The Physiology of Concussion

From Research to Recovery
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SPRING
DISCLOSURES

The Buffalo Sabres Foundation
Robert Rich Family Foundation
PUCCS Foundation
NFL Charities
Ralph and Mary Wilson Fund
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At the conclusion of this activity, the participant will be able to...

- Understand the use of the principle of Exercise Intolerance in concussion diagnosis, prognosis and recovery.
- Describe the systemic physiology of concussion during exercise with respect to:
  - Altered heart rate and blood pressure control.
  - Altered central sensitivity to arterial carbon dioxide level.
  - Altered control of ventilation and arterial carbon dioxide levels.
  - Altered cerebral blood flow (CBF).
Concussion is a physiological injury


- Concussion is an individual and a dynamic process during which the brain is susceptible to physiological factors:
  - Repeat trauma
  - Sleep deprivation
  - Dehydration, hypoglycemia
  - Physical exertion
    - or “Exercise intolerance…”
Concussion

• Is a medical problem from a physiological brain injury.
• There are symptoms but there are also SIGNS.
• SIGNS from dysautonomia (?)
  • Orthostatic Intolerance
  • Exercise intolerance
  • Abnormalities of the physical examination...
Concussion

- **SIGNS** provide for more reliable diagnosis and determination of recovery.
- Concussion recovery typically occurs in 1 to 4 weeks.
- Post concussion syndrome (PCS) = delayed recovery.
- Prolonged **SIGNS** = PCS = mild Traumatic Brain Injury (mTBI).

Autonomic Nervous System

- Heart rate variability (HRV)
  - Variation in the time interval between heartbeats.
  - Reflects the status of the autonomic nervous system.
  - High HRV (parasympathetic branch) is good (athletes)
  - Low (sympathetic branch) is bad (heart disease, anxiety, PTSD, mortality...)

![Heart Rate Variability Diagram]
Autonomic Nervous System

• Baroreflex
  • Baroreceptors are stretch receptors that monitor changes in blood pressure and relay them to the brainstem.
  • Increase BP and pulse when stand up so you don’t faint.
Concussion is a Brain Injury with Systemic Physiological Sequelae

Affects the Autonomic Nervous System, the Heart and the Vasculature

- Altered heart rate variability (HRV) and Baroreflex sensitivity in concussion at rest and when moving from supine to standing (Hilz et al. J Neurotrauma 2011)
- Reduced HRV and increased HRs during exercise (but not at rest) after reporting symptom resolution from SRC (Gall et al 2004a and 2004b)
- Increased diastolic BP during exercise in those still symptomatic (Leddy et al 2011; Kozlowski et al 2013)
ANS Dysfunction after Concussion

- 2 measures of cardiac vagal modulation, the QT interval variability index at rest and heart rate complexity during isometric hand-grip exercise, altered within 48 hours of concussion and resolved within 1 week. (La Fountaine MF et al 2009, 2011)

- University athletes clinically recovered from concussion (mean 95 days post injury) had less HF power and a greater LF/HF ratio during isometric hand-grip exercise, not at rest, than age- and team-matched controls with no history concussion. (Abaji JP et al. J Neurotrauma. 2015)

- Prospective study of adolescents 13–18 years old with PCS: 70% had abnormal cardiac tilt-table. (Heyer GL et al. Clin J Sport Med. 2016)
Altered ANS Function

- Reduced ability to adjust to postural changes (orthostasis, especially in kids).
- Control of CBF and cerebrovascular reactivity.

Symptoms...
Cardiovascular Dysfunction during Exercise in Adolescents

5 days after SRC (Acute) and at 14 days (Recovered)


(N=27) For both HR and RPE, time and group were significant (p<0.05) and a group-time interaction effect was significant for RPE (p<0.05)
Blood Pressure and Cardiac Function after Concussion
Pilot data

Exercise intolerance (PCS, n=37) and in those with normal exercise tolerance (Resolved, n=28)
Concussion is a metabolic and a physiological phenomenon inside and outside of the brain (Giza & Hovda, 2001).

The graph shows changes in Glutamate, Glucose, Calcium, and Cerebral Blood Flow over time. The y-axis represents % of normal, and the x-axis represents time in minutes, hours, and days.
Altered Autoregulation of Cerebral Blood Flow (CBF)

**Physiology**

- Deconditioning from resting interferes with CBF regulation

**Concussion**

- Reduced CBF at rest
  - Meier et al. JAMA Neurol 2015

- Increased CBF during exercise
  - Clausen et al JHTR 2015

**Effects**

- Fatigue
  - Altered CBF may influence cognition and other symptoms
    - Leddy et al. J Head Trauma Rehabil 2013

- Inability to exercise to maximum
Exercise and Concussion

• Concept of ‘exercise intolerance’ is consistent with the Zurich RTP Guidelines (McCrory et al. CJSM. 2013).
  • Patients may RTP once asymptomatic at rest and with provocative exercise.
  • Therefore, return of normal exercise tolerance = one criterion for recovery…
  • Ergo, exercise intolerant = not recovered.
Exercise and Concussion
UB Studies

• Systematic assessment of exercise tolerance after concussion.
  • Exercise intolerance is an objective sign of concussion (Kozlowski KF et al J Athl Train. 2013).
  • Exercise intolerance serves as a proxy for an abnormal concussion physiology (Clausen m et al. JHTR. 2015).
Systematic Evaluation of Provocative Exercise after Concussion
Buffalo Concussion Treadmill Test (BCTT)

• Modified Balke Protocol
  • Submaximal symptom-limited threshold = acutely concussed or not recovered.
    • Threshold is represented by the HR at symptom exacerbation.
    • HR used to prescribe a sub-threshold exercise prescription
  • Maximum exertion without symptom limit = physiologically recovered.

BCTT is safe and reliable
Stopping Criteria during the BCTT
Defines the symptom-exacerbation threshold

- Threshold $= \Delta \geq 3$ points from baseline
- Increase in headache or dizziness by 3 points or a new symptom appears (one point for each)

**Rate Your Overall Condition**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Feel terrific, no symptoms</td>
</tr>
<tr>
<td>1-2</td>
<td>Feel some symptoms but quite tolerable</td>
</tr>
<tr>
<td>3-4</td>
<td>Symptoms a little worse</td>
</tr>
<tr>
<td>5-6</td>
<td>Symptoms much worse</td>
</tr>
<tr>
<td>7-8</td>
<td>Feeling quite symptomatic</td>
</tr>
<tr>
<td>9-10</td>
<td>Feel terrible, worst I ever felt</td>
</tr>
</tbody>
</table>
CBF during Exercise in Males and Female Athletes Symptomatic after Concussion

Clausen et al. JHTR 2015
DTI Brainstem injury in Concussion
Polak et al J Head Trauma Rehabil 2014
Brainstem CO$_2$ sensitivity in Concussion
(n=6 females, before and after sub-threshold exercise Rx)

Clausen et al *JHTR* 2015
The Physiology of Concussion
Before and after Exercise Rx

Ventilation during exercise

Arterial CO₂ levels

Clausen et al JHTR 2015
The Physiology of Concussion
Before and after Exercise Rx

Arterial CO2 levels

Cerebral Blood Flow

Clausen et al JHTR 2015
CO₂ physiology and exercise tolerance may be biomarkers for concussion and PCS
Clausen et al JHTR 2015

- Exercise intolerance in female athletes with Physiological post-concussion disorder is associated with excessive CBF.
- A basic mechanism appears to be altered sensitivity to CO₂ that affects control of CBF.
- Return of normal CO₂ sensitivity and control of CBF is associated with resolution of symptoms and restoration of normal exercise tolerance.
Different regional cerebrovascular responsiveness on fMRI to provocative CO$_2$ challenge in PCS patients that was not present in healthy participants.

CO$_2$ physiology may be a biomarker for concussion/PCS

The relationship between exercise-induced increases in cerebral perfusion and headache exacerbation following sport-related concussion: A preliminary study
Exercise Effects on the Brain and on Systemic Physiology

Concussion and deconditioning adverse effects
- Autonomic Nervous System
- Cerebral Blood Flow
- Neuroplasticity
- Psychological
- Sleep

Exercise beneficial effects
- Improves PNS:SNS balance/control
- Improves CBF regulation
- Upregulates BDNF genes
- Improves Mood
- Improves sleep
Local CBF Regulation in Concussion Functional Imaging Study (fMRI)

Purpose

• To compare subjects with PCS and normal subjects on brain activation patterns during a simple math test.

• To compare subjects with PCS who received a sub-symptom threshold exercise program vs. a sham (stretching program) for recovery.
fMRI Study

fMRI measures changes in local CBF to areas of increased neural activity during a task.

\[5 + 6 - 4\]

\[> \text{ or } \leq 5?\]
fMRI in Athletes with PCS
Sub-threshold Exercise Rx vs. Placebo
Leddy J et al JHTR 2013

• Exercise
  • Controlled aerobic exercise treatment (n = 4)
    • 3F, 1M. 24 y.o.

• Stretch
  • Placebo stretching group (n = 4)
    • 3M, 1F. 21 y.o.

• Healthy Controls (HC)
  • No history of concussion (n = 4)
    • 4F. 21 y.o.
fMRI study

Two Time Points
  Time 1: baseline
  Time 2: 12 weeks later

No significant difference in cognitive performance between Concussion groups and Healthy control group Time 1 or Time 2:
  • Accuracy
  • Speed
Time 1 fMRI Results – before intervention
Inefficient brain function of PCS but normal cognitive performance
Time 2 (12 weeks)

- EXERCISE treated PCS subjects restored exercise capacity and experienced symptom reduction to control levels versus Placebo STRETCH PCS.
Time 2 fMRI
(12 weeks)

Stretch group

Exercise Rx = control
Summary
Leddy J et al JHTR 2013

- Brain function in PCS is different than healthy controls.
  - Not measurable on cognitive testing.
  - May represent cognitive intolerance (fatigue).
- Recovery is reflected by a return to normal fMRI brain activation patterns.
- Recovery is faster with sub-threshold aerobic exercise.
Days to Recovery by Age

- Elementary: X days
- Secondary: X days
- College: X days

Carson et al 2014 data. UB data.
Impact of puberty on the evolution of cerebral perfusion during adolescence
Satterthwaite TD et al. PNAS 2014
How do we diagnose SRC?

2016

• Zurich 2012: Clinical diagnosis based on recognition of injury, symptoms, cognitive and cranial nerve function, and balance.

• cNP testing: not validated as a diagnostic tool but can show cognitive deficits last longer than athletes are symptomatic. (Harmon. AMSSM Position Statement. CJSM 2013)

• SCAT 3 (symptoms, SAC, BESS)
  • current standard but needs validation. SCAT-2 validated by Dr. Putukian (CJSM 2015).
  • sens., spec. and predictive value unknown (Harmon. AMSSM Position Statement. CJSM 2013)
RCT

Purpose

• Primary
  • prospectively determine if early assessment of exercise tolerance after SRC is safe and which factors have prognostic utility for recovery in adolescents after SRC.

• Secondary
  • can principle of exercise intolerance be used to diagnose concussion?
Methods

Prospective study of 54 adolescents with SRC

66% male, mean age 15 y.

Mean 4 days since injury, range 1-9 d.

Enrollment

Assessed for eligibility (n=68)

Excluded (n=3)
- Not meeting inclusion criteria (n=0)
- Declined to participate (n=3)
- Other reasons (n=0)

Randomized (n=65)

Allocation

Allocated to receive treadmill test (n=32)
  - Received allocated intervention (n=32)

Allocated to not receive treadmill test (n=33)
  - Received allocated intervention (n=33)

Follow-Up

Lost to follow-up (n=0)
Discontinued participation (see text) (n=5)

Lost to follow-up (n=0)
Discontinued participation (see text) (n=6)

Analysis

Analysed (n=27)
  - Excluded from analysis (n=0)

Analysed (n=27)
  - Excluded from analysis (n=0)
Methods
Day 1

• All subjects completed ImPACT testing and had a physical examination.
• SRC diagnosis confirmed by study physician and then randomly assigned to BCTT (n=27) or no-BCTT (n=27).
Results

Day 1

- No difference in age, sex, # prior concussions, or days since injury before 1st visit between groups.
- 27 performed BCTT (mean of 4 days post-injury)
- ALL 27 had Exercise Intolerance- they stopped at a sub-maximal, symptom-limited threshold.
  - Mean treadmill time 11 min.
  - mean max HR = 145 bpm, ~70% of age-predicted max.
Recovery

- Asymptomatic (or a normal level of symptoms)
- Exercise tolerant (achieved 85% of predicted max HR without symptoms)
- Normal physical examination
  - by blinded physician assessment
Prognostic Study

• Day 21 (from injury, n=54)
  • 81% (22/27) randomized to BCTT and 78% (21/27) randomized to no BCTT were recovered by Day 21.

• BCTT group (n=27)
  • Gender, age, # prior concussions, and symptom severity score first visit did not predict recovery (p>0.05).
Prognostic Study
Significantly associated with days to recovery

#1: HRt (p=0.0032) lower = longer recovery.

#2: Physical Exam tests (p<0.05)

#3: Visual memory ImPACT score (p<0.05)
Brief Physical examination
Abnormal and/or symptom producing

• Eyes
  • Smooth pursuits (staccatic ± symptoms)
  • Saccades (abnormal ± symptoms)
  • Convergence (>10 cm diplopia)
  • VOR (vestibular ocular reflex. abnormal ± symptoms)

• Cervical
  • Tenderness, ROM, spasm

• Balance
  • Tandem gait forward and backward
  • Romberg combined with VOR
Physical Examination within First Week after Concussion
(% with abnormal physical signs on Visit #1, n=54)

Concussed n=54. Control n=30
Physical Examination 14 days later
(% with abnormal physical signs, n=54)
Heterogeneity of Delayed Recovery Group
Visit #2 (14 days after #1)

Recovered n=43. Delayed recovery n=11
Best Predictors of Recovery early after SRC

Stepwise Percent Variation with Days to Recovery as the Outcome Variable

- HR 30%
- VOR_dizzy 10%
- ImPACT 9%
- Romberg 5%
- Saccade 4%
- SmoothPur 3%
- UNEXPLAINED 39%
Exercise Intolerance

• Objective indicator of concussion within first week of SRC in adolescents.

• Safe to assess in a systematic way using pre-determined stopping criteria on the BCTT.

• Objective predictor of concussion severity or short-term prognosis (who will take >2.5-3 weeks from injury to recover).

• What about establishing readiness to safely return to sport?...
Zurich RTP Guidelines

Are these criteria valid?

<table>
<thead>
<tr>
<th>Rehabilitation Stage</th>
<th>Functional Exercise at Each Stage of Rehabilitation</th>
<th>Objective of Each Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No activity</td>
<td>Complete physical and cognitive rest</td>
<td>Recovery</td>
</tr>
<tr>
<td>2. Light aerobic exercise</td>
<td>Walking, swimming or stationary cycling keeping intensity &lt;70% MPHR; no resistance training</td>
<td>Increase HR</td>
</tr>
<tr>
<td>3. Sport-specific exercise</td>
<td>Skating drills in ice hockey, running drills in soccer; no head impact activities</td>
<td>Add movement</td>
</tr>
<tr>
<td>4. Non-contact training drills</td>
<td>Progression to more complex training drills, eg, passing drills in football and ice hockey; may start progressive resistance training</td>
<td>Exercise, coordination, and cognitive load</td>
</tr>
<tr>
<td>5. Full contact practice</td>
<td>Following medical clearance, participate in normal training activities</td>
<td>Restore confidence and assess functional skills by coaching staff</td>
</tr>
<tr>
<td>6. Return to play</td>
<td>Normal game play</td>
<td></td>
</tr>
</tbody>
</table>
Evaluation of the Zurich Guidelines and Exercise Testing for Return to Play in Adolescents Following Concussion
(Darling et al CJSM 2014)

• Retrospective study
  – 117 adolescent athletes with sport concussion.
  – 75% male. 15.4 years; range 13-19 years

• cNP testing prior to BCTT on day when athlete reported baseline level of symptoms.
  – mean 24 days post injury.

• **Upon passing BCTT, all athletes began Zurich RTP Protocol.
  – ATCs at schools to identify problems after RTP.
  – Telephone f/u 78% of athletes and parents.
Evaluation of the Zurich Guidelines and Exercise Testing for Return to Play in Adolescents Following Concussion
(Darling et al CJSM 2014)

• 100% proceeded through the Zurich guidelines without symptom exacerbation.
• 100% returned to sport successfully.
  – No symptoms, confirmed by team ATCs and team MDs.
  – Also confirmed by adolescent and parent on f/u.
  – *cNP test results were not predictive of RTP.

• **Conclusion:** Combined, normal exercise tolerance on the BCTT + Zurich Guidelines very effective for establishing safe RTP after SRC in adolescents.
Why is Objective Evaluation of Exercise Tolerance Important for Return to Sport?

Carson et al Canadian Family Physician 2014

- Retrospective 5 year study one family/sport medicine physician who recommended cognitive and physical rest based on existing consensus recommendations - SCAT2.
- Premature RTP and RTL = “recurrence or worsening of symptoms.”
- Concussions: 41 elementary, 95 high school, and 34 college.
- **44%** patients returned to sport too soon.
- **45%** patients returned to school too soon.
What does a Physiological Approach mean for Diagnosing SRC in the Office or the Clinic?

• Ask about symptoms with exertion
  • A history of clear symptom provocation with physical exertion strongly suggests that the presenting symptoms are consistent with concussion

• Look for physiological signs
  • **Physical Exam**: Orthostatic pulse and BP changes (with symptoms). Oculomotor, convergence, balance abnormalities.
  • If equipment available, systematically evaluate response to exertion to establish short-term prognosis in SRC or for the differential diagnosis in patients with prolonged recovery
If you are not sure your patient has suffered a concussion

• Systematically assess response to exercise
  • UB RCT
    • All 27 recently concussed adolescents (4 days from injury) were exercise intolerant.
    • Systematic evaluation of exercise tolerance is safe if you use pre-determined stopping criteria.
    • Degree of exercise tolerance when combined with a pertinent and brief PE predicts recovery very well.
The Principle of Exercise tolerance

Using pre-determined stopping criteria

• Diagnose concussion.
• Establish accurate short-term prognosis.
• Establish physiological recovery and readiness to RTP.
Thank you for your attention

Concussion.ubmd.com

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