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Exertional Tolerance Assessments after Mild Traumatic Brain Injury: A Systematic Review

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Abstract

Objective—The objective of this study was to review the literature to identify and summarize strategies for evaluating responses to physical exertion after mild traumatic brain injury (mTBI) for clinical and research purposes.

Data sources—PubMed and EBSCOHost through December 31, 2016.

Study Selection—Two independent reviewers selected studies based on the following criteria: 1) inclusion of participants with mTBI/concussion, 2) use of a measurement of physiological or psychosomatic response to exertion, 3) a repeatable description of the exertion protocol was provided, 4) a sample of at least 10 participants with a mean age between 8–65 years, and 5) the article was in English. The search process yielded 2,685 articles, of which 14 studies met the eligibility requirements.

Data Extraction—A quality assessment using a checklist was conducted for each study by two independent study team members and verified by a third team member. Data were extracted by a one team member and verified by a second team member.

Data Synthesis—A qualitative synthesis of the studies revealed that most protocols employed a treadmill or cycle ergometer as the exercise modality. Protocol methods varied across studies

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including differences in initial intensity determination, progression parameters, and exertion duration. Common outcome measures were self-reported symptoms, heart rate, and blood pressure.

Summary/conclusions—The strongest evidence indicates that exertional assessments can provide important insight about mTBI recovery and should be administered using symptoms as a guide. Additional studies are needed to verify an optimal modes and protocols for post-mTBI exertional assessments.

Keywords

exertion testing; concussion; mild traumatic brain injury

Introduction

Mild traumatic brain injuries (mTBIs), including concussions, affect an estimated 1.6 to 3.8 million individuals annually in the United States.[1, 2] Evidence increasingly indicates that mTBIs may alter the central nervous system's functioning leading to a variety of symptoms[3] and leaving the brain vulnerable to further injury for an unknown period of time.[4] Due to concerns that too much exertion in the acute recovery stages could impede recovery and potentially cause more damage,[5, 6] the standard of care for mTBI management has historically been rest from physical and cognitive activities.[6] However, recent studies and consensus statements increasingly emphasize that rest may be associated with prolonged symptoms and delayed recovery in at least some cases.[7–9] Thus, clinicians face a clinical conundrum when treating patients with mTBIs: how to determine when a patient is physiologically ready to return to higher levels of physical exertion. Exertional tolerance assessments could provide a mechanism to evaluate tolerance to increased physical exertion in a controlled and safe environment.

According to the latest American College of Sports Medicine's Guidelines for Exercise Testing and Prescription, clinical exercise testing can be useful for assessing a variety of medical conditions.[10] However, most of the research and protocols have been designed to assess patients with ischemic heart disease.[10] Treadmills and cycle ergometers (or stationary bicycles) are the two most common modes for clinical exercise testing, both of which offer advantages and disadvantages.[10, 11] Treadmill assessments may allow for testing higher levels of exercise capacity because evidence suggests peak exercise capacity during cycling can be 5%–20% lower due to regional muscle fatigue.[10] However, cycling may be the preferred mode of exercise testing for individuals who have orthopedic, neurologic, or other safety-related considerations (e.g., impaired standing balance or gait).[10–13] Additionally, cycling often entails less movement of arms and thorax, which can make it easier to obtain better quality physiologic measures and may be critical for the objective of the test in some cases.[13]

Regardless of the medical condition being assessed, clinical exercise testing protocols typically employ either a continuous approach (i.e., workload is consistent throughout test) or an incremental approach (i.e., workload is progressively increased as the test proceeds).[10, 13] Some incremental protocols increase workload in relatively large adjustments every few minutes (Bruce protocol), while others use what is known as a ramping method whereby workload increases occur in a more constant, steady, and continuous manner (e.g., Ball State University/Bruce ramp).[10, 13] Protocols with larger increases in workload increments such as the Bruce or Ellestad may be better suited for screening individuals who are younger and more physically active, to allow for optimally challenging exercise capacity within a more manageable total testing time.[13] In contrast, ramp protocols or protocols with smaller incremental increases (e.g., Balke-Ware or Naughton protocols) may be preferable for older individuals, deconditioned patients, or patients for whom large, quick increases in exertion levels may be a safety risk.[13]

Published exercise testing standards convey that it is important to select an exercise testing mode and protocol for each patient relative to purpose of the evaluation, the specific information desired, and the individual characteristics of the patient being tested (e.g., age, symptomatology, safety concerns).[10–12] Although there are a variety of consensus statements and general calls for the assessment of post-mTBI exertional tolerance to help determine physiological readiness to return to sport or identify physiologic impairment,[4, 5, 14] there is currently no gold standard protocol for activity assessments in these regards. Due to the potential multi-system effects and co-morbidities associated with mTBIs (e.g., vestibular dysfunction, autonomic dysfunction, musculoskeletal/cervicogenic dysfunction), an optimal exertional testing method for this patient population may differ from the graded exercise and cardiovascular exertion testing commonly performed in other patient populations. Likewise, unique outcome measures or interpretation of outcome measures may be necessary to adequately identify mTBI-related impairments as part of the individual's physiological responses to exertion. Therefore, the purpose of this study was to complete a systematic review of the literature in order to identify current clinical and research strategies and rationales for evaluating post-mTBI responses to physical exertion.

Methods

Data Sources

A literature search was conducted on July 15, 2016 using the following search terms: ((post concussion syndrome) OR (concussion) OR (mild traumatic brain injury) OR (closed head injury)) AND ((exercise test) OR (exercise assessment) OR (exercise) OR (exertion test) OR (exertion assessment) OR (exertion) OR (progressive exercise training) OR (autonomic assessment) OR (aerobic training) OR (aerobic rehabilitation) OR (active rehabilitation)). The search was performed using PubMed as well as an EBSCOHost package that included: CINAHL Plus with Full Text, MEDLINE with Full Text, Alt HealthWatch, Health Source-Consumer Edition, MEDLINE, SPORTDiscus with Full Text, Consumer Health Complete-EBSCOhost, and Academic Search Premier. The search was repeated on December 31st, 2016, and on July 20, 2017 to identify additional relevant studies that had been published since the initial search. The key word searches were also supplemented with manual searches of the bibliographies of the articles that were ultimately determined to meet the *a priori* inclusion and exclusion criteria and of any review articles that turned up in the initial search but were screened out during the abstract review stage. The search process was inclusive of grey literature (research disseminated outside of traditional commercial/

academic channels) in order to minimize publication bias. New articles that were published or available as an electronic version ahead of print and fit the final search criteria were added to the search pool. All duplicates were removed to yield a final initial pool of articles for review.

Study Selection

Study selection was completed using two phases (a title/abstract screening phase, followed by full text review) and managed using a web-based systematic review management software (Distiller SR). The initial screening for relevancy based on the titles and abstracts was performed by two independent reviewers according to a pre-determined set of inclusion/exclusion criteria. Any disagreements were resolved by a third independent reviewer. An article was deemed qualified for the systematic review if it met the following criteria: 1) included human participants who had sustained an mTBI, 2) measured a physiological or psychosomatic response to exertion, 3) provided a detailed description of the exercise protocol, 4) included a sample of at least 10 participants with a mean age between 8–65 years, and 5) had a full-text available in English. A full-text review of the article was completed if qualification could not be determined by title and abstract alone. Any disparities were resolved by a third reviewer. Case studies, non-empirical research articles, review papers, animal tests, and experiments done only in moderate or severe TBI populations were excluded.

Data Extraction and Quality Appraisals

Data extraction was completed by a single reviewer and verified by a second reviewer. Extracted characteristics included purpose, sample, exercise modality, protocol details, relevant outcome measures, results, and limitations. Because the studies were not the same study design and no existing quality assessment tools directly met our needs for our descriptive-oriented research question, we created a unique set of items modified from other critical appraisal tools (i.e., The Cochrane Risk of Bias Tool[15] and the Joanna Briggs Institute Critical Appraisal Tools Checklist for Cohort Studies[16]) to assess bias and relevance to our review purpose (see Table 1). The highest possible score was 10. It is important to note, that the ratings provided for each item on the appraisal tool were directly related to the purposes of the current systematic review. Therefore, a lower rating on an individual item or a lower overall score would not necessarily reflect a poorer quality study for the study's original purpose. Rather, a lower rating on the checklist here, simply reflects less direct relevancy or lower quality of study relative to the purposes of this systematic review. The methodological quality checklist was completed for each study individually by two reviewers. Any discrepancies were resolved and verified using a consensus generation process with a third reviewer.

Synthesis of Post-mTBI Exertional Testing for Research and Clinical Purposes

The authorship team identified key themes relative to the current post-mTBI exertional testing clinical and research strategies and rationales through a comprehensive review and comparison of the studies that met the inclusion and exclusion criteria for the systematic review. The themes were initially derived and drafted by the first author after considering the direct relevancy of each study for the systematic review purposes and evaluating the study design strengths and weaknesses, investigators' rationales for selecting exertional testing protocols and parameters, and investigators' discussions regarding post-mTBI exertional assessments and interventions. The other authors of this manuscript then discussed these themes both in-person and via written interactions as part of the development of the manuscript to generate a consensus on the themes, the presentation and discussion of the themes, and the analysis of the current state of the evidence. Additionally, the themes further evolved over the course of the peer review process through thoughtful critiques and feedback provided by the reviewers and editors.

Results

A total of 2,406 potential records were identified through the initial key word search (Figure 1). The second search yielded an additional 79 potential records and the third search identified 189 potential records. Eleven additional sources were found through a review of bibliographies for a total of 2,685 potential records. After the full text review relative to the eligibility criteria, 14 studies were identified as appropriate for the intended purposes of this review. Quality appraisals for each included study are provided in Table 1 and detailed study descriptions as they relate to the systematic review study question are provided in Table 2.

Sample Characteristics

Seven studies included samples with a mean age or age range of less than 18 years,[17–22] while the other seven utilized samples with a mean age of 18 years or older.[23–29] Four studies used a sample consisting of only athletes,[23–25, 30] three studies reported using a combination of athletes and non-athletes,[27, 28, 30] and seven studies were unclear in their reporting of athletes versus non-athletes within their samples.[17–20, 22, 26, 29]

Five studies performed exertional assessments with participants who were in the relatively acute post-concussion phases (1–3 weeks post injury).[18, 22–25] Seven studies used a sample of participants who were in a more sub-acute to chronic phase of recovery (3 weeks or more post injury).[17, 26–31] One study was a retrospective chart review that included exertion testing examples in both acute and more chronic patients.[20] The remaining study appeared to have an initial test that was performed in the acute phase and a second test when the participants were asymptomatic, but the timing of the second test was unclear.[19]

Exertion Protocols

Five of the 10 studies utilized a modified Balke progressive treadmill test referred to as the Buffalo Concussion Treadmill Test.[19, 20, 26–28] Seven of the studies used various forms of a cycle ergometer, or stationary bicycling test.[17, 22–25, 29, 31] One study utilized either a treadmill or cycle, depending on patient presentation and preference.[30] One study evaluated Nintendo Wii games.[18] All 14 of the studies entailed some form of intensity progression in the protocol. See Tables 1 and 2 for further details about study design and exertion testing protocols relative to the purposes of this review.

Outcome Measures

As the nature of the study questions varied among studies, a variety of outcome measures were used for the overall body of included studies. Multiple physiological and psychosomatic measures were used to assess response to exertion. All of the studies assessed and evaluated heart rate in some capacity, however one study also specifically considered heart rate variability metrics.[23] Eight of the studies included a post-concussion symptom checklist or assessment,[17, 24–26, 28–31] five studies evaluated blood pressure,[20, 26–29] and six evaluated rate of perceived exertion.[17, 19, 22, 26, 28, 29] Additional outcome measures (e.g., blood lactate levels, exercise duration, oxygen saturation and V02 estimates) were also measured in several studies.[17, 23, 24, 28, 29] }

Quality Appraisal Results

All but two of the studies used a prospective study design.[20, 30] Only three of the studies provided specific rationales for the mode used for exertion testing.[18, 29, 30] Five studies provided a rationale for exertional testing protocol type,[19, 20, 24, 29, 30] however, most of the rationales simply described that prior research on mTBI had used similar protocols. Seven of the studies investigated specific aspects of the body's response to an exertional test,[17, 19, 20, 23, 24, 3226–28] while this was an indirect purpose for the other studies.

Only the Buffalo Concussion Treadmill Test had available data associated with reliability relative to mTBI,[19, 20, 26–28, 30] while the studies that used the cycle ergometer and Nintendo Wii had no established data on the reliability or validity relative to samples with mTBI. One study specifically evaluated the retest reliability and interrater reliability of the Buffalo Concussion Treadmill Test.[27] Specifically, the study found that the Buffalo Concussion Treadmill Test had good test retest reliability for assessment of maximum heart rate in participants with a concussion and healthy controls and that raters achieved relatively high sensitivity (99%) and specificity (89%) for identifying participants with and without mTBI symptom exacerbation. It is important to note, however, that the study only had 11 participants with mTBI who were an average of 33.2 weeks post-injury.

Synthesis of Key Findings from Included Studies

Collectively, the body of evidence identified through the systematic search process was relatively limited with a variety of study designs, most of which were case series or case-control comparison studies. Given the wide variability in study designs, sample characteristics, and exertion testing protocols, a quantitative synthesis of the results of the studies was deemed inappropriate. Instead, a qualitative synthesis was used to identify key themes relative to the current clinical and research strategies found in the body of evidence for clinical evaluation and studying post-mTBI responses to physical exertion.

In general, the studies identified for this review provided foundational evidence that post-mTBI exertional testing can be safe and useful for identifying residual impairments including impaired physiologic responses to exertion (e.g., symptom emergence/exacerbation, altered heart rate variability with exertion, and blunted heart rate response to exertion). Cordingley et al. specifically found that the Buffalo Concussion Treadmill Test can be well-tolerated and safe for many youth ages 11–19 years even in the relatively acute stages of recovery.[20] A general expectation should be that exertional testing may exacerbate symptoms in many patients, however, this should be temporary. As DeMatteo et al's findings suggest, many patients may initially experience a worsening of symptoms with exertion, but within 24 hours many report an improvement in symptoms that exceeds the level of baseline symptoms reported prior to the exertional test.[17] Moreover, if certain metrics are utilized (e.g., heart rate variability), physiologic impairment may be discernable during exertion in ways that are unable to be captured through clinical assessments performed at rest.[19, 23, 24]

Overall, optimal testing mode and protocols for assessing and studying post-mTBI exertional responses remains unclear based on the current body of evidence. The studies identified for this systematic review primarily utilized either treadmill testing or cycle ergometer testing, with a modified Balke (Buffalo Concussion Treadmill Test) being the most frequently used in the literature. The rationales investigators used for selecting these modes and protocols were limited and lacking specific empirical and theoretical justifications. Additional, very little reliability and validity testing has been performed with the protocols. These are critical areas to clarify in order to improve the utility of exertional testing for clinical and research purposes.

Discussion

The purpose of this study was to review the literature to identify and summarize strategies for evaluating responses to physical exertion after mild traumatic brain injury (mTBI) for clinical and research purposes. Protocol characteristics for mode, workload, intensity, progression procedures, and test cessation determinants varied greatly across studies. The outcome measures used were inconsistent and often unique to each study's specific questions and design. The sample characteristics also varied widely across studies in terms of sex, age, time since injury, and pre-injury physical activity levels. Collectively, the large differences in protocols, sample compositions, and application of outcome measures greatly constrain the ability to draw strong conclusions about the best strategies to use for post-mTBI exertional tests. Further research is needed to provide more clarity around specific protocols and measures that can best identify post-mTBI exertion-related impairments. The benefits and limitations for the protocols and metrics identified through the systematic search process are discussed below to provide suggestions for refinement and optimization of post-mTBI exertional testing in future studies.

Exertional Testing Mode

A concern that may be particularly unique to exertional testing with patients with mTBI as compared to other patient populations who are frequently assessed with graded exercise tests (e.g., patients with cardiovascular disease) is the potential for a protocol to trigger symptoms that may confound the ability to specifically identify exertional intolerances.[33] For example, walking or running may trigger vestibular or oculomotor symptoms due to the visual and movement cues the body must process while on the treadmill. They may also trigger musculoskeletal or cervicogenic-related symptoms because of the forces that may go through the cervical spine or added stress on the neck and scapular postural muscles. This suggests that it may be important to perform impairment specific assessments (e.g., oculomotor, vestibular, and cervicogenic/musculoskeletal) in conjunction with exertional tolerance assessments.

Several investigators in the current review postulated that treadmill testing may be difficult or inappropriate for some patients.[29, 30] Additionally, since the symptoms associated with vestibular, oculomotor, and cervical spine related impairments are very similar to exertional intolerance impairments (e.g., headache, dizziness, nausea) and are also common after concussion, assessments with a high probability of producing vestibular, oculomotor, and cervical spine impairments may make it challenging to distinguish exertional-related impairments from these other impairments after concussion. There is potential that stationary biking may provide specific insight into physiological exertional tolerance by reducing the risk for confounding symptoms, however, no studies specific to post-concussion assessments have directly evaluated this contention. Additionally, stationary biking assessments may be less functional and transferable to everyday skills, particularly for those who engage in activities that require higher fitness levels.[33] This logically calls into question whether a single, gold-standard exertional testing mode can be identified for this patient population or if there is a need to demarcate certain types of testing modes relative to specific clinical and/or research questions.[34, 35]

Another important future research question to investigate is whether certain patient attributes lead to distinctive responses to different modes of testing. For example, patients who have previously used treadmills or stationary bicycles may tolerate these testing modes better than those who have not.[36] Other types of questions along these lines include: 1) do older patients respond differently to different modes of exertion testing compared to younger patients, 2) do post-mTBI athletes respond differently than non-athletes to different modes of exertion testing, and 3) does time since injury influence feasibility and effectiveness of different modes of exertion testing? All of these questions speak directly to the validity of post-mTBI exertional assessments and underlie justifications for why a clinician or researcher may choose to use one mode of exertion testing over another. Therefore, future studies investigating post-mTBI exertional testing modes in these regards would be beneficial.

Exertional Testing Protocols

All of the identified studies followed various levels of workload intensity. However, determinants for starting workloads, progressions of the workload, and the duration of the testing varied significantly across the studies. Additional studies comparing these parameters may help inform the determination of optimal testing protocols for use post-mTBI. In addition, all of the studies utilized staged progressions, whereby intensity was increased incrementally instead of continuously. Consequently, it may be hard to determine uniformity of responses and expected responses. For researchers interested in characterizing the mechanistic impairments that may be present post-mTBI, a ramped protocol, which increases work rate in a constant and continuous manner (as compared to staged progressions which introduce larger jumps in workload) may allow for more accurate estimates of exercise capacity, ventilatory threshold, and autonomic responsiveness to exertion.[13, 36] Regardless, it is clear that future studies that more comprehensively consider the theoretical foundations for protocol selection and empirically compare protocols for patients with mTBI would be beneficial.

Outcome Measures

Collectively, the studies indicated that mTBI may lead to changes in physiologic responses to exertion. However, the metrics used to capture altered physiologic responses may differ in their capacity to capture mTBI impairments as well as their clinical and research utilities. For example, many of the studies evaluated symptom responses to exertion, with mTBI-related symptom onset or exacerbation serving as test termination criteria. Symptom monitoring is a clear and useful way to help screen for readiness to return to higher levels of exertional activities as well as help identify patients who may benefit from progressive, active rehabilitation protocols.[3, 5, 26–28, 31, 34, 37] Nonetheless, symptom assessments are subjective and highly variable within and across patients. Additionally, there is insufficient evidence to clearly determine that physiologic impairments are not present even though a patient may be asymptomatic. For these reasons, there is a great need for further studies to identify more objective means to evaluate atypical physiologic responses to exertion as well as clarify implications for impaired physiologic responses to exertion relative to function and further injury risk.

The studies identified in this review highlighted some potential options for more comprehensive studies into metrics that may and may not be as useful for evaluating post-mTBI physiologic impairments. It has been theorized that mTBI can lead to a disruption of the autonomic nervous system and autoregulatory functions of the body[3]. Patients with persistent post-mTBI symptoms may have autonomic systems that are in a state of disequilibrium,[3] which could help explain the variety of impairments that emerge when they are confronted with physical and cognitive challenges.[40, 41, 43] Effectively capturing this phenomenon, however, may not be as simple as measuring heart rate and blood pressure as is done with conventional clinical screening techniques and exercise testing metrics used for other patient populations (e.g., cardiovascular exercise testing) because heart rate and blood pressure may not appear outside of what is expected as a normal response. However, protocols and metrics that specifically seek to consider autonomic responsiveness may reveal important differences between healthy and impaired post-mTBI states (e.g., heart rate variability).[23] Systematic studies specifically evaluating typical and atypical responses to exertion with a robust set of physiologic metrics are needed to provide a more comprehensive understanding of which metrics are most useful, relative to different protocols, and for which specific purposes.

Overall Considerations

As specified in the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription, the exercise modality, protocol, and outcome measures employed should be based on the purpose of the testing, the specific information desired, and the characteristics of the individual being tested.[33] There is a robust literature on exercise testing for cardiologic and respiratory-related diagnoses.[33, 36] However, the transferability and utility of the specific modalities, protocols, and outcome measures relative to patients with mTBI are currently unclear. Early work in this patient population suggests that exertional testing may be a useful clinical screening tool and a valuable line of inquiry to pursue to further understanding of the mechanisms and recovery trajectories associated with mTBI. Additional studies are needed to refine exertional testing protocols for this patient population and optimize recommendations and guidelines for specific clinical and research purposes.

Limitations

This systematic review has several notable limitations. First, although a comprehensive and thorough search strategy was used, there remains a potential for publication bias because the search was limited to peer-reviewed journal outlets in the English language. Therefore, it is possible that relevant studies may have been missed. Likewise, mTBI research is a rapidly evolving field of study. Consequently, the potential for relevant grey literature and new published works in the window of time that has passed since the search ended is relatively high. In addition, as with all systematic searches and critical appraisal processes, there is a certain degree of subjectivity involved. In particular, the quality appraisal process was completed through a self-generated form specifically targeting the purposes for this systematic review. We attempted to minimize the risk for this by using multiple screening rounds and multiple independent reviewers during all stages of the process. Nonetheless, it is possible that a different set of reviewers may have interpreted the studies differently. Finally, the small amount of available studies and the variable study purposes and study designs included in this review limit the conclusions that can be drawn from this research. It is clear that future research is needed to refine, extend, and validate the points discussed in this manuscript.

Conclusion

The current body of evidence provides a variety of post-mTBI exertional assessment options and protocols. The strongest evidence indicates that exertional assessments can provide important insight into recovery status after mTBI and should be administered using symptom presence and exacerbations as a guide. The synthesis and critical appraisal of the protocols identified through the systematic search process suggest that there is a great need for further research to evaluate optimal testing modes and protocols that can meet the unique and specific needs for clinically assessing and studying this patient population.

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Abbreviations

mTBI	Mild Traumatic Brain Injury

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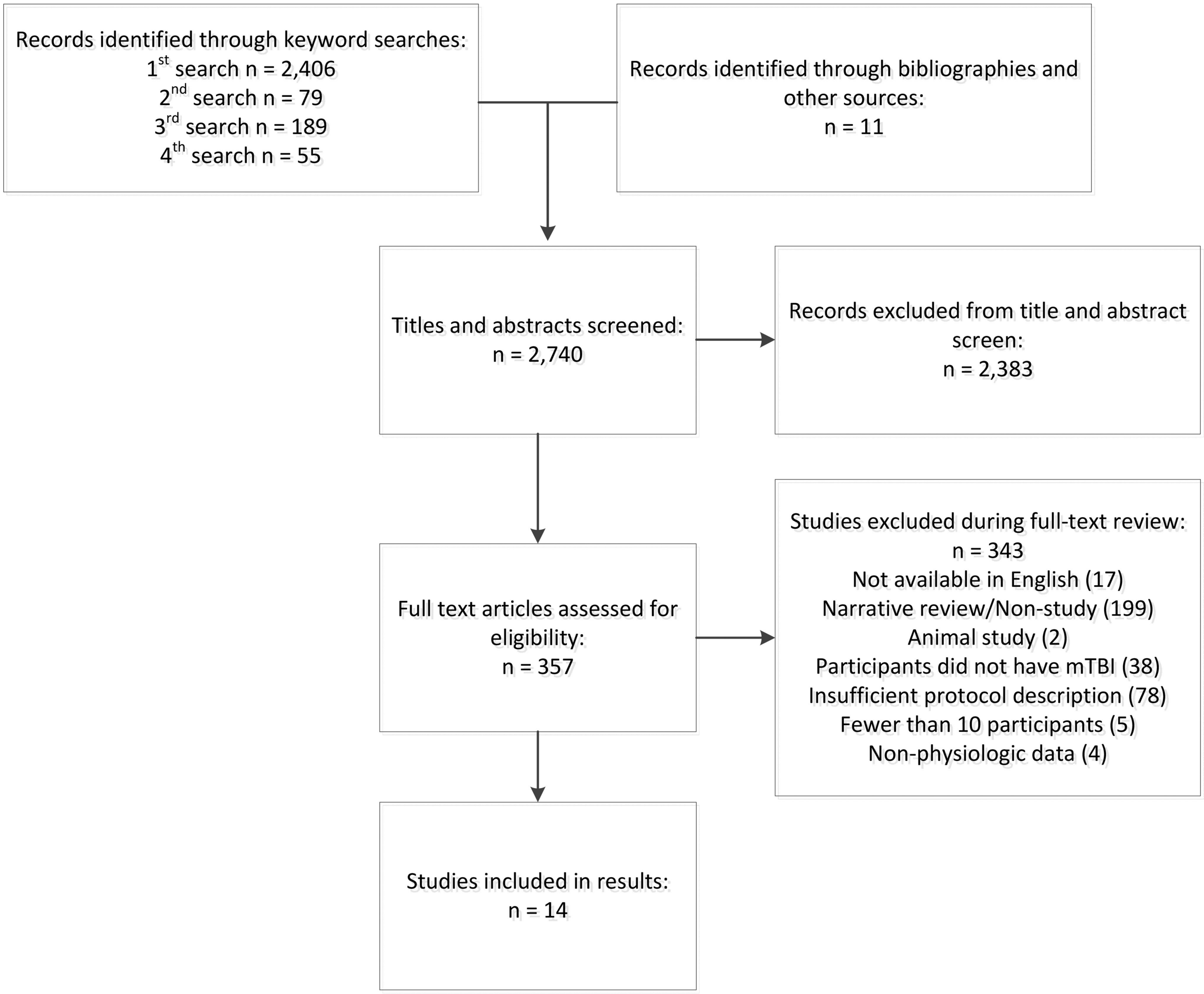

Figure 1.
PRISMA Diagram of Search and Record Selection Process

Table 1

Quality Appraisal Checklist Results

	Cordingley 2016	DeMatteo 2014	DeMatteo 2015	Gall 2004a	Gall 2004b	Grabowski 2017	Hinds 2016	Kozlowski 2013	Kurowski 2017	Leddy 2010	Leddy 2011	Manikas 2016	Moore 2016	Slobounov 2011
Did the study follow a prospective design? (1=yes)	0	1	1	1	1	0	1	1	1	1	1	1	1	1
Was a rationale regarding exertional testing mode provided by the authors? (1=yes)	0	1	0	0	0	1	0	0	0	0	0	0	1	0
Was a rationale regarding exertional testing protocol type provided by the authors? (1=yes)	1	0	0	0	1	1	1	0	0	0	0	0	1	0
Has the protocol been shown to be reliable or valid, either directly or through previous research? (1=yes)	1	0	1	0	0	0	1	1	0	1	1	1	1	1
Were funding sources or lack thereof described? (1=yes)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Was acknowledgment of conflict of interests or lack thereof provided? (1=yes)	1	1	1	0	1	0	0	0	1	1	1	1	1	0
Was evaluating physiologic response to exertion a primary purpose for the study (i.e. highly relevant for the purpose of the systematic review vs indirectly relevant)? (1=yes)	0	0	1	1	1	0	1	1	0	1	1	0	0	0

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	Cordingley 2016	DeMatteo 2014	DeMatteo 2015	Gall 2004a	Gall 2004b	Grabowski 2017	Hinds 2016	Kozlowski 2013	Kurowski 2017	Leddy 2010	Leddy 2011	Manikas 2016	Moore 2016	Slobounov 2011
Were there any significant risks of bias concerns relative to the outcomes of interest for this systematic review?* (1=no)	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Were potential confounding factors discussed? (1= yes)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Were appropriate statistical analyses used? (1=yes)	1	1	1	1	1	1	1	1	1	1	1	1	1	1
TOTAL	6	6	8	5	7	5	7	6	5	7	7	6	8	5

This table provides the individual ratings for each included study relative to the quality appraisal form created by the authors of this systematic review. It should be noted, that this set of questions was generated for the specific purposes of the current systematic review. Therefore, a lower score does not necessarily indicate a poorer quality study in general, but rather lower direct relevancy or lower level quality of study for the purposes of this systematic review.

*Criteria based on the Cochrane Risk of Bias Tool retrieved April 10, 2017 from http://handbook.cochrane.org. It should be noted, that this set of questions was generated for the specific purposes of the current systematic review. Therefore, a lower score does not necessarily indicate a poorer quality study in general, but rather lower direct relevancy or study design for the purposes of this systematic review.

Table 2

Exertion Assessment Protocols

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
Cordingley, 2016	Retrospective case series evaluating safety, clinical use, and patient outcomes	106 patients (46 M, 60 F); Mean age 15.1 years, range of 11–19 years SD 1.5 years; Median days from injury until initial testing 8 days (IQR 5–22 days)	**Mode and Type:** Treadmill with incremental progressions in treadmill grade (modified Balke protocol/ Buffalo Concussion Treadmill Test) **Rationale:** No specific rationale provided for mode, but protocol choice was noted as selected based on prior studies	- Speed of 3.2 miles per hour, 0% grade on treadmill. Grade increased by 1% per minute for the first 15 minutes, then increased .2 miles per hour every minute thereafter until exacerbation of symptoms or workload could not be maintained	- Physiologic measures - Adverse events	- No serious complications or adverse events - No persistent elevations in heart rate, blood pressure, or respiration rate	- The proportion of patients for whom test termination was due to symptom exacerbation vs exhaustion is unclear - It is also unclear if subgroups (e.g., those with vestibular or oculomotor impairments) had different responses or self-limiting behaviors leading to earlier termination of the tests
DeMatteo, 2014	Cross-sectional case series study evaluating the Nintendo Wii games for assessing return to activity readiness	24 participants (14 M, 10 F); Mean age 14.9 years, range of 9–18 years, time since injury range of 1–12 months with a mean of 5.5 months and SD of 3.68 months	**Mode and Type:** 6 Wii Games of progressive intensity **Rationale:** A rationale for Wii games for assessment was described as a way to assess functional mobility and	- First Wii game selected for lowest complexity and effort based on difficulty, quantity of movements, and balance and exertion requirements - 6 Wii games presented in increasing intensities with 3 minutes rest	- Physiologic measures	- Wii Fit Basic Run had the highest mean post-game HR and mean calorie expenditure - Wii UPC running had the highest mean post respiration rate	- The workload and ability to do this systematically is unclear based on the design of this study - Symptom responses to exertion were not reported - Unclear if subgroups (e.g., those with vestibular or oculomotor impairments) had different responses or self-limiting behaviors

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
			exertion. No specific rationale was provided for the games selected or protocol specifically	between each game			due to these impairments - There was some loss to follow-up with only 37 of 54 participants responding at the 24-hour follow-up - The fitness level of the participants prior to injury was not reported nor controlled through study design - A relatively young and small sample with a wide range in time since injury
DeMatteo, 2015	Case series of a single exercise testing bout with repeated measures of response to exertion and recovery from exertion	54 participants with recent mTBI (32 M, 22 F) Mean age of 14.8 years, SD of 2.3. Time from most recent injury range of .7–35.3 months with median of 4.1 months	**Mode and Type:** Cycle ergometer with incremental progressions in work rate (McMaster All-Out Progressive Continuous Cycling Test) **Rationale:** No specific rationale provided for mode or protocol selection	- Individualized starting work rate with fixed rotations per minute; cycling between 25–85 watts based on age, height, body mass, and level of fitness - Fixed increase in work rate every 2 minutes until exhaustion, dropping <50 rotations per minute, or concussion-like symptoms return	- Symptoms - Exertion duration - Physiologic measures	- 63% of participants had symptoms during exertion testing - Number and severity of symptoms significantly affected perception of exertion at 50% of peak mechanical power - Both the number and severity of symptoms significantly improved over 24 hours for 56.8% of participants	- Time from injury and age had significant effect on symptom scores at baseline and after exertion - Participants were all relatively young - No direct comparison group
Gall, 2004a	Repeated measure cohort	14 hockey players with	**Mode and Type:** Cycle	Low-moderate steady-state exercise at 80–90	- Symptoms	- No difference in number of high	- The sample size was relatively small and

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
	comparison study of 2 exercise testing bouts within 72 hours of being asymptomatic at rest and again 5 days later	mTBI and 14 players without mTBI matched 1:1 by investigators, no report of sex of participants in sample, mean age of participants reported by cohorts	ergometer with 10 minutes of steady-state cycling, followed by high intensity intervals **Rationale:** No specific rationale provided for mode or protocol selection	rpm against a constant load of 1.5W/kg of body weight for 10 minutes. High intensity bouts: 40 seconds at 4.7W/kg with a pedaling frequency of 90–100 rpm, followed by a 20 second free pedal (30 W), and then 20 second rest period - Test continued until the participant could no longer maintain the workload	- Number of high intensity exercise bouts completed - Physiologic measures	intensity bouts completed between cohort with concussion and matched controls - No difference in blood lactate levels between the groups - No difference was found in the symptoms reported between the groups - A subgroup of the cohort with concussion (those who missed playing time as a result of the concussion) exhibited a higher heart rate in the low-moderate exercise period and exhibited a greater rise in heart rate over the time - No significant differences between the groups were observed in blood lactate levels at rest or after exertion	focused solely on athletes - Sex of participants was not reported, so it is unclear if this is generalizable across sexes
Gall, 2004b	Repeated measure cohort comparison study of 2	14 hockey players with mTBI and 14 players without	**Mode and Type:** Cycle ergometer with 10	Low-moderate steady-state exercise at 80–90 rpm against a constant load of 1.5W/kg of body	-- Physiologic measures	- No difference in HR or heart rate variability metrics between	- The sample size was relatively small and focused solely on athletes

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
	exercise testing bouts within 72 hours of being asymptomatic at rest and again 5 days later	mTBI matched 1:1 by investigators, no report of sex of participants in sample, mean age of participants reported by cohorts	minutes of steady-state cycling, followed by high intensity intervals **Rationale:** The authors noted that the protocol was designed to reflect high intensity intervals that often occur while playing ice hockey.	weight for 10 minutes. - High intensity bouts: 40 seconds at 4.7 W/kg with a pedaling frequency of 90–100 rpm, followed by a 20 second free pedal (30 W), and then 20 second rest period - Test continued until the participant could no longer maintain the workload		the cohort with concussion and matched controls - HRV metrics revealed lower RR, LF and HF power during exercise for the cohort with concussion	- Sex of participants was not reported, so it is unclear if this is generalizable across sexes
Grabowski, 2017	Retrospective case series evaluating the implementation, safety, and feasibility of multimodal impairment-based physical therapy (including vestibular therapy, manual therapy and exercise therapy for cervical and thoracic spine, and aerobic training)	25 patients (11 M/14 F) mean age of 15 years (range 12–20 years) following sport-related concussion with a mean of 41 days post-injury (range 21–228 days) prior to first visit	**Mode and Type:** Patient specific treadmill (modified Balke protocol/ Buffalo Concussion Treadmill Test) vs cycle ergometer incremental increases in bike resistance **Rationale:** The treadmill protocol was the default, with the cycle ergometer used according to patient preference and/or in the	- Treadmill: initial speed of 3.3 mph with 0% grade. Grade was increased to 2.0% at start of second minute and increased by 1% for every minute thereafter until 15% was reached. If test continued beyond that point, speed was increased by .1 miles per hour each minute until exacerbation of symptoms or exhaustion - Cycle ergometer: Cadence was maintained on an electronically braked-cycle ergometer with	- Symptoms - Symptom-free exercise duration - Maximum symptom-free heart rate - Instances of symptom exacerbation with exercise on two consecutive days	- 88% of patients reported an improvement in symptom scores after intervention, with 24% reporting symptom-free state at end of the treatment - 55% of patients who terminated exercise due to symptom exacerbation at initial session achieved a symptom-free maximal effort test by end of treatment - Mean duration of exercise was greater at the last exercise test compared to the initial baseline test	- The sample size was relatively small and the nature of the study was retrospective - 28% of the patients discontinued for reasons unrelated to safety or efficacy (e.g., non-compliance, insurance changes)—however, some showed improvement in symptom score and maximum symptom-free heart rate

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
			presence of significant vestibular symptoms in order to minimize head movement	initial resistance set at level 1 and increased by 1 level every minute until exacerbation of symptoms or exhaustion		- Two instances of minor symptom exacerbations were reported while performing cardiovascular exercise at home	
Hinds, 2016	Case series and case-control comparisons using a repeated measure design investigating exercise assessment while symptomatic and after deemed recovered	40 athletes (23 M, 17 F) ages 12–18 years (mean 15.5 years) and comparison of 30 athletes without a history of recent concussion (18 M, 12 F)	**Mode and Type:** Treadmill: Incremental progressions in treadmill grade (modified Balke protocol/ Buffalo Concussion Treadmill Test) **Rationale:** No specific rationale provided for mode, but protocol choice was noted as selected based on prior studies	- Speed of 3.3 miles per hour, 0% grade on treadmill. Grade was increased by 1% per minute for the first 15 minutes, then increased . 2 miles per hour every minute thereafter until exacerbation of symptoms or workload could not be maintained	- Physiologic measures - RPE	- Resting HR did not differ between bout while symptomatic and bout when recovered - HR was significantly lower when participants were symptomatic at the start of exercise but the relative increase in HR relative to increased intensity did not differ while symptomatic compared to when recovered - RPE was consistently rated higher for comparable work while symptomatic compared to when recovered - No differences in HR or relative change in HR or RPE with repeated administration for youth	- The timing between the first and second testing sessions relative to the time since injury were unclear, however, the results allude to most of the testing taking place in the acute phase post-recovery - Participants were all relatively young

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
						without a recent concussion	
Kozlowski, 2013	Case control comparisons for a single exercise bout comparing exercise tolerance for individuals with persistent postconcussion symptoms compared to a healthy control cohort	59 participants 34 injured (17 M, 17 F; mean age = 25.9 SD 10.9 years), 22 controls (11 M, 11 F; mean age = 23.3 SD 6.2 years)	**Mode and Type:** Treadmill Walking: Incremental progressions in treadmill grade (modified Balke protocol/ Buffalo Concussion Treadmill Test) **Rationale:** No specific rationale provided for mode or protocol selection	Constant speed of 3.3 miles per hour, starting at 0% incline. After 1 minute, fixed 2% grade increase; after 2 minutes, fixed 1% grade increase each minute until speed could not be maintained, post-mTBI symptoms returned, or max of 21 minutes was reached	- Symptoms - Exertion duration - Physiologic measures	- No difference between groups in resting heart rate or blood pressure measures - Injured group demonstrated shorter test duration, lower max HR at test termination, lower max blood pressure at test termination, and a lower achieved workload - Systolic blood pressure was the only measure to show a sex effect within the injured cohort with males having higher blood pressure throughout the testing	- Convenience sample compared to historical dataset with a widespread of ages and days since injury
Kurowski, 2017	Randomized clinical trial investigating aerobic exercise training versus a stretching control group for a 6 week program	30 adolescents (13 M, 17 F ages 12–17 years between 4 – 16 weeks post-injury with 87% reporting regular participation in an organized sport; randomization	**Mode and Type:** Cycle ergometer with incremental progressions in intensity **Rationale:** No specific rationale provided for mode or	Self-selected speed consistent with their personal Borg rate of perceived exertion of level 11 (fairly light pace) with fixed resistance at level 2, progressions of intensity occurred every five minutes with participants increasing workload by a Borg rating of 1 level until	- Patient-reported symptoms - Parent-reported perception of symptoms - Adherence to exercise program - Adverse events	- A greater rate of improvement in symptom scores was observed in the group that followed the aerobic exercise program - Adherence was lower in the aerobic training group	- The sample size was relatively small with a set of young participants with fairly high premorbid activity levels - No report of participants’ physiological responses to exertional test at the start or after the interventions

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
		was performed within stratified age and gender blocks	protocol selection	they started to experience an increase in symptoms or for a maximum of 30 minutes		- No intervention-specific adverse events	-- The exertion testing was an indirect focus of the study with the emphasis instead being on reporting on intervention results relative to symptoms at rest and adherence between the two groups
Leddy, 2010	Case series of exercise training with pre- and post-intervention exertional testing	13 participants (7M, 5F) 6 – 52 weeks post-injury, with age range of 16 – 53 years (mean = 27.9, SD 14.3 years); 6 of 12 participants were athletes	**Mode and Type:** Treadmill Walking: Incremental progressions in treadmill grade (modified Balke protocol/ Buffalo Concussion Treadmill Test) **Rationale:** No specific rationale provided for mode or protocol selection	- Constant speed of 3.3 miles per hour, starting at 0% incline. After 1 minutes, fixed 2% grade increase; after 2 minutes, fixed 1% grade increase each minute until speed could not be maintained, post-mTBI symptoms returned, or max of 21 minute was reached	- Symptoms - Exertion duration - RPE - Physiologic measures	- No unexpected adverse events were reported, however 1 subject reported a mild, temporary increase in symptoms early in the treatment phase - After treatment, participants were able to exercise longer and able to achieve higher peak HR and blood pressure during exercises without symptom exacerbations	- Relatively small sample that were in a sub-acute recovery period - V02 was estimated but not directly measured
Leddy, 2011	Case series with participants who had a recent concussion to assess retest reliability on effort and physiologic measures and a set of actors without	21 participants with concussion (11 M, 10 F), age range of 1554 (mean = 29.8, SD 14.8 years) who were an average of 33.2 weeks postinjury, 11	**Mode and Type:** Treadmill Walking: Incremental progressions in treadmill grade (modified Balke protocol/	- Constant speed of 3.3 miles per hour, starting at 0% incline. After 1 minute, fixed 2% grade increase; after 2 minute, fixed 1% grade increase each minute until	- Test-retest reliability of physiologic measures and RPE - Interrater reliability for identifying symptom exacerbation	- The protocol had good retest reliability for assessment of max HR in participants with a concussion and healthy controls (ICC of .79 and .64, respectively)	- Relatively large age range with small sample, which makes it difficult to determine if age may affect the test retest reliability -- Unclear if different subgroups (e.g., those with vestibular or oculomotor

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
	concussion to evaluate interrater reliability to determine symptom exacerbation	were athletes; 10 healthy, sedentary participants (4 M, 6 F) age range of 18 – 45 years (mean = 26.5, SD 8.2 years)	Buffalo Concussion Treadmill Test) **Rationale:** No specific rationale provided for mode, but protocol choice was noted as selected based on prior studies	speed could not be maintained, post-mTBI symptoms returned, or max of 21 minute was reached		- For max systolic blood pressure, the participants with concussion showed more variability (ICC of .37) compared to healthy controls (ICC of .90) - Max diastolic blood pressure reliability was low (ICC of .20) for participants with concussion compared to healthy controls (ICC of .50) - Reliability for RPE was relatively low (ICC of .42) compared to healthy controls (ICC of .80) - Raters achieved a sensitivity and specificity of 99% and 89%, respectively for ruling out concussion symptom exacerbation and agreed 304 of 320 observations an accuracy of 95%	impairments) may respond differently since classifications were not a comparison parameter
Manikas, 2016	Experimental study investigating the impact of exercise on symptom exacerbation and	30 patients (25 M, 5 F) between the ages of 10 and 17 years of age; participants were tested two	**Mode and Type:** Cycle ergometer-modified version of the McMaster	- After a 2 minute warm-up, the resistance on the bike was increased by 25 or 50 Watts over 3 stages, based	- Physiologic measures - RPE	- No report on HR outcomes in results - Maximum RPE was lower at Day 10	- The exertional testing was an indirect focus of the study as the emphasis was on how exertion affected neurocognitive functioning

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
	neurocognition at 2 time points (Days 2 and 10 post selfreport of symptom resolution	days and ten days after they reported resolution of symptoms; mean of 5.4 (range of 0–24) days until self-report of resolution of symptoms	All-Out Progressive Continuous Cycling Test **Rationale** "shown to be suitable for children"	on participant height. Participants were instructed to keep the rotations on the bicycle constant for 6 minutes.		compared to Day 2 - Reduction in symptoms reported on Day 10 compared to Day 2	- Limited physiologic results were available
Moore, 2016	Case series describing functional changes in adults with persistent post mTBI symptoms and disability after completing a supervised home exercise program with combination of vestibular and aerobic training	14 patients (6 M, 8 F) median age of 43 years (range 18–72) referred for vestibular rehabilitation; median time between injury and initial evaluation was 107 days (range 14–992)	**Mode and Type:** Cycle ergometer using a modified Balke protocol/ Buffalo Concussion Test **Rationale:** A cycle ergometer was used instead of a treadmill due to the likelihood of head excursion that occurs while walking or running on a treadmill and to minimize conflicting sensory stimulation; no rationale for Balke protocol was specifically cited though prior mTBI studies were cited	- Incremental increases by a factor of two units every 2 minutes until participants reported exacerbation or until they reached 60–80% of their maximum heart rate or until they reported a 17 on RPE scale indicating the perception of "very hard" exertional level	- Symptoms - Physiologic measures - RPE - Return to Work/ Study/Activity	- No report of BP, HR, oxygen saturation responses, or RPE to exertion, but these variables were used to guide home intervention program - Improvements were observed in symptom reports, function, and return to work and meaningful-activities	- No control group for comparison - Sample consisted of participants with identified vestibular impairments making it hard to know how this would generalize to patients without vestibular symptoms - Large range in age - Minimal reporting of specific exercise physiologic changes

Author	Purpose and Study Design	Sample	Protocol Exertion Mode, Type, and Rationale	Protocol Intensity and Progression Parameters	Relevant Observed Measures	Relevant Results	Pertinent Study Limitations
Slobounov, 2011	Observational cohort comparison study of brain connectivity patterns at rest and in response to a physical exertion test	17 college athletes with a recent concussion and 17 college athletes with no history of concussion	**Mode and Type:** Cycle Ergometer: 4 stages of increasing resistance **Rationale:** No specific rationale provided for mode or protocol selection	Resistance determined by YMCA stress test, 4 stages of increasing resistance, 3 min per stage, progression to next stage was determined by heart rate	- Symptoms - Brain imaging before and after biking - Physiologic measures	- Imaging identified differences in connectivity patterns at rest and in response to exertion, although no differences in HR responses to exertion were identified between the cohorts	- The exertion testing was an indirect focus of the study, with the physiologic response results being of secondary interest - Limited physiologic results were available

*M = male, F = female; HR = heart rate; RPE = Ratings of perceived exertion