Joint Session with ACOFP, AOASM and AAO:

Post Concussion Research and Therapy Options

P. Gunnar Brolinson, DO, FAOASM
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Post Concussion Research Update and Treatment Options

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OMED 2017
Philadelphia, PA

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Concussive Brain Injuries

- Nearly 90% of estimated 2.5 million TBIs in the US each year are mild
- Gross underestimates since most do not go to ED for care
- Up to 3.8 million sports-related TBIs each year
- Research suggests potential links between repetitive concussions and long-term neurodegenerative processes

www.nytimes.com
www.wired.com
Concussive Rates by Sport

<table>
<thead>
<tr>
<th>Sport</th>
<th>Rate per 10,000 athlete-exposures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men's Ice Hockey</td>
<td>1</td>
</tr>
<tr>
<td>Women's Ice Hockey</td>
<td>3</td>
</tr>
<tr>
<td>Men's Football</td>
<td>5</td>
</tr>
<tr>
<td>Women's Soccer</td>
<td>8</td>
</tr>
<tr>
<td>Women's Basketball</td>
<td>7</td>
</tr>
<tr>
<td>Women's Field Hockey</td>
<td>6</td>
</tr>
<tr>
<td>Men's Basketball</td>
<td>4</td>
</tr>
<tr>
<td>Men's Soccer</td>
<td>2</td>
</tr>
</tbody>
</table>

* Rates are reported per 10,000 athlete-exposures

Concussion Biomechanics

- **Heading a soccer ball** results in head accelerations from 16 to 20g lasting 25 ms
- The average collegiate football impact:
  - From 21 and 32g lasting 14-15 ms
- Impacts to the **top of the head** yielded the greatest linear acceleration and impact force magnitude
- **Improper tackling techniques**
- Offensive and Defensive line players sustained the lowest-magnitude impacts but the highest number of impacts during games and practices

Sensor Systems....

- Can they be clinically useful?
- Research tool only?
- How validated?
  - Industry standards?
Field Deployed Head Impact Sensor History

Peak head acceleration of athletes during competition—football

2000: CART Racing Instrumentation, Air Force Research Lab
Hill, Knox, Crockett, Handman, Poff, Olvey, Cohn, Pelletiere, Bonfeld, Plaga
2008: CART Racing New Sensors
Smaller sensor located further in ear canal
Knox, Pelletiere, Panzer, Bass

"Yep, I'm flying through the air, this is not good" Ricky Bobby
“Sensorgate”…Lights out on concussion????

Concussion Biomechanics

- Over 225,000 head impacts recorded at Virginia Tech
  - Games (30%)
  - Practice (70%)
  - 13 years of data collection: 2003-2016

- Clinically diagnosed concussive impacts recorded for instrumented players

- Unbiased exposure data
  - Previous football work over-sampled injury data

A Head Impact Detection System Using SVM Classification and Proximity Sensing in an Instrumented Mouthguard

Hernandez et al., 2014
Wu et al., 2014
Wu et al., 2015
Kuo et al., 2016

Stanford CAMlab MIG

Stanford Tab MIG

Stanford MIG1.0

Stanford MIG2.0
Validation of an “Intelligent Mouthguard” Single Event Head Impact Dosimeter

Adam Bartch, Sergey Samozenko, Edward Bensus
Cleveland Clinic

Vincent Maio
University of Pittsburgh, Cleveland Clinic

Daniel Betti
Sportguard Laboratories Inc.

ABSTRACT - During the 2013-14 National Collegiate Athletic Association men’s lacrosse season, we evaluated the feasibility of using a compact, lightweight impact sensor to accurately and efficiently capture head impact data. The Sensor Headgear was used in conjunction with a custom mouthguard to provide single event head impact data on a real-time basis.

Player-specific ear molds used to create custom-fit ear piece sensors: DASHR (Duke-Bass) MVTrak

Lacrosse Summary Data
Linear Acceleration
18 ± 13 g
Wake Forest Retainer System

20 g, 14 rad/s

Soccer Summary Data
Linear Acceleration
23 ± 11 g
Rotational Velocity
11 ± 5 rad/s
Concussions in Ice Hockey

- Among the highest rates of concussion in sports
- Most result from player-player contact (45%), followed by player-boards/glass (28.8%), and player-ice contact (20%) (Marar et al. 2012)
- Higher rates of concussion associated with body checking

Laboratory Testing Methods

Pendulum Impactor:
- Improved repeatability
- Variable impact energy (pendulum arm angle)
- Rigid impactor face

NOCSAE headform mounted on Hybrid III neck

Impact Response Corridors

Average response for Hybrid III to boards, glass, and ice at an ice rink
Front Impact: Medium Energy Level

\[ RISK = \frac{1}{1 + e^{-(v_2 \cdot v_3 \cdot \alpha \cdot \omega)}} \]

\[ RISK \times EXPOSURE = INCIENCE \]

\[ 0.032 \times 4.6 = 0.148 \%

3.2% risk

1%

5%

10%

25%

50%

75%

90%

99%

Football

115 g

3646 rad/s/s

8.2% risk

Hockey

164 g

6333 rad/s/s

82% risk

Injury Risk Comparison
Front Impact, High Severity

Cascade M11

Xenith X2E

Helmets in study

5 stars: 0

4 stars: 0

3 stars: 1

2 stars: 6

1 star: 17

0 stars: 13
Hockey Helmets
- Bauer 5100
- CCM Resistance 100
- Schutt Air XP Pro VTD

Football Helmets
- Riddell SpeedFlex

Padding Thickness
(Bauer 5100 helmet and Bauer Nexus padding)
- Head: 0.7 in (18 mm)
- Shoulders: 1.0 in (25 mm)
- Elbows: 1.5 in (38 mm)
- Hands: 1.5 in (38 mm)
- Hips: 1.5 in (38 mm)
- Knees: 2.2 in (56 mm)
- Shins: 1.6 in (41 mm)

Manufacturers using methods to improve helmet designs
Bauer just released a new top rated helmet.
Effects of Helmet Safety Standards

Helmet standards reduced rate of fatal head injuries 74%.

Quantifying Head Impact Exposure

Exposure:
- All results from video analysis only

Sensor Performance:
- Comparison between video analysis and data collected by sensors

Virginia Tech Women's Soccer Team

Concussion History

<table>
<thead>
<tr>
<th># Previous Concussions</th>
<th>0</th>
<th>≥1</th>
<th>≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td># Players (26 total)</td>
<td>15</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>
Data Processing

- Downloaded and processed following each game and practice
- Two games excluded due to poor video quality

Distribution Functions

Head impacts per season across all players

Acceleration Distributions

<table>
<thead>
<tr>
<th>Linear Acceleration (g)</th>
<th>Rotational Acceleration (rad/s²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min: 9</td>
<td>Max: 115</td>
</tr>
</tbody>
</table>
88g, 12,039 rad/s²

X2 xPatch Study – Women’s Soccer

- VT Women’s Soccer
  - 26 players
  - 26 practices
  - 20 games
- Instrumented with xPatch
- Video footage of each practice/game used to verify every head impact event

X2 xPatch did not accurately:
- count head impacts
- measure head acceleration

X2 xPatch Study – Women’s Soccer

<table>
<thead>
<tr>
<th>Player Position</th>
<th>Average # of Impacts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.0 ± 8.2</td>
</tr>
<tr>
<td>2</td>
<td>52.6 ± 27.8</td>
</tr>
<tr>
<td>4</td>
<td>60.2 ± 32.4</td>
</tr>
<tr>
<td>6</td>
<td>96.4 ± 63.3</td>
</tr>
</tbody>
</table>

From Video Analysis

X2 xPatch: 8,999 events classified as head impacts
Video: 1,703 head impact events identified

Head Impact Count Comparison

Head Acceleration Measurements
- Peak Linear Acceleration: 26 g
- Peak Rotational Acceleration: 12,039 rad/s²

X2 Data
- 1,463 True Positives
- 7,536 False Positives
- 8,626 True Negatives
- 240 False Negatives

- In identifying head impacts:
  - Sensitivity: 86%
  - Specificity: 53%
**X2 Coupling Limitation**  
Over-prediction of Rotational Acceleration

![Graphs showing X2 Coupling Limitation](image)

**Sensor STAR (Fall 2017)**

- **Dummy Testing**
- **Volunteer Testing**

![Images of sensor STAR](image)

**Preliminary results:**

- Ball-to-Head
- Head-to-Head

**Biomechanical Performance of Headgear Used in Soccer**

![Images showing biomechanical performance](image)
Ball-to-Head Impacts

Little Effect with Protective Headgear

Concussion Risk Below 1%
Head-to-Head Impacts

- Side Location
- Back Location

- Bare Head to Bare Head
- Bare Head to Headgear
- Headgear to Headgear

9/25/2017
Bare Head to Headgear

35% average reduction in linear head accelerations

Headgear to Headgear

53% average reduction in linear head accelerations

Differences in Headgear Performance

<table>
<thead>
<tr>
<th>Headgear</th>
<th>Overall Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTRL</td>
<td>3.06</td>
</tr>
<tr>
<td>STOR</td>
<td>0.37</td>
</tr>
<tr>
<td>UN10</td>
<td>0.64</td>
</tr>
<tr>
<td>UN6</td>
<td>1.12</td>
</tr>
<tr>
<td>DJ</td>
<td>1.63</td>
</tr>
<tr>
<td>F90P</td>
<td>1.81</td>
</tr>
<tr>
<td>FFU</td>
<td>2.00</td>
</tr>
<tr>
<td>FN1</td>
<td>2.03</td>
</tr>
<tr>
<td>F90S</td>
<td>2.29</td>
</tr>
<tr>
<td>HB</td>
<td>2.55</td>
</tr>
</tbody>
</table>

1 exposure to each impact (6 total)
Differences in Headgear Performance

Impact Protection Summary

- Not effective for ball-to-head impacts
- Meaningful reductions for head-to-head impacts
  - Not all headgear performed equally
- Use of protective headgear could reduce concussion incidence significantly

The Concussion “crisis” and Chronic Traumatic Encephalopathy

- “Unlike other neurology specialties, sports concussion is driven not by science but opinion in the form of the numerous consensus conferences”.
- “Accepting the assertion that football causes CTE requires the well-read and knowledgeable clinician to make a sizable leap of faith”.

The Concussion “crisis” and Chronic Traumatic Encephalopathy

• In a convenience sample of 202 deceased players of American football from a brain donation program, CTE was neuropathologically diagnosed in 177 players across all levels of play (87%), including 110 of 111 former National Football League players (99%).

• In a convenience sample of deceased players of American football, a high proportion showed pathological evidence of CTE, suggesting that CTE may be related to prior participation in football.


The Concussion “crisis” and Chronic Traumatic Encephalopathy

• What are the potential issues with this study?
  – ascertainment bias associated with participation in this brain donation program
    • public awareness of a possible link between repetitive head trauma and CTE may have motivated players and their families with symptoms and signs of brain injury to participate in this research
  – the VA-BU-CLF brain bank is not representative of the overall population of former players of American football
  – this study lacked a comparison group that is representative of all individuals exposed to American football at the college or professional level

Incidence of neurodegenerative disease

• 9% of Americans over 65 have dementia
  – About 5 million people
  – Expected to triple by 2050
• NFL players are 3X more likely to develop neurodegenerative disease
HS Football and Risk of Neurodegenerative Disease

- To assess whether high school football played between 1946 and 1956, when headgear was less protective than today, was associated with development of neurodegenerative disease later in life.
- Compared 438 FB players to 140 non FB players from HS in Rochester, MN.
- High school students who played American football from 1946 to 1956 did not have an increased risk of later developing dementia, PD, or ALS compared with non–football-playing high school males, despite poorer equipment and less regard for concussions compared with today and no rules prohibiting head-first tackling (spearing). These results should be somewhat reassuring to high school players from 50 years ago, they should give no reassurance to today’s players.


What is Chronic Traumatic Encephalopathy???

- Dementia Pugilistica
  - Primary Sport-Specific?
  - Dr. Harrison M. 1928
  - CTE with Post Traumatic Encephalopathy
- Accumulation of Tau Protein in neurologic tissue
  - Genetically determined?
  - Head trauma triggered?
  - Cellular type of “Yo-yo disease”?
  - An epileptogenic syndrome?
- A composite syndrome of mood disorders
  - Associated with neurologic and psychiatric symptoms
- Is NOT Alzheimer’s Disease
  - Not associated with central amyloid
  - Relationship to Lou Gehrig’s Disease?
- definitive Diagnosis by direct tissue analysis post mortem

WE HAD NO IDEA THAT THIS COULD CAUSE WHAT IT’S CAUSING. CTE? THAT’S SCARY STUFF. THAT, WE DIDN’T EVEN KNOW ABOUT UNTIL THREE YEARS AGO OR SO. ALZHEIMER’S? WE NEVER HEARD THE WORD ALZHEIMER’S IN THE ’60s OR ’70s.

Manny Fernandez, Defensive Tackle on 1972 Miami Dolphins

Fernandez doesn’t remember the end of Super Bowl VII, which capped the Dolphins’ 17-0 season, because of blow he took to the head.

Fernandez estimates he sustained “dozens” of concussions during his playing career. And yet, his mind is strong.

We had no idea that this could cause what it’s causing.

CTE? That’s scary stuff. That, we didn’t even know about until three years ago or so. Alzheimer’s? We never heard the word Alzheimer’s in the ’60s or ’70s.

Manny Fernandez, defensive tackle on 1972 Miami Dolphins

What is Chronic Traumatic Encephalopathy???
What is Post Traumatic Encephalopathy?

• A clinicopathologic syndrome that follows focal or diffuse brain trauma
  – Associated with gross or microscopic destruction of brain tissue
  – Lacerations, contusions, hemorrhages, etc

• Not neurodegenerative and not progressive
• Can co-exist with CTE

Does “Advanced Imaging” help? Maybe…

• Functional MRI
  – Measures neuronal glucose uptake while the patient performs a “task” in the magnet
  – Can see changes in brain activation patterns for “acutely injured” patients vs controls

• Diffusion Tensor Imaging
  – Can identify structural changes in the white matter of the brain that correlates to cognitive deficits even in patients with mild traumatic brain injury.
  – When white matter is damaged, other areas of the brain may appear healthy but they are actually “unplugged” and cannot function optimally.

Kraus, Little, Guzman et al, Brain: Oct 2012
Future Diagnostic Considerations

- **Biomarkers**
  - Term often used to refer to a protein measured in blood whose concentration reflects the severity or presence of some disease state.
  - Troponin is a biomarker used to diagnose acute myocardial infarction (AMI) in Emergency Rooms.

Banyan Biomarker Panel for TBI

- **GFAP**
  - Gliarial fibrillary acidic protein
  - Structural protein of the intermediate filament of Astroglia 50 kDa
  - Highly enriched in the nervous system
  - 1% of total brain protein

- **UCH-L1**
  - Ubiquitin Carboxyl-terminal Esterase L1
  - Small compact 24 kDa protein
  - Expressed at a high level in neurons
  - 5% of total brain protein

TBI study

Levels of Serum GFAP Are Associated With Severity Of Injury In Patients With Mild And Moderate Traumatic Brain Injury

**SUMMARY:**

GFAP was systematically assessed in human serum following mild and moderate TBI. GFAP levels were significantly elevated in this population using ELISA analysis, including those with mild TBI. GFAP was able to discriminate TBI patients from uninjured controls and serum levels were able to distinguish orthopedic and motor vehicle controls from TBI patients.
Mild and moderate TBI study (GFAP)

Elevated Levels of Serum Gliial Fibrillary Acidic Protein Breakdown Products in Mild and Moderate Traumatic Brain Injury Are Associated With Intracranial Lesions and Neurosurgical Intervention

SUMMARY:
GFAP-BDP is detectable in serum within an hour of injury. It is associated with measures of injury severity, including the GCS score, CT lesions, and neurosurgical intervention. Further study is required to validate these findings before clinical application.

Mild and moderate TBI Study (UCHL-1)

Serum levels of UCHL-1 distinguishes mild and moderate traumatic brain injury from trauma controls and is associated with lesions on computed tomography.

SUMMARY:
UCHL-1 was detected in the serum of mild and moderate TBI (MMTBI) patients within an hour of injury.

What about repetitive “sub concussive” impacts?

- Millions of individuals have played contact sports for many years without obvious functionally significant adverse effects, and without developing progressive neurodegenerative disorders.

- Nevertheless, we are concerned that repetitive head impacts may have an adverse affect on some athletes.
  - It is reasonable to speculate that individual differences such as polymorphisms in genes modulating response to neurotrauma (e.g., APOE, BDNF, A2M) or other host factors may play a role.
  - It is tempting to hypothesize that risk of chronic traumatic encephalopathy or other long term effects of contact sports may represent a gene-environment interaction between repetitive mild neurotrauma and genetic vulnerability to heightened injury response or attenuated neural repair.

**Post Concussion Syndrome**

- This Dx is a function of the length of symptom persistence:
  - 3 months duration of at least 3 symptoms
- Retired NFL players who were diagnosed with post-concussion related depression:
  - 87% continued to have lifelong symptoms
- Medications that address symptoms may be considered in the treatment of PCS:
  - Dosing should begin low and titrated upward slowly

<table>
<thead>
<tr>
<th>Drug</th>
<th>Side Effects</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flexeril 10mg</td>
<td>Moderate muscle stiffness</td>
<td>10mg at bedtime</td>
</tr>
<tr>
<td>Elavil 10-25mg</td>
<td>Sedation, insomnia</td>
<td>10-25mg at bedtime</td>
</tr>
<tr>
<td>NSIDs</td>
<td>Gastrointestinal issues</td>
<td>As needed</td>
</tr>
<tr>
<td>Topamax 25-50mg</td>
<td>Nausea, diarrhea</td>
<td>25-50mg twice daily</td>
</tr>
<tr>
<td>Effexor and Cymbalta</td>
<td>Nausea, dizziness</td>
<td>Initial 37.5mg twice daily, titrated as needed</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>Sedation, dizziness</td>
<td>Initial 10-25mg daily, titrated as needed</td>
</tr>
<tr>
<td>SSRI's</td>
<td>Insomnia, sedation</td>
<td>Initial 10-20mg daily, titrated as needed</td>
</tr>
<tr>
<td>Omega 3 supplements</td>
<td>Nausea</td>
<td>1000mg daily</td>
</tr>
<tr>
<td>Antioxidants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha Lipoic Acid 100mg</td>
<td>Nausea</td>
<td>100-200mg daily</td>
</tr>
<tr>
<td>Co Q 10 100-200mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amantadine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of Gunnar’s clinical treatment Pearls for PCS

- Remember that dx and tx is a “team event”
  - Psychologists, neurologists, PM&R, PT’s and ATC’s can all be involved
- You are treating “symptoms”
  - For mild insomnia with head/neck pain:
    - Flexeril 10mg at hs
    - Elavil 10-25mg at hs
  - For headache:
    - NSIDs
    - Topamax 25-50mg BID
    - OMT
  - For depression with diffuse “body pain”:
    - Effexor and Cymbalta (SNRIs)
    - Tricyclics
    - SSRI’s don’t seem to work well
  - For “fogginess”:
    - Omega 3 supplements
    - Antioxidants
    - Alpha Lipoic Acid 100mg QD
    - Co Q 10 100-200mg QD
    - Amantadine
    - 100-200mg BID
- Remember to include physical therapy and neurocognitive rehab as appropriate
- In general avoid narcotics

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Placebo-Controlled Trial of Amantadine for Severe Traumatic Brain Injury; Gianco et al; N Engl J Med 2012; 366:819-826