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 Responses to TOF

TOF Ratio ≥ 0.9 for adequate reversal

(Viby-Mogensen, 1988)
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


Mechanomyography

- **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 Newton's 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 $\omega$
  • Proportional to the force of the muscle contraction

• Integration of area under curve of angular velocity vs time
Kinemyography Studies Compared to MMG

  - Acceptable repeatability
  - Reasonable agreement with MMG for recovery of TOF
  - Can be used clinically, but not for research applications

  - 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
Hydraulomyography 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.
Hydraulomyography

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 an 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 Frequency

- 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 $A_2/A_1 = 0.3$
  - 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

Square Wave Impulse

$A_1 = \ldots$

$A_2 = \ldots$
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

![Graph showing calibration: Transducer Pressure vs Force Applied]  

- Transducer Pressure (mmHg) vs Force Applied (N)
- Regression equation: $y = 1.8068x$
- $R^2 = 0.9975$

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

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