



HAL
open science

Journal of Cardiopulmonary Rehabilitation and Prevention Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review

Isabelle J Andrew Vivodtzev, J. Andrew Taylor

► To cite this version:

Isabelle J Andrew Vivodtzev, J. Andrew Taylor. Journal of Cardiopulmonary Rehabilitation and Prevention Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review. Journal of Cardiopulmonary Rehabilitation, 2021, 41 (1), pp.6-12. 10.1097/HCR.0000000000000564 . hal-03551325

HAL Id: hal-03551325

<https://hal.sorbonne-universite.fr/hal-03551325v1>

Submitted on 1 Feb 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Journal of Cardiopulmonary Rehabilitation and Prevention
Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review
 --Manuscript Draft--

Manuscript Number:	JCRP-D-20-00150R2
Full Title:	Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review
Short Title:	Cardiac rehabilitation in spinal cord injury
Article Type:	Invited Review Article
Keywords:	Spinal cord injury; cardiac rehabilitation; Autonomic Function; FES-rowing; cardiometabolic
Corresponding Author:	Isabelle Vivodtzev, Ph.D. Harvard Medical School Cambridge, MA UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Harvard Medical School
Corresponding Author's Secondary Institution:	
First Author:	Isabelle Vivodtzev, Ph.D.
First Author Secondary Information:	
Order of Authors:	Isabelle Vivodtzev, Ph.D. J. Andrew Taylor, PhD
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED STATES
Abstract:	<p>Introduction</p> <p>Direct and indirect effects of spinal cord injury (SCI) lead to important cardiovascular complications that are further increased by years of injury and the process of “accelerated aging”. The present review examines the current evidence in the literature for the potential cardio-protective effect of exercise training in SCI.</p> <p>Review Methods</p> <p>PubMed and Web of Science databases were screened for original studies investigating the effect of exercise-based interventions on aerobic capacity, cardiac structure/function, autonomic function, cardiovascular function and/or cardiometabolic markers. We compared the effects in individuals <40 yrs. old with time since injury (TSI) <10 yrs. with those in older individuals (> 40 yrs. old) with longer TSI (>10 yrs.), reasoning that the two can be considered individuals with low- vs. high- cardiovascular risk factors (CVRF).</p> <p>Summary</p> <p>Studies showed similar exercise effects in both groups (n = 31 in low-CVRF vs. n = 15 in high-CVRF). The evidence does not support any effect of exercise training on autonomic function but does support an increase peripheral blood flow, improved left ventricular mass, higher peak cardiac output, greater lean body mass, better anti-oxidant capacity, and improved endothelial function. In addition, some evidence suggests that it can result in lower blood lipids, systemic inflammation (IL-6, TNF-α and CRP), and arterial stiffness. Training intensity, volume, and frequency were key factors determining cardiovascular gains. Future studies with larger sample sizes, well-</p>

	<p>matched groups of subjects, and randomized controlled designs will be needed to determine if high-intensity hybrid forms of training result in greater cardiovascular gains.</p>
<p>Response to Reviewers:</p>	<p>JCRP-D-20-00150R1 Responses to the reviewer Reviewer Comments:</p> <p>The revised manuscript is substantially improved from the original submission. We believe a few more minor revisions as suggested will further improve it.</p> <p>1. Page 10, para 1. It would be useful to add a statement that the effects of exercise training on orthostatic hypotension in this population has not been systematically studied. Ok, done, page 10.</p> <p>2. Future Directions paragraph. Remove "hence" from the first sentence. Ok, done.</p> <p>3. Tables. Please spell out all abbreviations in table titles or include the abbreviations in the table footnote. Ok done.</p> <p>4. Table 1. A few organizational suggestions: Since orthostatic hypotension does not reflect resting vagal tone, consider grouping it with baroreflex sensitivity in a separate category "Autonomic Reflexes". The category Resting Hemodynamics should include HR, BP, SV, CO, and diastolic function. The category Cardiovascular Function should be renamed Vascular Structure & Function and moved just below Resting Hemodynamics. Ok done.</p> <p>5. A new table should be created to parallel Table 1 summarizing the effects of exercise training on cardiac, autonomic, and metabolic function. These effects are not readily evident from the individual studies in current Tables 2 and 3. Also, we ask that your change Tables 2 and 3 to Supplemental Digital Content (that are available 'free' as online supplements for readers) to reduce manuscript length.</p> <p>We have created a new table named Table 2 to summarize the content of the previous Tables 2 and 3.</p> <p>Editorial Office:</p> <p>Please use a footnote with Table 1 to list all the abbreviations (with expansion). Ok done</p> <p>Please add the reference number (superscripted) for all cited in Tables 2 and 3. Per request of the reviewer, these tables have been moved to supplemental material and therefore renamed Table E1 and E2. We have included the reference number for all citations.</p> <p>On Page 10 – please provide the reference for (Solinsky et al) Ok done</p> <p>Please use a subscript for the 2peak in VO₂peak, note also express it this way in the Tables including for the L/min values Ok done</p> <p>Please use yr as the abbreviation for both year and years Ok done</p>

Type of submission: Invited review

Title: Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review

Running title: Cardiac rehabilitation in spinal cord injury

Authors: Isabelle Vivodtzev^{1,2,3}, PhD and J. Andrew Taylor^{1,2} PhD

Affiliations: ¹Harvard Medical School, Department of Physical Medicine and Rehabilitation, Boston MA, USA; ²Spaulding Rehabilitation Hospital, Cardiovascular Research Laboratory, Cambridge, MA, USA; ³Sorbonne Université, INSERM, UMRS1158, Neurophysiologie Respiratoire Expérimentale et Clinique, F-75005 Paris

Key words: Spinal cord injury; cardiac rehabilitation; exercise training; cardiovascular; autonomic

Funding: Support for this study was provided by NIH Grant (R01-HL-117037) and ACL Grant 90SI5021-01, USA. IV was supported by the Ellen R. and Melvin J. Gordon Center for the Cure and Treatment of Paralysis, USA.

Corresponding Author:

Isabelle Vivodtzev,

Cardiovascular Research Laboratory,

Spaulding Rehabilitation Hospital,

1575 Cambridge St., Cambridge, MA, USA 02138

Phone: +1 (617)758 5504

ivivodtzev@partners.org; isabelle.vivodtzev@sorbonne-universite.fr

Conflict of interest: The Authors have no conflict of interest to disclose

The authors have read and approved the manuscript

Text-only words count: 3761

Number of tables: 2

Number of figures: 0

Number of references: n = 80

**Structured Abstract (Purpose or Objective; Review Methods; Summary) ≤ 250 words
(n =249)**

Introduction: Direct and indirect effects of spinal cord injury (SCI) lead to important cardiovascular complications that are further increased by years of injury and the process of “accelerated aging”. The present review examines the current evidence in the literature for the potential cardio-protective effect of exercise training in SCI.

Review Methods: PubMed and Web of Science databases were screened for original studies investigating the effect of exercise-based interventions on aerobic capacity, cardiac structure/function, autonomic function, cardiovascular function and/or cardiometabolic markers. We compared the effects in individuals <40 yr. old with time since injury (TSI) <10 yr. with those in older individuals (> 40 yr. old) with longer TSI (>10 yr.), reasoning that the two can be considered individuals with low- vs. high- cardiovascular risk factors (CVRF).

Summary: Studies showed similar exercise effects in both groups (n = 31 in low-CVRF vs. n = 15 in high-CVRF). The evidence does not support any effect of exercise training on autonomic function but does support an increase peripheral blood flow, improved left ventricular mass, higher peak cardiac output, greater lean body mass, better anti-oxidant capacity, and improved endothelial function. In addition, some evidence suggests that it can result in lower blood lipids, systemic inflammation (IL-6, TNF- α and CRP), and arterial stiffness. Training intensity, volume, and frequency were key factors determining cardiovascular gains. Future studies with larger sample sizes, well-matched groups of subjects, and randomized controlled designs will be needed to determine if high-intensity hybrid forms of training result in greater cardiovascular gains.

JCRP SUBMISSION CHECKLIST FOR AUTHORS

Please refer to the Information for Authors (edmgr.ovid.com/jcrp/ifauth.htm) for more detailed information. The following is a checklist for authors to help insure that a submission is complete and uses the correct format and JCRP conventions. JCRP requires that the corresponding author complete the checklist and include it with the initial manuscript submission in Editorial Manager. Manuscripts submitted without this checklist will be returned to the authors with a request to complete and submit a completed checklist.

Corresponding Author: [Click here to enter text.](#)

Manuscript Title: [Click here to enter text.](#)

General Manuscript Formatting and Requirements:

- Corresponding Author has reviewed the [Information for Authors](#) and followed the instructions for submission of a manuscript
- The manuscript was prepared following the formatting requirement of the JCRP Style Guide (available on the Information for Authors page)
- The manuscript text has been submitted as a Microsoft Word file (not as a PDF) using Times New Roman font, 12-point. The entire manuscript and references are double-spaced. Page numbers are on each text page, appearing in the upper right header.
 - Note: Do not use bold, italics, or underline for any terms or phrases in the abstract or manuscript, as these should only be used for headings.

Title page is formatted correctly and includes all elements:

- Type of submission
- Both a full title and a shortened form (≤ 50 characters) of the title (running title)
- Name, terminal degree, and professional affiliation information for each author
- List of 3-5 key words
- Name, complete mailing address, fax, phone, and email for the corresponding author
- Statements regarding both financial support and any conflicts of interest for all authors. If no sources of support or no conflicts are present, please explicitly list this on the title page.
- Statement that all authors have read and approved the manuscript
- List of the total text-only word count, number of tables, number of figures, and number of references

Abstracts:

- Structured abstract of ≤ 250 words (using subheadings appropriate for submission type)

- Condensed abstract of ≤ 50 words; no subheadings

Text-only/Manuscript File:

- Text-only manuscript file only includes body of manuscript, references, and figure legends
 - Do not include: title page, abstracts, figures, tables, or cover letter in the manuscript file. These items should be submitted as separate files as indicated below

Text-only word limits^a for the types of submissions:

- Original investigation: $\leq 3,000$ words
- Scientific reviews: $\leq 4,000$ words (limited to ≤ 75 references)
- Brief Report or Case Report: $\leq 2,000$ words (limited to ≤ 20 references and 2 figures or tables in total)

^aApplies to initial and revised submissions

References:

- Cited in the text in the order they appear using superscript numbers
- Citations formatted following the AMA Manual of Style, 10th edition as summarized in the Instructions for Authors.
- Adhered to the limit specific to the submission type.

Figures:

- Standard figures should be created using a Microsoft Office program file type or PDF file type (Note: importing figures created using other software into a Microsoft Office program file or PDF is not acceptable). This prohibition does not apply to figures that can only be created using statistical software (eg, forest plot).
- Each separate figure submitted as a separate file (not embedded in manuscript file)
- Manuscript figures in black and white unless authors pay the costs of for color
 - Note: Figures submitted as supplemental digital content (SDC) may be in color at no additional expense
- Figure legends included in the manuscript file, appearing after the References

Tables:

- Tables submitted as a Microsoft Word file type;
- Submit each table as a separate file (not embedded in manuscript file)
- Call outs for any footnotes should use superscripted letters (a, b, c, ...); do not use other symbols
- Any abbreviations used are listed and spelled out in a footnote to the table.

Supplemental Digital Content (SDC):

- SDC material in accepted articles will be available to the reader in digital format only and is linked within the article using a unique URL

SDC may include figures, tables or appendices

Type of submission: Invited review

Title: Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review

Running title: Cardiac rehabilitation in spinal cord injury

Authors: Isabelle Vivodtzev^{1,2,3}, PhD and J. Andrew Taylor^{1,2} PhD

Affiliations: ¹Harvard Medical School, Department of Physical Medicine and Rehabilitation, Boston MA, USA; ²Spaulding Rehabilitation Hospital, Cardiovascular Research Laboratory, Cambridge, MA, USA; ³Sorbonne Université, INSERM, UMRS1158, Neurophysiologie Respiratoire Expérimentale et Clinique, F-75005 Paris

Key words: Spinal cord injury; cardiac rehabilitation; exercise training; cardiovascular; autonomic

Funding: Support for this study was provided by NIH Grant (R01-HL-117037) and ACL Grant 90SI5021-01, USA. IV was supported by the Ellen R. and Melvin J. Gordon Center for the Cure and Treatment of Paralysis, USA.

Corresponding Author:

Isabelle Vivodtzev,

Cardiovascular Research Laboratory,

Spaulding Rehabilitation Hospital,

1575 Cambridge St., Cambridge, MA, USA 02138

Phone: +1 (617)758 5504

ivivodtzev@partners.org; isabelle.vivodtzev@sorbonne-universite.fr

Conflict of interest: The Authors have no conflict of interest to disclose

The authors have read and approved the manuscript

Text-only words count: 3761

Number of tables: 2

Number of figures: 0

Number of references: n = 80

Structured Abstract (Purpose or Objective; Review Methods; Summary) ≤ 250 words

(n =249)

Introduction: Direct and indirect effects of spinal cord injury (SCI) lead to important cardiovascular complications that are further increased by years of injury and the process of “accelerated aging”. The present review examines the current evidence in the literature for the potential cardio-protective effect of exercise training in SCI.

Review Methods: PubMed and Web of Science databases were screened for original studies investigating the effect of exercise-based interventions on aerobic capacity, cardiac structure/function, autonomic function, cardiovascular function and/or cardiometabolic markers. We compared the effects in individuals <40 yr. old with time since injury (TSI) <10 yr. with those in older individuals (> 40 yr. old) with longer TSI (>10 yr.), reasoning that the two can be considered individuals with low- vs. high- cardiovascular risk factors (CVRF).

Summary: Studies showed similar exercise effects in both groups (n = 31 in low-CVRF vs. n = 15 in high-CVRF). The evidence does not support any effect of exercise training on autonomic function but does support an increase peripheral blood flow, improved left ventricular mass, higher peak cardiac output, greater lean body mass, better anti-oxidant capacity, and improved endothelial function. In addition, some evidence suggests that it can result in lower blood lipids, systemic inflammation (IL-6, TNF- α and CRP), and arterial stiffness. Training intensity, volume, and frequency were key factors determining cardiovascular gains. Future studies with larger sample sizes, well-matched groups of subjects, and randomized controlled designs will be needed to determine if high-intensity hybrid forms of training result in greater cardiovascular gains.

Condensed Abstract ≤ 50 words

1 This review examines original studies investigating the impact of exercise-based interventions
2 on cardiac, autonomic, and cardiometabolic outcomes in spinal cord injury (SCI). Exercise
3 training does not alter autonomic function but it increases peripheral blood flow and
4 counterbalances many deleterious effects of deconditioning, improving cardiac function and
5 cardiometabolic outcomes in SCI.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

INTRODUCTION

The cardioprotective effect of regular aerobic exercise in the general population is broadly accepted, but its importance for those with spinal cord injury (SCI) may be even greater. Indeed, SCI is associated with greater risk for cardiovascular disease compared to the general population.¹ Both symptomatic and asymptomatic cardiovascular disease prevalence is alarming in these patients² who have almost three times the odd ratio of developing heart disease and up to six times the risk for stroke compared to general population.³ Furthermore, early death occurs due to higher rates of obesity,³ type 2 diabetes,⁴ and cardiovascular disease.⁵

Autonomic dysfunction

Alterations in autonomic function are a direct consequence of SCI that may explain higher susceptibility to cardiovascular disease⁶ (Table 1). Indeed, damage to the spinal and/or central components of the autonomic nervous system lead to impaired neural control of the heart and blood vessels.⁷ Cardiac sympathetic nerve fibers which innervate the heart arise from the thoracic cord between T1 and T5⁸. As a result, cardiovascular sympathetic control is impaired or absent in individuals with SCI above the T6 spinal segment. Therefore, most individuals with SCI > T6 experience persistent hypotension and bradycardia on a daily basis, with episodic falls in blood pressure with the upright posture. Furthermore, transient episodes of aberrantly low and high blood pressure can be life-threatening, presenting as clinical complications known as orthostatic hypotension and autonomic dysreflexia.⁹ In addition, heart rate variability (HRV), a non-invasive tool for assessing cardiac autonomic control, is markedly impacted with implications for the development of cardiovascular disease after SCI.¹⁰ For example, lesser HRV is associated with cardiac diseases¹¹ and is prognostic for those with known cardiovascular disease.¹² Moreover, HRV decreases with age, is lower in those with a sedentary life style, and is inversely related to inflammatory markers in both healthy individuals

1 and those with cardiovascular disease¹³. On the other hand, there is a greater blood pressure
2 variability in SCI, and greater variability has been associated with cardiac, vascular, and renal
3 damage and with increased risk of cardiovascular events and mortality.¹⁴ We recently reported
4 that the HRV decrease is seen within the first 24 months after SCI, suggesting that this decline
5 is due, in part, to a direct impact of SCI itself rather than long-term effect of living with SCI.¹⁵
6
7
8
9
10
11
12

13 *Reduced cardiopulmonary fitness*

14
15

16 The loss of metabolically active tissue and reduced capacity to routinely engage in
17 aerobic exercise is another major effect of SCI.¹⁶ Aerobic capacity, a key component of
18 cardiopulmonary fitness, is related to the level and extent of SCI and decreases by ~5% with
19 each level of injury from T11 to C4 such that those with high-level injuries have aerobic
20 capacities <40% of their able-bodied peers.¹⁷ The demands of producing aerobic work require
21 integrated responses across a number of systems.¹⁸ The functional limit of aerobic work,
22 maximal oxygen consumption, is by definition the product of maximal systemic flow (i.e.,
23 cardiac output) and active muscle oxygen use (i.e., arteriovenous oxygen difference). On both
24 fronts, individuals with SCI have much greater obstacles to overcome in achieving and
25 maintaining high levels of aerobic fitness. For example, impaired sympathetic outflow
26 precludes the normal vasoconstriction in non-exercising tissue to redistribute blood flow to
27 active muscle. Indeed, to achieve high intensity exercise levels, it is critical that blood flow is
28 diverted from inactive tissues, including non-active skeletal muscle. In those with low maximal
29 cardiac output, maximal aerobic capacity can be reduced as much as 40% without regional
30 vasoconstriction.¹⁸ This is of particular relevance to those with injuries at T6 and above who
31 have lessened sympathetically mediated tachycardia and contractility, with subsequent reduced
32 stroke volume and cardiac output.¹⁹ Moreover, the loss of muscle function and trunk control in
33 those with tetraplegia impacts stability and hence the ability to engage in strenuous exercise.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2 As a result, individuals with the highest level of SCI may not achieve exercise intensities
3 required to reduce cardio metabolic risk.²⁰
4

5 *Metabolic dysfunction*

6

7
8
9 Due to a 'forced' sedentary life-style, cardiovascular and metabolic diseases develop
10 (such as hyperlipidaemia, glucose intolerance, and systemic inflammation) that are
11 superimposed upon the direct impact of SCI. Years of cumulative stresses due to nervous
12 system dysfunction, limited mobility, and increased inflammation lead to a process of
13 accelerated aging.²¹ For example, chronic hyperglycemia promotes arterial wall hypertrophy
14 and fibrosis and impairs endothelial function.²² Moreover, systemic inflammation (IL-6, TNF-
15 α and CRP) alters NO production, further contributing to endothelial dysfunction²³ and
16 increasing expression of adhesion molecules on activated endothelium, facilitating the
17 formation of atheromatous plaque. Hence, although increased arterial stiffness is part of the
18 normal aging process, systemic complications of SCI may contribute to a premature vascular
19 aging effect. This is particularly true in older individuals with SCI and those with longer time
20 of injury who have the greatest clustering of cardiometabolic risk factors.²⁴
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 One main goal of rehabilitation is therefore to increase aerobic capacity and reduce the
40 cardiovascular impact of SCI. For example, greater aerobic capacity decreases the risk for
41 cardiovascular disease mortality independent of age, ethnicity, and health conditions in able-
42 bodied adults²⁵. A 3.5 ml/kg/min improvement in aerobic capacity relates to a 19% decrease in
43 cardiovascular disease mortality.²⁶ Furthermore, the risk for all-cause mortality decreases in
44 direct relation to exercise training intensity²⁷. However, the impact of exercise rehabilitation
45 may differ in SCI depending on the nature of the injury. Though exercise is necessary in the
46 acute/subacute phase of SCI, it may be even more important for older individuals with longer
47 TSI who could benefit from its cardioprotective effect.
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

In the present review, we searched for published studies investigating the cardiovascular impact of exercise training in SCI. PubMed and Web of Science databases were screened using the following key words and MeSH terms: [spinal cord injury] AND [training or exercise or rehabilitation] AND [cardiac or autonomic or cardiovascular or cardiometabolic]. Original studies that met the following criteria were included: i) study design: within-group studies, non-randomized between-groups studies, randomized controlled studies, cross-sectional studies and cohort studies; ii) participants: individuals with spinal cord injury and iii) outcomes: effect of an exercise-based intervention on VO_{2peak} , cardiac structure or function, autonomic function, cardiovascular function, and/or cardiometabolic blood markers. Non-English language articles, case studies, review articles and congress abstracts were excluded. Only original studies with a minimum number of subjects of $n = 5$ and training duration of 7 days were included. Furthermore, we dichotomized the effect of exercise training into two categories of patients: younger individuals (<40-45 yr old) with shorter time since injury (< 10 yr), considered as those with low cardiovascular risk (low-CVRF) vs. older Individuals (~40-45 yr or older) with longer time since injury (> 10 yr) and higher cardiovascular risk (high-CVRF).

40 **REVIEW OF RELEVANT LITERATURE**

43 **Exercise training and aerobic capacity**

46 *Training modalities*

49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Our search identified 46 unique studies that fulfilled eligibility criteria. Thirty-one were in individuals with low-CVRF and 15 in those with high-CVRF. A substantial number of training modalities have been investigated, from wheelchair training to exoskeleton adapted walking (Table E1 and E2). Most exercise training programs require only arms or only leg engagement (either voluntarily or using electrical-stimulation devices), such as arm crank, hand cycling,

1 functional electrical stimulation (FES)-cycling, or body weight support treadmill training
2 (BWSTT).²⁸⁻⁵⁶ These are the most commonly used in SCI rehabilitation due accessibility and
3
4 low cost. Less frequently, exercise training programs have employed FES of the lower
5
6 extremities in combination with voluntary contraction of the arms, such as FES cycling + arm
7
8 or FES-rowing.^{15,57-62} These forms of exercise are considered as hybrid training since they allow
9
10 simultaneous contractions of the upper and lower limb muscle groups. Nevertheless, hybrid
11
12 forms of exercise require more assistance and learning (at least initially) but allow for greater
13
14 exercise intensities for longer periods⁶³.
15
16
17
18

19 *Aerobic capacity*

20
21
22
23 On the whole, exercise training positively affects VO_{2peak} in those with SCI. Indeed, we found
24
25 13 out of 16 studies reporting increase in VO_{2peak} after training in low-CVRF^{15,28-32,43-46,57,58,64,65}
26
27 and 9 out of 12 in high-CVRF^{48,49,51,53,54,59,61,62,66} (i.e., >75% of all studies; see Table 2 for
28
29 summary and Table E1 and E2 for details). However, the range of increases in VO_{2peak} was
30
31 highly variable, from 10 to 70% in both low and high CVRF individuals. For example, some
32
33 studies showed > 50% increase after only 8 weeks of training³⁰ while others showed only 12%
34
35 improvement after more than 16 weeks of training^{54,60}. This disparity may be due to the extreme
36
37 variability in subjects' characteristics and training protocols. Adaptations to training can be
38
39 impacted by level and completeness of injury. For example, patients with cervical injuries and
40
41 or complete injury have lower baseline VO_{2peak} and potentially lower ability to sustain high
42
43 intensity exercise. Indeed, two studies reported improvement in VO_{2peak} in subjects with
44
45 thoracic but not cervical injuries, despite similar training program.^{30,32} As a result, a smaller
46
47 improvement may be found in studies with a higher proportion of subjects with high-level SCI.
48
49
50 Another factor which can account for different adaptation to training is the level of physical
51
52 activity before or during the training program. Indeed, in most studies, patients are new to
53
54 training but not always.³¹ This can explain lower response to training in studies with patients
55
56
57
58
59
60
61
62
63
64
65

1 already engaged in rehabilitation. In addition, level of activity outside the study is almost never
2 described, and it is important to note that cohort studies show that when individuals engaged in
3 regular physical activity have considerably higher VO_{2peak} compared to those who are sedentary
4
5
6
7 ($\sim+60\%$)^{64,66}.
8
9

14 **Impact of exercise training on the cardiovascular system**

17 *Cardiac function*

20 An important question is whether exercise training improves cardiac and cardiovascular health
21 in SCI. As VO_{2peak} is the product of cardiac output and arteriovenous O_2 difference, hence
22 increases in VO_{2peak} reflect changes at the cardiac and/or at the peripheral level. A first
23
24 interesting finding is that 4 weeks of quadriceps muscle training using electrical stimulation
25 followed by 6 months of functional electrical stimulation (FES)-cycling increased left
26 ventricular (LV) mass in young individuals within ~ 6 yr. after complete injury³⁵ (Table 2, E1
27 and E2). This may relate to increased leg muscle mass (+70%) and thigh blood flow (+115%)
28 as reported in Taylor et al.³⁶ In addition, FES-cycle training has been shown to increase
29 peak cardiac output.³⁴ This 12-16-week program of FES-cycling led to a 24% improvement in
30
31 VO_{2peak} associated with a 13% increase in peak CO.³⁴ These results suggest that the leg muscle
32 pump may be important to gains in CO after training in SCI. In fact, CO may be enhanced via
33 increased venous return to the heart leading to increased LV mass and stroke volume. Greater
34 LV mass and/or diameter is, indeed, the most commonly reported finding in cross-sectional
35 studies^{64,66-68}. Furthermore, only 8 weeks of hybrid exercise can result in significant
36 improvement in cardiac structure and function both in low and high-CVRF individuals with
37 SCI.^{58,61} This was obtained with concomitant improvement in VO_{2peak} . Hence, changes in
38
39 VO_{2peak} seems to be mainly due to improvements at the cardiac level (peak CO, SV, LV) in
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 both subcategories. However, there is one report of increases in haemoglobin mass and
2 concentration that could also be a factor in improved in VO_{2peak} , even without cardiac changes
3
4 in individuals with SCI and high-CVRF.⁶⁶
5
6

7 *Autonomic function*

8
9
10 Few studies have investigated the effect of training on autonomic function in SCI and most of
11 them enrolled subjects with low CVRF. These studies are uniform in finding no effect of
12 endurance training on autonomic function in SCI (Table 2, E1 and E2). This was found despite
13 improved VO_{2peak} ¹⁵ and despite training modalities that engaged the whole body.^{15,37,54,69} This
14
15 lack of change may indicate that damaged autonomic pathways after SCI cannot adapt to
16 exercise training as in uninjured individuals. There could be an effect of endurance training on
17
18 peak heart rate during training sessions⁵⁵ but this does not seem to impact HRV. Nevertheless,
19
20 we recently reported that high-intensity exercise training (FES-rowing) improved baroreflex
21
22 gain by 30% after 6 months of training, compared to a decrease in a matched control group
23
24 (Solinsky et al, American Spinal Injury Association Annual Meeting 2019)⁷⁰. Here, again, only
25
26 individuals in the subacute period after injury (< 2 yr.) were investigated. In addition, the effects
27
28 of exercise training on orthostatic hypotension has not been systematically studied in SCI. Further
29
30 studies will be needed to confirm this result and to understand the mechanisms. Importantly,
31
32 studies should investigate if exercise training could have an impact on baroreflex sensitivity in
33
34 those with high CVRF. Furthermore, more studies should provide quantitative assessment of
35
36 change in orthostatic tolerance with exercise training in SCI
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51

52 *Metabolic markers and cardiovascular function*

53
54
55 A substantial number of studies have investigated the cardiovascular and metabolic impact of
56
57 exercise training in SCI. Studies agree on an overall positive effect of exercise on cardio
58
59
60
61
62
63
64
65

1 metabolic parameters in SCI (Table 2, E1 and E2). Indeed, at least four studies in individuals
2 with low CVRF and two in those with high CVRF report an increase in lean body mass^{30,45,62}
3 and/or a reduction in plasma lipids with training.^{43-45,47} In addition, training can decrease
4 plasma leptin,⁴⁷ a well-known hormone associated with obesity-linked metabolic and vascular
5 diseases in SCI. All but one study also reported concomitant improvement in VO_{2peak} with
6 training, suggesting that metabolic improvements occur when intensity is sufficient to increase
7 aerobic capacity. Furthermore, both resistance training⁴⁵ and high intensity aerobic exercise
8 (75% Heart rate reserve)⁴³ can improve insulin sensitivity, suggesting muscular anabolism is
9 involved in this adaptation. For example, lower limb FES training increases both muscle mass
10 and insulin sensitivity after only 10 sessions in mice.⁷¹ Lastly, exercise training can reduce
11 systemic inflammation and oxidative stress in SCI. The inflammatory cytokines IL-6, TNF- α ,
12 and CRP, as well as lipid and protein peroxidation were decreased by exercise training,^{46,47,56}
13 while anti-oxidant capacity was increased.⁴⁶ Interestingly, femoral and aortic compliances were
14 also improved after training^{38,42,72} while carotid intima-media thickness was decreased.⁴¹ This
15 could be the result of a concomitant reduction in hyperglycemia and systemic inflammation,
16 two main factors of cardiovascular function alteration in SCI. These observations are confirmed
17 by cross-sectional comparisons of athletes vs. sedentary or non-elite individuals with SCI,^{73,74}
18 suggesting once again that a high volume and/or intensity of exercise are key components for
19 cardiovascular protection in SCI. However, most studies have been in individuals with low
20 CVRF and more studies are needed to confirm a positive impact in those with high CVRF.

51 **DISCUSSION**

52 The current body of literature suggest that the cardioprotective goal of exercise training is
53 partially reached in SCI. Indeed, aerobic capacity is increased by training in ~75% of the studies
54 analysed. Furthermore, improvement in VO_{2peak} is almost always associated with improvements
55
56
57
58
59
60
61
62
63
64
65

1 in cardiovascular health. Indeed, although it fails to alter autonomic function, exercise training
2 can increase peripheral blood flow and reverse the deleterious effects of deconditioning.
3
4 Improvements in cardiac structure and function (mainly increased LV mass and CO), body
5 composition (increased lean body mass), lipid status, systemic inflammation (reduced
6 circulatory cytokines and increased anti-oxidant capacity), and cardiovascular function
7 (reduced arterial stiffness and improved endothelial function) have been consistently reported
8 across studies. Given the increased risk of cardiovascular mortality in SCI, such adaptations are
9 of primary importance. Moreover, these adaptations occur not only in those in the acute phase
10 of recovery post injury but also in those with longer time since injury and considered at high
11 cardiovascular risk. Hence, adaptations to training are not dependent on baseline CVRF but
12 rather on the ability to engage in high-intensity level of exercise. Indeed, cardiovascular stress
13 during exercise needs to be sufficient to obtain a cardiovascular effect of training. One main
14 outcome seems to be the magnitude of oxygen consumption that can be achieved during
15 exercise training. The lack of cardiovascular adaptations with training approaches using low
16 intensity of exercise^{52,60} strongly support this observation. Furthermore, cross sectional studies
17 between athletes and sedentary subjects show the greatest differences between trained and
18 untrained individuals. On the contrary, functional improvement after training (increase in power
19 output) does not necessarily relate to increases in VO_{2peak} . Indeed, increase in power output
20 often occurs before changes at the metabolic level due to a learning effect and a better
21 coordination at the muscular level during exercise. Hence, a training program may improve the
22 ability to perform a task, but not result in cardiovascular adaptations.
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51 *The benefit of hybrid forms of training*

52 Studies of whole-body hybrid approaches (FES-cycling + arms or FES-rowing) have led to
53 more consistent (~12%, range 8-24%) improvements in VO_{2peak} than arms or legs-only training,
54 in those with both low and high CVRF.^{15,57,58,60-62} This level of improvement may reflect a
55
56
57
58
59
60
61
62
63
64
65

1 certain specific physiological adaptation. Hybrid forms of exercise create a leg muscle pump in
2 synchrony with the upper body exercise. Moreover, hybrid exercise can require a high
3
4 cardiopulmonary demand compared to arms/legs-only exercise in SCI due to the greater muscle
5
6 mass engaged⁶³. Hence, higher gains in VO_{2peak} from hybrid FES row training should be
7
8 expected compared with FES cycling alone.⁶³ Furthermore, these forms of exercise may lead
9
10 to greater cardio-protection. Given that risk for mortality decreases in association with higher
11
12 exercise intensities²⁷ and that there is a 6 metabolic equivalent exercise intensity threshold
13
14 below which the reduction in risk may be minimal,⁷⁵ there is need for training approaches that
15
16 generate the greatest oxygen consumption demand. Hence, combined form of exercise might
17
18 be most appropriate for those with SCI given the more consistent improvements in VO_{2peak} with
19
20 training.
21
22
23
24
25

26 **Innovative approaches**

27 *Ventilatory capacity and VO_{2peak} in high-level SCI*

28
29 Although active muscle oxygen use is a key determinant of VO_{2peak} , aerobic exercise also
30
31 requires sufficient ventilation to provide oxygen to working muscles.⁷⁶ In most able-bodied
32
33 individuals, ventilatory capacity is more than adequate to meet metabolic demands for all
34
35 exercise intensities.⁷⁷ However, SCI is characterized by profound respiratory compromise
36
37 usually proportional to the level of injury, with those with injuries above T3 having the most
38
39 profound loss.⁶ There is little impact during arms only exercise, due to the proportional
40
41 denervation of both skeletal and pulmonary muscle such that the respiratory system is still able
42
43 to cope with the demands of arms-only exercise, even after training.⁷⁸ However, as mentioned
44
45 above, hybrid FES exercise can overcome the limited muscle mass and result in higher peak
46
47 aerobic capacity than arms-only or FES legs-only exercise. As a result, aerobic adaptations to
48
49 exercise in those with high-level injuries can be constrained by reduced ventilatory capacity.⁵⁷
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2 If this ventilatory limitation could be overcome, greater improvements in aerobic capacity could
3 be expected with hybrid FES exercise training.
4

5 *Ventilatory support during exercise*

6

7 Ventilatory support during exercise could be one approach to overcome this ventilatory
8 limitation. Indeed, we previously found that one single session of non-invasive ventilation led
9 to 12% improvement in aerobic capacity during hybrid FES-rowing in an individual with an
10 acute, high-level SCI whose aerobic capacity had been plateauing for 18 months despite regular
11 training⁷⁹. Moreover, we recently showed that changes in peak alveolar ventilation and VO_{2peak}
12 were strongly correlated such that improvement in peak ventilation with NIV resulted in
13 improvement in VO_{2peak} during a single session of FES-rowing.⁸⁰ In fact, ventilatory support
14 can improve respiratory pattern, resulting in slower and deeper breathing, a potentially more
15 efficient pattern for the increasing oxygen demand of exercise.⁸⁰ Not all patients would respond
16 to ventilatory support, but those with higher level of injury, shorter time since injury, and
17 incomplete injury seem to be the best responders with a potential increased exercise capacity.⁸⁰
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

34 *Limitation of the current literature*

35

36 One important limitation of the current literature, however, is the low quality of the studies.
37
38 Studies have a relatively small sample size (sometimes $n \leq 5$), and are underpowered. In
39 addition, many studies are not controlled, making the contribution of natural recovery during
40 the subacute period or spontaneous activity independent of the study difficult to ascertain. When
41 studies are randomized as exercise vs. control, significant changes with training are usually
42 found compared to baseline only, not supporting the superiority of training. Furthermore,
43 important selection or methodological bias make any comparison difficult. For example, some
44 studies include unmatched groups of subjects (up to >10 yr. difference in age or > 5 yr.
45 difference in TSI).^{33,53} In general, study discrepancies (level of injury, TSI, training
46 procedures) do not allow for comparison among studies. In addition, some studies omitted to
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 consider criteria of maximality for $\text{VO}_{2\text{peak}}$ testing. Indeed, some authors have termed their
2 values $\text{VO}_{2\text{peak}}$ but did not use standardized protocol or follow the widely accepted criteria to
3 ensure achievement of true maximum O_2 consumption. Other studies do not provide details on
4 either protocol or criteria. Only a few studies reported objective $\text{VO}_{2\text{peak}}$ using at least 3 criteria
5 of maximality^{15,57,58,61,63}. As a result, the magnitude of physiological adaptations could have
6 been mis-estimated in some studies. Lastly, whether training effects are maintained has never
7 been investigated prospectively. Studying training effects in SCI is very difficult due to
8 significant inter- individual differences, a relatively small patient population, and complexity
9 of care. Despite these constraints, prospective and randomized controlled studies, with larger
10 samples of well-matched individuals, will be required to provide more robust evidence of
11 cardiac and cardiovascular improvements after training in SCI.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26

27 *Future directions*

28
29 Any forms of exercise allowing for high-intensity level of exercise training should be
30 developed and further investigated. Among them, combinatorial therapies are promising
31 approaches in SCI. For example, endurance training can be associated with muscle
32 strengthening⁴⁵ and/or with ventilatory support for high-level injury⁸⁰. Furthermore, new
33 technologies will soon allow for greater intensity level of exercise with robotic-assisted training
34 or underwater training approaches⁵⁵. Lastly, motivation is a key determinant of long-term
35 training compliance. New technologies with digitalized platform and social networking may
36 offer longer adherence to training which could be interesting to investigate in SCI.
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 **SUMMARY**

54
55
56 Cardiovascular complications are the result of the direct and indirect consequences of SCI.
57
58 Years of accumulated relative inactivity lead to an accelerated aging and a high risk of
59
60
61
62
63
64
65

1 cardiovascular death. Exercise training is a cornerstone of rehabilitation in SCI due to its
2 potential cardio protection. Although its effect on autonomic dysfunction seems to be lacking,
3
4 exercise training does have an important role in counterbalancing the effect of deconditioning,
5
6 preserving cardiac function and improving cardiometabolic outcomes such as lean body mass,
7
8 blood lipids, and systemic inflammation. However, a major facet of exercise as underscored
9
10 from current studies is that adequate training intensity, volume, and frequency are essential for
11
12 cardiovascular gains. More recently, forms of combined exercise training (whole-body hybrid
13
14 leg FES + arms) have been shown to produce the highest O₂ consumption during exercise.
15
16
17 However, increasing peak ventilatory capacity may be necessary for those with high level SCI
18
19 to allow for increased aerobic capacity with this form of exercise. Nonetheless, there is a need
20
21 for future studies with bigger sample sizes, well-matched subject groups, and randomized
22
23 controlled designs to investigate whether high-intensity hybrid forms of training result in
24
25 greater cardiovascular gains.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References

1. Garshick E, Kelley A, Cohen SA, et al. A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord*. 2005;43(7):408-416.
2. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil*. 2007;86(2):142-152.
3. Cragg JJ, Noonan VK, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury: results from a national population health survey. *Neurology*. 2013;81(8):723-728.
4. Lai YJ, Lin CL, Chang YJ, et al. Spinal cord injury increases the risk of type 2 diabetes: a population-based cohort study. *Spine J*. 2014;14(9):1957-1964.
5. Groah SL, Nash MS, Ward EA, et al. Cardiometabolic risk in community-dwelling persons with chronic spinal cord injury. *J Cardiopulm Rehabil Prev*. 2011;31(2):73-80.
6. Shields RK. Muscular, skeletal, and neural adaptations following spinal cord injury. *J Orthop Sports Phys Ther*. 2002;32(2):65-74.
7. West CR, Bellantoni A, Krassioukov AV. Cardiovascular function in individuals with incomplete spinal cord injury: a systematic review. *Top Spinal Cord Inj Rehabil*. 2013;19(4):267-278.
8. Calaresu FR, Yardley CP. Medullary basal sympathetic tone. *Annu Rev Physiol*. 1988;50:511-524.
9. Solinsky R, Kirshblum SC, Burns SP. Exploring detailed characteristics of autonomic dysreflexia. *J Spinal Cord Med*. 2018;41(5):549-555.
10. Buker DB, Oyarce CC, Plaza RS. Effects of Spinal Cord Injury in Heart Rate Variability After Acute and Chronic Exercise: A Systematic Review. *Top Spinal Cord Inj Rehabil*. 2018;24(2):167-176.
11. Szabo BM, van Veldhuisen DJ, Brouwer J, Haaksma J, Lie KI. Relation between severity of disease and impairment of heart rate variability parameters in patients with chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1995;76(10):713-716.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
12. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol.* 2008;51(18):1725-1733.
13. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. *Psychoneuroendocrinology.* 2008;33(10):1305-1312.
14. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol.* 2013;10(3):143-155.
15. Solinsky R, Vivodtzev I, Hamner JW, Taylor JA. The effect of heart rate variability on blood pressure is augmented in spinal cord injury and is unaltered by exercise training. *Clin Auton Res.* 2020.
16. Hicks AL, Martin Ginis KA, Pelletier CA, Ditor DS, Foulon B, Wolfe DL. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. *Spinal Cord.* 2011;49(11):1103-1127.
17. 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(5):397-405.
18. Rowell LB. Human circulation - regulation during physical stress 1986.
19. Krassioukov A, Claydon VE. The clinical problems in cardiovascular control following spinal cord injury: an overview. *Prog Brain Res.* 2006;152:223-229.
20. van der Scheer JW, Martin Ginis KA, Ditor DS, et al. Effects of exercise on fitness and health of adults with spinal cord injury: A systematic review. *Neurology.* 2017.
21. LaVela SL, Evans CT, Prohaska TR, Miskevics S, Ganesh SP, Weaver FM. Males aging with a spinal cord injury: prevalence of cardiovascular and metabolic conditions. *Arch Phys Med Rehabil.* 2012;93(1):90-95.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
22. Wendt T, Harja E, Bucciarelli L, et al. RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. *Atherosclerosis*. 2006;185(1):70-77.
 23. Eickhoff P, Valipour A, Kiss D, et al. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;178(12):1211-1218.
 24. Haisma JA, van der Woude LH, Stam HJ, Bergen MP, Sluis TA, Bussmann JB. Physical capacity in wheelchair-dependent persons with a spinal cord injury: a critical review of the literature. *Spinal Cord*. 2006;44(11):642-652.
 25. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation*. 2008;117(5):614-622.
 26. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation*. 2011;124(23):2483-2490.
 27. Williams PT, Thompson PD. The relationship of walking intensity to total and cause-specific mortality. Results from the National Walkers' Health Study. *PLoS One*. 2013;8(11):e81098.
 28. Mohr T, Andersen JL, Biering-Sorensen F, et al. Long-term adaptation to electrically induced cycle training in severe spinal cord injured individuals. *Spinal Cord*. 1997;35(1):1-16.
 29. Tordi N, Dugue B, Klupzinski D, Rasseneur L, Rouillon JD, Lonsdorfer J. Interval training program on a wheelchair ergometer for paraplegic subjects. *Spinal Cord*. 2001;39(10):532-537.
 30. Hjeltnes N, Wallberg-Henriksson H. Improved work capacity but unchanged peak oxygen uptake during primary rehabilitation in tetraplegic patients. *Spinal Cord*. 1998;36(10):691-698.
 31. 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(6):819-830.
 32. Valent LJ, Dallmeijer AJ, Houdijk H, Sloopman 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(6):1016-1022.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
33. Wouda MF, Lundgaard E, Becker F, Strom V. Effects of moderate- and high-intensity aerobic training program in ambulatory subjects with incomplete spinal cord injury-a randomized controlled trial. *Spinal Cord*. 2018;56(10):955-963.
 34. Hooker SP, Figoni SF, Rodgers MM, et al. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. *Arch Phys Med Rehabil*. 1992;73(5):470-476.
 35. Nash MS, Bilsker S, Marcillo AE, et al. Reversal of adaptive left ventricular atrophy following electrically-stimulated exercise training in human tetraplegics. *Paraplegia*. 1991;29(9):590-599.
 36. Taylor PN, Ewins DJ, Fox B, Grundy D, Swain ID. Limb blood flow, cardiac output and quadriceps muscle bulk following spinal cord injury and the effect of training for the Odstock functional electrical stimulation standing system. *Paraplegia*. 1993;31(5):303-310.
 37. Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N, Hicks AL. Effects of body weight-supported treadmill training on heart rate variability and blood pressure variability in individuals with spinal cord injury. *J Appl Physiol (1985)*. 2005;98(4):1519-1525.
 38. Ditor DS, Macdonald MJ, Kamath MV, et al. The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI. *Spinal Cord*. 2005;43(11):664-673.
 39. Bloomfield SA, Jackson RD, Mysiw WJ. Catecholamine response to exercise and training in individuals with spinal cord injury. *Med Sci Sports Exerc*. 1994;26(10):1213-1219.
 40. Millar PJ, Rakobowchuk M, Adams MM, Hicks AL, McCartney N, MacDonald MJ. Effects of short-term training on heart rate dynamics in individuals with spinal cord injury. *Auton Neurosci*. 2009;150(1-2):116-121.
 41. Matos-Souza JR, de Rossi G, Costa ESAA, et al. Impact of Adapted Sports Activities on the Progression of Carotid Atherosclerosis in Subjects With Spinal Cord Injury. *Arch Phys Med Rehabil*. 2016;97(6):1034-1037.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
42. Faulkner J, Martinelli L, Cook K, et al. Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study. *J Spinal Cord Med.* 2019;1-7.
 43. 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(12):673-679.
 44. Midha M, Schmitt JK, Sclater M. Exercise effect with the wheelchair aerobic fitness trainer on conditioning and metabolic function in disabled persons: a pilot study. *Arch Phys Med Rehabil.* 1999;80(3):258-261.
 45. Kim DI, Taylor JA, Tan CO, et al. A pilot randomized controlled trial of 6-week combined exercise program on fasting insulin and fitness levels in individuals with spinal cord injury. *Eur Spine J.* 2019;28(5):1082-1091.
 46. Ordonez FJ, Rosety MA, Camacho A, et al. Arm-cranking exercise reduced oxidative damage in adults with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2013;94(12):2336-2341.
 47. Rosety-Rodriguez M, Rosety I, Fornieles G, et al. A short-term arm-crank exercise program improved testosterone deficiency in adults with chronic spinal cord injury. *Int Braz J Urol.* 2014;40(3):367-372.
 48. Berry HR, Perret C, Saunders BA, et al. Cardiorespiratory and power adaptations to stimulated cycle training in paraplegia. *Med Sci Sports Exerc.* 2008;40(9):1573-1580.
 49. 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(5):790-795.
 50. Hoekstra F, van Nunen MP, Gerrits KH, Stolwijk-Swuste JM, Crins MH, Janssen TW. Effect of robotic gait training on cardiorespiratory system in incomplete spinal cord injury. *J Rehabil Res Dev.* 2013;50(10):1411-1422.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
51. Valent LJ, Dallmeijer AJ, Houdijk H, et al. Effects of hand cycle training on physical capacity in individuals with tetraplegia: a clinical trial. *Phys Ther.* 2009;89(10):1051-1060.
 52. van der Scheer JW, de Groot S, Tepper M, Faber W, Veeger DH, van der Woude LH. Low-intensity wheelchair training in inactive people with long-term spinal cord injury: A randomized controlled trial on fitness, wheelchair skill performance and physical activity levels. *J Rehabil Med.* 2016;48(1):33-42.
 53. Gorman PH, Scott W, VanHiel L, Tansey KE, Sweatman WM, Geigle PR. Comparison of peak oxygen consumption response to aquatic and robotic therapy in individuals with chronic motor incomplete spinal cord injury: a randomized controlled trial. *Spinal Cord.* 2019;57(6):471-481.
 54. Milia R, Roberto S, Marongiu E, et al. Improvement in hemodynamic responses to metaboreflex activation after one year of training in spinal cord injured humans. *Biomed Res Int.* 2014;2014:893468.
 55. Stevens SL, Caputo JL, Fuller DK, Morgan DW. Effects of underwater treadmill training on leg strength, balance, and walking performance in adults with incomplete spinal cord injury. *J Spinal Cord Med.* 2015;38(1):91-101.
 56. Griffin L, Decker MJ, Hwang JY, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *J Electromyogr Kinesiol.* 2009;19(4):614-622.
 57. Qiu S, Alzhab S, Picard G, Taylor JA. Ventilation Limits Aerobic Capacity after Functional Electrical Stimulation Row Training in High Spinal Cord Injury. *Med Sci Sports Exerc.* 2016;48(6):1111-1118.
 58. Gibbons RS, Stock CG, Andrews BJ, Gall A, Shave RE. The effect of FES-rowing training on cardiac structure and function: pilot studies in people with spinal cord injury. *Spinal Cord.* 2016;54(10):822-829.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
59. Wheeler GD, Andrews B, Lederer R, 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(8):1093-1099.
60. Bakkum AJ, de Groot S, Stolwijk-Swuste JM, van Kuppevelt DJ, van der Woude LH, Janssen TW. 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(5):395-401.
61. Brurok 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(5):407-414.
62. 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(12):1957-1959.
63. 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(9):817-824.
64. Maggioni MA, Ferratini M, Pezzano A, et al. Heart adaptations to long-term aerobic training in paraplegic subjects: an echocardiographic study. *Spinal Cord.* 2012;50(7):538-542.
65. 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(3 Pt 2):R1072-1079.
66. Schumacher YO, Ruthardt S, Schmidt M, Ahlgrim C, Roecker K, Pottgiesser T. Total haemoglobin mass but not cardiac volume adapts to long-term endurance exercise in highly trained spinal cord injured athletes. *Eur J Appl Physiol.* 2009;105(5):779-785.
67. Gates PE, Campbell IG, George KP. Absence of training-specific cardiac adaptation in paraplegic athletes. *Med Sci Sports Exerc.* 2002;34(11):1699-1704.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
68. G DER, Matos-Souza JR, Costa ESAD, et al. Physical activity and improved diastolic function in spinal cord-injured subjects. *Med Sci Sports Exerc.* 2014;46(5):887-892.
 69. Ditor DS, Kamath MV, Macdonald MJ, Bugaresti J, McCartney N, Hicks AL. Reproducibility of heart rate variability and blood pressure variability in individuals with spinal cord injury. *Clin Auton Res.* 2005;15(6):387-393.
 70. Solinsky R DA, Taylor J. . Autonomic gains associated with 6 months of high-intensity FES Assisted rowing after SCI. *Topics in spinal cord injury rehabilitation.* 2019;25:s1:90.
 71. Lotri-Koffi A, Pauly M, Lemarie E, et al. Chronic neuromuscular electrical stimulation improves muscle mass and insulin sensitivity in a mouse model. *Sci Rep.* 2019;9(1):7252.
 72. 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(8):808-814.
 73. Hubli M, Currie KD, West CR, Gee CM, Krassioukov AV. Physical exercise improves arterial stiffness after spinal cord injury. *J Spinal Cord Med.* 2014;37(6):782-785.
 74. Schreiber R, Souza CM, Paim LR, et al. Impact of Regular Physical Activity on Adipocytokines and Cardiovascular Characteristics in Spinal Cord-Injured Subjects. *Arch Phys Med Rehabil.* 2018;99(8):1561-1567 e1561.
 75. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA.* 2002;288(16):1994-2000.
 76. McArdle W, Katch F, Katch V. Exercise physiology: energy, nutrition, and human performance. 4th ed. . 1996.
 77. Casaburi R, Barstow TJ, Robinson T, Wasserman K. Dynamic and steady-state ventilatory and gas exchange responses to arm exercise. *Med Sci Sports Exerc.* 1992;24(12):1365-1374.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
78. Taylor BJ, West CR, Romer LM. No effect of arm-crank exercise on diaphragmatic fatigue or ventilatory constraint in Paralympic athletes with cervical spinal cord injury. *J Appl Physiol (1985)*. 2010;109(2):358-366.
79. Morgan JW, Ferrazzani E, Taylor JA, Vivodtzev I. Augmenting exercise capacity with noninvasive ventilation in high-level spinal cord injury. *J Appl Physiol (1985)*. 2018;124(5):1294-1296.
80. Vivodtzev I, Picard G, Cepeda FX, Taylor JA. Acute Ventilatory Support During Whole-Body Hybrid Rowing in Patients With High-Level Spinal Cord Injury: A Randomized Controlled Crossover Trial. *Chest*. 2020;157(5):1230-1240.

Table 1: Baseline autonomic, cardiac, and metabolic deficiencies in Spinal cord injury

AUTONOMIC CONTROL	Sympathetic activity	↓ vasoconstriction in the periphery ↓ cardiovascular sympathetic control above T6 (complete loss above T1)
	Resting vagal tone	= but possible orthostatic hypotension and autonomic dysreflexia above T6
	Heart rate variability	↓
	Blood pressure variability	↑
AUTONOMIC REFLEXES	Baroreflex gain	↓ across almost all levels Relies solely on cardiac vagal modulation above T1
RESTING HEMODYNAMIC	Resting HR	=
	Resting BP	↓ across almost all levels of injury
	Stroke volume	=
	Resting CO	= or slightly lower
	Diastolic function	↓
VASCULAR STRUCTURE & FUNCTION	Endothelial function	↓ (impaired)
	Arterial stiffness	↑
	Intima media thickness	↑
CARDIAC FUNCTION	Left ventricular mass	↓
EXERCISE RESPONSES	Maximal HR	= up to T3 ↓ above T3
	Maximal Stroke Volume	↓ across all levels
	Peak VO ₂	Decreased across all levels ↓ with ↑ level of injury
	Peak CO	↓ mostly above T6
METABOLISM	Fat free mass	↓
	Fat mass	↑ higher obesity rate
	Type 2 diabetes	↑

Definition of abbreviation: BP, Blood pressure; CO, Cardiac output; HR, heart rate variability; VO₂, O₂ consumption.

Table 2: Training effects on fitness, cardiac, autonomic, cardiometabolic functions in Spinal cord injury

		LOW CVRF*	HIGH CVRF*
FITNESS, VO₂ TESTING	Peak VO ₂	↑↑↑	↑↑↑
	Peak PO	↑↑↑	↑↑
	Peak HR	= or ↓	↑↑
	Peak VE	= or ↑	=
	Peak Lactate	=	No study
	Peak CO	↑	↑
CARDIAC STRUCTURE & FUNCTION	Left ventricular mass	↑↑	↑
	Stroke volume	= or ↑	↑
	Resting CO	=	No study
	Diastolic function	↑↑	↑
AUTONOMIC FUNCTION	Resting HR	= or ↓	No study
	Maximal HR during training	No study	↓
	Heart rate variability	=	No study
	Blood pressure variability	=	No study
	Resting BP	=	No study
	Baroreflex gain	↑	No study
CARDIOVASCULAR FUNCTION	Endothelial function	↑↑	No study
	Femoral compliance	↑↑	No study
	Thigh blood flow	↑	No study
	Arterial stiffness	↓	↓
	Intima media thickness	↓↓	No study
BLOOD MARKERS OF CARDIOVASCULAR RISK	Fat free mass	↑	No study
	Fat mass	↓	↓
	Insulin sensitivity	= or ↑	=
	HDL-Cholesterol	↑↑	↓
	Triglycerides	↓↓	=
	IL-6	↓	↓
	TNF-α	↓	↓
	CRP	No study	↓
PTAS	↑	No study	

Definition of abbreviation: BP, Blood pressure; CO, Cardiac output; CRP, C reactive protein; Hb, Haemoglobin; HR, heart rate variability; IL-6, interleukin 6; PTAS, Plasmatic total antioxidant status; TNF-α, Tumor necrosis factor alpha; VO₂, O₂ consumption. *One arrow: only one study reporting the effect of training; Two arrows: ≥ 2 and < 5 studies agreeing on the same effect of training; Three arrows ≥ 5 studies agreeing on the same effect of training.

Table E1: Effect of exercise training on cardiac, autonomic and cardiometabolic outcomes in SCI with low-CVRF

Authors, date	Training	n	Age (yr.)	TSI (yr.)	Level of injury	Methods / VO ₂ testing	Main outcomes	Baseline value	Changes after training
<i>VO_{2peak} and Fitness</i>									
<i>Cervical injuries</i>									
Mohr, 1997 ²⁸	FES-cycling	10	27 - 45	3-23	C6-T4	Uncontrolled study	Peak VO ₂ , L/min	1.20 ± 0.08	↑ 23%, <i>P</i> < .05
					ASIA A-C	52 wks. 3x/wk, 30'	Peak PO, W	4 ± 1	↑ 425%
						Testing: FES-cycling ergometer	Peak lactate	9.0 ± 1.2	NS ↑ up to 11.8 ± 0.9
							MHC isoform IIA	33%	↑ 61%
Hjeltnes, 1998 ³⁰	Arm cycling	10	25 ± 2	< 0.5	C6-C8	Case -controlled study	Peak VO ₂ , L/min - Cervical	0.78 ± 0.07	No changes in Cervicals
			31 ± 4	< 0.5	T7 - T11	Arm cycling	Peak VO ₂ , L/min - Thoracic	1.37 ± 0.08	↑ 28%, <i>P</i> < .001
					Asia A-B	12-16 wks 3x/wk, 30'	Peak PO, W	22 ± 2	↑ 45%, <i>P</i> < .01
						Testing: Arm crank ergometer	Peak HR, pbm	110 ± 5	No changes
							Peak Lactate, mmol/L	5.86 ± 1.32	No changes
Janssen, 2008 ³¹	FES-cycling	12	36 ± 16	11 ± 9	C4-T11	Uncontrolled study	Peak VO ₂ , L/min	0.81 ± 0.28	NS ↑ 30%
					ASIA A-C	6 wks 3x/wk, 30'	Peak PO, W	8.6 ± 9.9	↑ 56%
						Interval training	Peak HR, pbm	97.4 ± 11.2	NS ↑ to 113.3 ± 23.0
						Testing: FES-cycling ergometer	Peak VE, L/min	41.3 ± 12.3	NS ↑ to 49.1 ± 9.1
							Peak CO, L/min	8.6 ± 1.9	NS ↑ to 9.5 ± 2.3
							Peak lactate, mmol/L	6.6 ± 1.9	NS ↑ to 8.7 ± 1.0
Qiu, 2016 ⁵⁷	FES rowing	12	33 ± 4	8 ± 3	C4 - T2	Uncontrolled study	Peak VO ₂ , mL/min/kg	15.3 ± 1.5	↑ 12% (<i>P</i> = .02)
						24 wks 2-3x/wk, 75%, 30'	Peak PO, W	34.6 ± 4.4	↑ 28% (<i>P</i> < .01)
						Testing: FES-rowing	Peak VE, L/min	37.5 ± 4.4	tendency <i>P</i> = .09
							Peak HR, pbm		No changes

							RER		No changes
							R. Peak VO ₂ vs. Peak VE	R2 = 0.62	↑ to r2 = 0.84
Wouda, 2018 ³³	Treadmill-85-95%	10	50 ± 15	< 0.5	7C/1T/2L	Randomized controlled trial	Peak VO ₂ , L/min	2.70 ± 0.81	↑ ~10% no ≠ btw gps
	Treadmill 70%	10	34 ± 15	< 0.5	4C/4T/2L	12 wks, 2x/wk, 35' vs. 45'	6MWD, m	561 ± 93	↑ ~15% no ≠ btw gps
	Usual care	10	41 ± 19	< 0.5	7C/2T/2L	Testing: Treadmill	Daily energy expenditure, KJ	2666 ± 528	No changes
					ASIA C-D		Peak lactate, mmol/L	6.6 ± 1.9	NS ↑ to 8.7 ± 1.0
<i>Thoracic injuries</i>									
Valent, 2009 ⁵¹	Hand cycle	35	42 ± 14	< 0.5	T1-T12	Cohort study	Peak VO ₂ , Para, L/min	1.10 ± 0.23	↑ 29% vs. bsl
	Control	56	40 ± 15	< 0.5	T1-T12	20-30 wks, 1-3/wk, 20-30'	Peak VO ₂ Para – Cont.	1.22 ± 0.48	↑ 7% vs. bsl
	Hand cycle	20	33 ± 10	< 0.5	C5-C8	Testing: Wheelchair treadmill	Peak VO ₂ Tetra, L/min	0.86 ± 0.32	No changes
	Control	26	44 ± 14	< 0.5	C5-C8		Peak VO ₂ Tetra – Cont.	0.97 ± 0.38	No changes
Tordi, 2001 ²⁹	Wheelchair	5	27 ± 8.1	~ 2	T6-L4	Uncontrolled study	Peak VO ₂ , mL/min/kg	21 (17 - 33)	↑ 18.5%
					ASIA A	4 wks 3x/wk, 30'	Peak PO, W	45 (35 - 45)	↑ 27.9%
						interval training	Peak HR, pbm	176	↓ 5%
						Testing: Wheelchair treadmill	Peak VE, L/min	64 (47 - 78)	No changes
<i>Cardiac structure and function</i>									
<i>Cervical injuries</i>									
Nash, 1991 ³⁵	NMES Quad + FES-cycling	8	28 ± 5	6 ± 3	C5-C7 ASIA A	Uncontrolled study	LV internal dimension, mm	48.9 ± 3.4	↑ 6.5% (P < .02)
						24 wks, 3/wk, 30'	ISWT, mm	7.5 ± 1.3	↑ 18% (P < .002)
						Echocardiography	Posterior wall thickness, mm	7.4 ± 1.2	↑ 20% (P < .01)
						End-diastolic measurements			
Hooker, 1992 ³⁴	FES-cycling	18	30 ± 2	6 ± 1	C4-T11	Uncontrolled study	Peak VO ₂ , L/min	0.78 ± 0.05	↑ 23% P < .05
						12-16 wks, 2/3x/wk, 10-30'	Peak CO, L/min	8.5 ± 0.5	↑ 13% P < .05
						Impedance cardiography	Total peripheral resistance, mmHg/l/min	11.3 ± 0.9	↓ 14% P < .05
							Peak VE, L/min	28.1 ± 1.2	↑ 27% P < .05

Taylor, 1993 ³⁶	NMES + stand ES	7	27 ± 7	2 ± 1	C5-T12	Uncontrolled study	Resting CO ml/min resting?	4360 ± 2790	NS ↑ to 5230 ± 1750		
			3 months program	Thigh blood flow ml/min		167 ± 70	↑ 115% <i>P</i> < .001				
			300 ms, 20 Hz, up to 150mA	Quadriceps depth, mm		14.5 ± 4.2	↑ 70% <i>P</i> < .001				
			Impedance cardiography	Subcutaneous fat,		15.9 ± 4.4	NS ↑ to 17 ± 4				
Hjeltnes, 1998 ³⁰	Arm cycling	10	25 ± 2	< 0.5	C6-C8	Case controlled study	Peak VO ₂ , L/min - Cervical	0.78 ± 0.07	No changes in Cervicals		
			10	31 ± 4	< 0.5	T7 - T11	Arm cycling	Peak VO ₂ , L/min - Thoracic	1.37 ± 0.08	↑ 28%, <i>P</i> < .001	
		CO ₂ -rebreathing method	Submax CO - Cervical	5.5 ± 0.6	NS ↑ to 6.8 ± 1.2						
			Submax CO - Thoracic	7.3 ± 0.4	No changes						
			Submax SV - Cervical	50 ± 4	NS ↑ to 69 ± 14						
			Submax SV - Thoracic	52 ± 4	No changes						
D.E. Rossi, 2014 ⁶⁸	Sedentary	29	31 ± 1	7 ± 1	C4-T12	Cross-sectional analysis	Stroke volume, mL	61.2 ± 2.3	> 15% in athletes, <i>P</i> < .05		
			Athletes	29	29 ± 1	9 ± 1	C4-T12	> 1 yr sport practice	LV end-diastolic diameter, mm	44.6 ± 0.7	> 7% in athletes, <i>P</i> < .05
								ASIA A/B	Echocardiography	LV end-systolic diameter, mm	28.0 ± 0.6
Gibbons, 2016 ⁵⁸	FES-rowing	5	32 ± 5	7 ± 7	C4-T10	Uncontrolled study	VO _{2peak} , L/min	0.97 ± 0.22	↑ 11%, <i>P</i> < .05		
							8 wks, 3/wk, 30'	Peak heart rate	151 ± 7	↑ 8%, <i>P</i> < .05	
							Doppler	LV mass, g	110 ± 6	↑ 7%, <i>P</i> < .05	
							Echocardiography	EDV, mL	65 ± 8	↑ 40% <i>P</i> < .05	
								ESV, mL	28 ± 5	↑ 25%, <i>P</i> < .05	
								Diastolic function (E/A)	1.38 ± 0.05	↑ 9%, <i>P</i> < .05	
<i>Thoracic injuries</i>											
Gates, 2002 ^{*67}	Power	11	25 ± 7	5-24	T1-T10	Cross-sectional analysis	Wall thickness, cm	0.83 ± 0.10	Tend to ↑ in whole group		
			Endurance	10	30 ± 9	8-18	T4-L1	Doppler	LV mass (g)	164 ± 66	Tend to ↑ in whole group
			Sedentary	5	29 ± 6	3-16	T1-T4	Echocardiography			no ≠ between groups
Maggioni, 2012 ⁶⁴	Endurance	10	33 ± 7	NA	T1-L1	Cross-sectional analysis	VO _{2peak} , ml/min/kg	13.3 ± 3.3	> 61% in trained, <i>P</i> = .001		
			Untrained	7	36 ± 10	T1-L3	5 yr / 3-5h /wk	IVST, mm	8.6 ± 0.8	>18% in trained, <i>P</i> = .01	

					ASIA A	Echocardiography	posterior wall thickness, mm	8.4 ± 1.1	NS ≠ in trained
							LV mass, g/m ²	56.3 ± 17.5	> 48% in trained, <i>P</i> = .01
							E/A ratio	1.64 ± 0.80	NS ≠ in trained
<i>Autonomic function</i>									
Bloomfield, 1994 ³⁹	FES-cycling	7	28 ± 2	5 ± 1	C5-T7	Uncontrolled study	VO _{2peak} , L/min	0.72 ± 0.1	No changes
						Catecholamine	Resting EPI pmol/L	163 ± 32	↓ 80%, <i>P</i> < .05
							Exercise NE pmol/L	1350 ± 610	No changes
							Exercise EPI pmol/L	510 ± 293	No changes
Ditor, JAP 2005 ³⁷	BWSTT	8	27.6	9.6 ± 7.5	C4-C5	Uncontrolled study	HR b/min	61.9 ± 6.9	↓10%, <i>P</i> < .05
					ASIA B-C	24 wks, 3x/wk, 15'	LF HRV (0.04-0.15 Hz) b/min	5894 ± 815	↓13%, <i>P</i> < .05
						10' Finapres	HF HRV (0.15-0.40 Hz) b/min	5493 ± 1472	No changes
							LF-to-HF ratio	1.23 ± 0.47	↓19%, <i>P</i> < .05
							LF SBP (0.04-0.15 Hz) mmHg ²	183.1 ± 46.8	↓14%, <i>P</i> < .01
							LF DBP (0.15-0.40 Hz) mmHg ²	191.0 ± 26.4	No changes
Ditor, SC 2005 ³⁸	BWSTT	6	37 ± 15	7.6 ± 9.4	C4-T12	Uncontrolled study	HR b/min	61.9 ± 9.7	No changes
						16 wks 15-60 min	LF HRV (0.04-0.15 Hz) b/min	6302 ± 1251	No changes
						10' Finapres	HF HRV (0.15-0.40 Hz) b/min	4647 ± 664	No changes
							LF/HF ratio	1.45 ± 0.44	No changes
Millar, 2009 ⁴⁰	BWSTT	6	37 ± 8	5.0 ± 4.4	C5-T10	Cross-over study	Normalized LF HRV	68.1 ± 10.3	No changes
					ASIA A-C	4 wks, 3x/wk	Normalized HF HRV	31.9 ± 10.3	No changes
						5' Finapres	LF/HF ratio	4.45 ± 1.32	No changes
						(breathing 12/min)	RMSSD	40.1 ± 23.0	No changes
Solinsky, 2020 ¹⁵	FES-rowing	15	30 ± 1	0.8 ± 0.1	C1-T10	Randomized controlled	VO _{2peak} , ml/min/kg	18.3 ± 1.3	↑ 11% vs. bsl
	Control	17	25 ± 1		C1-T10	24 wks, 2x/wk, 30'	LF HRV (0.05-0.15 Hz) ms ²	316 ± 55	No changes
					ASIA A-C	5' Finapres	HF HRV (0.20-0.30 Hz) ms ²	682 ± 135	No changes
						(breathing 15/min)	LF BPV (0.05-0.15 Hz) mmHg ²	1.39 ± 0.18	No changes

							HF BPV (0.20–0.30 Hz) mmHg ²	3.23 ± 0.51	No changes
<i>Cardiovascular function</i>									
<i>Cervical injuries</i>									
Ditor, SC 2005 ³⁸	BWSTT	6	37 ± 15	7.6 ± 9.4	C4-T12	Uncontrolled study 16 wks, 15-60 min Doppler ultrasound	Femoral compliance (mm ² /mmHg)	0.07 ± 0.03	↑42%, <i>P</i> = .07
Matos-Souza, 2016 ⁴¹	Upperbody	8	28 ± 2	5.1 ± 1.3	C5-T9	Non randomized controlled	Resting HR, b/m	71.4 ± 5.4	↑ in controls only
	Controls	9	33 ± 2	7.6 ± 1.5	C4-T8 ASIA A-B	5 yr follow up Carotid ultrasonography	Resting Stroke volume, mL Resting cardiac output, L/min Carotid IMT, mm CCA diameter, mm CCA resistive index	71.4 ± 5.4 5.0 ± 0.3 0.74 ± 0.05 5.3 ± 0.2 0.82 ± 0.02	No changes No changes ↓ 24% in trained only No changes No changes
Schreiber, 2018 ⁷⁴	Athletes	25	30 ± 6	9.7 ± 4.5	C4 to < T6	Cross-sectional comparison	Carotid IMT, mm	0.69 ± 0.10	< 19% in athletes, <i>P</i> < .01
	Sedentary	16	34 ± 7	8.2 ± 3.0	C4 to < T6	Athletes: 5 yr, 11 h/wk Carotid ultrasonography Echocardiography	E/A ratio E/Em ratio Adipocytokines	1.43 ± 0.38 7.7 ± 2.5 -	> 13% in athletes, <i>P</i> = .14 NS ≠ in trained NS ≠ in trained
Faulkner, 2019 ⁴²	Exoskeleton	6	30 (13)	2.7 (1.3)	ASIA A-C	Non-randomized trial	Augmentation index (Aix), %	30 ± 18	↓ 30%, <i>P</i> = .001
	Usual care	6	38 (17)	3.6 (2.5)	ASIA A-C	5 days, 90 min SphygmoCor	Normalized Aix to HR, % MAP, mmHg Central SBP, mmHg Central DBP, mmHg	21 ± 18 89 ± 11 117 ± 17 72 ± 8	↓ 33%, <i>P</i> = .001 NS ↓, <i>P</i> = .47 No changes No changes
<i>Thoracic injuries</i>									
Nash, 1997 ⁷²	FES-walking	12	28 ± 7	3.9 ± 3.1	T4-T11	Uncontrolled study Doppler ultrasound CFA = common femoral artery	Cross-sectional area, cm CFA Flow velocity integral, cm CFA pulse volume, mL	0.36 ± 0.06 16.8 ± 3.8 6.0 ± 1.7	↑ 33%, <i>P</i> < .0001 ↑ 26%, <i>P</i> < .05 ↑ 67% (<i>P</i> = .001)

CFA inflow mL/min	417.1 ± 122	↑ 56% (<i>P</i> < .01)
Resting HR, b/m	70.1 ± 10.1	↓ 7% (<i>P</i> < .05)

Blood markers of cardiovascular risk

Cervical injuries

Hjeltnes, 1997⁶⁵	FES-cycling	5	35 ± 3	10 ± 3	C5-C7	Uncontrolled study	VO _{2peak} , ml/min/kg	~7.5 ± 2.0	↑ 70% (<i>P</i> < .05)	
							DEXA and CT scan	Whole body fat	29.7 ± 2.6	↓ 7% (<i>P</i> < .05)
							Lower limb muscles CSA, cm ²	267 ± 27	↑ 21% (<i>P</i> < .05)	
Midha, 1999⁴⁴	Wheelchair	12	22-58	12 ± 7	C6-L3	Uncontrolled study	VO _{2peak} , ml/min/kg	19 + 6	↑ 25%, <i>P</i> = .02	
							10 wks, 2-3/wk, 30'	Resting HR, b/m	93 ± 14	↓ 29%, <i>P</i> = .02
							Blood samples	Fasting serum cholesterol (mg/dL)	185 ± 42	↓ 8%, <i>P</i> = .04
de Groot, 2003⁴³	Arm-crank High	3	39 (2)	0.3 ± 0.3	C5 to L1	Randomized controlled study	VO _{2peak} , ml/min/kg	~14 ± 6	↑ +33% High vs. Low	
	Arm-crank Low	3	52 (2)	0.3 ± 0.3	C5 to L1	8 wks, 3/wk [75% vs. 45%HRR]	Total Chol/HDL (post/pre)	100 (20)	↓ 23% High vs. Low	
						Fasting blood samples	Triglycerides (post/pre)	95 (14)	↓ 32% High vs. Low	
						HOMA-CIGMA test	Insulin sensitivity	156 (55)	NS↓ High vs. NS↑ Low	
Kim, 2019⁴⁵	Aerobic + resistance	11	36 ± 6	(2-27)	C4-L1	Randomized controlled trial	VO _{2peak} , ml/min/kg	11.7 ± 8.1	↑ 35% vs. bsl, <i>P</i> < .05	
	Control	6				6 wks, 3/wk, 60'	Insulin, μU/ml	7.5 ± 4.7	↓ 40%, <i>P</i> < .05	
						Fasting blood samples	HOMA-IR	1.5 ± 1.0 vs	↓ 40%, <i>P</i> < .05	
							Fat mass, %	35.3 ± 10.8	↓ 6%, <i>P</i> < .05	
							Total Chol (mg/dl)	162.3 ± 34.1	No change	
							HDL-C (mg/dl)	48.7 ± 21.3	↑ 12%, <i>P</i> < .05	

Thoracic injuries

Ordenez, 2013⁴⁶	Arm-crank	9	29 ± 3	4.6 ± 0.3	< T5	Randomized controlled trial	VO _{2peak} , ml/min/kg	23.2 ± 2.1	↑ 10% vs. pretest
	Control	8	30 ± 3	4.6 ± 0.3	< T5	12 wks, 3/wk, 30'	PTAS, mmol/L	0.64 ± 0.2	↑ 37% vs. pretest
						50% to 65%HRR	GP activity, U/g Hb	23.6 ± 2.4	↑ 18% vs. pretest
						Fasting blood samples	Lipid peroxidation, mmol/L	0.48 ± 0.13	↓ 27% vs. pretest

							Protein oxidation, nmol/mg	1.92 ± 0.3	↓ 31% vs. pretest
Rosety-Rodriguez, 2014⁴⁷	Arm-crank	9	29 ± 3	4.6 ± 0.3	< T5	Randomized controlled trial	PAI-1, ng/dL	29.8 ± 6.2	No change
	Controls	8	30 ± 3	4.6 ± 0.3	< T5	12 wks, 3/wk, 30'	Adiponectin (ng/mL)	18.8 ± 4.1	No change
						Fasting blood samples	Leptin (ng/mL)	9.6 ± 2.7	↓ 20% vs. pretest and Control
							TNF-α (pg/mL)	23.3 ± 5.6	↓ 13% vs. pretest and Control
							IL-6 (pg/mL)	6.7 ± 2.2	↓ 61% vs. pretest and Control

*SCI and spina bifida

Definition of abbreviation: Aix, Augmentation index; ASIA, American spinal injury association impairment scale; BPV, Blood pressure variability; Bsl = baseline; CCA, Common carotid artery; CFA = common femoral artery; CO, Cardiac output; DBP, diastolic blood pressure; E/A, peak early/atrial velocity ratio; EDV = end diastolic volume; E, peak early inflow velocity; EPI, Epinephrine; ESV, End-systolic volume; GP, Glutathione peroxidase ; Hb, hemoglobin; HDL, high density lipoprotein, HF, high frequency; HOMA-IR, Homeostatic model assessment of insulin resistance; HR, heart rate; HRV, Heart rate variability; IMT, Intima media thickness; ISWT, Interventricular septal wall thickness; IVST, intra-ventricular septum thickness; LF, Low frequency; IL-6, interleukin 6; LV, left ventricle; MAP, Mean arterial pressure; MHC, Myosin Heavy chain; NE, Norepinephrine; PA, physical activity; PAI-1, plasminogen activator inhibitor type 1; PO, power output; PTAS, Plasmatic total antioxidant status; PWV, Pulse wave velocity; RER, respiratory equivalent ratio; RMSSD, Root means square standard deviation; SBP, systolic blood pressure; SV, stroke volume; TNF-α, Tumor necrosis factor alpha; VE, minute ventilation; VFR = ventricular filling rate; VO_{2peak}, peak O₂ consumption; 6MWD, 6 minute walking distance.

Table E2: Effect of exercise training on cardiac, autonomic and cardiometabolic outcomes in SCI with high-CVRF

Authors, date	Training	n	Age (yr.)	TSI (yr.)	Level of injury	Methods / VO ₂ test	Main outcomes	Baseline value	Changes after training
<i>VO_{2peak} and Fitness</i>									
<i>Cervical injuries</i>									
Wheeler, 2002⁵⁹	FES rowing	6	42 ± 18	14 ± 12	C7–T12	Uncontrolled study	Peak VO ₂ , L/min	1.81 ± 0.41	↑ 11.2%, <i>P</i> < .001
						12 wks. 3x/wk., 75%, 30'	Peak HR, pbm	167.5 ± 20.9	No changes
						Test: FES-rowing	Peak VE, L/min	84 ± 27.2	No changes
							Peak RER	0.98 ± 0.12	NS ↑ up to 1.07
Valent, 2009⁵¹	Hand cycling	22	39 ± 12	10 ± 7	C5-T1 ASIA A-D	Uncontrolled study	Peak VO ₂ , L/min	1.32 ± 0.40	↑ ~10% <i>P</i> < .05
						12 wks. 2x/wk., 35-45'	Peak PO, W	42.5 ± 21.9	↑ ~20% <i>P</i> < .05
						Test: Hand-cycling treadmill			
Hoekstra, 2013⁵⁰	Robotic gait	10	49 ± 14	>1 - 35	C3-T10 ASIA C-D	Uncontrolled study	Peak VO ₂ , L/min	1.16 ± 0.40	No changes
						10-16 wks., 2-3/wk., 20-40'	Submax VO ₂ , L/min	0.75 ± 0.18	No changes
						Test: Armcrank ergometer	submax HR, pbm	116 ± 14	↓ 6%, <i>P</i> = .02
							Exercise Intensity - METs	2.1 ± 0.9	No changes
Bakkum, 2015⁶⁰	FES cycle + arms	10	48 ± 10	20 ± 8	C3-T10	Randomized controlled trial 16-wks., x/wk., 30' Test in respective mode	Peak VO ₂ , L/min	1.19 ± 0.20	↑12% vs. +3%, (NS ≠ gps)
	Hand cycle	10	47 ± 9	16 ± 6	C2-L2		Peak PO, W	35.9 ± 9.5	↑15% vs. +4%, (NS ≠ gps)
					ASIA A-D		Resting HR, pbm	73 ± 2	↓ 8% overall (NS ≠ gps)
							PA score, (PASIPD) h/wk.	6.3 ± 1.9	↑ 224 % vs. 150%, <i>P</i> = .10
Van des Scheer, 2016⁵²	Wheelchair treadmill	14	42–64	13–29	C4-L5	Randomized controlled trial	Peak VO ₂ , L/min	1.02	No changes and no ≠
	Control	15	46–62	14–31	C4-L5 Asia A-D	16 wks. 2x/wk., 30' Test: Wheelchair treadmill	Peak PO, W	43.6	No changes and no ≠
							PA score, h/wk	5.3	No changes and no ≠
							Distance km/week	7.4	No changes and no ≠
Gorman, 2019⁵³	Aquatic	15	47 ± 10	12 ± 12	C2-T12	Randomized controlled trial	Peak VO ₂ , Aqua, ml/kg/min	13.3 ± 3.1	↑8% vs. Robotic
	Robotic gait	18	45 ± 13	6 ± 4	C2-T12	12 wks., 3x/wk., 40-45'	Peak VO ₂ Robo, ml/kg/min	16.5 ± 5.4	No change

					ASIA C-D	Test: Armcrank ergometer	Peak VO ₂ robotic treadmill CO 80% of peak, L/min	14.9 ± 4.3	↑ 15% vs. baseline
<i>Thoracic injuries</i>									
Berry, 2008 ⁴⁸	FES-cycling	11	42 ± 8	10 ± 7	T3-T9 ASIA A	Uncontrolled study 52 wks. 5x/wk., 60' Test: FES-cycling ergometer	Peak VO ₂ , L/min Peak PO ₂ , W Peak HR, pbm Training duration vs. VO ₂ Peak	0.54 ± 0.14 8.4 ± 3.2 82 ± 8	↑ 56% ↑ 132%, <i>P</i> = .001 ↑ 14%, <i>P</i> < .05 (9 mth) <i>r</i> ² = 0.52, <i>P</i> = .012
Carty, 2012 ⁴⁹	NMES (2–8Hz) Quad + Hamstring	14	45 ± 8	11 ± 11	T4-T11 ASIA A-B	Prospective cohort study 8 wks., 5/wk., 60' Test: Wheelchair treadmill	Peak VO ₂ , L/min Peak HR, pbm	1.09 ± 0.20 159 ± 17	↑ 21%, <i>P</i> = .001 ↑ 3%, <i>P</i> = .03
<i>Cardiac structure and function</i>									
Schumacher, 2009 ⁶⁶	Elite athletes	25	36 ± 11	> 3	C6-S5	Cross-sectional analysis	VO _{2peak} , L/min	1.4 ± 0.3	> 85% in athletes, <i>P</i> < .05
	Untrained	10	45 ± 18	> 3	C6-S5	> 3 yr. 15h/wk. endurance CO ₂ rebreathing method Echocardiography	HRmax (beats/min) Cardiac volume Hb concentration (mmol/l) Total Hb mass, mmol	153 ± 42 793 ± 164 8.8 ± 1.4 390 ± 130	> 13% in athletes, <i>P</i> < .05 < 4% in athletes, <i>P</i> < .05 > 8% in athletes, <i>P</i> < .05 > 19% in athletes, <i>P</i> < .05
Brurok, 2011 ⁶¹	FES cycling + arm	6	40 ± 11	17 ± 8	C7, T1-T9 ASIA A	Uncontrolled study 8 wks., 3/wk., intervals Single breath acetylene	VO _{2peak} , ml/min/kg CO 80% of peak, L/min SV 80% of peak, ml/beat	24.6 ± 3.9 12.4 ± 1.9 77.7 ± 9.9	↑ 24%, <i>P</i> < 0.05 ↑ 27%, <i>P</i> < 0.05 ↑ 33%, <i>P</i> < 0.05
Milia, 2014 ⁵⁴	Arm crank	9	41 ± 11	5-15	T4–L1 ASIA A	Uncontrolled study 1 yr. / 3-5h /wk., 60%Wmax Impedance cardiography Resting post-ischemia	VO _{2peak} , L/min ΔCO post Ischemia, mL/min ΔVFR post Ischemia, mL/sec	1.4 ± 0.2 220 ± 745 –15 ± 35	↑ 11%, <i>P</i> < 0.05 ↑ 247%, <i>P</i> < 0.05 ↑ to +51 ± 50
<i>Autonomic function</i>									
Stevens, 2015 ⁵⁵	Submerged	11	48 ± 13	5 ± 8	C4-L2	Uncontrolled study	HR wks. 2/3, b/m	102 (93-115)	↓ 7% d6 vs. d1, <i>P</i> < .001
	treadmill				ASIA C-D	8 wks., 3x/wk., 15-24' Chest monitor last 15"	HR wks. 4/5, b/m (> speed) HR wks. 6/7, b/m (>> speed)	118 (108-126) 126 (121-138)	↓ 14% d6 vs. d1, <i>P</i> < .001 ↓ 17% d6 vs. d1, <i>P</i> < .001
<i>Cardiovascular function and blood markers of cardiovascular risk</i>									
Griffin, 2009 ⁵⁶	FES cycling	18	40 ± 2	11 ± 3	C4-T7	Uncontrolled study	Total Chol (mg/dl)	157.9 ± 6.3	No change

						10 wks., 2-3/wk., 30' Blood samples	HDL-C, (mg/dl) IL-6, pg/ml TNF- α , pg/ml CRP, mg/L	34.2 \pm 2.0 4.91 \pm 1.10 11.8 \pm 0.6 15.9 \pm 1.5	\downarrow 11% $P < .05$ \downarrow 22% $P < .05$ \downarrow 4% $P < .05$ \downarrow 19% $P < .05$
Hubli, 2014 ⁷³	Elite hand-cycle Non-elite	10 10	41 \pm 6 42 \pm 11	19 \pm 6 17 \pm 11	C2-T5 C4-T3	Cross-sectional comparison 17 \pm 4 vs. 1 \pm 2 h/wk. Applanation tonometry	Aortic PWV, m/sec Resting supine MAP, mmHg EDV 3' post Ischemia, mL	8.7 \pm 2.5 91 \pm 19 7.2 \pm 22.2	< 21% in athletes, $P = .04$ NS \neq in trained (81 \pm 10) \uparrow 370%
Jeon, 2010 ⁶²	FES-rowing	6	48.6 \pm 6	NA	T4-T10	Uncontrolled study 12 wks., 3-4/wk., 30' Fasting blood samples	VO _{2peak} , ml/min/kg plasma glucose, mg/dL plasma leptin, ng/dL Fat mass, % insulin sensitivity	21.4 \pm 1.23 103.2 \pm 6.8 6.9 \pm 1.7 25.5 \pm 1.8 3.6 0.8	\uparrow 8%, $P < .05$ \downarrow 10%, $P .28$ \downarrow 28%, $P .28$ \downarrow 5%, $P = .07$ No change

Definition of abbreviation: ASIA, American spinal injury association impairment scale; Bsl = baseline; CO = Cardiac output; CRP, C reactive protein; EDV = end diastolic volume; Gp, group; Hb, hemoglobin; HDL, high density lipoprotein, HR, heart rate; IL-6, interleukin 6; PA, physical activity; PO, power output; PWV, Pulse wave velocity; RER, respiratory equivalent ratio; SV, stroke volume; TNF- α , Tumor necrosis factor alpha; VE, minute ventilation; VFR = ventricular filling rate; VO_{2peak}, peak O₂ consumption.

Type of submission: Invited review

Title: Cardiac, autonomic and cardiometabolic impact of exercise training in spinal cord injury: A qualitative review

Running title: Cardiac rehabilitation in spinal cord injury

Authors: Isabelle Vivodtzev^{1,2,3}, PhD and J. Andrew Taylor^{1,2} PhD

Affiliations: ¹Harvard Medical School, Department of Physical Medicine and Rehabilitation, Boston MA, USA; ²Spaulding Rehabilitation Hospital, Cardiovascular Research Laboratory, Cambridge, MA, USA; ³Sorbonne Université, INSERM, UMRS1158, Neurophysiologie Respiratoire Expérimentale et Clinique, F-75005 Paris

Key words: Spinal cord injury; cardiac rehabilitation; exercise training; cardiovascular; autonomic

Funding: Support for this study was provided by NIH Grant (R01-HL-117037) and ACL Grant 90SI5021-01, USA. IV was supported by the Ellen R. and Melvin J. Gordon Center for the Cure and Treatment of Paralysis, USA.

Corresponding Author:

Isabelle Vivodtzev,
Cardiovascular Research Laboratory,
Spaulding Rehabilitation Hospital,
1575 Cambridge St., Cambridge, MA, USA 02138

Phone: +1 (617)758 5504

ivivodtzev@partners.org; isabelle.vivodtzev@sorbonne-universite.fr

Conflict of interest: The Authors have no conflict of interest to disclose

The authors have read and approved the manuscript

Text-only words count: 3761

Number of tables: 2

Number of figures: 0

Number of references: n = 80

Structured Abstract (Purpose or Objective; Review Methods; Summary) ≤ 250 words

(n =249)

Introduction: Direct and indirect effects of spinal cord injury (SCI) lead to important cardiovascular complications that are further increased by years of injury and the process of “accelerated aging”. The present review examines the current evidence in the literature for the potential cardio-protective effect of exercise training in SCI.

Review Methods: PubMed and Web of Science databases were screened for original studies investigating the effect of exercise-based interventions on aerobic capacity, cardiac structure/function, autonomic function, cardiovascular function and/or cardiometabolic markers. We compared the effects in individuals <40 yr. old with time since injury (TSI) <10 yr. with those in older individuals (> 40 yr. old) with longer TSI (>10 yr.), reasoning that the two can be considered individuals with low- vs. high- cardiovascular risk factors (CVRF).

Summary: Studies showed similar exercise effects in both groups (n = 31 in low-CVRF vs. n = 15 in high-CVRF). The evidence does not support any effect of exercise training on autonomic function but does support an increase peripheral blood flow, improved left ventricular mass, higher peak cardiac output, greater lean body mass, better anti-oxidant capacity, and improved endothelial function. In addition, some evidence suggests that it can result in lower blood lipids, systemic inflammation (IL-6, TNF- α and CRP), and arterial stiffness. Training intensity, volume, and frequency were key factors determining cardiovascular gains. Future studies with larger sample sizes, well-matched groups of subjects, and randomized controlled designs will be needed to determine if high-intensity hybrid forms of training result in greater cardiovascular gains.

Condensed Abstract ≤ 50 words

1 This review examines original studies investigating the impact of exercise-based interventions
2 on cardiac, autonomic, and cardiometabolic outcomes in spinal cord injury (SCI). Exercise
3 training does not alter autonomic function but it increases peripheral blood flow and
4 counterbalances many deleterious effects of deconditioning, improving cardiac function and
5 cardiometabolic outcomes in SCI.
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

INTRODUCTION

The cardioprotective effect of regular aerobic exercise in the general population is broadly accepted, but its importance for those with spinal cord injury (SCI) may be even greater. Indeed, SCI is associated with greater risk for cardiovascular disease compared to the general population.¹ Both symptomatic and asymptomatic cardiovascular disease prevalence is alarming in these patients² who have almost three times the odd ratio of developing heart disease and up to six times the risk for stroke compared to general population.³ Furthermore, early death occurs due to higher rates of obesity,³ type 2 diabetes,⁴ and cardiovascular disease.⁵

Autonomic dysfunction

Alterations in autonomic function are a direct consequence of SCI that may explain higher susceptibility to cardiovascular disease⁶ (Table 1). Indeed, damage to the spinal and/or central components of the autonomic nervous system lead to impaired neural control of the heart and blood vessels.⁷ Cardiac sympathetic nerve fibers which innervate the heart arise from the thoracic cord between T1 and T5⁸. As a result, cardiovascular sympathetic control is impaired or absent in individuals with SCI above the T6 spinal segment. Therefore, most individuals with SCI > T6 experience persistent hypotension and bradycardia on a daily basis, with episodic falls in blood pressure with the upright posture. Furthermore, transient episodes of aberrantly low and high blood pressure can be life-threatening, presenting as clinical complications known as orthostatic hypotension and autonomic dysreflexia.⁹ In addition, heart rate variability (HRV), a non-invasive tool for assessing cardiac autonomic control, is markedly impacted with implications for the development of cardiovascular disease after SCI.¹⁰ For example, lesser HRV is associated with cardiac diseases¹¹ and is prognostic for those with known cardiovascular disease.¹² Moreover, HRV decreases with age, is lower in those with a sedentary life style, and is inversely related to inflammatory markers in both healthy individuals

1 and those with cardiovascular disease¹³. On the other hand, there is a greater blood pressure
2 variability in SCI, and greater variability has been associated with cardiac, vascular, and renal
3 damage and with increased risk of cardiovascular events and mortality.¹⁴ We recently reported
4 that the HRV decrease is seen within the first 24 months after SCI, suggesting that this decline
5 is due, in part, to a direct impact of SCI itself rather than long-term effect of living with SCI.¹⁵
6
7
8
9
10
11
12

13 *Reduced cardiopulmonary fitness*

14
15

16 The loss of metabolically active tissue and reduced capacity to routinely engage in
17 aerobic exercise is another major effect of SCI.¹⁶ Aerobic capacity, a key component of
18 cardiopulmonary fitness, is related to the level and extent of SCI and decreases by ~5% with
19 each level of injury from T11 to C4 such that those with high-level injuries have aerobic
20 capacities <40% of their able-bodied peers.¹⁷ The demands of producing aerobic work require
21 integrated responses across a number of systems.¹⁸ The functional limit of aerobic work,
22 maximal oxygen consumption, is by definition the product of maximal systemic flow (i.e.,
23 cardiac output) and active muscle oxygen use (i.e., arteriovenous oxygen difference). On both
24 fronts, individuals with SCI have much greater obstacles to overcome in achieving and
25 maintaining high levels of aerobic fitness. For example, impaired sympathetic outflow
26 precludes the normal vasoconstriction in non-exercising tissue to redistribute blood flow to
27 active muscle. Indeed, to achieve high intensity exercise levels, it is critical that blood flow is
28 diverted from inactive tissues, including non-active skeletal muscle. In those with low maximal
29 cardiac output, maximal aerobic capacity can be reduced as much as 40% without regional
30 vasoconstriction.¹⁸ This is of particular relevance to those with injuries at T6 and above who
31 have lessened sympathetically mediated tachycardia and contractility, with subsequent reduced
32 stroke volume and cardiac output.¹⁹ Moreover, the loss of muscle function and trunk control in
33 those with tetraplegia impacts stability and hence the ability to engage in strenuous exercise.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2 As a result, individuals with the highest level of SCI may not achieve exercise intensities
3 required to reduce cardio metabolic risk.²⁰
4

5
6 *Metabolic dysfunction*
7

8
9 Due to a 'forced' sedentary life-style, cardiovascular and metabolic diseases develop
10 (such as hyperlipidaemia, glucose intolerance, and systemic inflammation) that are
11 superimposed upon the direct impact of SCI. Years of cumulative stresses due to nervous
12 system dysfunction, limited mobility, and increased inflammation lead to a process of
13 accelerated aging.²¹ For example, chronic hyperglycemia promotes arterial wall hypertrophy
14 and fibrosis and impairs endothelial function.²² Moreover, systemic inflammation (IL-6, TNF-
15 α and CRP) alters NO production, further contributing to endothelial dysfunction²³ and
16 increasing expression of adhesion molecules on activated endothelium, facilitating the
17 formation of atheromatous plaque. Hence, although increased arterial stiffness is part of the
18 normal aging process, systemic complications of SCI may contribute to a premature vascular
19 aging effect. This is particularly true in older individuals with SCI and those with longer time
20 of injury who have the greatest clustering of cardiometabolic risk factors.²⁴
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 One main goal of rehabilitation is therefore to increase aerobic capacity and reduce the
40 cardiovascular impact of SCI. For example, greater aerobic capacity decreases the risk for
41 cardiovascular disease mortality independent of age, ethnicity, and health conditions in able-
42 bodied adults²⁵. A 3.5 ml/kg/min improvement in aerobic capacity relates to a 19% decrease in
43 cardiovascular disease mortality.²⁶ Furthermore, the risk for all-cause mortality decreases in
44 direct relation to exercise training intensity²⁷. However, the impact of exercise rehabilitation
45 may differ in SCI depending on the nature of the injury. Though exercise is necessary in the
46 acute/subacute phase of SCI, it may be even more important for older individuals with longer
47 TSI who could benefit from its cardioprotective effect.
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

In the present review, we searched for published studies investigating the cardiovascular impact of exercise training in SCI. PubMed and Web of Science databases were screened using the following key words and MeSH terms: [spinal cord injury] AND [training or exercise or rehabilitation] AND [cardiac or autonomic or cardiovascular or cardiometabolic]. Original studies that met the following criteria were included: i) study design: within-group studies, non-randomized between-groups studies, randomized controlled studies, cross-sectional studies and cohort studies; ii) participants: individuals with spinal cord injury and iii) outcomes: effect of an exercise-based intervention on VO_{2peak} , cardiac structure or function, autonomic function, cardiovascular function, and/or cardiometabolic blood markers. Non-English language articles, case studies, review articles and congress abstracts were excluded. Only original studies with a minimum number of subjects of $n = 5$ and training duration of 7 days were included. Furthermore, we dichotomized the effect of exercise training into two categories of patients: younger individuals (<40-45 yr old) with shorter time since injury (< 10 yr), considered as those with low cardiovascular risk (low-CVRF) vs. older Individuals (~40-45 yr or older) with longer time since injury (> 10 yr) and higher cardiovascular risk (high-CVRF).

41 **REVIEW OF RELEVANT LITERATURE**

43 **Exercise training and aerobic capacity**

46 *Training modalities*

49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Our search identified 46 unique studies that fulfilled eligibility criteria. Thirty-one were in individuals with low-CVRF and 15 in those with high-CVRF. A substantial number of training modalities have been investigated, from wheelchair training to exoskeleton adapted walking (Table E1 and E2). Most exercise training programs require only arms or only leg engagement (either voluntarily or using electrical-stimulation devices), such as arm crank, hand cycling,

1 functional electrical stimulation (FES)-cycling, or body weight support treadmill training
2 (BWSTT).²⁸⁻⁵⁶ These are the most commonly used in SCI rehabilitation due accessibility and
3
4 low cost. Less frequently, exercise training programs have employed FES of the lower
5
6 extremities in combination with voluntary contraction of the arms, such as FES cycling + arm
7
8 or FES-rowing.^{15,57-62} These forms of exercise are considered as hybrid training since they allow
9
10 simultaneous contractions of the upper and lower limb muscle groups. Nevertheless, hybrid
11
12 forms of exercise require more assistance and learning (at least initially) but allow for greater
13
14 exercise intensities for longer periods⁶³.
15
16
17
18

19 *Aerobic capacity*

20
21
22
23 On the whole, exercise training positively affects VO_{2peak} in those with SCI. Indeed, we found
24
25 13 out of 16 studies reporting increase in VO_{2peak} after training in low-CVRF^{15,28-32,43-46,57,58,64,65}
26
27 and 9 out of 12 in high-CVRF^{48,49,51,53,54,59,61,62,66} (i.e., >75% of all studies; [see Table 2 for](#)
28
29 [summary and Table E1 and E2 for details](#)). However, the range of increases in VO_{2peak} was
30
31 highly variable, from 10 to 70% in both low and high CVRF individuals. For example, some
32
33 studies showed > 50% increase after only 8 weeks of training³⁰ while others showed only 12%
34
35 improvement after more than 16 weeks of training^{54,60}. This disparity may be due to the extreme
36
37 variability in subjects' characteristics and training protocols. Adaptations to training can be
38
39 impacted by level and completeness of injury. For example, patients with cervical injuries and
40
41 or complete injury have lower baseline VO_{2peak} and potentially lower ability to sustain high
42
43 intensity exercise. Indeed, two studies reported improvement in VO_{2peak} in subjects with
44
45 thoracic but not cervical injuries, despite similar training program.^{30,32} As a result, a smaller
46
47 improvement may be found in studies with a higher proportion of subjects with high-level SCI.
48
49
50 Another factor which can account for different adaptation to training is the level of physical
51
52 activity before or during the training program. Indeed, in most studies, patients are new to
53
54 training but not always.³¹ This can explain lower response to training in studies with patients
55
56
57
58
59
60
61
62
63
64
65

1 already engaged in rehabilitation. In addition, level of activity outside the study is almost never
2 described, and it is important to note that cohort studies show that when individuals engaged in
3 regular physical activity have considerably higher VO_{2peak} compared to those who are sedentary
4
5
6
7 ($\sim+60\%$)^{64,66}.
8
9

10 11 12 13 14 **Impact of exercise training on the cardiovascular system**

15 16 17 *Cardiac function*

18
19 An important question is whether exercise training improves cardiac and cardiovascular health
20 in SCI. As VO_{2peak} is the product of cardiac output and arteriovenous O_2 difference, hence
21 increases in VO_{2peak} reflect changes at the cardiac and/or at the peripheral level. A first
22 interesting finding is that 4 weeks of quadriceps muscle training using electrical stimulation
23 followed by 6 months of functional electrical stimulation (FES)-cycling increased left
24 ventricular (LV) mass in young individuals within ~ 6 yr. after complete injury³⁵ ([Table 2, E1](#)
25 [and E2](#)). This may relate to increased leg muscle mass (+70%) and thigh blood flow (+115%)
26 as reported in Taylor et al.³⁶ In addition, FES-cycle training has been shown to increase
27 peak cardiac output.³⁴ This 12-16-week program of FES-cycling led to a 24% improvement in
28 VO_{2peak} associated with a 13% increase in peak CO.³⁴ These results suggest that the leg muscle
29 pump may be important to gains in CO after training in SCI. In fact, CO may be enhanced via
30 increased venous return to the heart leading to increased LV mass and stroke volume. Greater
31 LV mass and/or diameter is, indeed, the most commonly reported finding in cross-sectional
32 studies^{64,66-68}. Furthermore, only 8 weeks of hybrid exercise can result in significant
33 improvement in cardiac structure and function both in low and high-CVRF individuals with
34 SCI.^{58,61} This was obtained with concomitant improvement in VO_{2peak} . Hence, changes in
35 VO_{2peak} seems to be mainly due to improvements at the cardiac level (peak CO, SV, LV) in
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 both subcategories. However, there is one report of increases in haemoglobin mass and
2 concentration that could also be a factor in improved in VO_{2peak} , even without cardiac changes
3
4 in individuals with SCI and high-CVRF.⁶⁶
5
6

7 *Autonomic function*

8
9
10 Few studies have investigated the effect of training on autonomic function in SCI and most of
11 them enrolled subjects with low CVRF. These studies are uniform in finding no effect of
12 endurance training on autonomic function in SCI ([Table 2, E1 and E2](#)). This was found despite
13 improved VO_{2peak} ¹⁵ and despite training modalities that engaged the whole body.^{15,37,54,69} This
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

lack of change may indicate that damaged autonomic pathways after SCI cannot adapt to
exercise training as in uninjured individuals. There could be an effect of endurance training on
peak heart rate during training sessions⁵⁵ but this does not seem to impact HRV. Nevertheless,
we recently reported that high-intensity exercise training (FES-rowing) improved baroreflex
gain by 30% after 6 months of training, compared to a decrease in a matched control group
(Solinsky et al, American Spinal Injury Association Annual Meeting 2019)⁷⁰. Here, again, only
individuals in the subacute period after injury (< 2 yr.) were investigated. In addition, the effects
of exercise training on orthostatic hypotension has not been systematically studied in SCI.
Further studies will be needed to confirm this result and to understand the mechanisms.
Importantly, studies should investigate if exercise training could have an impact on baroreflex
sensitivity in those with high CVRF. Furthermore, more studies should provide quantitative
assessment of change in orthostatic tolerance with exercise training in SCI

66 *Metabolic markers and cardiovascular function*

67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100

A substantial number of studies have investigated the cardiovascular and metabolic impact of
exercise training in SCI. Studies agree on an overall positive effect of exercise on cardio
metabolic parameters in SCI ([Table 2, E1 and E2](#)). Indeed, at least four studies in individuals

1 with low CVRF and two in those with high CVRF report an increase in lean body mass^{30,45,62}
2 and/or a reduction in plasma lipids with training.^{43-45,47} In addition, training can decrease
3 plasma leptin,⁴⁷ a well-known hormone associated with obesity-linked metabolic and vascular
4 diseases in SCI. All but one study also reported concomitant improvement in VO_{2peak} with
5 training, suggesting that metabolic improvements occur when intensity is sufficient to increase
6 aerobic capacity. Furthermore, both resistance training⁴⁵ and high intensity aerobic exercise
7 (75% Heart rate reserve)⁴³ can improve insulin sensitivity, suggesting muscular anabolism is
8 involved in this adaptation. For example, lower limb FES training increases both muscle mass
9 and insulin sensitivity after only 10 sessions in mice.⁷¹ Lastly, exercise training can reduce
10 systemic inflammation and oxidative stress in SCI. The inflammatory cytokines IL-6, TNF- α ,
11 and CRP, as well as lipid and protein peroxidation were decreased by exercise training,^{46,47,56}
12 while anti-oxidant capacity was increased.⁴⁶ Interestingly, femoral and aortic compliances were
13 also improved after training^{38,42,72} while carotid intima-media thickness was decreased.⁴¹ This
14 could be the result of a concomitant reduction in hyperglycemia and systemic inflammation,
15 two main factors of cardiovascular function alteration in SCI. These observations are confirmed
16 by cross-sectional comparisons of athletes vs. sedentary or non-elite individuals with SCI,^{73,74}
17 suggesting once again that a high volume and/or intensity of exercise are key components for
18 cardiovascular protection in SCI. However, most studies have been in individuals with low
19 CVFR and more studies are needed to confirm a positive impact in those with high CVRF.

49 DISCUSSION

50
51
52 The current body of literature suggest that the cardioprotective goal of exercise training is
53 partially reached in SCI. Indeed, aerobic capacity is increased by training in ~75% of the studies
54 analysed. Furthermore, improvement in VO_{2peak} is almost always associated with improvements
55 in cardiovascular health. Indeed, although it fails to alter autonomic function, exercise training
56
57
58
59
60
61
62
63
64
65

1 can increase peripheral blood flow and reverse the deleterious effects of deconditioning.
2 Improvements in cardiac structure and function (mainly increased LV mass and CO), body
3 composition (increased lean body mass), lipid status, systemic inflammation (reduced
4 circulatory cytokines and increased anti-oxidant capacity), and cardiovascular function
5 (reduced arterial stiffness and improved endothelial function) have been consistently reported
6 across studies. Given the increased risk of cardiovascular mortality in SCI, such adaptations are
7 of primary importance. Moreover, these adaptations occur not only in those in the acute phase
8 of recovery post injury but also in those with longer time since injury and considered at high
9 cardiovascular risk. Hence, adaptations to training are not dependent on baseline CVRF but
10 rather on the ability to engage in high-intensity level of exercise. Indeed, cardiovascular stress
11 during exercise needs to be sufficient to obtain a cardiovascular effect of training. One main
12 outcome seems to be the magnitude of oxygen consumption that can be achieved during
13 exercise training. The lack of cardiovascular adaptations with training approaches using low
14 intensity of exercise^{52,60} strongly support this observation. Furthermore, cross sectional studies
15 between athletes and sedentary subjects show the greatest differences between trained and
16 untrained individuals. On the contrary, functional improvement after training (increase in power
17 output) does not necessarily relate to increases in VO_{2peak} . Indeed, increase in power output
18 often occurs before changes at the metabolic level due to a learning effect and a better
19 coordination at the muscular level during exercise. Hence, a training program may improve the
20 ability to perform a task, but not result in cardiovascular adaptations.

21 *The benefit of hybrid forms of training*

22 Studies of whole-body hybrid approaches (FES-cycling + arms or FES-rowing) have led to
23 more consistent (~12%, range 8-24%) improvements in VO_{2peak} than arms or legs-only training,
24 in those with both low and high CVRF.^{15,57,58,60-62} This level of improvement may reflect a
25 certain specific physiological adaptation. Hybrid forms of exercise create a leg muscle pump in
26

1 synchrony with the upper body exercise. Moreover, hybrid exercise can require a high
2 cardiopulmonary demand compared to arms/legs-only exercise in SCI due to the greater muscle
3 mass engaged⁶³. Hence, higher gains in VO_{2peak} from hybrid FES row training should be
4 expected compared with FES cycling alone.⁶³ Furthermore, these forms of exercise may lead
5 to greater cardio-protection. Given that risk for mortality decreases in association with higher
6 exercise intensities²⁷ and that there is a 6 metabolic equivalent exercise intensity threshold
7 below which the reduction in risk may be minimal,⁷⁵ there is need for training approaches that
8 generate the greatest oxygen consumption demand. Hence, combined form of exercise might
9 be most appropriate for those with SCI given the more consistent improvements in VO_{2peak} with
10 training.
11
12
13
14
15
16
17
18
19
20
21
22

23 **Innovative approaches**

24 *Ventilatory capacity and VO_{2peak} in high-level SCI*

25
26
27 Although active muscle oxygen use is a key determinant of VO_{2peak} , aerobic exercise also
28 requires sufficient ventilation to provide oxygen to working muscles.⁷⁶ In most able-bodied
29 individuals, ventilatory capacity is more than adequate to meet metabolic demands for all
30 exercise intensities.⁷⁷ However, SCI is characterized by profound respiratory compromise
31 usually proportional to the level of injury, with those with injuries above T3 having the most
32 profound loss.⁶ There is little impact during arms only exercise, due to the proportional
33 denervation of both skeletal and pulmonary muscle such that the respiratory system is still able
34 to cope with the demands of arms-only exercise, even after training.⁷⁸ However, as mentioned
35 above, hybrid FES exercise can overcome the limited muscle mass and result in higher peak
36 aerobic capacity than arms-only or FES legs-only exercise. As a result, aerobic adaptations to
37 exercise in those with high-level injuries can be constrained by reduced ventilatory capacity.⁵⁷
38
39 If this ventilatory limitation could be overcome, greater improvements in aerobic capacity could
40 be expected with hybrid FES exercise training.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Ventilatory support during exercise

Ventilatory support during exercise could be one approach to overcome this ventilatory limitation. Indeed, we previously found that one single session of non-invasive ventilation led to 12% improvement in aerobic capacity during hybrid FES-rowing in an individual with an acute, high-level SCI whose aerobic capacity had been plateauing for 18 months despite regular training⁷⁹. Moreover, we recently showed that changes in peak alveolar ventilation and VO_{2peak} were strongly correlated such that improvement in peak ventilation with NIV resulted in improvement in VO_{2peak} during a single session of FES-rowing.⁸⁰ In fact, ventilatory support can improve respiratory pattern, resulting in slower and deeper breathing, a potentially more efficient pattern for the increasing oxygen demand of exercise.⁸⁰ Not all patients would respond to ventilatory support, but those with higher level of injury, shorter time since injury, and incomplete injury seem to be the best responders with a potential increased exercise capacity.⁸⁰

Limitation of the current literature

One important limitation of the current literature, however, is the low quality of the studies. Studies have a relatively small sample size (sometimes $n \leq 5$), and are underpowered. In addition, many studies are not controlled, making the contribution of natural recovery during the subacute period or spontaneous activity independent of the study difficult to ascertain. When studies are randomized as exercise vs. control, significant changes with training are usually found compared to baseline only, not supporting the superiority of training. Furthermore, important selection or methodological bias make any comparison difficult. For example, some studies include unmatched groups of subjects (up to >10 yr. difference in age or > 5 yr. difference in TSI).^{33,53} In general, study discrepancies (level of injury, TSI, training procedures) do not allow for comparison among studies. In addition, some studies omitted to consider criteria of maximality for VO_{2peak} testing. Indeed, some authors have termed their values VO_{2peak} but did not use standardized protocol or follow the widely accepted criteria to

1 ensure achievement of true maximum O₂ consumption. Other studies do not provide details on
2 either protocol or criteria. Only a few studies reported objective VO_{2peak} using at least 3 criteria
3 of maximality^{15,57,58,61,63}. As a result, the magnitude of physiological adaptations could have
4 been mis-estimated in some studies. Lastly, whether training effects are maintained has never
5 been investigated prospectively. Studying training effects in SCI is very difficult due to
6 significant inter- individual differences, a relatively small patient population, and complexity
7 of care. Despite these constraints, prospective and randomized controlled studies, with larger
8 samples of well-matched individuals, will be required to provide more robust evidence of
9 cardiac and cardiovascular improvements after training in SCI.
10
11
12
13
14
15
16
17
18
19
20
21

22 *Future directions*

23 ~~Hence,~~ Any forms of exercise allowing for high-intensity level of exercise training should be
24 developed and further investigated. Among them, combinatorial therapies are promising
25 approaches in SCI. For example, endurance training can be associated with muscle
26 strengthening⁴⁵ and/or with ventilatory support for high-level injury⁸⁰. Furthermore, new
27 technologies will soon allow for greater intensity level of exercise with robotic-assisted training
28 or underwater training approaches⁵⁵. Lastly, motivation is a key determinant of long-term
29 training compliance. New technologies with digitalized platform and social networking may
30 offer longer adherence to training which could be interesting to investigate in SCI.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

48 **SUMMARY**

49
50
51 Cardiovascular complications are the result of the direct and indirect consequences of SCI.
52 Years of accumulated relative inactivity lead to an accelerated aging and a high risk of
53 cardiovascular death. Exercise training is a cornerstone of rehabilitation in SCI due to its
54 potential cardio protection. Although its effect on autonomic dysfunction seems to be lacking,
55
56
57
58
59
60
61
62
63
64
65

1 exercise training does have an important role in counterbalancing the effect of deconditioning,
2 preserving cardiac function and improving cardiometabolic outcomes such as lean body mass,
3
4 blood lipids, and systemic inflammation. However, a major facet of exercise as underscored
5
6 from current studies is that adequate training intensity, volume, and frequency are essential for
7
8 cardiovascular gains. More recently, forms of combined exercise training (whole-body hybrid
9
10 leg FES + arms) have been shown to produce the highest O₂ consumption during exercise.
11
12 However, increasing peak ventilatory capacity may be necessary for those with high level SCI
13
14 to allow for increased aerobic capacity with this form of exercise. Nonetheless, there is a need
15
16 for future studies with bigger sample sizes, well-matched subject groups, and randomized
17
18 controlled designs to investigate whether high-intensity hybrid forms of training result in
19
20 greater cardiovascular gains.
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

References

1. Garshick E, Kelley A, Cohen SA, et al. A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord*. 2005;43(7):408-416.
2. Myers J, Lee M, Kiratli J. Cardiovascular disease in spinal cord injury: an overview of prevalence, risk, evaluation, and management. *Am J Phys Med Rehabil*. 2007;86(2):142-152.
3. Cragg JJ, Noonan VK, Krassioukov A, Borisoff J. Cardiovascular disease and spinal cord injury: results from a national population health survey. *Neurology*. 2013;81(8):723-728.
4. Lai YJ, Lin CL, Chang YJ, et al. Spinal cord injury increases the risk of type 2 diabetes: a population-based cohort study. *Spine J*. 2014;14(9):1957-1964.
5. Groah SL, Nash MS, Ward EA, et al. Cardiometabolic risk in community-dwelling persons with chronic spinal cord injury. *J Cardiopulm Rehabil Prev*. 2011;31(2):73-80.
6. Shields RK. Muscular, skeletal, and neural adaptations following spinal cord injury. *J Orthop Sports Phys Ther*. 2002;32(2):65-74.
7. West CR, Bellantoni A, Krassioukov AV. Cardiovascular function in individuals with incomplete spinal cord injury: a systematic review. *Top Spinal Cord Inj Rehabil*. 2013;19(4):267-278.
8. Calaresu FR, Yardley CP. Medullary basal sympathetic tone. *Annu Rev Physiol*. 1988;50:511-524.
9. Solinsky R, Kirshblum SC, Burns SP. Exploring detailed characteristics of autonomic dysreflexia. *J Spinal Cord Med*. 2018;41(5):549-555.
10. Buker DB, Oyarce CC, Plaza RS. Effects of Spinal Cord Injury in Heart Rate Variability After Acute and Chronic Exercise: A Systematic Review. *Top Spinal Cord Inj Rehabil*. 2018;24(2):167-176.
11. Szabo BM, van Veldhuisen DJ, Brouwer J, Haaksma J, Lie KI. Relation between severity of disease and impairment of heart rate variability parameters in patients with chronic congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1995;76(10):713-716.

12. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease: physiological basis and prognostic implications. *J Am Coll Cardiol.* 2008;51(18):1725-1733.
13. Haensel A, Mills PJ, Nelesen RA, Ziegler MG, Dimsdale JE. The relationship between heart rate variability and inflammatory markers in cardiovascular diseases. *Psychoneuroendocrinology.* 2008;33(10):1305-1312.
14. Parati G, Ochoa JE, Lombardi C, Bilo G. Assessment and management of blood-pressure variability. *Nat Rev Cardiol.* 2013;10(3):143-155.
15. Solinsky R, Vivodtzev I, Hamner JW, Taylor JA. The effect of heart rate variability on blood pressure is augmented in spinal cord injury and is unaltered by exercise training. *Clin Auton Res.* 2020.
16. Hicks AL, Martin Ginis KA, Pelletier CA, Ditor DS, Foulon B, Wolfe DL. The effects of exercise training on physical capacity, strength, body composition and functional performance among adults with spinal cord injury: a systematic review. *Spinal Cord.* 2011;49(11):1103-1127.
17. 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(5):397-405.
18. Rowell LB. Human circulation - regulation during physical stress 1986.
19. Krassioukov A, Claydon VE. The clinical problems in cardiovascular control following spinal cord injury: an overview. *Prog Brain Res.* 2006;152:223-229.
20. van der Scheer JW, Martin Ginis KA, Ditor DS, et al. Effects of exercise on fitness and health of adults with spinal cord injury: A systematic review. *Neurology.* 2017.
21. LaVela SL, Evans CT, Prohaska TR, Miskevics S, Ganesh SP, Weaver FM. Males aging with a spinal cord injury: prevalence of cardiovascular and metabolic conditions. *Arch Phys Med Rehabil.* 2012;93(1):90-95.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
22. Wendt T, Harja E, Bucciarelli L, et al. RAGE modulates vascular inflammation and atherosclerosis in a murine model of type 2 diabetes. *Atherosclerosis*. 2006;185(1):70-77.
 23. Eickhoff P, Valipour A, Kiss D, et al. Determinants of systemic vascular function in patients with stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2008;178(12):1211-1218.
 24. Haisma JA, van der Woude LH, Stam HJ, Bergen MP, Sluis TA, Bussmann JB. Physical capacity in wheelchair-dependent persons with a spinal cord injury: a critical review of the literature. *Spinal Cord*. 2006;44(11):642-652.
 25. Kokkinos P, Myers J, Kokkinos JP, et al. Exercise capacity and mortality in black and white men. *Circulation*. 2008;117(5):614-622.
 26. Lee DC, Sui X, Artero EG, et al. Long-term effects of changes in cardiorespiratory fitness and body mass index on all-cause and cardiovascular disease mortality in men: the Aerobics Center Longitudinal Study. *Circulation*. 2011;124(23):2483-2490.
 27. Williams PT, Thompson PD. The relationship of walking intensity to total and cause-specific mortality. Results from the National Walkers' Health Study. *PLoS One*. 2013;8(11):e81098.
 28. Mohr T, Andersen JL, Biering-Sorensen F, et al. Long-term adaptation to electrically induced cycle training in severe spinal cord injured individuals. *Spinal Cord*. 1997;35(1):1-16.
 29. Tordi N, Dugue B, Klupzinski D, Rasseneur L, Rouillon JD, Lonsdorfer J. Interval training program on a wheelchair ergometer for paraplegic subjects. *Spinal Cord*. 2001;39(10):532-537.
 30. Hjeltnes N, Wallberg-Henriksson H. Improved work capacity but unchanged peak oxygen uptake during primary rehabilitation in tetraplegic patients. *Spinal Cord*. 1998;36(10):691-698.
 31. 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(6):819-830.
 32. Valent LJ, Dallmeijer AJ, Houdijk H, Sloopman 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(6):1016-1022.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
33. Wouda MF, Lundgaard E, Becker F, Strom V. Effects of moderate- and high-intensity aerobic training program in ambulatory subjects with incomplete spinal cord injury-a randomized controlled trial. *Spinal Cord*. 2018;56(10):955-963.
34. Hooker SP, Figoni SF, Rodgers MM, et al. Physiologic effects of electrical stimulation leg cycle exercise training in spinal cord injured persons. *Arch Phys Med Rehabil*. 1992;73(5):470-476.
35. Nash MS, Bilsker S, Marcillo AE, et al. Reversal of adaptive left ventricular atrophy following electrically-stimulated exercise training in human tetraplegics. *Paraplegia*. 1991;29(9):590-599.
36. Taylor PN, Ewins DJ, Fox B, Grundy D, Swain ID. Limb blood flow, cardiac output and quadriceps muscle bulk following spinal cord injury and the effect of training for the Odstock functional electrical stimulation standing system. *Paraplegia*. 1993;31(5):303-310.
37. Ditor DS, Kamath MV, MacDonald MJ, Bugaresti J, McCartney N, Hicks AL. Effects of body weight-supported treadmill training on heart rate variability and blood pressure variability in individuals with spinal cord injury. *J Appl Physiol (1985)*. 2005;98(4):1519-1525.
38. Ditor DS, Macdonald MJ, Kamath MV, et al. The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI. *Spinal Cord*. 2005;43(11):664-673.
39. Bloomfield SA, Jackson RD, Mysiw WJ. Catecholamine response to exercise and training in individuals with spinal cord injury. *Med Sci Sports Exerc*. 1994;26(10):1213-1219.
40. Millar PJ, Rakobowchuk M, Adams MM, Hicks AL, McCartney N, MacDonald MJ. Effects of short-term training on heart rate dynamics in individuals with spinal cord injury. *Auton Neurosci*. 2009;150(1-2):116-121.
41. Matos-Souza JR, de Rossi G, Costa ESAA, et al. Impact of Adapted Sports Activities on the Progression of Carotid Atherosclerosis in Subjects With Spinal Cord Injury. *Arch Phys Med Rehabil*. 2016;97(6):1034-1037.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
42. Faulkner J, Martinelli L, Cook K, et al. Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study. *J Spinal Cord Med.* 2019;1-7.
 43. de Groot PC, Hjeltnes 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(12):673-679.
 44. Midha M, Schmitt JK, Sclater M. Exercise effect with the wheelchair aerobic fitness trainer on conditioning and metabolic function in disabled persons: a pilot study. *Arch Phys Med Rehabil.* 1999;80(3):258-261.
 45. Kim DI, Taylor JA, Tan CO, et al. A pilot randomized controlled trial of 6-week combined exercise program on fasting insulin and fitness levels in individuals with spinal cord injury. *Eur Spine J.* 2019;28(5):1082-1091.
 46. Ordonez FJ, Rosety MA, Camacho A, et al. Arm-cranking exercise reduced oxidative damage in adults with chronic spinal cord injury. *Arch Phys Med Rehabil.* 2013;94(12):2336-2341.
 47. Rosety-Rodriguez M, Rosety I, Fornieles G, et al. A short-term arm-crank exercise program improved testosterone deficiency in adults with chronic spinal cord injury. *Int Braz J Urol.* 2014;40(3):367-372.
 48. Berry HR, Perret C, Saunders BA, et al. Cardiorespiratory and power adaptations to stimulated cycle training in paraplegia. *Med Sci Sports Exerc.* 2008;40(9):1573-1580.
 49. 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(5):790-795.
 50. Hoekstra F, van Nunen MP, Gerrits KH, Stolwijk-Swuste JM, Crins MH, Janssen TW. Effect of robotic gait training on cardiorespiratory system in incomplete spinal cord injury. *J Rehabil Res Dev.* 2013;50(10):1411-1422.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
51. Valent LJ, Dallmeijer AJ, Houdijk H, et al. Effects of hand cycle training on physical capacity in individuals with tetraplegia: a clinical trial. *Phys Ther.* 2009;89(10):1051-1060.
 52. van der Scheer JW, de Groot S, Tepper M, Faber W, Veeger DH, van der Woude LH. Low-intensity wheelchair training in inactive people with long-term spinal cord injury: A randomized controlled trial on fitness, wheelchair skill performance and physical activity levels. *J Rehabil Med.* 2016;48(1):33-42.
 53. Gorman PH, Scott W, VanHiel L, Tansey KE, Sweatman WM, Geigle PR. Comparison of peak oxygen consumption response to aquatic and robotic therapy in individuals with chronic motor incomplete spinal cord injury: a randomized controlled trial. *Spinal Cord.* 2019;57(6):471-481.
 54. Milia R, Roberto S, Marongiu E, et al. Improvement in hemodynamic responses to metaboreflex activation after one year of training in spinal cord injured humans. *Biomed Res Int.* 2014;2014:893468.
 55. Stevens SL, Caputo JL, Fuller DK, Morgan DW. Effects of underwater treadmill training on leg strength, balance, and walking performance in adults with incomplete spinal cord injury. *J Spinal Cord Med.* 2015;38(1):91-101.
 56. Griffin L, Decker MJ, Hwang JY, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *J Electromyogr Kinesiol.* 2009;19(4):614-622.
 57. Qiu S, Alzhab S, Picard G, Taylor JA. Ventilation Limits Aerobic Capacity after Functional Electrical Stimulation Row Training in High Spinal Cord Injury. *Med Sci Sports Exerc.* 2016;48(6):1111-1118.
 58. Gibbons RS, Stock CG, Andrews BJ, Gall A, Shave RE. The effect of FES-rowing training on cardiac structure and function: pilot studies in people with spinal cord injury. *Spinal Cord.* 2016;54(10):822-829.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
59. Wheeler GD, Andrews B, Lederer R, 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(8):1093-1099.
 60. Bakkum AJ, de Groot S, Stolwijk-Swuste JM, van Kuppevelt DJ, van der Woude LH, Janssen TW. 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(5):395-401.
 61. Brurok 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(5):407-414.
 62. 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(12):1957-1959.
 63. 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(9):817-824.
 64. Maggioni MA, Ferratini M, Pezzano A, et al. Heart adaptations to long-term aerobic training in paraplegic subjects: an echocardiographic study. *Spinal Cord.* 2012;50(7):538-542.
 65. 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(3 Pt 2):R1072-1079.
 66. Schumacher YO, Ruthardt S, Schmidt M, Ahlgrim C, Roecker K, Pottgiesser T. Total haemoglobin mass but not cardiac volume adapts to long-term endurance exercise in highly trained spinal cord injured athletes. *Eur J Appl Physiol.* 2009;105(5):779-785.
 67. Gates PE, Campbell IG, George KP. Absence of training-specific cardiac adaptation in paraplegic athletes. *Med Sci Sports Exerc.* 2002;34(11):1699-1704.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
68. G DER, Matos-Souza JR, Costa ESAD, et al. Physical activity and improved diastolic function in spinal cord-injured subjects. *Med Sci Sports Exerc.* 2014;46(5):887-892.
 69. Ditor DS, Kamath MV, Macdonald MJ, Bugaresti J, McCartney N, Hicks AL. Reproducibility of heart rate variability and blood pressure variability in individuals with spinal cord injury. *Clin Auton Res.* 2005;15(6):387-393.
 70. Solinsky R DA, Taylor J. . Autonomic gains associated with 6 months of high-intensity FES Assisted rowing after SCI. *Topics in spinal cord injury rehabilitation.* 2019;25:s1:90.
 71. Lotri-Koffi A, Pauly M, Lemarie E, et al. Chronic neuromuscular electrical stimulation improves muscle mass and insulin sensitivity in a mouse model. *Sci Rep.* 2019;9(1):7252.
 72. 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(8):808-814.
 73. Hubli M, Currie KD, West CR, Gee CM, Krassioukov AV. Physical exercise improves arterial stiffness after spinal cord injury. *J Spinal Cord Med.* 2014;37(6):782-785.
 74. Schreiber R, Souza CM, Paim LR, et al. Impact of Regular Physical Activity on Adipocytokines and Cardiovascular Characteristics in Spinal Cord-Injured Subjects. *Arch Phys Med Rehabil.* 2018;99(8):1561-1567 e1561.
 75. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. *JAMA.* 2002;288(16):1994-2000.
 76. McArdle W, Katch F, Katch V. Exercise physiology: energy, nutrition, and human performance. 4th ed. . 1996.
 77. Casaburi R, Barstow TJ, Robinson T, Wasserman K. Dynamic and steady-state ventilatory and gas exchange responses to arm exercise. *Med Sci Sports Exerc.* 1992;24(12):1365-1374.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
78. Taylor BJ, West CR, Romer LM. No effect of arm-crank exercise on diaphragmatic fatigue or ventilatory constraint in Paralympic athletes with cervical spinal cord injury. *J Appl Physiol (1985)*. 2010;109(2):358-366.
79. Morgan JW, Ferrazzani E, Taylor JA, Vivodtzev I. Augmenting exercise capacity with noninvasive ventilation in high-level spinal cord injury. *J Appl Physiol (1985)*. 2018;124(5):1294-1296.
80. Vivodtzev I, Picard G, Cepeda FX, Taylor JA. Acute Ventilatory Support During Whole-Body Hybrid Rowing in Patients With High-Level Spinal Cord Injury: A Randomized Controlled Crossover Trial. *Chest*. 2020;157(5):1230-1240.