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

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Abstract:	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 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). 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.
Response to Reviewers:	JCRP-D-20-00150R1 Responses to the reviewer Reviewer Comments: The revised manuscript is substantially improved from the original submission. We believe a few more minor revisions as suggested will further improve it. 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. 2. Future Directions paragraph. Remove "hence" from the first sentence. Ok, done. 3. Tables. Please spell out all abbreviations in table titles or include the abbreviations in the table footnote. Ok done. 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. 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. We have created a new table named Table 2 to summarize the content of the previous Tables 2 and 3. Editorial Office: Please use a footnote with Table 1 to list all the abbreviations (with expansion). Ok done 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. On Page 10 – please provide the reference for (Solinsky et al) Ok done 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 Please use yr as the abbreviation for both year and years Ok done

Type of submission: Invited review

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Running title: Cardiac rehabilitation in spinal cord injury

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Condensed Abstract ≤ 50 words

This review examines original studies investigating the impact of exercise-based interventions on cardiac, autonomic, and cardiometabolic outcomes in spinal cord injury (SCI). Exercise training does not alter autonomic function but it increases peripheral blood flow and counterbalances many deleterious effects of deconditioning, improving cardiac function and cardiometabolic outcomes in SCI.

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 patients[2] 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 disease[6] (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 T5[8]. 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 diseases[11] 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

and those with cardiovascular disease[13]. On the other hand, there is a greater blood pressure variability in SCI, and greater variability has been associated with cardiac, vascular, and renal damage and with increased risk of cardiovascular events and mortality.[14] We recently reported that the HRV decrease is seen within the first 24 months after SCI, suggesting that this decline is due, in part, to a direct impact of SCI itself rather than long-term effect of living with SCI.[15]

Reduced cardiopulmonary fitness

The loss of metabolically active tissue and reduced capacity to routinely engage in aerobic exercise is another major effect of SCI.[16] Aerobic capacity, a key component of cardiopulmonary fitness, is related to the level and extent of SCI and decreases by ~5% with each level of injury from T11 to C4 such that those with high-level injuries have aerobic capacities <40% of their able-bodied peers.[17] The demands of producing aerobic work require integrated responses across a number of systems.[18] The functional limit of aerobic work, maximal oxygen consumption, is by definition the product of maximal systemic flow (i.e., cardiac output) and active muscle oxygen use (i.e., arteriovenous oxygen difference). On both fronts, individuals with SCI have much greater obstacles to overcome in achieving and maintaining high levels of aerobic fitness. For example, impaired sympathetic outflow precludes the normal vasoconstriction in non-exercising tissue to redistribute blood flow to active muscle. Indeed, to achieve high intensity exercise levels, it is critical that blood flow is diverted from inactive tissues, including non-active skeletal muscle. In those with low maximal cardiac output, maximal aerobic capacity can be reduced as much as 40% without regional vasoconstriction.[18] This is of particular relevance to those with injuries at T6 and above who have lessened sympathetically mediated tachycardia and contractility, with subsequent reduced stroke volume and cardiac output.[19] Moreover, the loss of muscle function and trunk control in those with tetraplegia impacts stability and hence the ability to engage in strenuous exercise.

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

Metabolic dysfunction

Due to a 'forced' sedentary life-style, cardiovascular and metabolic diseases develop (such as hyperlipidaemia, glucose intolerance, and systemic inflammation) that are superimposed upon the direct impact of SCI. Years of cumulative stresses due to nervous system dysfunction, limited mobility, and increased inflammation lead to a process of accelerated aging.[21] For example, chronic hyperglycemia promotes arterial wall hypertrophy and fibrosis and impairs endothelial function.[22] Moreover, systemic inflammation (IL-6, TNF-α and CRP) alters NO production, further contributing to endothelial dysfunction[23] and increasing expression of adhesion molecules on activated endothelium, facilitating the formation of atheromatous plaque. Hence, although increased arterial stiffness is part of the normal aging process, systemic complications of SCI may contribute to a premature vascular aging effect. This is particularly true in older individuals with SCI and those with longer time of injury who have the greatest clustering of cardiometabolic risk factors.[24]

One main goal of rehabilitation is therefore to increase aerobic capacity and reduce the cardiovascular impact of SCI. For example, greater aerobic capacity decreases the risk for cardiovascular disease mortality independent of age, ethnicity, and health conditions in able-bodied adults[25]. A 3.5 ml/kg/min improvement in aerobic capacity relates to a 19% decrease in cardiovascular disease mortality.[26] Furthermore, the risk for all-cause mortality decreases in direct relation to exercise training intensity[27]. However, the impact of exercise rehabilitation may differ in SCI depending on the nature of the injury. Though exercise is necessary in the acute/subacute phase of SCI, it may be even more important for older individuals with longer TSI who could benefit from its cardioprotective effect.

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).

REVIEW OF RELEVANT LITERATURE

Exercise training and aerobic capacity

Training modalities

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,

functional electrical stimulation (FES)-cycling, or body weight support treadmill training (BWSTT).[28-56] These are the most commonly used in SCI rehabilitation due accessibility and low cost. Less frequently, exercise training programs have employed FES of the lower extremities in combination with voluntary contraction of the arms, such as FES cycling + arm or FES-rowing.[15,57-62] These forms of exercise are considered as hybrid training since they allow simultaneous contractions of the upper and lower limb muscle groups. Nevertheless, hybrid forms of exercise require more assistance and learning (at least initially) but allow for greater exercise intensities for longer periods[63].

Aerobic capacity

On the whole, exercise training positively affects VO_{2peak} in those with SCI. Indeed, we found 13 out of 16 studies reporting increase in VO_{2peak} after training in low-CVRF[15,28-32,43-46,57,58,64,65] 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 summary and Table E1 and E2 for details). However, the range of increases in VO_{2peak} was highly variable, from 10 to 70% in both low and high CVRF individuals. For example, some studies showed > 50% increase after only 8 weeks of training[30] while others showed only 12% improvement after more than 16 weeks of training[54,60]. This disparity may be due to the extreme variability in subjects' characteristics and training protocols. Adaptations to training can be impacted by level and completeness of injury. For example, patients with cervical injuries and or complete injury have lower baseline VO_{2peak} and potentially lower ability to sustain high intensity exercise. Indeed, two studies reported improvement in VO_{2peak} in subjects with thoracic but not cervical injuries, despite similar training program.[30,32] As a result, a smaller improvement may be found in studies with a higher proportion of subjects with high-level SCI. Another factor which can account for different adaptation to training is the level of physical activity before or during the training program. Indeed, in most studies, patients are new to training but not always.[31] This can explain lower response to training in studies with patients

already engaged in rehabilitation. In addition, level of activity outside the study is almost never described, and it is important to note that cohort studies show that when individuals engaged in regular physical activity have considerably higher VO_{2peak} compared to those who are sedentary (~+60%)[64,66].

Impact of exercise training on the cardiovascular system

Cardiac function

An important question is whether exercise training improves cardiac and cardiovascular health in SCI. As VO_{2peak} is the product of cardiac output and arteriovenous O_2 difference, hence increases in VO_{2peak} reflect changes at the cardiac and/or at the peripheral level. A first interesting finding is that 4 weeks of quadriceps muscle training using electrical stimulation followed by 6 months of functional electrical stimulation (FES)-cycling increased left ventricular (LV) mass in young individuals within ~6 yr. after complete injury[35] (Table 2, E1 and E2). This may relate to increased leg muscle mass (+70%) and thigh blood flow (+115%) as reported in Taylor et al.[36] In addition, FES-cycle training has been shown to increase peak cardiac output.[34] This 12-16-week program of FES-cycling led to a 24% improvement in VO_{2peak} associated with a 13% increase in peak CO.[34] These results suggest that the leg muscle pump may be important to gains in CO after training in SCI. In fact, CO may be enhanced via increased venous return to the heart leading to increased LV mass and stroke volume. Greater LV mass and/or diameter is, indeed, the most commonly reported finding in cross-sectional studies[64,66-68]. Furthermore, only 8 weeks of hybrid exercise can result in significant improvement in cardiac structure and function both in low and high-CVRF individuals with SCI.[58,61] This was obtained with concomitant improvement in VO_{2peak}. Hence, changes in VO_{2peak} seems to be mainly due to improvements at the cardiac level (peak CO, SV, LV) in

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

Autonomic function

Few studies have investigated the effect of training on autonomic function in SCI and most of them enrolled subjects with low CVRF. These studies are uniform in finding no effect of endurance training on autonomic function in SCI (Table 2, E1 and E2). This was found despite improved VO_{2peak}[15] and despite training modalities that engaged the whole body.[15,37,54,69]. This 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 sessions[55] 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

Metabolic markers and cardiovascular function

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

DISCUSSION

The current body of literature suggest that the cardioprotective goal of exercise training is partially reached in SCI. Indeed, aerobic capacity is increased by training in ~75% of the studies analysed. Furthermore, improvement in VO_{2peak} is almost always associated with improvements

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

The benefit of hybrid forms of training

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

certain specific physiological adaptation. Hybrid forms of exercise create a leg muscle pump in synchrony with the upper body exercise. Moreover, hybrid exercise can require a high cardiopulmonary demand compared to arms/legs-only exercise in SCI due to the greater muscle mass engaged[63]. Hence, higher gains in VO_{2peak} from hybrid FES row training should be expected compared with FES cycling alone.[63] Furthermore, these forms of exercise may lead to greater cardio-protection. Given that risk for mortality decreases in association with higher exercise intensities[27] and that there is a 6 metabolic equivalent exercise intensity threshold below which the reduction in risk may be minimal,[75] there is need for training approaches that generate the greatest oxygen consumption demand. Hence, combined form of exercise might be most appropriate for those with SCI given the more consistent improvements in VO_{2peak} with training.

Innovative approaches

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

Although active muscle oxygen use is a key determinant of VO_{2peak}, aerobic exercise also requires sufficient ventilation to provide oxygen to working muscles.[76] In most able-bodied individuals, ventilatory capacity is more than adequate to meet metabolic demands for all exercise intensities.[77] However, SCI is characterized by profound respiratory compromise usually proportional to the level of injury, with those with injuries above T3 having the most profound loss.[6] There is little impact during arms only exercise, due to the proportional denervation of both skeletal and pulmonary muscle such that the respiratory system is still able to cope with the demands of arms-only exercise, even after training.[78] However, as mentioned above, hybrid FES exercise can overcome the limited muscle mass and result in higher peak aerobic capacity than arms-only or FES legs-only exercise. As a result, aerobic adaptations to exercise in those with high-level injuries can be constrained by reduced ventilatory capacity.[57]

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

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 training[79]. 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 ensure achievement of true maximum O_2 consumption. Other studies do not provide details on either protocol or criteria. Only a few studies reported objective VO_{2peak} using at least 3 criteria of maximality[15,57,58,61,63]. As a result, the magnitude of physiological adaptations could have been mis-estimated in some studies. Lastly, whether training effects are maintained has never been investigated prospectively. Studying training effects in SCI is very difficult due to significant inter- individual differences, a relatively small patient population, and complexity of care. Despite these constraints, prospective and randomized controlled studies, with larger samples of well-matched individuals, will be required to provide more robust evidence of cardiac and cardiovascular improvements after training in SCI.

Future directions

Any forms of exercise allowing for high-intensity level of exercise training should be developed and further investigated. Among them, combinatorial therapies are promising approaches in SCI. For example, endurance training can be associated with muscle strengthening[45] and/or with ventilatory support for high-level injury[80]. Furthermore, new technologies will soon allow for greater intensity level of exercise with robotic-assisted training or underwater training approaches[55]. Lastly, motivation is a key determinant of long-term training compliance. New technologies with digitalized platform and social networking may offer longer adherence to training which could be interesting to investigate in SCI.

SUMMARY

Cardiovascular complications are the result of the direct and indirect consequences of SCI. Years of accumulated relative inactivity lead to an accelerated aging and a high risk of

cardiovascular death. Exercise training is a cornerstone of rehabilitation in SCI due to its potential cardio protection. Although its effect on autonomic dysfunction seems to be lacking, exercise training does have an important role in counterbalancing the effect of deconditioning, preserving cardiac function and improving cardiometabolic outcomes such as lean body mass, blood lipids, and systemic inflammation. However, a major facet of exercise as underscored from current studies is that adequate training intensity, volume, and frequency are essential for cardiovascular gains. More recently, forms of combined exercise training (whole-body hybrid leg FES + arms) have been shown to produce the highest O_2 consumption during exercise. However, increasing peak ventilatory capacity may be necessary for those with high level SCI to allow for increased aerobic capacity with this form of exercise. Nonetheless, there is a need for future studies with bigger sample sizes, well-matched subject groups, and randomized controlled designs to investigate whether high-intensity hybrid forms of training result in greater cardiovascular gains.

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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; VO_2, O_2 consumption.

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

		LOW CVRF*	HIGH CVRF*
FITNESS, VO_2 TESTING	Peak VO_2	↑↑↑	↑↑↑
	Peak PO	↑↑↑	↑↑
	Peak HR	= or ↓	↑↑
	Peak VE	= or ↑	=
	Peak Lactate	=	No study
	Peak CO	↑	↑
CARDIAC STRUTURE & 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; VO_2, O_2 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
VO_{2peak} and Fitness									
Cervical injuries									
Mohr, 1997[28]	FES-cycling	10	27 - 45	3–23	C6-T4	Uncontrolled study	Peak VO_2, L/min	1.20 ± 0.08	↑23%, *P* < .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
		10	31 ± 4	< 0.5	T7 - T11	Arm cycling	Peak VO2, L/min - Thoracic	1.37 ± 0.08	↑ 28%, *P* < .001
					Asia A-B	12-16 wks 3x/wk, 30'	Peak PO, W	22 ± 2	↑ 45%, *P* < .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% (*P* = .02)
						24 wks 2-3x/wk, 75%, 30'	Peak PO, W	34.6 ± 4.4	↑ 28% (*P* < .01)
						Testing: FES-rowing	Peak VE, L/min	37.5± 4.4	tendency *P* = .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
Thoracic injuries									
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 VO2 Para – Cont.	1.22 ± 0.48	↑7% vs. bsl
	Hand cycle	20	33 ± 10	< 0.5	C5-C8	Testing: Wheelchair treadmill	Peak VO2 Tetra, L/min	0.86 ± 0.32	No changes
	Control	26	44 ± 14	< 0.5	C5-C8		Peak VO2 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
Cardiac structure and function									
Cervical injuries									
Nash, 1991[35]	NMES Quad + FES-cycling	8	28 ± 5	6 ± 3	C5-C7	Uncontrolled study	LV internal dimension, mm	48.9 ± 3.4	↑ 6.5% (*P* <·02)
					ASIA A	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% *P* < .001
						300 ms, 20 Hz, up to 150mA	Quadriceps depth, mm	14.5 ± 4.2	↑ 70% *P* < .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 VO2, L/min - Thoracic	1.37 ± 0.08	↑ 28%, *P* <.001
						CO2-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, *P* < .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, *P* < .05
					ASIA A/B	Echocardiography	LV end-systolic diameter, mm	28.0 ± 0.6	> 8% in athletes, *P* < .05
Gibbons, 2016[58]	FES-rowing	5	32 ± 5	7 ± 7	C4-T10	Uncontrolled study	VO_{2peak}, L/min	0.97 ± 0.22	↑ 11%, *P* < .05
					ASIA A-B	8 wks, 3/wk, 30'	Peak heart rate	151 ± 7	↑ 8%, *P* < .05
						Doppler	LV mass, g	110 ± 6	↑ 7%, *P* < .05
						Echocardiography	EDV, mL	65 ± 8	↑ 40% *P* < .05
							ESV, mL	28 ± 5	↑ 25%, *P* < .05
							Diastolic function (E/A)	1.38 ± 0.05	↑ 9%, *P* < .05
Thoracic injuries									
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, *P* = .001
	Untrained	7	36 ± 10		T1–L3	5 yr / 3-5h /wk	IVST, mm	8.6 ± 0.8	>18% in trained, *P* = .01

					ASIA A	Echocardiography	posterior wall thickness, mm	8.4 ± 1.1	NS ≠ in trained
							LV mass, g/m2	56.3 ± 17.5	> 48% in trained, *P* = .01
							E/A ratio	1.64 ± 0.80	NS ≠ in trained
Autonomic function									
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%, *P* < .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%, *P* < .05
					ASIA B-C	24 wks, 3x/wk, 15'	LF HRV (0.04-0.15 Hz) b/min	5894 ± 815	↓13%, *P* < .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%, *P* < .05
							LF SBP (0.04-0.15 Hz) mmHg2	183.1 ± 46.8	↓14%, *P* < .01
							LF DBP (0.15-0.40 Hz) mmHg2	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) ms2	316 ± 55	No changes
					ASIA A-C	5' Finapres	HF HRV (0.20–0.30 Hz) ms2	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) mmHg2	3.23 ± 0.51	No changes
Cardiovascular function									
Cervical injuries									
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 (mm2/mmHg)	0.07 ± 0.03	↑42%, *P* = .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	5 yr follow up	Resting Stroke volume, mL	71.4 ± 5.4	No changes
					ASIA A-B	Carotid ultrasonography	Resting cardiac output, L/min	5.0 ± 0.3	No changes
							Carotid IMT, mm	0.74 ± 0.05	↓ 24% in trained only
							CCA diameter, mm	5.3 ± 0.2	No changes
							CCA resistive index	0.82 ± 0.02	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, *P* < .01
	Sedentary	16	34 ± 7	8.2 ± 3.0	C4 to < T6	Athletes: 5 yr, 11 h/wk	E/A ratio	1.43 ± 0.38	> 13% in athletes, *P* = .14
						Carotid ultrasonography	E/Em ratio	7.7 ± 2.5	NS ≠ in trained
						Echocardiography	Adipocytokines	-	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% , *P* = .001
	Usual care	6	38 (17)	3.6 (2.5)	ASIA A-C	5 days, 90 min	Normalized AIx to HR, %	21 ± 18	↓ 33% , *P* = .001
						SphygmoCor	MAP, mmHg	89 ± 11	NS ↓, *P* = .47
							Central SBP, mmHg	117 ± 17	No changes
							Central DBP, mmHg	72 ± 8	No changes
Thoracic injuries									
Nash, 1997[72]	FES-walking	12	28 ± 7	3.9 ± 3.1	T4-T11	Uncontrolled study	Cross-sectional area, cm	0.36 ± 0.06	↑ 33%, *P* < .0001
						Doppler ultrasound	CFA Flow velocity integral, cm	16.8 ± 3.8	↑ 26%, *P* < .05
						CFA = common femoral artery	CFA pulse volume, mL	6.0 ± 1.7	↑ 67% (*P* = .001)

							CFA inflow mL/min	417.1 ± 122	↑ 56% (*P* < .01)
							Resting HR, b/m	70.1 ± 10.1	↓ 7% (*P* < .05)
Blood markers of cardiovascular risk									
Cervical injuries									
Hjeltnes, 1997[65]	FES-cycling	5	35 ± 3	10 ± 3	C5-C7	Uncontrolled study	VO_{2peak}, ml/min/kg	~7.5 ± 2.0	↑70% (*P* < .05)
						DEXA and CT scan	Whole body fat	29.7 ± 2.6	↓ 7% (*P* < .05)
							Lower limb muscles CSA, cm2	267 ± 27	↑ 21% (*P* < .05)
Midha, 1999[44]	Wheelchair	12	22-58	12 ± 7	C6-L3	Uncontrolled study	VO_{2peak}, ml/min/kg	19 + 6	↑ 25%, *P* = .02
						10 wks, 2-3/wk, 30'	Resting HR, b/m	93 ± 14	↓ 29%, *P* = .02
						Blood samples	Fasting serum cholesterol (mg/dL)	185 ± 42	↓ 8%, *P* = .04
de Groot, 2003[43]	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, 2019[45]	Aerobic + resistance	11	36 ± 6	(2-27)	C4-L1	Randomized controlled trial	VO_{2peak}, ml/min/kg	11.7 ± 8.1	↑ 35%vs. bsl, *P* < .05
	Control	6				6 wks, 3/wk, 60'	Insulin, µU/ml	7.5 ± 4.7	↓ 40%, *P* < .05
						Fasting blood samples	HOMA-IR	1.5 ± 1.0 vs	↓ 40%, *P* < .05
							Fat mass, %	35.3 ± 10.8	↓ 6%, *P* < .05
							Total Chol (mg/dl)	162.3 ± 34.1	No change
							HDL-C (mg/dl)	48.7 ± 21.3	↑ 12%, *P* < .05
Thoracic injuries									
Ordonez, 2013[46]	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, 2014[47]	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-a (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, Homeostasic 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 O_2 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
VO_{2peak} and Fitness									
Cervical injuries									
Wheeler, 2002[59]	FES rowing	6	42 ± 18	14 ± 12	C7–T12	Uncontrolled study	Peak VO_2, L/min	1.81 ± 0.41	↑ 11.2%, *P* < .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, 2009[51]	Hand cycling	22	39 ± 12	10 ± 7	C5-T1	Uncontrolled study	Peak VO_2, L/min	1.32 ± 0.40	↑~10% *P* < .05
					ASIA A-D	12 wks. 2x/wk., 35-45'	Peak PO, W	42.5 ± 21.9	↑~20% *P* < .05
						Test: Hand-cycling treadmill			
Hoekstra, 2013[50]	Robotic gait	10	49 ± 14	>1 - 35	C3-T10	Uncontrolled study	Peak VO_2, L/min	1.16 ± 0.40	No changes
					ASIA C-D	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%, *P* = .02
							Exercise Intensity - METs	2.1 ± 0.9	No changes
Bakkum, 2015[60]	FES cycle + arms	10	48 ± 10	20 ± 8	C3-T10	Randomized controlled trial	Peak VO_2, L/min	1.19 ± 0.20	↑12% vs. +3%, (NS ≠ gps)
	Hand cycle	10	47 ± 9	16 ± 6	C2-L2	16-wks., x/wk., 30'	Peak PO, W	35.9 ± 9.5	↑15% vs. +4%, (NS ≠ gps)
					ASIA A-D	Test in respective mode	Resting HR, pbm	73 ± 2	↓ 8% overall (NS ≠ gps)
							PA score, (PASIPD) h/wk.	6.3 ± 1.9	↑ 224 % vs. 150%, *P* = .10
Van des Scheer, 2016[52]	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	16 wks. 2x/wk., 30'	Peak PO, W	43.6	No changes and no ≠
					Asia A-D	Test: Wheelchair treadmill	PA score, h/wk	5.3	No changes and no ≠
							Distance km/week	7.4	No changes and no ≠
Gorman, 2019[53]	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
Thoracic injuries									
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, W Peak HR, pbm Training duration vs. VO_2Peak	0.54 ± 0.14 8.4 ± 3.2 82 ± 8	↑ 56% ↑ 132%, *P* = .001 ↑ 14%, *P* < .05 (9 mth) r2 = 0.52, *P* = .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%, *P* = .001 ↑ 3%, *P* = .03
Cardiac structure and function									
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, *P* < .05
	Untrained	10	45 ± 18	> 3	C6-S5	> 3 yr. 15h/wk. endurance CO2 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, *P* < .05 < 4% in athletes, *P* < .05 > 8% in athletes, *P* < .05 > 19% in athletes, *P* < .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%, *P* < 0.05 ↑ 27%, *P* < 0.05 ↑ 33%, *P* < 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%, *P* < 0.05 ↑ 247%, *P* < 0.05 ↑ to +51 ± 50
Autonomic function									
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, *P* < .001
	treadmill				ASIA C-D	8 wks., 3x/wk., 15-24'	HR wks. 4/5, b/m (> speed)	118 (108-126)	↓14% d6 vs. d1, *P* < .001
						Chest monitor last 15"	HR wks. 6/7, b/m (>> speed)	126 (121-138)	↓ 17% d6 vs. d1, *P* < .001
Cardiovascular function and blood markers of cardiovascular risk									
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 ± 2.0 4.91 ± 1.10 11.8 ± 0.6 15.9 ± 1.5	↓11% *P* < .05 ↓22% *P* < .05 ↓4% *P* < .05 ↓19% *P* < .05
Hubli, 2014[73]	Elite hand-cycle Non-elite	10 10	41 ± 6 42 ± 11	19 ± 6 17 ± 11	C2–T5 C4-T3	Cross-sectional comparison 17 ± 4 vs. 1 ± 2 h/wk. Applanation tonometry	Aortic PWV, m/sec Resting supine MAP, mmHg EDV 3' post Ischemia, mL	8.7 ± 2.5 91 ± 19 7.2 ± 22.2	< 21% in athletes, *P* =.04 NS ≠ in trained (81 ± 10) ↑ 370%
Jeon, 2010[62]	FES-rowing	6	48.6 ±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 ± 1.23 103.2 ± 6.8 6.9 ± 1.7 25.5 ± 1.8 3.6 0.8	↑ 8%, *P* < .05 ↓ 10%, *P* .28 ↓ 28%, *P* .28 ↓ 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 O_2 consumption.

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

Running title: Cardiac rehabilitation in spinal cord injury

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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

This review examines original studies investigating the impact of exercise-based interventions on cardiac, autonomic, and cardiometabolic outcomes in spinal cord injury (SCI). Exercise training does not alter autonomic function but it increases peripheral blood flow and counterbalances many deleterious effects of deconditioning, improving cardiac function and cardiometabolic outcomes in SCI.

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 patients[2] 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 disease[6] (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 T5[8]. 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 diseases[11] 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

and those with cardiovascular disease[13]. On the other hand, there is a greater blood pressure variability in SCI, and greater variability has been associated with cardiac, vascular, and renal damage and with increased risk of cardiovascular events and mortality.[14] We recently reported that the HRV decrease is seen within the first 24 months after SCI, suggesting that this decline is due, in part, to a direct impact of SCI itself rather than long-term effect of living with SCI.[15]

Reduced cardiopulmonary fitness

The loss of metabolically active tissue and reduced capacity to routinely engage in aerobic exercise is another major effect of SCI.[16] Aerobic capacity, a key component of cardiopulmonary fitness, is related to the level and extent of SCI and decreases by ~5% with each level of injury from T11 to C4 such that those with high-level injuries have aerobic capacities <40% of their able-bodied peers.[17] The demands of producing aerobic work require integrated responses across a number of systems.[18] The functional limit of aerobic work, maximal oxygen consumption, is by definition the product of maximal systemic flow (i.e., cardiac output) and active muscle oxygen use (i.e., arteriovenous oxygen difference). On both fronts, individuals with SCI have much greater obstacles to overcome in achieving and maintaining high levels of aerobic fitness. For example, impaired sympathetic outflow precludes the normal vasoconstriction in non-exercising tissue to redistribute blood flow to active muscle. Indeed, to achieve high intensity exercise levels, it is critical that blood flow is diverted from inactive tissues, including non-active skeletal muscle. In those with low maximal cardiac output, maximal aerobic capacity can be reduced as much as 40% without regional vasoconstriction.[18] This is of particular relevance to those with injuries at T6 and above who have lessened sympathetically mediated tachycardia and contractility, with subsequent reduced stroke volume and cardiac output.[19] Moreover, the loss of muscle function and trunk control in those with tetraplegia impacts stability and hence the ability to engage in strenuous exercise.

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

Metabolic dysfunction

Due to a 'forced' sedentary life-style, cardiovascular and metabolic diseases develop (such as hyperlipidaemia, glucose intolerance, and systemic inflammation) that are superimposed upon the direct impact of SCI. Years of cumulative stresses due to nervous system dysfunction, limited mobility, and increased inflammation lead to a process of accelerated aging.[21] For example, chronic hyperglycemia promotes arterial wall hypertrophy and fibrosis and impairs endothelial function.[22] Moreover, systemic inflammation (IL-6, TNF-α and CRP) alters NO production, further contributing to endothelial dysfunction[23] and increasing expression of adhesion molecules on activated endothelium, facilitating the formation of atheromatous plaque. Hence, although increased arterial stiffness is part of the normal aging process, systemic complications of SCI may contribute to a premature vascular aging effect. This is particularly true in older individuals with SCI and those with longer time of injury who have the greatest clustering of cardiometabolic risk factors.[24]

One main goal of rehabilitation is therefore to increase aerobic capacity and reduce the cardiovascular impact of SCI. For example, greater aerobic capacity decreases the risk for cardiovascular disease mortality independent of age, ethnicity, and health conditions in able-bodied adults[25]. A 3.5 ml/kg/min improvement in aerobic capacity relates to a 19% decrease in cardiovascular disease mortality.[26] Furthermore, the risk for all-cause mortality decreases in direct relation to exercise training intensity[27]. However, the impact of exercise rehabilitation may differ in SCI depending on the nature of the injury. Though exercise is necessary in the acute/subacute phase of SCI, it may be even more important for older individuals with longer TSI who could benefit from its cardioprotective effect.

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).

REVIEW OF RELEVANT LITERATURE

Exercise training and aerobic capacity

Training modalities

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,

functional electrical stimulation (FES)-cycling, or body weight support treadmill training (BWSTT).[28-56] These are the most commonly used in SCI rehabilitation due accessibility and low cost. Less frequently, exercise training programs have employed FES of the lower extremities in combination with voluntary contraction of the arms, such as FES cycling + arm or FES-rowing.[15,57-62] These forms of exercise are considered as hybrid training since they allow simultaneous contractions of the upper and lower limb muscle groups. Nevertheless, hybrid forms of exercise require more assistance and learning (at least initially) but allow for greater exercise intensities for longer periods[63].

Aerobic capacity

On the whole, exercise training positively affects VO_{2peak} in those with SCI. Indeed, we found 13 out of 16 studies reporting increase in VO_{2peak} after training in low-CVRF[15,28-32,43-46,57,58,64,65] 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 summary and Table E1 and E2 for details). However, the range of increases in VO_{2peak} was highly variable, from 10 to 70% in both low and high CVRF individuals. For example, some studies showed > 50% increase after only 8 weeks of training[30] while others showed only 12% improvement after more than 16 weeks of training[54,60]. This disparity may be due to the extreme variability in subjects' characteristics and training protocols. Adaptations to training can be impacted by level and completeness of injury. For example, patients with cervical injuries and or complete injury have lower baseline VO_{2peak} and potentially lower ability to sustain high intensity exercise. Indeed, two studies reported improvement in VO_{2peak} in subjects with thoracic but not cervical injuries, despite similar training program.[30,32] As a result, a smaller improvement may be found in studies with a higher proportion of subjects with high-level SCI. Another factor which can account for different adaptation to training is the level of physical activity before or during the training program. Indeed, in most studies, patients are new to training but not always.[31] This can explain lower response to training in studies with patients

already engaged in rehabilitation. In addition, level of activity outside the study is almost never described, and it is important to note that cohort studies show that when individuals engaged in regular physical activity have considerably higher VO_{2peak} compared to those who are sedentary (~+60%)[64,66].

Impact of exercise training on the cardiovascular system

Cardiac function

An important question is whether exercise training improves cardiac and cardiovascular health in SCI. As VO_{2peak} is the product of cardiac output and arteriovenous O_2 difference, hence increases in VO_{2peak} reflect changes at the cardiac and/or at the peripheral level. A first interesting finding is that 4 weeks of quadriceps muscle training using electrical stimulation followed by 6 months of functional electrical stimulation (FES)-cycling increased left ventricular (LV) mass in young individuals within ~6 yr. after complete injury[35] (Table 2, E1 and E2). This may relate to increased leg muscle mass (+70%) and thigh blood flow (+115%) as reported in Taylor et al.[36] In addition, FES-cycle training has been shown to increase peak cardiac output.[34] This 12-16-week program of FES-cycling led to a 24% improvement in VO_{2peak} associated with a 13% increase in peak CO.[34] These results suggest that the leg muscle pump may be important to gains in CO after training in SCI. In fact, CO may be enhanced via increased venous return to the heart leading to increased LV mass and stroke volume. Greater LV mass and/or diameter is, indeed, the most commonly reported finding in cross-sectional studies[64,66-68]. Furthermore, only 8 weeks of hybrid exercise can result in significant improvement in cardiac structure and function both in low and high-CVRF individuals with SCI.[58,61] This was obtained with concomitant improvement in VO_{2peak}. Hence, changes in VO_{2peak} seems to be mainly due to improvements at the cardiac level (peak CO, SV, LV) in

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

Autonomic function

Few studies have investigated the effect of training on autonomic function in SCI and most of them enrolled subjects with low CVRF. These studies are uniform in finding no effect of endurance training on autonomic function in SCI (Table 2, E1 and E2). This was found despite improved VO_{2peak}[15] and despite training modalities that engaged the whole body.[15,37,54,69]. This 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 sessions[55] 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

Metabolic markers and cardiovascular function

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

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

DISCUSSION

The current body of literature suggest that the cardioprotective goal of exercise training is partially reached in SCI. Indeed, aerobic capacity is increased by training in ~75% of the studies analysed. Furthermore, improvement in VO_{2peak} is almost always associated with improvements in cardiovascular health. Indeed, although it fails to alter autonomic function, exercise training

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

The benefit of hybrid forms of training

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

synchrony with the upper body exercise. Moreover, hybrid exercise can require a high cardiopulmonary demand compared to arms/legs-only exercise in SCI due to the greater muscle mass engaged[63]. Hence, higher gains in VO_{2peak} from hybrid FES row training should be expected compared with FES cycling alone.[63] Furthermore, these forms of exercise may lead to greater cardio-protection. Given that risk for mortality decreases in association with higher exercise intensities[27] and that there is a 6 metabolic equivalent exercise intensity threshold below which the reduction in risk may be minimal,[75] there is need for training approaches that generate the greatest oxygen consumption demand. Hence, combined form of exercise might be most appropriate for those with SCI given the more consistent improvements in VO_{2peak} with training.

Innovative approaches

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

Although active muscle oxygen use is a key determinant of VO_{2peak}, aerobic exercise also requires sufficient ventilation to provide oxygen to working muscles.[76] In most able-bodied individuals, ventilatory capacity is more than adequate to meet metabolic demands for all exercise intensities.[77] However, SCI is characterized by profound respiratory compromise usually proportional to the level of injury, with those with injuries above T3 having the most profound loss.[6] There is little impact during arms only exercise, due to the proportional denervation of both skeletal and pulmonary muscle such that the respiratory system is still able to cope with the demands of arms-only exercise, even after training.[78] However, as mentioned above, hybrid FES exercise can overcome the limited muscle mass and result in higher peak aerobic capacity than arms-only or FES legs-only exercise. As a result, aerobic adaptations to exercise in those with high-level injuries can be constrained by reduced ventilatory capacity.[57] If this ventilatory limitation could be overcome, greater improvements in aerobic capacity could be expected with hybrid FES exercise training.

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 training[79]. 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

ensure achievement of true maximum O_2 consumption. Other studies do not provide details on either protocol or criteria. Only a few studies reported objective VO_{2peak} using at least 3 criteria of maximality[15,57,58,61,63]. As a result, the magnitude of physiological adaptations could have been mis-estimated in some studies. Lastly, whether training effects are maintained has never been investigated prospectively. Studying training effects in SCI is very difficult due to significant inter- individual differences, a relatively small patient population, and complexity of care. Despite these constraints, prospective and randomized controlled studies, with larger samples of well-matched individuals, will be required to provide more robust evidence of cardiac and cardiovascular improvements after training in SCI.

Future directions

~~Hence,~~ Any forms of exercise allowing for high-intensity level of exercise training should be developed and further investigated. Among them, combinatorial therapies are promising approaches in SCI. For example, endurance training can be associated with muscle strengthening[45] and/or with ventilatory support for high-level injury[80]. Furthermore, new technologies will soon allow for greater intensity level of exercise with robotic-assisted training or underwater training approaches[55]. Lastly, motivation is a key determinant of long-term training compliance. New technologies with digitalized platform and social networking may offer longer adherence to training which could be interesting to investigate in SCI.

SUMMARY

Cardiovascular complications are the result of the direct and indirect consequences of SCI. Years of accumulated relative inactivity lead to an accelerated aging and a high risk of cardiovascular death. Exercise training is a cornerstone of rehabilitation in SCI due to its potential cardio protection. Although its effect on autonomic dysfunction seems to be lacking,

exercise training does have an important role in counterbalancing the effect of deconditioning, preserving cardiac function and improving cardiometabolic outcomes such as lean body mass, blood lipids, and systemic inflammation. However, a major facet of exercise as underscored from current studies is that adequate training intensity, volume, and frequency are essential for cardiovascular gains. More recently, forms of combined exercise training (whole-body hybrid leg FES + arms) have been shown to produce the highest O_2 consumption during exercise. However, increasing peak ventilatory capacity may be necessary for those with high level SCI to allow for increased aerobic capacity with this form of exercise. Nonetheless, there is a need for future studies with bigger sample sizes, well-matched subject groups, and randomized controlled designs to investigate whether high-intensity hybrid forms of training result in greater cardiovascular gains.

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