Physical Activity Intolerance and Cardiorespiratory Dysfunction in Patients with Moderate-to-Severe Traumatic Brain Injury

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Abstract

Moderate-to-severe traumatic brain injury (TBI) is a chronic health condition with multi-systemic effects. Survivors face significant long-term functional limitations, including physical activity intolerance and disordered sleep. Persistent cardiorespiratory dysfunction is a potentially modifiable yet often overlooked major contributor to the alarmingly high long-term morbidity and mortality rates in these patients. This narrative review was developed through systematic and non-systematic searches for research relating cardiorespiratory function to moderate-to-severe TBI. The literature reveals patients who have survived moderate-to-severe TBI have ~25–35% reduction in maximal aerobic capacity 6–18 months post-injury, resting pulmonary capacity parameters that are reduced 25–40% for weeks to years post-injury, increased sedentary behavior, and elevated risk of cardiorespiratory-related morbidity and mortality. Synthesis of data from other patient populations reveals that cardiorespiratory dysfunction is likely a consequence of ventilator-induced diaphragmatic dysfunction (VIDD), which is not currently addressed in TBI management. Thus, cardiopulmonary exercise testing should be routinely performed in this patient population and those with cardiorespiratory deficits should be further evaluated for diaphragmatic dysfunction. Lack of targeted treatment for underlying cardiorespiratory dysfunction, including VIDD, likely contributes to physical activity intolerance and poor functional outcomes in these patients. Interventional studies have demonstrated that short-term exercise training programs are effective in patients with moderate-to-severe TBI, though improvement is variable. Inspiratory muscle training is beneficial in other patient populations with diaphragmatic dysfunction, and may be valuable for patients with TBI who have been mechanically ventilated. Thus, clinicians with expertise in cardiorespiratory fitness assessment and exercise training interventions should be included in patient management for individuals with moderate-to-severe TBI.

1 Introduction

Traumatic brain injury (TBI) is a major public health crisis that affects all demographics and impacts approximately half of the world's population [1, 2]. After initial injury, TBI has significant long-term consequences, supporting its conceptualization as a chronic health condition. Among adolescents and adults who received rehabilitation for moderate-to-severe TBI, mortality rate is six times higher 13 years post-TBI, life expectancy is shortened by 6–7 years, and nearly four in ten will demonstrate a significant decline in function from the level of recovery attained 1–2 years after

injury [2–4]. Additionally, survivors of TBI face a number of other impairments, including physical activity intolerance, fatigue, emotional and behavioral changes, and disordered sleep [5, 6]. Thus, there is a clear need to address these factors, which contribute to significant morbidity and mortality in survivors [7, 8].

Cardiorespiratory dysfunction and exercise intolerance in patients with TBI have been described in the literature [9–13] but have generally not been a priority in patient management, and the long-term consequences of these issues remain largely overlooked. Cardiorespiratory dysfunction in the moderate-to-severe TBI population is rooted in a combination of physical deconditioning and changes in contractility and atrophy of the diaphragm in those who have been mechanically ventilated during the acute phase of TBI management. Patients with a history of moderate-to-severe TBI display similar cardiorespiratory changes, co-morbidities, and functional deficits to patients with known diaphragmatic dysfunction [14–17], as well as those who have received long-term ventilation [18–21]. These morbidities contribute

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Key Points

A small but growing number of studies demonstrate that patients with moderate-to-severe traumatic brain injury (TBI) commonly experience physical activity intolerance and impaired cardiorespiratory function, and have increased risk of cardiorespiratory-related co-morbidities and elevated mortality.

Maximal aerobic capacity is severely diminished (mean 24.6 mL O₂/kg/min, ~5th percentile) and submaximal cardiorespiratory responses are abnormal for weeks to years following moderate-to-severe TBI, which may be responsible for the sedentary behavior common in this population.

A few studies directly address this issue, but ventilator-induced diaphragmatic dysfunction and its sequelae are generally not addressed in patients with moderate-to-severe TBI, despite their history of mechanical ventilation during the acute phase of care.

A number of interventional studies have demonstrated that short-term exercise training programs are effective in patients with moderate-to-severe TBI, but are generally not sufficiently emphasized at any point of rehabilitation.

Synthesis of the available evidence suggests that recognition and proper management of cardiorespiratory dysfunction in patients with moderate-to-severe TBI has potential to substantially improve patient outcomes and quality of life, and long-term interventional studies are necessary to confirm this.

to various functional deficits including decreased activity tolerance and participation restrictions, which are common in the sub-acute and chronic phases of recovery from TBI. Additionally, these morbidities increase the mortality rate in this population. While the long-term health issues related to mechanical ventilation [22, 23] and extended hospital stays [24, 25] are well-documented, inpatient and long-term rehabilitation strategies for patients with TBI do not adequately target cardiorespiratory outcomes. Thus, the purpose of this narrative review is to synthesize available research regarding the contributors to and management of cardiorespiratory dysfunction following moderate-to-severe TBI.

2 Search Methodology

A systematic review was originally attempted to capture all literature on the topic relating TBI to cardiorespiratory dysfunction. The following search strategy was utilized on

PubMed, PsycINFO and CINAHL in the attempt to comprehensively identify the original research on this topic: (“traumatic brain injury” OR “TBI” OR “brain trauma” OR “head injury” OR “brain injury”) AND (dyspnea OR dyspneic OR dyspnoea OR dyspnoeic OR breathless OR breathlessness OR “short of breath” OR “shortness of breath” OR “respiratory distress” OR hypoxemia OR hypoxemic OR hypoxaemia OR hypoxaemic OR desaturation OR desaturate OR “pulse oximeter” OR “pulse oximetry” OR “oxygen saturation” OR “hemoglobin saturation” OR “haemoglobin saturation” OR “PAO₂” OR “SAO₂” OR exercise OR “physical activity” OR exertion OR deconditioned OR deconditioning OR decondition OR aerobic OR endurance OR ventilator OR breathing OR respiratory OR respiration OR inhale OR inhalation OR inspiratory OR inspiration OR diaphragm OR diaphragmatic OR pulmonary OR ventilatory OR ventilation OR VIDD OR spirometry OR spirometer OR lung OR intubation OR intubated OR intubate OR tracheotomy OR tracheostomy OR extubation OR extubate OR extubated OR diaphragm OR diaphragmatic OR spirometry OR spirometer OR cardiac OR cardiorespiratory OR cardiorespiratory OR cardiovascular).

While many results were obtained, thorough screening of titles and abstracts by both authors revealed very few relevant original research articles that specifically examined the connection between moderate-to-severe TBI and cardiorespiratory dysfunction. The relevant articles identified by this search strategy also did not fit into discrete categories. The relative dearth of literature directly relating cardiorespiratory dysfunction and moderate-to-severe TBI reflects a lack of attention to this topic, both in research settings and clinical practice. As such, the authors opted to utilize a narrative review format, which includes some literature from other (i.e., non-TBI) patient populations, and synthesize this evidence to demonstrate that persistent cardiorespiratory dysfunction is present and has significant deleterious effects in patients who survive a moderate-to-severe TBI.

3 Contributors to Physical Activity Intolerance and Cardiorespiratory Dysfunction

3.1 Hospital-Acquired Deconditioning

Patients with moderate-to-severe TBI undergo lengthy inpatient hospital and rehabilitation center stays during which they are largely physically inactive [26, 27]. Such prolonged inactivity, including bed rest and other sedentary behaviors, combined with sleep disturbances and nutritional deficits, leads to hospital-acquired deconditioning (HAD) [24, 25], which is a factor in post-hospital syndrome [28]. Catabolic changes in muscle during this time ultimately lead to an

overall decrease in physical fitness, including muscular strength and cardiorespiratory endurance [24]. The magnitude of dysfunction is often beyond that expected from immobilization itself [29], which suggests that a history of mechanical ventilation also likely exacerbates HAD.

3.2 Ventilator-Induced Diaphragmatic Dysfunction

A majority of individuals with moderate TBI and all persons with severe TBI receive mechanical ventilation as part of required life-saving standards of care [27]. It is well-established that those who undergo mechanical ventilation for > 24 h can experience lung injuries and ventilator-induced diaphragmatic dysfunction (VIDD) [22, 30]. VIDD ultimately impairs cardiorespiratory function in human and animal models [23, 31, 32]. Though VIDD has received much attention in patients undergoing critical care [33, 34], it receives little attention in the moderate-to-severe TBI population despite their prolonged mechanical ventilation. While studies examining VIDD often do not report the specific medical condition that led to mechanical ventilation, Levine's landmark study characterizing VIDD in humans includes brain dead subjects, of which presumably some were due to TBI (i.e., motor vehicle accidents) [18, 22].

VIDD is characterized by protein degradation in myofibrils of the diaphragm through the ATP-dependent ubiquitin–proteasome pathway [22]. Mechanical ventilation increases oxidative stress in the diaphragm, causing decreased protein synthesis and increased activity of proteolytic pathways, further accelerating the atrophy process [35, 36]. Animal model research has demonstrated that neuromuscular-blocking agents commonly used in the intensive care unit may also exacerbate this degradation [37], though it is unknown how this translates to mechanically ventilated humans. As few as 12–18 h of mechanical ventilation can result in significant diaphragm atrophy and contractile dysfunction, with longer durations causing more severe muscle injury [22, 38–40]. VIDD can quickly become a 'downward spiral' due to the systemic implications that result from diaphragmatic atrophy and weakness [39]. VIDD may also progress and become seemingly irreversible, causing significant cost in terms of both healthcare dollars and lives [39].

Diaphragmatic weakness and dysfunction ultimately decrease inspiratory pressure [22]. This causes significant deterioration of pulmonary function in patients with poor cardiorespiratory reserve and may lead to secondary complications, including hypoxemia, pneumonia, and prolonged dependence on a ventilator [41]. Additionally, observational studies have consistently demonstrated that diaphragmatic dysfunction is associated with various sleep disturbances [14, 15, 42], which also impact long-term quality of life. The consequences of impaired ventilatory capacity rooted in VIDD and HAD are magnified when metabolic demands

are increased beyond resting values, leading to fatigue and physical activity intolerance [16]. Therefore, unaddressed cardiorespiratory dysfunction due to unrecognized VIDD likely causes or exacerbates other common co-morbidities, contributes to poor clinical outcomes, and significantly impairs quality of life.

Prevention of VIDD would likely have a significant impact on morbidity, mortality, and cost of TBI care of critically ill individuals. Unfortunately, VIDD cannot be easily prevented in patients with moderate-to-severe TBI because mechanical ventilation is absolutely necessary in the acute stages of care. New strategies to attenuate diaphragmatic dysfunction during ventilation, such as phrenic nerve stimulation [43], may be of value in the future but are not common practice at this time.

4 Clinical Indicators of Cardiorespiratory Dysfunction in Patients with a History of Moderate-to-Severe Traumatic Brain Injury (TBI)

A summary of the evolution and sequelae of cardiorespiratory dysfunction in patients with TBI is presented in Fig. 1.

4.1 Fatigue

The chief indicator of cardiorespiratory dysfunction in patients with moderate-to-severe TBI is physical activity intolerance, which is often conflated with the broader symptom of 'fatigue'. The general symptom of 'fatigue' is prevalent in the TBI population and is generally attributed to primary central nervous system dysfunction and sleep-related issues [44–47]. However, the combination of VIDD and HAD results in cardiorespiratory dysfunction and few resources consider the relevance of cardiorespiratory dysfunction in fatigue [48]. As such, it is necessary for clinicians to differentiate this physical activity intolerance from a sense of general tiredness when considering factors related to 'fatigue' in this patient population.

4.2 Sedentary Lifestyle

Following moderate-to-severe TBI, patients often adopt a sedentary lifestyle [49], which ultimately impairs long-term health. The literature on physical activity levels following TBI is relatively scant, but a recent systematic review identified six studies on the topic, which consistently demonstrated insufficient activity for health maintenance across a wide range of post-injury timepoints [50]. Cross-sectional studies have revealed post-TBI decreases in physically demanding physical activities [51] and discontinuation of sports participation in exchange for sedentary behaviors

attributable to brain trauma, it is possible they may also be exacerbated by cardiorespiratory-related hypoxia (including nocturnal hypoxia [see Sect. 4.3]).

4.5 Infectious Disease

Chronically impaired ventilation may also substantially impair the respiratory system's defenses against infectious disease. Individuals who survive more than 1 year after moderate-to-severe TBI are 12 times more likely to die from septicemia, four times more likely to die from pneumonia, and three times more likely to die from other respiratory disorders than a matched control group from the general population [70]. This is consistent with data from acutely ill patients who received mechanical ventilation, who also have high rates of morbidity and mortality from secondary complications attributed to cardiorespiratory dysfunction [29]. Inability to generate strong inspiratory pressures due to VIDD may ultimately impair the effectiveness of coughing and other respiratory-mediated defenses, thereby raising the risk of pneumonia, similar to what has been described in patients with stroke [71].

4.6 Autonomic Nervous System Dysfunction

Patients with TBI may develop autonomic nervous system dysfunction, most commonly known as autonomic dysreflexia and dysautonomia [72]. Autonomic nervous system dysfunction ultimately results in impaired regulation of blood pressure and regional blood flow, both at rest and during exercise, and is therefore inter-related to other aspects of cardiorespiratory dysfunction. Clinical signs of autonomic dysregulation frequently include tachycardia, tachypnea, hypertension, and impaired thermoregulation [72]. Various aspects of autonomic nervous system dysfunction appear to begin immediately in the acute stages of TBI [73] and persist into the sub-acute stage [74]. There is some evidence that measurements of autonomic nervous system function during the acute stage of injury can predict long-term outcomes and mortality in patients with moderate-to-severe TBI [75–78]. Although autonomic nervous system dysfunction does appear to improve during recovery [79], it often remains present in the chronic stages [80] of TBI. Additionally, autonomic nervous system dysfunction has been demonstrated following prolonged periods of mechanical ventilation in the general patient population [81].

5 Evaluation of Cardiorespiratory Dysfunction in Patients with Moderate-to-Severe TBI

Accurate diagnosis in patients recovering from moderate-to-severe TBI may be challenging due to cognitive or behavioral issues which impair one's ability to accurately self-report symptoms indicative of cardiorespiratory dysfunction. Therefore, the presence of this pathology is likely missed during its clinical course. A thorough history, including information regarding physical activity tolerance, combined with exercise and pulmonary testing procedures is necessary to determine whether a patient with TBI has cardiorespiratory dysfunction, including HAD and/or VIDD.

Exercise testing may be especially useful in identifying cardiorespiratory dysfunction in patients with TBI, since signs and symptoms of cardiorespiratory deficits may not be readily recognizable during the sedentary or low-intensity activities in which they are normally engaged. In the presence of cardiorespiratory dysfunction, $\dot{V}O_{2peak}$, which is the highest volume of oxygen consumption ($\dot{V}O_2$) attained during high-intensity exercise testing, should be decreased. Since pre-TBI baseline data are not available for most patients, $\dot{V}O_{2peak}$ data generally should be interpreted in the context of age- and sex-specific normative reference ranges (e.g., Kaminsky et al. [82]). If diaphragmatic dysfunction is present, decreased tidal volume would be expected, which would necessitate an increased respiratory rate to meet ventilation demands [17]. Since this combination should result in increased dead space ventilation, and thus decreased gas exchange for a given minute ventilation (VE), $VE/\dot{V}O_2$ and $VE/\dot{V}CO_2$ (carbon dioxide consumption) ratios would be expected to be greater than those of a healthy population. Indeed, the relationship between VE and $\dot{V}O_2$ is disrupted in patients during peak exercise with diaphragmatic paralysis [16], and animal models suggest this is due to increased metabolic requirements for ventilation [84]. Initially, one could expect these abnormal ventilatory responses to become magnified as submaximal exercise intensity increases. However, with a diaphragmatic limitation, maximal VE would be expected to be substantially reduced [16]. With greater ventilation necessary to achieve a given $\dot{V}O_2$, increased respiratory muscle activity would be necessary at a given workload, which would therefore increase cardiovascular demand. This could theoretically increase heart rate (HR) and blood lactate at submaximal intensities. Oxyhemoglobin desaturation (i.e., pulse oximeter measurement < 92%) during exercise has not been observed in patients with unilateral or bilateral diaphragmatic paralysis [16, 85], but it is unclear whether other co-morbidities could induce this during exercise in patients with moderate-to-severe TBI.

5.1 Exercise Testing

Cardiorespiratory responses to exercise are severely compromised in the months following moderate-to-severe TBI and remain so years afterwards, as summarized in Table 1. In Table 1, we included only studies that objectively measured $\dot{V}O_2$ during exercise, and focused on patients with moderate-to-severe TBI. Studies that included patients with mild TBI as > 50% of the sample were not included. If TBI severity was not stated, it was assumed that patients who were in a post-injury coma, described as having “brain damage”, or recruited from an inpatient neurological rehabilitation center or long-term care facility had a history of moderate-to-severe TBI. For datasets that included other neurological conditions (e.g., cerebrovascular accident), only those that had a sample > 80% moderate-to-severe TBI were included. When a given research group published more than one study, attempts were made to determine if there was any overlap between samples through evaluating the methods sections (i.e., specific mentions of overlap, institutional review board protocol numbers, and data collection dates), as well as attempted personal communication with corresponding authors.

In ten studies involving 203 patients (127 men, 41 women, 35 sex not reported; mean age ~31 years) at various post-injury timepoints, the weighted mean (standard deviation) of $\dot{V}O_{2peak}$ was ~24.6 (6.2) mL O_2 /kg/min. Though a comparison of this average $\dot{V}O_{2peak}$ to normative values is difficult due to mixed-sex data (~75% men), many of the values reported would fall below the fifth percentile for healthy individuals in their respective age groups [82]. This substantial reduction in cardiorespiratory capacity equates to 65–75% of predicted [10, 11] and is consistently lower than sedentary healthy individuals in studies using a control group [12, 86]. However, there may be substantial inter-individual variation within this patient population, depending on injury severity and time since initial injury. For instance, Chin et al. [87] report the highest group mean for $\dot{V}O_{2peak}$ (37.1 mL O_2 /kg/min) of any of the included studies, and their representative figure is that of a patient who achieved a $\dot{V}O_{2peak}$ ~55 mL O_2 /kg/min [87].

In many of the studies examining aerobic capacity, respiratory exchange ratios (RERs) indicated that patients had provided sufficient effort for a valid measurement (i.e., $RER > 1.10$), and thus were not limited by other factors (e.g., motivation). However, it is striking that four studies (across two research teams) reported RER at peak exercise ≥ 1.20 [12, 86–88], with Chin et al. [87] reporting a mean of 1.35. These values exceed that expected from other factors that elevate maximal RER in healthy patients, such as diet [89], and from populations known to have poor ventilation and pulmonary gas exchange [90, 91]. It is unknown whether these high RER values reflect a combination of ventilatory

and metabolic issues in this patient population (e.g., hypercapnia due to increased buffering of hydrogen ions formed during glycolysis, altered renal acid–base balance), a mismatch between volitional exercise tolerance and cardiorespiratory capacity, dietary factors, or measurement error.

The absolute $\dot{V}O_2$ at which the anaerobic threshold occurs has been demonstrated to be reduced in patients with TBI compared with healthy controls [86]. However, it is noteworthy that the relative intensity at which anaerobic threshold occurred was lower in patients with TBI (~52% $\dot{V}O_{2peak}$) than in healthy sedentary controls (~60% $\dot{V}O_{2peak}$) [86], and a similar relative intensity (~51% $\dot{V}O_{2peak}$) was reported in a separate study without a control group [87]. As exercise intensity increases beyond the anaerobic threshold, glycolytic metabolism would be expected to substantially increase and further drive ventilation. Together, these metabolic and respiratory stressors would be expected to increase the rating of perceived exertion substantially and lead to fatigue. As such, the reduced absolute and relative intensity at which anaerobic threshold occurs in this patient population may serve as a key barrier to physical activity participation.

VE may be decreased at anaerobic threshold [86] and during maximal exercise [12, 86]. The $VE/\dot{V}O_2$ ratio may be significantly elevated in TBI patients during submaximal exercise [9], which strongly suggests compromised pulmonary function, though this is not consistent across studies [12, 86]. Impaired pulmonary function during exercise is consistent with an earlier cross-sectional study which revealed lung capacity and pulmonary function are reduced ~25–40% in patients who have recovered from TBI compared with healthy controls [9]. These pulmonary function deficits are present despite normal functional residual capacity and are not responsive to bronchodilators, which implicates respiratory muscle weakness [9]. Though the data seem convincing, this seems to be the only published report of spirometry/pulmonary function evaluation in patients with TBI without other known major respiratory complications (e.g., tracheotomy, lung resection, etc.). Given that patients with moderate-to-severe TBI are prime candidates for VIDD, pulmonary deficits at rest and exercise (i.e., decreased VE and increased $VE/\dot{V}O_2$ at submaximal intensities) and substantially decreased aerobic capacity (i.e., $\dot{V}O_{2peak}$) are likely attributable to at least some degree of unaddressed diaphragmatic dysfunction.

Existing data do seem convincing in demonstrating cardiorespiratory deficits in this patient population, but there are some limitations to be aware of. Though many of these studies exclusively examine moderate-to-severe TBI [88, 92–94], a few datasets do include a relatively small number of patients with mild TBI [12, 13, 86, 87] or non-traumatic brain injuries [10, 11, 95]. Given that patients with mild TBI are unlikely to have received mechanical ventilation or experienced long inpatient stays, these less-injured individuals

Table 1 Summary of published data regarding cardiorespiratory function in patients with a history of moderate-to-severe traumatic brain injury

Study	TBI patient characteristics ^a	Control group	$\dot{V}O_{2\text{peak}}$ (mL/kg/min) [exercise type]	Other relevant cardiorespiratory measurements
Amonette and Mossberg [86]	<i>n</i> = 19 (14 male, 5 female) Age: 28.2 (8.4) years BMI: 27.8 (5.0) kg/m ² Mild or moderate TBI patients, current or former residents in post-acute rehabilitation center 4.2 (4.3) years post-injury	19 healthy sedentary controls, age- and sex-matched	$\dot{V}O_{2\text{peak}}$: 28.2 (6.2) Control: 37.2 (6.3) <i>p</i> < 0.001 [Treadmill]	At ventilatory anaerobic threshold: Lower $\dot{V}O_2$ in TBI [14.6 (2.2)] vs. control [22.3 (4.0)], <i>p</i> < 0.001 Lower VE in TBI [29.4 (8.1)] vs. control [40.3 (10.6)], <i>p</i> = 0.001 Similar effort during test [RER = 0.9 (0.1 for each group), <i>p</i> = 0.44] At peak exercise: Significantly lower VE in TBI [81.6 (24.3)] vs. control [106.2 (26.3)], <i>p</i> = 0.005 Similar effort during test [RER = 1.2 (0.1 for each group), <i>p</i> = 0.32] Similar $\dot{V}E/\dot{V}O_2$ for TBI [35.8 (5.8)] and control [36.1 (4.0)], <i>p</i> = 0.87
Becker et al. [9]	<i>n</i> = 19 (men and women, not categorized by sex) Mean ~ 1.6 years post-injury	14 sedentary individuals without disease, similar body weight and height	Not reported	Non-significant <i>p</i> -values not reported in original text At rest: Lower vital capacity in TBI [70 (18)] vs. control [101 (16)], <i>p</i> < 0.01 Lower inspiratory capacity in TBI [77 (19)] vs. control [100 (21)], <i>p</i> < 0.05 Lower total lung capacity in TBI [78 (9)] vs. control [93 (14)], <i>p</i> < 0.05 Similar functional residual capacity in TBI [81 (15)] and control [85 (20)] During cycle ergometry exercise—lower workloads (150 kpm/min): Similar VE in TBI [22.9 (5.9)] and control [19.2 (2.3)] Similar $\dot{V}E/\dot{V}O_2$ in TBI [37.1 (12.7)] and control [33.0 (6.6)] Similar oxygen pulse in TBI [5.8 (1.3)] and control [6.4 (1.1)] During cycle ergometry exercise—higher workloads (300 kpm/min): Similar VE in TBI [33.7 (12.0)] and control [31.8 (6.9)] Greater $\dot{V}E/\dot{V}O_2$ in TBI [40.2 (13.2)] vs. control [31.5 (8.4)], <i>p</i> < 0.05 Lower oxygen pulse in TBI [7.2 (1.9)] vs. control [9.8 (2.2)]

Table 1 (continued)

Study	TBI patient characteristics ^a	Control group	$\dot{V}O_{2\text{peak}}$ (mL/kg/min) [exercise type]	Other relevant cardiorespiratory measurements
Bhambhani et al. [10]	<i>n</i> = 34 (28 male, 6 female) Medically stable, ambulatory patients in an inpatient brain injury rehabilitation facility 1.5 (1.4) years post-injury 29 patients with TBI, 7 with non-traumatic brain injuries Age: 31.8 (9.9) years GCS: 4.6 (1.4) FAM: 6.3 (1.1) <i>n</i> = 10 (4 male, 6 female) 5 mild, 4 moderate, 1 severe TBI Age: 32.9 (6.5) years 6.7 (6.8) years post-injury BMI: 23.8 (4.4) kg/m ²	N/A	22.3 (8.7) ~65% of predicted for age- and sex-matched healthy individuals [Cycle ergometer]	Peak VE: 54.5 (26.7) Peak RER: 1.04 (0.14) Peak VE/ $\dot{V}O_2$: 31.2 (4.8) Peak oxygen pulse: 12.1 (4.8) Peak HR: 141.6 (22.8) (~75% of predicted)
Chin et al. [87]	<i>n</i> = 12 (9 male, 3 female) 10 patients with TBI, 2 patients with cerebrovascular accident Age: 31.0 (6.3) years Ideal body weight: 111% (24%) Patients at inpatient post-acute brain injury rehabilitation center > 1 year post-injury	N/A	37.1 (8.2) [Treadmill]	Peak HR: 177 (7) Peak RER: 1.35 (0.1) At anaerobic threshold: $\dot{V}O_2$: 18.9 (4.1)
Hunter et al. [11]	<i>n</i> = 14 (13 male, 1 female) Age: 28.8 (2.3) years Body fat (skinfold): 19.5 (7.3%) Patients with a history of brain damage from TBI who completed physical and occupational therapy and discharged from rehabilitation center TBI-specific information not provided	N/A	2.1 (0.5) L O ₂ /min 74% (4%) of predicted [Treadmill, cycle ergometer, or mechanical stairs]	Note: actual values not provided in Hunter [11], but Bhambhani [10] extrapolated data from figures in Hunter Peak VE: 88 (24) Peak VE/ $\dot{V}O_2$: 46.3 Peak oxygen pulse: 11.1 Peak HR: 170 (18)
Jankowski and Sullivan [92]	<i>n</i> = 40 (29 male, 11 female) Age: 33 (11) years Patients at inpatient post-acute brain injury center, able to ambulate independently 2.1 (4.2) years post-injury	N/A	31.3 (2.4) [Treadmill]	Peak HR: 168 (20)
Mossberg et al. [95]	<i>n</i> = 35 individuals with TBI, 5 with cerebrovascular accident Age: 33 (11) years Patients at inpatient post-acute brain injury center, able to ambulate independently 2.1 (4.2) years post-injury	N/A	23.5 (6.6) [Treadmill]	

Table 1 (continued)

Study	TBI patient characteristics ^a	Control group	$\dot{V}O_{2peak}$ (mL/kg/min) [exercise type]	Other relevant cardiorespiratory measurements
Mossberg and Greene [88]	<i>n</i> = 15 (11 male, 4 female) Age: 28.5 (9.2) years BMI: 23.7 (4.2) kg/m ² TBI patients at post-acute inpatient rehabilitation facility, able to ambulate independently 14 patients with GCS = 3–7, 1 patient GCS = 11 ~0.8 years post-injury	N/A	21.7 (5.1) [Treadmill]	Peak HR: 167 (16) Peak VE: 60.1 (14.6) Peak RER: 1.24 (0.11)
Mossberg et al. [12]	<i>n</i> = 13 (12 male, 1 female) Age: 31.2 (7.9) years TBI patients at inpatient post-acute brain injury center, able to ambulate independently, no cardiovascular medications or known cardiovascular disease 0.9 (0.8) years post-injury 11 subjects with severe injury (GCS = 3–8), 1 moderate (GCS = 9), 1 mild (GCS = 13)	13 age- and sex-matched healthy non-disabled individuals	TBI: 27.0 (4.6) Control: 35.4 (4.3) <i>p</i> < 0.01 [Treadmill]	Lower VE in TBI [71.7 (14.7)] vs. control [105.7 (17.9)], <i>p</i> < 0.01 Lower oxygen pulse in TBI [12.0 (2.0)] vs. control [15.8 (2.2)], <i>p</i> < 0.01 Lower HR in TBI [166 (18)] vs. control [193 (9)], <i>p</i> < 0.01 Similar RER [1.22 (0.10 for each)] Similar $\dot{V}E/\dot{V}O_2$ for TBI [36.4 (3.9)] and control [34.9 (4.7)]
Mossberg et al. [13] ^b	<i>n</i> = 35 (sex unspecified) Age: 32.9 (10.7) years BMI: 27.5 (3.6) kg/m ² 30 TBI patients in post-acute phase of recovery with moderate-to-severe injury (GCS = 3–12), 5 patients with mild injury (GCS = 13–15) 3.5 years post-injury	N/A	22.3 (5.5) [Treadmill]	Patients with greater growth hormone levels had greater cardiovascular fitness parameters Peak HR: 159.4 (18.3) Peak VE: 64.8 (20.6) Peak $\dot{V}E/\dot{V}O_2$: 34.6 (7.2) Peak RER: 1.15 (0.13) Peak oxygen pulse: 11.8 (3.0)
Mossberg et al. [94]	<i>n</i> = 2 TBI patients Patient 1: 25-year-old male 0.3 years post-injury GCS = 3 Patient 2: 18-year-old female 1 year post-injury GCS = 6	N/A	Patient 1: 17.1 Patient 2: 14.6 [Treadmill]	Patient 1: Peak HR: 114 Peak VE: 44.2 Peak $\dot{V}E/\dot{V}O_2$: 24.9 Peak oxygen pulse: 10.3 Peak RER: 1.05 Patient 2: Peak HR: 172 Peak VE: 32.0 Peak $\dot{V}E/\dot{V}O_2$: 33.4 Peak oxygen pulse: 8.4 Peak RER: 1.09

Table 1 (continued)

Study	TBI patient characteristics ^a	Control group	$\dot{V}O_{2\text{peak}}$ (mL/kg/min) [exercise type]	Other relevant cardiorespiratory measurements
Mossberg and Fortini [93]	$n = 21$ (15 male, 6 female) Age: 30.1 (11.6) years TBI patients at post-acute rehabilitation center, no overt cardiovascular disease 1.3 (1.1) years post-injury 20 patients with GCS = 3–8, 1 patient with GCS = 10	N/A	21.9 (3.6) (Extrapolated data from Fig. 1 of text) [Treadmill]	6-min walk test performance was related to peak $\dot{V}O_2$

All values are reported as mean (standard deviation)

Across all studies, $\dot{V}O_{2\text{peak}}$ was 24.6 mL O_2 /kg/min. Note: only studies that included an objective measurement of maximal cardiorespiratory function during exercise (i.e., $\dot{V}O_{2\text{peak}}$) or pulmonary function (e.g., spirometry data) are included. Studies reporting functional tests (e.g., 6-min walk test) without actual cardiorespiratory data are not included. Only datasets focused on patients with moderate and/or severe TBI are included, though some studies do include patients with mild TBI

BMI body mass index, FAM Functional Assessment Measure score for locomotion, GCS Glasgow Coma Score, HR heart rate (bpm), N/A not applicable, RER respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$), TBI traumatic brain injury, VE minute ventilation (L air/min), $\dot{V}O_2$ oxygen consumption, $\dot{V}O_{2\text{peak}}$ peak oxygen consumption during exercise (mL O_2 /kg/min) unless otherwise stated, $\dot{V}CO_2$ carbon dioxide consumption

^aAvailable patient characteristics all reported at time of study, except GCS which was reported at time of injury

^bStudy data presented across three TBI groups. All values here reflect weighted average and standard deviations

are not necessarily representative of the moderate-to-severe patient population. Aside from intermixing patient populations, there is considerable variation of the duration since initial injury within many studies. Therefore, it is difficult to determine how injury severity and the recovery period ultimately influence cardiorespiratory dysfunction. Though a number of different research groups have found similar results, it must be noted that the majority of datapoints come from various studies by Mossberg et al. [12, 13, 88, 93–95, 111], and it is not known whether each paper represents a unique dataset or if there is overlap in patients between studies. Thus, there is a need for further research in examining physiologic responses to exercise testing in this patient population.

5.2 Diaphragmatic Function Evaluation

An unusually poor exercise tolerance and response to exercise training in a patient with TBI may suggest the presence of VIDD. A detailed description of the diagnosis of VIDD is beyond the scope of this article, and the American Thoracic Society/European Respiratory Society's joint statement on respiratory muscle testing provides detailed information regarding measurement of diaphragmatic function [96]. Briefly, inspiratory pressure during phrenic nerve stimulation can provide insight regarding the diaphragm's ability to generate force. While this is the gold standard technique, there are multiple logistical barriers that preclude it from being a commonly utilized procedure. Standard pulmonary function testing can provide some insight into a patient's ability to generate inspiratory pressure, though this is effort dependent and does not test the diaphragm in isolation from other respiratory muscles. Additionally, there may be value in performing pulmonary function testing in both the upright and supine positions [97]. Fluoroscopy and ultrasound can be used to determine movement of the diaphragm, as well as its length and thickness across various lung volumes [96]. Unfortunately, these diaphragmatic assessments do not appear to be routinely provided to those with TBI who receive mechanical ventilation.

5.3 Autonomic Nervous System Function

A number of different measurements have been used to evaluate autonomic nervous system status in patients with moderate-to-severe TBI, including HR variability (HRV), blood pressure variability, and baroreflex sensitivity [98]. However, these measurements are generally used for prognostic information during the acute or sub-acute stages of injury [100], rather than as a component of cardiorespiratory functional evaluation during the chronic stage. There are limited data reporting measurements of autonomic nervous system function in ambulatory survivors of moderate-to-severe TBI,

and the literature in this realm is currently limited to children and adolescents. In children, HR is greater and HRV is lower, both at rest and during exercise, 3–5 years following severe TBI [101, 102]. Similar HR and HRV results were reported in a mixed population of brain-injured adolescents (including both traumatic and non-traumatic injuries) [98].

HRV data can be relatively easy to record using a standard HR monitor: there are a multitude of different parameters used to evaluate HRV, indicative of different aspects of autonomic function [103, 104], and a variety of different procedures to collect and analyze the data [105]. Although resting and exercise measurements of HRV may provide some insight into the status of the autonomic nervous system, and potentially cardiorespiratory function, it remains unclear how to apply these data in evaluating and managing this patient population in a TBI rehabilitation setting. There is growing interest in using biofeedback to modify abnormal HRV status, based on successes in healthy populations [106]. Though much of this work has focused on patients with mild TBI (i.e., post-concussion syndrome), one recent study demonstrated a single session of HRV biofeedback was effective in increasing multiple HRV parameters in patients with a history of severe TBI [107]. Other highly relevant measurements of autonomic nervous system function, such as arterial pulse wave characteristics [99], have been studied in relation to mild TBI, but their applicability to patients with moderate-to-severe TBI remain unknown.

6 Management of Cardiorespiratory Dysfunction in Patients with Moderate-to-Severe TBI

Although impaired cardiorespiratory function and subsequent poor functional outcomes indicative of VIDD and HAD are common in patients with TBI, these issues receive limited attention from researchers and are not adequately considered in any phase of TBI patient care [44]. Management of patients with TBI initially focuses upon lifesaving care, and later aims to restore functional capabilities. Inpatient and outpatient rehabilitation generally address neurologic deficits. While some cardiorespiratory functional assessments may be performed, this is a relatively minor component of evaluation and management in this patient population. Though outpatient rehabilitation may include some physical activity to counter this deconditioning, improvement is highly variable and may be very limited, leading to poor cardiorespiratory fitness [10, 44].

It is important for clinicians not to incorrectly attribute an observation of improved physical function to an improvement in cardiorespiratory function during typical rehabilitation. For instance, patients with TBI (mean 2.1 years post-injury) who underwent rehabilitation that included

15–20 min of low-intensity aerobic exercise for three sessions per week significantly increased treadmill walking time and movement efficiency but did not improve $\dot{V}O_{2peak}$ over a mean treatment time of 17.7 weeks [95]. This demonstrates that patients who may appear to have greater function (i.e., prolonged treadmill time) following rehabilitation do not necessarily have improved cardiorespiratory function. This may be due to insufficient exercise training stimulus, such as intensity and duration of each individual training session. The observed improvements in functional outcomes are likely related to peripheral adaptations to the physical activity, including skeletal muscle metabolism, rather than improvement in cardiorespiratory capacity—an outcome seen in other patient populations undergoing exercise training [110]. Thus, these patients may remain at increased risk of various co-morbidities associated with the cardiovascular and respiratory systems, and may also be more likely to gravitate towards sedentary behaviors.

6.1 Exercise Training

There is evidence that patients with TBI can positively respond to intentional exercise training, though such targeted cardiorespiratory programming is generally not part of standard inpatient or outpatient rehabilitation [111, 112]. Indeed, patients with TBI who exercise report better general health and emotional health than patients who do not exercise [113]. Approximately 3 months of a structured exercise training program has been demonstrated to improve $\dot{V}O_{2peak}$ and decrease resting HR in patients with moderate-to-severe [11, 114, 115] and mild-to-severe TBI [87]. Studies with less structured programs have also been found to improve $\dot{V}O_{2peak}$ [92]. In addition, case series have demonstrated similar effects of post-TBI exercise training on $\dot{V}O_{2peak}$ [94] and found reductions in HR and reduced rating of perceived exertion for a given exercise intensity [116]. Exercise training has also been demonstrated to substantially increase absolute and relative $\dot{V}O_2$ at anaerobic threshold, while increasing work rate and duration at this point [87]. Improvements in these parameters should reduce fatigue, and this has been confirmed through questionnaires examining fatigue severity [87].

Although improvements in $\dot{V}O_{2peak}$ have been noted in those with low baseline values, exercise training was insufficient to restore $\dot{V}O_{2peak}$ to that of healthy individuals and did not improve ventilatory efficiency [11]. This suggests that exercise training must be viewed as a longer-term part of rehabilitation, as the full benefits cannot be achieved within 12 weeks. It also is possible that typical exercise training does not sufficiently address underlying diaphragmatic dysfunction in patients who have been mechanically ventilated. Aerobic exercise at an intensity of 70–85% of age-predicted maximal HR for 30–40 min three to four times per week is

recommended by the American Heart Association [117], and these guidelines are commonly used in the rehabilitation of HAD. These goals may be very difficult to achieve for patients with diaphragmatic weakness and respiratory insufficiency resulting from VIDD. As such, VIDD likely accelerates and exacerbates HAD in persons with moderate-to-severe TBI, intensifying physical activity intolerance and facilitating further cardiorespiratory deterioration. Therefore, targeted strategies for improving diaphragmatic function must be applied to patients with TBI following mechanical ventilation, as they are for critically ill and other patient populations who also receive mechanical ventilation [33, 34, 118].

While this paper is focused on the cardiorespiratory benefits of exercise training for patients with moderate-to-severe TBI, it must be noted that exercise training has also been demonstrated to be beneficial for improving emotional status in patients with moderate-to-severe TBI. Given the interrelationships between physical activity participation, emotional health, quality of life, and cardiorespiratory fitness in the general population and various clinical populations [119–121], it is important for clinicians to appreciate that the multifaceted benefits of exercise training may extend beyond typical indicators of exercise performance in this patient population. Even a single 30-min session of moderate or high intensity exercise can immediately reduce symptoms of depression and anxiety [122] and improve mood [123] in patients with a history of mild-to-moderate TBI. A recent systematic review found that exercise training programs can reduce depressive symptoms in the general TBI patient population [124]. Previously sedentary patients with mild-to-severe TBI may experience long-term changes in mood state within 4 weeks of beginning an exercise training program [123]. The mood-related benefits of such multi-week exercise training programs exceed those from standard neurorehabilitation alone [125].

6.2 Inspiratory Muscle Training

Targeted inspiratory muscle training during rehabilitation has been demonstrated to be effective in various patient populations with diaphragmatic dysfunction, including improved quality of life in a mixed cohort of patients who have undergone mechanical ventilation (~7–12 days) [20], and may also be valuable for patients with moderate-to-severe TBI who have received mechanical ventilation. Twelve weeks (6 weeks supervised, 6 weeks unsupervised) of physical therapy emphasizing diaphragmatic breathing and coughing, combined with strength training exercise and functional movements, has been shown to improve 1-year survival and various functional outcomes in non-TBI patients who had undergone prolonged (~50 days) mechanical ventilation [21]. Inspiratory muscle training has been

demonstrated to improve diaphragmatic function compared to sham treatment following major heart surgery [126]. Likewise, 6 weeks of inspiratory muscle training results in diaphragmatic hypertrophy and increased aerobic performance compared to sham treatment in Paralympic athletes with motor-complete spinal cord injuries at the C5–C7 level [127]. Beyond the direct effects on the diaphragm itself, inspiratory muscle training may improve blood flow to the skeletal muscles while reducing sympathetically mediated peripheral vasoconstriction [128]. This has been observed in patients with chronic heart failure, who had improved diaphragm thickness and blood flow to arm and leg muscles during exercise following 4 weeks of inspiratory muscle training [129]. Similarly, 10 weeks of inspiratory muscle training reduced dyspnea, increased exercise capacity, and improved quality of life compared with controls in patients with chronic heart failure [130]. Nocturnal desaturation during sleep has also been demonstrated to improve compared to sham treatment following 10 weeks of inspiratory muscle training in patients with chronic obstructive pulmonary disease [131].

Inspiratory muscle training may theoretically begin during weaning from the ventilator [132], though cognitive and behavioral issues in patients with TBI may make this challenging to implement. Thus, based on successes in other patient populations with exercise intolerance and sub-optimal diaphragmatic function, inspiratory muscle training may be recommended as soon as a patient with a history of TBI is capable of doing so. However, further interventional research in this population is needed.

7 Conclusion

High rates of cardiorespiratory-related morbidity and mortality [7, 8] combined with evidence for cardiorespiratory dysfunction [9, 10, 12, 13, 44, 95] indicate that cardiorespiratory health should be a priority topic of research in the moderate-to-severe TBI population. Thus, there is a need for those with expertise in exercise medicine to be part of the interdisciplinary team managing this medically complex patient population. Epidemiologic research is needed to further elucidate how cardiorespiratory health relates to long-term morbidity and mortality in patients with moderate-to-severe TBI, as has been performed in other patient populations. There is also a specific need for epidemiological studies exploring VIDD in this population, due to the commonalities with other deconditioned patient populations who have been mechanically ventilated and experienced long inpatient stays.

Cardiorespiratory fitness, including diaphragmatic dysfunction, is generally not addressed by current rehabilitation standards for the TBI population [26, 133]. Recognition of

the significance of cardiorespiratory dysfunction in moderate-to-severe TBI may result in breakthroughs in medical and rehabilitative management to ultimately reduce health-care costs, decrease complications and high mortality, and improve functional outcomes and quality of life. Likewise, healthcare providers with expertise in cardiorespiratory fitness evaluation and interventions should be an integral part of management for patients with TBI. Thus, future studies should also explore best practice precision medicine for TBI to determine if long-term targeted cardiorespiratory interventions positively impact morbidity, mortality, secondary complications, and quality of life.

Compliance with Ethical Standards

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