Development of a Simple, Hydraulically-Coupled Device to Monitor Quantitatively the Extent of Neuromuscular Blockade

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- Acknowledge support of the STA in this project
- Goal of project is to validate a device that can be assembled using supplies readily available in the OR to provide quantitative assessment of neuromuscular blockade
- Compare accuracy to a standard clinical NMB monitor
- Current talk is review of progress to date

Disclosures

- No financial disclosures
- No interests in commercial development related to the project
- Will be discussing the use of a non-FDA approved device

Topic of Presentation

- Not as far along as hoped…
  - TOF-Watch went out of production so had to switch to a different device
  - Investigational device exemption as “nonsignificant risk”
    - Even though the “device” is no more than a bag of saline
    - Many hoops to jump through to be granted an IDE
  - Navigation of the IRB bureaucracy at UM
- Focus on engineering aspects and pre-clinical validation of the device

Importance of Monitoring Neuromuscular Blockade

- To determine optimal timing of intubation
- To provide optimal surgical conditions during surgery when muscle relaxation is necessary
- To assess return of sufficient motor function to permit monitoring of nerve function
- To assess return of NM function after succinylcholine prior to administration of a non-depolarizing blocker

Importance of Monitoring Neuromuscular Blockade

- To assess reversibility of blockade at the end of procedures
- To determine dose of sugammadex
- To assess that sufficient return of neuromuscular function has occurred to permit safe extubation

Surgeons are increasingly asking for profound levels of NMB

- Laparoscopic and robotic procedures
- Facilitated by the availability of sugammadex

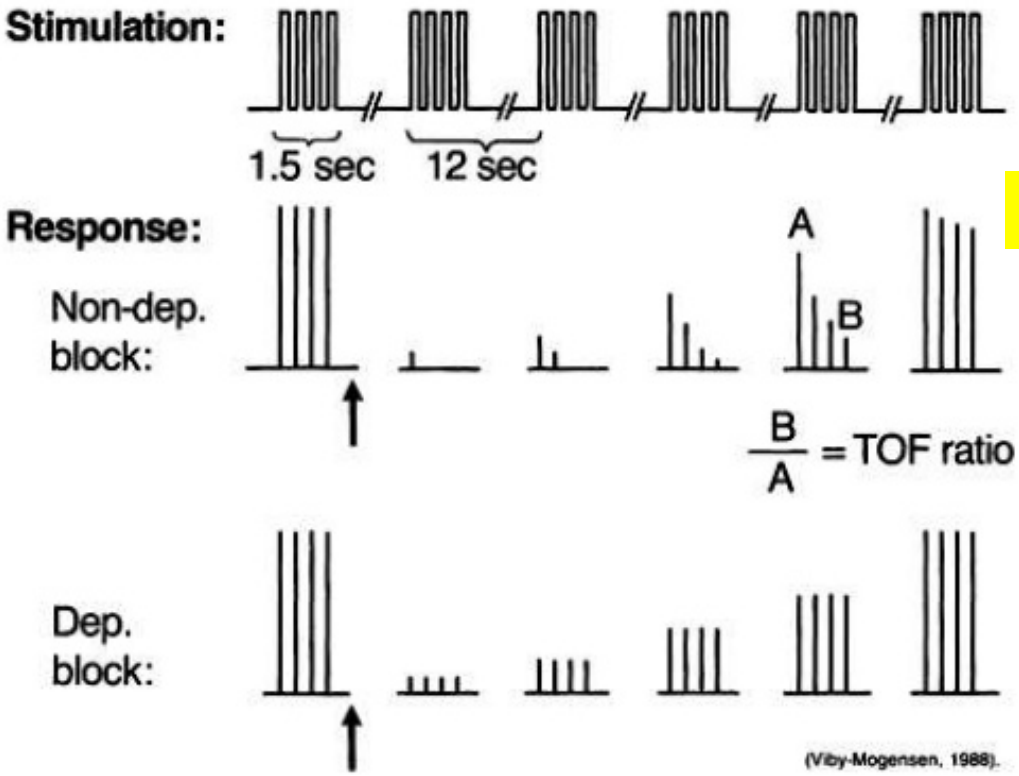
Consequences of Unrecognized Residual NMB

- Aspiration
  - Pharyngeal dysfunction
- Post-operative pneumonia
  - Inability to cough and clear secretions
  - Aspiration (may be silent)
- Hypoxemia
  - Atelectasis
  - Mucous plugging
- Multiple clinical studies in the PACU have demonstrated that unappreciated residual NMB occurs frequently

Various Modes of Peripheral Nerve Stimulation

- Single twitch
  - 1 constant current, square wave of 0.2 msec duration
- TOF
  - 4 single twitches at 2 Hz
- Double-Burst stimulation
  - 2 sets of 50-Hz tetanic stimuli, each over 2 msec, 750 msec between sets
    - 3:3 or 3:2
- Tetanic stimulation (5 or 10 sec)
  - 50-Hz or 100-Hz
- TOF Count
  - Tetanic stimulation for 5 sec
  - Wait 3 sec
  - 20 single stimuli at 1 Hz interval

Patterns of Muscle Reponses to TOF



TOF Ratio ≥ 0.9 for adequate reversal

Why Quantitative NMB Monitoring is Necessary

- Visual inspection of TOF inadequate to assess degree of recovery
  - Even experienced anesthesiologists cannot detect substantial fade in the TOF
  - Absence of apparent fade is not a reliable indicator of adequate recovery
  - Can be difficult to detect fade visually when TOF ratio = 50%
  - If fade is visible, then there is residual blockade
- Clinical assessment of strength correlates poorly with TOF Ratio
  - Sustained head lift
  - Hand squeeze
  - Negative inspiratory pressure
- Even absence of fade on tetanic stimulation is not completely reliable
  - Very painful

Modalities for Quantitative NMB Monitoring

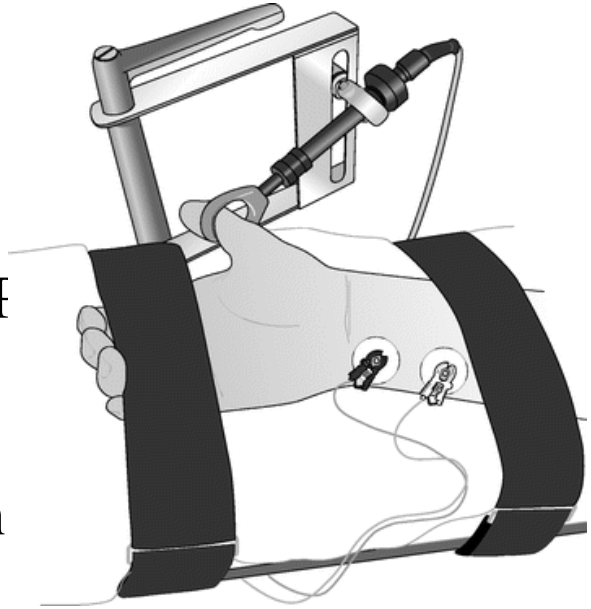
- Mechanomyography
- Electromyography
- Phonomyography
- Accelerometry
- Compressomyography
- Kinemyography

Hemmerling TM, Le N. Neuromuscular Monitoring: an update for the clinician. Can J Anaesth 2007; 54:58-72

Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring: Challenges and opportunities. Anesthesiology 2017; 126:173-90

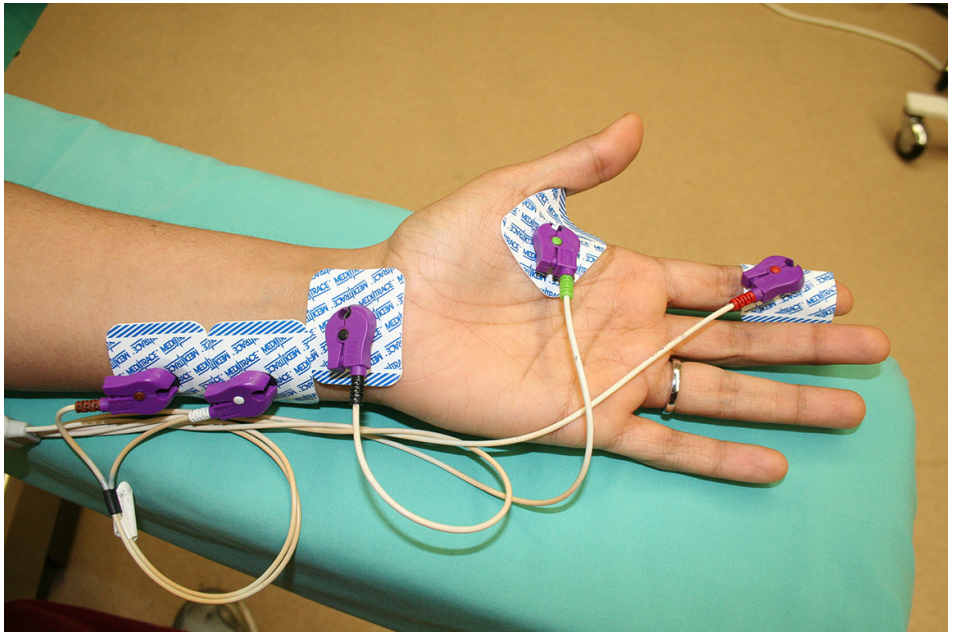
Mechanomygraphy

- **Gold standard method for NMB research**
- Measured at the adductor pollicis (AP)
- Thumb is placed under preload attached to strain gauge
- Electrical stimulus at the ulnar nerve causes the AP to contract isometrically
- Deformation of the strain gauge results in a electrical signal that is proportional to the strength of contraction
- Bulky, need arm extended
- Not clinically available



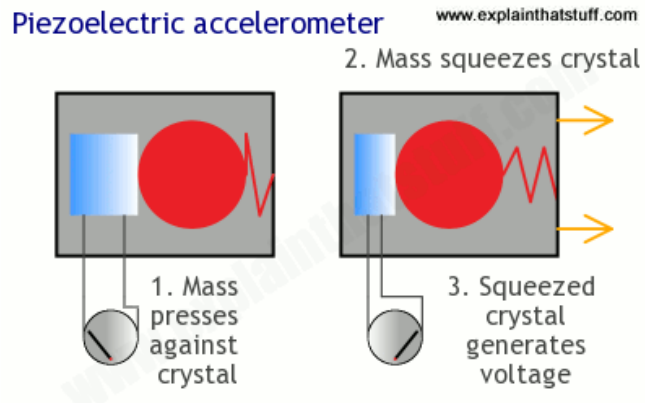
Electromyography

- Can be measured at many muscle sites
  - Typically over AP
  - Also diaphragm, larynx, face
- Compound action potential is recorded, amplified, rectified, and integrated
- Results as % of control or as TOF ratio
- Also used for NMB research
- Used by neurophysiologists during intraoperative monitoring, but not



Accelerometry

- Based on Newtons 2nd Law of Motion
  - force = mass x acceleration
- Piezoelectric ceramic transducer attached to the thumb
  - When thumb accelerates, voltage generated
  - Since mass of thumb is constant, voltage is proportional to the force
- Generally not regarded as sufficiently accurate for NMB drug evaluation
- OK for clinical use
  - Many studies showing utility in detection of residual neuromuscular blockade

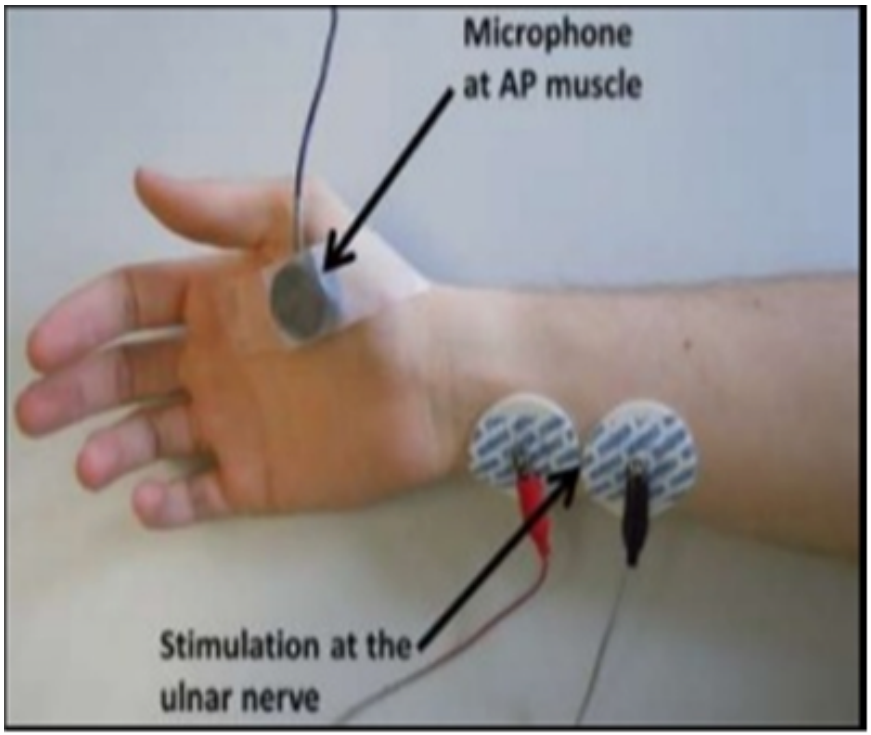


Accelerometry

- TOF Watch
  - MIPM – Mammendorfer Institut für Physik und Medizin GmbH
  - Discontinued production as of June 2016
- Stimpod NMS 450
  - Xavant Technologies (South Africa)
  - Only commercial accelerometer

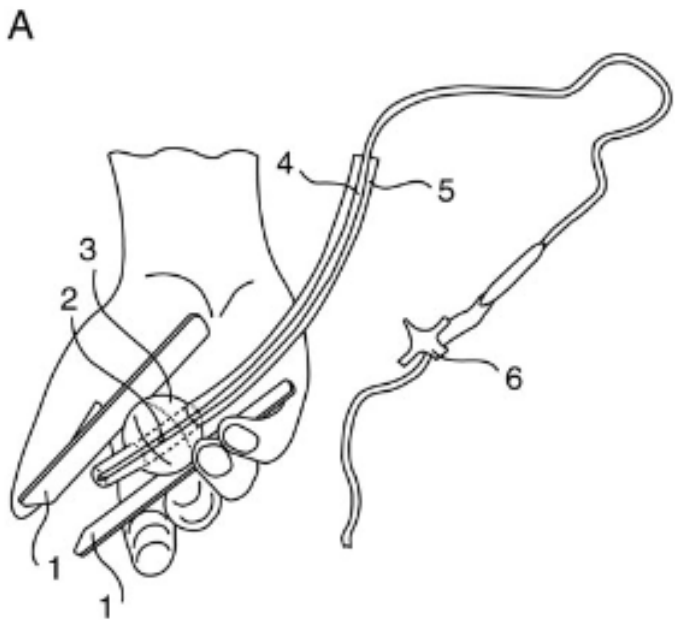
Phonomyography

- Stimulus of ulnar nerve
- Muscle contraction of the AP generates low frequency sounds
- Special microphone over the muscle records and amplifies the sounds
- Force of contraction is proportional to the intensity of the sound
- Not commercially available



Compressomyography

- Uses two strips compressing an air-filled balloon
- Pressure transducer measures the increase in pressure in the balloon due to compression of the balloon
- Patented EU and US
- Not commercially available
- Brit J Anaesth 2008;100;344–50

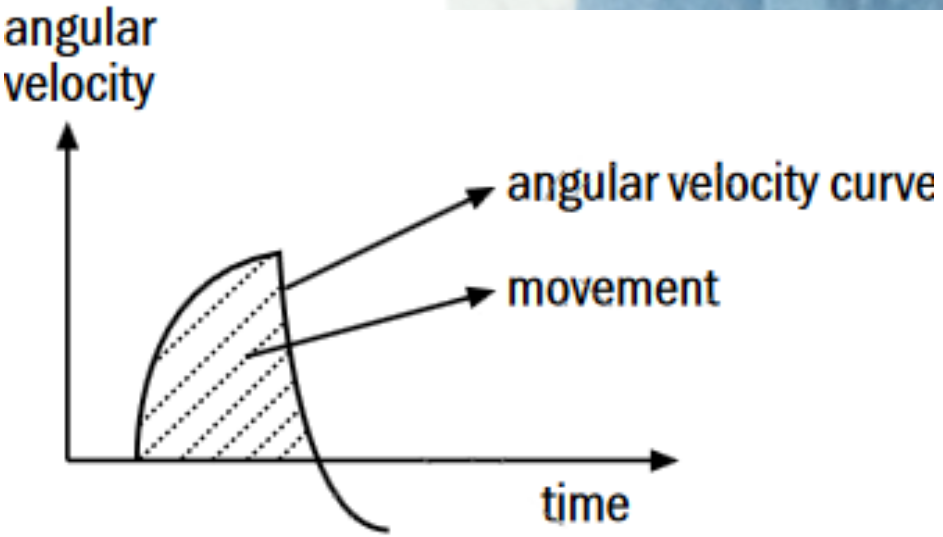


Kinemyography

- Technique originally developed by Joe Orr and Dwayne Westenskow
  - US Patent 5131401 A
- Also uses a piezoelectric sensor, embedded in the plastic strip in the web space between the thumb and index finger
- Available clinically (GE)
  - In all the operating rooms at UMH
- Switched to this as comparative device, as TOF-Watch not

Kinemyography

- Output voltage is proportional to the angular velocity of the thumb ω
  - Proportional to the force of the muscle contraction
- Integration of area under curve of angular velocity vs time



Kinemyography Studies Compared to MMG

- Motamed C, Kirov K, Combes X, Duvaldestin P. Comparison between the Datex-Ohmeda M-NMT module and a force displacement transducer for monitoring neuromuscular blockade. Eur J Anaesth. 2003;20:467–9
  - Acceptable repeatability
  - Reasonable agreement with MMG for recovery of TOF
  - Can be used clinically, but not for research applications
- Dahaba AA, von Klobucar F, Rehak PH, List WF. The neuromuscular transmission module versus the relaxometer mechanomyograph for neuromuscular block monitoring. Anesth Analg. 2002;94:591–6
  - Reasonable agreement with MMG for onset of block and full recovery
  - Lagged behind MMG for determination of T1 recovery to 25% (repeat dose)
  - Can be used clinically, but not interchangeable with MMG

Why develop another device to measure NMB?

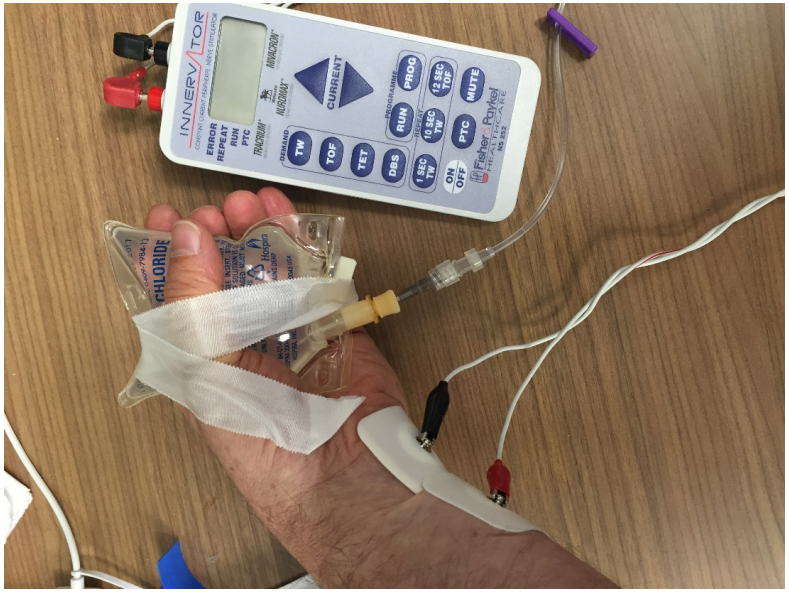
- Quantitative NMB monitors are not widely available in most ORs
- Technology is expensive
- Wanted to develop a simple method that could be assembled easily using readily available materials in the OR
  - Bag of saline and a standard arterial pressure transducer
- Potential benefits
  - Clinical assessment of NMB where commercial devices are not available
  - Teaching purposes in the OR
  - Use in countries with limited resources

Description and Validation

- Named this technique “hydraulomyography”
- Validation
  - Engineering aspects of the device
  - Preliminary application results

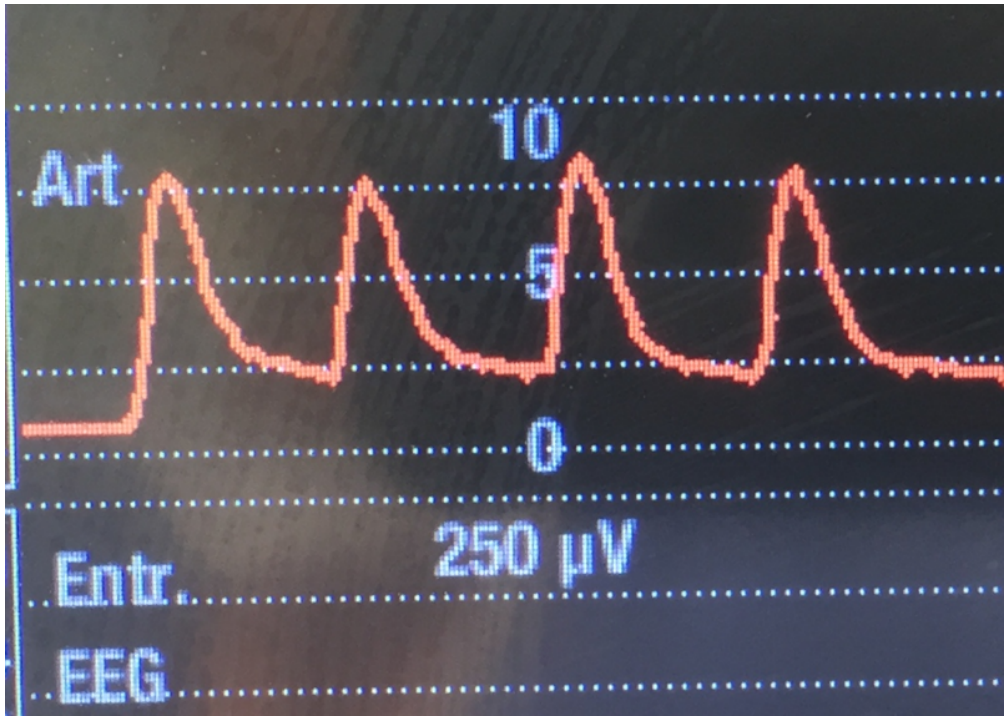
Hydraulomyograph Device Description

Overfilled 50-ml bag of saline spiked with an IV catheter and connected to a pressure transducer.

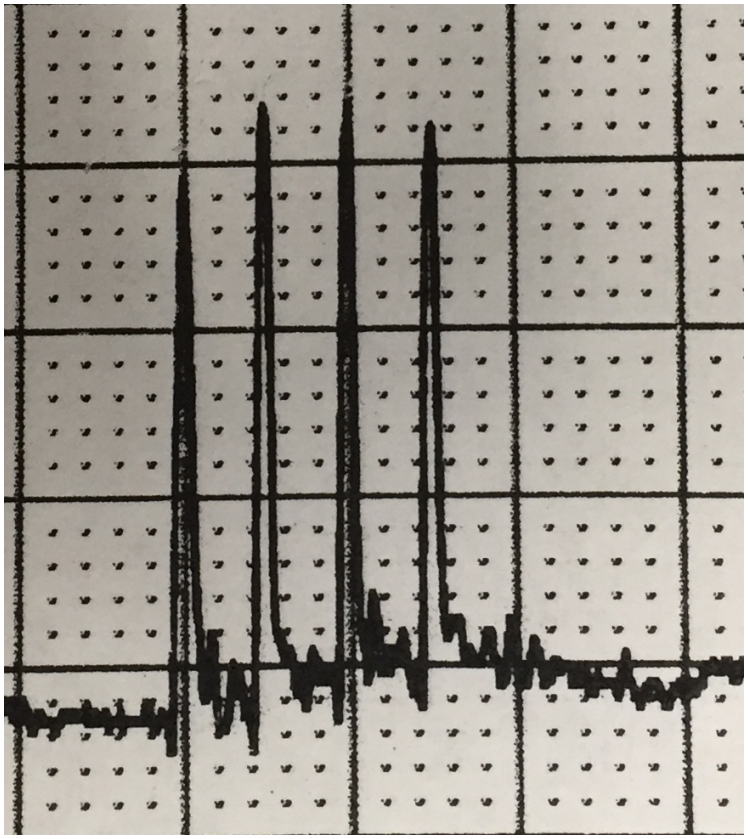


Secured with tape and used with commercial nerve stimulator at the ulnar nerve at the wrist.

Hydaulomyography



Monitor Screen



Strip Recorder

Engineering Aspects of the Device

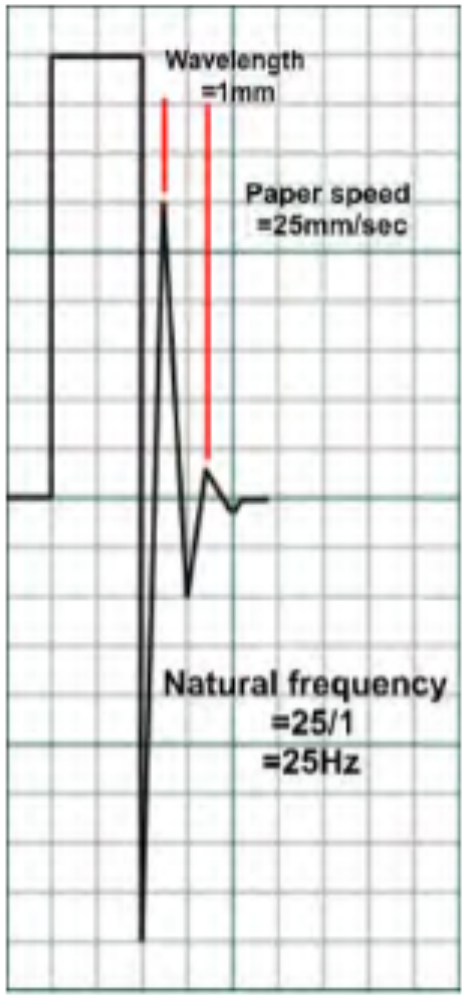
- Device is a pressure transduction system
- Force generated by contraction of the adductor pollicis is transmitted to the saline bag in the patients' hand
- Results in a increase in pressure in the bag
- Pressure is measured by the transducer
- Force of contraction will be proportional to the pressure

Pressure Measurement Considerations

- Resonant Frequency of pressure monitoring systems
  - If too close to the input frequency, can lead to wave amplification
  - Would like a high resonant frequency
  - For arterial pressure monitoring systems, 8-10x the HR frequency is desirable
    - HR = 180 BP = 3 Hz
    - Minimum resonant frequency 24 Hz
- TOF input frequency is 2 Hz
  - However, duration is only for 1.5 sec with 12 sec pauses between TOF
  - Unclear what the minimum resonance frequency needs to be
  - Higher RF would be better to mitigate waveform distortion

Measurement of Resonant Frequenc

- Turn on strip chart recorder at 25 or 50 mm/sec
- Square wave impulse
  - "Fast flush" for arterial pressure systems
- Wavelength = distance between peaks in mm
- Resonant frequency = chart speed / wavelength



Steps to Maximize Resonant Frequency

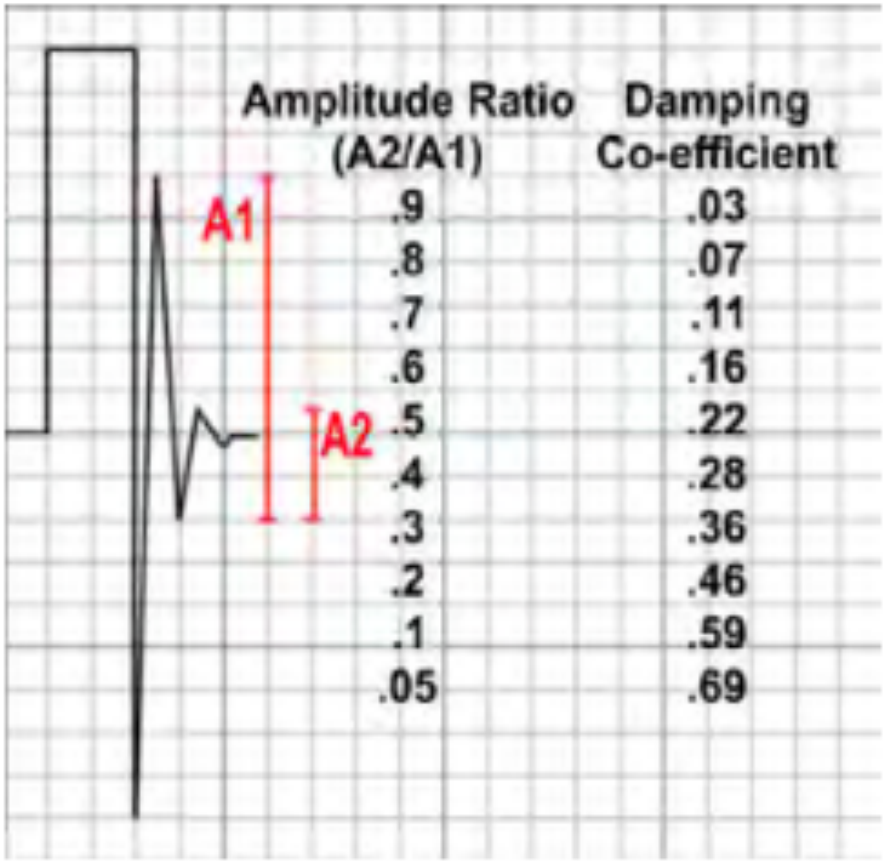
- Short length of tubing
- Wide bore, non-compressible tubing
- Avoid kinks
- Minimize stopcocks
- Use low viscosity fluid

Pressure Measurement Considerations

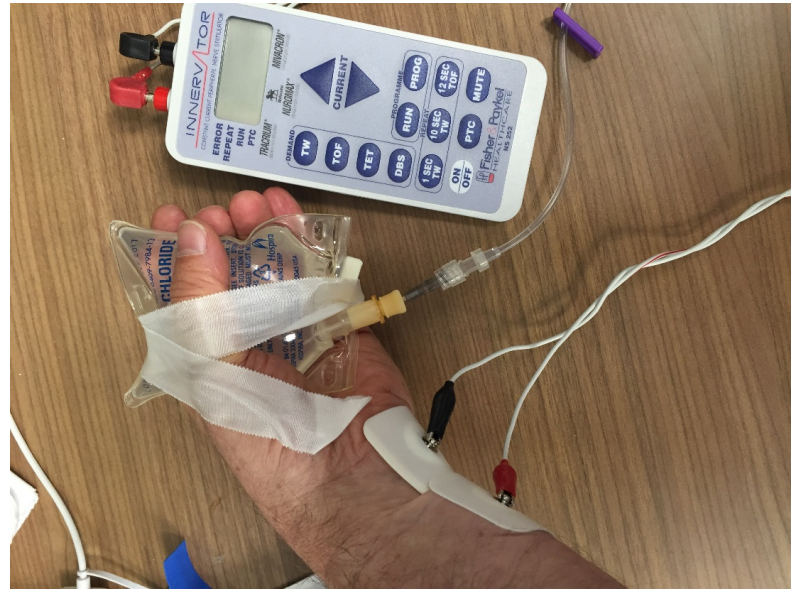
- Damping
  - Counteracts effects of oscillation by reducing the energy in the system
  - Excessive damping in arterial pressure measuring systems
    - Underestimate SBP
    - Overestimate DBP
    - Slow to respond to pressure changes
    - Loss of details of waveform
  - Underdamping in arterial pressure measuring systems
    - Overshoot of pressure waves
    - Overestimate SBP
    - Underestimate DBP
- Damping decreases the natural frequency of the system
  - Balance between natural frequency and damping coefficient

Damping

- Can measure with a fast flush test
- Generates a high pressure square wave with a subsequent undershoot
- Measure the ratio of 2 successive wave amplitudes (damping ratio)
  - Here A2/A1 = 0.3
  - Damping coefficient = 0.36
- Optimal damping coefficient = 0.7
  - Underdamped

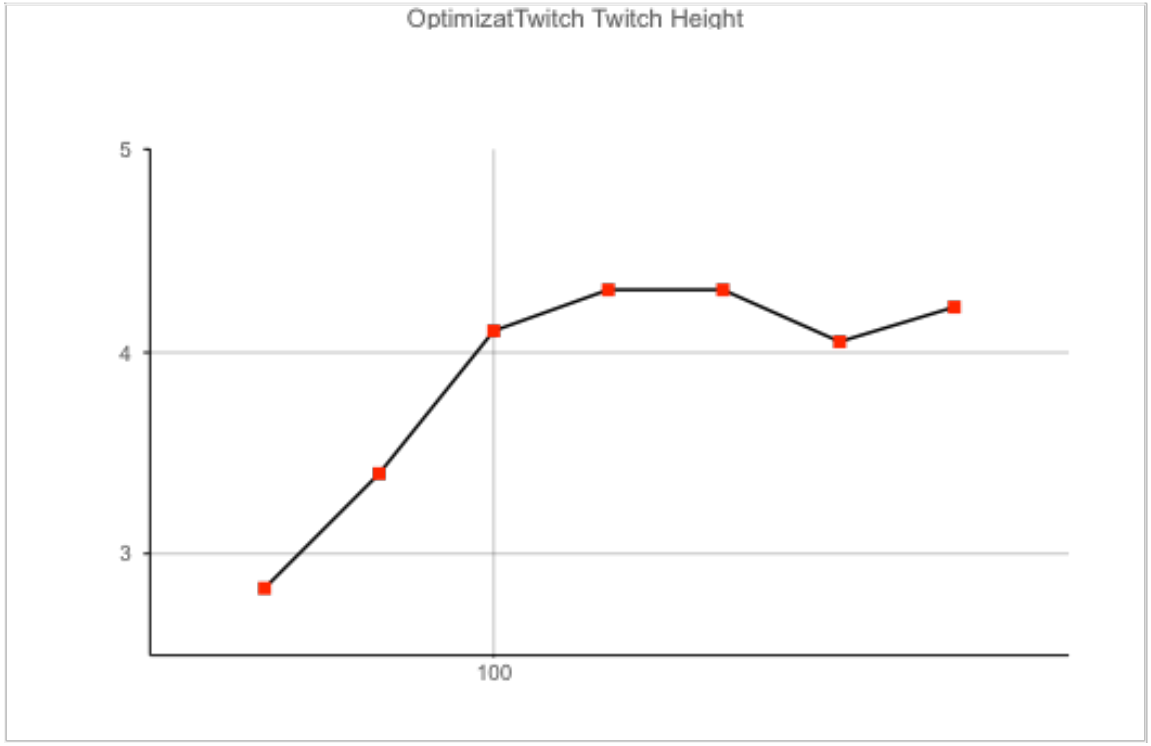


Resonant Frequency and Damping of Hydraulic Device

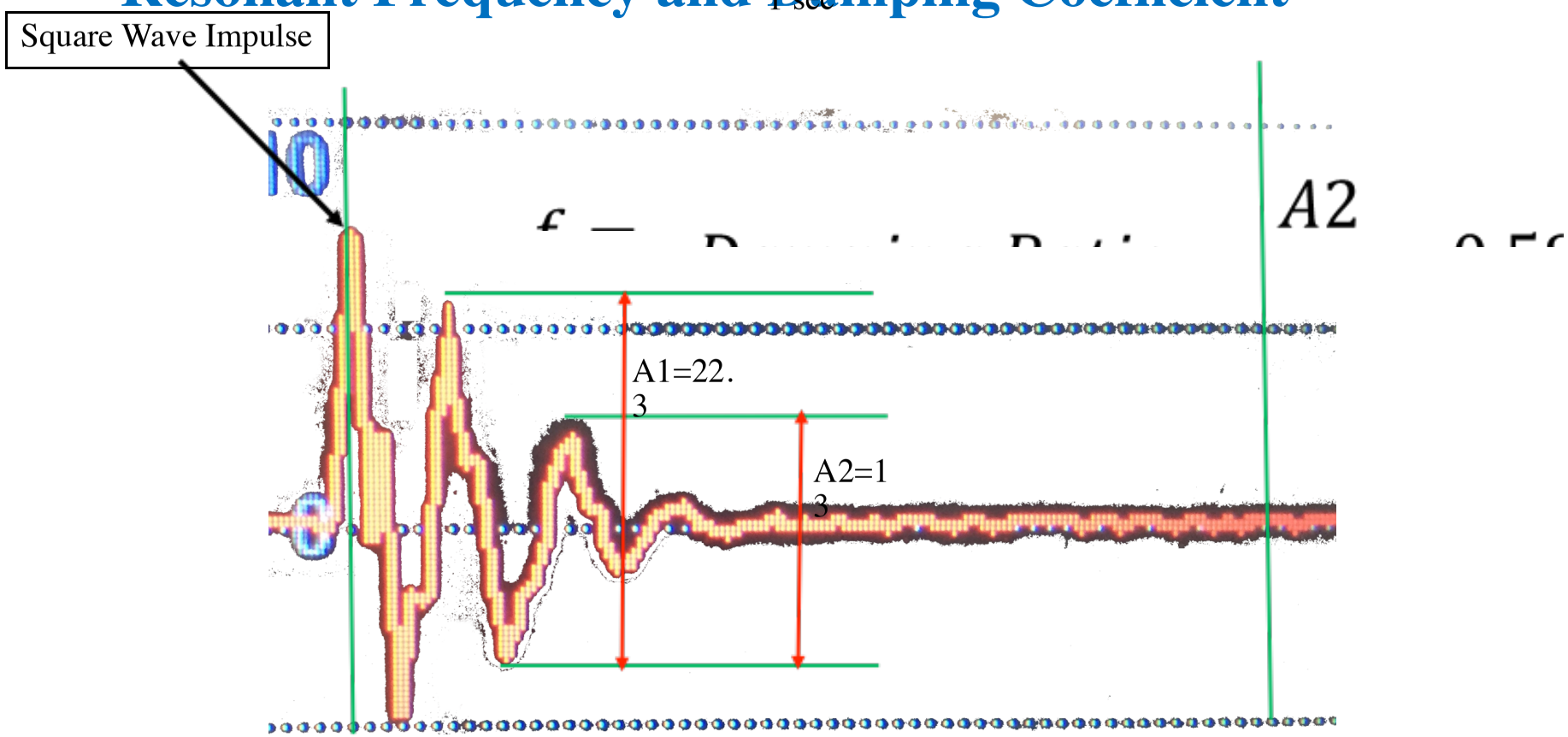


Optimal Amount of Fluid to Add to Bag

- 50 ml saline bag
- Added volume to bag and measured twitch height
  - No relaxant
  - Supramaximal stimulus
  - Replicates of 5 measurements
- Add 110 ml to the bag to achieve maximum twitch height

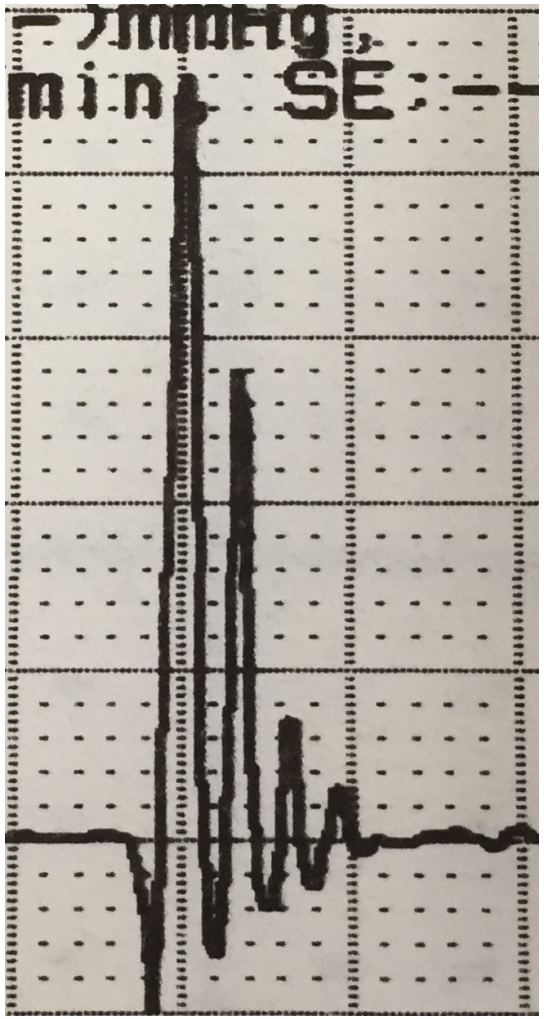


Hydraulic Twitch Monitor with 16 g Catheter and Long Tubing:
Resonant Frequency and Damping Coefficient

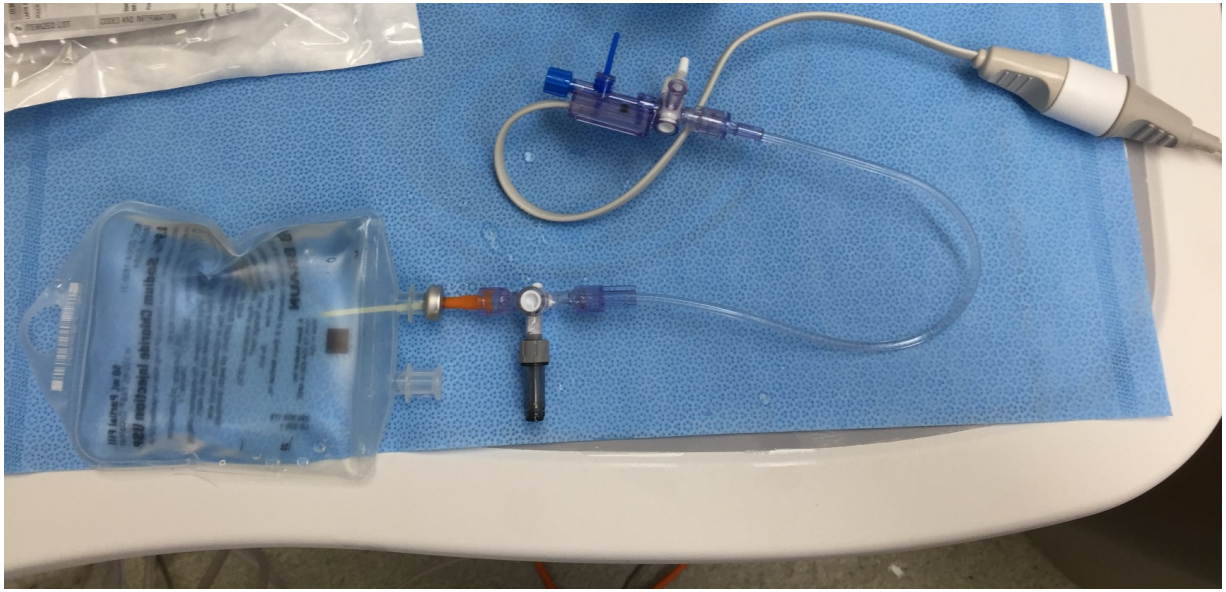


Resonant Frequency: 14 g Catheter and Short Tubing

- Resonant Frequency
  - chart speed mm·sec-1 / wavelength mm
    - Chart speed = 50 mm·sec-1
    - Wavelength = 2 mm
  - 50/2 = 25 Hz
  - RF/Input Freq = 25/2 = 12.5
    - High fidelity system
- Damping ratio = 0.45 ± 0.09 (SD)
  - Damping coefficient = 0.25
  - Better than with 16 g catheter
  - Still underdamped
- Final Device
  - 14 g catheter



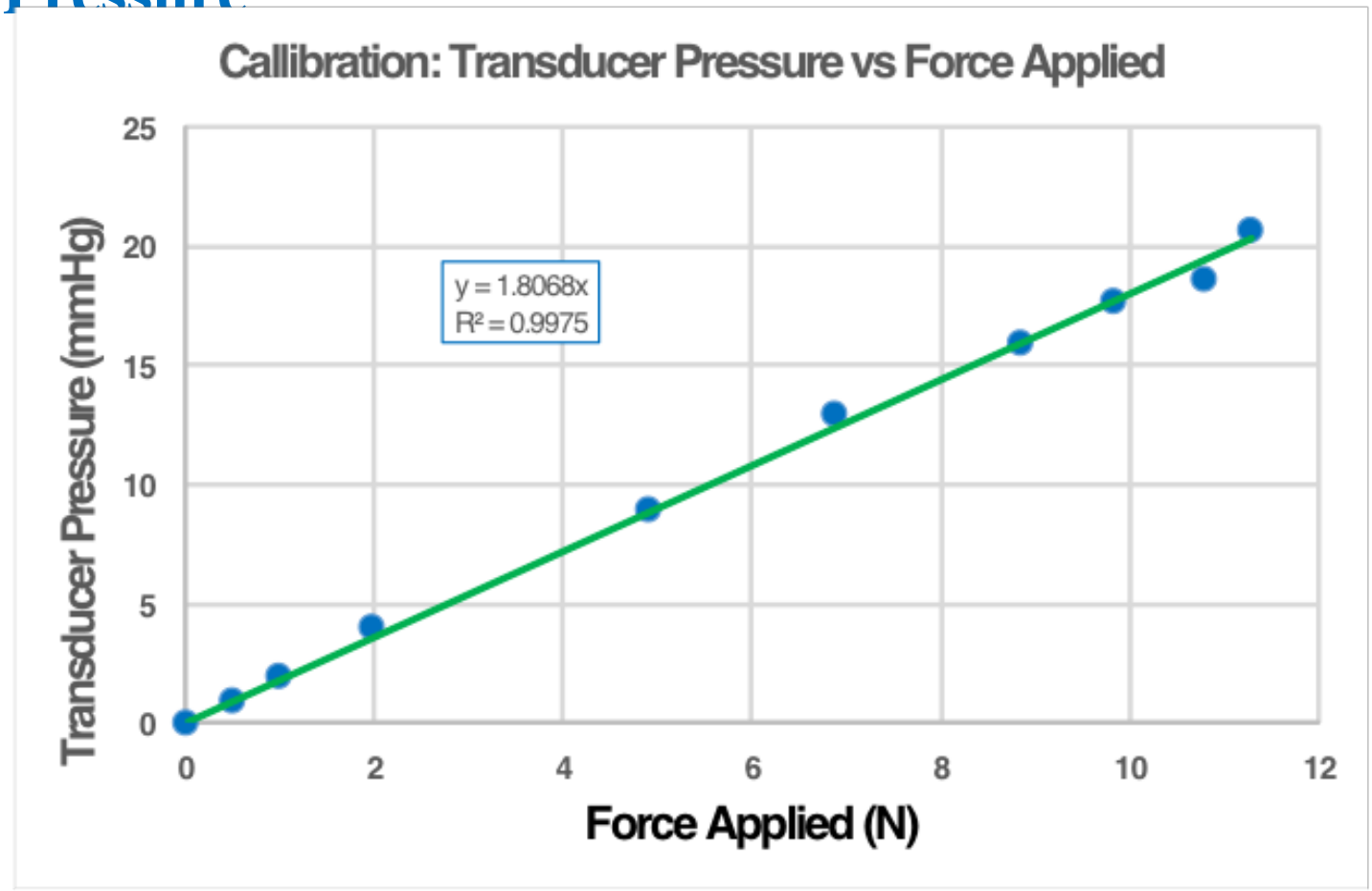
Hydraulic Twitch Monitor: Final Device



Hydraulic Twitch Monitor: Conversion of Pressure to Force

- Pressure = Force / Area
- Area of transducer is constant
- Should be a linear relationship between the pressure measured and the force
- Tested by adding static external weights to the pressure bag and measuring the resulting pressure
  - Converted mass of weight to units of force in Newtons (kg·m·sec-2)

Static Weight to Hydraulic Twitch Monitor vs. Transducer Pressure

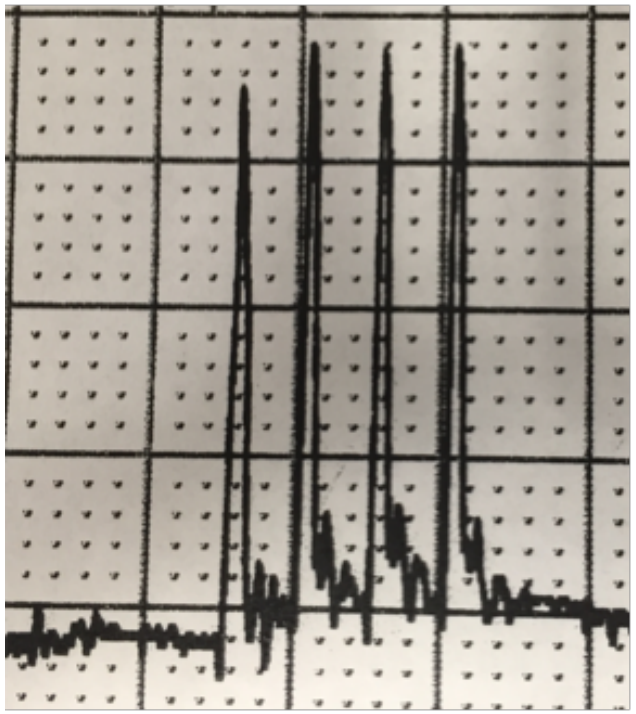


Typical force at measured with device around 5 N

Static Calibration

- Highly linear relationship between force and pressure
  - System adequate for clinical measurement of expected forces of contraction
- System might not be adequate for precise quantitative management of continuous infusion of NMB drugs to very deep levels of block
  - 5% of T1 control would be 0.25 N
  - 0.5 N corresponds to 1 mmHg pressure
  - Might still be able to detect presence of tiny twitch on the screen

Consistency of Baseline Twitch Heights T1-T4



Consistent twitch height
No evidence of "reverse fade"

Next Steps

- IDE approval from the UM IRB (in review)
- Protocol approval from UM IRB (in review)
- Register trial at ClinicalTrials.gov
- Enroll patients

Conclusions

- Hydraulic measurement of twitch height appears to be a reasonable device to use clinically
  - Simple to construct usually readily available materials in the OR
  - Display of twitches on monitor convenient
  - Accuracy needs to be confirmed before recommending use
- If one has resources to purchase a commercial device to do quantitative monitoring of NMB, this is preferable
- Come back next year to the annual meeting for the study results!
  - Turnberry Isle Miami
  - I promise better weather

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Questions?