Maybe we need to reverse more conservatively?

- 120 patients maintained at TOF= 2
- Reversed with TOF 2-4 using neostigmine
- Patients met extubation criteria
- Before extubation, 58% had TOFR <0.7
- 88% had TOFR < 0.9
- In PACU, 8% were < 0.7; 32% < 0.9

Murphy, G. et al. Residual paralysis at the time of tracheal extubation. *Anes Analg.* 2005;100:1840-5.

Neostigmine after recovery may impair neuromuscular function

- Neostigmine after recovery increases upper airway collapsibility and impairs the genioglossus electromyogram in response to negative pharyngeal pressure.

Herbstreit, Frank; Zigrann, Daniela; Ochterbeck, Christof; Peters, Jürgen; Eikermann, Matthias
Anesthesiology. 113(6):1280-1288, December 2010.

Confused yet?

Can we compensate with more effective monitoring?

Methods of stimulation

Mode	Characteristics	Main Uses	Interpretation
Single Twitch	0.2 ms in duration 	Onset Monitor <i>depolarizing</i> block	Divide twitch height by height of control twitch prior to relaxation. Depression of twitch relates to degree of block.

Methods of stimulation

Mode	Characteristics	Main Uses	Interpretation
Train Of Four	4 stimuli 500 ms apart 	Onset, Maintenance, Recovery, Extubation (ratio) No potentiation (freq. use O.K.)	1. Count responses to determine block of 75-100% (4/4 response) 2. Compare height of fourth to first twitch ("T ₄ /T ₁ , or TOF ratio") >0.9 = adequate pulmonary function for extubation.

Limitations of PNS information

	Sensitivity		Specificity	
	TOF <.7	TOF <.9	TOF <.7	TOF <.9
Head lift	19	11	85	87
TOF	27	11	98	99

Sensitivity and specificity of head lift and TOF ratio to detect TOF ratios <.7 or .9

Debaene, B, Plaud, B, Dilly, M, Donati, F (2003) Residual Paralysis in the PACU after a Single Intubating Dose of Nondepolarizing Muscle Relaxant with an Intermediate Duration of Action. *Anesthesiology*, 98(5): 1042-1048

Methods of stimulation

Mode	Characteristics	Main Uses	Interpretation
Double Burst Stim.	3 rapid stimuli followed in 750 ms by 2 or 3 more 	Extubation- (easier to evaluate fade clinically than TOF) More sensitive than TOF, less painful than tetany.	Equal twitch height corresponds to T4/T1 > 0.7 No discernable fade = no significant block

Benefit of Double Burst Stimulation

Pancuronium guided by:	Mean TOFR in PACU
Clinical criteria	0.53
TOF	0.67
Double Burst	0.81

- Ueda N, Muteki T, Tsuda H, Inoue S, Nishina H. Is the diagnosis of significant residual neuromuscular blockade improved by using double-burst nerve stimulation?. *European Journal of Anaesthesiology*. 8(3):213-8, 1991.

Limitations of PNS information

	Sensitivity		Specificity	
	TOF <.7	TOF <.9	TOF <.7	TOF <.9
Head lift	19	11	85	87
TOF	27	11	98	99
DBS	35	14	98	99

Sensitivity and specificity of head lift, TOF ratio and Double burst stimulation to detect TOF ratios <.7 or .9

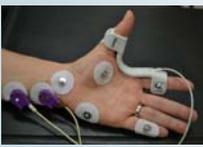
Debaene, B, Plaud, B, Dilly, M, Donati, F (2003) Residual Paralysis in the PACU after a Single Intubating Dose of Nondepolarizing Muscle Relaxant with an Intermediate Duration of Action. *Anesthesiology*, 98(5): 1042-1048

Methods of stimulation

Mode	Characteristics	Main Uses	Interpretation
Tetany 50 Hz	0.2 ms repeated q 20µs 	Extubation- IDs small amt of residual block	5-second sustained response (no fade) = ready for extubation (not necessarily complete reversal) Indicates muscle strength equivalent to 5-second head lift.
Tetany 100 Hz	0.2 ms repeated q 10µs 	Extubation- more sensitive, but less specific. Can cause fade in absence of relaxant	

Nerve stimulators

- Various models; similar functions
- Increasing occurrence of automated monitors and new modalities

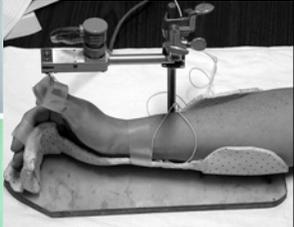



Nerve stimulators- Myographs

- Mechanomyography measures the force exerted by a muscle
- Relaxometer (Groningen University)
- Myograph 2000 (Biometer)



Mechanomyography

Nerve stimulators- Accelerometers

- Accelerometry- if mass is constant, acceleration is equal to force
- TOF-Guard (Biometer)
- TOF-Watch (Phillips Co.)

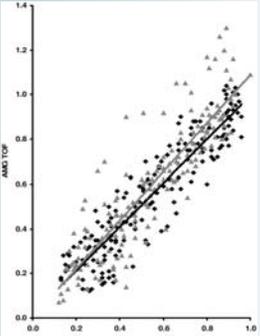



Nerve stimulators- Accelerometers vs. Myographs

- Wider variability in results
- Onset same; recover appears slower with accelerometer.
- Advantage: no prep calibration needed



Nerve stimulators- Accelerometers vs. Myographs



Capron, Fortier, Racine, & Donati. (2006) Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. *Anesth. Analg* 102(5) 1578-1584.

Nerve stimulators- Accelerometers vs. Myographs

- Accelerometry performs better than DBS or tetanus, but does not reliably detect low degrees of residual paralysis
- Samet A. Capron F. Alla F. Meistelman C. Fuchs-Buder T. Single acceleromyographic train-of-four, 100-Hertz tetanus or double-burst stimulation: which test performs better to detect residual paralysis?. *Anesthesiology*. 102(1):51-6, 2005 Jan.



Accelerometry- Sensitivity

TOFR by MMG	TOF	DBS	50hZ TET	100hZ TET	AMG
0.1-0.19	71%	100%	42%	89%	100%
0.4-0.49	22%	95%	24%	75%	100%
0.5-0.59	8%	72%	6%	90%	100%
0.9-1.0	0%	4%	0%	59%	69%

Capron, Fortier, Racine, & Donati. (2006) Tactile fade detection with hand or wrist stimulation using train-of-four, double-burst stimulation, 50-hertz tetanus, 100-hertz tetanus, and acceleromyography. *Anesth. Analg* 102(5) 1578-1584.

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Nerve stimulators- Kinemyography

- Neuromuscular Transmission Module (Datex)
- Like AMG, but measures degree of movement

New Technology Tri-axial Accelerometry

Neuro-Trace III

New Technology Phonomygraphy

- Phonomygraphy- measurement of low-frequency sounds created during muscle contraction.
- Preliminary results similar to MMG

Phonomygraphy

- Good agreement between mechanomyographic measurements at the adductor pollicis muscle and phonomygraphic measurements at the thenar and the first dorsal interosseus muscles.
- Phonomygraphy of those two muscles could be used interchangeably with mechanomyography of adductor pollicis for clinical purposes.
- *Canadian Journal of Anaesthesia*, 2004



What do you think?

Which of these is most reliable at reducing residual relaxation?

- A. administer only a half-dose of relaxant (e.g. 0.3mg/kg rocuronium)
- B. administer a double dose of neostigmine (e.g., 0.1 mg/kg)
- C. monitor via train of four
- D. monitor via double burst stimulation

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Residual Relaxation is...

- Prevalent
- Associated with complications
- Difficult to detect
- Present regardless of monitoring or reversal



Minimizing residual relaxation

- Reduce dosage of drugs:
 - Low dose Rocuronium-

Dose (mg/kg)	Time to TOFR recovery to 0.8 (min)
0.15	13
0.22	16
0.3	27

- Use ED₅₀ or ED₉₅ Instead of intubating dose
- Use drugs with rapid elimination profiles; infuse for better control
 - Recovery index of Cis faster than Roc after infusion

Jellish, WS, Brody, M, Sawicki, K, Slogoff, S. Recovery from neuromuscular blockade after either bolus and prolonged infusions of cisatracurium or rocuronium using either isoflurane or propofol-based anesthetics. (2000) Anesthesia & Analgesia. 91(5):1250



Minimizing residual relaxation

- Spontaneous recovery prior to reversal does not guarantee complete reversal
- Provide additional time when possible
- Avoid long-acting drugs (Pancuronium)
 - Can achieve same stability with infusion of other agents



Practical Pearls

- Recognize limitations of “human interpreted” nerve stimulators- Low sensitivity for residual relaxation.
- Always monitor; automated monitors are best



Practical Pearls

- Reverse conservatively
 - TIVA: at least 2 twitches
 - Volatile: 4 twitches
 - If TOFR > .9 (determined quantitatively), do not reverse
 - Reverse with 15 minute lead time prior to extubation.
- Brull, Sorin J (2010). Residual neuromuscular block: lessons unlearned. Part II: methods to reduce the risk of residual weakness. *Anesthesia and analgesia*, 111(1):129.
- Kopman AF, Zank LM, Ng J, Neuman GG. (2004) Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? *Anesthesia & Analgesia*, 98(1):102.



Practical Pearls

- Balance reversal decisions against potential for residual relaxation and complications:
 - Advanced age
 - Hypothermia
 - Recent or ample dosing of relaxant or prolonged surgery
 - Concurrent medical conditions (COPD)
 - Abdominal, chest, or any prolonged surgery



Summary

- Residual relaxation is a common problem, which may lead to complications.
- Human-interpreted PNS data is not sensitive to residual relaxation.
- Choice of PNS mode (such as double burst stim.), and monitoring site may improve decision-making process re: relaxants.
- Use of rapidly-metabolized drugs or lower doses of relaxants may improve safety.