Everything You Believe About Neuromuscular Blockade and Monitoring is WRONG

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History – 1st Use

THE USE OF CURARE IN GENERAL ANESTHESIA

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EVERY anesthetist has wished at times that he might be able to produce rapid and complete muscular relaxation in resistant patients under general anesthesia. This is a preliminary report on the clinical use of a drug which will give this kind of relaxation, temporarily and apparently quite harmlessly.

The physiological action of curare as an interrupter of the neuromuscular mechanism has long been recognized, and its best known practical applications have been by South American Indians as an arrow poison and in the physiological laboratory. The crude curare of the South American forests contains numerous toxic substances, but it has been possible so to refine the drug that the elements of cardiac and respiratory depression are removed and only the "pure" curare effect remains.

For several years this purified curare has been used experimentally in psychiatric hospitals to prevent traumatic complications in convulsive shock therapy. Bennett (1), Gray (2) and others have reported on the efficiency and harmlessness of curare when used for this purpose in quite a large number of patients.

Anesthesiology 3: 418, 1942

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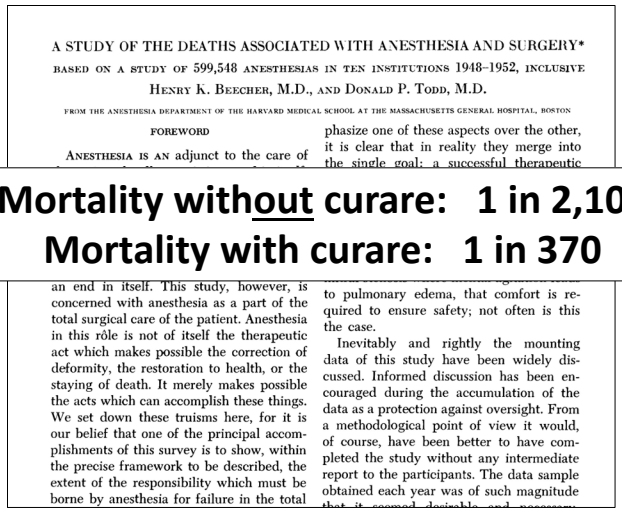
History – 1st Concern



A STUDY OF THE DEATHS ASSOCIATED WITH ANESTHESIA AND SURGERY*

BASED ON A STUDY OF 599,548 ANESTHESIAS IN TEN INSTITUTIONS 1948–1952, INCLUSIVE

HENRY K. BEECHER, M.D., AND DONALD P. TODD, M.D.

FROM THE ANESTHESIA DEPARTMENT OF THE HARVARD MEDICAL SCHOOL AT THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON

FOREWORD

ANESTHESIA IS AN adjunct to the care of

phasize one of these aspects over the other, it is clear that in reality they merge into the single goal: a successful therapeutic

an end in itself. This study, however, is concerned with anesthesia as a part of the total surgical care of the patient. Anesthesia in this rôle is not of itself the therapeutic act which makes possible the correction of deformity, the restoration to health, or the staying of death. It merely makes possible the acts which can accomplish these things. We set down these truisms here, for it is our belief that one of the principal accomplishments of this survey is to show, within the precise framework to be described, the extent of the responsibility which must be borne by anesthesia for failure in the total

to pulmonary edema, that comfort is required to ensure safety; not often is this the case.

Inevitably and rightly the mounting data of this study have been widely discussed. Informed discussion has been encouraged during the accumulation of the data as a protection against oversight. From a methodological point of view it would, of course, have been better to have completed the study without any intermediate report to the participants. The data sample obtained each year was of such magnitude

Mortality without curare: 1 in 2,100
Mortality with curare: 1 in 370

Annals of Surgery 140: 2, 1954

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History – Beecher & Todd

- This might have killed the use of curare EXCEPT that it occurred at a time of rapid growth in our understanding of ventilation, oxygenation and of the neuromuscular junction.
  - Endotracheal tubes and ventilators
  - Neostigmine Reversal (mid 50s)
  - **Peripheral Nerve Stimulators (1956)**
    - Single Twitch and Tetanus Only

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Monitoring of NMB - History

- Modern monitoring started with the introduction of the "Train of Four" by Hasan Ali in 1970:
  - Ali HH, Utting JE, Gray C. *Stimulus Frequency in the Detection of Neuromuscular Block in Humans.* BJA 42: 967, 1970

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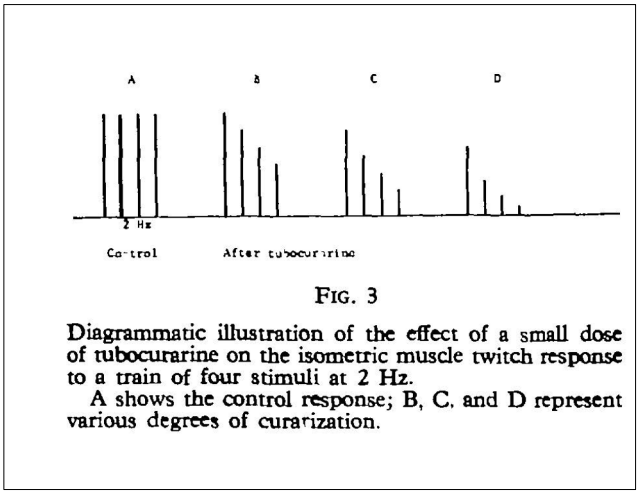

FIG. 3

Diagrammatic illustration of the effect of a small dose of tubocurarine on the isometric muscle twitch response to a train of four stimuli at 2 Hz.
A shows the control response; B, C, and D represent various degrees of curarization.

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Monitoring of NMB - History

- This work was done quantitatively (with the thumb attached to a strain gauge).
- 1st described the "Train of Four Ratio" (height of the 4th twitch/height of the 1st twitch) to quantitate the degree of fade
- **BUT** also commented on its qualitative value
  - You can easily "see" each of the 4 twitches. If you see fade, you know there is residual block.

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Monitoring - History

- So Peripheral Nerve Stimulators with TOF became common.
- BUT the monitoring never became universal in the USA.
- NMB monitoring is NOT an ASA Standard
- Many American providers NEVER monitor (or only sporadically).
- In the 2020 paper by Kherterpal (later), 36% of cases (out of 44,000) had **no** documented monitoring.

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OK, So We Don't Monitor. Is this a Problem?

- Yes, we have known for >40 years that incomplete reversal of patients in the PACU is common – even with rocuronium.
  - Viby Mogensen 1979: 42% (curare, gallamine, pancuronium)
  - Maybauer 2007: 44% (rocuronium)
  - Murphy 2008: 30% (rocuronium)
  - Todd 2014: 31% (rocuronium)
  - RECITE 2015: 56.5% (rocuronium)
  - Todd 2017 (UMN): 48% (rocuronium)

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OK, But Does Residual Paralysis Matter Clinically?

- YES!!!! There is a clear relationship between residual paralysis and postop respiratory problems.

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Just One Example

- Murphy et al. Anesthesiology 123: 1322-1335, 2015.
  - 150 patients age ≤ 50. 30% incidence residual paralysis in PACU (TOF <0.9).
  - 150 patients age ≥ 70. 57% incidence of residual paralysis in PACU.

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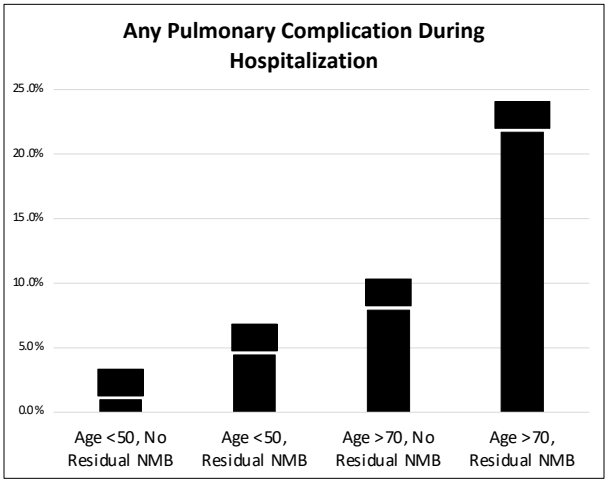

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Why, with data this clear, do we (providers) seem to be BLIND to this problem.

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- **Reasons – The Mythology of NMB Pharmacology, Reversal and Monitoring**
  - Rocuronium is short-acting and predictable. If I time it right, reversal is not needed.
  - Reversing rocuronium is fast, easy and dependable. Give neostigmine, wait 5 minutes and extubate. With sugammadex, even easier.
  - Qualitative twitch monitoring is sufficient to avoid residual paralysis.
  - Clinical signs (head lift etc.) are sufficient to avoid residual paralysis
  - Patient breathing well, good ETCO2 – he's OK to extubate.

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EVERY ONE OF THESE STATEMENTS IS WRONG!

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Myths: Roc is short acting and predictable. Textbooks say duration is 25-35minutes

- Debaene et al 2003.
  - 402 patients received 0.6mg/kg rocuronium (2x ED95) at induction. NO ADDITIONAL rocuronium given. NO REVERSAL.
  - Examined TOF ratio (quantitatively) at case end or PACU, along with clinical assessments.

Debaene et al. Anesthesiology 98: 1042, 2003

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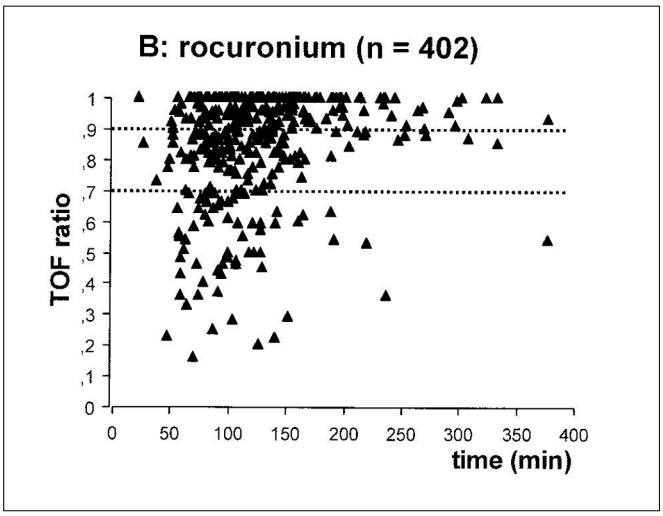

45% of Patients Had TOF <0.9

Even after 120 minutes, >30% Had TOF <0.9, and 10% <0.7!

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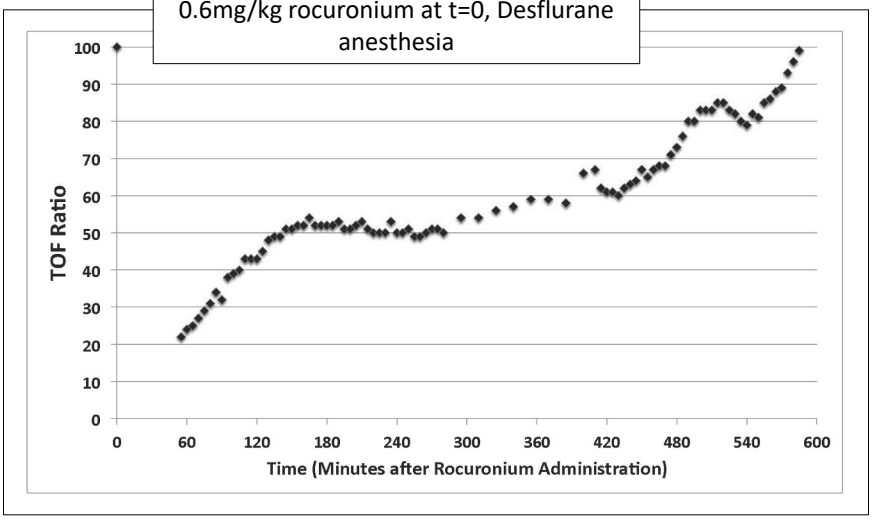
54y/o F, ASA 2, No renal disease, no meds.
0.6mg/kg rocuronium at t=0, Desflurane anesthesia



Leonard and Todd. A&A Case Reports. 9: 190-192, 2017

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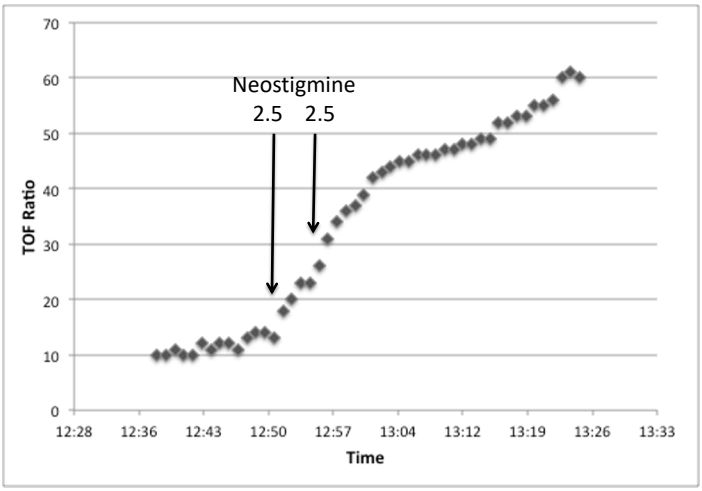
Rocuronium is Easy To Reverse



Even 4 Twitches Don't Guarantee Easy Reversal

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And if rocuronium is so easy to reverse with neostigmine, then why do we have such a high incidence of residual paralysis?

And we'll talk about sugammadex in a minute

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Myth: Qualitative Monitoring is Adequate

Visual and Tactile Assessment of Fade to TOF vs Quantitative Measurement

Assessment Method	Threshold	Range
Visual	0.51	0.38 - 0.73
Manual - Thumb	0.66	0.42 - 0.92
Manual - Hand	0.66	0.46 - 0.95

You cannot SEE (or feel) fade if the TOF ratio is >0.4.

Viby-Mogensen et al. Anesthesiology 63: 440, 1985.

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Myth: Clinical Measures

Clinical Measure	Sensitivity	Specificity
General weakness	0.35	0.78
Inability to lift head for 5 sec	0.19	0.88
Inability to lift leg for 5 sec	0.25	0.84
Inability to sustain hand grip for 5 sec	0.18	0.89
Inability to perform sustained tongue depressor test	0.22	0.88

Brull & Murphy Anesth & Analg 111: 129, 2010

In Debaene 2003, a successful sustained head lift was seen in 82% of patients who actually had a TOF ratio <0.9. And in 80% of patients with a TOF ratio <0.7.

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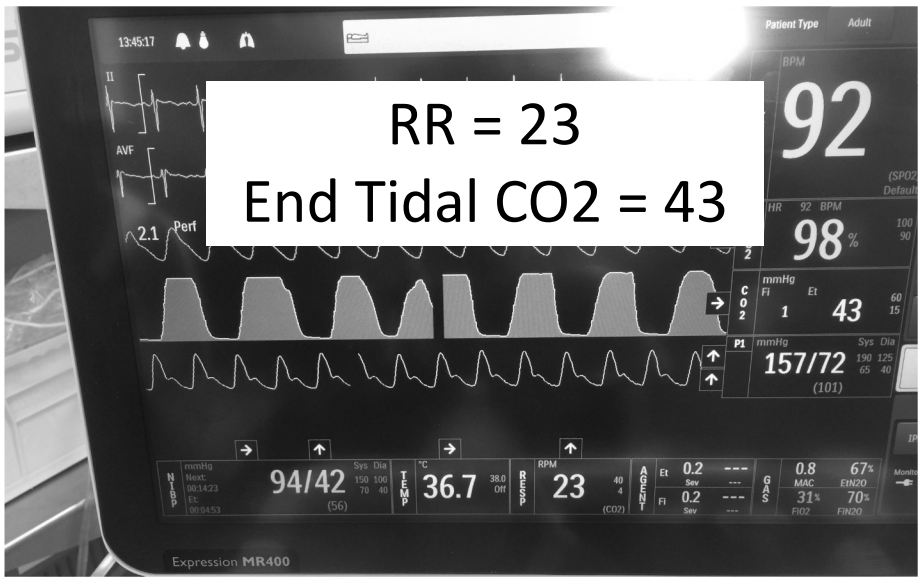
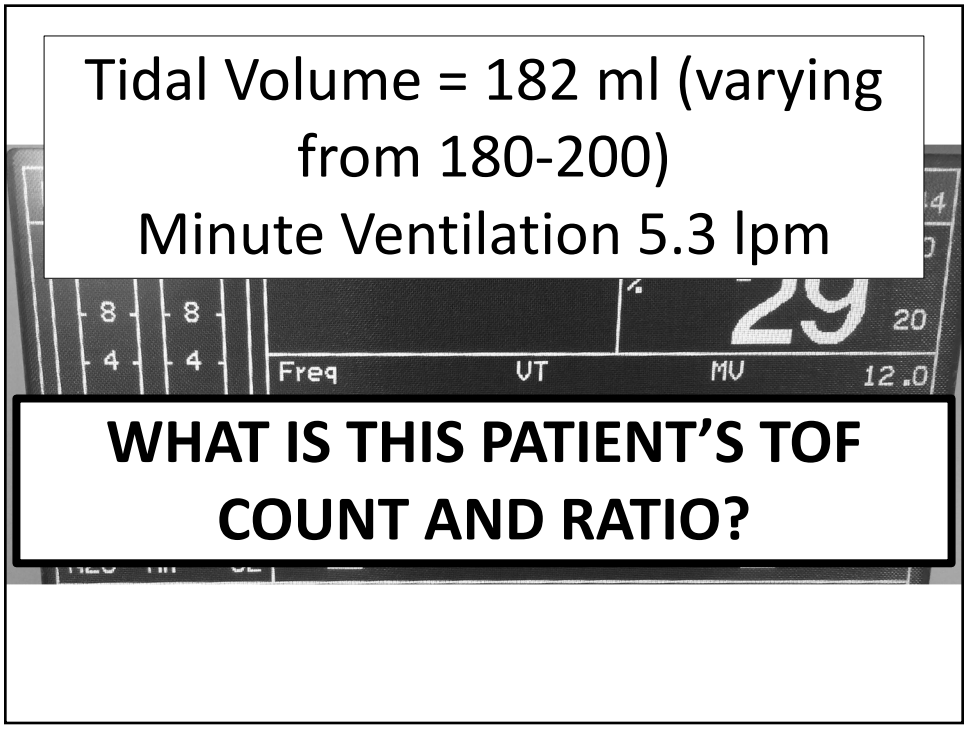
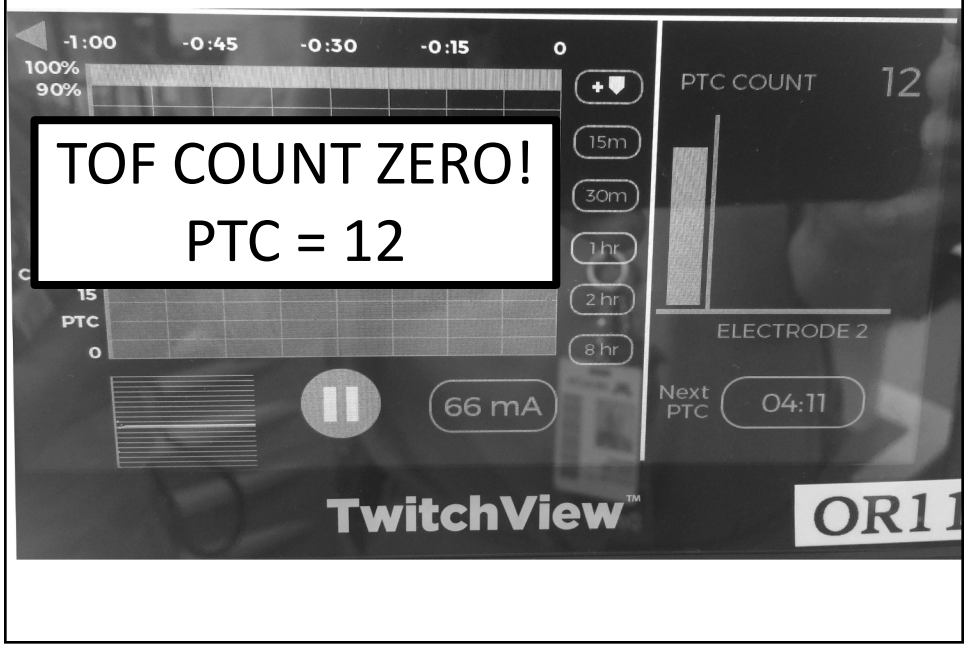

RR = 23
End Tidal CO2 = 43
13:45:17
Patient Type
Adult
92
98
43
157/72
94/42
36.7
23
Expression MR400

23


Tidal Volume = 182 ml (varying from 180-200)
Minute Ventilation 5.3 lpm
WHAT IS THIS PATIENT'S TOF COUNT AND RATIO?
Freq
VT
MV
12.0

24



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- If you SEE fade to TOF, or if you SEE a failure to sustain a head-lift, you KNOW the patient is paralyzed (hi specificity).
- If you DO NOT SEE fade or DO NOT SEE a failure to sustain a head-lift, YOU KNOW NOTHING! (low sensitivity).
- And respiration is totally meaningless.

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- The ONLY way to reliably detect residual paralysis is QUANTITATIVE monitoring, specifically the direct assessment of the TOF ratio (height of the 4th twitch divided by the height of the first).
- Why don't we all do this?
- Because until about 2 years ago, the monitoring technology SUCKED.

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Quantitative Monitoring Technology

- 3 basic (clinical) methods
  - Mechanomyography (or Kinetomyography) – GE Only
  - Accelerometry – Philips, TOFScan, StimPod.
  - Electromyography – GE, Blink Twitchview, Senzime Tetragraph

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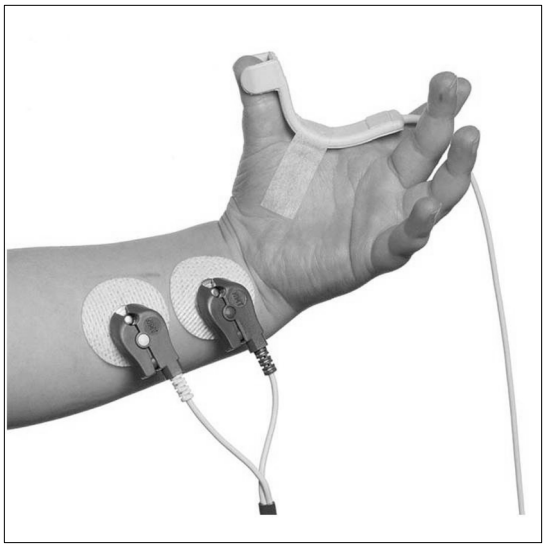
Mechanomyography (Kinetomyography) - GE



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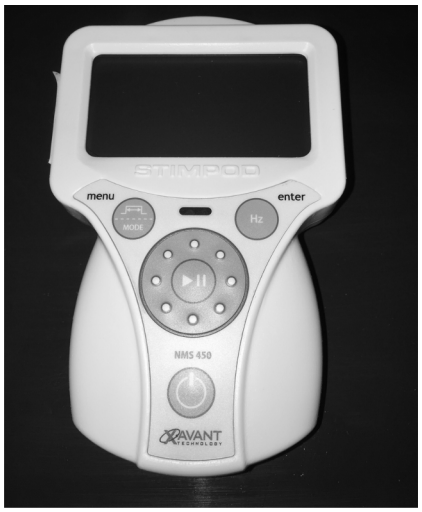
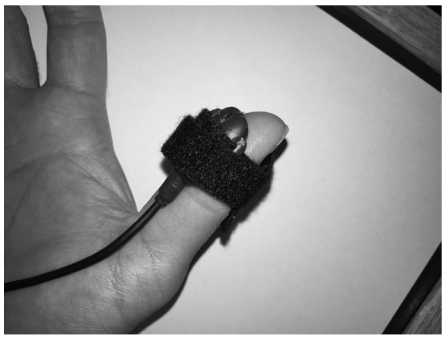
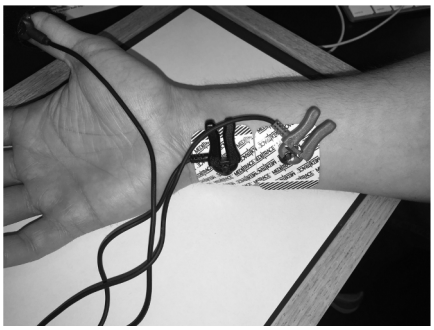
Accelerometry – Stimpod 450







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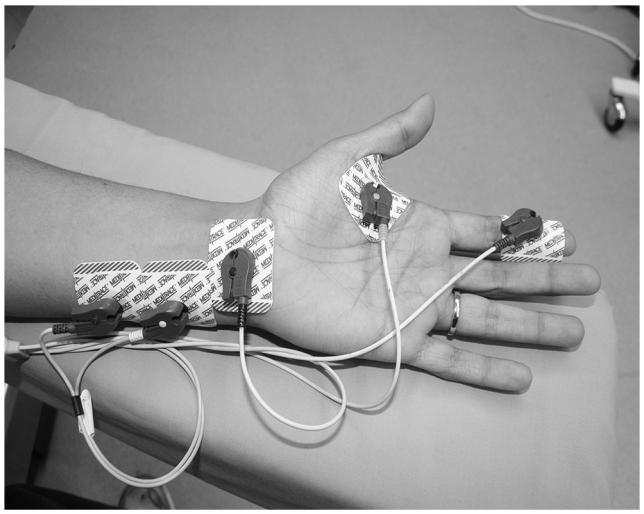
Electromyography - GE



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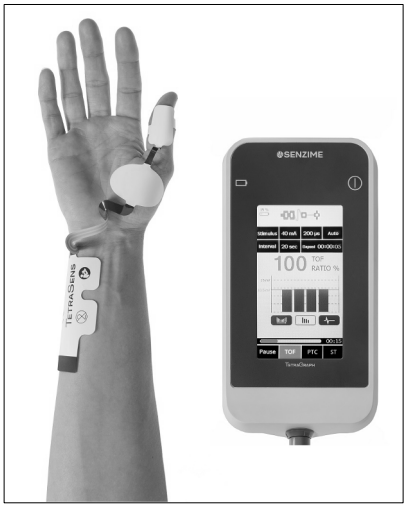
EMG - TwitchView

EMG - Tetragraph



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Comment

- Kinetomyography and Accelerometry record MOVEMENT. If movement restricted (e.g tucked hards), they may not work. Also "baseline problems" (>100%).
- Electromyography DOES NOT depend on movement. Works just fine with with tucked arms.
- But in terms of clinical outcomes, there is no reason to believe that one method is "better" than another IF used correctly.
- But the new generation EMG systems are clearly EASIEST to use.

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- But it takes more than just buying equipment. You have to convince clinicians to USE the equipment and to properly interpret what they are seeing.
- Let me tell you a story.

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The University of Iowa

- In January 2011, we purchased GE EMG twitch-monitoring equipment for ALL of our Main OR's. This was accompanied by an extensive educational program.
- By July 2011, the system was only being used in <50% of patients given NMB (data in Epic).
- In August 2011, we had a "sentinel event" in PACU.
- So we started twitching patients in the PACU.
-

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- Our initial residual paralysis rate was 31%. These results were presented to the Department. Then we did it again. And again. And again. And again. And again – final round in June-July 2014. We twitched over 1000 PACU patients!

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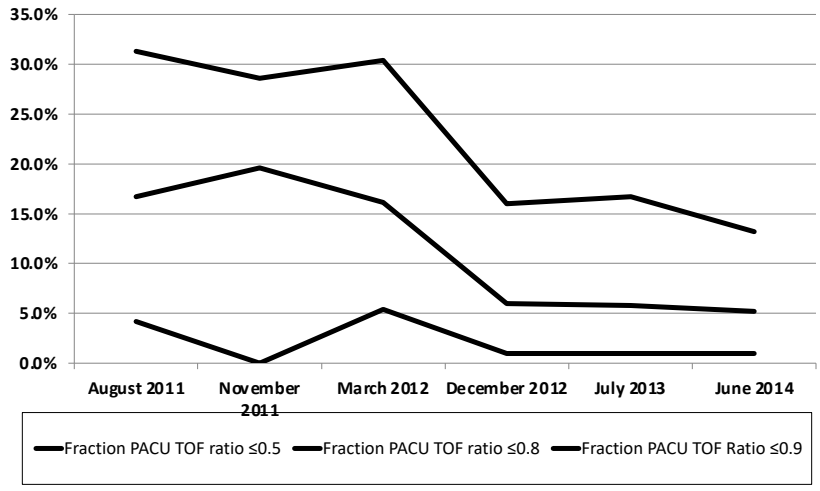

In 2013-14, only TWO PACU reintubations – both in UNMONITORED PATIENTS

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Conclusions

- But why didn't we reduce the incidence of residual paralysis to ZERO?
- Three thoughts
  - 1. Technology (Datex EMG poor)
  - 2. Limitations inherent in neostigmine.
- How do we beat this?
  - 1. Better monitoring
  - 2. Sugammadex

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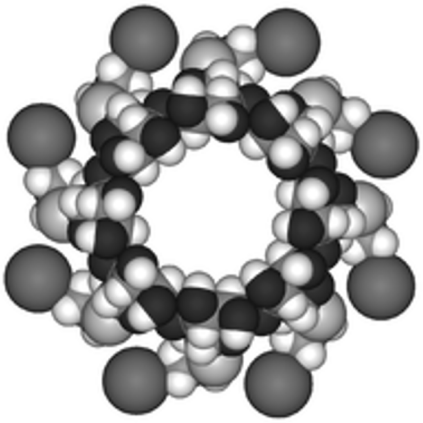
Sugammadex. Approved USA December 2017



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University of Minnesota

- NO intraoperative quantitative monitoring, no consistent qualitative monitoring (often none).
- PACU Survey in 2017 (accelerometry – old TOF Watch of Rich Priellip's)
  - With Neostigmine, 48.6% incidence residual paralysis (accelerometry)
  - With Sugammadex, 24.5% incidence of residual paralysis

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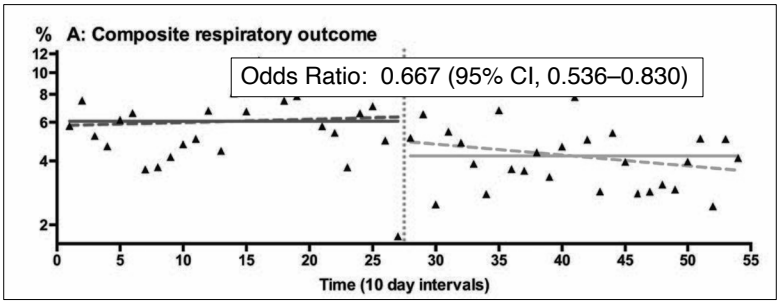
Sugammadex and Outcomes

- Time Series analysis during an institutional transition from neostigmine to sugammadex. Minimal OR monitoring
- 7316 patients, primary outcome: reintubation or non-invasive ventilation at any time postop.



Krause et al. A & A, 131: 141-151, 2020

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Sugammadex and Outcomes

- Retrospective Study
- 22,856 patients reversed with sugammadex MATCHED to 22,856 patients reversed with neostigmine.
- Outcome: composite respiratory complications: pneumonia, respiratory failure, or other pulmonary complications)

Kherterpal et al. Anesthesiology 132: 1371-1381, 2020

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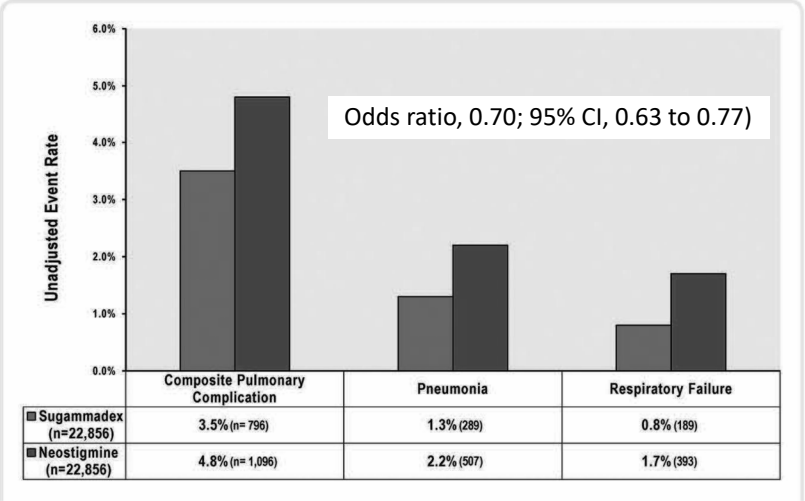

Kherterpal et al. Anesthesiology 132: 1371-1381, 2020

CAVEATS: 1). Retrospective, uncontrolled. 2) Little reliable info on intraop monitoring. 3) All key authors supported by or employed by Merck.

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Our Experience

- Survey, 36 months, 2013-2015
  - 41 PACU Reintubations
    - 31 deemed LIKELY to be related to residual paralysis
    - Incidence 0.9/month
- Event Reporting System 44 months, 2017-2021. AFTER UNIVERSAL CHANGE TO SUGAMMADEX
  - 82 PACU/Immediate ICU Reintubations
    - 26 deemed LIKELY to be related to residual paralysis
    - Incidence 0.6/month

Risk Reduction Similar to Kraus et al. and Kherterpal et al

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Conclusion re. Neostigmine and Sugammadex!!!

- Neostigmine is a lousy drug.
- Sugammadex is clearly a MUCH better reversal agent.
- Reduces incidence of residual paralysis even without monitoring - but NOT to zero!
- Reduces postop respiratory complications

BUT SIMPLY CHANGING TO SUGAMMADEX WILL NOT ELIMINATE THE PROBLEMS OF RESIDUAL PARALYSIS OF RELAXANT-RELATED COMPLICATIONS.

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Conclusions re. Sugammadex

- **SUGAMMADEX IS NOT A "GET OF JAIL FREE CARD"**
- Fixed mg/kg doses of Sugammadex do NOT always reverse patients.
- And stupid use of rocuronium (huge doses) will still get you in trouble. (seen it many times)

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Conclusions re. Sugammadex

- If you REALLY want to avoid trouble, think "Sugammadex + Quantitative Monitoring".
- I believe that this combination is the ONLY way to achieve ZERO residual paralysis.

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Additional Thoughts

- Question: Why do we manage to “get away with it” (residual paralysis) so frequently?
- Answer: Because in MOST patients, residual paralysis is tolerated (young patients, thin patients, healthy patients). This is at the root of a lack of national standards.
- But in a fraction of patients (old, sick, obese, respiratory disease), you won’t “get away with it” – although you may not recognize that your actions are the cause of their problems.

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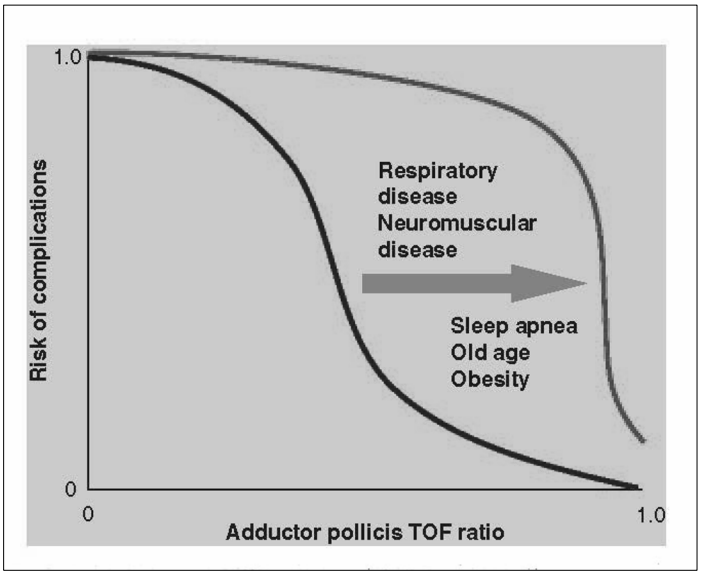

Donati, Anesthesiology 117: 934, 2012

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Thank You

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