Review

Does aerobic exercise benefit persons with tetraplegia from spinal cord injury?

A systematic review

Stephen F. Figoni¹, David R. Dolbow², Edwin C. Crawford², Margaret L. White², Sambit Pattanaik³

¹Spinal Cord Injury/Disorders Healthcare Group (128), Tibor Rubin VA Medical Center, Long Beach, California, USA, ²Physical Therapy Program, William Carey University, Hattiesburg, Mississippi, USA, ³College of Osteopathic Medicine, William Carey University, Hattiesburg, Mississippi, USA

Context: This review synthesizes the findings of previous research studies on the cardiovascular and metabolic benefits of aerobic exercise for individuals with tetraplegia secondary to spinal cord injury. They are often less active due to muscular paralysis, sensory loss, and sympathetic nervous system dysfunction that result from injury. Consequently, these persons are at higher risk for exercise intolerance and secondary health conditions.

Objective: To evaluate the evidence concerning efficacy of aerobic exercise training for improving health and exercise performance in persons with tetraplegia from cervical injury.

Methods: The search engines PubMed and Google Scholar were used to locate published research. The final 75 papers were selected on the basis of inclusion criteria. The studies were then rank-ordered using Physiotherapy Evidence Database.

Results: Studies combining individuals with tetraplegia and paraplegia show that voluntary arm-crank training can increase mean peak power output by 33%. Functional electrical stimulation leg cycling was shown to induce higher peak cardiac output and stroke volume than arm-crank exercise. A range of peak oxygen uptake (VO_{2peak}) values have been reported (0.57–1.32 L/min). Both VO_{2peak} and cardiac output may be enhanced via increased muscle pump in the legs and venous return to the heart. Hybrid exercise (arm-crank and functional electrical stimulation leg cycling) can result in greater peak oxygen uptake and cardiovascular responses.

Conclusion: Evidence gathered from this systematic review of literature is inconclusive due to the lack of research focusing on those with tetraplegia. Higher power studies (level 1–3) are needed with the focus on those with tetraplegia.

Keywords: Tetraplegia, Spinal cord injuries, Rehabilitation, Exercise therapy

Introduction

It is well known that spinal cord injury/disorder (SCI/D) results in muscular paralysis, sensory loss, and sympathetic nervous system dysfunction, and that these impairments negatively affect body composition, mobility, and ability to exercise.^{1,2} The physical activity of the SCI population has been found to be 40% below that of the able-bodied population.³ Consequently, persons

with SCI often are less physically active and are at higher risk for many secondary health conditions including cardiometabolic/vascular disease than their able-bodied peers (Appendix 1). Figoni and Chen⁴ reviewed medical records of 178 SCI/D Veteran outpatients referred to Kinesiotherapy for exercise services. The prevalence of cardiometabolic risk factors were as follows: dyslipidemia 72%, obesity (BMI > 25 kg/m²) 67%, hypertension 62%, impaired fasting glucose or glucose tolerance (prediabetes or diabetes) 46%, and diagnosed atherosclerotic cardiovascular disease (CVD) 28%. Median 10-year CVD risk in those without CVD and age less than 80 years was calculated as 16.8%

Correspondence to: David R. Dolbow, William Carey University, 710 William Carey Parkway, Hattiesburg, MS 39401, USA; Ph: 615-513-0279. Email: ddolbow@wmcarey.edu

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/yscm.

This article has been republished with minor changes. These changes do not impact the academic content of the article.

compared to the risk if risk factors were optimized (7.5%). Groah *et al.*⁵ had also found that surviving tetraplegia for at least 25 years was associated with a 16% increase in CVD risk and five-fold increases in CVD diagnosis and stroke risk compared to non-SCI able-bodied peers. Additionally, complete SCI conferred a 44% greater risk of overall CVD compared to incomplete SCI.⁵

Tetraplegia results in greater neuromuscular impairments and immobility than those with paraplegia, resulting in lower aerobic exercise tolerance and capacity.¹ Many physiological, health, and functional benefits of exercise are evident for persons with paraplegia or heterogeneous groups with tetraplegia or paraplegia.⁶ However, given the more severe impairments of tetraplegia, it cannot be assumed that these benefits will extend to the entire population.

The primary objective of this paper is to evaluate the evidence concerning efficacy of aerobic exercise training (voluntary arm ergometry, functional electrical stimulation cycling and hybrid exercise combining the first two forms of exercise) for improving health and exercise performance in persons with tetraplegia from cervical SCI.

Methods

Search strategy for identification of studies

In order to refine the research question the authors relied on highlighting the best evidence-based rehabilitation components, i.e. participants, intervention, comparison, and outcome (PICO).⁷

The initial search for literature on this topic was conducted in September 2016 by one author. Information was initially gathered for a symposium at a health/medical conference held in November 2016. Follow-up literature searches were conducted on January 10, 2019 and March 6, 2019 by two additional authors using the same format as before to capture any relevant articles that had been published since the initial search. PubMed and Google Scholar were searched to find relevant articles. The bibliographies from the selected articles were also reviewed to locate additional useful articles. The searches were performed using the keywords and phrases “spinal cord injury AND aerobic exercise” which produced 1959 articles initially and “tetraplegia AND aerobic exercise” which produced 1605 articles initially. To narrow the search we then searched “tetraplegia AND aerobic exercise AND adult” from years 2000 to 2019 which decreased the number of articles to 1035. Titles and abstracts were screened to identify appropriate articles followed by a more in-depth review of the papers that made it through the screening process. We captured an additional 23 articles

from the reference pages of the articles that met our inclusion criteria for an overall total of 75 papers selected (Fig. 1).

Inclusion criteria

- (1) Studies involving individuals (18–65 years) with tetraplegia
- (2) Studies that included aerobic exercise (voluntary arm exercise, electrical stimulation-induced leg cycling, hybrid exercise combining voluntary arm exercise and electrical stimulation leg cycling)
- (3) Articles that included cardiovascular and metabolic measures such as peak oxygen uptake (VO_2), cardiac output, stroke volume, heart rate, blood pressure
- (4) Studies that included $\geq$ ten participants involving voluntary arm exercise
- (5) Studies that included $\geq$ four participants involving electrically induced leg cycling

Physiology Evidence Database (PEDro) scale level determinations were made by two separate authors independently and then compared. When discrepancies occurred, resolution was determined through discussion between the two scoring authors (Appendices 2 and 3).⁸

Reporting of items

The “Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols” (PRISMA-P) 2015 Checklist was used to ensure the accuracy of the systematic review process.

Results

Peak physiologic responses during aerobic exercise testing

Persons with tetraplegia are usually capable of three basic types of aerobic exercise: (a) voluntary arm exercise, (b) functional electrical stimulation leg cycle ergometry (FES-LCE) using paralyzed muscles, and (c) “hybrid exercise” (voluntary arm exercise combined with FES-LCE). The metabolic responses to any form of aerobic exercise is the fundamental stimulus for cardiovascular training, i.e. the potential for inducing adaptations in the cardiovascular system such as increasing aerobic metabolic enzyme concentrations; plasma, red blood cell, and blood volumes; venous return and end-diastolic volume; stroke volume and peak cardiac output; heart size, O_2 delivery to and extraction by active muscle tissues, arterial diameters, myocardial and skeletal muscle perfusion, and peak O_2 uptake ($\text{VO}_{2\text{peak}}$).⁹

$\text{VO}_{2\text{peak}}$ is the highest rate of oxygen consumption measured during incremental exercise. It is the most commonly reported metabolic variable during graded exercise testing. It is measured in L/min or mL/min (absolute rate) or mL/kg/min (relative to body mass),

Figure 1 PRISMA 2009 Flow Diagram.

and is the gold standard measure of aerobic/cardiorespiratory fitness. For simplicity in the clinical setting, VO_2 is often converted to metabolic equivalents (METs, multiples of the resting metabolic rate). With the general population, 1 MET is assumed to be 3.5 mL/kg/min.^{10,11} However, Collins *et al.*¹² reported that the resting metabolic rate in persons with tetraplegia is 2.7 mL/kg/min (23% < 3.5 mL/kg/min) due to their paralysis and sarcopenia.

$\text{VO}_{2\text{peak}}$ depends on the integrated ability of cardiovascular and pulmonary systems to deliver O_2 . Muscle metabolism to utilize/consume O_2 is limited primarily by the size of active muscle mass, peak cardiac output and blood flow in active muscles, hemoglobin in blood, and ability of cells to extract O_2 . “ $\text{VO}_{2\text{peak}}$ ” is used here instead of “ $\text{VO}_{2\text{maximum}}$ ” to indicate that it is the highest VO_2 measured under pathological conditions that constrain VO_2 due to limited muscle mass and autonomic dysfunction.

Evidence of benefit from exercise training Voluntary arm exercise

Tables 1–2 contain data from published research to illustrate the magnitude of physiologic responses during peak voluntary arm exercise testing. Individuals with cervical SCI (tetraplegia) performed exercise using the residual innervated muscle mass of their upper body. Studies with sample sizes ≥ 10 were selected. Note the heterogeneity of exercise modes (arm-crank ergometry, wheelchair ergometry/propulsion, handcycling), levels of SCI (C3–C8), completeness of SCI (American Spinal Injury Association Impairment Scale, AIS A–D), and training status (trained and untrained) – all factors are known to be important determinants of $\text{VO}_{2\text{peak}}$.^{13,14} Additionally, women are not well represented in the sample ($n = 8$). The average peak cardiac output in the male group (5.96 L/min) is similar to the 5.75 L/min supine resting value for 23 able-bodied (non-SCI) male and female adults

Table 1 Description of published studies of peak physiologic responses during upright arm exercise in subjects with tetraplegia.

Study	N	Sex	SCI Level	AIS	Training status	Ergometry mode	PEDro Level
Van Loan <i>et al.</i> ⁷³	13	M & F	C5-8	*	T & U	Arm-crank	5
Figoni ⁷⁴	11	M	C6-7	A	U	Arm-crank	5
Lasko-McCarthy <i>et al.</i> ⁷⁵	22	M	C5-8	A-C	U	Wheelchair	5
Hjeltnes <i>et al.</i> ¹⁷	10	M	C6-8	A-B	U	Arm-crank	2
Morrison <i>et al.</i> ⁷⁶	24	32 M, 4 F	C6-8	A-B	U	Arm-crank or wheelchair	4
Figoni <i>et al.</i> ⁷⁷	11	M & F	C5-8	A-D	U	Arm-crank	5
Janssen <i>et al.</i> ⁷⁸	34	M	C4-8	*	T & U	Wheelchair	3
Simmons <i>et al.</i> ⁷⁹	60	M & F	C3-8	A-D	U	Arm-crank	3
Total:	175						

Note: AIS: American Spinal Injury Association Impairment Scale (A-D).

SCI level: C: cervical.

Sex: M: male, F: female.

Training status: T: trained, U: untrained.

*Completeness of SCI or Frankel level were not specified.

measured by dye-dilution.¹⁵ Subjects demonstrate low peak heart rate and blood pressures compared to abled-bodied individuals (117 bpm, 97/60 mmHg). This is consistent with sympathetic dysfunction and/or insufficient active muscle mass to induce substantial cardiovascular adjustments to meet the demands of exercise. Blood pressure responses were measured on only 11 male subjects, probably reflecting the technical difficulty of brachial auscultatory sphygmomanometry during or immediately after peak upper-body exercise.

Exercise training adaptations

Researchers have investigated the effects of exercise training on many outcome measures: physiology (e.g. $\text{VO}_{2\text{peak}}$), fitness (e.g. muscular strength), health (e.g. CVD risk, morbidity, mortality), and function (e.g. mobility, physical activity). Tables 3–4 contain data from published research to illustrate the magnitude of changes in peak physiologic

responses during peak voluntary arm exercise testing following a training intervention. Individuals with cervical SCI (tetraplegia) performed 10–37 weeks of exercise training using their residual innervated upper-body muscle mass. Training studies were selected on the basis of sample sizes ≥ 10 . Initial training status was “untrained”. No peak blood pressures were reported. Statistical analyses were not possible without complete raw data. However, the mean peak power output appeared to increase by 33% without substantial changes in peak VO_2 or central hemodynamic variables. Increased muscular strength, endurance or coordination/efficiency could explain the increased power output. The apparent 9% increase in mean $\text{VO}_{2\text{peak}}$ might be associated with increased O_2 extraction by active muscles as indicated by the 24% increase in body arteriovenous O_2 difference reflecting blood shunting toward active muscle tissues. These results are consistent with the earlier suggestion from exercise testing data that exercise training at lower intensities would not be sufficient to induce cardiovascular and metabolic adaptations associated with high-level fitness due to sympathetic dysfunction and/or insufficient active muscle mass to require substantial cardiovascular adaptations to exercise training.¹⁶ (Note: All research findings cited below are statistically significant unless stated otherwise.)

Table 2 Mean peak physiologic responses during upright arm exercise testing in subjects with tetraplegia from studies listed in Table 1.

	Male		Female	
	N	Mean	N	Mean
Power (W)	185	25.5	6	16.7
O_2 uptake (L/min)	183	0.77	8	0.68
O_2 uptake (mL/kg/min)	183	10.5	8	9.37
SCI-METs	183	3.9	8	3.5
Arteriovenous O_2 difference (mL/100 mL)	183	12.0	0	*
Cardiac output (L/min)	34	5.96	0	*
Stroke volume (mL/b)	34	51	0	*
Heart rate (bpm)	81	117	0	*
Systolic/diastolic blood pressure (mmHg)	11	97/60	0	*

Note: SCI-METs: metabolic equivalents (multiples of resting metabolic rate) for persons with spinal cord injury. 1 SCI-MET = 2.7 mL/kg/min (Collins *et al.*¹²).

*not specified.

Functional electrical stimulation leg cycle ergometry (FES-LCE)

FES-LCE is the application of electrical currents through skin electrodes to induce muscle contractions of paralyzed muscle by an external stimulator/controller, thereby bypassing the central nervous system. The goal is to activate a sufficiently large muscle mass to elicit substantial acute physiological responses to

Table 3 Description of published studies of upright arm exercise training responses.

	N	Sex (n)		Age (yr)	SCI Level	AIS	Training	PEDro Level
		M	F					
McLean <i>et al.</i> ⁸⁰	14	*	*	18–55	C5-T1	A-B	Arm-crank ergometry, 3x/wk × 10 wk	2
Hjeltnes <i>et al.</i> ¹⁷	10	10	0	25 ± 2*	C6-8	A-B	Arm-crank ergometry and wheelchair propulsion, 3x/wk × 16 wk	2
Hicks <i>et al.</i> ⁸¹	11	*	*	19–65	C4-8	A-D	Arm-crank ergometry and progressive resistance exercise, 2x/wk × 37 wk	1b
Valent <i>et al.</i> ⁸²	22	18	4	18–65	C5-T1	A-D	Handcycling, 2x/wk × 10 wk	2
Total:	57	28	4					

Note: AIS: American Spinal Injury Association Impairment Scale (classes A-D).

Sex: M: male; F: female.

SCI levels: C: cervical, T: thoracic.

*not specified.

induce aerobic training adaptations that may result in health benefits.

Bilateral FES-LCE is designed to induce 200–400 muscle contractions/minute, depending on the FES-LCE system used: 4–8 muscle groups × 50 rpm cycling cadence. The typical muscle groups activated are the quadriceps, hamstrings and gluteus maximus; some systems also utilize the gastrocnemius. FES-LCE can be performed with or without voluntary upper-body exercises such as arm-cranking or rowing; these hybrid exercises will be discussed in a separate section later.

FES-LCE may activate a larger lower-body muscle mass and elicit a higher $\text{VO}_{2\text{peak}}$ compared to voluntary arm exercise, especially for persons with higher-level tetraplegia (above level C7, AIS A-B). Research has shown that peak FES-LCE power outputs in tetraplegia are low (mean 9 W) due to low efficiency, i.e. recruitment of large fast-twitch type-2 motor units.

Table 4 Mean metabolic and cardiovascular responses to upright arm exercise training in subjects with tetraplegia from studies listed in Table 3.

	N	Pre-training	Post-training	Δ	Δ%
Power (W)	54	30	40	+10	+33
O ₂ uptake (L/min)	43	1.05	1.12	+0.07	+9
O ₂ uptake (mL/kg/min)	43	16.3	17.7	+1.4	+9
SCI-METs	43	4.6	5.1	+0.5	+9
Arteriovenous O ₂ difference (mL/100 mL)	11	14.6	18.1	+3.5	+24
Cardiac output (L/min)	11	7.2	6.2	−1.0	−14
Stroke volume (mL/b)	11	74	73	−1	−1
Heart rate (bpm)	21	110	119	+9	+8

Note: SCI-METs: metabolic equivalents (multiples of resting metabolic rate) for persons with spinal cord injury. 1 SCI-MET = 2.7 mL/kg/min (Collins *et al.*¹²).

However, individuals with tetraplegia using FES-LCE have demonstrated a wide range of $\text{VO}_{2\text{peak}}$ results (0.57–1.32 L/min)^{17,18} with Figoni *et al.*¹⁹ and Janssen and Pringle²⁰ both reporting 0.72 $\text{VO}_{2\text{peak}}$ which is similar to arm-cranking at 25 W or walking at 2 mph (3–3.5 METs) by able-bodied individuals. FES-LCE has been shown to elicit higher peak cardiac output and stroke volume (higher cardiac volume-loading) than arm-crank exercise^{19–21} perhaps due to activation of peripheral venous muscle pump in the legs. See Tables 5, 6 and 7.

Baldi *et al.*²² demonstrated the prevention of gluteal muscle atrophy and hypertrophy of gluteal lean body mass compared to the non-treatment control group after 6 months of FES training. Similarly, Skold *et al.*²³ and Demchak *et al.*²⁴ demonstrated that FES-LCE training increased leg muscle volume and cross-sectional area versus non-treatment control groups.

Several years later, Warburton *et al.*⁶ identified one longitudinal study,²⁵ one post study,²⁶ twenty-four pre-post studies,^{20,21,27–49} and one prospective cohort study⁵⁰ that examined effects of other FES-assisted training programs on cardiovascular fitness and/or health in persons with SCI (not specifically tetraplegia).

Overall, Warburton *et al.*⁶ concluded the available Level 4 evidence from multiple pre-post studies using FES-LCE training have been shown to increase peak power output and VO_2 20–40%, improve cardiac function during rest and exercise, decrease vascular resistance and increase muscle blood flow at rest and during exercise, and decrease platelet aggregation and blood coagulation. Warburton and associates also found that FES-LCE training can improve musculoskeletal fitness, oxidative potential of muscle, muscle tolerance, and cardiovascular fitness when performed at least 3 days per week for 2 months.⁶

Five additional noteworthy studies include a pre-post study by Nash *et al.*⁵¹ conducted with eight tetraplegic

Table 5 Description of published studies of peak physiologic responses during FES-LCE testing in subjects with SCI.

Study	N	Sex (n)		SCI Levels	Tetra N	Para N	Frankel/AIS/C-I	Training status	PEDro Level
		M	F						
Pollock <i>et al.</i> ⁸³	11	7	4	C4-T6	7	4	Frankel A-B	FES-trained	4
Figoni <i>et al.</i> ¹⁹	17	15	2	C5-T1	17	0	Frankel A-D	untrained	5
	13	11	2	C5-T1	0	17	Frankel A-D	untrained	3
Petrofsky & Stacy ⁸⁴	8	*	*	T4-T12	0	8	Frankel A	FES-KE trained	4
Hooker <i>et al.</i> ²¹	18	*	*	C5-T1	10	8	Frankel A-C	FES-LCE trained	4
Hooker <i>et al.</i> ⁸⁵	8	*	*	C5-8	8	0	Frankel A-C	FES-LCE trained	4
Faghri <i>et al.</i> ²⁸	13	12	1	C6-T10	7	6	Frankel A-D	*	4
Krauss <i>et al.</i> ⁶⁰	8	7	1	C7-L1	1	7	*	*	4
Barstow <i>et al.</i> ²⁹	8	8	0	C5-L1	2	6	AIS A	*	4
Mutton <i>et al.</i> ⁸⁶	11	11	0	C5-L1	2	9	AIS A	untrained	2
Hjeltnes <i>et al.</i> ³⁰	5	5	0	C5-7	5	0	AIS A-B	FES-LCE trained	4
Mohr <i>et al.</i> ³¹	10	8	2	C6, T4	6	2	Frankel A	untrained	4
Gurney <i>et al.</i> ⁶¹	6	6	0	C4-T4	2	4	*	untrained	2
Chilibeck <i>et al.</i> ⁶⁷	5	4	1	*	*	*	AIS A-B	untrained	4
Bhambhani <i>et al.</i> ⁸⁷	7	5	2	C5-T12	3	4	AIS A-B	N = 6 FES-trained	2
Barstow <i>et al.</i> ⁸⁸	8	8	0	T4-L1	0	8	AIS A	*	4
Gerrits <i>et al.</i> ³²	9	9	0	C4-T8	4	5	AIS A	*	4
Kjaer <i>et al.</i> ⁸⁹	10	8	2	C6-T4	6	4	AIS A-B	untrained	2
Holme <i>et al.</i> ¹⁸	7	6	1	C5-T7	3	4	Frankel A	FES-LCE trained	5
Hopman <i>et al.</i> ³³	9	9	0	T4-T12	0	9	AIS A	untrained	2
Raymond <i>et al.</i> ⁹⁰	6	6	0	T5-9	0	6	AIS A	FES-LCE trained	2
Skold <i>et al.</i> ²³	8	8	0	*	*	*	AIS A-B	*	2
Verellen <i>et al.</i> ⁹¹	5	5	0	C7-T12	1	4	AIS A-C	FES-LCE/rowing trained	4
Berry <i>et al.</i> ³⁵	12	10	2	T3-T12	0	12	AIS A	untrained	4
Fornusek & Davis ⁹²	9	7	2	T4-T10	0	9	AIS A	FES-LCE trained	4
Zbogor <i>et al.</i> ³⁶	4	0	4	C4-T7	2	2	AIS A-C	*	4
Janssen & Pringle ²⁰	12	12	0	C4-T11	6	6	C & I	FES-LCE trained	4
Griffin <i>et al.</i> ³⁷	18	13	5	C4-T7	8	10	5 C & 13 I	*	4
Kahn <i>et al.</i> ³⁸	10	*	*	C4-T10	*	*	*	untrained	4
Berry <i>et al.</i> ²⁵	11	9	2	T3-9	0	11	AIS A	FES-LCE trained	4
Hakansson & Hull ²⁶	11	8	3	T4-T12	0	11	AIS A	untrained	5
Fornusek <i>et al.</i> ⁹³	8	?	?	C7-T11	?	?	AIS A & C	untrained	4
Thrasher <i>et al.</i> ⁹⁴	11	8	3	C5-T12	3	8	C & I	untrained	4
Hasnan <i>et al.</i> ⁹⁵	9	9	0	C6-T12	*	*	AIS A-C	FES-LCE trained	4
Mazzoleni <i>et al.</i> ⁹⁶	5	4	1	C7-T12	2	3	AIS A-C	*	4
Sadowsky <i>et al.</i> ⁵⁴	25	22	3	*	13	12	AIS A-C	FES-LCE trained	3
Kuhn <i>et al.</i> ⁹⁷	30	30	0	C4-L5	13	17	AIS A-D	untrained	4
Johnston <i>et al.</i> ^{98**}	15	14	3	C3-T6	8	9	AIS A-B	untrained	4
Gorgey <i>et al.</i> ⁹⁹	10	9	1	C5-T10	8	2	AIS A-B	untrained	4
Total:	405	310	45	—	148	221	—	—	

Note: AIS: American Spinal Injury Association Impairment Scale (classes A–C).

SCI Levels: C: cervical, T: thoracic, L: lumbar.

C-I: complete or incomplete SCI.

FCE-LCE: functional electrical stimulation leg cycle ergometry.

FES-KE: functional electrical stimulation knee extension training.

Frankel: The Frankel Grade classification (grades A–E) provides an assessment of spinal cord function before the development of the current AIS system.

Sex: M: male; F: female.

*not specified.

**no metabolic/cardiovascular data.

men (C5-6, AIS A) and no control groups. Subjects trained one month with FES knee extension progressive resistance exercise followed by six months of FES-LCE. Subjects increased their mean left ventricular (LV) mass by 33% and septal wall thickness by 18–20%. Therefore, LV volume- and pressure-loading during FES exercise reversed left ventricular atrophy.

A second study by Nash *et al.*⁵² compared blood flow responses in ten trained tetraplegic men and ten sedentary

tetraplegic men (C5-7, AIS A–B, mean age 27). Subjects trained with FES-LCE 0.4–7.0 years. Before and after training, supine resting Doppler blood flow measurements were made at the common femoral artery during an occlusion test. The trained group increased their average peak systolic flow velocity by 15%, cross-sectional area by 30% and inflow volume by 51%.

Mohr *et al.*⁵³ trained ten SCI subjects, including six with C6 tetraplegia (mean age 35, mean time since

Table 6 Mean $\pm$ SD peak physiologic responses during FCE-LCE testing in subjects with tetraplegia from five studies listed in Table 5.

N	Figoni <i>et al.</i> ¹⁹ 17	Hooker <i>et al.</i> ²¹ 8	Hjeltnes <i>et al.</i> ¹⁷ 5	Holme <i>et al.</i> ¹⁸ 3	Janssen & Pringle ²⁰ 6	n
Power Output, W	9 $\pm$ 7	2.3 $\pm$ 1.7	6	*	5.6 $\pm$ 2.5	36
O ₂ uptake, L/min	0.72 $\pm$ 0.19	0.66 $\pm$ 0.06	0.57	1.32 $\pm$ 0.1	0.72 $\pm$ 0.13	39
O ₂ uptake, mL/kg/min	10.6	8.9	7.5	8.8 $\pm$ 0.7	*	33
SCI-METs ^a	3.9	3.3	2.8	3.2 $\pm$ 0.2	*	33
Arteriovenous O ₂ difference, mL/100 ml	10.2 $\pm$ 2.3	8.8 $\pm$ 0.8	*	*	8.4	31
Cardiac output, L/min	7.3 $\pm$ 1.5	7.6 $\pm$ 0.6	*	*	8.5 $\pm$ 2.1	31
Stroke volume, mL/b	83 $\pm$ 16	89 $\pm$ 8	*	*	88 $\pm$ 24	31
Heart rate, bpm	89 $\pm$ 18	88 $\pm$ 6	118	111 $\pm$ 16	115 $\pm$ 25	39
Systolic blood pressure, mmHg ^b	103 $\pm$ 19	*	100	*	*	22
Diastolic blood pressure, mmHg ^b	68 $\pm$ 15	*	*	*	*	17
Mean arterial blood pressure, mmHg ^c	80	68 $\pm$ 4	*	*	*	25
Total peripheral vascular resistance, mmHg/ L/min ^c	10.9	9.1 $\pm$ 0.2	*	*	*	25

Note: FCE-LCE: functional electrical stimulation leg cycle ergometry.

^aSCI-MET: metabolic equivalents (multiples of resting metabolic rate) for persons with spinal cord injury. 1 SCI-MET = 2.7 ml/kg/min (Collins *et al.*¹²).

^bbased on Figoni *et al.*¹⁹ and Hjeltnes *et al.*¹⁷

^cbased on Figoni *et al.*¹⁹ and Hooker *et al.*²¹

*not specified.

SCI 12 yr), using FES-LCE 3x/wk, 30 min/day for one year. They noted increased insulin sensitivity and GLUT 4 concentration (glucose transporter type 4, the insulin-regulated glucose transporter found primarily in adipose tissues and striated muscle).

Table 7 Summary of data from the only study containing metabolic and cardiovascular responses to FES-LCE training of subjects with tetraplegia (Hjeltnes *et al.*¹⁷).

	N	Pre-training	Post-training	Δ	$\Delta\%$
Power (W)	5	6.0	22.4	16.4	273
O ₂ uptake (L/min)	5	0.57	0.97	0.40	71
O ₂ uptake (mL/kg/min)	5	7.5	12.8	5.3	71
SCI-METs ^a	5	2.8	4.8	2.0	71
Arteriovenous O ₂ difference (mL/100 mL)	*	*	*	*	*
Cardiac output (L/min)	*	*	*	*	*
Stroke volume (mL/b)	*	*	*	*	*
Heart rate (bpm)	5	118	*	*	*
(estimated from graph)					
Systolic blood pressure, mmHg ^b	5	100	*	*	*
Diastolic blood pressure, mmHg ^b	*	*	*	*	*
Mean arterial pressure, mmHg ^c	*	*	*	*	*
Total peripheral resistance, mmHg/L/min ^c	*	*	*	*	*

Note: FCE-LCE: functional electrical stimulation leg cycle ergometry.

^aSCI-METs: metabolic equivalents (multiples of resting metabolic rate) for persons with spinal cord injury; 1 SCI-MET = 2.7 mL/kg/min (Collins *et al.*¹²).

^bestimated from graph.

Sadowsky *et al.*⁵⁴ conducted a nonrandomized retrospective cross-sectional study in which they compared training effects of 25 SCI subjects (including 13 with tetraplegia in a training group) to 20 SCI subjects (including 15 with tetraplegia in a “standard of care” control group). Subjects’ with tetraplegia levels of SCI were C5-7, AIS A-C, mean age 36, 84% male. Training involved FES-LCE 45–60 min/session, 3x/wk, for an average of 29 months plus other undefined activities in “activity-based restorative therapy”,⁵⁵ a potential major confounder. From the baseline measures the FES-LCE-trained group showed a 17% increase in ASIA sensory and motor scores, 23% increase in ASIA motor scores, 36% increase in quadriceps mass, 44% decrease in fat mass, 30/35% increase in quadriceps/hamstring strength, decreased quadriceps spasticity and baclofen use, increased Functional Independence Measure transfer, bowel and bladder scores, increased SF-36 physical functioning score and decreased role limitations due to physical problems score; decreased total cholesterol, LDL, and triglycerides; and increased blood urea nitrogen (BUN) and creatinine indicating improved renal function. It is unknown how much of the changes were due to FES-LCE or other concurrent activities.

Dolbow *et al.*⁵⁶ conducted a one-group, pre–post-training study with no controls with 11 SCI Veterans including nine with C4-7 tetraplegia, AIS A-C, mean age 40 yr. FES-LCE training was home-based and utilized the Restorative Therapies RT300 for 40–60 min/session, 3x/wk for 8 wk. Outcome measurements

included the World Health Organization Quality of Life Assessment short version questionnaire. Results included a 12% increase in physical quality of life score (physical health, work capacity, comfort) and a 9% increase in environmental quality of life (physical safety, freedom, and comfort in home) with no significant changes in psychosocial test items.

Hybrid exercise: voluntary arm exercise + FES-LCE

“Hybrid exercise” consists of concurrent voluntary arm + FES leg exercise including FES-LCE + arm-cranking, FES- rowing, and FES-assisted gait.^{1,53,54,57,58} The objective of hybrid exercise is to engage a larger active muscle mass than either FES-leg or voluntary arm exercise alone. The objectives of hybrid exercise are to enable greater acute metabolic and cardiovascular responses, training adaptations, and potential health benefits. Tables 8 and 9 report peak physiologic responses during hybrid exercise in individuals with SCI. Figoni *et al.*⁵⁹ demonstrated that, when untrained persons with tetraplegia performed concurrent FES-LCE and graded arm-cranking to maximal effort, peak values of VO₂, HR, stroke volume and cardiac output increased significantly by 35, 46, 26, and 18%, respectively.

Warburton *et al.*⁶ identified six pre–post studies that examined the effects of hybrid (FES-LCE + arm) training on cardiovascular fitness in persons with SCI, not specifically tetraplegia.^{60–65} Warburton and colleagues

Table 9 Mean ± SD peak physiologic responses during hybrid exercise testing in subjects with tetraplegia/paresis from two studies listed in Table 8.

	Hooker <i>et al.</i> ⁸⁴
Exercise modes	FES-LCE + ACE
N	8
Power output, W	22 ± 57
O ₂ uptake, L/min	1.02 ± 0.06
O ₂ uptake, mL/kg/min	13.8
SCI-METs ^a	5.1
Arteriovenous O ₂ difference, mL/100 ml	11.2 ± 0.8
Cardiac output, L/min	9.4 ± 0.7
Stroke volume, mL/b	80 ± 1
Heart rate, bpm	117 ± 3
Systolic blood pressure, mmHg	*
Diastolic blood pressure, mmHg	*
Mean arterial pressure, mmHg	71 ± 6 ^b
Total peripheral resistance, mmHg/L/min	7.2 ± 0.6 ^b

Note: ACE: arm-crank ergometry.

FES-LCE: functional electrical stimulation leg cycle ergometry.

*not specified.

^aSCI-MET: metabolic equivalents (multiples of resting metabolic rate) for persons with spinal cord injury; 1 SCI-MET = 2.7 mL/kg/min (Collins *et al.*¹²).

^bn = 5.

summarized the strength of the scientific evidence for health benefits of hybrid exercise reporting level 4 evidence that hybrid exercise increases peak power output and VO₂, and improves exercise cardiac function in those with SCI, including those with tetraplegia.^{60–65} Additionally, they found level 2 evidence that FES

Table 8 Description of published studies of peak physiologic responses during hybrid exercise testing in subjects with SCI.

Study	N	Sex (n)		Levels	Tetra	Para	Frankel/AIS, C/I	Training status	PEDro Level
		M	F						
Edwards & Marsolais ¹⁰⁰	4	4	0	T6-11	0	4	AIS A	*	5
Hooker <i>et al.</i> ⁸⁵	8	7	1	C5-8	8	0	Frankel A-C	FES-LCE trained	5
Laskin <i>et al.</i> ¹⁰¹	8	7	1	C6-T6	6	2	*	*	5
Figoni <i>et al.</i> ⁵⁹	14	10	4	C5-T1	14	0	*	FES-LCE trained	4
Raymond <i>et al.</i> ¹⁰²	7	5	2	T4-12	0	7	*	FES-LCE trained	5
Raymond <i>et al.</i> ¹⁰³	10	10	0	T5-12	0	10	*	FES-LCE trained	5
Weiss <i>et al.</i> ¹⁰⁴	8	7	1	C6-T6	6	2	AIS A-C	FES-LCE trained	4
Wheeler <i>et al.</i> ⁴²	5	*	*	T4-12	1	4	AIS A-C	some FES trained	4
Heesterbeek <i>et al.</i> ¹⁰⁵	10	9	1	T2-12	0	10	AIS A-C	AE trained, FES-LCE untrained	4
Brurok <i>et al.</i> ⁶⁵	6	6	0	T5-9	1	5	AIS A	untrained	4
Paulson <i>et al.</i> ¹⁰⁶	5	4	1	T5-6	0	5	AIS A-B	FES-LCE trained	5
Taylor <i>et al.</i> ¹⁰⁷	14	13	1	T3-11	0	5	AIS A	*	4
Bakkum <i>et al.</i> ¹⁰⁸	10	10	0	C3-T10	5	5	AIS A-C	*	4
Bakkum <i>et al.</i> ¹⁰⁹	10	10	0	C3-T10	4	6	AIS A-C	untrained	4
Draghici <i>et al.</i> ¹¹⁰	6	5	1	C6-T4	1	5	AIS A	FES-rowing	2
Total:	105	88	10	—	34	59	—	—	—

Note: AIS: American Spinal Injury Association Impairment Scale (classes A-C).

C/I: complete or incomplete SCI.

Frankel: The Frankel Grade classification (grades A–E) provides an assessment of spinal cord function before the development of the current AIS system.

SCI levels: C: cervical, T: thoracic, L: lumbar.

Sex: M: male; F: female.

*not specified.

gait training increases peak metabolic and cardiorespiratory responses in tetraplegia.⁶⁴

Metabolic and cardiovascular risk factors in SCI
Glucose homeostasis in SCI

Warburton *et al.*⁶ summarized the strength of the scientific evidence for metabolic and cardiovascular benefits of hybrid exercise reporting that a minimum of 30 min of exercise 3 times per week can achieve health benefits. Specifically, they reported level 1b (very strong) evidence from one RCT⁶⁶ and five Level 4 studies that combined both arm-cranking and FES-LCE, and FES-rowing training to improve glucose homeostasis, i.e. decreased insulin sensitivity and insulin resistance, and/or improved glucose tolerance.^{37,47,53,67,68} Additionally, Warburton and associates reported that there is level 4 evidence from multiple pre-post studies that improvements in glucose homeostasis are clinically significant for prevention and/or treatment of type II diabetes.⁶

Cardiovascular fitness and disease risk factor management in SCI

Table 10 highlights reports of cardiovascular fitness and disease risk factor management in SCI. While an optimal training program for changes in lipid lipoprotein profile remains to be determined aerobic exercise

intensity of 70% of HR_{reserve} on most days of the week appears to be a good general recommendation for improving lipid lipoprotein profile. Preliminary Level 4 data also indicate that FES training (3 hr/wk × 14 wk) may improve lipid lipoprotein profiles.

Discussion

The original question of this paper was “Does aerobic exercise benefit persons with tetraplegia resulting from SCI?” Evidence gathered from this systematic review of literature is inconclusive but rather indicates a probability that persons with tetraplegia can benefit from aerobic exercise. The strength of the experimental designs in much of the literature is weak increasing the chances of uncontrolled confounding variables influencing the results. Experimental design deficiencies include small sample sizes, mixed injury levels and completeness of SCI, varied training interventions (modes, training durations), and the lack of randomized controlled trials.

Almost all of the studies tested/trained individuals with paraplegia or mixed groups of individuals with paraplegia and tetraplegia without providing separate results for those with tetraplegia. Only one study reported pre- and post-training data in individuals with tetraplegia, and those data were only power output and VO₂ responses – no cardiovascular data.¹⁷ Although peak power output and VO₂ uptake improved with FES-LCE training, both remained low, 22.4 W and 0.97 L/min, respectively, which is equivalent to 2.8 SCI-METS.¹⁷ This suggests that exercise training at this and lower intensities may not be sufficient to induce cardiovascular and metabolic adaptations associated with high-level fitness or wellness.

Two additional training studies have involved the effects of wheelchair rugby training in male tetraplegic athletes. Currie *et al.*⁶⁹ tested 8 trained Paralympic wheelchair rugby athletes (mean age 34 years, C5-7, AIS A-B). Resting echocardiographic data revealed normal diastolic function but low systolic function (low cardiac output, stroke volume, heart rate, and blood pressure), presumably from chronic low cardiac volume- and pressure-loading and myocardial deconditioning. Gorla *et al.*⁷⁰ also tested body composition of tetraplegic wheelchair rugby athletes (mean age 27 years, unspecified SCI levels, AIS A-C) before and after an average of 8 months (3–11 months) of rugby training 4 sessions/week. Training consisted of aerobic and anaerobic activities, and technical and tactical aspects of rugby. Subjects decreased their mean % fat mass by 13% and increased their ulnar bone mineral content and forearm fat-free (muscle) mass by 7% and 11%, respectively.

Table 10 Research on cardiovascular fitness and disease risk factor management in SCI.

Cardiovascular fitness	
Parameter	Level 4 Evidence (References)
Increased peak exercise tolerance	Pollack <i>et al.</i> ; ⁸³ Hooker <i>et al.</i> ; ²¹ Barstow <i>et al.</i> ; ²⁹ Mohr <i>et al.</i> ; ³¹ Wheeler <i>et al.</i> ; ⁴² Thijssen <i>et al.</i> ⁶²
Increased VO _{2peak}	Pollack <i>et al.</i> ; ⁸³ Hooker <i>et al.</i> ; ²¹ Barstow <i>et al.</i> ; ²⁹ Hjeltnes <i>et al.</i> ; ¹⁷ Mohr <i>et al.</i> ; ³¹ Wheeler <i>et al.</i> ; ⁴² Thijssen <i>et al.</i> ⁶²
Increased peak cardiac output	Hooker <i>et al.</i> ²¹
Decreased submaximal exercise HR	Faghri <i>et al.</i> ²⁸
Increased peak stroke volume	
Decreased peak total peripheral vascular resistance	
Increased peak power output	Faghri <i>et al.</i> ; ²⁸ Hooker <i>et al.</i> ; ²¹ Thijssen <i>et al.</i> ⁶²
Increased peak oxidative metabolic cellular adaptations	Mohr <i>et al.</i> ; ³¹ Crameri <i>et al.</i> ; ¹¹¹ Crameri <i>et al.</i> ³⁴
Lipid profile	
Risk factor	Level 4 Evidence (Reference)
Decreased LDL cholesterol	Solomonow <i>et al.</i> ⁴¹
Decreased total cholesterol	

A systematic review of literature by Hamzaid & Davis⁷¹ concluded that insufficient evidence existed to document health/fitness benefits of FES exercise for persons with SCI (not specifically tetraplegia). Cited reasons included lack of consistency of approach (varying experimental designs and FES instrumentation; frequency, intensity, and duration of training programs); small group sample sizes ($N = 5-10$, predominantly younger males), and lack of randomization and control of extraneous variables.

The lack of health/fitness benefits after FES exercise may indicate that VO_{2peak} is limited more by peripheral factors (active muscle mass and peripheral blood flow) than by central cardiac reserve which was not exhausted by arm-cranking alone. Higher training intensities and volumes during hybrid exercise training should enable higher peak fitness, function and health outcomes.

One additional factor to consider is the pre-training aerobic capacity which is typically associated with the level of injury and completeness of injury in those with SCI. Swain and Franklin's⁷² literature review supported the presumption that the higher the level of injury the less active muscle mass available to do work, which in turn results in lower potential to develop cardiovascular fitness.

Conclusion

In conclusion, the literature is lacking on the primary point of training efficacy, especially data involving implications for cardiovascular and metabolic benefits of FES-LCE for individuals with tetraplegia secondary to SCI. However, the existing evidence indicates that the greatest improvements in cardiovascular exercise performance (peak power output, VO_2 , and METs) are likely to occur with 30–45 min of a FES-LCE regimen at a frequency of three or more times per week for 8–12 weeks as seen by several Level 4 pre-post studies (Tables 5 and 6) and a few level 2 nonrandomized studies (Table 7). These benefits can be maintained with moderate intensity training 3 days/week as seen by the previous Systematic Review on this topic.⁶ While many of the hybrid studies have promising results, higher power studies (i.e. Level 1–3) need to be performed in order to more directly compare or contrast the results with FES-LCE alone. Additionally, studies regarding the effects of FES-LCE on hyperlipidemia are also lacking.

Acknowledgements

This paper was adapted from a presentation by one of the authors at an Annual International Conference, Orlando, FL in November 2016.

Disclaimer statements

Conflicts of interest The authors report no conflicts of interest.

Ethics approval. None.

Disclosures. None.

References

- Figoni SF. Exercise responses and quadriplegia. *Med Sci Sports Exerc* 1993;25:433–41.
- Gorgey AS, Dolbow DR, Dolbow JD, Gater DR. Effects of spinal cord injury on body composition and metabolic profile-Part I. *J Spinal Cord Med* Nov 2014;37(6):693–702.
- van den Berg-Emons RJ, Bussmann JB, Stam HJ. Accelerometry-based activity spectrum in persons with chronic physical conditions. *Arch Phys Med Rehabil* 2010;91:1856–61.
- Figoni SF, Chen LK. Cardiovascular characteristics of SCI/D outpatients referred to a Kinesiotherapy wellness exercise program. *Clin Kinesiol* 2015;69:11–20.
- Groah SL, Weitzkamp D, Sett P P, Soni B, Savic G. Relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. *Spinal Cord* 2001;39:310–7.
- Warburton DER, Krassioukov A, Sproule S, Eng JJ, et al. Cardiovascular health and exercise following spinal cord injury. In: JJ Eng, (ed.) *Spinal Cord Injury Rehabilitation Evidence*. version 5.0. Vancouver, BC, Canada; 2014. p. 1–48.
- Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice*. 3rd ed. Philadelphia (PA): F. A. Davis Company; Pages 9–11, 2015a.
- Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice*. 3rd ed. Philadelphia (PA): F. A. Davis Company; Pages 368–9, 2015b.
- Hulke SM, Phatak MS, Vaidya YP. Cardiorespiratory response to aerobic exercise programs with different intensity: 20 weeks longitudinal study. *J Res Med Sci* Jul 2012;17(7):649–655.
- McArdle WD, Katch FI, Katch VL. *Exercise Physiology: Nutrition, Energy, and Human Performance*. 8th ed. Baltimore (MD): Wolters Kluwer Health/ Lippincott Williams & Wilkins; Page 200, 2015.
- Jette M, Sidney K, Blumchen G. Metabolic equivalents (METs) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol* 1990;13:555–65f.
- Collins EG, Gater D, Kiratli J, Butler J, Hanson K, Langbein WE. Energy cost of physical activities in persons with spinal cord injury. *Med Sci Sports Exerc* 2010;42:691–700.
- Niewland W, Berkhuisen MA, Landsman MLJ, Lie KI, Rispen P. Training effects on peak VO_2 , specific of the mode of movement, in rehabilitation of patients with coronary artery disease. *Int J Sports Med* 1998;19(5):358–363.
- Martin D, O'Kroy J. Effects of acute hypoxia on VO_2 max of trained and untrained subjects. *J Sports Sciences* 1993;11(1):37–42.
- Bruce TA, Shillingford JP. The normal resting cardiac output: serial determinations by a dye dilution method. *Br Heart J* 1962;24:69–75.
- Nightingale TE, Metcalfe RS, Niels B, Vollaard NB, Bilzon JL. Exercise guidelines to promote cardiometabolic health in spinal cord injured humans: time to raise the intensity? *Arch Phys Med Rehabil* 2017;98(8):1693–1704.
- Hjeltnes N, Wallberg-Henriksson H. Improved work capacity but unchanged peak oxygen uptake during primary rehabilitation in tetraplegic patients. *Spinal Cord* 1998;36:691–8.
- Holme E, Mohr T, Kjaer M, Nielsen B. Temperature responses to electrically induced cycling in spinal cord injured persons. *Med Sci Sports Exerc* 2001;33:431–5.
- Figoni SF, et al. Physiologic responses of paraplegics and quadriplegics to passive and active leg cycle ergometry. *J Am Paraplegia Soc* 1990b;13:33–9.

- 20 Janssen TW, Pringle DD. Effects of modified electrical stimulation-induced leg cycle ergometer training for individuals with spinal cord injury. *J Rehabil Res Dev* 2008; 45:819–30.
- 21 Hooker SP, Figoni SF, Rodgers MM, Glaser GM, Mathews T, Suryaprasad AG, Gupta SC. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. *Arch Phys Med Rehabil* 1992a;73:470–6.
- 22 Baldi JC, Jackson RD, Moraille R, Mysiw WJ. Muscle atrophy is prevented in patients with acute spinal cord injury using functional electrical stimulation. *Spinal Cord* 1998;36:463–9.
- 23 Sköld C, Lönn L, Harms-Ringdahl K, Hultling C, Levi R, Nash M, Seiger A. Effects of functional electrical stimulation training for six months on body composition and spasticity in motor complete tetraplegic spinal cord-injured individuals. *J Rehabil Med* 2002;34:25–32.
- 24 Demchak TJ, Linderman JK, Mysiw WJ, Jackson R, Suun J, Devor ST. Effects of functional electric stimulation cycle ergometry training on lower limb musculature in acute SCI individuals. *J Sports Sci Med* 2005;4:263–71.
- 25 Berry HR, Kakebeeke TH, Donaldson N, Perret C, Hunt KJ. Energetics of paraplegic cycling: adaptations to 12 months of high-volume training. *Technol Health Care* 2012;20 (2):73–84.
- 26 Hakansson NA, Hull ML. Can the efficacy of electrically stimulating pedaling using a commercially available ergometer be improved by minimizing the muscle stress-time integral? *Muscle Nerve* 2012;45:393–402.
- 27 Ragnarsson KT, Pollack S, O'Daniel W Jr., Edgar R, Petrofsky J, Nash MS. Clinical evaluation of computerized functional electrical stimulation after spinal cord injury: a multicenter pilot study. *Arch Phys Med Rehabil* 1988;69:672–7.
- 28 Faghri PD, Glaser RM, Figoni SF. Functional electrical stimulation leg cycle ergometer exercise: training effects on cardiorespiratory responses of spinal cord injured subjects at rest and during submaximal exercise. *Arch Phys Med Rehabil* 1992;73: 1085–93.
- 29 Barstow TJ, Scremin AM, Mutton DL, Kunkel CF, Cagle TG, Whipp BJ. Changes in gas exchange kinetics with training in patients with spinal cord injury. *Med Sci Sports Exerc* 1996;28: 1221–8.
- 30 Hjeltnes N, Aksnes AK, Birkeland KI, Johansen J, Lannem A, Wallberg-Henriksson H. Improved body composition after 8 wk of electrically stimulated leg cycling in tetraplegic patients. *Am J Physiol* 1997;273:R1072–9.
- 31 Mohr T, Andersen JL, Biering-Sørensen F, Galbo H, Bangsbo J, Wagner A, Kjaer M. Long-term adaptation to electrically induced cycle training in severe spinal cord injured individuals. *Spinal Cord* 1997;35:1–16.
- 32 Gerrits HL, de Haan A, Sargeant AJ, van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with spinal cord injury. *Arch Phys Med Rehabil* 2001;82:832–9.
- 33 Hopman MT, Groothuis JT, Flendrie M, Gerrits KH, Houtman S. Increased vascular resistance in paralyzed legs after spinal cord injury is reversible by training. *J Appl Physiol* 2002;93:1966–72.
- 34 Cramer RM, Cooper P, Sinclair PJ, Bryant G, Weston A. Effect of load during electrical stimulation training in spinal cord injury. *Muscle Nerve* 2004;29:104–11.
- 35 Berry HR, Perret C, Saunders BA, Kakebeeke TH, Donaldson N, Allan DB, Hunt KJ. Cardiorespiratory and power adaptations to stimulated cycle training in paraplegia. *Med Sci Sports Exerc* Sep 2008;40(9):1573–80.
- 36 Zbogor D, Eng JJ, Krassioukov AV, Scott JM, Esch BT, Warburton DE. The effects of functional electrical stimulation leg cycle ergometry training on arterial compliance in individuals with spinal cord injury. *Spinal Cord* 2008;46:722–6.
- 37 Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z, Ivy JL. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *J Electromyogr Kinesiol* 2009; 19:614–22.
- 38 Kahn NN, Feldman SP, Bauman WA. Lower-extremity functional electrical stimulation decreases platelet aggregation and blood coagulation in persons with chronic spinal cord injury: a pilot study. *J Spinal Cord Med* 2010;33:150–8.
- 39 Jacobs PL, Nash MS, Klose KJ, Guest RS, Needham-Shropshire BM, Green BA. Evaluation of a training program for persons with SCI paraplegia using the Parastep 1 ambulation system: part 2. effects on physiological responses to peak arm ergometry. *Arch Phys Med Rehabil* 1997;78:794–8.
- 40 Nash MS, Jacobs PL, Montalvo BM, Klose KJ, Guest RS, Needham-Shropshire BM. Evaluation of a training program for persons with SCI paraplegia using the Parastep 1 ambulation system: part 5. lower extremity blood flow and hyperemic responses to occlusion are augmented by ambulation training. *Arch Phys Med Rehabil* 1997;78:808–14.
- 41 Solomonow M, Reisin E, Aguilar E, Baratta RV, Best R, D'Ambrosia R. Reciprocating gait orthosis powered with electrical muscle stimulation (RGO II). Part II: medical evaluation of 70 paraplegic patients. *Orthopedics* 1997;20:411–8.
- 42 Wheeler GD, et al. Functional electric stimulation-assisted rowing: increasing cardiovascular fitness through functional electric stimulation rowing training in persons with spinal cord injury. *Arch Phys Med Rehabil* 2002;83:1093–9.
- 43 de Groot P, Crozier J, Rakobowchuk M, Hopman M, MacDonald M. Electrical stimulation alters FMD and arterial compliance in extremely inactive legs. *Med Sci Sports Exerc* 2005;37:1356–64.
- 44 Sabatier MJ, Stoner L, Mahoney ET, Black C, Elder C, Dudley GA, McCully K. Electrically stimulated resistance training in SCI individuals increases muscle fatigue resistance but not femoral artery size or blood flow. *Spinal Cord* 2006;44: 227–33.
- 45 Stoner L, Sabatier MJ, Mahoney ET, Dudley GA, McCully KK. Electrical stimulation-evoked resistance exercise therapy improves arterial health after chronic spinal cord injury. *Spinal Cord* 2007; 45:49–56.
- 46 Berry HR, Perret C, Saunders BA, Kakebeeke TH, Donaldson Nde N, Allan DB, Hunt KJ. Quadriceps muscle deoxygenation during functional electrical stimulation in adults with spinal cord injury. *Spinal Cord* 2000 Oct;38(10):630–8.
- 47 Jeon JY, Hettinga D, Steadward RD, Wheeler GD, Bell G, Harber V. Reduced plasma glucose and leptin after 12 weeks of functional electrical stimulation-rowing exercise training in spinal cord injury patients. *Arch Phys Med Rehabil* 2010;91: 1957–9.
- 48 Taylor JA, Picard G, Widrick JJ. Aerobic capacity with hybrid FES rowing in spinal cord injury: comparison with arms-only exercise and preliminary findings with regular training. *PM R* 2011;3:817–24.
- 49 Ryan TE, Brizendine JT, Backus D, McCully KK. Electrically induced resistance training in individuals with motor complete spinal cord injury. *Arch Phys Med Rehabil* 2013;94:2166–73.
- 50 Carty A, McCormack K, Coughlan GF, Crowe L, Caulfield B. Increased aerobic fitness after neuromuscular electrical stimulation training in adults with spinal cord injury. *Arch Phys Med Rehabil* 2012;93:790–95.
- 51 Nash MS, et al. Reversal of adaptive left ventricular atrophy following electrically-stimulated exercise training in human tetraplegics. *Paraplegia* 1991;29:590–9.
- 52 Nash MS, Montalvo BM, Applegate B. Lower extremity blood flow and responses to occlusion ischemia differ in exercise-trained and sedentary tetraplegic persons. *Arch Phys Med Rehabil* 1996;77:1260–5.
- 53 Mohr T, Dela F, Handberg A, Biering-Sørensen F, Galbo H, Kjaer M. Insulin action and long-term electrically induced training in individuals with spinal cord injuries. *Med Sci Sports Exerc* 2001;33:1247–52.
- 54 Sadowsky CL, et al. Lower extremity functional electrical stimulation cycling promotes physical and functional recovery in chronic spinal cord injury. *J Spinal Cord Med* 2013; 36:623–31.
- 55 Dolbow DR, et al. Activity-Based restorative Therapies after spinal cord injury: Inter-institutional conceptions and perceptions. *Aging Dis* 2015 August;6(4):254–261.
- 56 Dolbow DR, Gorgey AS, Ketchum JM, Gater DR. Home-based functional electrical stimulation cycling enhances quality of life in

- individuals with spinal cord injury. *Top Spinal Cord Inj Rehabil* 2013;19:324-9.
- 57 Glaser RM, Strayer JR, May KF. Combined FES leg and voluntary arm exercise of SCI patients. *Proc 7th Ann IEEE Conf Eng Med Biol Soc* 1985;308-313.
 - 58 Strayer JR, Glaser RM, May KP. Metabolic responses to voluntary and electrically stimulated leg exercise in spinal cord injured individuals. *Fed Proc* 1985;44:1369.
 - 59 Figoni SF, Rodgers MM, Glaser RM, Hooker SP, Faghri PD, Gupta SC. Hemodynamic responses of quadriplegics to arm, ES-leg, and combined arm + ES-leg ergometry. *Med Sci Sports Exerc* 1989;21(Suppl. 2):S96.
 - 60 Krauss JC, Robergs RA, Depaepe JL, Kopriva LM, Aisenbrey JA, Anderson MA, Lange EK. Effects of electrical stimulation and upper body training after spinal cord injury. *Med Sci Sports Exerc* 1993;25:1054-61.
 - 61 Gurney AB, Robergs RA, Aisenbrey J, Cordova JC, McClanahan L. Detraining from total body exercise ergometry in individuals with spinal cord injury. *Spinal Cord* 1998;36:782-9.
 - 62 Thijssen DH, Heesterbeek P, van Kuppevelt DJ, Duysens J, Hopman MT. Local vascular adaptations after hybrid training in spinal cord-injured subjects. *Med Sci Sports Exerc* 2005;37:112-8.
 - 63 Thijssen DH, Ellenkamp R, Smits P P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. *Arch Phys Med Rehabil* 2006;87:474-81.
 - 64 de Carvalho DC, Martins CL, Cardoso SD, Cliquet A. Improvement of metabolic and cardiorespiratory responses through treadmill gait training with neuromuscular electrical stimulation in quadriplegic subjects. *Artif Organs* 2006;30:56-63.
 - 65 Brurak B, Helgerud J, Karlsen T, Leivseth G, Hoff J. Effect of aerobic high-intensity hybrid training on stroke volume and peak oxygen consumption in men with spinal cord injury. *Am J Phys Med Rehabil* 2011;90:407-14.
 - 66 de Groot PC, Hjeltne N, Heijboer AC, Stal W, Birkeland K. Effect of training intensity on physical capacity, lipid profile and insulin sensitivity in early rehabilitation of spinal cord injured individuals. *Spinal Cord* 2003;41:673-9.
 - 67 Chilibeck PD, et al. Functional electrical stimulation exercise increases GLUT-1 and GLUT-4 in paralyzed skeletal muscle. *Metabolism* 1999;48:1409-13.
 - 68 Jeon JY, et al. Improved glucose tolerance and insulin sensitivity after electrical stimulation-assisted cycling in people with spinal cord injury. *Spinal Cord* 2002;40:110-7.
 - 69 Currie KD, West CR, Krassioukov AV. Differences in left ventricular global function and mechanics in Paralympic athletes with cervical and thoracic spinal cord injuries. *Front Physiol* 2016;29(7):110-7.
 - 70 Gorla JJ, et al. Impact of wheelchair rugby on body composition of subjects with tetraplegia: a pilot study. *Arch Phys Med Rehabil* 2016;97:92-6.
 - 71 Hamzaid NA, Davis GM. Health and fitness benefits of functional electrical stimulation-evoked leg exercise for spinal cord-injured individual: a position review. *Top Spinal Cord Inj Rehabil* 2009;14:88-121.
 - 72 Swain DP, Franklin BA. VO₂ reserve and the minimal intensity for improving cardiorespiratory fitness. *Med Sci Sports Exerc* 2002;34:152-7.
 - 73 Van Loan MD, McCluer S, Loftin JM, Boileau RA. Comparison of physiological responses to maximal arm exercise among able-bodied, paraplegics and quadriplegics. *Paraplegia* 1987;25:397-405.
 - 74 Figoni SF. Circulorespiratory responses of spinal cord injured, quadriplegic men to dynamic physical exercise Doctoral Dissertation, 1987 Dept. of Physical Education, University of Illinois at Urbana-Champaign, Available at: <http://hdl.handle.net/2142/71888>.
 - 75 Lasko-McCarthy P, Davis JA. Effect of work rate increment on peak oxygen uptake during wheelchair ergometry in men with quadriplegia. *Eur J Appl Physiol Occup Physiol* 1991;63:349-53.
 - 76 Morrison SA, Melton-Rogers SL, Hooker SP. Changes in physical capacity and physical strain in persons with acute spinal cord injury. *Top Spinal Cord Inj Rehabil* 1997;3:1-15.
 - 77 Figoni SF, Glaser RM, Gupta SC. Effects of posture on arm exercise performance and cardiovascular responses of adults with tetraplegia. *Clin Exerc Physiol* 1999;1:74-85.
 - 78 Janssen TW, Dallmeijer AJ, Veeger DJ, van der Woude LH. Normative values and determinants of physical capacity in individuals with spinal cord injury. *J Rehabil Res Dev* 2002;39:29-39.
 - 79 Simmons OL, Kressler J, Nash MS. Reference fitness values in the untrained spinal cord injury population. *Arch Phys Med Rehabil* 2014;95:2272-8.
 - 80 McLean KP, Skinner JS. Effect of body training position on outcomes of an aerobic training study on individuals with quadriplegia. *Arch Phys Med Rehabil* 1995;76:139-50.
 - 81 Hicks AL, Martin KA, Ditor DS, Latimer AE, Craven C, Bugaresti J, McCartney N. Long-term exercise training in persons with spinal cord injury: effects on strength, arm ergometry performance and psychological well-being. *Spinal Cord* 2003;41:34-43.
 - 82 Valent LJ, Dallmeijer AJ, Houdijk H, Slootman HJ, Post MW, van der Woude LH. Influence of hand cycling on physical capacity in the rehabilitation of persons with a spinal cord injury: a longitudinal cohort study. *Arch Phys Med Rehabil* 2008;89:1016-22.
 - 83 Pollack SF, Axen K, Spielholz N, Levin N, Haas F, Ragnarsson KT. Aerobic training effects of electrically induced lower extremity exercises in spinal cord injured people. *Arch Phys Med Rehabil* 1989;70:214-9.
 - 84 Petrofsky JS, Stacy R. The effect of training on endurance and the cardiovascular responses of individuals with paraplegia during dynamic exercise induced by functional electrical stimulation. *Eur J Appl Physiol Occup Physiol* 1992;64:487-92.
 - 85 Hooker SP, Figoni SF, Rodgers MM, Glaser RM, Mathews T, Suryaprasad AG, Gupta SC. Metabolic and hemodynamic responses to concurrent submaximal voluntary arm crank and electrical stimulation leg cycle exercise in quadriplegics. *J Rehabil Res Dev* 1992b;29:1-11.
 - 86 Mutton DL, Scremin AM, Barstow TJ, Scott MD, Kunkel CF, Cagle TG. Physiologic responses during functional electrical stimulation leg cycling and hybrid exercise in spinal cord injured subjects. *Arch Phys Med Rehabil* 1997;78:712-8.
 - 87 Bhambhani Y, Tuchak C, Burnham R, Jeon J, Maikala R. Quadriceps muscle deoxygenation during functional electrical stimulation in adults with spinal cord injury. *Spinal Cord* 2000;38(10):630-8.
 - 88 Barstow TJ, Scremin AM, Mutton DL, Kunkel CF, Cagle TG, Whipp BJ. Peak and kinetic cardiorespiratory responses during arm and leg exercise in patients with spinal cord injury. *Spinal Cord* 2000;38:340-345.
 - 89 Kjaer M, et al. Leg uptake of calcitonin generated peptide during exercise in spinal cord injury humans. *Clin Physiol* Jan 2001;21(1):32-8.
 - 90 Raymond J, Schoneveld K, Van Kemenade CH, Davis GM. Onset of electrical stimulation leg cycling in individuals with paraplegia. *Med Sci Sports Exerc*. Oct 2002;34(10):1557-62.
 - 91 Verellen J, Vanlandewijck Y, Andrews B, Wheeler GD. Cardiorespiratory responses during arm ergometry, functional electrical stimulation cycling, and two hybrid exercise conditions in spinal cord injured. *Disabil Rehabil Assist Technol* 2007;2:127-32.
 - 92 Fornusek C, Davis GM. Cardiovascular and metabolic responses during functional electric stimulation cycling at different cadences. *Arch Phys Med Rehabil* 2008;89:719-25. doi: 10.1016/j.apmr.2007.09.035.
 - 93 Fornusek C, Davis GM, Russold MF. Pilot study of the effect of low-cadence functional electrical stimulation cycling after spinal cord injury on thigh girth and strength. *Arch Phys Med Rehabil* 2013;94:990-3.
 - 94 Thrasher TA, Ward JS, Fisher S. Strength and endurance adaptations to functional electrical stimulation leg cycle ergometry in spinal cord injury. *NeuroRehabilitation* 2013;33:133-8. doi: 10.3233/NRE-130937.
 - 95 Hasnan N, et al. Exercise responses during functional electrical stimulation cycling in individuals with spinal cord injury.

- Med Sci Sports Exerc 2013;45:1131–8. doi: 10.1249/MSS.0b013e3182805d5a.
- 96 Mazzoleni S, Stampacchia G, Gerini A, Tombini T, Carrozza MC. FES-cycling training in spinal cord injured patients. 35th Proc Annu Int Conf IEEE EMBS. Osaka, Japan, 5339–41, 2013.
 - 97 Kuhn D, Leichtfried V, Schobersberger W. Four weeks of functional electrical stimulation cycling after spinal cord injury: a clinical cohort study. Int J Rehabil Res 2014;37:243–50. doi: 10.1097/MRR.0000000000000062.
 - 98 Johnston TE, et al. Musculoskeletal effects of 2 functional electrical stimulation cycling paradigms conducted at different cadences for people with spinal cord injury: a pilot study. Arch Phys Med Rehabil 2016;97:1413–22. doi:10.1016/j.apmr.2015.11.014.
 - 99 Gorgey AS, Poarch HJ, Dolbow DR, Castillo T, Gater DR. Effect of adjusting pulse durations of functional electrical stimulation cycling on energy expenditure and fatigue after spinal cord injury. J Rehabil Res Dev 2014; 51(9):1455–68.
 - 100 Edwards BG, Marsolais EB. Metabolic responses to arm ergometry and functional neuromuscular stimulation. J Rehabil Res Dev 1990; 27(2):107–13. discussion 113–4 Spring.
 - 101 Laskin JJ, Ashley EA, Olenik LM, Burnham R, Cumming DC, Steadward RD, Wheeler GD, et al. Electrical stimulation-assisted rowing exercise in spinal cord injured people. a pilot study. Paraplegia 1993;31:534–41.
 - 102 Raymond J, Davis GM, Fahey A, Climstein M, Sutton JR. Oxygen uptake and heart rate responses during arm vs combined arm/electrically stimulated leg exercise in people with paraplegia. Spinal Cord 1997;35:680–5.
 - 103 Raymond J, Davis GM, Climstein M, Sutton JR. Cardiorespiratory responses to arm cranking and electrical stimulation leg cycling in people with paraplegia. Med Sci Sports Exerc 1999;31:822–8.
 - 104 Weiss C. Effects of acute moderate intensity FES-Leg cycle, arm crank, and hybrid ergometer exercise on lipid-lipoprotein profile in persons with spinal cord injury Master's thesis, University of Alberta, Edmonton, Alberta, Canada, 1999.
 - 105 Heesterbeek PJC, Berkelmans HWA, Thijssen DHJ, van Kuppevelt HJM, Hopman MTE, Duysens J. Increased physical fitness after 4-week training on a new hybrid FES-cycle in persons with spinal cord injury. Technol Disabil 2005;17: 103–10.
 - 106 Paulson TA, Bishop NC, Smith BM, Goosey-Tolfrey VL. Inflammation-mediated cytokine response to acute handcycling exercise with/without functional electrical stimulation-evoked lower-limb cycling. Journal Rehabil Res Dev 2014;51(4): 645–654.
 - 107 Taylor JA, Picard G, Porter A, Morse LR, Pronovost MF, Deley G. Hybrid functional electrical stimulation exercise training alters the relationship between spinal cord injury level and aerobic capacity. Arch Phys Med Rehabil Nov 2014;95(11): 2172–9.
 - 108 Bakkum AJ, de Groot S, Stolwijk-Swuste JM, van Kuppevelt DJ, Allrisc van der Woude LH, Janssen TWJ. Effects of hybrid cycling versus handcycling on wheelchair-specific fitness and physical activity in people with long term spinal cord injury: a 16-week randomized controlled trial. Spinal Cord 2015;53: 395–401.
 - 109 Bakkum AJ, et al. Effects of hybrid cycle and handcycle exercise on cardiovascular disease risk factors in people with spinal cord injury: A randomized controlled trial. J Rehabil Med. Jun 2015; 47(6):523–30.
 - 110 Draghici AE, Picard G, Taylor JA, Shefelbine SJ. Assessing kinematics and kinetics of functional electrical stimulation rowing. J Biomech Feb 2017;28(53):120–126.
 - 111 Crameri RM, Weston A, Climstein M, Davis GM, Sutton JR. Effects of electrical stimulation-induced leg training on skeletal muscle adaptability in spinal cord injury. Scand J Med Sci Sports 2002;12:316–22.
 - 112 Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM, Knipschild PG. The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. J Clin Epidemiol 1998;51:1235–41.

Appendix 1. Common secondary health conditions after SCI.

Acute/Sub-acute	Chronic
<ul style="list-style-type: none"> Physical inactivity, Deconditioning ↓ % lean mass, ↑ % fat mass Bladder/bowel incontinence Orthostatic/exercise hypotension, Exercise intolerance Autonomic dysreflexia Hypertension Prediabetes Dyslipidemia Anxiety/Depression Urinary tract infection Restrictive lung disease Osteopenia, Heterotopic bone Spasticity, Joint contracture Pressure ulcer Deep venous thrombosis, Pulmonary embolism Musculoskeletal/neuropathic pain 	<ul style="list-style-type: none"> Metabolic syndrome: Obesity, Diabetes, Stroke, Cardiovascular disease, Peripheral arterial disease Chronic renal insufficiency, Hemodialysis Pneumonia, Respiratory failure Sepsis Pathological fractures Frequent hospitalizations Chronic pain Suicide

Appendix 2. PEDro Scale: Physiotherapy Evidence Database (Verhagen et al.¹¹²) used to evaluate the strength of the experimental design of individual studies.

	Yes	No
	1	0
1	Eligibility criteria were specified.	
2	Subjects were randomly allocated to groups. In crossover study, subjects were randomly allocated in order in which treatments were received.	
3	Allocation was concealed.	
4	Groups were similar at baseline re: most important prognostic indicators.	
5	Blinding of all subjects	
6	Blinding of all therapists who administered therapy	
7	Blinding of all assessors who measured at least one key outcome	
8	Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.	
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by "intention to treat".	
10	Results of between-group statistical comparisons are reported for at least one key outcome.	
11	Study provides both point measures and measures of variability for at least one key outcome.	
TOTAL SCORE:		

Appendix 3. Methods of systematic review: 5 levels of evidence. A lower level number indicates stronger research design and higher level of evidence.

Level	Research design	Description
1a	Randomized controlled trial (RCT) ^a	"≥ 1 human subject is prospectively assigned to ≥ 1 interventions or placebo or other control groups) to evaluate the effects of interventions on health-related biomedical or behavioral outcomes" (NIH, 2016) > 1 RCT with PEDro score ≥ 6, including within-subjects comparison with randomized conditions and cross-over designs
1b	RCT	1 RCT with PEDro score ≥ 6
2	RCT	1 RCT with PEDro score < 6
	Prospective controlled trial ^b	Prospective nonrandomized controlled trial
	Cohort ^c	Prospective longitudinal study using ≥ 2 similar groups with 1 exposed to a particular condition
3	Case control ^d	Retrospective study comparing conditions, including historical controls
4	Pre-post ^e	Prospective trial with baseline measure, intervention, and post-test using 1 group
	Post-test ^f	Prospective post-test with ≥ 2 groups (intervention followed by post-test and no re-test or baseline measurement), 1 group
	Case Series ^g	Retrospective study usually collecting variables from a chart review
5	Observational ^h	Study using cross-sectional analysis to interpret relations
	Clinical Consensus ⁱ	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or "first principles"
	Case Report ^j	Pre-post or case series involving 1 subject

PEDro: Physiotherapy evidence database (Verhagen *et al.*¹¹²)