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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 yr with time since injury (TSI) <10 yr with those in older individuals (> 40 yr) 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 (interleukin-6, tumor necrosis factor alpha, and C reactive protein), 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

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

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deleterious effects of deconditioning, improving cardiac function and cardiometabolic outcomes in SCI.

Keywords

Spinal cord injury; cardiac rehabilitation; exercise training; cardiovascular; autonomic

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 (CVD) compared to the general population.[1] Both symptomatic and asymptomatic CVD 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 CVD.[5]

Autonomic dysfunction

Alterations in autonomic function are a direct consequence of SCI that may explain higher susceptibility to CVD.[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 (CV) 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 CVD after SCI.[10] For example, lesser HRV is associated with cardiac diseases[11] and is prognostic for those with known CVD.[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 CVD[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 CV events and mortality.[14] We recently reported that the HRV decrease is seen within the first 24 mo 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 cardiorespiratory fitness

The loss of metabolically active tissue and reduced capacity to routinely engage in aerobic exercise is another major effect of SCI.[16] Cardiorespiratory fitness (CRF), 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 uptake, 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 cardiorespiratory 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 CRF 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 cardiometabolic risk.[20]

Metabolic dysfunction

Due to a forced sedentary life-style, CV and metabolic diseases develop (such as hyperlipidemia, 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 (interleukin-6, tumor necrosis factor alpha, and C reactive protein) alters nitric oxide 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 CRF and reduce the CV impact of SCI. For example, greater CRF decreases the risk for CVD mortality independent of age, ethnicity, and health conditions in able-bodied adults[25]. A 3.5 ml/kg/min (1 metabolic equivalent [MET]) improvement in CRF relates to a 19% decrease in CVD 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 CV 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 CV 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 peak oxygen uptake (VO_{2peak}), cardiac structure or function, autonomic function, CV 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 d were included. Furthermore, we dichotomized the effect of exercise training into two categories of patients: younger individuals (<40-45 yr) with shorter time since injury (< 10 yr), considered as those with low CV risk (low-CVRF) vs. older Individuals (~≥40-45 yr) with longer time since injury (> 10 yr) and higher CV 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 (SDC1 and SDC2). 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.[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].

Cardiorespiratory Fitness—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 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 SDC1 and SDC2 for details). However, the range of increases in VO_{2peak} was highly variable, from 10 - 70% in both low and high CVRF individuals. For example, some studies showed > 50% increase after only 8 wk of training[30] while others showed only 12% improvement after more than 16 wk 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 CV 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 wk of quadriceps muscle training using electrical stimulation followed by 6 mo of functional electrical stimulation (FES)-cycling increased left ventricular (LV) mass in young individuals within ~6 yr after complete injury[35] (Table 2, SDC1 and SDC2). 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 wk 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 wk 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, stroke volume, LV mass) in both subcategories. However, there is one report of increases in hemoglobin 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 mo 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 CV and metabolic impact of exercise training in SCI. Studies agree on an overall positive effect of exercise on cardiometabolic parameters in SCI (Table 2, SDC1 and SDC2). 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 cardiorespiratory fitness. 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 interleukin-6, tumor necrosis factor alpha, and C reactive protein, 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 CV 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 CV 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, CRF is increased by training in ~75% of the studies analysed. Furthermore, improvement in VO_{2peak} is almost always associated with improvements in CV 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 CV function (reduced arterial stiffness and improved endothelial function) have been consistently reported across studies. Given the increased risk of CV 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 CV 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, CV stress during exercise needs to be sufficient to obtain a CV effect of training. One main outcome seems to be the magnitude of VO_2 that can be achieved during exercise training. The lack of CV 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 CV 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 MET exercise intensity threshold below which the reduction in risk may be minimal,[75] there is need for training approaches that generate the greatest VO_2 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 CRF 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 CRF 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 CRF during hybrid FES-rowing in an individual with an acute, high-level SCI whose CRF had been plateauing for 18 mo 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 VO_{2max}. Other studies do not provide details on either protocol or criteria. Only a few studies reported objective VO_{2peak} using at least three 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 CV 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 CV 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 CV 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 CRF 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 CV gains.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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
	HR variability	↓
	BP 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	↑

Abbreviations: BP, blood pressure; CO, cardiac output; HR, heart rate variability; VO_2, oxygen uptake.

Table 2:

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

		LOW CVRF*	HIGH CVRF*
EXERCISE TESTING	Peak VO_2	↑↑↑	↑↑↑
	Peak PO	↑↑↑	↑↑
	Peak HR	= or ↓	↑↑
	Peak VE	= or ↑	=
	Peak Lactate	=	NS
	Peak CO	↑	↑
CARDIAC STRUTURE & FUNCTION	Left ventricular mass	↑↑	↑
	Stroke volume	= or ↑	↑
	Resting CO	=	NS
	Diastolic function	↑↑	↑
AUTONOMIC FUNCTION	Resting HR	= or ↓	NS
	Maximal HR during training	NS	↓
	HR variability	=	NS
	BP variability	=	NS
	Resting BP	=	NS
	Baroreflex gain	↑	NS
CARDIOVASCULAR FUNCTION	Endothelial function	↑↑	NS
	Femoral compliance	↑↑	NS
	Thigh blood flow	↑	NS
	Arterial stiffness	↓	↓
	Intima media thickness	↓↓	NS
BLOOD MARKERS OF CARDIOVASCULAR RISK	Fat free mass	↑	No study
	Fat mass	↓	↓
	Insulin sensitivity	= or ↑	=
	HDL-Cholesterol	↑↑	↓
	Triglycerides	↓↓	=
	IL-6	↓	↓
	TNF-α	↓	↓
	CRP	NS	↓
	PTAS	↑	NS

Definition of abbreviation: BP, blood pressure; CO, cardiac output; CRP, C reactive protein; Hb, hemoglobin; HDL, high-density lipoprotein; HR, heart rate; IL-6, interleukin 6; NS, no study; PO, power output; PTAS, plasmatic total antioxidant status; TNF-α, tumor necrosis factor alpha; VE, ventilation; VO_2, O_2 uptake.

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.