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"A Randomized Controlled Trial of Exercise Treatment for Concussion"

Abstract

Background: The University at Buffalo (UB) Concussion Clinic has developed a treadmill test (The Buffalo Concussion Treadmill Test, BCTT) that is the most systematic and only validated approach to the assessment of exercise tolerance in patients with concussion. We have shown that sub-symptom threshold aerobic exercise improves recovery in patients who are slow to recover. The mechanism may involve beneficial effects of exercise on neuroplasticity and upon the abnormal physiology of concussion (autonomic nervous system and control of cerebral blood flow, CBF). We want to evaluate controlled aerobic exercise as a non-pharmacological treatment for concussion during the acute recovery phase in adolescents.

Methods: Subjects (13-18 years old, male and female) who sustained a concussion within the past 4-7 days. We chose this timeframe to make the sample as homogeneous as possible. Subjects will undergo the BCTT on the day of clinic presentation and will then be randomly assigned to daily sub-threshold aerobic or to a progressive stretching program, which is an ideal placebo condition because participants receive equal attention but stretching does not confer a cardiovascular training effect. Polar HR monitors will record their daily activity and HRs and subjects will report symptoms daily on a dedicated website. They will return weekly to see the physician who is blinded to group assignment to determine clinical recovery.

Specific Aim: To determine the efficacy of early sub-threshold aerobic exercise treatment in adolescents with concussion. We hypothesize that sub-threshold aerobic exercise as opposed to placebo stretching will safely speed recovery in patients acutely after concussion.

Dependent variable: Time to concussion recovery.

Impact of the project: There is no known active intervention or medication that speeds recovery acutely from concussion. Rest is the most prescribed "treatment". While a few days of rest are helpful, prolonged rest is actually detrimental to recovery. We are the first group in the world to use the physiological effects of sub-threshold aerobic exercise to safely treat humans with delayed recovery from concussion. There are no data on the use of exercise treatment in the acute phase of concussion recovery although we have completed an RCT that showed it is safe to test exercise tolerance (on the BCTT using our pre-determined stopping criterion) early (within one week) after concussion. The logical next step is to use sub-threshold exercise in those with exercise intolerance shortly after injury to see if it speeds recovery; theoretically because of the beneficial effects of aerobic exercise on autonomic function, CBF control, and neuroplasticity. If successful, this would represent a paradigm shift in the way concussion is assessed and treated. Such an approach may also prevent some of the 20% of adolescents who would have gone on to experience post-concussion syndrome. *We have already enrolled 21 subjects into each group but we need funding to extend this pilot study to satisfy our sample size of 54 in each group in order to obtain an effect size to apply to NIH for a multicenter RCT of early exercise intervention in adolescent concussion. Child and adolescent concussion is an emerging interest area for NIH (Dr. Leddy was an invited panel member of the recent NIH Pediatric Concussion Workshop held at the NIH on October 13-14, 2016).*

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5 Key words: exercise, aerobic, concussion, treatment, physiology

Background/Significance

Concussion is a physiological brain injury that has systemic effects.[1] One of these effects is exercise intolerance, which is defined as inability to exercise to the level predicted for a given age. In previous work we showed that exercise intolerance is an objective sign of ongoing physiological dysfunction after concussion.[2] Using the principle of exercise intolerance as an objective sign of concussion, we developed a standard treadmill test- the Buffalo Concussion Treadmill Test (BCTT)- that is the only functional test thus far shown to safely[3] and reliably[4] diagnose physiological dysfunction in concussion, help to differentiate it from other conditions with similar subjective symptoms (e.g., cervical and vestibular injury, depression, migraines),[5] and quantify the clinical severity and exercise capacity of concussed patients.[3, 4] The BCTT is now used by many others throughout the world to assess concussed patients.

Animal studies have shown that aerobic exercise is beneficial to cognitive recovery if administered three or more weeks after simulated concussion.[6, 7] Other animal studies show that the motivation for exercise after brain injury is important. Rats *forced* to exercise 28-32 days and 35-39 days after mild traumatic brain injury (mTBI) markedly stimulated the corticotrophic axis and did not increase brain derived neurotrophic factor (BDNF, which is involved in neuron repair after injury and increases hippocampal volume and improves spatial memory[8]) whereas

BDNF levels increased following *voluntary* exercise.[9] In another study, rats forced to exercise soon after mTBI increased stress hormone levels whereas rats who voluntarily exercised did not, suggesting that exercise regimens with strong stress responses (i.e., forced exercise) may not be beneficial during the early post-TBI period.[10] Voluntary physical exercise immediately after or within days of TBI has been shown in other animal studies to have beneficial effects on aspects of brain neuroplasticity such as: reduced interhemispheric differences in hippocampal formation and lateral ventricle volumes and in the density of mature neurons in the hilus of the dentate gyrus and the perirhinal cortex,[11] increased proliferation of neuronal stem cells,[12] reduced neuronal degeneration and apoptotic cell death around the damaged area,[13] increased Purkinje neurons and suppressed formation of reactive astrocytes,[14] and better cognitive performance in association with decreased DNA fragmentation in the hippocampus.[15] Similarly, human data suggest that exercise improves brain function via favorable effects on brain neuroplasticity[16] as early as 6 weeks.[17] The rapidity of the beneficial effect of exercise on the brain suggests that the mechanism is not reduced cerebrovascular disease risk but improved neuronal function.

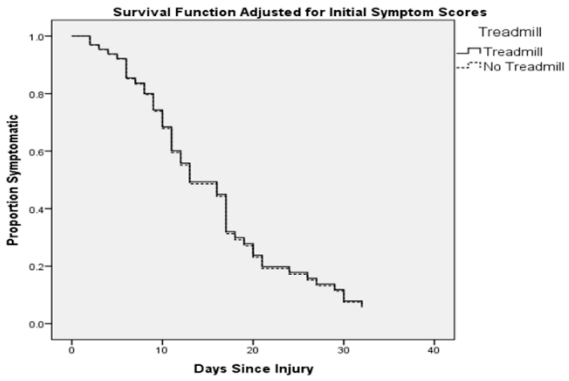
We were the first group to use the animal data to develop an assessment for human patients suffering with prolonged symptoms after concussion (called post-concussion syndrome, PCS). We used the BCTT to establish the symptom-exacerbation exercise threshold and prescribed an individualized, progressive sub-symptom threshold aerobic exercise program for patients with PCS. This controlled exercise program (which is akin to voluntary exercise in animals) safely improved recovery and helped restore function (i.e., return to sport and work) in most patients suffering from PCS.[3, 5]

The results of our early studies led us to query if, in addition to relieving symptoms, exercise might improve the physiology of concussion, which includes abnormal autonomic nervous system (ANS) function and altered control of cerebral blood flow (CBF).[1] In a recent controlled study,[18] we showed that female athletes with PCS had abnormally low sensitivity to the arterial CO_2 tension ($PaCO_2$) that caused a relative hypoventilation during exercise that raised their $PaCO_2$ levels out of proportion to exercise intensity. CBF is directly proportional to $PaCO_2$; hence, elevated $PaCO_2$ raised exercise CBF disproportionately to exercise intensity. This was associated with symptoms of headache and dizziness that limited their exercise tolerance to low levels. A program of sub-threshold aerobic exercise treatment increased their CO_2 sensitivity to normal, which normalized exercise ventilation, $PaCO_2$ levels, and exercise tolerance. Thus, sub-threshold aerobic exercise had salutary effects not only on the symptoms but on the physiology of the concussed brain in active patients suffering with PCS. In a different study we showed that sub-threshold aerobic exercise treatment restored abnormal local CBF regulation (as indicated by brain functional MRI, fMRI, activation patterns) to normal in PCS patients whereas a placebo stretching program did not.[19] Thus, these studies suggest that concussion symptoms and exercise intolerance may be related to abnormal CBF regulation and, furthermore, that individualized, controlled aerobic exercise treatment can restore CBF regulation and exercise tolerance to normal and improve outcome.

The traditional therapy for concussion and for PCS has been rest and avoidance of activity that exacerbates symptoms.[20] Physical deconditoning from prolonged rest can, however, impair control of CBF[21] whereas exercise training improves CBF control[22] as well as ANS balance.[2] The ability to exercise to exhaustion on a treadmill test without symptom exacerbation defines physiological recovery from concussion,[19] which conforms to expert consensus opinion about

recovery from concussion and readiness to return to activity.[20] Individualized exercise treatment for PCS patients is well accepted as < 10% of subjects refuse exercise treatment.[5] We have recently completed an RCT (paper in review) of giving the BCTT to concussed adolescents within 4 days from injury (range 1-9 d) and showed that it was completely safe (Figure) without short term increase in symptoms or delayed recovery when compared with standard assessment (i.e., no exercise testing).

While adults typically recover within 10-14 days after concussion,[20] adolescents may take 3-4 weeks to recover.[23, 24]Since we have shown that it is safe to assess exercise capacity shortly after concussion (Figure), the use of sub-threshold aerobic exercise as a non-pharmacological treatment to speed recovery acutely after concussion in adolescents should be tested in a randomized controlled trial (RCT).



Methods: Patients will be screened for eligibility at the UB Concussion Management Clinics in Buffalo and in Niagara Falls**.** Potential subjects will be identified after a standard clinical evaluation that consists of a thorough history and physical examination by physicians with extensive experience in concussion management. Concussion will be diagnosed according to international consensus definition.[20]

Inclusion Criteria: Age 13-18 years; any race, ethnicity, or sex; concussion within 4-7 days of first clinic visit; symptom score >5 on the Post-Concussion Scale;[25] low risk for cardiac disease (defined as no cardiopulmonary symptoms and meet no more than one risk factor for heart disease);[26] submaximal symptom-limited threshold on the BCTT;[27] willing to exercise; and medications, except for βeta-blockers, are acceptable.

Our symptom-limited graded exercise test (BCTT) is terminated when concussed subjects have an increase of ≥ 3 points on the VAS. We have shown that performing the BCTT within one week of concussion does

Exclusion Criteria: Glasgow Coma Scale (GCS) score <12 at time of injury. Justification: indicates moderate or severe TBI; Lesion on CT/MRI (via review of emergency room medical records) and/or focal neurologic deficit. Justification: indicates moderate or severe TBI; Inability to exercise because of orthopedic injury, significant vestibular dysfunction, visual abnormality, or increased cardiac risk. Justification: unsafe to perform treadmill test or undergo exercise as treatment; βeta-blocker use. Justification: affects autonomic function, reduces exercise capacity, and blunts exercise heart rate, invalidating interpretation of the treadmill test; Major depression. Justification: affects autonomic function, unlikely to comply with intervention; Unwilling to exercise. Justification: will not be compliant with intervention or control condition; and cannot understand English. Justification: cannot be compliant with intervention.

Specific Aim: To determine the efficacy of early sub-threshold aerobic exercise treatment in patients with concussion. We hypothesize that sub-threshold aerobic exercise as opposed to placebo stretching will safely speed recovery in patients acutely after concussion.

Approach (*we already have IRB approval***)**

If eligible, subjects will meet immediately with the research assistant to obtain consent. Subjects will fill out a validated concussion symptom checklist that has normative data.[25] Subjects will be treadmill tested for exercise tolerance on day of enrollment (or the next day if too symptomatic, which we define as a score of ≥ 7 on our 1-10 VAS) using our pre-determined stopping criterion (symptom exacerbation).[27] Subjects will be randomly assigned to sub-threshold aerobic exercise or to placebo (low level stretching that does not raise HR) therapy.

Subjects will be given a Polar HR monitor that records daily activity (via accelerometer) and HR (via chest strap) and asked to wear it at all times at home but for shower and swimming. Subjects randomized to aerobic exercise will exercise at a target HR intensity (80% of the HR achieved on the treadmill) 20 minutes per day (on a stationary bike or treadmill under supervision of parent/partner, at home or in a gym). They will be instructed to stop exercise at symptom exacerbation or at 20 min, whichever comes first. We have shown that this is safe.[3] They will be prompted by text/email to do their exercise at the same time each day. Subjects randomized to placebo will be contacted by text/email each day to prompt them to stretch for 20 minutes per day (stretching program provided via written instructions with visual examples of each stretch).[19] Subjects will complete an activity log to document exercise times. We used a similar intervention in a small controlled trial of exercise vs. placebo stretching in PCS patients and showed that aerobic exercise improved symptoms and returned brain fMRI activation patterns to control levels whereas placebo stretching did not.[19] After randomization, subjects will be seen weekly by a physician blinded to treatment group until they are declared recovered (by normal symptoms and physical examination). They also will have treadmill testing and have accelerometer/HR data downloaded weekly for up to 3 weeks (Visits 3-5). A new exercise prescription will be given to subjects based upon the treadmill results (a new target HR or a new stretching prescription). Concussion care provided by the blinded physician will be otherwise the same for each group.

Research personnel administering physiological testing will be blinded to subject group assignment; specifically, the research assistant (RA) obtaining consent will be different from the person performing the physiological testing, who will be blinded to group assignment. Subjects will be prompted by text/email to report their symptoms daily online in the evening for up to 4 weeks using the Post-Concussion Scale, a validated instrument with normative data for males and females.[25] Subjects in each group will have the same amount of contact with and attention from the study staff. It is not possible to blind subjects to treatment but the evaluating physician will be blinded to group assignment. Subjects will be instructed to do only their assigned exercise program during the trial and to avoid all other forms of exercise. The HR monitor will confirm the degree of compliance with each intervention (i.e., documentation of elevated HR during exercise in aerobic group and no significant elevation of HR in stretching group. This makes stretching an ideal placebo since it is active but does not confer an aerobic training effect) and will provide data on daily activity. Once deemed recovered, the subject is finished with the study except that subjects and parents will fill out a follow-up survey at the final visit and a telephonic survey at six weeks from the date of injury to document degree of recovery. We stop the active intervention at clinical recovery because our studies have shown that subject retention is very low once they have recovered. We can achieve the sample size for this pilot study since we have a demonstrated track record of recruiting acutely concussed subjects into

trials *but we need more funding to complete this trial.* We have a sports medicine clinic with a direct referral base from athletic trainers in local high schools who contact us immediately upon injury and we see them within several days of concussion.

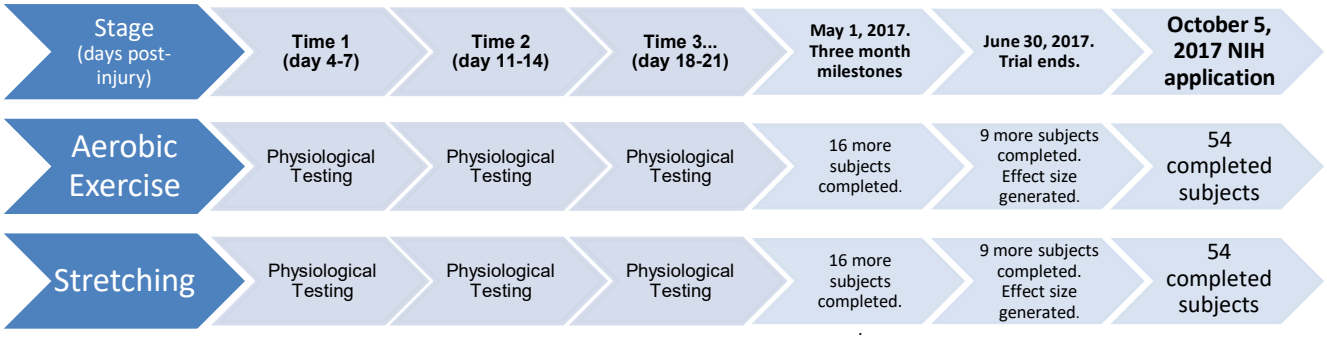
Dependent variable: Time to concussion recovery, which is defined as reporting a normal level of symptoms on the PCS scale and a normal physical examination (i.e., normal cognitive, cervical, vestibular, neurological and oculomotor systems) by blinded physician assessment.

Statistical Analysis: We will analyze the mean time to concussion recovery (days) for significance between the aerobic exercise group and the stretching group using standard regression procedures at α level 0.05.

Sample size: We used our pilot control data from a previous study of the safety of the BCTT (*paper in revision at Clinical Journal of Sports Medicine*) to estimate the standard deviation for the days to recovery calculated from the time of injury. Using a two sample t-test (size =0.05) and the estimated standard deviation for recovery time, we have an 80 percent chance to detect a clinically significant mean difference of 4 days in recovery time between the two groups (exercise vs. placebo stretching) with *54 subjects in each group*.

Impact of the project: There is no known active intervention or medication that speeds recovery acutely from concussion. Rest is the most prescribed “treatment” and a few days of rest is helpful[28] but prolonged rest is actually detrimental to recovery.[29] We are the first group in the world to use the physiological effects of sub-threshold aerobic exercise to safely treat humans with delayed recovery from concussion. There are no data on the use of exercise treatment in the *acute phase of concussion recovery,* although we have completed an RCT that showed it is safe to test exercise tolerance (using our pre-determined stopping criterion) early (within one week) after concussion. The logical next step is to use sub-threshold exercise in those with exercise intolerance shortly after injury to see if it speeds recovery; theoretically, because of the beneficial effects of aerobic exercise on ANS function, CBF control, and neuroplasticity. If successful, this would represent a paradigm shift in the way concussion is assessed and treated- that is, using an active as opposed to a passive approach. *We need CTSA funding to extend our study to double our current sample size. This will allow us to obtain an effect size to power a larger randomized trial for an NIH grant application.*

Study Timeline (assuming a February 1, 2017 start date)



Extramural Funding: Based upon the results, we will submit a grant to NIH (NINDS, study section BINP) to solicit funding for a larger RCT on the effect of sub-threshold aerobic exercise on recovery during the acute phase after concussion. *We have spoken with Patrick Bellgowan, PhD, Program Director, Repair and Plasticity, NIH/NINDS, who says that BINP would be interested in this study. We will aim for submission June of 2017.* We are also submitting an R24 NIH multicenter trial application in February 2017 with Children's Hospital of Philadelphia, Harvard Medical School and Boston Children's Hospital, and the Mind Research Network in New Mexico for a study to develop consensus criteria and objective biomarkers of pediatric concussion that predict clinical symptoms, guide treatment decisions, and inform the development of new interventions. *The data from this proposed CTSA project will provide critical pilot data to support this application, which is of interest to NINDS, study sections BINP (PO Patrick Bellgowan, Ph.D) and ANIE (PO Seetha Bhagavan, Ph.D).*

References

1. Leddy JJ, Kozlowski K, Fung M, Pendergast DR, Willer B. Regulatory and autoregulatory physiological dysfunction as a primary characteristic of post concussion syndrome: implications for treatment. NeuroRehabilitation. 2007;22(3):199-205. Epub 2007/10/06. PubMed PMID: 17917170.
2. Kozlowski KF, Graham J, Leddy JJ, Devinney-Boymel L, Willer BS. Exercise Intolerance in Individuals With Postconcussion Syndrome. J Athl Train. 2013. Epub 2013/08/21. doi: 10.4085/1062-6050-48.5.02. PubMed PMID: 23952041.
3. Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. Clinical Journal of Sport Medicine. 2010;20(1):21-7. Epub 2010/01/07. doi: 10.1097/JSM.0b013e3181c6c22c 00042752-201001000-00004 [pii]. PubMed PMID: 20051730.

4. Leddy JJ, Baker JG, Kozlowski K, Bisson L, Willer B. Reliability of a graded exercise test for assessing recovery from concussion. Clin J Sport Med. 2011;21(2):89-94. Epub 2011/03/02. doi: 10.1097/JSM.0b013e3181fdc72100042752-201103000-00003 [pii]. PubMed PMID: 21358497.

5. Baker JG, Freitas MS, Leddy JJ, Kozlowski KF, Willer BS. Return to full functioning after graded exercise assessment and progressive exercise treatment of postconcussion syndrome.

Rehabilitation research and practice. 2012;2012:705309. Epub 2012/02/01. doi: 10.1155/2012/705309. PubMed PMID: 22292122; PMCID: 3265107.
6. Griesbach GS, Gomez-Pinilla F, Hovda DA. The upregulation of plasticity-related proteins following TBI is disrupted with acute voluntary exercise. Brain Res. 2004;1016(2):154-62. PubMed PMID: 15246851.
7. Griesbach GS, Hovda DA, Molteni R, Wu A, Gomez-Pinilla F. Voluntary exercise following traumatic brain injury: brain-derived neurotrophic factor upregulation and recovery of function. Neuroscience. 2004;125(1):129-39. PubMed PMID: 15051152.
8. Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF. Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci U S A. 2011;108(7):3017-22. Epub 2011/02/02. doi: 10.1073/pnas.1015950108. PubMed PMID: 21282661; PMCID: 3041121.
9. Griesbach GS, Tio DL, Nair S, Hovda DA. Recovery of stress response coincides with responsiveness to voluntary exercise after traumatic brain injury. J Neurotrauma. 2014;31(7):674-82. doi: 10.1089/neu.2013.3151. PubMed PMID: 24151829; PMCID: 3961793.
10. Griesbach GS, Tio DL, Vincelli J, McArthur DL, Taylor AN. Differential effects of voluntary and forced exercise on stress responses after traumatic brain injury. J Neurotrauma. 2012;29(7):1426-33. Epub 2012/01/12. doi: 10.1089/neu.2011.2229. PubMed PMID: 22233388; PMCID: 3335105.
11. Jacotte-Simancas A, Costa-Miserachs D, Coll-Andreu M, Torras-Garcia M, Borlongan CV, Portell-Cortes I. Effects of voluntary physical exercise, citicoline, and combined treatment on object recognition memory, neurogenesis, and neuroprotection after traumatic brain injury in rats. J Neurotrauma. 2015;32(10):739-51. doi: 10.1089/neu.2014.3502. PubMed PMID: 25144903.
12. Itoh T, Imano M, Nishida S, Tsubaki M, Hashimoto S, Ito A, Satou T. Exercise increases neural stem cell proliferation surrounding the area of damage following rat traumatic brain injury. J Neural Transm. 2011;118(2):193-202. doi: 10.1007/s00702-010-0495-3. PubMed PMID: 20924619.
13. Itoh T, Imano M, Nishida S, Tsubaki M, Hashimoto S, Ito A, Satou T. Exercise inhibits neuronal apoptosis and improves cerebral function following rat traumatic brain injury. J Neural Transm. 2011;118(9):1263-72. doi: 10.1007/s00702-011-0629-2. PubMed PMID: 21442353.
14. Seo TB, Kim BK, Ko IG, Kim DH, Shin MS, Kim CJ, Yoon JH, Kim H. Effect of treadmill exercise on Purkinje cell loss and astrocytic reaction in the cerebellum after traumatic brain injury. Neurosci Lett. 2010;481(3):178-82. doi: 10.1016/j.neulet.2010.06.087. PubMed PMID: 20603186.
15. Kim DH, Ko IG, Kim BK, Kim TW, Kim SE, Shin MS, Kim CJ, Kim H, Kim KM, Baek SS. Treadmill exercise inhibits traumatic brain injury-induced hippocampal apoptosis. Physiol Behav. 2010;101(5):660-5. doi: 10.1016/j.physbeh.2010.09.021. PubMed PMID: 20888848.
16. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. Mayo Clinic proceedings Mayo Clinic. 2011;86(9):876-84. Epub 2011/09/01. doi: 10.4065/mcp.2011.0252. PubMed PMID: 21878600; PMCID: 3258000.
17. Stroth S, Hille K, Spitzer M, Reinhardt R. Aerobic endurance exercise benefits memory and affect in young adults. Neuropsychological rehabilitation. 2009;19(2):223-43. Epub 2008/07/09. doi: 10.1080/09602010802091183. PubMed PMID: 18609015.
18. Clausen M, Pendergast DR, Willer B, Leddy J. Cerebral Blood Flow During Treadmill Exercise Is a Marker of Physiological Postconcussion Syndrome in Female Athletes. J Head Trauma Rehabil. 2015. doi: 10.1097/HTR.0000000000000145. PubMed PMID: 26098254.
19. Leddy JJ, Cox JL, Baker JG, Wack DS, Pendergast DR, Zivadinov R, Willer B. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic

resonance imaging activation, physiology, and symptoms. J Head Trauma Rehabil. 2013;28(4):241-9. Epub 2012/12/20. doi: 10.1097/HTR.0b013e31826da964. PubMed PMID: 23249769.
20. McCrory P, Meeuwisse W, Aubry M, Cantu B, Dvorak J, Echemendia RJ, Engebretsen L, Johnston K, Kutcher JS, Raftery M, Sills A, Kathryn Schneider PTPCHTMDPHD, Benson BW, Davis GA, Ellenbogen RG, Guskiewicz KM, Herring SA, Iverson G, Jordan BD, Kissick J, McCrea M, McIntosh AS, Maddocks DL, Makdissi M, Purcell L, Putukian M, Turner M, Schneider K, Tator CH. Consensus statement on concussion in sport--the 4th International Conference on Concussion in Sport held in Zurich, November 2012. Clin J Sport Med. 2013;23(2):89-117. doi: 10.1097/JSM.0b013e31828b67cf. PubMed PMID: 23478784.
21. Zhang R, Zuckerman JH, Pawelczyk JA, Levine BD. Effects of head-down-tilt bed rest on cerebral hemodynamics during orthostatic stress. J Appl Physiol. 1997;83(6):2139-45. Epub 1998/02/14. PubMed PMID: 9390992.
22. Alderman BL, Arent SM, Landers DM, Rogers TJ. Aerobic exercise intensity and time of stressor administration influence cardiovascular responses to psychological stress. Psychophysiology. 2007;44(5):759-66. Epub 2007/06/23. doi: 10.1111/j.1469-8986.2007.00548.x. PubMed PMID: 17584185.
23. Carson JD, Lawrence DW, Kraft SA, Garel A, Snow CL, Chatterjee A, Libfeld P, MacKenzie HM, Thornton JS, Moineddin R, Fremont P. Premature return to play and return to learn after a sport-related concussion: physician's chart review. Canadian family physician Medecin de famille canadien. 2014;60(6):e310, e2-5. PubMed PMID: 24925965; PMCID: 4055342.
24. Kostyun RO, Hafeez I. Protracted recovery from a concussion: a focus on gender and treatment interventions in an adolescent population. Sports health. 2015;7(1):52-7. doi: 10.1177/1941738114555075. PubMed PMID: 25553213; PMCID: 4272696.
25. Lovell MR, Iverson GL, Collins MW, Podell K, Johnston KM, Pardini D, Pardini J, Norwig J, Maroon JC. Measurement of symptoms following sports-related concussion: reliability and normative data for the post-concussion scale. Appl Neuropsychol. 2006;13(3):166-74. PubMed PMID: 17361669.
26. ACSM’s Guidelines for Exercise Testing and Prescription 7th ed. Whaley MH, editor. Philadelphia: Lippincott Williams & Wilkins; 2006.
27. Leddy JJ, Willer B. Use of Graded Exercise Testing in Concussion and Return-to-Activity Management. Curr Sports Med Rep. 2013;12(6):370-6. doi: 10.1249/JSR.0000000000000008. PubMed PMID: 24225521.
28. Thomas DG, Apps JN, Hoffmann RG, McCrea M, Hammeke T. Benefits of Strict Rest After Acute Concussion: A Randomized Controlled Trial. Pediatrics. 2015;135(2):213-23. doi: 10.1542/peds.2014-0966. PubMed PMID: 25560444.
29. Silverberg ND, Iverson GL. Is Rest After Concussion "The Best Medicine?": Recommendations for Activity Resumption Following Concussion in Athletes, Civilians, and Military Service Members. J Head Trauma Rehabil. 2012;28(4):250-59. Epub 2012/06/13. doi: 10.1097/HTR.0b013e31825ad658. PubMed PMID: 22688215.

Sample Size

We used data from a pilot study of exercise versus stretching in concussed patients[30] and estimated 4.2 and 7.8 as the standard deviation of the days to recovery for the aerobic exercise and stretching exercise groups, respectively. We used an underlying normal distribution to simulate time to recovery data with the above standard deviations. Using a two sample two-sided t-test, we calculated an 80 percent chance to detect a clinically significant mean difference of 3.7 days in recovery time between groups with 50 participants in each group. No interim analysis was planned. Adverse events and near misses were recorded and evaluated by the treating physician.

Data Analysis

Analyses were based on per protocol analysis. Baseline characteristics were analyzed to assess cluster differences between aerobic and stretching groups. We assessed group-wise differences in normally distributed variables (age, total physical examination findings, total symptom severity scores on initial visit, and days to initial visit) using ANOVA. Chi-square test was used to assess group-wise differences in sex and prior concussions. The Mann-Whitney test was used for the main outcome measure (days to recovery), which was not normally distributed. This outcome was demonstrated by Kaplan-Meier curves and assessed using multivariable Cox proportional hazards models, which were adjusted for patient characteristics (age, sex, prior concussion, and time since injury) based on prior literature.[34] The Mann-Whitney test was also used for the analysis of days to recovery from first clinical visit. Mean daily symptom severity score with 95% CI for the first three weeks was considered in linear regression models and distributional checks of residuals were undertaken to determine the most appropriate model. Missing values were calculated as the average of day-before and day-after scores. A repeated

measures ANOVA was used to assess differences in symptom recovery time between groups. A p-value less than 0.05 determined statistical significance and all tests were 2-sided. Statistical analyses were performed using STATA version 14 (College Station, Texas).