Controlled Exercise in the Evaluation and Treatment of Concussion

2018 Traumatic Brain Injury Conference

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Disclosures

- The Buffalo Sabres Foundation
- Robert Rich Family Foundation
- PUCCS Foundation
- NFL Charities
- Ralph and Mary Wilson Fund
- NIH (1 R01 NS094444-01A1)
- Some Forensic Work (on SRC only)

Objectives

- 1. Describe the effects of concussion on the autonomic nervous system and control of cerebral blood flow.
- 2. Identify the utility of the Buffalo Concussion Treadmill Test for diagnosing concussion and establishing recovery based upon the principle of exercise intolerance.
- 3. Discuss the implications for clinical practice of using controlled exercise for the treatment of acute concussion and in those with persistent post-concussion symptoms.

REST till Symptom-free?

5th international conference on concussion in sport
Berlin, October 2016

Most consensus and agreement statements for managing SRC recommend that athletes rest until they become symptom-free.

> Rest may promote recovery by minimizing brain energy demands following concussion.

There is currently insufficient evidence that prescribing complete rest achieves these objectives.

After a brief period of rest during the acute phase (24-48 hours) after injury, patients can be encouraged to become gradually and progressively more active while staying below their cognitive and physical symptom-exacerbation thresholds (i.e. activity level should not bring on or worsen their symptoms).

> Avoid vigorous exertion/sport while they are recovering.

Concussion is a *physiological injury*

McKeag and Kutcher. Clin J Sport Med 2009

Concussion is a 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…"*

Why aerobic exercise for Concussion Treatment?

- Concussion is a physiological injury that affects the heart as well as the brain.
- Concussion affects the Autonomic Nervous System, which controls cerebral blood flow and cardiac and vascular function (cardiac output and vascular resistance).
- Aerobic exercise has salutary effects on ANS balance, CBF, cardiac and vascular function.

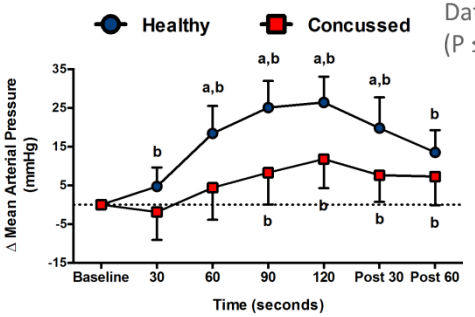
Exercise Effects on the Brain and on Central and Systemic Physiology

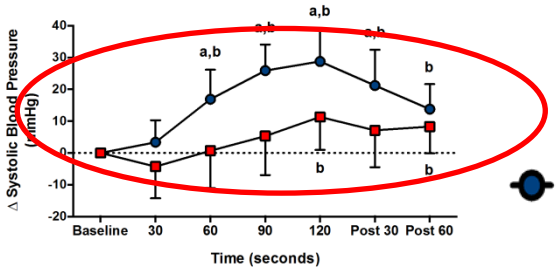
Concussion and deconditioning adverse effects		Exercise beneficial effects
• Autonomic Nervous System	→	• Improves ANS balance and CO_2 sensitivity
• Cerebral Blood Flow	→	• Improves CBF regulation
• Neuroplasticity	→	• Upregulates BDNF genes
• Psychological	→	• Improves Mood
• Sleep	→	• Improves sleep

SNS function in College athletes within 1 week of SRC

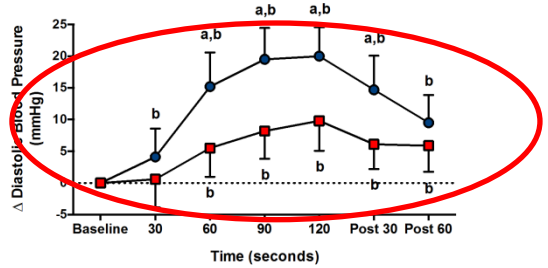
10 concussed v. 10 HC after Cold Water Immersion. (20 y, 5 d from injury)- Blair Johnson

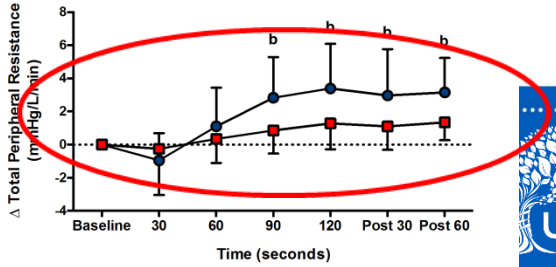
Data are presented as mean ± SD. B = different from baseline ($P \leq 0.025$), * = different from concussed athletes ($P < 0.001$).

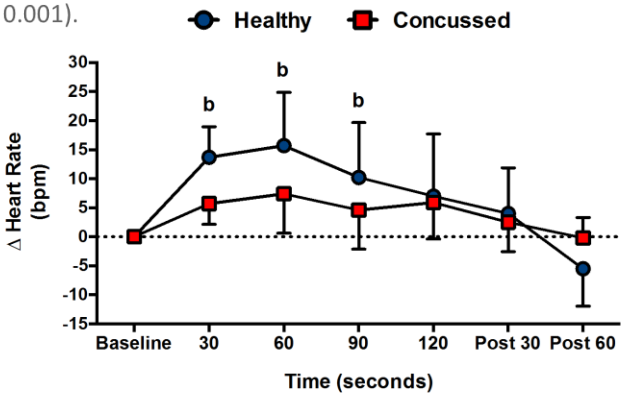


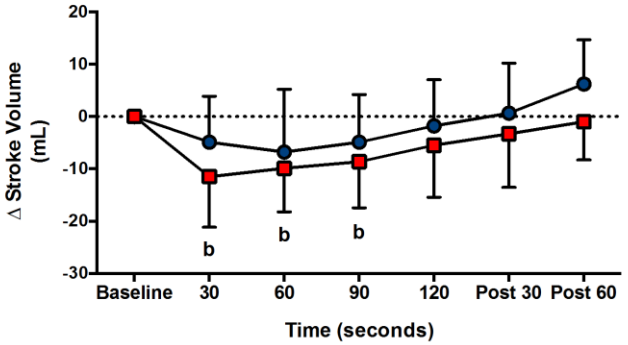


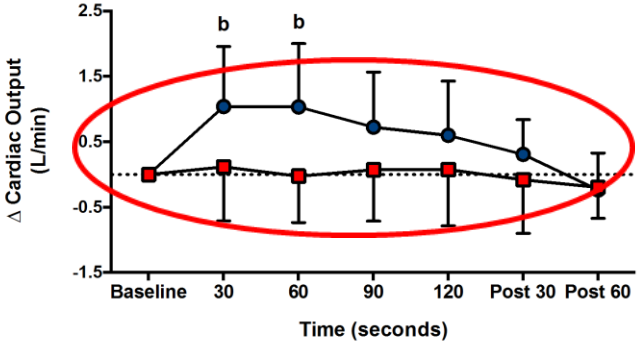
Healthy Concussed







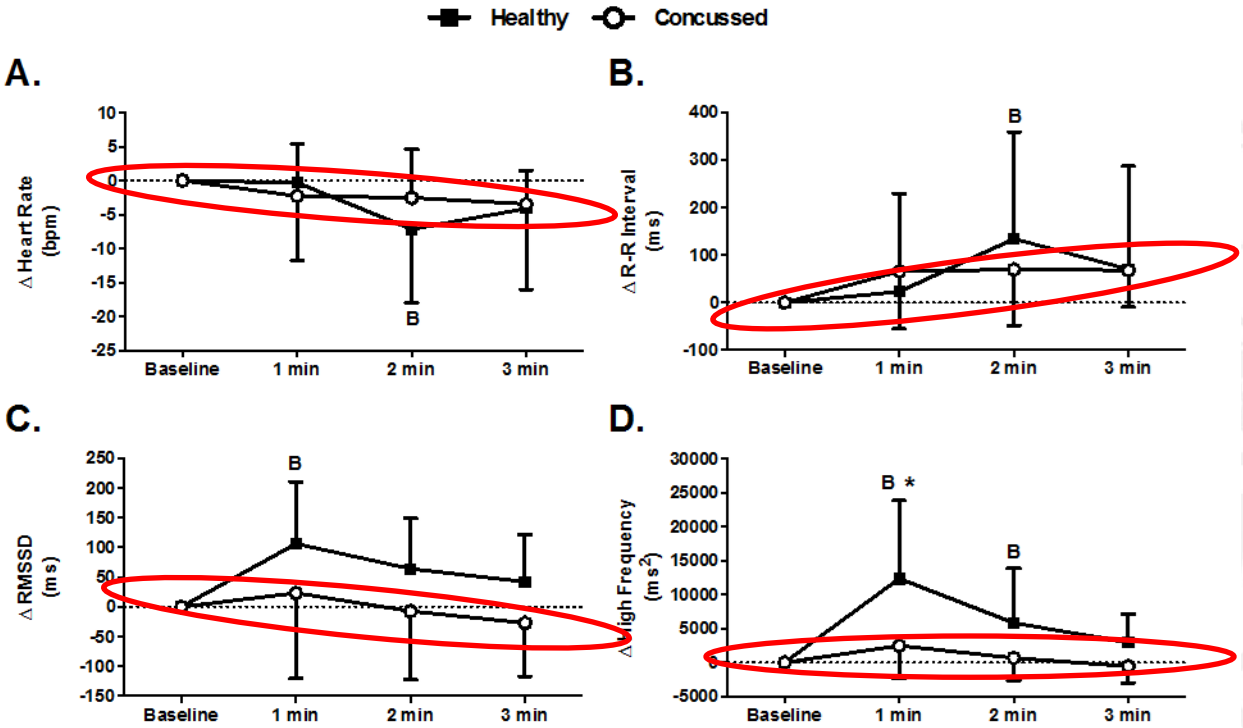




UB MD ORTHOPAEDICS & SPORTS MEDICINE

PNS function in College athletes within 1 week of SRC

11concussed v. 10 HC after Facial Cooling (20 y, 5 d from injury)- Blair Johnson

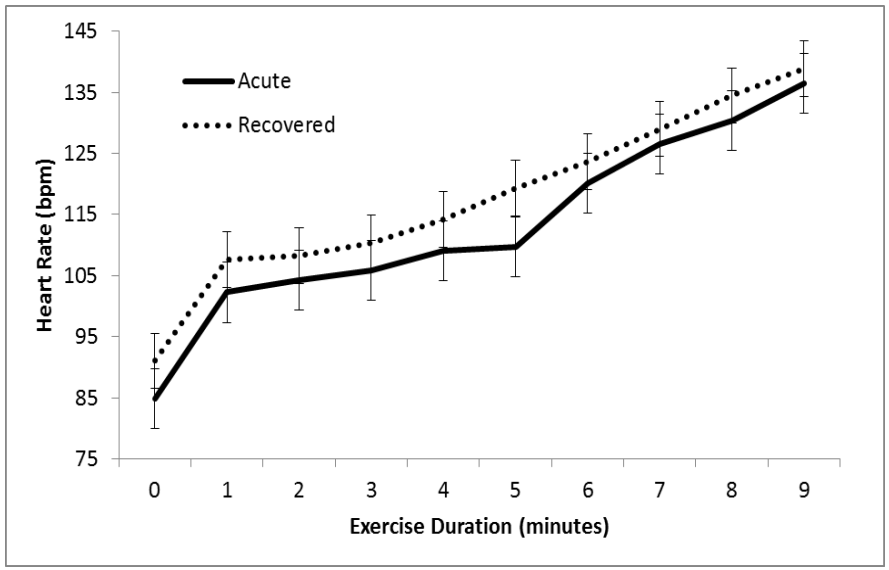


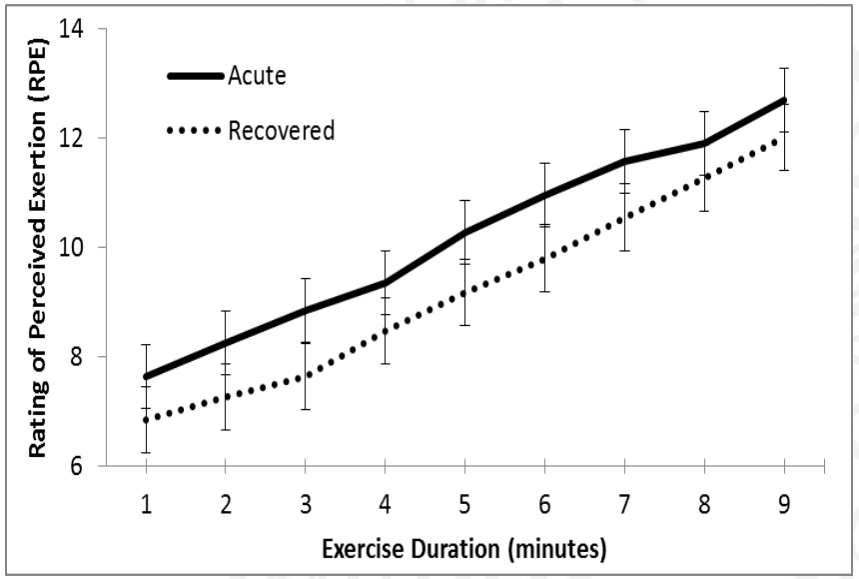
Data are presented as mean ± SD. B = different from baseline ($P \leq 0.025$), * = different from concussed athletes ($P < 0.001$).

Cardiovascular Dysfunction during Exercise in Adolescents

5 days after SRC (Acute) and at 14 days (Recovered), (N=27)

Hinds A et al. J Neurol Neurophysiol 2016, 7:4.

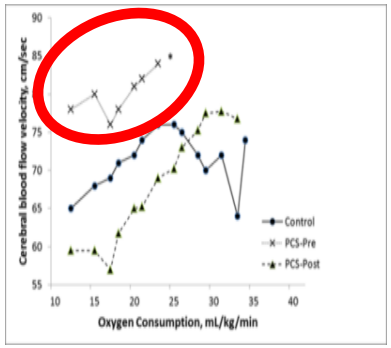


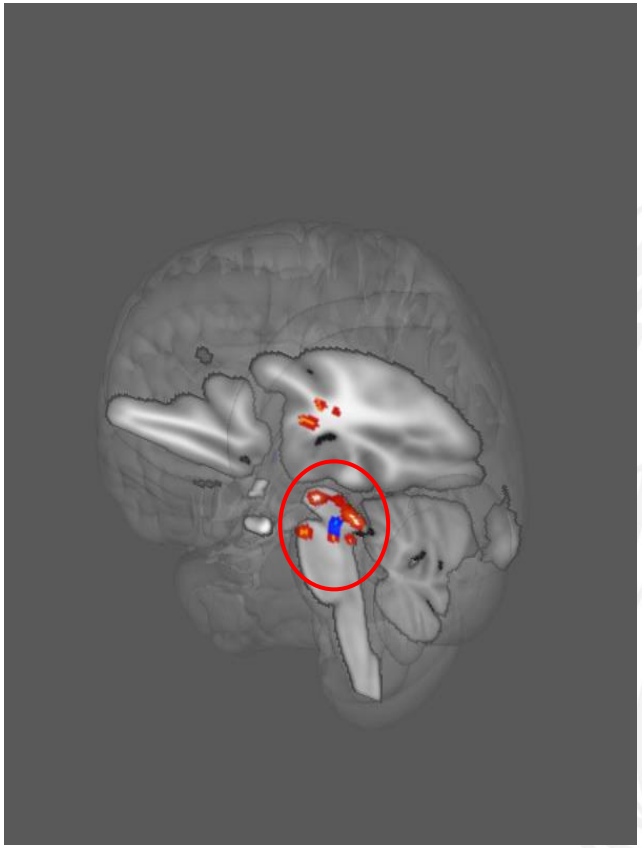


For both HR and RPE, time and group were significant ($p<0.05$) and a group-time interaction effect was significant for RPE ($p<0.05$)

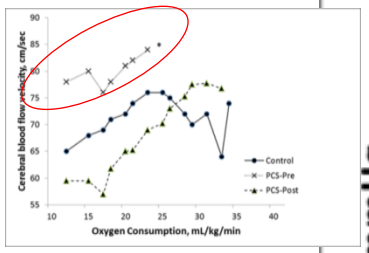
DTI Brainstem injury in Concussion

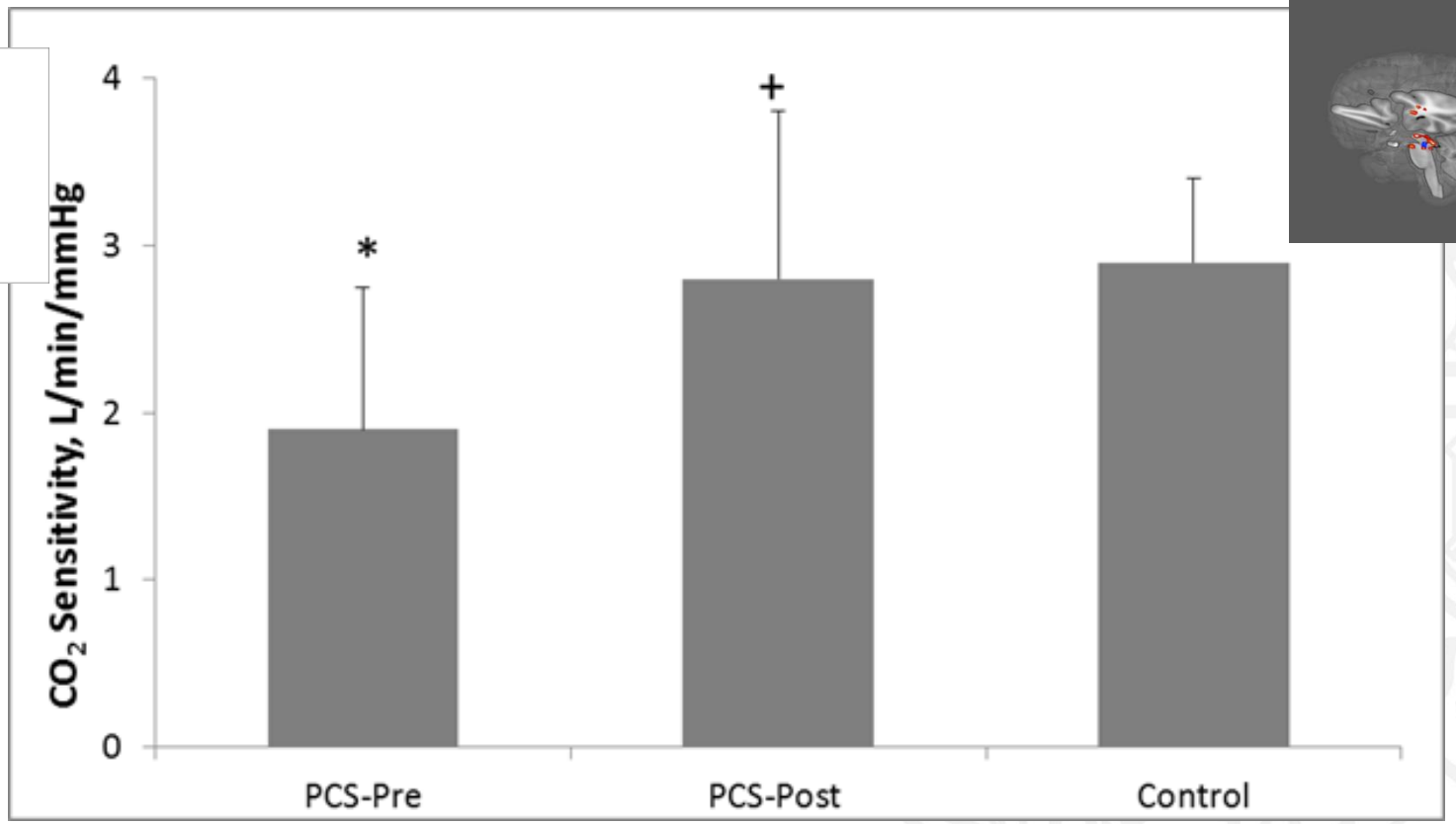
Polak et al *J Head Trauma Rehabil* 2014

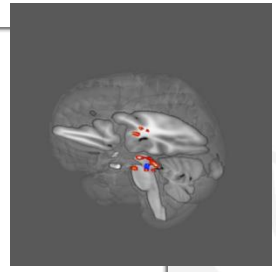




Brainstem CO_2 sensitivity in Concussion
(n=6 females, before and after sub-threshold exercise Rx)



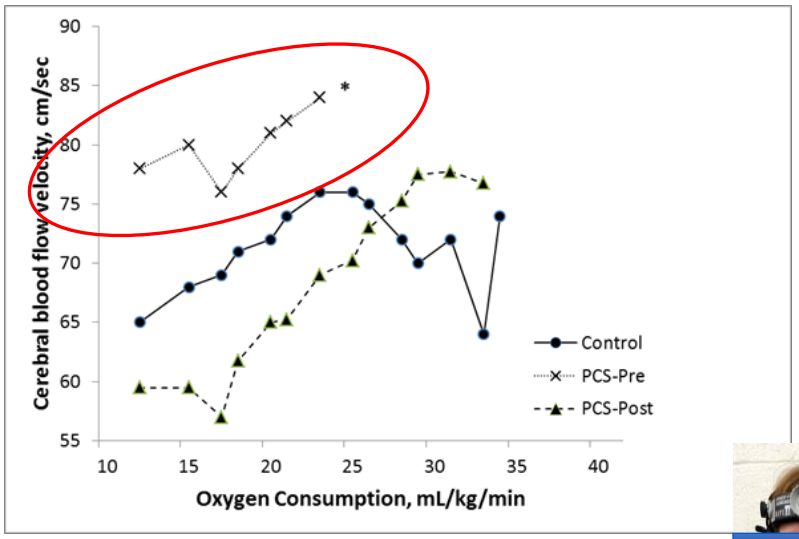


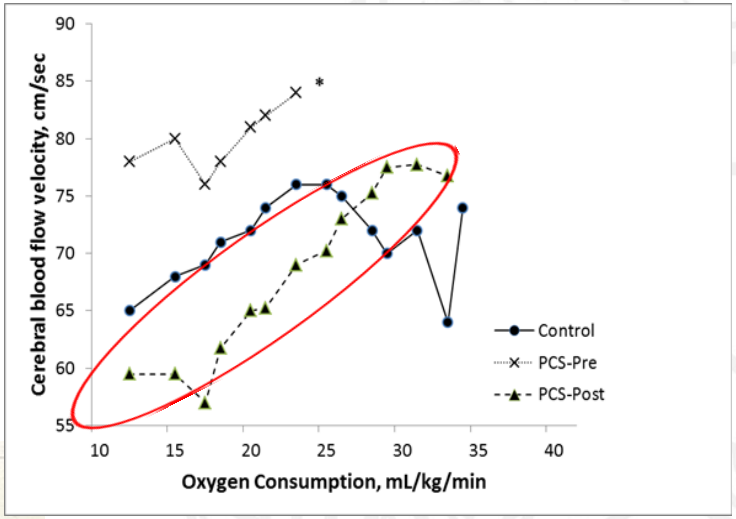


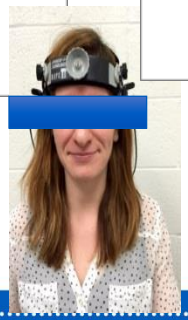
Clausen et al *JHTR* 2015

CBF before and after Controlled Exercise in Female Athletes Persistently Symptomatic after Concussion (n=6)

Clausen et al JHTR 2015







Why could sub-threshold exercise improve CBF regulation?

- Exercise training increases parasympathetic activity at rest and may have restored ANS balance. (Carter et al. Med Sci Sports Exerc 2003)
- Progressive stepwise aerobic training may improve CA by conditioning the brain to gradually adapt to repetitive mild elevations of systolic BP. (Brys et al. Am J Physiol Heart Circ Physiol 2003)
- Physical deconditioning is associated with reduced CA (Zhang et al. J Appl Physiol 1997) whereas regular exercise improves control of CBF. (Guiney et al. Neuropsychology 2014)
- A controlled progressive breathing training program can increase CO_2 sensitivity in subjects with low CO_2 sensitivity to begin with

CISG recommendations- Berlin

Active Treatment of Concussion and PPCS- Schneider et al BJSM 2017

- Research supports interventions including
  - Cervical and vestibular rehabilitation (for individuals with persisting dizziness, cervical spine pain, and headaches).
  - Closely monitored active rehabilitation programs involving sub-symptom threshold and submaximal exercise have been shown to be safe and may be of benefit to facilitate recovery.
  - Multifaceted collaborative treatments (including CBT, school accommodations, and pharmacotherapy) may also be of benefit.
- Future studies should evaluate the optimal timing, mode, duration, intensity, and frequency of treatment during the post-acute time period following concussion.

Current standard is the Berlin RTP Strategy

Why not test the principle of exercise tolerance systematically?...

Exercise step	Functional exercise at each step	Goal of each step
1. Symptom-limited activity	Daily activities that do not provoke symptoms.	Gradual reintroduction of work/school activities.
2. Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training.	Increase heart rate.
3. Sport-specific exercise	Running or skating drills. No head impact activities.	Add movement.
4. Non-contact training drills	Harder training drills, e.g., passing drills. May start progressive resistance training.	Exercise, coordination, and increased thinking.
5. Full contact practice	Following medical clearance, participate in normal training activities.	Restore confidence and assess functional skills by coaching staff.
6. Return to sport	Normal game play.	

The 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

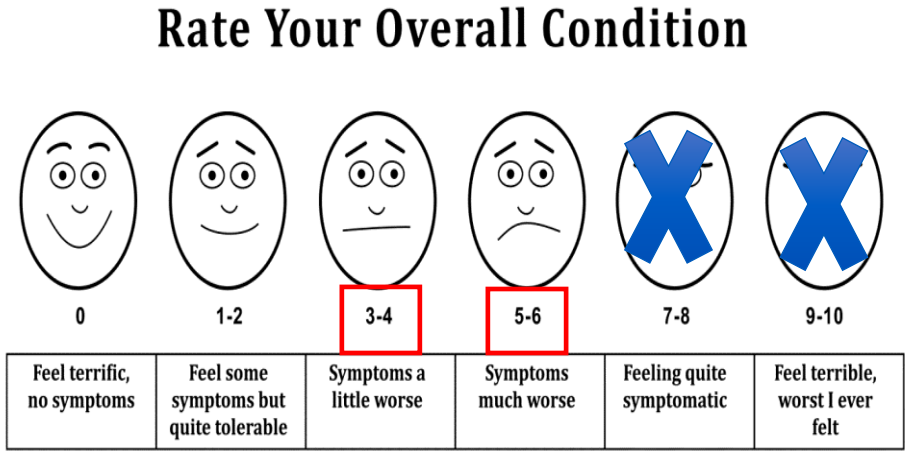
(Leddy et al Clin J Sport Med 2010, 2011)

Stopping Criteria during the BCTT

Defines the symptom-exacerbation threshold

Threshold =Δ ≥3 points from baseline

- Increase in headache or dizziness by 3 points or a new symptom appears (one point for each)



Establishing the Threshold

Symptom exacerbation described as a feeling that one's head is "full", dizziness, increased headache…

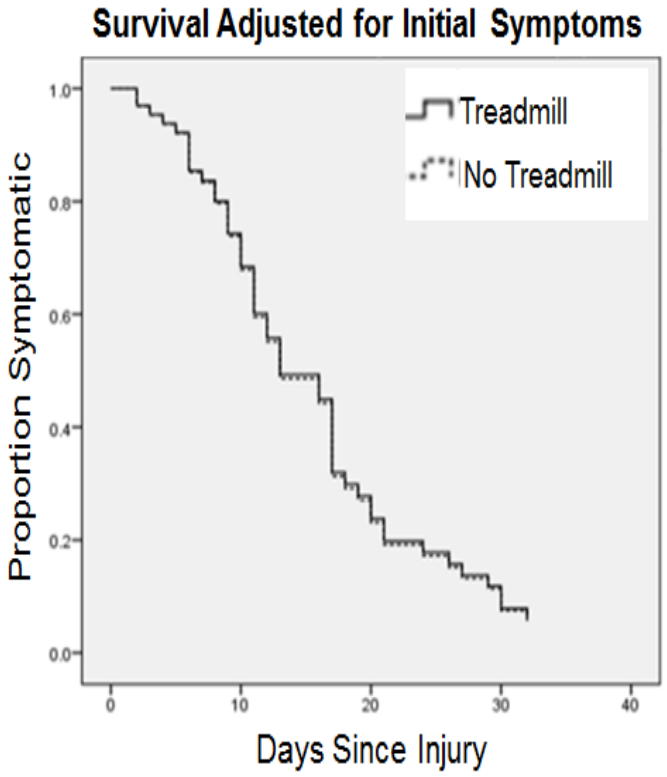
- –Athlete cannot continue, push through.

Must be distinguished from symptoms at near maximal or maximal exercise

- –Physiologic concussion symptoms occur earlier in test (at lower RPE and HR), well before maximum exertion
- –More obvious signs of distress

Assessment of Exercise Tolerance within First Week of SRC is safe

(Leddy et al. CJSM in press)

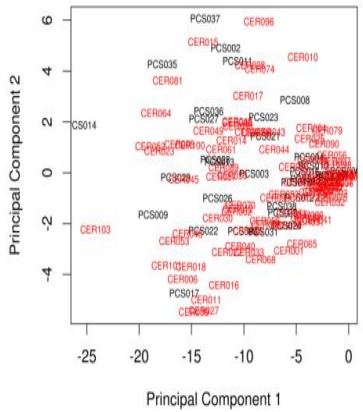


Cannot use Symptoms to Diagnose Concussion

N=128

(Leddy et al. 2014)

- P-PCD (n=36)
  - Headache
  - Dizziness
  - Foggy
  - Can't concentrate
- Cervical/vestibular injury (n=92)
  - Headache
  - Dizziness
  - Foggy
  - Can't concentrate



No significant separation of symptoms

Systematic assessment of exercise tolerance after concussion.

Is Exercise Intolerance an Early Physiological Biomarker for SRC and Prognosis?

- Exercise intolerance is an objective physiological *sign* of acute concussion:
  - Recent RCT of BCTT within first week
    - all 27 adolescents were significantly exercise intolerant (achieved only 50-70% of predicted max.) (Leddy et al in press CJSM)
- Exercise intolerance serves as a proxy for an abnormal concussion physiology (Clausen m et al. JHTR. 2015).
  - Altered autonomic control of cerebral blood flow

The Buffalo Concussion Bike Test (BCBT)

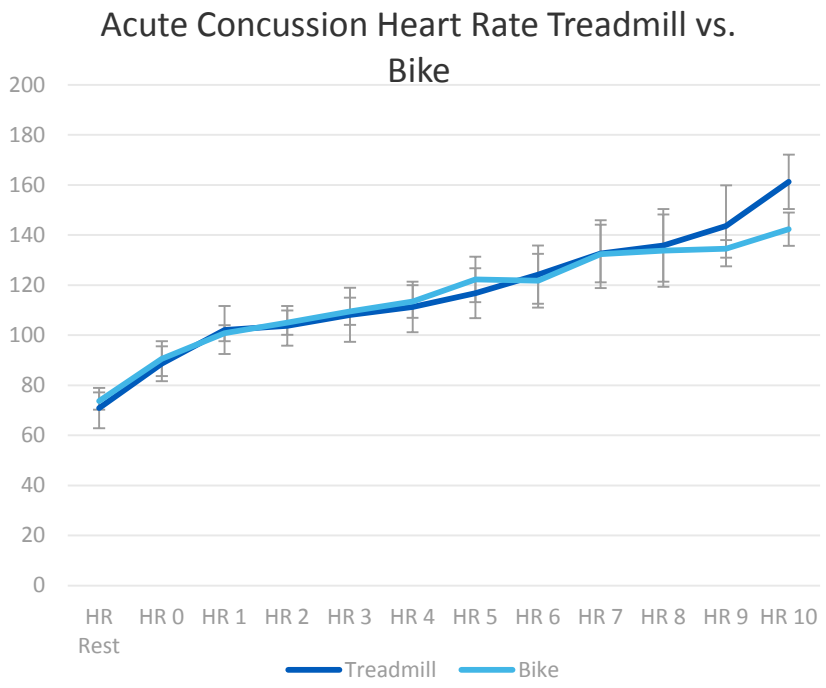
Each bike stage is equivalent to an increase of 1 degree incline on the treadmill.
Sample resistance for 70 kg

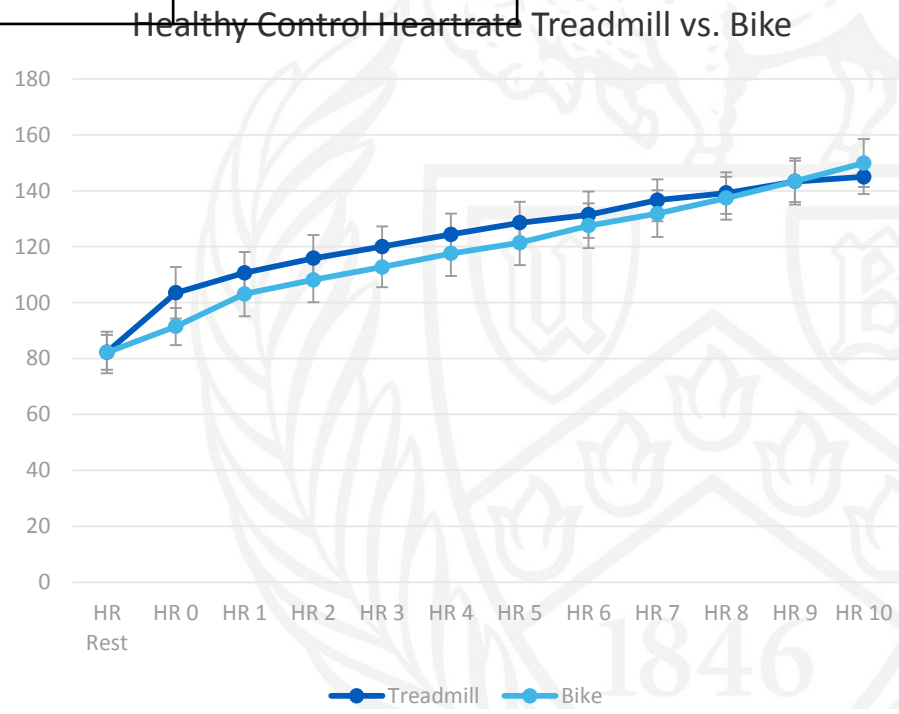
Stage (2-minutes)	VO2	METs	BW (KG)	Resistance (Watts)
0	13.1	3.74	70	35.014
1	14.83	4.24		44.9442
2	16.56	4.73		54.8744
3	18.28	5.22		64.7472
4	20.01	5.72		74.6774
5	21.74	6.21		84.6076
6	23.47	6.71		94.5378
7	25.2	7.2		104.468
8	26.92	7.69		114.3408
9	28.67	8.19		124.3858
10	30.38	8.68		134.2012
11	32.12	9.17		144.1888
12	33.85	9.67		154.119
13	35.56	10.16		163.9344
14	37.92	10.65		177.4808
15	39.03	11.15		183.8522

The Buffalo Concussion Bike Test (BCBT)

Heart rates of Acute Concussion and Healthy Control Subjects: Treadmill vs. Bike

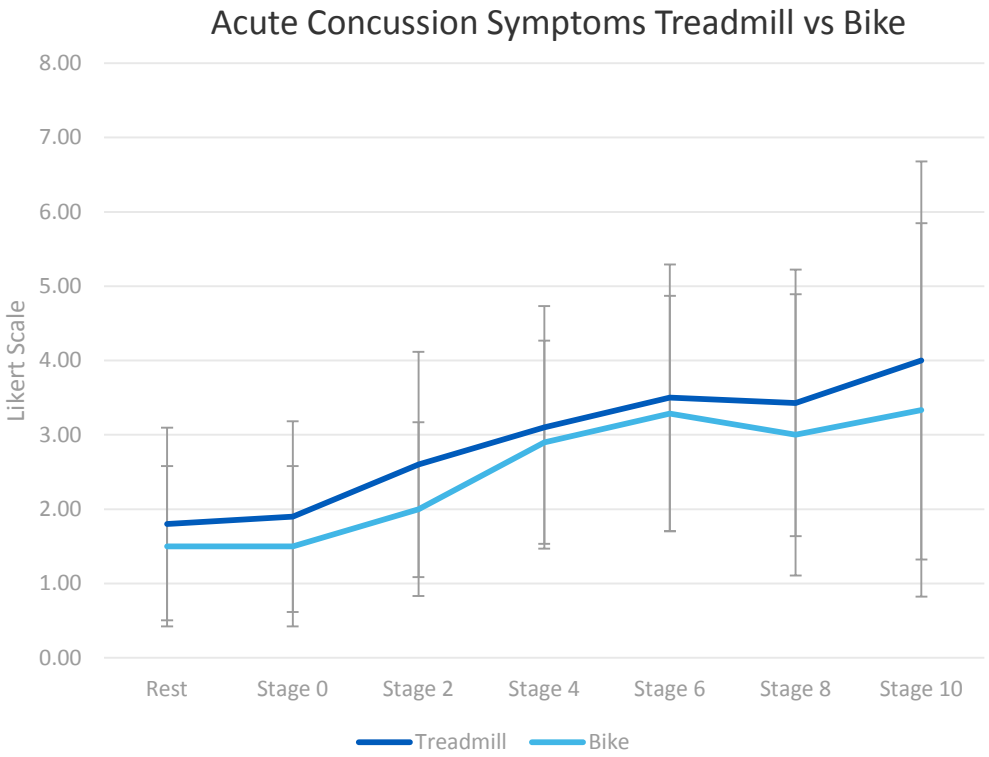
	Acute Concussion (n = 10)	Healthy Controls (n = 19)
Age (years)	15.7 ± 1.06	16.42 ± 1.17
Gender	70% male	42% male
Previous Concussion	0.80 ± 0.79	0.37 ± 0.83
Time To Recovery (days)	27.28 ± 20	-





The Buffalo Concussion Bike Test (BCBT)

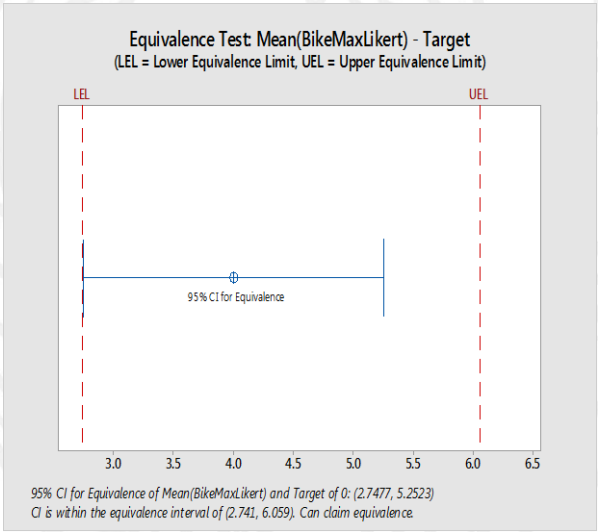
Symptoms reports in Acute Concussion: Treadmill vs. Bike



Two one-sided T-tests of equivalence with 95% CI show that the symptom exacerbation reported at each stage is equivalent.

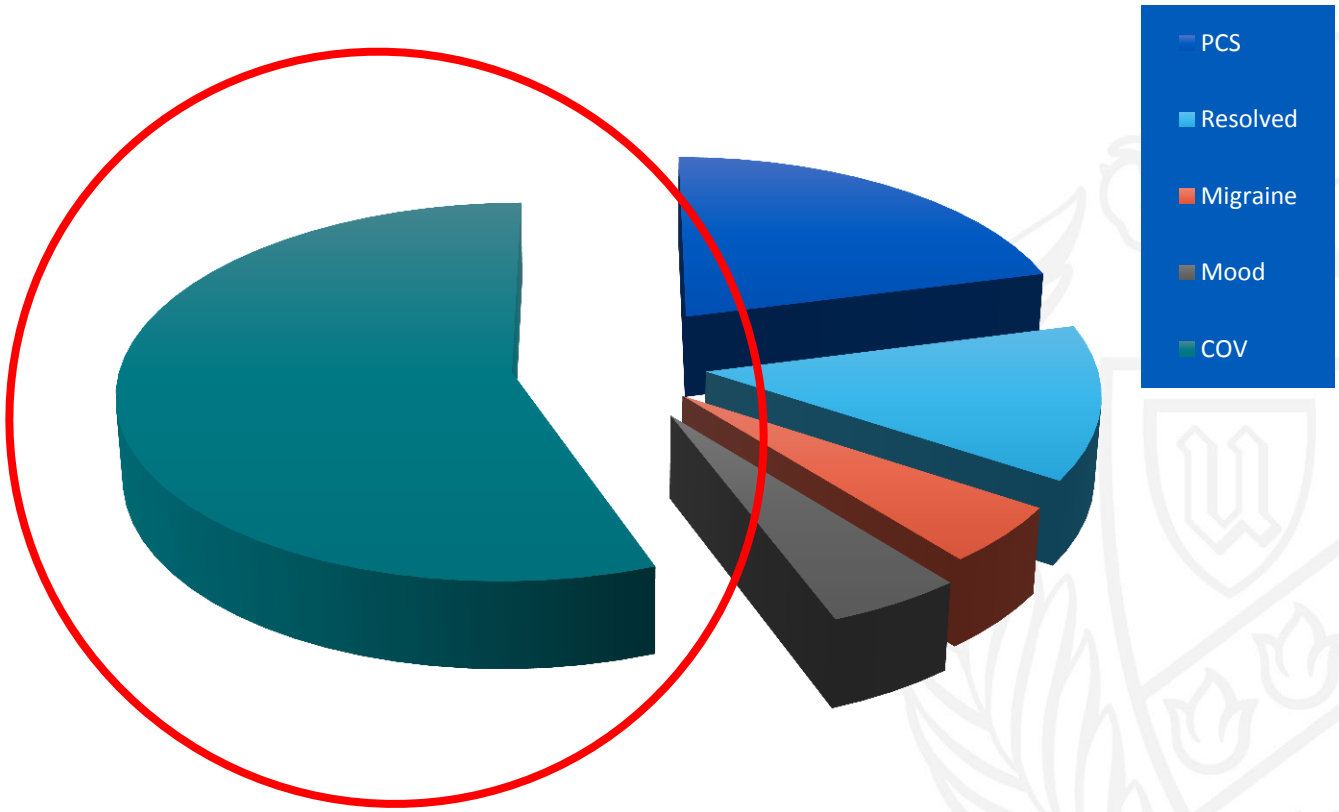
LEL p-value = 0.049

UEL p-value = 0.007



The Differential Diagnosis of PPCS According to Primary Diagnosis (Exercise Tolerance + Physical Exam)

(Leddy et al PM&R 2016)



A proactive approach to treating "Physiological Post Concussion Disorder" in PPCS

- Establish the diagnosis by systematic evaluation of exercise tolerance
  - Symptom-limited threshold on the treadmill (or other exercise modality, e.g., bike).
- Sub-threshold exercise prescription ("Exercise is Medicine")
  - 80-90% of achieved HR = target HR.
    - HR monitor is KEY to prevent athlete from over-exertion.
  - 20 min/day at target HR with 5 min warmup and longer cool down.
    - Stop at symptom exacerbation or at 30 minutes, whichever is first.
  - Bike first, then running. 6-7 d/wk.
  - Increase 5-10 bpm q1-2 weeks.

A proactive approach to treating Physiological PPCS

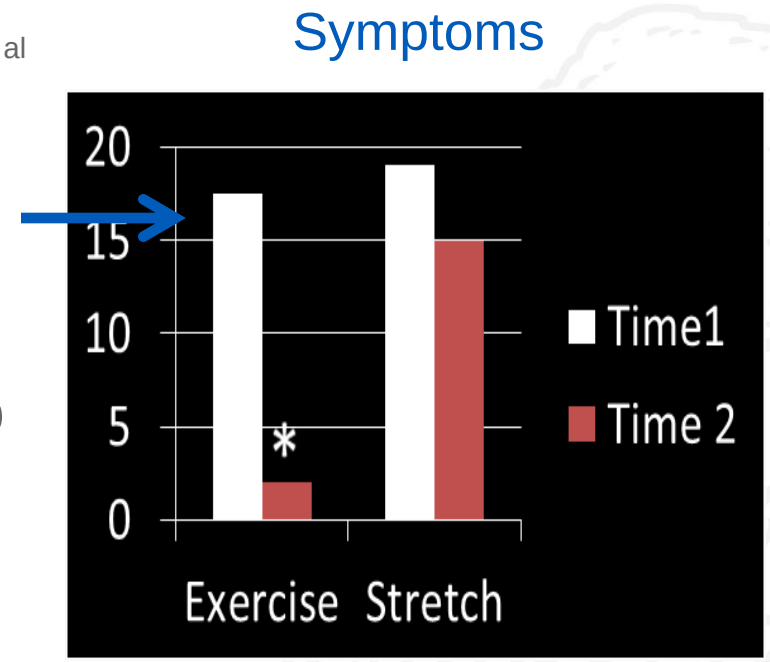
≥ 85% age-predicted max HR x 20 min without symptoms- "Physiological Recovery"

May need concomitant Rx for cervical, vestibular and/or ocular dysfunction before RTP.

Advice on RTP based on history (e.g. number of prior concussions) and other signs and symptoms.

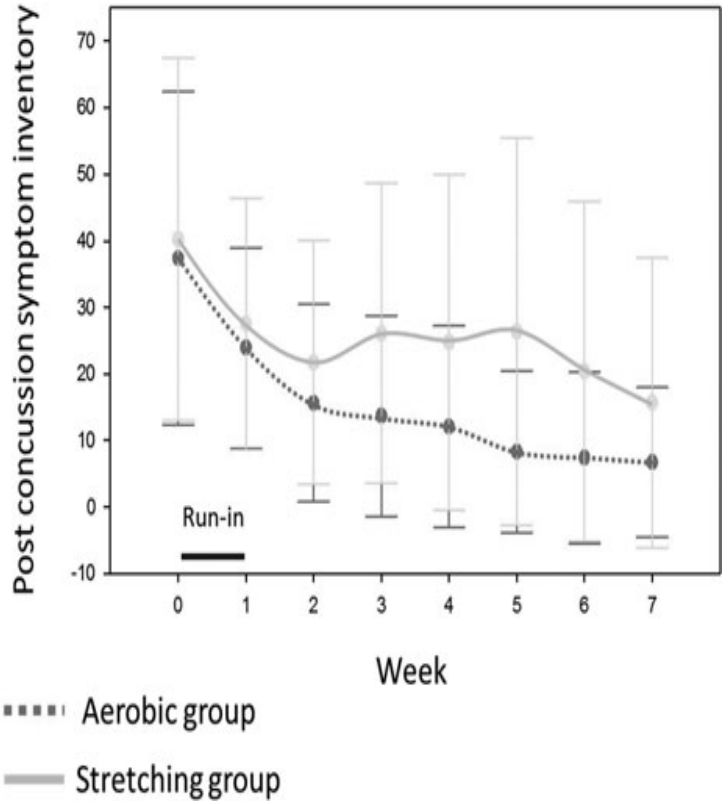
Exercise Treatment Outcomes in P-PCD

- 12/12 subjects returned to full sport or work (Leddy et al CJSM 2010)
- 4/4 exercise treated subjects had symptom resolution v. stretching placebo control (Leddy et al. Jl Head Trauma Rehabil 2013)
- 77% of P-PCD (n=65) treated with aerobic exercise returned to full sport or work (Baker et al. Rehabilitation Research and Practice. 2012)



Aerobic Exercise for Adolescents With Prolonged Symptoms After Mild Traumatic Brain Injury: An Exploratory RCT

Kurowski et al J Head Trauma Rehabil 2016



Greater rate of improvement in the sub-symptom threshold aerobic training group than in stretching group ($P = .044$).

"Potential benefit of active rehabilitation programs for adolescents with persistent symptoms after mTBI"…

What about establishing physiological recovery from SRC?

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; range13-19 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.
- **Conclusion**: Combined BCTT + Zurich Guidelines is very effective for establishing safe RT
  adolesc

TABLE 1. Graduated Return to Play Protocol

Rehabilitation Stage	Functional Exercise at Each Stage of Rehabilitation	Objective of Each Stage
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity <70% MPHR; no resistance training	Increase HR
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer; no head impact activities	Add movement
4. Non-contact training drills	Progression to more complex training drills, eg, passing drills in football and ice hockey; may start progressive resistance training	Exercise, coordination, and cognitive load
5. Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

Exercise as a Treatment for Acute Sport-related Concussion??

Association Between Early Participation in Physical Activity Following Acute Concussion and Persistent Post-concussive Symptoms in Children and Adolescents

Grool AM et al JAMA 2017

Prospective study of 3063 children and adolescents (5 to 18 years) with acute concussion (9 Canadian EDs).

Follow up survey of association between early participation in Physical Activity within 7 days of injury and symptoms at one month.

Physical activity within 7 days of injury compared with no physical activity was significantly associated with *reduced* risk of symptoms at 28 days (*24.6% vs. 43.5%*).

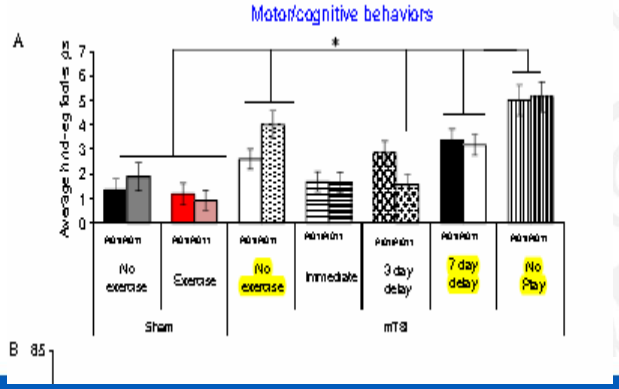
Reducing the time interval between concussion and voluntary exercise restores motor impairment, short-term memory, and alterations to gene expression

Mychasiuk R et al. European Journal of Neuroscience 2016

Voluntary initiation of exercise therapy within 1-3 days of concussion significantly improved motor and cognitive functioning and BDNF expression.

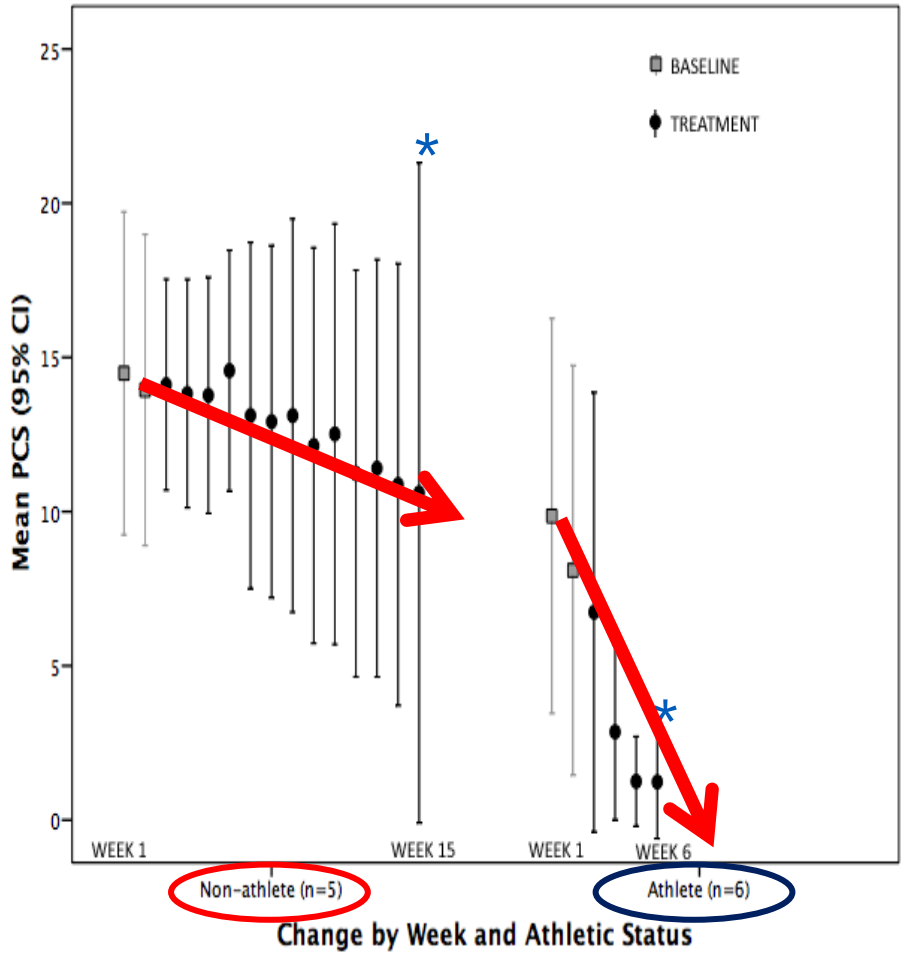
The group that responded to exercise had previous training on the wheel ("rat athletes").

Social and physical sequestration, akin to prolonged periods of full rest in the home ("cocoon therapy") were detrimental to recovery.



Rest Symptoms

Athletes recovered faster than non-athletes (25 ± 8.7 vs. 74.8 ± 27.2 days, p=. 01).



Leddy et al 2010

Symptom Improvement by HR Improvement

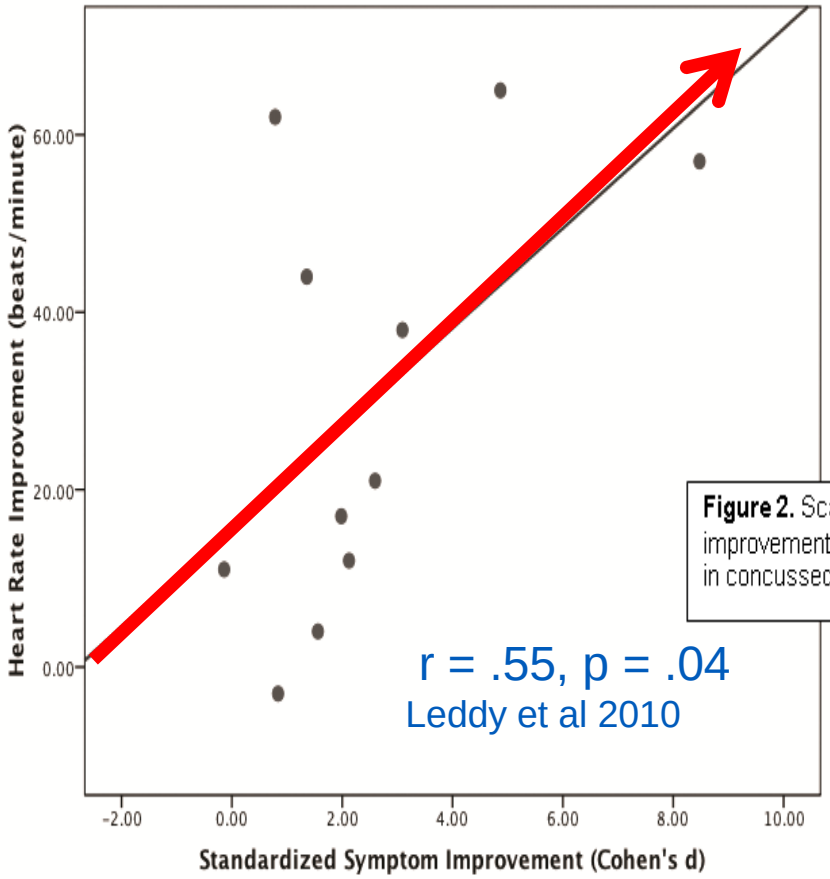


Figure 2. Scatterplot of heart rate improvement by symptom improvement in concussed subjects (r=.55, p= .04).

r = .55, p = .04

Leddy et al 2010

Leddy et al 2010

Rx of SRC?

Rest is the most prescribed treatment for SRC.

- Few days of rest is helpful (Thomas et al., 2015).
- Prolonged rest is detrimental to recovery (Silverberg and Iverson, 2013).

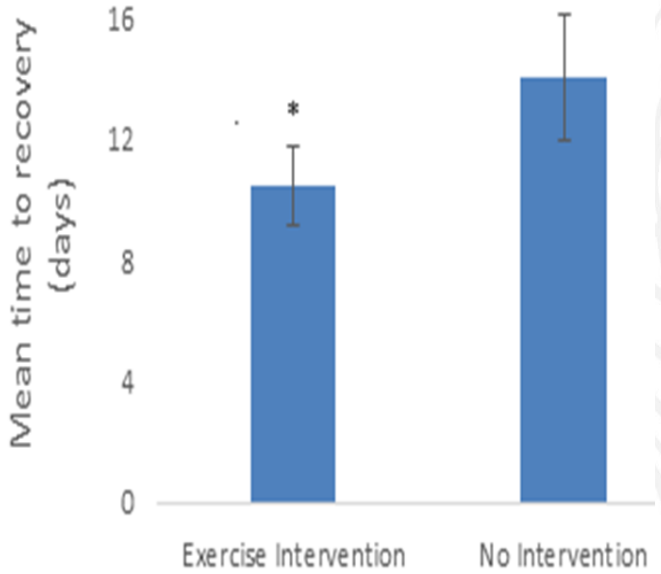
Currently, no active interventions or medications exist that to speed recovery from SRC or reduce PPCS incidence.

Active vs. Passive Recovery in SRC

RCT Pilot Data of intervention within one week of injury, in those recovering within 3 weeks of injury.

Active intervention (N=39, mean age 15.8 y, aerobic exercise *or* stretching).

Relative rest (N=48: mean age 15 y) (Leddy et al CJSM in press)



*10.5 ± 4.2 v. 14.1 ± 7.8 days, *p=0.016*

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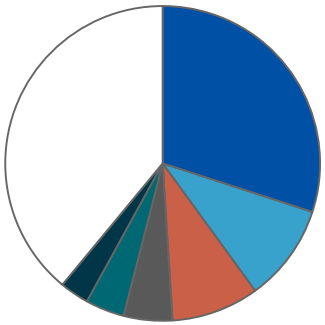
Early Exercise Tolerance Testing and Early Physical Examination Findings are Useful for Prognosis after SRC.

UB RCT (Leddy et al. CJSM in press)

Degree of early exercise tolerance was strongest predictor of recovery: lower tolerance = longer recovery (p=0.0032)

Stepwise Percent Variation with
Days to Recovery as t
Outcome Variable



BCTT within 4 days injury	Low HR Threshold (≤135 BPM)	High HR Threshold (>135 BPM)
Re	1	17
Recovery (>21 days)	7	2

13.2 ±7 days

60.9 55.1± days

Every 1 beat per minute increase in heart rate threshold resulted in a .82 day shorter recovery.

The Principle of Exercise tolerance

Diagnose concussion.

Establish accurate short-term prognosis.

Establish physiological recovery and readiness to RTP.

Develop a sub-threshold aerobic “exercise is medicine” program to treat physiological post-concussion disorder…

and may  and may help prevent PPCS?

Studies Showing Benefit or No Harm of Moderate Physical Activity or Controlled Exercise for Concussion and PPCS

• Physical Activity

- Majerske et al. (2008)- Retrospective
- Brown et al. (2014)- Retrospective.
- Thomas et al. (2015)- RCT
- Buckley et al. (2015)- Prospective cohort
- Silverberg et al. (2016)- Secondary analysis RCT
- Grool et al. (2016)- Prospective multicenter cohort
- Howell et al. (2016)- Prospective cohort
- Taubman et al. (2016)- Prospective cohort
- Sufrinko et al. (2017)- Secondary analysis RCT

• Aerobic Exercise

- Gagnon et al. (2009)-Prospective case series
- Leddy et al. (2010)-Prospective case series
- Baker et al. (2012)- Retrospective
- Leddy et al. (2013)-Quasi experimental
- Clausen et al (2015)-Prospective cohort
- *Maerlender et al. (2015)- RCT
- Dematteo et al. (2015)- Prospective X-sectional
- Cordingley et al. (2016)- Retrospective
- Gagnon et al. (2016)-Prospective case series
- *Kurowski et al. (2017)- RCT
- Chrisman et al. (2017)- Retrospective
- *Leddy et al (2017, in press)

Activity After Concussion

Old view

Rest until symptoms resolve

Activity After Concussion - New view
Berlin CISG 2016

- Radical Rest for a couple of days.
- Once symptoms stabilize, get back into activity gradually staying below cognitive and physical symptom thresholds.
- There are active treatments for the physiological disturbances seen in SRC and PPCS:
  - ANS (with sub-threshold exercise),
  - Oculomoto[illegible] cervical, and cognitive/b[illegible]erapies.

Want to establish physiological recovery from SRC?

Don’t need a blood test (right now at least…)

Don’t need a DTI, fMRI, SWI or “I don’t know why” MRI…

Use Clinical information

- Return of symptoms to baseline.
- Return of physical examination to baseline.
- Return of cognition to baseline.
- Return of exercise tolerance to normal without early symptom exacerbation.

"Some cause happiness wherever they go; others whenever they go"

Oscar Wilde

I'm gone….

Concussion.ubmd.com

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