# Traumatic Brain Injury in Modern War
# Pre Hospital Resuscitation Implications

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# Disclosures

## Co-Founder

- On Demand Pharmaceuticals, Inc
- Host Response, Inc
- SunQ, LLC

## Board Member

- Facebook B8
- KnoLimits, LLC
- Caivis Fund
- Camden Partners Fund
- BioElectron Pharma
- DNARx, Inc
- National Football League Health Fdn
- NFL Players Association Health Cmt
- NIH-NCATS Advisory Council

# THOR

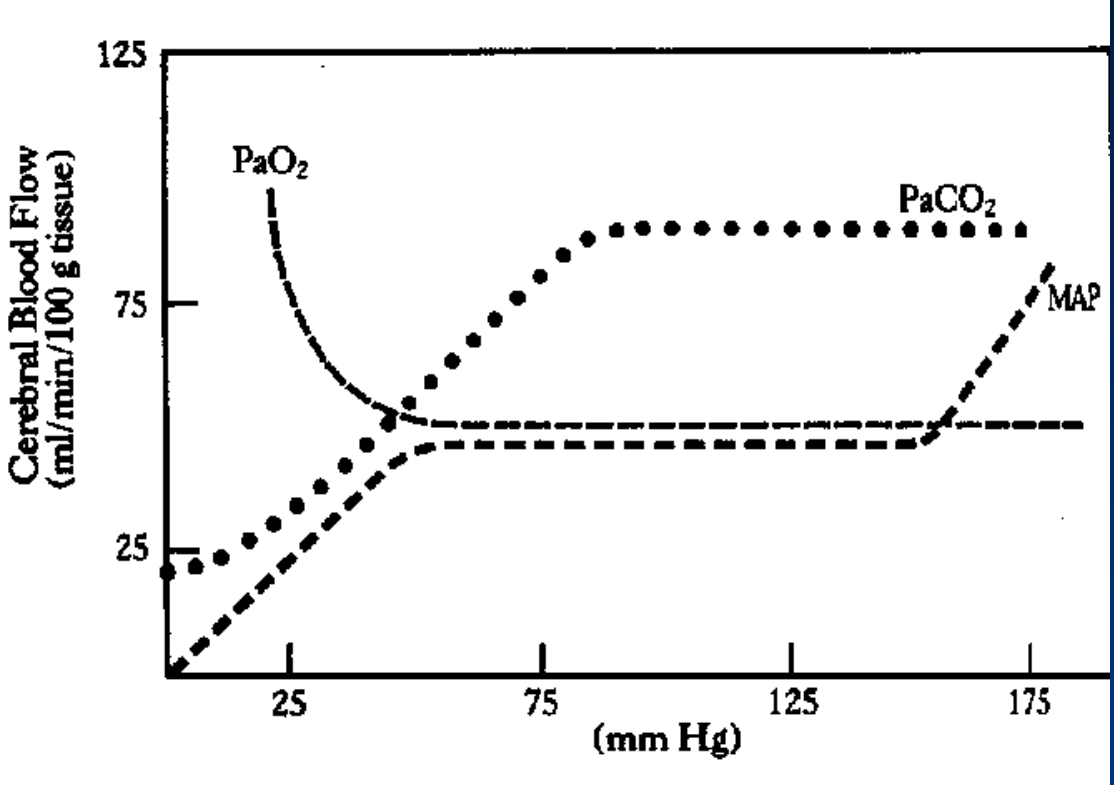
- Save life first ….then worry about the brain
- ABCs are also the first steps in TBI management
- Learning from the resuscitation community

# Brain Physiology

- 25% of total body oxygen consumption
- 94% devoted to gray matter
  - % changes depending on regional brain activity
  - 12mM ATP/min for normal function
- Brain produce 12mM ATP/min but reserves: 8mM
- Glucose (brain) in anaerobic state: 15mM ATP
- Autoregulation of CBF between MAP 50-150mmHg
  - 50cc/100gm tissue but regional differences are key
- If only hypoxic, adequate CPP with glucose and normal pCO2 can still maintain normal ATP levels
  - ?? Protection via in reduced CMRO2??
- Ischemia leads rapidly to neuron death

http://www.humanneurophysiology.com/cbfo2consumption.htm

# CPP - CBF Relationship




Hayek and Veremakis, in Critical Care, Lippincott, 1992

# Cerebral Perfusion Pressure
## TBI Resuscitation Important Principal

CPP=MAP-ICP

- Prospective studies have shown 50% increase in survival
- 50% increase in “good” outcome
- No increase in ICP or adverse clinical outcomes by actively maintaining CPP
- Impractical prehospital as need ICP

Marion et al, J Neurosurg **75**:354-362 (1993)
Marshall et al, J Neurosurg **73**:S28-S36 (1991)

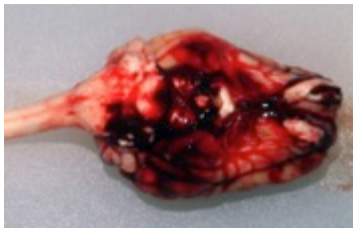
# It all starts with a whack, bang or boom

Google images

# Blast Wave

Courtesy of Steve Parks, ORA, Inc

# PREVENT Studies: injury severity vs. overpressure



> 130 PSI: Severe TBI; Death

80 PSI: Overpressure induced brain edema observed in pigs; EDH/SDH; lung collapse of unarmored pigs

< 60 PSI: Pigs had altered gait and short-term behavioral changes that faded after weeks ; Some evidence of long term neuronal injury but no behavioral correlate

16 PSI: Humans had no neurologic reaction to single exposure

< 4 PSI: Humans had no neurologic reaction or change in cognitive status following repeated exposure to low-level blast

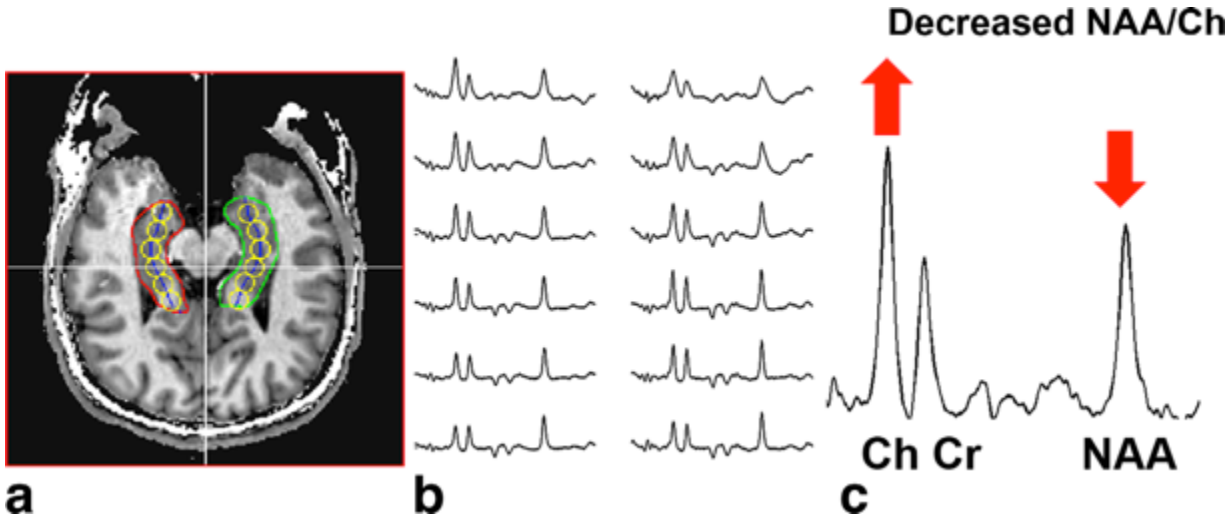
Fatal
Severe
Moderate
Mild
Injury Severity

4 PSI
Overpressure
60 PSI
80 PSI
150 PSI

# Explosive Blasts TBI
# Not Seen on Regular MRI or CT

- **7T MRSI reveals hippocampal injury in patients which correlates with memory impairments determined by cognitive testing.**
  - Anterior hippocampus significantly injured on both sides evidence by decreased NAA/Ch ratio (> 2 SD) compared to controls.

**Ref:** Hetherington H, Hamid H, Kulas J, Ling G, Bandak F, de Lanerolle N, Pan J . MRSI of the medial temporal lobe at 7T in explosive blast mTBI. Magn Reson Med (2013)



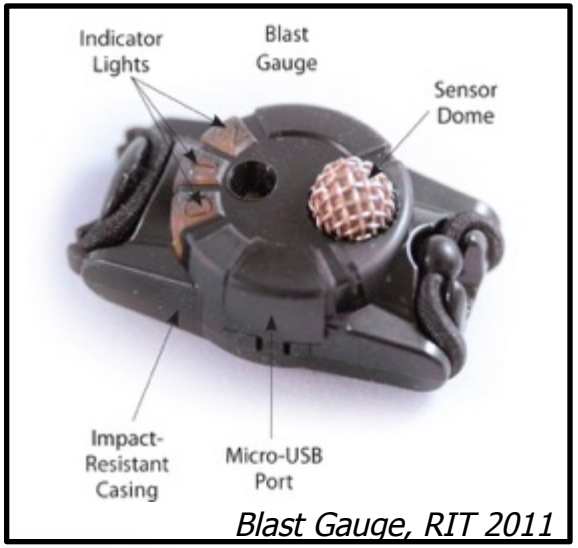

**Data from a veteran with explosive blast mTBI. (a) locations of the single voxel reconstructions (yellow circles) numbered 1 to 6 from posterior to anterior; (b) spectra from these loci from a veteran with explosive blast mTBI; (c) spectrum from the most anterior location of the eight hippocampal formation**

# The DARPA Blast Gauge System

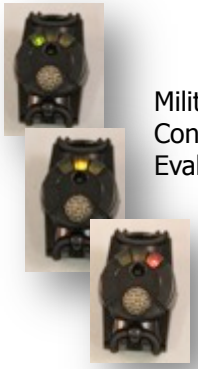
**•A wristwatch-sized device that measures pressure and acceleration changes caused by explosive blast**

- Attached at the neck, shoulder and the base of the skull
- Rate of false alarm <1%
- Wiith > 7100 active combat soldiers

**Dr. Jeff Rogers, MTO**

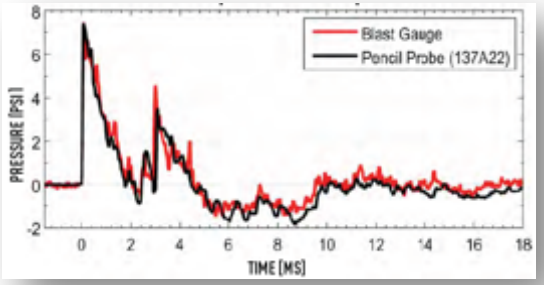


*Blast Gauge, RIT 2011*



Military Acute Concussion Evaluation (MACE)


Accurate Measurement of overpressure waveforms, pressure impulse, and acceleration.




**Weight < 1 ounce**

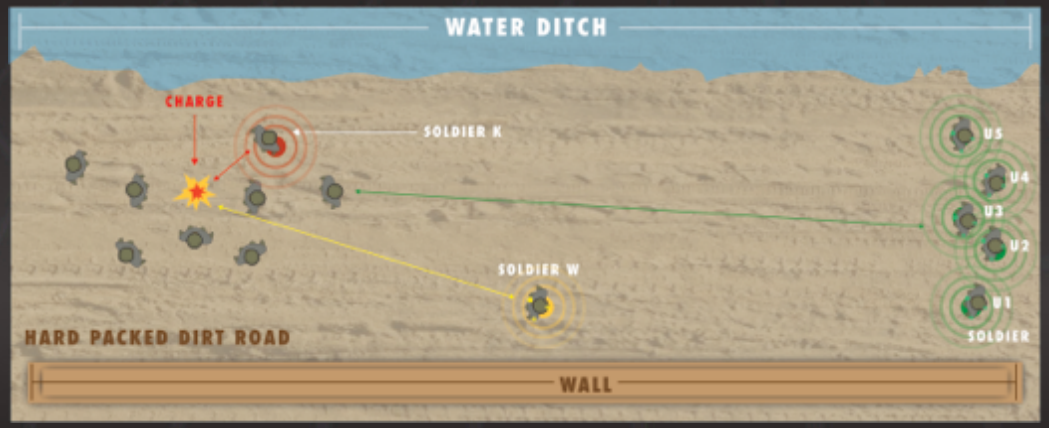
**Tracking Cumulative Exposure for correlation to acute injury and long term deficits via integrated data base**

The Blast Gauge System, © 2013 BlackBox Biometrics, Inc.

# UNDERSTANDING BLAST ENVIRONMENT

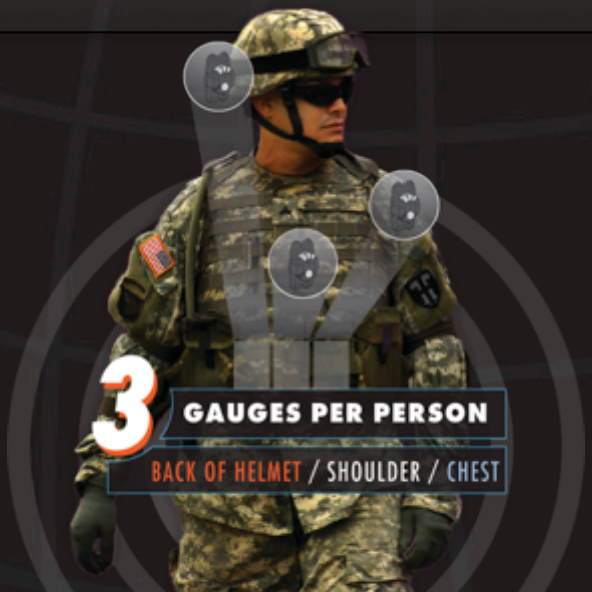
**SENSOR MEASUREMENTS ALLOW:**
operationally relevant recreations of blast events,
individual Exposures HISTORIES,
Better operating procedures and improved equipment.

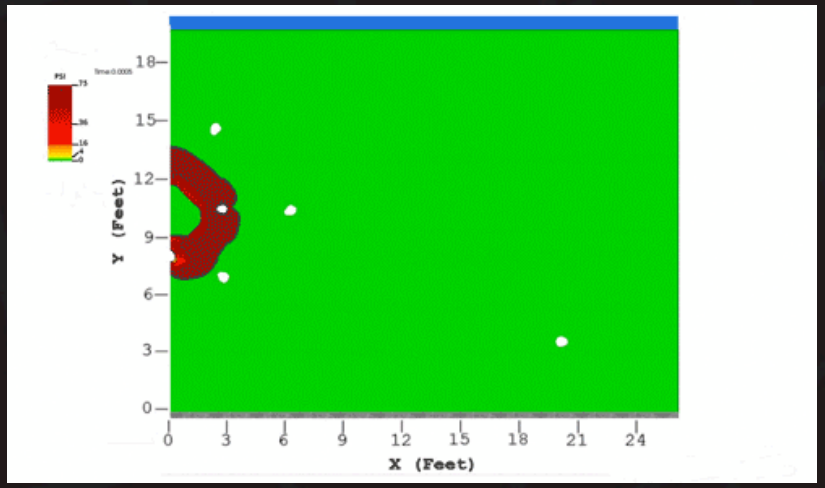
RETURN TO MENU









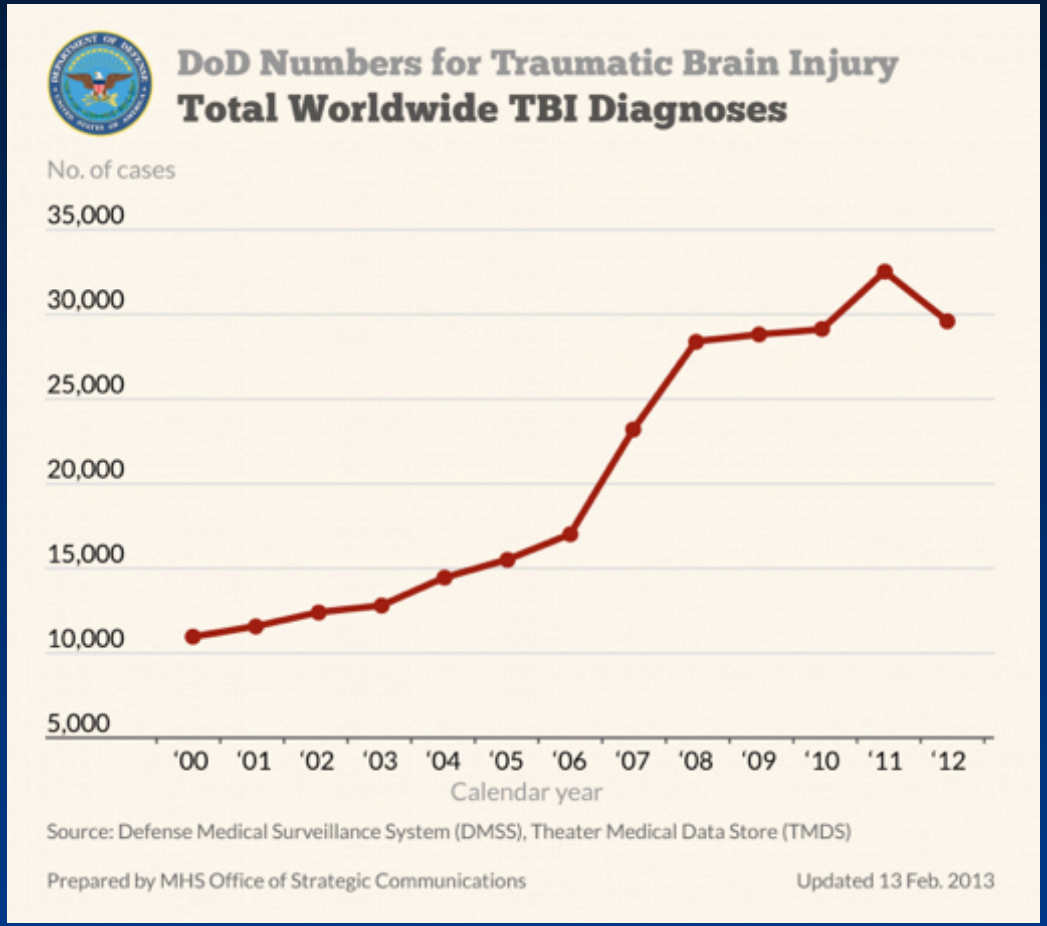
Afghanistan 2003

Iraq 2005

# Is TBI New disease?

Or an old one that is now gained importance?

# TBI and Iraq and Afghanistan Wars




***Total : 266,810***
***(2001-2012)***

**> 80% is mild TBI**

***Source: DVBIC and AFHSC***

# TBI

Lessons from Civilians

# State of Civilian TBI Management at the beginning

- Greatest advances are for moderate-severe TBI due to the Clinical Practice Guidelines developed by AANS and CNS
- Mild TBI/Concussion care is inconsistent
  - Only 10-15% of mild TBI victims seen by MD
  - Most are seen by lay person (coach, parent, etc)
  - Epidemiology is incomplete
- No standard approach to mild TBI treatment
- No effective neuro rescue medications in clinical practice

# TBI Management
# Learning from the war

Evolving continuously

# TBI "Good News"
# Military Medical Care is "Leading the Way"

- Creation of the first large system-wide approach to concussion
- Concussion diagnostic tool being used widely by first providers
  - MACE (military acute concussion evaluation)
- Clinical practice guidelines (CPG) for TBI care
  - DoD-VA CPG mTBI/Concussion
  - Guidelines for the Field Management of Combat Related Head Injury
  - Use of civilian CPGs for moderate to severe TBI
    - Additional advances made through war experience
- Clinical guidelines for return to duty
  - "3 strikes and you are out"
  - DTM 09-033: mandatory screening
- Neuro Teams (neurosurgeon and neurointensivist)
- Neurosurgical advances in hemicraniectomy, endovascular techniques and neuro critical care

"There is always room for improvement"

Ling et al, Explosive blast neurotrauma, J Neurotrauma 26:815 (2009)
Knuth, Letarte, Ling et al, "Field management of combat related head injury, "Brain Trauma Foundation (2005)
Cifu, Labutta and Ling (eds), "VA/DoD Clinical Practice Guidelines for Management of Concussion/mTBI" (2009)

# Mild TBI

- Pt suffered blast TBI from about 8 feet
- Wearing helmet/body armor/googles
- No LOC but confusion/amnesia for at least 15min (Grade 2 concussion)
- CT: normal
- Alert and Oriented X 4
- Persistent neuro cognitive deficits
  - Frontal lobe based tasks (digit span, word list generation)
  - Normal by Day 7, returned to duty

# Second Impact Syndrome (SIS)

## Avoiding Second Impact Syndrome

- Patients who sustain initial mild TBI (usually a concussion) sustains a second head injury before having fully recovered
- Leads to
  - loss of cerebral autoregulation
  - diffuse cerebral swelling
  - uncontrolled elevated ICP (even without intracranial hematoma)
  - death
- Rare
- Mortality rate ~50%

# Not being satisfied with “good enough”

Learn from providers who are making it happen

# Get leaders the evidence that change is needed

Gray Team missions (I-IV) sent by ADM Mullens, CJCS

# Paradigm Shift
# Take medicine "to" patient

- Empower first providers (medics) with new clinical tool to identify TBI
- Order: every "at risk" solider must be screened by medic
- At Risk: within 50m of blast or in vehicle in front of or behind damaged vehicle
- If soldier has TBI and was not seen by medic, the blame is on the leaders (officer and sergeant)

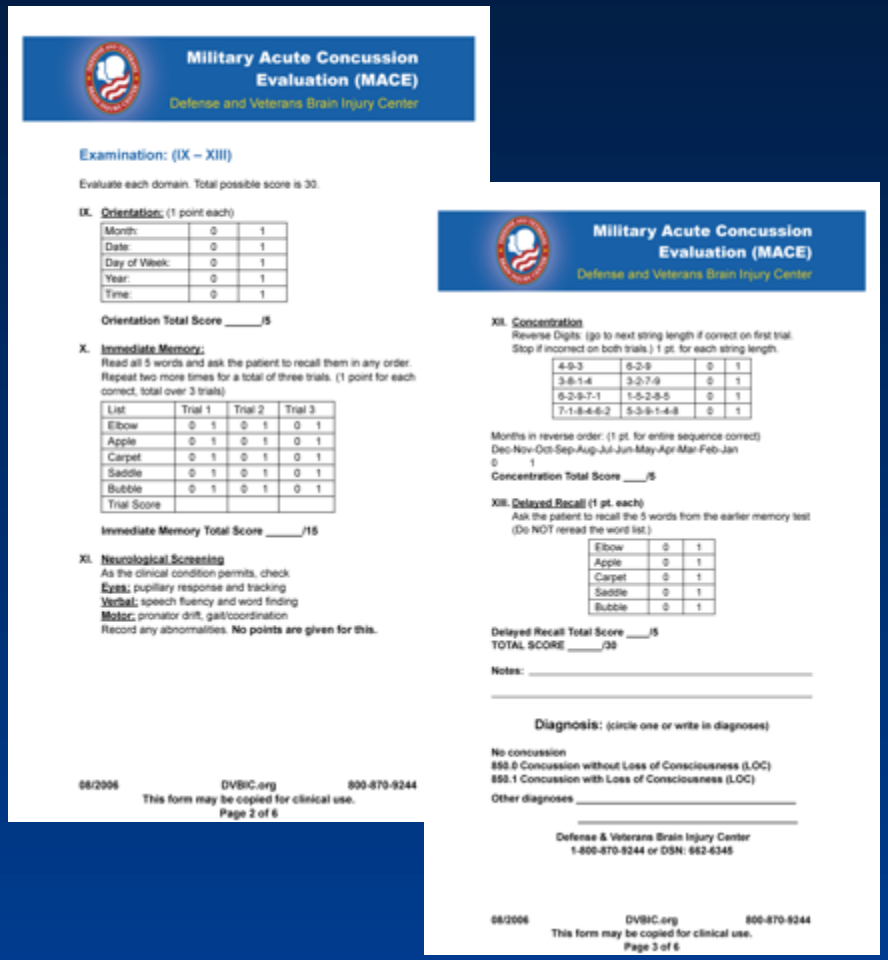
**DTM 09-033**

# MACE and SAC

## Military Acute Concussion Evaluation
## Standardized Assessment of Concussion

- Embedded in the MACE is the Standardized Assessment of Concussion (SAC), a widely used, validated, brief cognitive tool.
- Gross cognitive tool addressing 4 domains
  - Orientation
  - Immediate memory
  - Concentration
  - Memory recall

  - Max score is 30
  - ≤ 25 is significant



**Military Acute Concussion Evaluation (MACE)**
Defense and Veterans Brain Injury Center

**Examination: (IX – XIII)**

Evaluate each domain. Total possible score is 30.

**IX. Orientation:** (1 point each)

| | | |
|---|---|---|
| Month: | 0 | 1 |
| Date: | 0 | 1 |
| Day of Week: | 0 | 1 |
| Year: | 0 | 1 |
| Time: | 0 | 1 |

**Orientation Total Score _____/5**

**X. Immediate Memory:**
Read all 5 words and ask the patient to recall them in any order. Repeat two more times for a total of three trials. (1 point for each correct, total over 3 trials)

| List | Trial 1 | Trial 2 | Trial 3 |
|---|---|---|---|
| Elbow | 0 1 | 0 1 | 0 1 |
| Apple | 0 1 | 0 1 | 0 1 |
| Carpet | 0 1 | 0 1 | 0 1 |
| Saddle | 0 1 | 0 1 | 0 1 |
| Bubble | 0 1 | 0 1 | 0 1 |
| Trial Score | | | |

**Immediate Memory Total Score _____/15**

**XI. Neurological Screening**
As the clinical condition permits, check
**Eyes:** pupillary response and tracking
**Verbal:** speech fluency and word finding
**Motor:** pronator drift, gait/coordination
Record any abnormalities. **No points are given for this.**

08/2006 DVBIC.org 800-870-9244
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**Military Acute Concussion Evaluation (MACE)**
Defense and Veterans Brain Injury Center

**XII. Concentration**
Reverse Digits: (go to next string length if correct on first trial. Stop if incorrect on both trials.) 1 pt. for each string length.

| | | | |
|---|---|---|---|
| 4-9-3 | 6-2-9 | 0 | 1 |
| 3-8-1-4 | 3-2-7-9 | 0 | 1 |
| 6-2-9-7-1 | 1-5-2-8-5 | 0 | 1 |
| 7-1-8-4-6-2 | 5-3-9-1-4-8 | 0 | 1 |

Months in reverse order: (1 pt. for entire sequence correct)
Dec-Nov-Oct-Sep-Aug-Jul-Jun-May-Apr-Mar-Feb-Jan
0 1
**Concentration Total Score ____/5**

**XIII. Delayed Recall (1 pt. each)**
Ask the patient to recall the 5 words from the earlier memory test (Do NOT reread the word list.)

| | | |
|---|---|---|
| Elbow | 0 | 1 |
| Apple | 0 | 1 |
| Carpet | 0 | 1 |
| Saddle | 0 | 1 |
| Bubble | 0 | 1 |

**Delayed Recall Total Score ____/5**
**TOTAL SCORE _____/30**

**Notes:** _____

**Diagnosis:** (circle one or write in diagnoses)

No concussion
850.0 Concussion without Loss of Consciousness (LOC)
850.1 Concussion with Loss of Consciousness (LOC)
**Other diagnoses** _____

Defense & Veterans Brain Injury Center
1-800-870-9244 or DSN: 662-6345

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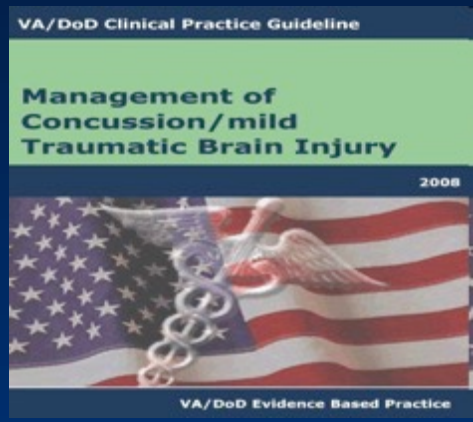
www.dvbic.mil

# Clinical Management of mTBI

## First large system-wide CPG

- VA/DoD Clinical Practice Guidelines for Management of Concussion/mTBI
  - **Evidence based**
  - Released in March, 2009
- Focused on **symptoms treatment**




Cifu, Labutta and Ling (eds),
"VA/DoD Clinical Practice Guidelines for Management of Concussion/ mTBI" (2009)

Download free at:
www.mirecc.va.gov/docs/visn6/VADoD_CPG-Concussion-mTBImarch09.pdf

# Initial Preliminary Results

- Return To Duty: 97.36%
- 90% of Blast pts are symptom free by 3 days
- No cases to date of prolonged post-concussive syndrome

Rafols, Advance for Occup Therap 2010

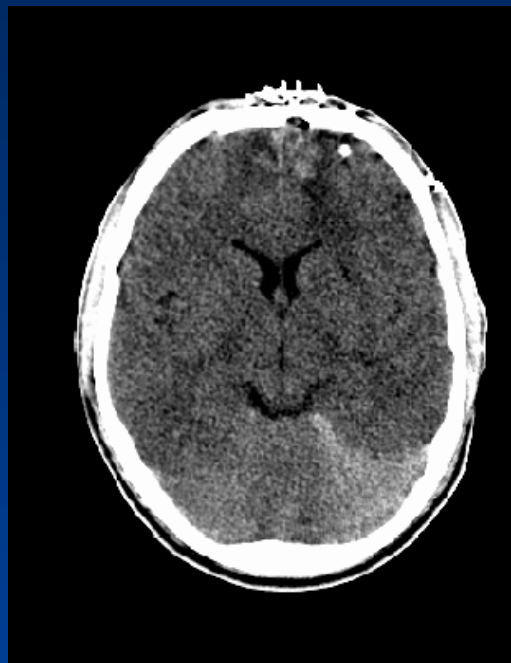
# Moderate to Severe TBI

No head injury is too severe to despair of,  nor too trivial to ignore

- Hippocrates

# Moderate TBI

- Pt exposed to mortar explosion and struck by frag
- GCS 12 at scene, brought to CSH
- CT: frag track w/ hematoma, no SAH

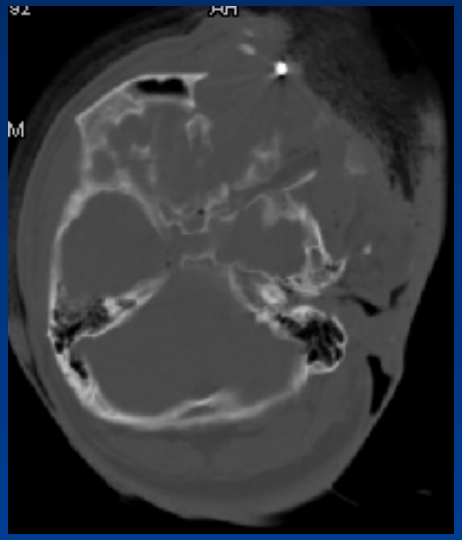


# Moderate Injury to Brain Outcome

- Bifrontal craniotomy with debridement
- ICP monitor placed, treated with HTS
- TCDs increased flow velocities so patient was treated with HHH
  - Peaks at HD#7 and
  - Normal by HD#11
- Discharge to home
  - But stayed in theater

# Severe TBI

- Pt suffered TBI from hanging IED
- CT: Early edema, L brain herniation, L SDH, SAH, L temp fx, L orbital roof fx



# Severe Blast TBI Outcome

- No evid of hemorrhagic shock
- Initial Left hemi-craniectomy with SDH evac
- Partial frontal lobectomy (of herniated portion)
- ICP control with HTS
- CPP directed therapy
- Seizures but controlled
- Autonomic dysfunction syndrome controlled with propanolol and morphine
- Vasospasm successfully tx with HHH
- Followed commands by Day #7
- Followed multi-step commands by Day #12 and extubated
- Transferred to civilian hospital on Day #14

# Blast TBI and Shock

- IED blast, GCS 12 then 6
- Airway, Tourniquet in field
- A/E to CSH but cardiac arrest during landing
- EMD, Pulseless, Pupils 3 NR,
- Hb 6, pH 6.9, INR 6, T 93$^{o}$F
- Lots of warm RBC/plasma (1:1), platelets, cryo,fVIIa, NS
- Hemicraniectomy, amputation, ICU care
- Today, recovered, prosthetic leg

# In Triage Area

- Neuro Critical Care assigned primary care
- Regained pulse with 2U PRBC, 2L NS
- Central lines placed and resuscitation advanced
- BP 60/30, additional 7U PRBC (warmed with Belmont), 7U FFP, 6-pk Plt, 6 cyro, 6L NS
- Factor VIIa administered
- Peak airway pressures over 50
  - reintubated
  - high rate low volume mode instituted
- Within 2 hours, T 97.2$^{o}$F, INR 1.9, pH 7.2, INR 1.1, HCT 30, Plt 95, PAP 20's
- Pupils: sluggish but reactive bilaterally

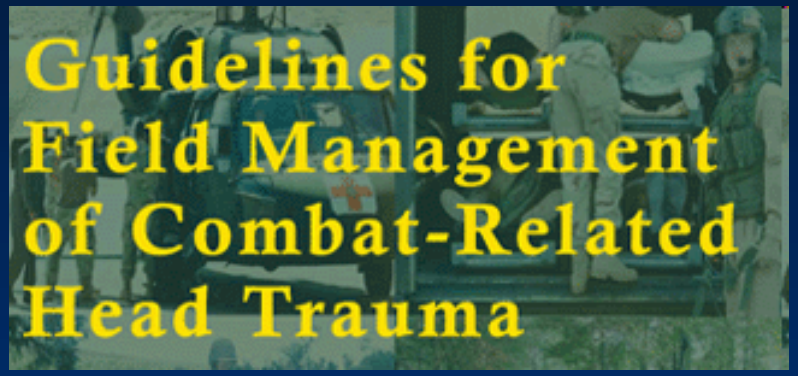
# In OR

- Right fronto-parietal-temporal craniectomy with evac of SDH, debrided ODSF
- IVC placed with ICP 7

## Post-OP

- A/E to Germany.  There, pupils reactive, moved RUE purposefully, L to pain, ICP 12, CPP 70s
- Transferred to WRAMC, awoke to oriented X 3, in rehab due to R BKA as left HP resolved
- Recovered, prosthetic leg

# Battlefield Treatment




Knuth, Letarte, Ling, Moores et al

Brain Trauma Foundation (2005)

Download available: www.braintrauma.org

# Pre-Hospital Guidelines for Management of TBI

- Avoid hypoxia
  - $O_2$ Sats > 90 or $pO_2$> 60mmHg
- Artificial airway for GCS $\leq$ 8
- Hyperventilation for cerebral herniation
  - Not for ICP prophylaxis or routine use
- Systolic BP > 100mmHg
- No specific resuscitation fluid is recommended
  - Hypertonic saline has logistical advantages
- Hypertonic saline at $\leq$ 500cc boluses is acceptable
  - Use for ICP management is an option
- +/- Mannitol for cerebral herniation if intravascular volume can be maintained

# Pre-Hospital Guidelines for TBI

- Determine **GCS and pupil** function as soon as possible
- Triage GCS 9 – 13 to CSH
- GCS < 15 should not return to duty until normalized
- **Sedation and analgesia as needed for transport**
- Analgesics in small doses with proper monitoring
- Antibiotics for penetrating TBI is an option

# Early Prognostic Signs Trauma

Design: Retrospective study of adults and children

Pts: 846 (668M:178F), MVA 50%, motorcycle 22%, falls 15%

Outcome: 1 year GOS

Results: GCS 8 (40% good recovery) to 3 (7%), death 8 (12% death) to 3 (73%), Pupils: Bilat abn (62% death, 5% PVS) vs normal (16% death, 0 PVS, 53% good).

Conclude: Outcome assoc with GCS, pupils, body temp, age

Jiang et al, J Neurotrauma 19: 869 (2002)

# Clinical Management of Moderate – Severe TBI

"Guidelines for the management of severe traumatic brain injury"
Carney et al, Neurosurgery 80:6-15 (2017)
Download available: www.braintrauma.org

"Explosive Blast Neurotrauma"
Ling, Bandak, Armonda, Grant and Ecklund
Journal of Neurotrauma 26:815–825 (2009)

"Traumatic Brain Injury in Modern War"
Ling and Ecklund
Curr Opin Anesth 24: 124-130 (2011)

# Key Guidelines

- CPP goal: 60 – 70mmHg
- SBP > 100mmHg (50-69yo) & >110 mmHg (15-49 or > 70yo)
- ICP < 22 mmHg
- Antiepileptic drug for 7 days (begin w/in 24 hours)
- No hypothermia
- No steroids
- pCO2 35mmHg if hyperventilating for herniation, 24Hrs only

In 3rd Ed CPG

- pO2 > 60mmHg or O2 sats > 90%
- Hypertonic resuscitation fluids (NS or higher)
- Artificial airway for GCS ≤8
- Head of Bed at 30°

Guidelines for the management of severe TBI, 4th Ed, Brain Trauma Foundation, 2016

# Additional Interventions

- Brain Code
  - HOB 30º, Hypervent $pCO_2$ 35, +/- mannitol
- Hypertonic Saline (HTS) for ICP control
  - 23.4% HTS bullet, 3% HTS infusion
- Hemicraniectomy (early)
- Transcranial Doppler (TCD) for blast related vasospasm detection
- Endovascular techniques for vasospasm intervention

# Hypertonic Saline "Bullet"

- Emergency treatment for herniation
- Saline bullet = 30cc bolus of 23.4% saline
  - Can be repeated
- Up to 50% reduction of ICP
  - 65% of pts below 20mmHg ICP
- Preserves intravascular volume state
  - Increase osmolality without diuresis
- Effect lasts for hours
- Potential toxicity
  - ATN

Suarez et al, Crit Care Med **26**: 1118 (1998)
Koenig et al, Neurology **70**: 1023 (2008)

# Hypertonic Saline Infusion

- Maintain blood:brain osmotic gradient
- Initiate therapy with 3% saline at 75 cc/hr (or higher if requiring fluid resuscitation)
  - use 50% chloride/50% acetate to minimize risk of hyperchloremia
  - Central venous access to avoid phlebitis
- Infuse to a goal Na (ex. 145-150)
- Check serum Na frequently (q 4-6 hrs)
  - "ballpark" serum osm will be double serum Na
- After "edema window," simply turn off infusion to autotaper

# Emerging Evidence for Improving TBI goals of Resuscitation

# TBI and Optimal Hb

Study: RCT of EPO with restrictive Hb <7 vs liberal Hb <10 goals, CHI TBI, n=200 pts

Methods: EPO vs placebo, transfusion if Hb < 7 (restrictive) or Hb < 10 (liberal)

Results: Restrictive Hb threshold had more favorable outcome (42.5%) than liberal (33%) and less thromboembolic events, 8.1% vs 21.8%

Conclusions: **Restrictive Hb trigger level (< 7) had greater benefit.** EPO or liberal Hb goal did not improved outcome.

Robertson et al, JAMA 312: 36-47 (2014)

# TBI and Optimal Systolic BP

Study: Retrospective analysis of 3844 pts from Excellence in Pre-Hospital TBI study

Methods: SBP and TBI outcome

Results: SBP 40-119 mmHg associated with worse outcome, Compared to 40mmHg, every 10mmHg higher assoc with lower mortality (18.8%)

Conclusions: Higher SBP associated with better outcome. Challenges SBP> 90 goal as standard of care.

Spaite et al, JAMA Surg 152:360 (2017)

# TBI and Optimal Resuscitation Fluid

## Unknown

- NS assoc less mortality than albumin (humans)
- FFP decreases lesion size and edema (pigs)
- Hextend decreases edema (pigs)
- Vasopressors increase risk of ARDS (humans)
  - Epi by 5.8X, Dopamine by 10.8X

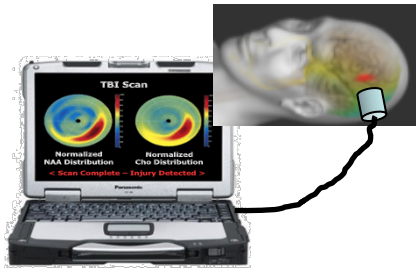
Contant et al, J Neurosurg 95:560 (2001)
Finfer et al, SAFE, NEJM 3:2247 (2004)
Myburgh et al, NEJM 357:874 (2007)
Jin et al, Shock 38: 49 (2012)

# Research to Improve Diagnosis and Treatment

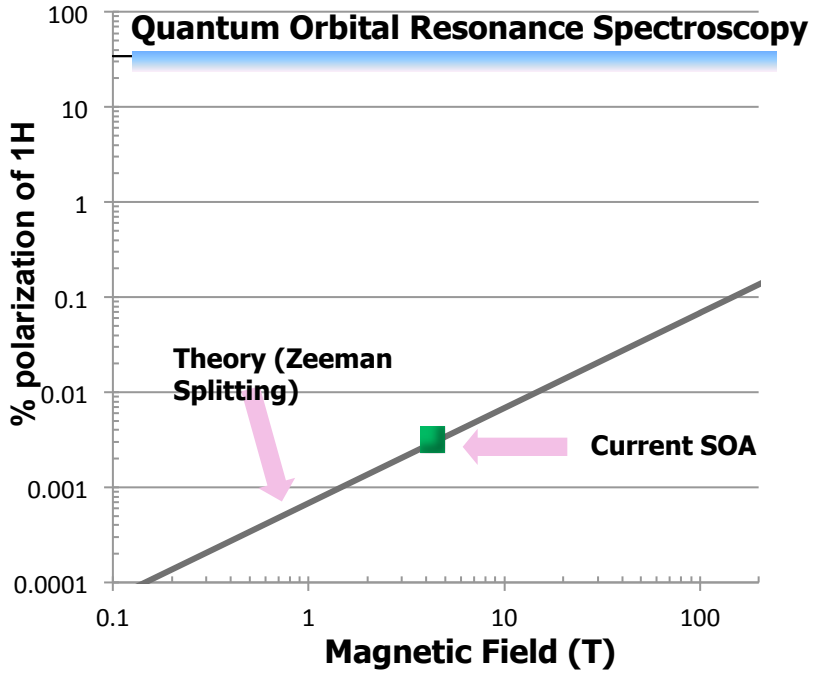
What is on the horizon?

# Portable Brain Imaging (better than MRI)

## Quantum Orbital Resonance Spectroscopy




**Today**




**What is needed:**

**A new non-invasive method for directly hyperpolarizing tissues that does not require a large magnet.**

- **High polarization (>10%)**
- **Fast (sec to min)**
- **Compact, inexpensive system**
- **Other atomic spectra (e.g., $^{13}C$)**

**Problem:**

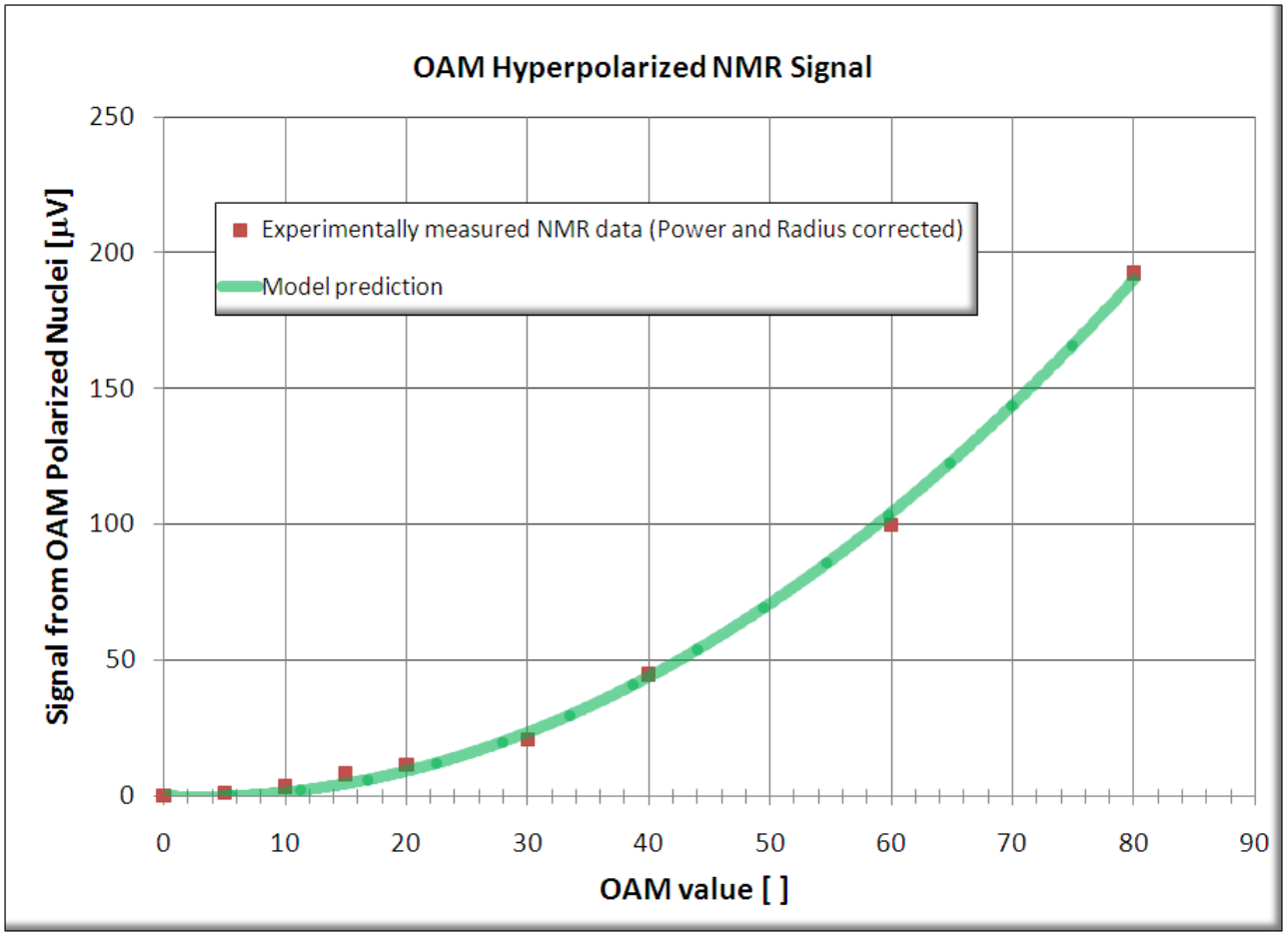
**Current Magnetic Resonance Spectroscopy is hampered by:**

- **Low polarization (~0.001%)**
- **Slow (30 min)**
- **Large, expensive magnets**
- **Restricted to $^{1}H$ spectra**

Dr. Matt Goodman, DSO, DARPA

**It's hard to beat thermodynamics….so change the game. Use different physics!**

# Initial Results: Hyperpolarization using visible light



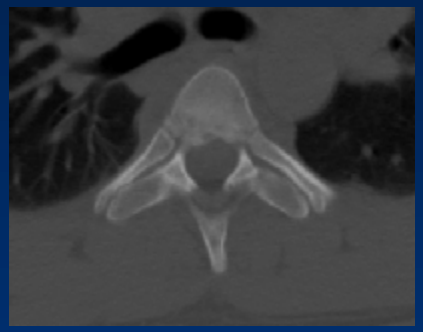
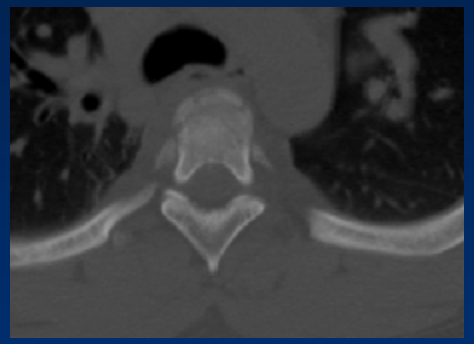

**Team achieved 1% polarization**

**Initial measurements indicated 100-1000x more polarization using this method.**

**Dr. Matt Goodman, DSO, DARPA**

# Today's Soldier

- Pt thrown from vehicle by IED blast
- CT: Spine fractures at T4 and T5

•Plan to A/E back home
•Cried when told he would be sent out of theater.
•"Back home, what do I do? Here, I am helping these people help build a nation."

Afghanistan, 2003

# Conclusion

Iraq 2005

Providing medical care to the most deserving patients --- our soldiers at war defending the principles of freedom, self-rule, and equality that define our countries--- is the most personally rewarding experience one can have