Concussion: Is there a role of TCD

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Disclosure

- A. Razumovsky, PhD, FAHA is FTE for the private practice (Sentient NeuroCare Services, Inc.)
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TBI

- TBI accounts for one-third of all injury-related deaths in the United States (CDC, 2010)
- Each year, 1.7 million Americans sustain a TBI. Of these, more than 1.3 million are treated and released from a health care facility, 275,000 are hospitalized, and 52,000 die (CDC, 2010)
- Approximately 75–90% of recorded TBI cases are classified as mTBI (Cassidy et al, 2004; Thornhill et al, 2000)
- TBI in prison population: Of the overall sample, 16% had experienced moderate-to-severe TBI and 48% mild TBI. Adults with TBI were younger at entry into custodial systems and reported higher rates of repeat offending (Williams WH et al. 2010)
- The actual number of people who sustain an mTBI is unknown; however, it is likely much higher than these estimates; individuals having less visible symptoms may not seek medical attention for their injuries or be diagnosed with mTBI at the hospital

Monetary Cost of TBI

- Direct and indirect costs may exceed $60 billion per year in the US
- Costs of inpatient rehabilitation often exceed $100,000/patient
- Outpatient cognitive rehabilitation approximately $20,000 to $30,000/patient
- Employment drops from 69% to 31% by end of 1st year of injury for civilian TBI
- US civilian TBI result in $642 million in lost wages yearly, $96 million in lost taxes yearly, and $353 million in increased public assistance expenditures.
Mild TBI/Concussion Statistics

- Up to 3.8 million sport-related concussions every year
  - 10% young athletes ever year
  - Up to 50% playing collision sports have concussion symptoms – only 10% report them
- 7.6 million athletes participate in high school sports; 44 million in non-scholastic sports

Sport and Concussion

- You cannot see a concussion – TRUE
- There is no correlation between imaging and physical or cognitive deficits - TRUE
- Many physicians believe that if you cannot see a lesion in brain imaging studies, then the patient with persistent symptoms must be malingering – FALSE

Mild TBI

- Myth: All mild TBI typically associated with short-term difficulties that resolve in 3 months to one year following injury
  - "Mild TBI" term is oxymoron (nothing mild about it)
- Reality: Mild TBI is a contradiction in terms, all brain injuries are very serious

Mild TBI (cont..)

- The impact of mild TBI is still mostly unknown
- Current methods and approaches can only describe/detect the visible brain injury
- Neuropsychology can detect functional impairment but may not be repeatable at frequency to monitor recovery
**mTBI Pathophysiology**

- Rotational and/or acceleration/deceleration forces differentially affect brain tissues, i.e. shearing
- Complex cascade of neurochemical/metabolic events
- Disruption of neuronal cell membranes and axonal stretching with indiscriminate ion flux
- Changes in CBF
- Neuronal dysfunction without significant acute cell death
- Post concussive metabolic vulnerability

**mTBI Pathophysiology (cont.)**

- Neurovascular deficiency:

  Impaired axonal function/diffuse axonal injury, neuronal metabolism, perfusion, and inflammation, suggesting involvement of the neurovascular unit in the presence of persistent symptoms in mTBI patients

**mTBI Pathophysiology (cont.)**

- mTBI patients suffering from acute mTBI experience impaired CBF autoregulation and cerebral vascular reactivity (CVR), reducing CBF despite increased metabolic demand
- Recent theories postulate that generalized autonomic dysfunction, includes abnormal CVR. However, limited information is available on the prevalence of CVR impairment in SM with chronic symptoms of mTBI

**Post-Concussive Syndrome (PCS)**

- First longitudinal PCS study to focus on PCS defined specifically as a minimum of 3 months of symptoms, negative CT and/or MRI, negative TOMM test, and no litigation. **PCS may be permanent if recovery has not occurred by 3 years.** Symptoms appear in a predictable order, and each additional PCS symptom reduces recovery rate by 20%. More long-term follow-up studies are needed to examine recovery from PCS (Hippolyte et al, 2016)
- Most neuropsychological and functional differences abate by 1 year, reporting three or more posttraumatic symptoms remain for about half of individuals (Dikmen et al, 2016)
CBF AUTOREGULATION

- CVR maintained via CBF autoregulation mechanism
- CVR is the ability of the cerebral arterioles to auto-regulate in response to changes in PCO$_2$ and BP
- One possible contributor to sustained PCS may be compromised CVR regulation or injury-related cerebrovascular dysfunction
- Evaluating CVR can help improve treatment strategies

CBF Autoregulation

- CBF/CBFV Autoregulation: Changes in cerebrovascular resistance in response to a change in systemic BP
- CO2 Vasomotor Reactivity: Changes in cerebrovascular resistance in response to a changes in PCO2
CEREBROVASCULAR (CVR) OR VASOMOTOR REACTIVITY (VMR) AND mTBI

The diagnostic and prognostic value of breath-holding
McMechan FH, Cal State J Med. 1922

• The breath-holding test in connection with the patient's response to other tests, when indicated, may be of diagnostic and prognostic significance, and may not only indicate therapeutic measures, but may also serve as a guiding sign to their effectiveness.

• Used routinely at the bedside, in the office, and in the hospital, it can be made one of the most valuable assets of daily practice.

Carbon Dioxide Pressure or PCO2 is potent regulator of cerebral arterioles and CBF

More CO2 – more CBF/CBFV

Less CO2 – less CBF/CBFV

How CVR could be tested

Carbon dioxide injection
Transcranial Doppler Ultrasound for Concussion in Amateur Athletes. Work In Progress
Tegeler et al, 2009

- This pilot study assessed TCD changes after Sport Related Concussion (SRC) in amateur athletes
- METHODS: TCD testing at rest, and with continuous bilateral MCA monitoring during hyperventilation, breath holding (BH), and leg up tilt. Neurological exam, and computerized NPSY (ImPACT) were done at baseline and following SRC in 91 athletes at Wake Forest University (82 football, 1 soccer) and Forsyth Country Day School (4 football, 4 soccer)
- RESULTS: There were 8 SRC’s (3 with baseline testing). NPSY showed impairment after all SRC. Initial TCD analysis shows differences in response to breath holding after SRC
- CONCLUSION: This work in-progress pilot study shows that TCD is feasible in amateur athletes at risk for SRC, and can assess cerebral hemodynamics and responsiveness. Initial results suggest differences in response to BH after SRC. TCD may reveal pathophysiological mechanisms of SRC, identify opportunities for acute treatments, and provide an additional objective measure to assist with return to play decisions

Serial monitoring of CO2 reactivity following sport concussion using hypocapnia and hypercapnia.
Len TK et al, Brain Inj, 2013

- PRIMARY OBJECTIVE: This study examined the effects of mild traumatic brain injury (mTBI) on cerebrovascular reactivity (CVR)
- METHODS AND PROCEDURES: Twenty subjects who recently suffered a mTBI were subjected to a respiratory challenge consisting of repeated 20-s breath-holds (BH) and hyperventilations (HV). Testing occurred on days 2 (D2), 4 (D4) and 8 (D8) post-injury as well as a baseline (BASE) assessment (after return-to-play). Transcranial Doppler was used to assess mean cerebral blood velocity (vMCA) and expired gas analysis provided end-tidal carbon dioxide (PETCO2) levels
- RESULTS: There was no significant difference in resting vMCA across all testing days for mTBI. No significant differences in PETCO2 were found throughout the testing protocol. A significant effect (p < 0.001) of testing day on vMCA was found during BH and HV challenges for mTBI. Post-hoc analysis revealed significant differences (p < 0.05) in vMCA between D2 and the other testing days
- CONCLUSIONS: These data suggest that, following mTBI: (1) CVR is not impaired at rest; (2) CVR is impaired in response to respiratory stress; and (3) the impairment may be resolved as early as 4 days post-injury

Neuroimaging Assessment of Cerebrovascular Reactivity in Concussion

- There is a correlation between lower grey matter (GM) CVR indexes and lower performance on SCAT2 in patients with mTBI, which seems to be associated with more symptoms. This correlation seems to persist well beyond 120 days. mTBI may lead to a decrease in GM volume in these patients. da Costa et al, Front Neurol, 2016
- Standardized brain MRI CO2 stress testing is capable of providing a longitudinal assessment of CVR in individual SRC patients. Consequently, larger prospective studies are needed to examine the utility of brain MRI CO2 stress testing as a clinical tool to help guide the evaluation, classification, and longitudinal management of SRC patients. Mutch et al, Front Neurol, 2016

Breath Holding

- Using a breath holding paradigm, TCD can reliably measure the cerebral vasculature dilatory response to elevated CO2 and provide a breath holding index (BHI) as an indirect measure of cerebral autoregulation
Cerebrovascular Reactivity

BHI Normal Values

- The mean MCA BHI value was 1.48 %/s (Silvestrini et al, 1996)
- The mean MCA BHI were 1.59 ± 0.3 in women and in young (1.34 ± 0.5) and old men (1.20 ± 0.4) (normal population) (Matteis et al, Stroke, 1998)
- The mean MCA BHI was 1.03-1.65 %/s (Zavoreo et al. Acta Clinica Groatica, 2004)
- The mean MCA BHI value was 1.45 +/- 0.50 %/s (Jiménez-Caballero et al. Rev Neurol. 2006)
- The mean MCA BHI value was 1.28 +/- 0.71 %/s (Molnari et al, J Neuroeng Rehabil. 2006)

Physiologic Testing of CVR with Breath-Holding Index (BHI). Protocol

- 2 MHz PW TCD probes bilaterally with helmet with any modern TCD machine
- Before the BHI test, the procedure must be explained to the patient in detail: “Please, breath normally, then take a normal breath and hold for 30 seconds, until I say okay, thereafter you are allowed to breath again normally.”
- Careful instruction provided to patient to avoid or minimize a Valsalva maneuver during the breath-holding
Physiologic Testing of CVR with Breath-Holding Index (BHI). Protocol

- For each MCA, the percent change in CBFV calculated for each three breath-holds obtained. This is determined by formula \((\frac{V2 - V1}{V1}) \times 100\%\), where \(V1\) is the baseline CBFV and \(V2\) is the mean CBFV at the end of 30-35 sec. Therefore we are determining percentage of mean CBFV change for each of three breath-holds.
- Dividing each percent change by its respective length of breath-hold (30 sec) is providing the percent per second change which is analogous to the...
- Calculate mean BHI
- Based on literature, normal MCA BHI ranges between 1.2 to 1.8

mTBI and CVR

- Although assessment of cerebrovascular responses to changes in arterial gases (i.e., CVR) after neurotrauma is not a new concept; this concept has been underexplored in long-term effect of mTBI.

Transcranial Doppler measure of persistent cerebral vasomotor reactivity abnormality in service members with chronic mTBI

- A retrospective review of TCD studies and subjective questionnaires (Neurobehavioral Symptom Index, NSI; PTSD Symptom Checklist-Military Version, PCL-M; and Patient Health Questionnaire-9, PHQ-9) was performed on 145 SMs admitted to the NCoE with post-concussive headaches and TBI and PH conditions.
- 64 of 145 subjects (44.1%) had abnormal BHI’s indicating impaired CVR
- Abnormal BHI group had significantly higher scores on the PCL-M than the Normal BHI group suggesting higher levels of PTSD in those with abnormal BHIs

Transcranial Doppler measure of persistent cerebral vasomotor reactivity abnormality in service members with chronic mTBI

- TCD in patients with chronic PCS revealed a high prevalence of cerebral autonomic disturbance. This autonomic disturbance is correlated with increased PCL-M
- These autonomic disturbances may be associated with post traumatic stress or may be an independent entity of PCS that overlaps with PTSD.
Disruption of the autonomic nervous system, including CVR, has been observed following TBI and may also be associated with chronic PCS

- To address this physiological disturbance, NICoE at WRNMMC integrated mind-body techniques, known to affect parasympathetic tone and autonomic balance, into a four-week intensive interdisciplinary outpatient treatment program for service members with combat-related TBI and post-traumatic stress (PTS)
- TCD BHI testing performed in patients with chronic mTBI revealed a high prevalence of cerebral autonomic disturbance
- Dr. DeGraba and colleagues reported the change in BHI obtained on admission and discharge of the four-week program
- Exposure to mind-body training was associated with improved cerebral autoregulation as measured by changes in BHI, suggesting that this TCD BHI test might have utility as a quantitative biomarker of treatment response in patients with mTBI and PTS

Role of TCD BHI as a Biomarker for CVR evaluation in Patients with mTBI

- Current results support the use of TCD measured CVR as a non-expensive and easy implemented research tool for identifying altered neurophysiology and monitoring recovery in long-term effects of mTBI
- Larger cross-sectional, prospective and longitudinal studies are required to understand the sensitivity and prognostic value of CVR in mTBI

Clinical Material

- 389 (9 female) consecutive SMs with mTBI from Apr. 10, 2014 to Jan. 16, 2016
- Mean age 39.0 ± 6.6 years
- All SMs had a range of post-concussive symptoms (PCS)
- Mean time between last mTBI and TCD test was 4.7 ± 3.8 years (range 1 and 24 years)
- Single mTBI – 46 SMs; Multiple mTBI – 343 SMs
- Mechanism of mTBI:
  - Blast only 138
  - Falls only 33
  - Combination of blast and falls 215
  - Other 3

CEREBRAL HEMODYNAMICS AND mTBI
Methods

- All subjects were consented to Protocol #362504 prior to any data collection and analysis.
- Comprehensive TCD protocol was applied in all cases recordings of mean cerebral blood flow velocities (CBFV, in cm/s) and Pulsatility Indices (PI) were recorded using a 2-MHz transducer (Doppler Box, DWL/Compumedics, USA).
- All TCD tests were done at the same time during circadian clock and by the same neurosonographer.
- Data were analyzed and abnormal values for the MCA (M1 segm), ICA (C1 segm) and proximal BA were defined according to published normative data as:
  - 2 SD from the mean CBFV in any direction labeled as an abnormal.
  - PI assumed normal with values between 0.7 and 0.9.

PCS duration after last mTBI

- 35 SMs with 10 years or more after last mTBI
  - multiple mTBI 31 SMs (88%)
- 330 SMs with less than 10 years after mTBI
  - multiple mTBI 291 SMs (88%)
- 24 SMs were not able to provide data about last TBI

Percentage of vessels with abnormal CBFV’s and PI’s values

<table>
<thead>
<tr>
<th>Vessels</th>
<th>“Normal” mean CBFV ± SD (cm/sec)</th>
<th>“Abnormal” mean CBFV ± 2SD (cm/sec)</th>
<th>“Normal” PI ± SD</th>
<th>“Abnormal” PI ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCA Left</td>
<td>63.0 ± 9.4</td>
<td>88 ± 10.7</td>
<td>0.76 ± .03</td>
<td>0.58 ± .03</td>
</tr>
<tr>
<td>MCA Right</td>
<td>61.9 ± 8.8</td>
<td>86.5 ± 6.1</td>
<td>0.75 ± .06</td>
<td>0.59 ± .02</td>
</tr>
<tr>
<td>ICA Left</td>
<td>58.8 ± 7.7</td>
<td>79 ± 7.3</td>
<td>0.76 ± .07</td>
<td>0.58 ± .03</td>
</tr>
<tr>
<td>ICA Right</td>
<td>59.4 ± 7.2</td>
<td>80 ± 8.7</td>
<td>0.76 ± .006</td>
<td>0.59 ± .03</td>
</tr>
<tr>
<td>BA proximal</td>
<td>42.4 ± 6.7</td>
<td>62.2 ± 6.1</td>
<td>0.78 ± .07</td>
<td>0.58 ± .03</td>
</tr>
</tbody>
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Abnormally high CBFV & low PI vs. “normal” CBFV & PI
**Results**

- Abnormally elevated CBFV’s or low PI’s were observed frequently in isolated artery or in a few arteries (uni- or bilaterally)
- Abnormally low CBFV’s or high PI’s were observed significantly less frequently in isolated artery or in a few arteries (uni- or bilaterally)
- Abnormal cerebral hemodynamics was present equally in 33% of SMs with single or multiple mTBI
- Abnormal cerebral hemodynamics was evident in 32%, 34% and 31% in SMs who were younger than 30 yo, between 31 and 40 yo and 41 and older, respectively
- Overall higher percentage of elevated CBFV was present at terminal ICA (C1 segm) 48%

**Distribution of abnormally elevated CBFV’s and low PI’s**

**Conclusions**

- Our data demonstrates that abnormal TCD findings are frequent (approx. one third) in patients with mTBI many years after last impact
- This is a first study to provide data on cerebral hemodynamics abnormalities in patients with a history of mTBI and chronic PCS
- TCD illuminates status of cerebral hemodynamics and could be offered as a good screening test to detect abnormal changes in patients after mTBI
Conclusions (cont..)

- Consider available information it is possible suggest the following:
  - mTBI leads to the impairment of NVU function that is reflected in abnormally elevated CBFV's due to the enduring stenotic process
  - Sequentially presence of low PI's most likely due to the compensatory effect of CBF autoregulation
  
- **evaluation of mTBI must involve understanding potential of CVD presence and its treatment**

What we do know today

- Chronic mTBI patients have a brain regions with abnormal perfusion compared to controls (Newberg A. et al, 2014)
- Extensive cerebral microvascular injury in humans and experimental animals seen in acute and chronic TBI, and in CTE (Kenney et al, Exp. Neurology, 2016)
- Vascular amyloid deposits render blood vessels rigid and reduce the dynamic range of affected vessel segments: potential mechanism that could account in part for the reduction in CBF in patients with Alzheimer's disease (Kimbraugh L. et al, Brain, 2015)
- mTBI has been proposed as a risk factor for the development of Alzheimer's disease, Parkinson's disease, depression, and other illnesses. Meta-analysis, 27 studies, mTBI is a risk factor for heterogeneous pathological processes or may contribute to a common pathological processes (Perry DC et al, J Neurosurgery, 2016)

Post-Concussive Symptoms Development Hypothesis

**Concussion/Mild TBI**

- Cerebral microvascular changes, cholinergic dysfunction, β-amyloid (Aβ) oligomers, impaired CBF and ANS regulation will contribute to vascular injury and abnormal neurovascular unit function
- Biomechanical forces influence the initiation of atherosclerosis, with plaques developing predominantly near to side branches and/or bends in arteries

**Dementia/CTE!?**
Limitations

- We were not able to correlate clinical data and combine TCD data with other neuroimaging methods: work in progress
- Prospective descriptive observational study
- Effect of medications not reflected

Invisible wounds of war are nothing new...

- Old as warfare itself
- World War I
  - Shell shock;
  - Soldier’s heart;
  - Battle fatigue
- World War II
  - Combat stress reaction
- PTSD (Trimbble et al., 1985)
- PTSD* labeled as a “mental disorder”?!
- Medical science has evolved
  - Better screening tools?
  - More effective treatment?

TCD as a Quantitative Biomarker in Evaluation of Patients with mTBI

- TCD represent a biomarker to detect disturbed CVR in patients after mTBI
- Current results support the use of TCD measured CVR as a research tool for identifying altered neurophysiology and monitoring recovery in long-term effects of mTBI
- TCD represent a biomarker to detect CVD presence and in patients with long-term effect of mild TBI

Not Imaging but:

TCD as a non-invasive and simple procedure must be engaged in the management of mTBI patients and must be utilized as a quantitative screening test to detect CVD presence

CBFV and PI measurements will permit detection of abnormal cerebral hemodynamics and allow physicians better define future management strategies
QUESTIONS?

The European Brain Injury Consortium:
Nemo solus satis sapit: nobody knows
enough alone

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