Feasibility of Aerobic Exercise in the Subacute Phase of Recovery from Traumatic Brain Injury: A Case Series

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Abstract

Background and purpose: Injuries associated with traumatic brain injury (TBI) are common and can complicate rehabilitation. The objective of this study is to examine the feasibility of introducing aerobic physical exercise programs into the subacute phase of multidisciplinary rehabilitation from moderate-to-severe TBI, which includes computerized cognitive training.

Case description: Five individuals undergoing inpatient rehabilitation with moderate or severe TBIs who also have concomitant physical injuries. All of these individuals are in the subacute phase of recovery from their TBIs.

Intervention: An 8-week progressive aerobic physical exercise program. Participants were monitored to ensure that they could both adhere to and tolerate the exercise program. In addition to the physical exercise, individuals were undergoing their standard rehabilitation procedures which included cognitive training. Neuropsychological testing was performed to gain an understanding of each individuals' cognitive function.

Outcomes: Two minor adverse events were reported. Participants adhered to both aerobic exercise and cognitive training. Poor correlations were noted between heart rate reserve and ratings of perceived effort.

Discussion: Despite concomitant injuries and cognitive impairments, progressive aerobic exercise programs seem feasible and well tolerated in subacute rehabilitation from moderate-to-severe TBI. Some findings highlight the difficulty in measuring exercise intensity in this population.

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1. Introduction

Traumatic brain injury (TBI) leads to many behavioural, sensorimotor and cognitive deficits, which result in significant social, personal and economic burdens. Cognitive impairment is an important statistical predictor of return to work [1] and with a mere 40% of individuals with severe TBI returning to work within 1-year of injury [2], long-term treatments aimed at combating these deficits are critical for quality of life. Aerobic exercise, an inexpensive, easily administered and potentially long-term therapeutic intervention has been shown to have many physiological, structural and cognitive effects on the brain [3–7]. In non-injured adults, aerobic exercise appears capable of improving a variety of cognitive functions including attentional processes [8] and executive functions such as working memory and task switching [9,10]. In clinical studies improved attention, delayed memory and executive functions [11,12] have been observed in individuals with traumatic brain injury who participated in aerobic exercise. Additionally, a cardiorespiratory benefit of aerobic exercise in individuals with TBI has been shown [13,14]. However, these studies are few, with small sample sizes. A recent systematic review on aerobic exercise and cognitive recovery after TBI [15] highlighted some shortcomings inherent in these studies, including grouping together of individuals in different phases of recovery (subacute and chronic) and inadequate information on multidisciplinary rehabilitation procedures. Moreover, cognitive impairment and concomitant physical injuries may limit the participation in, and adherence to, an aerobic exercise program.

Common concomitant injuries associated with TBI include musculoskeletal injuries [16] and gait and balance impairments [17]. Apraxia and/or hypokinesia [18], pain [19] and spasticity [20] are also seen. These injuries may constitute barriers to aerobic exercise, especially in the subacute phase of injury. It is possible that the duration, intensity and frequency needed to induce an adaptive plastic response to enhance functional and cognitive recovery may not be achieved in individuals who present with serious concomitant injuries. It has been suggested that individuals with TBI have poor awareness of subjective fatigue however [21]. Assessing the feasibility of how to measure and control for these exercise parameters (frequency, duration and intensity), is therefore important

Inpatient, as well as early outpatient rehabilitation for TBI includes intensive sessions of physical therapy, occupational therapy, behavioural speech therapy and cognitive rehabilitation. This multidisciplinary approach means outcomes are unlikely to be influenced greatly by any single therapeutic input [22]. Meta-analyses on cognitive rehabilitation outcomes suggest computerized cognitive training is beneficial for improving cognitive functions such as executive function and attention [23,24] and is a common therapeutic tool in neurorehabilitation clinics [25]. Research has postulated that the combination of aerobic exercise with cognitive training may be more effective than either one alone [26]. Since fatigue [27] and apathy [28] are common symptoms in subacute TBI, the addition of aerobic exercise to traditional rehabilitation may pose challenges regarding the adherence to both programs. Should both interventions prove efficacious, it is important that individuals can participate in both.

Therefore, the development of successful aerobic exercise programs early after TBI requires the assessment of their feasibility. The aim of this case series study is to assess the feasibility of the inclusion of an 8-week progressive aerobic exercise program in addition to standard multidisciplinary rehabilitation, which includes computerized cognitive training, for moderate-to-severe TBI in the subacute phase of recovery.

2. Case description

The demographics of five individuals with moderate or severe TBIs who were undertaking inpatient rehabilitation at the time of recruitment are seen in Table 1.

A.A – The participant was a 19-year-old male who collided at high velocity with a wooden shed whilst skiing. He was wearing a helmet at the time but the impact caused the helmet to split into two. He lost consciousness immediately and upon being admitted to the hospital was awake but minimally conscious. His injury resulted in gait impairments including ataxia and apraxia. He had been an active adult prior to the injury, participating in regular sport and activity. He had undertaken the first year of undergraduate studies in computer engineering and spoke four languages.

B.B – The participant was a 56-year-old male who sustained a head injury in a motorcycle accident. He lost control of the motorcycle and was subsequently hit by a moving car. He presented with concomitant injuries of a cervical fracture at C4. He had been an active adult prior to injury participating in cycling multiple days per week. He had vocational education in mechanics.

C.C – The participant was a 34-year old male who sustained a head injury in a motor traffic accident. He fell from a motor cycle and hit the pavement with the front part of his head, breaking his helmet in two. He sustained a brachial plexus injury to the right arm, which caused severe pain as well as cervical compression myelopathy and a fractured right clavicle. He was an active adult prior to his injury participating in sport and resistance exercises multiple times per week. He worked as a computer engineer.

D.D – The participant was a 43-year-old male who sustained a head injury caused by a fall. He was found with anisocorous pupils with mydriasis of the right pupil. An urgent craniotomy on the right side was performed. He sustained no concomitant injuries as a result of his accident. He was active prior to his injury participating in sport and exercise multiple times per week.

E.E – The participant was a 32-year-old male who sustained a head injury after a collision with a motor vehicle while riding a bicycle. He presented with concomitant injuries consisting of atelectasis contusion in the left posterobasal pulmonary segments associated with mild hemothorax and fractures of the posterior costal arches of ribs 10 and 11. He was physically active prior to the injury.

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3. Intervention

3.1 Recruitment

The education and ethics committee of the participating institution approved this study. All patients signed an informed consent prior to participating in the study. The informed consent documents were left with the participant and family members overnight and family members were active in all consent processes. This manuscript has been prepared under the CARE guidelines: consensus-based clinical case reporting guideline development [29]. Participants were recruited from an acquired brain injury inpatient ward and were assessed by both a trained neuropsychologist and physiotherapist to assure they met the inclusion criteria for the study. Participants were considered eligible to participate in this study if they: i) had a diagnosis of moderate or severe TBI (3-8 or 9-13 on the Glasgow Coma Scale, respectively [30]) ii) had sufficient cognitive ability to understand written and verbal instructions (>6 on the Rancho Los Amigos Scale [31]); and iii) if they no longer displayed post-traumatic amnesia (measured by an average score of >75 on the Galveston Orientation Amnesia Scale over 3 consecutive days). Participants were excluded from the study if they had a history of a previous moderate or severe TBI, if they presented with any neurological or cardiorespiratory complications that were a contraindication to perform physical exercise, as described by the American College of Sports Medicine [32] or if they presented with aphasia, which would limit their ability to perform the cognitive assessments and study procedures. All participants began the study as inpatients and were discharged from the hospital during the 8-week intervention period. A.A, B.B and C.C returned as outpatients to continue their rehabilitation and the study whereas D.D and E.E did not live in the local area and did not come back for treatment in the outpatient clinic.

3.1.2 Description of rehabilitation procedures

All participants were undergoing standard and individualised multidisciplinary rehabilitation programs throughout the entire study period, which involved intensive 5 hours a day, 5-7 days a week of occupational therapy, physical therapy, and behavioural speech therapy. Cognitive training using a computerized cognitive training platform (Guttmann NeuroPersonal Trainer®, Barcelona, Spain) was performed by each participant at a similar frequency to the physical exercise (three times per week for one hour during the 8-week study period). The cognitive training consists of a set of computerised cognitive tasks that cover different cognitive functions (attention, memory and executive functions) and sub-functions. For a full list of sub-functions see Solana et al., (2015) [25]. A baseline neuropsychological assessment determines the cognitive training program (which tasks, at what frequency and at what difficulty level to begin) and an automated algorithm, 'Intelligent therapy assist' [33] continuously monitors and updates an individual's progress.

Measures of neuropsychological function

Participants were administered a clinical battery of neuropsychological tests by a trained neuropsychologist prior to (<1-week) the 8-week intervention period. The trail making test A [34], where the participant is instructed to connect 25 numbered dots consecutively, as quickly and accurately as possible was used as a measure of processing speed and attention. The digit span forward, digit span backward and letter/numbers tests of the Wechsler adult intelligence scale part III (WAIS [35]), a series of tests during which the participant is read a series of numbers (or numbers and letters for letters/numbers) and asked to repeat them in the same order, or backwards were undertaken and which have been asserted to measure working memory. The Rey auditory verbal learning tests (RAVLT [36]) which measures episodic memory using a word-list learning task where 15 unrelated words are verbally presented and the participant is asked to recall as many as possible was performed. Five trials are presented which give measures of immediate word span (trial 1), total acquisition (all trials) and retention (after 20 to 45-minute delay). The block design task from the WAIS was also administered which measures visual abstract processing, spatial perception and problem solving. The participant is presented with red and white blocks (with two red sides and two white) and is asked to construct replicas of designs previously presented by the examiner. Lastly, the verbal fluency task (FAS [37]) which consists of three word-naming trials where the participant has to say as many words beginning with a given letter of the alphabet (typically F A or S although in this study P M and R were used as part of the Spanish language version [38]) was administered.

3.2 Progressive aerobic exercise program

The aerobic exercise intervention took place 3 times per week for 8-weeks. An introductory session took place to introduce participants to the equipment and aerobic exercise program. Each participant's physical abilities dictated which exercise equipment was used. Two machines was available- an active/passive exercise trainer that delivered resistance for active exercising of the arm, leg or arms and legs (Motomed Muvi, RECK, Betzenweiler, Germany), and an upright cycle ergometer (Keiser M3 indoor, Fresno, CA). As an example, if the participant was non-ambulatory they initially began with the active/passive trainer, performing arm cycling only. Weekly assessments by the participant's physiotherapist assessed whether a move from active/passive arm cycling to both arm and leg cycling or to the cycle ergometer was appropriate. Decisions were based on functional capacity of the participant (e.g has the participant regained sufficient leg strength to perform active leg cycling? Or, has the participant regained ambulation and sufficient balance to ride the cycle ergometer?). The target exercise intensity zone was defined as 50-70% of heart rate reserve (HRR). The corresponding heart rate (HR) in beats per minute (BPM) was calculated using the Karvonen equation ([220-age]-resting heart rate * intended goal % of HRR + heart rate rest) and monitored continuously by a Polar A380 wrist-based photoplethysmographic heart rate monitor (Polar Electro, Kemple, Finland). Nursing staff recorded resting heart rate periodically during the early mornings, according to standard hospital protocol, and the average of the three lowest values in the three days prior to enrolment in study was recorded as pre-intervention resting heart rate. Ratings of perceived exertion using the 6-20 Borg scale [39] were taken every 15-minutes. Borg's scale of perceived exertion is a widely used rating scale with both verbal anchors and corresponding numbers whereby 6 represents "no exertion at all" and 20 represents "maximal effort". The scale is based on the physical sensations a person experiences during exercise, including increases in HR. A high correlation between the numerical anchors (times by 10) and actual heart rate during exercise has been shown [40].The target HR zones of 50-70% of HRR are said to correspond to 12-14 ("somewhat hard") on this scale [32]. Each aerobic exercise session was designed to last between 45 minutes and one hour with a 10-minute warm-up and cool-down worked into each session. Warm-up sessions consisted of light resistance exercise. The exercise protocol aimed to allow each participant to become familiar with aerobic exercise, thus initially, participants were asked to undertake exercise at their own pace and were allowed to stop at any time. Upon having completed week one, the physical therapy staff asked participants to attempt to progressively increase their intensity (HR) and the duration of each session until they reached a consistent performance in each session that comprised 25 to 35 minutes of aerobic exercise within the target HRR zone. As patient engagement in health care may lead to greater outcomes [41] physical therapy staff attempted to engage participants to play a role in increasing the resistance of the exercise by using positive language as verbal motivation and feedback. The physical therapy staff monitored the participants HR and RPE to ensure intensity was increased in a progressive manner (i.e. not abruptly). Figure 1 shows a decision diagram of the aerobic exercise program.

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3.3 Outcome measures

Feasibility was measured using the following outcomes: number of adverse events reported, adherence to the aerobic exercise program (session durations and number of session attended), time spent in HRR training zones, the correlation between RPE and HRR and adherence to the cognitive rehabilitation training program (number of sessions attended and tasks performed).

Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.00 for Macintosh, GraphPad software, La Jolla California, USA, www.graphpad.com. Pearson's correlation coefficients were calculated for the relationship between RPE and HRR. HRR was measured as the average HRR (calculated from bpm using the Karvonen equation) in the 30-seconds before and after the measurement of RPE at 15-minute intervals. Heart rate in beats per minute was recorded second-by-second and time spent in HRR training zones calculated by the amount of time (seconds) each participants' corresponding heart rate was at or above individual 50% HRR.

4 **Outcomes**

Table 2 shows the neuropsychological profile of each participant at the beginning of the intervention. Two adverse events were reported during the study. A.A complained of feelings of nausea during one session and B.B complained of feeling light-headed after one session within the first week. Throughout the study period no participant took beta-blockers or any other antiarrhythmic medications or medications that directly affect heart rate. Three participants (A.A, B.B, C.C) were being treated with benzodiazepines and antipsychotic medications, which could be associated with adverse effects on heart rate but all participants were prescribed the recommended dosages and no adverse events were reported. One participant (A.A) was taking clonidine but no side effects related to heart rate were reported.

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Table 3 presents feasibility data from the aerobic exercise program. Adherence percentages are presented as % of 15 sessions for D.D and E.E. All participants had adherence rates above 80% to the cognitive training program except D.D (73%). D.D and E.E spent 55% and 56%, respectively, of the aerobic exercise program within the target heart rate zone. B.B spent 4% of their time within the target zone, with a mean HRR of 40% over all sessions. A.A and C.C did not exercise within the target zone for any amount of time during the 8-week program. Individual mean %HRR every 15-minutes is shown in Figure 2A. RPE values for case E.E were not collected due to investigator error and therefore missing. Figure 2B-E displays mean individual plots of % HRR and RPE every 15-minutes. Pearson’s correlation coefficients show low correlation between HRR and RPE in all participants (A.A r = 0.33; B.B r = 0.5; C.C r = 0.28; D.D r = 0.17).

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5 Discussion

This case series aimed to assess the feasibility of introducing progressive aerobic exercise programs into subacute rehabilitation of moderate-to-severe TBI. Despite cognitive impairments and concomitant physical injuries, participants adhered to the exercise program with minimal adverse events. Nevertheless, just two participants exercised for more than 50% of the time within the target heart rate zones and poor correlations between HRR and perception of effort were seen.

Inpatient as well as early outpatient rehabilitation from severe TBI involves intensive multidisciplinary treatments. However, damage to frontal lobes and networks integral to drive and motivation can be problematic to the rehabilitation process [42]. Low motivation in individuals with TBI is often observed and commitment to, and perseverance in, rehabilitation can be negatively affected [43]. Fatigue [27] and apathy [28] are also common in this phase of recovery and so, aerobic exercise may be challenging to initiate and sustain. More recently, adherence to minimally supervised aerobic exercise programs within community-dwelling individuals with TBI was deemed feasible [44]. Importantly, such aerobic exercise programs may improve mood in chronic TBI [45,46]. Less is known about adherence to aerobic exercise in sub-acute rehabilitation however, and so the results from the present study suggest the addition of three, one-hour sessions of aerobic exercise per week for 8-weeks to the multidisciplinary rehabilitation schedule can be feasible.

Up to 78% of individuals with TBI may present with concomitant extracranial injuries, which have been significantly associated with long-term disability [47]. These physical barriers to aerobic exercise can also contribute to a sedentary lifestyle and result in long-term sedentary behaviour upon discharge from the hospital [48]. Therefore, the re-introduction of aerobic exercise soon after injury may be important. Indeed, aerobic exercise has been shown to improve clinical disability scores in other clinical populations [49] and so successful adherence to an early 8-week aerobic exercise program in individuals with concomitant injuries to TBI, such as loss of ambulation (A.A), cervical and clavicle and rib fractures (B.B and C.C and E.E) has the potential to improve long term disability. Nevertheless, despite adhering to both the exercise program and traditional rehabilitation, only two participants exercised for more than 50% of the time within the target intensity zones. A previous study showed that just 28% of individuals with severe TBI exercised above 50% of their heart rate reserve (HRR) during circuit class therapy [13]. The authors did not report on physical limitations of participants in that study. It is possible that the concomitant injuries sustained by the participants in this case series limited their ability to exercise at higher HR intensities. However, contributions beyond physical limitations (which dictated exercise type) may also account for this. Participants A.A and B.B performed different exercises (arm/leg cycling and static upright cycling, respectively) and neither participant exercised within the target HR training zones. The Karvonen equation, used to calculate HR training zones, uses 220-age to predict HR maximum and may be a contributing factor. The peak aerobic capacity of individuals with TBI has been reported at 65-74% of non-injured adults [50–52] and so this widely used equation may underestimate intensity zones in this population.

The possible inability of the Karvonen equation to capture true HRR in individuals who have lower peak aerobic capacity could also explain the poor correlation between HRR and RPE seen. However, participant D.D reported the same RPE value at most time points regardless of HR and so it is more likely that this individual had difficulty in accurately communicating their true perception of effort. Indeed poor awareness of subjective fatigue in individuals with TBI compared to healthy controls has previously been reported [21]. Importantly, the Borg scale is not validated in individuals with TBI and discrepancies in the meaning of the verbal anchors may exist in this population [53]. Nevertheless, RPE is the preferred method to assess intensity in individuals who take medications that affect HR or pulse [54]. This is of particular importance as if the peak aerobic capacity of individuals with TBI is reduced [50–52] and/or medications that affect resting heart rate are taken, then heart rate measures to control for the intensity of exercise may be invalid. Yet the use of RPE may also prove inaccurate [53,55]. Larger studies to assess this phenomenon in individuals in this phase of recovery and a search for optimal methods to control for exercise intensity are required.

The results from this case series should be interpreted in light of their limitations. The recording of RPE at 15-minute intervals in a small sample is a limitation. Yet implementation of RPE recordings at greater frequencies within the clinic might be impractical. The use of wrist-based photoplethysmograpghy (PPG) technology to monitor HR is also a limitation with its susceptibility to motion artifact [56]. However, this may represent a best-case scenario as the use of the gold standard chest straps may be impractical in individuals with severe TBI who present with behavioral and cognitive impairments. Additionally, by not re-measuring resting heart rate prior to each exercise session changes in resting heart rate (which dictates heart rate training zones) over the 8-week intervention period an unaccounted for.

4. Summary

The inclusion of three, one-hour sessions of aerobic exercise for 8-weeks into intensive multidisciplinary rehabilitation for moderate-to-severe TBI was feasible. Individuals tolerated the aerobic exercise well and concomitant physical injuries did not hinder their participation. Despite this feasibility, future studies are required to better understand how the intensity of exercise can be controlled in this population.

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Tables

Table 1. Demographics

Participant	**A.A**	**B.B**	**C.C**	**D.D**	**E.E**
Age	19	56	34	43	32
Gender	M	M	M	M	M
Severity of Injury (GCS)	Severe (4)	Moderate (10)	Severe (3)	Moderate (11)	Severe (5)
Pre-intervention resting HR	58	79	67	58	58
Time since injury (days)	91	24	30	51	48
PTA time (days)	78	24	18	36	38
Cause of injury	Skiing accident	Traffic accident	Traffic accident	Traffic accident	Traffic accident
Concomitant injuries / barriers to exercise	Complete loss of independent ambulation, Apraxia / ataxia	C4 vertebral fracture	Brachial plexus injury / fractured clavicle / chronic pain	n/a	Rib fractures 10/11
Pre-injury activity level	Active	Active	Active	Active	Active

GCS, Glasgow coma score; PTA, post traumatic amnesia

Table 2. Neuropsychological test scores

Participant	**A.A**		**B.B**		**C.C**		**D.D**		**E.E**	
Test										
RAVLT Short term *(verbal*	28	VS	33	M	34	VS	42	S	20	VS

memory)										
RAVLT long term *(verbal memory)*	n/a*	VS	5	M	1	M	8	S	2	VS
RAVLT retention *(verbal memory)*	n/a*	VS	12	N	9	M	12	S	5	VS
WAIS digit span forward *(short term memory)*	6	N	4	S	6	N	6	N	5	S
WAIS digit span backwards *(working memory)*	7	N	4	N	4	N	5	N	3	S
WAIS letters/numbers *(working memory)*	5	S	10	N	11	N	8	S	n/a*	VS
WAIS block design *(visual construction)*	n/a^		26	N	46	N	27	M	15	S
TMT-A *(attention)*	77	VS	84	S	56	N	31	N	57	M
FAS *(executive function)*	20	VS	n/a*	VS	20	VS	19	VS	16	VS

Left column = test score, right column = level of deficit, based on age and level of education: VS = very severe, S = severe, M = moderate, N = normal. RAVLT, Rey auditory verbal learning test; WAIS, Wechsler adult intelligence scale; TMT-A, trail making test part A; FAS, phonemic verbal fluency test. n/a*, participant unable to complete test due to severe deficit; n/a^, participant unable to complete test due to motor impairment.

Table 3. Feasibility data from the aerobic exercise and cognitive training programs

Participant	**A.A**	**B.B**	**C.C**	**D.D**	**E.E**
Aerobic exercise					
Total number of sessions	24	23	23	12	13
% adherence	100%	95%	95%	80%	87%
Mean session duration (mins)	45	47	41	45	49
Mean % HRR	33%	40%	40%	55%	56%
Mean time spent in HRR training zone (%)	0	4%	0%	55%	62%

Mean BPM	102	109	108	116	128
Mean RPE	12	13	11	12	
Cognitive training					
Total number of sessions	24	24	24	11	12
% adherence	100%	100%	100%	73%	80%
# tasks performed	363	222	252	157	234

% adherence based on 24 sessions for A.A, B.B AND C.C and on 15 sessions for D.D and E.E. HRR, heart rate reserve; BPM, beats per minute; RPE, ratings of perceived exertion.

Figure Legends

Figure 1. Flow diagram of the progressive aerobic exercise intervention

Figure 2. **A.** Individual mean %HRR at 15-minute intervals (1 minute average of HRR before and after each 15-minute mark) with standard error bars.**B-E.** Scatter plots for individual mean %HRR and mean RPE at 15-minutes intervals with Pearson's correlation coefficient values.