Chronic exercise effects on vascular function and structure in persons living with spinal cord injury: a systematic review

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Study design: A systematic review

Objective: The purpose of this study was to systematically identify, review, synthesize, and appraise current chronic exercise intervention literature on arterial dynamics in people with spinal cord injury (SCI). By doing so, this study aimed to highlight gaps and compelling evidence, and guide future research directions that will help to advance understanding and application of different training modalities.

Setting: Literature searches were carried out for appropriate articles using several databases (e.g. PubMed, MEDLINE, EMBASE).

Methods: Two independent reviewers evaluated the quality of each article, using the physiotherapy Evidence Database Scale (PEDro) for randomized controlled trials and Downs and Black Scale for all other studies. A table with all outcomes from each investigation were listed, and levels of evidence assigned.

Results: A total of 337 studies were found through the systematic literature search. Through examination, 27 articles were included. The articles were distinguished into the arterial benefits from the chronic exercise interventions. The potential to improve arterial function and structure in those with SCI was supported by limited to good methodological quality. It appears from the evidence that a variety of exercise modalities, passive cycling, arm exercises, functional electrical stimulation (FES), hybrid electrically stimulated, body weight supported treadmill (BWST), electrically stimulated knee extension, endurance and resistance training can improve arterial function in those living with SCI.

Conclusion: The overall quality and volume of evidence was low-to-average. There is limited literature that supports exercise as a useful intervention technique for improving arterial function and structure in those with SCI.

Keywords: Systematic review; therapeutic; exercise; spinal cord injury; tetraplegia; paraplegia

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Resume

Aterosklerose (areforkalkning) er en betegnelse for ophobning af fedtstoffer (kolesterol), bindevæv og kalk i blodkarrenes vægge, som derved bliver stive, fortykkede og med forsnævringer. Dette fører til en nedsat blodgennemstrømning og derved nedsat forsyning af iltet blod. Efter en rygmarvsskade har man ikke de samme muligheder for at bevæge sig som før skaden. Derfor er det meget vigtigt, at disse personer kan holde sig sunde, og forebygge alvorlige følgesygdomme som f.eks.: hjerte-karsygdomme.

Endotel celler udsættes for blodstrøm, hvilket bidrager til opretholdelse af karstruktur og bevarelse af vaskulære funktioner. Endotel dysfunktion er et tidligt tegn på åreforkalkning og er associeret til de traditionelle risikofaktorer for hjerte-karsygdom. En af årsagerne til endotel dysfunktion af det vaskulære endotel ses typisk i de tidlige faser af åreforkalkning. Flow-medieret dilatation (FMD) kan forudsige fremtidige kardiovaskulære begivenheder. Træning forbedrer det vaskulære helbred hos sunde personer, men meget mindre kendes til den rygmarvsskadede population.

Alle arterier har relative tykke vægge, der kan modstå det høje blodtryk som kommer fra hjertet. Hvis arterievæggene er stive, og ikke er i stand til at udvide sig og rekylere, vil modstanden i blodgennemstrømningen øges, og blodtrykket vil stige til et endnu højere niveau, hvilket igen kræver, at hjertet pumper hårdere for at øge blodvolumen som kommer fra hvert hjerteslag (slagvolumen) og oprethold et passende tryk og flow. Arterievæggene bliver hermed tykkere som et udtryk for det øgede blodtryk. Det forhøjet blodtryk efter en rygmarvsskade initierer en proces med arteriel ombygning. Blodkarrene udviser nedsat arteriediameter og øget tykkelse af arterievæggene, hvilket gør arterierne stivere end den normale. Dette påvirker i høj grad blodgennemstrømningen og det arterielle tryk og bidrager til en øget risiko for hjerte-karsygdomme.

På baggrund af eksisterende viden på området forventes det at finde varierende resultater i effekterne af fundne træningsmodaliteter i personer med rygmarvsskade. Dertil forventes det, at projektet gruppen kan give en omfattende gennemgang af effekterne af længerevarende træningsinterventioner, som giver indblik i hvilke modaliteter man med fordel kan benytte for at forbedre vaskulær funktion og struktur.

Introduction

Cardiovascular diseases (CVD) are a major cause of morbidity and mortality among people aging with spinal cord injury (SCI)[1] and is the leading cause of death[2]. The endothelium plays a central role in the process of atherosclerosis at the early stages through the more advanced stages and leads to impairment of endothelial function, which precedes development of atherosclerosis that is evident of thickening the arterial wall[3]. Endothelium dysfunction is characterized by reduced nitric oxide (NO) availability[4]. The SCI population have activity levels less than 40% of the able-bodied population[5]. Increased vascular stiffness is a primary marker of CVD risk[6–8]. Vascular stiffness is related to smoking,[9] advancing age,[10,11] and physical inactivity[12]. Individuals with a SCI demonstrate an increase in arterial stiffness in both central[13] and peripheral arteries[14]. SCI results in muscular paralysis, sensory loss, and sympathetic nervous system dysfunction, and these impairments negatively affect body composition and ability to exercise[15]. The impaired loss of motor function after a SCI results in lower limb deconditioning and extreme physical inactivity below the level of the lesion, and this result in arterial remodeling and changes in vascular function, both below and above the level of the lesion[16]. It appears that decreases in brachial artery FMD after SCI and the differences in FMD above and below the lesion may be consequences of structural adaptations that occur following SCI, although, changes in diameter do not fully explain the differences in FMD[17]. SCI has a significant impact on the structure and function of the cardiovascular system, which in general leads to more diminutive sized vessels below the lesion and impairment of endothelial function throughout the body[16]. A low flow-mediated dilation (FMD) response is associated with cardiovascular morbidity and mortality,[18] but lower limb deconditioning does not lead to a decrease in FMD, however it can be related to marked remodeling of the vessel (i.e. smaller diameter, larger wall-to-lumen ratio)[19–21].

Individuals with SCI have an increased risk for CVD compared with their able-bodied (AB) counterparts[22]. Prediction of CVD risk is generally based on factors such as smoking status, sex, age, blood lipid profile, elevated systolic blood pressure, diabetes and smoking status[23]. However, these traditional risk factors do not fully explain the increased CVD risk in individuals with SCI[24]. People with high (lesions above the T6) SCI lesions exhibit autonomic disturbances that result in a low resting arterial blood pressure[25]. In the AB population, studies that investigated the reduction in CVD risk with exercise have reported that only 40–60% of the risk reduction were explained by improvements in traditional CVD risk factors[26]. Exercise-induced hemodynamics may induce adaptations in vascular function and structure that contribute to the cardiovascular benefits of exercise training which can explain the 'risk factor gap'[27].

It is evident that exercise benefit cardiovascular health in persons with tetraplegia or paraplegia[28], but there is limited evidence on how chronic exercise benefits arterial dynamics in SCI subjects[29]. A few papers have been published explaining some of these effects of exercise on cardiovascular adaptations in those with SCI[30,31]. Philips et al.[31] found strong evidence to support passive leg exercise programs as a technique to improve vascular function among individuals with paraplegia, although many other various modes of exercises presented, did not have insufficient evidence or mixed evidence[31]. It is currently challenging to provide evidence-based exercise prescriptions because of a considerable variability in the existing exercise training literature with regards to the exercise interventions tested within the SCI population[32]. Offering therapeutic activities, exercise programs, sports modalities, and adequate recreational activities to SCI individuals is very important to promote their participation in physical exercise programs[33]. Due to the lack of evidence of chronic exercise effects on arterial dynamics, the objective of this systematic review is to evaluate various chronic exercise modalities and present a synopsis of the scientific literature of the beneficial effects in arterial function and structure. The aim of this systematic review is to evaluate the evidence concerning the chronic exercise effects on vascular adaptations in individuals with SCI.

Techniques to asses arterial function and structure

Ultrasound, pulse wave velocity and pulse wave analysis are non-invasive techniques that have reliability and validity for their usage in the general population. These techniques are considered very useful in clinical assessments to guide individual treatment strategies in the SCI population. Ultrasound technology with duplex-Doppler gives researchers the ability to obtain conduit arterial images and corresponding blood velocity signals at the same time of the artery in real-time. Arterial diameters are measured by B-mode images with automated image analysis software, and these devices are able to assess beat-to-beat blood flow and shear stress to exercise. Blood flow is calculated as vessel cross-sectional area and mean blood velocity. Shear stress creates friction to the endothelium and is a stimulus in regulating the vascular health by causing dilatation. The diameter of a particular vessel is dependent on structural properties of the vessel and the tone of the vessel. Arterial tone can measure from a 10-minute occlusion period, providing the minimum and maximal diameters used to calculate arterial range. Maximal dilation can be achieved with a combination of ischemia, exercise and, the use of an endothelium-independent vasodilator (nitroglycerine, (NTG)), after 10 min of ischemia to induce a near maximal response. The intima-media thickness of the carotid artery reflects the generalized status of subclinical atherosclerosis and can be measured from ultrasound images.[34]

The term ‘arterial stiffness’ is a general expression that describes distensibility, compliance and elastic modulus of the arterial vascular system. Arterial stiffness can be measured at different levels: locally, regionally and centrally. Local carotid stiffness can be estimated by change in area of an artery to distending pressure.[34]

The evaluation of peripheral endothelial function, includes venous occlusion forearm Plethysmography, peripheral arterial tonometry, laser Doppler flowmetry, and flow-mediated dilation (FMD)[34]. FMD express the vasodilatation of a conduit artery following an increase in shear stress, typically induced by a 5-min period of ischemia induced by a limb cuff[35]. The brachial artery has been used widely as a global endothelial health index, although it may not representative in the SCI population[34].

The pulse wave velocity is measured by the speed at which the forward pressure wave moves through the vascular tree. Pulse wave velocity is calculated from the time taken for the arterial waveform to pass between two sites e.g. the carotid and femoral artery. Pulse wave analysis estimates central blood pressure, systemic arterial wave reflections (augmentation index) and wave reflection magnitude. This is normally measured by the pressure (tonometry) in the radial artery.[34]

Method

The primary data was obtained by a systematic search of multiple databases (including Embase, PubMed/Medline, SPORTSDiscus and PsycInfo). A keyword literature search for all scientific publications with no date range restriction was organized to extract studies that incorporated measures of arterial structure or function. To increase chance of finding important information the authors searched in reference lists of the investigated literature to find additional studies. The search strategy included a combination of AND and OR operators. Population key words: spinal cord injury, spinal cord injuries, paraplegia, tetraplegia OR quadriplegia - paired with vascular adaptations: blood flow, arterial flow, artery flow, vascular compliance, vascular function, vascular elasticity, arterial stiffness, arterial compliance, arterial resistance, arterial function, arterial elasticity, endothelial function, artery stiffness, artery compliance, artery function, artery elasticity OR vascular resistance – paired with exercises: running, jogging, swimming, walking, weight lifting, endurance training, resistance training, exercise therapy, physical activity OR functional electrical stimulation. Abstracts were reviewed to identify relevant studies, and where the relevant information was not available in the abstract, the method section was also reviewed. All studies published in English that incorporated measures of arterial structure or function in response chronic exercise in humans with SCI were included. 'Chronic exercise' is defined as a repeated amount of bouts of exercise during a short or long-term period of time[36]. Only studies that fit the definition were included. A total of 337 papers were found, after which duplicates, review papers, letters to the editor, those not in English and those not evaluating arterial function or structural outcomes were removed from the sample leaving a total of 27 articles (Figure 1).

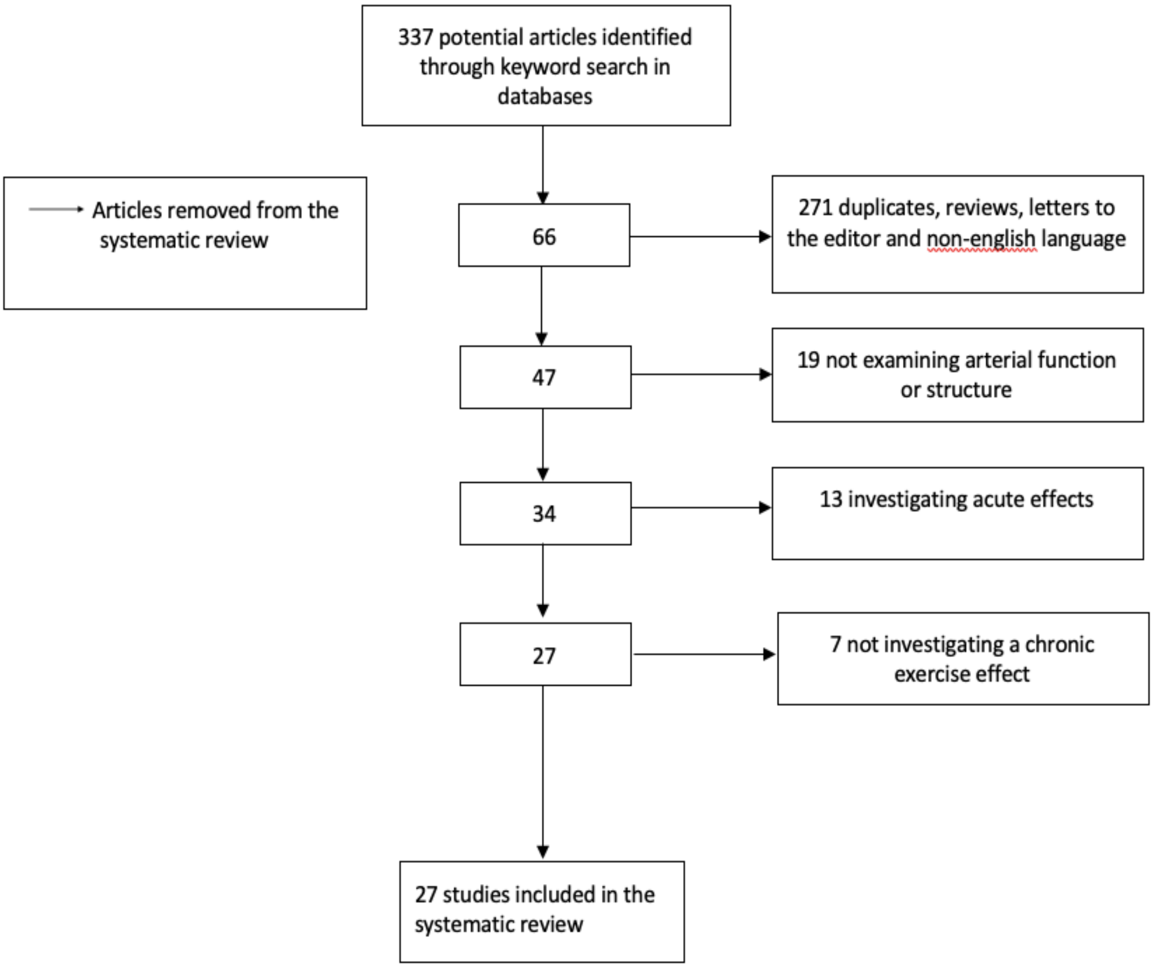

Figure 1 Flow of studies through the systematic review

The methodological quality of each article was evaluated by two independent reviewers (NM and DM) using the 11-item PEDro Scale[37] for randomized controlled trials (RCT). For methodological quality of non-randomized trials (NRT), studies were evaluated with the Downs and Black Tool[38]. The highest and strongest possible methodologically score for an article is 10 using the PEDro Scale and 27 for the Down and Black Tool. The level of evidence was evaluated using a five-level scale[38] where level 1 is the highest level of evidence with a PEDro score ≥6 and level 5 being the lowest. There was no sample size requirement for the individual studies because of a low number of publications in SCI research.

Results

The articles selected for investigation were categorized as chronic exercise. Within this group of articles, 4 RCT received a PEDro Scale score of 6-7 out of 10 (good methodological quality)[39], whereas the remaining 23 NRT studies ranged from 9 to 20 out of 27 on the Down and Black Scale (considered limited to moderate methodological quality)[40].

This study found 27 papers that met the systematic search criteria that examined arterial function and structure resulting from chronic exercise effects. Seven articles were case–control studies, 14 were of the pre–post studies, 2 was case reports and 4 was RCTs. This included exercise protocols of passive cycling, body weighted supported treadmill training (BWSTT) and tilt-table standing (TTS) training. Passive standing - Whole body vibration (PS-WBV), electrically stimulated knee extension (NMES), arm exercise (upper body), functional electrical stimulation (FES), hybrid electrical stimulation, endurance or endurance and resistance training. Table 1 is a summary of published investigations examining the effect of chronic exercise on arterial function and structure in those with SCI. The scale of injury is listed based on American Spinal Injury Association Impairment Scale[41]

Table 2: Effects of chronic exercise interventions on arterial dynamics in people with SCI

Author, year, country, study design, level of evidence, sample size	Methods	Outcome
Ballaz et al.[42] France Score 6/1 level 1 N = 17 (9 SCI-E, 8 SCI-Control)	Population: T3–T12 SCI (ASIA: A–C) Intervention: Passive cycling training 6 times per week for 6 weeks (36 sessions at home) done up to 30min at 50 r.p.m. Outcome measures: Maximum and minimum femoral artery blood flow velocity (duplex Doppler) using a velocity index (VI) (peripheral resistance) before and after 10min of passive cycling	1. No difference in vascular characteristics after 6 weeks passive cycling between trained and untrained groups at rest (P=0.08) 2. Increase in mean femoral artery blood flow velocity after 10-min passive cycling and a reduction in VI (P<.05)
Cotie et al.[43] Canada Score = 7/10 RCT Crossover Level 1 N = 7	Population: C5-T12 (ASIA: A-C) Intervention: body-weight-supported treadmill (BWST) and tilt-table standing (TTS) training which consisted of 4 weeks of BWST or TTS for 30 min, 3 times per week for a total of 12 training sessions. Outcome measures: Blood flow was assessed at the common femoral artery using Doppler ultrasound. Microcirculation was assessed by skin temperature, measured on the anterior aspect of the thigh and shin and posterior calf of both legs, using DermaTemp Infrared Surface Skin Scanner.	1. No changes in blood flow from either training method. 2. BWST training resulted in decreases in resting leg skin temperature at four of the six sites examined, whereas TTS training only resulted in decreases in resting skin temperature at one of the six sites.
Menéndez et al.[44] Spain Score = 7/10 RCT Level 1 N = 17 (9 SCI-E, 8 SCI-control)	Population: C3-L1 SCI (ASIA: A-B) Treatment: Whole-body vibration (WBV) and electromyostimulation treatment (WBV+ES) for 12 weeks. Outcome measures: Adaptations on the popliteal artery (mean blood velocity (MBV), peak blood velocity (PBV), arterial resting diameter (RD) and blood flow (BF). Measurement at baseline, after 6 weeks and 12 weeks of the treatment + 8 weeks after end treatment.	1. Increase from baseline in arterial resting diameter after post-6, post-12 and returned above baseline after 8 detraining in exercise group - no difference between groups. 2. Improved blood flow after WBV+ES was significant compared with the control group. Blood flow returned to baseline following 8 weeks of detraining.
Totosy et al.[45] Canada Score = 6/10 RCT Level 1 N = 23 (12 SCI-E, 11 SCI-control)	Population: C3-T11 SCI (ASIA: A-C) Intervention: Hybrid training (PAG) for 16 weeks with 20 minutes of moderate-vigorous aerobic exercise (rating of perceived exertion 3-6 on 10-point scale) and 3x10 repetitions of upper-body strengthening exercises (50%-70% 1 repetition maximum) 2 times per week. Outcome measures: Arterial stiffness measured via	1. improved carotid artery stiffness in the PAG group concurrent with declines in the control group. 2. No changes in carotid artery structure (pulse pressure, IMT, WLR), regional stiffness (PWV), or endothelial function (BA or SFA FMD or NTG)

	carotid distensibility with PWV (Central and peripheral), and endothelial function via flow-mediated-dilation (duplex ultrasound)	
Hubli et al.[46] Canada D & B Score = 15/27 Case control level 3 N = 20 (10 SCI-ex, 10 SCI-sedentary)	Population: C2–T5 SCI (ASIA: A-B) Characteristics: 10 elitehand-cyclists matched by sex to 10 sedentary non-athletes' individuals with SCI Outcome measures: Assessment of central arterial stiffness to compare PWV in athletes and non-athletes with SCI.	1. PWV was lower in athletes compared to non-athletes.
Jae et al.[47] South Korea D & B Score = 17/27 Case control level 3 N = 52 (28 SCI, 24 AB)	Population: Below T6 SCI (ASIA: A-E) Group Characteristics: SCI-trained (wheelchair athletes). AB (recreational) age-matched controls Outcome measures: Common carotid artery intima-media thickness, arterial compliance and β stiffness. Aortic augmentation index (applanation tonometry of radial artery)	1. No differences in any of the arterial values between the groups
Katzelnick et al.[48] USA D & B Score = 15/27 Case control level 3 N = 73 (46 SCI, 27 AB)	Population: C3-T12 (ASIA: A-C) Characteristics: 29 individuals with SCI C3-T5, 17 individuals with SCI T7-T12, and 27 AB controls Outcome measures: Pulse Wave Analysis of radial artery measured by an augmentation index (AI@75) used to estimate aortic arterial stiffness. PAL (physical activity level) measured at radial artery AI among groups	1. Increase in arterial stiffness in individuals with self-reported no physical activity compared to mild ($p<0.05$), moderate and intense exercise ($p<0.01$)
Nash et al.[49] USA D & B Score = 15/27 Case control level 3 N = 30 (20 SCI, 10 AB)	Population: C5–C7 SCI (ASIA: A) Group characteristics: FES (0.4-7 years) SCI-trained group. SCI-untrained group with no FES experience. 10 AB-control age-matched Outcome measures: Femoral artery end diastolic diameter and flow–velocity profiles at rest and after 5-min thigh occlusion	1. Increase in femoral peak systolic volume, cross-sectional area and inflow volume at rest in SCI-trained compared with SCI-untrained. 2. Increase in cross-sectional area and inflow volume after 5-min thigh occlusion femoral peak systolic volume in SCI-trained compared to SCI-untrained 3. Reduced resting and post-occlusive femoral artery cross-sectional area in SCI-trained compared to AB-control. No other differences in vascular parameters between SCI-trained and AB-control
Paim et al.[50] Brazil D & B Score = 17/27 Case control level 3 N = 63 (40 SCI, 23 AB)	Population: C4-T6 SCI (ASIA: A-C) Group characteristics: Wheelchair sport athletes (SCI-A and sedentary (SCI-S) and able-bodied (AB) control individuals Outcome measures: carotid intima-media thickness (cIMT) (ultrasonography)	1. Increase in cIMT in SCI-S compared to both SCI-A and AB.
Phillips et al.[51] Canada D & B Score = 17/27 Case control level 3 N = 34 (17 SCI, 17 AB)	Population: C5-L3 SCI (ASIA: A-C) Characteristics: The control matched the SCI subjects by age, sex and psychical activity. Outcome measures: Comparison of arterial stiffness between SCI and AB individuals when matched for habitual level of physical activity, including central carotid-femoral PWV, and lower limb femoral-toe PWV as well as large and small arterial compliance.	1. Both large and small artery compliance is associated with habitual physical activity (moderate to vigorous physical activity), but not with PWV in physically active individuals with SCI. 2. Increase in cfPWV with no other measures of arterial stiffness were different between the groups 3. No evidence of physical activity is

		associated with PWV in physically active individuals with SCI
Wong et al.[52] Canada D & B Score = 14/27 Case control level 3 N = 36 (18 SCI, 18 AB)	Population: C3-T12 SCI (ASIA: A-B) Characteristics: Age-, height-, weight- and sex-matched able-bodied participants were used as the control groups for the SCI groups. The SCI groups (untrained vs endurance-trained) were matched for level and severity of injury. Outcome measures: Large and small artery compliance were measured at the radial artery and physical activity was assessed via questionnaire.	1. No difference in large artery compliance between groups 2. Reduced small artery compliance markedly in SCI-untrained compared to SCI-trained, AB-trained and AB-untrained. 3. 4% increase in small artery compliance of SCI-trained compared to AB-untrained 4. Greater small artery compliance found in AB-trained compared to SCI-trained, SCI-untrained and AB-untrained.
De Groot et al.[53] The Netherlands D & B Score = 11/27 Pre–post level 4 N = 14 (6 SCI, 8 AB)	Population: T4–L2 SCI (ASIA: A-B) Intervention: FES training for 4 weeks, sessions of 30min of single leg daily (2-s stimulation followed by 3-s rest) Outcome measures: Arterial diameter, arterial compliance, FMD (superficial femoral artery) and mean wall shear rate of the common femoral artery, brachial artery and carotid artery (echo Doppler). Measurements performed at 1, 2 and 4 weeks	1. Increased artery compliance in trained leg femoral artery compliance after 4 weeks FES training 2. Reduced FMD in trained leg femoral artery after 2 weeks FES training
Ditor et al.[54] Canada D & B Score = 14/27 Pre-post level 4 N = 6	Population: C4-T12 SCI (ASIA: A-B) Intervention: Progressive increase from 15 to 60min BWSTT training 3 times per week for 16 weeks Outcome measures: Beat-to-beat blood pressure, mean femoral and carotid artery blood flow velocity and cross-sectional area (Doppler ultrasound). Calculation of femoral and carotid blood flow, compliance and resistance	1. Increased femoral artery compliance 2. No changes in any other carotid or femoral arterial characteristics
Gerrits et al.[55] The Netherlands D & B Score = 14/27 Pre–post level 4 N = 9	Population: C4–T8 SCI (ASIA: A-C) Intervention: FES training 30min sessions 3 times per week for 6 weeks (50 r.p.m.) Outcome measures: Arterial diameter, peak systolic inflow volume, mean inflow volume and velocity index (peripheral resistance) were evaluated at the common carotid and femoral arteries after 20min of femoral artery occlusion	1. Increase in femoral artery diameter, peak systolic inflow volume, mean inflow volume and reduced velocity index after the intervention 2. No change in any vascular measures of the common carotid artery after training 3. Improved hyperemic response improved (increased peak systolic inflow volume and velocity index) after training.
Hopman et al.[56] The Netherlands D & B Score = 14/27 Pre–post level 4 N = 9	Population: T4–T12 SCI (ASIA: A) Intervention: FES cycling training 30min sessions 3 times per week for 6 weeks Outcome measures: Blood flow and vascular resistance of calf and forearm (occlusion plethysmography), common femoral artery diameter, blood flow (color- coded Doppler)	1. Reduced baseline arterial blood flow and increased leg vascular resistance in SCI compared to AB control 2. Increased arterial blood flow and vascular resistance reduced in arms vs legs within the SCI group. 3. 30% increase in SCI in leg blood flow with unchanged blood pressure levels, indicating a marked reduction in vascular resistance after training.
Lammers et al.[57] The Netherlands	Population: C5-T11 SCI (ASIA: A-B) Intervention: FES cycling training for 8 weeks and	1. Increased femoral artery baseline diameter in SCI compared to control

D & B Score 14/27 Pre-post level 4 N = 14 (8 SCI, 6 AB)	sessions of 30min (20 sessions). Outcome measures: Peak hyperaemic (Doppler), baseline diameter and IMT of the superficial femoral artery were measured (echo ultrasound)	after exercise in SCI subjects. 2. No change in peak hyperaemic flow after 8 weeks of FES 3. Decrease in IMT/lumen ratio in SCI after 8 weeks of FES. 4. VEGF signalling pathway was identified as major potential players in these vascular adaptations.
Nash et al.[58] USA D & B Score = 11/27 Pre–post level 4 N = 12	Population: T4–T11 SCI (ASIA: A) Intervention: Parastep training with assisted FES 3 times per week for 12 weeks (32 sessions). Duration based on comfort of the participant Outcome measures: Femoral artery end diastolic diameter and flow–velocity profiles (Doppler Ultrasound) at rest and after 5- min thigh occlusion	1. Increased resting common femoral cross-sectional area, computed pulse volume and arterial inflow volume. Peak systolic velocity not significantly different (P = 0.083) 2. Increase in flow velocity integral and arterial inflow volume after 5-min thigh occlusion femoral pulse volume after intervention.
Sabatier et al.[59] USA D & B Score 15/27 Pre–post level 4 N = 5	Population: C5–T10 SCI (ASIA: A) Intervention: NMES training. 4x10 dynamic knee extensions, twice a week for 18 weeks Outcome measures: Femoral artery end diastolic diameter and flow–velocity profiles (Doppler ultrasound). Measurements were performed before training and after 8, 12, and 18 weeks of training	1. No changes in any vascular measures after training 2. Resting, reactive hyperemic, and exercise blood flow did not appear to change with training
Stoner et al.[60] USA D & B Score = 16/27 Pre–post level 4 N = 5	Population: C5–T10 SCI (ASIA: A) Intervention: NMES induced resistance training twice a week with 4x10 repetitions of unilateral, dynamic knee extension for 18 weeks Outcome measures: Resting diameter, FMD and arterial range (maximum–minimum diameter) of the posterior tibial artery.	1. Increase in FMD and arterial range 2. Resting diameter did not change
Taylor et al.[61] England D & B Score = 10/27 Pre–post level 4 N = 7	Population: Mid-low thoracic SCI (ASIA: Not documented) Intervention: FES knee extensions, increasing joint range (intensity) and duration in the 12-week program Outcome measures: Thigh blood flow (electrical impedance plethysmography)	1. Increase in thigh blood flow by 115% after training 2. Similar thigh blood flow after training in SCI compared to AB
Thijssen et al.[62] The Netherlands D & B Score 16/27 Pre-post level 4 N = 10	Population: T1-T12 SCI (ASIA: A-C) Intervention: 4 weeks of voluntary arm and electrically stimulated leg exercise (8 –12 sessions, 2-3 times a week) Outcome measures: active tissue vs adjacent inactive areas measured by plethysmography (blood flow and vascular resistance) and echo Doppler (diameter and flow-mediated dilation (FMD)	1. Increased thigh baseline and peak blood flow, decreased thigh baseline vascular resistance, and increased diameter of the common femoral artery in stimulated tissue. 2. No change in FMD of superficial femoral artery 3. No change in calf or forearm vascular parameters
Thijssen et al.[63] The Netherlands D & B Score = 20/27 Pre–post level 4 N = 9	Population: C5–T12 SCI (ASIA: A-C) Intervention: Hybrid training (FES cycling voluntary synchronous arm cranking) 2 times per week for 6 weeks consisted of 25min-sessions (tested after 2 and 6 weeks of training). Measured time course of detraining after 1 and 6 weeks. Outcome measures: Blood flow and vascular resistance of thigh and forearm (occlusion plethysmography), common femoral artery diameter,	1. After 2 weeks of hybrid training, increased in thigh baseline and peak blood flow, increase in femoral artery diameter, decrease in FMD of the femoral artery. 2. 1 week of detraining reversed baseline and peak thigh blood flow, vascular resistance, and femoral diameter toward pre-training values - 6

	blood flow (echo Doppler). Brachial and femoral FMD (echo Doppler)	weeks of detraining did not return FMD baseline of the femoral artery.
Totosy et al.[64] Canada D & B Score 11/27 Pre-post level 4 N = 15	Population: T4-T10 SCI (ASIA: A-D) Intervention: 45 min sessions of PS-WBV for 40 weeks (3 times a week) Outcome measures: Arterial stiffness (Aortic and leg) measured by PWV was collected at baseline, week 20 and week 40.	1. No observable change in arterial stiffness after 20 or 40 weeks for Aortic PWV (P = 0.46) or Leg PWV (P = 0.54)
Van Duijnhoven et al.[65] The Netherlands D & B Score 18/27 Pre–post level 4 N = 35 (18 SCI, 17 AB)	Population: T1-T12 SCI (ASIA: A-C) Intervention: FES cycling training for 8-wk, sessions of 30-min stimulation per training. SCI individuals trained twice a week during the first 4 week, while frequency was increased three times a week during the last 4 weeks. Outcome measures: Arm and leg skin blood flow - cutaneous vascular conductance (CVC) responses to local heating measured by laser-Doppler flowmetry.	1. The 8-wk intervention did not change forearm and leg CVC responses to local heating in SCI-C and SCI-EX but increased femoral artery diameter in SCI-EX (P=0.05). 2. Different impact on skin microcirculatory function than on conduit arteries.
Zbogar et al.[66] Canada D & B Score = 18/27 Pre–post level 4 N = 4	Population: C4–T7 SCI (ASIA: A-C) Intervention: FES training 30-min (50 r.p.m.), 3 times per week for 12 weeks Outcome measures: Large and small artery compliance	1. Increase in small artery compliance 2. No change in large artery compliance
Dolbow et al.[67] USA D & B Score 10/27 Case report level 5 N = 1	Population: T10 SCI (ASIA: B) Intervention: Resistance-guided, high intensity interval training functional electrical stimulation (RG-HIIT-FES) cycling program 3 times per week for 10 weeks and 30min sessions of 30/30 seconds intervals at 50-80% low-high intensity were used. Outcome measures: Reactive hyperemia (AUC), Shear stimulus (AUC), resting artery diameter, peak diameter and vascular endothelial function of the brachial artery via flow-mediated dilation (Duplex-Doppler)	1. Increase in FMD% in Brachial Artery and reactive hyperemia. 2. No significans in other vascular measures.
Tordi et al.[68] France D & B Score = 13/27 Case report level 5 N = 1	Population: T11 SCI (ASIA: A) Intervention: Wheelchair ergometry 3 times per week for 6 weeks for 30 min each session, 4:1 min interval training moderate 50% and high-intensity 80% Maximal Tolerated Power (MTP, watts). Increased watts by 10 when subject did not reach target HR. Outcome measures: Carotid–wrist and carotid–ankle pulse wave velocity	1. Decrease in both upper body and lower body pulse wave velocity after training (improved arterial stiffness)

Figur 2 Abbreviations: AB, able bodied; BWSTT, body weight supported treadmill training; D & B Score, Downs and Black quality score; FES, functional electrical stimulation; FMD, flow-mediated;; RCT, randomized controlled trials; SCI, spinal cord injury;

Passive leg exercise

Only one study examined the chronic exercise effect from passive leg exercise on arterial function in SCI[42]. This study showed subjects (N=9) with paraplegia and AIS A-C improving femoral artery hemodynamic response due to a 6 week (30min twice a week) home-based cycling program. Femoral blood velocity increased after 10-min passive cycling exercise (P=0.01) but no changes in resting femoral artery blood flow (P=0.08). The control group (N=8) continued with their daily activities across the 6 weeks and showed no change in either measure.

Conclusions: There is currently level 1 evidence[42] (highly reliable) supporting a passive leg exercise program as a technique to improve vascular function in subjects with paraplegia. Although the level of evidence show confidence in the effects of this type of training, there no prior studies which make it more uncertain even if the study was of high quality. There is a need for more studies examining this effect in subjects with tetraplegia and paraplegia and with larger sample sizes that does not limit the impact of the results.

Passive standing: Whole body vibration

A single study used a PS-WBV intervention where subjects (N=9) with SCI comparing AIS A-B (N=7) and AIS C-D (N=2) participated to improve arterial stiffness measured by PWV[64]. Subjects underwent therapy for 45min three times weekly for 40 weeks and showed no changes over time (measured after 20 and 40 weeks) for either aortic PWV (P=0.46) or leg PWV (P=0.54).

Conclusions: This study appear to suggest that chronic PS-WBV does not improve arterial function in subjects with paraplegia or between AIS. The study design (level 4[64] evidence (somewhat reliable)) of this investigation is in need of prospective research of chronic exercise effects of PS-WBV on arterial function in SCI participants with larger sample sizes and proper controls.

Body weighted supported treadmill (BWST) and tilt-table standing (TTS) training

Two studies examined the effects of BWST[43,54] or TTS[43] on arterial function in those with paraplegia and tetraplagia. Overall BWSTT did not change femoral artery[43,54] and carotid artery blood flow[43], although 4 months of BWSTT training 3 days per week showed improved femoral arterial compliance (N=6)[37]. Cotie et al.[43] showed that BWSTT training decreased resting skin temperature and skin temperature reactivity at several sites in the leg after 4 weeks (3 times per week) and TTS improved skin temperature in several sites in SCI subjects (N=7)

Conclusions: It appears from these level 1[43] and level 4[54] evidence studies, (somewhat reliable to reliable) that BWSTT has the potential to improve vascular function in SCI participants of the femoral artery and microcirculatory in the legs. Although more studies are needed to examine levels of injury to clarify the maximum and minimum potential benefit, as well a time course of the functional effects from BWSTT and TTS. Furthermore, studies should investigate the effects of this modality on blood flow in both skin microcirculation and conduit arteries.

Electrically stimulated knee extension

A total of three studies has investigated NMES (Neuromuscular Electrical Stimulation) as a potential modality for improving arterial structure and function in SCI subjects with AIS A[59–61]. Two studies used the same protocol of exercise for 18 weeks (twice a week). Sabatier et al.[59] (N=5) found no improvement in femoral arterial structure or function (artery diameter, blood flow, hyperemic response). Stoner et al.[60] (N=5) performed a follow-up study from the same group and improved femoral artery FMD after 18 weeks. Taylor et al.[61] used a progressive training regime of 3 month which demonstrated increased muscle thickness and thigh blood flow.

Conclusion: This level 4 evidence[59–61] (limited to average reliable) present that NMES may improve some arterial function in SCI. The lack of control groups reduces the evidence, it is therefore suggested that future studies should investigate the effects of this training modality with SCI controls.

Arm exercise

Four papers have evaluated the effect of upper body exercise on arterial function or structure. Jae et al.[47] found no differences in a cross-sectional design in the common carotid artery IMT, arterial compliance and stiffness between active wheelchair athletes with paraplegia and recreationally active AB controls (N=28 SCI vs 24 AB). Paim et al.[50] found a larger carotid IMT in sedentary SCI (N=17) compared with active SCI that participated in wheelchair sport utilizing the upper body (N=23) and sedentary AB (N=22). Hubli et al.[46] showed that elitehand-cyclists (N=10) had improved arterial stiffness compared to sedentary SCI (N=10). Tordi et al.[68] examining a case study of the aortic pulse wave velocity values of a single SCI participant (N=1) before and after 6 weeks of upper body endurance training (30 min, 3 times per week) showing significant improvements in central aortic stiffness post-training.

Conclusions: It appear from these studies, that chronic upper body exercise may improve arterial structure and function in those with SCI. The study design (level 3[46,47,50] and level 5[68] evidence (somewhat to adequate reliable)) of these four investigations is appreciable, although it also demonstrate the need for prospective research examining the impact of chronic exercise effects on arterial dynamics in SCI participants with larger sample sizes and proper controls.

FES

Eight studies have examined the chronic effects of FES training for improving arterial dynamics in SCI. All studies found improvements in arterial function or structure in SCI subjects (tetraplegia and paraplegia), and across AIS A-C. Findings from FES training were: increased femoral diameter,[55,57,65] decrease in IMT/lumen ratio,[57] increased brachial artery FMD,[67] normalized femoral artery FMD,[53] femoral artery compliance,[53] improved small artery compliance,[66] reduced leg vascular resistance,[56] increased femoral artery blood flow,[49,53,55,49] improved hyperemic response, [49,55,67]. De groot et al.[69] found that 2 weeks of FES training was required to improve femoral artery FMD. Hence, femoral artery compliance and blood flow responses were significant after 4 weeks of FES training.

Conclusion: These studies shows several improvements in arterial function and structure. The quality of design (Level 3 (N=1), level 4 (N=6), level 5 (N=1) is adequate reliable) show favorable outcome for FES training. Future studies should examine prospective research with larger sample sizes to determine the effects of FES on functional and structural adaptations.

Hybrid electrical stimulation

Four studies found improvements from hybrid electrical stimulation training in arterial function or structure in SCI subjects. Two studies used FES cycling combined with voluntary arm cranking (N=10),[62] (N=9)[63]. Nash et al.[58] combined FES and parastep in SCI subjects (N=12). Menéndez et al.[44] examined SCI subjects (N=17) that trained WBV with electrical stimulation for 12 weeks. These studies showed improvements in vascular function and structure for both tetraplegia and paraplegia subjects: increased baseline femoral artery blood flow,[62,63]larger femoral artery cross-sectional area,[58] increased peak thigh blood flow,[63] increased femoral artery diameter,[62] increased femoral artery

FMD[62] and post-occlusion femoral artery hyperemic response[58,63]. Thijssen et al.[63] showed that these improvements occur after only 2 weeks of hybrid training and all vascular changes, except of FMD, disappear after just 1 week of detraining. Menéndez et al.[44] showed improvements in the popliteal artery: resting diameter and blood flow.

Conclusions: Hybrid exercise using electrical stimulation can improve vascular function and structure in those with SCI. There is a need for more studies investigating a comparison of FES with hybrid exercise to identify whether hybrid exercise yields more vascular function benefits than traditional FES training. Future studies could compare PS-WBV and WBV+ES and investigate the vascular exercise effects between PS-WBV and WBV+ES training. The low to high level of evidence (level 1[44] and level 4[,58,62,63] (limited-to-highly reliable)) showed that effects of chronic FES exercise interventions on arterial function and structure is in need for larger sample sizes. Hence, future research should investigate if the improved popliteal artery can be found in the femoral artery and vice versa.

Endurance or endurance and resistance training

Four papers have evaluated the effect of endurance or endurance and resistance training on vascular function and structure. One study[45] examined the effects of 16 weeks endurance and resistance training. Three case-control studies[48,51,52] compared SCI subjects with SCI or AB based on physical activity level. Totosy et al.[45] found improved arterial function of carotid artery stiffness in tetraplegia and paraplegia, although the study found no changes in carotid artery structure (pulse pressure, IMT, WLR), regional stiffness (PWV), or endothelial function (BA and SFA FMD or NTG). Three studies[48,51,52] examined the physical activity level of endurance exercises through questionnaire and found improvements in trained SCI individuals (tetraplegia and paraplegia). The findings were increased small artery compliance, [60,62]increased large artery compliance[60] - large and small artery compliance were correlated with intensity (moderate-vigorous physical activity))[60]. Reduced central arterial stiffness[60]. Reduced peripheral arterial stiffness with intensity (mild ($P<0.05$), moderate and vigorous exercise ($P<0.01$))[63].

Conclusion: Based on the available evidence, including level 1[45] and level 3[48,51,52] (somewhat to reasonable reliable) investigation, there is promising support for endurance and resistance training can improve vascular function in individuals with tetraplegia and paraplegia. Although, there is a need for more research to distinguish between endurance and resistance training effects. Therefore, future research could help the overall reliability by implementing crossover designs to examine the individual effects of endurance and resistance training on arterial function and structure. Hence, crossover designs could also solve the problem of adherence (44% ± 34%) in the control group which was demonstrated in Totosy et al.[45].

Discussion

The purpose of this systematic review was to evaluate relevant literature that examined the chronic exercise effects on arterial function and structure.

Researches use various recruitment strategies while planning exercise interventions, because there is a limited assess of people with SCI and other low incidence disabilities[70]. The SCI population is at higher risk of CVD[22] and this population is less physical active than AB[5]. Therefore, researchers hesitate to design studies where a SCI control group would receive no intervention. The majority of the studies investigating the chronic exercise effects have either poorly matched controls or no control group at all (level 2-5 evidence: 21 out of 24 studies). Many of these intervention studies could improve the overall evidence by applying a control phase before and after the intervention which would improve the level of evidence for studies limited in sample size. Hence, studies in the future should use crossover designs to prevent SCI control groups not receiving an intervention effect.

In this review, the evidence demonstrated supports a lot of different exercises and viable method of improving vascular function and structural adaptations in those with SCI. FES and hybrid electrical stimulation showed increased femoral diameter, decrease in femoral IMT/lumen ratio, increased popliteal artery diameter[44,55,57,65]. There were seen improvements in femoral artery FMD, femoral and popliteal artery blood flow, arterial stiffness and hyperemic response[44,55,56,62,63,66]. It appears, that improvement in arterial function can be found after 2 weeks of training and may stay above baseline values after 6 weeks of detraining. Structural adaptation was found after 6-8 weeks of FES or hybrid electrical stimulation and stayed above baseline after 8 weeks of detraining. SCI with cardiovascular diseases (endothelial dysfunction) as well as in healthy controls (with normal endothelial function) have shown that exercise enhances FMD responses. However, De Groot et al.[53] (electrical stimulation) showed decreased femoral artery FMD in the inactive and paralyzed leg following a chronic exercise FES intervention. The current findings of normalized FMD in femoral artery is still to be investigated. De Groot et al.[53] argued that extreme inactivity result in a total lack of peak shear rate levels, and the exercise intervention have normalized the NO release and/or NO sensitivity.

The evidence of BWST illustrates improved vascular function in paraplegia and tetraplegia. Improvements in microcirculation vascular function were found in several local leg sites: decreased resting skin temperature and skin temperature reactivity[43]. Participating in regular exercises activities can be dangerous for people with SCI because of impaired thermoregulation which limits tolerance to exercise and creates negative incentive for persons with SCI to participate in regular exercise. However, lower resting skin temperature could prove advantageous for facilitating heat loss during exercise. Although, future studies are required to determine whether BWST actually provides any thermoregulatory benefit during exercise and/or during heat exposure. Chronic effects were found from BWST after 4 weeks (30 min, 3 times per week) and BWST can be a helpful modality for improving microvascular function and health in tetraplegia and paraplegia. The improved resting skin temperature suggest improved NO availability in the skin,[27] but there was no improvement in the femoral artery blood flow. Interestingly, data from AB population have demonstrated that exercise-induced improvements in vascular function may be dose-dependent and represent a balance between oxidative stress and NO availability with moderate-intensity exercise[71]. The BWST modality showed no change in blood flow which could be caused by the low-level intensity in Cotie et al[43]. Van Duijnhoven et al.[65] showed that FES cycling did not change cutaneous vascular conductance (function of central venous pressure during heating) in arms or legs in paraplegia, although the study used low intensity. There is little known of microvascular changes compared with conduit artery function after SCI[17].

The evidence of arm exercise indicates a tendency that upper body trained SCI have improved arterial function and structure. Overall, arm exercises improved arterial stiffness[46] and carotid IMT[50]. Although, there is a need for prospective research to establish more evidence on arm exercises.

The evidence of endurance or endurance and resistance training showed improvement in carotid arterial stiffness. Totosy et al.[45] combined 16 weeks of endurance and resistance training which improved carotid arterial stiffness. Normally, there is a difference when comparing the endurance and resistance effects on vascular function in AB[27]. The combination of aerobic and resistance training may have opposite effects on arterial function when comparing the changes in AB population: Spence et al.[72] compared upper body resistance training for 6 months, which improved brachial artery FMD, but not femoral artery FMD, whereas lower limb endurance exercise training did not improve brachial artery vascular function in AB. This may also indicate a site-specific changes; 10 weeks of endurance training improved BA FMD,[73] but 12 weeks of whole-body resistance training did not have an effect on BA FMD[74]. Hence, Totosy et al.[45] measured vascular function after 16 weeks, this may have prevented them from finding an effect in vascular function if compared when functional and structural changes that occur in AB. In the healthy AB population, BA and popliteal FMD increased after 2 weeks of endurance training but returned to baseline levels by 8 weeks, accompanied by increased structural adaptations[27]. Hence, the control group lacked adherence (44% ± 34%) in Totosy et al.[45] and there is a need of crossover designs to examine the individual effects of endurance and resistance training on arterial function and structure, and this can be a solution to give every participant an intervention. Crossover designs can be more time consuming, but more researchers should consider the benefits and produce such research.

Conclusions

There is a discrepancy in the available research evidence when the magnitude of cardiovascular disease is the leading cause of death in people with spinal cord injury and it being overlooked. It is concluded from the available literature, that chronic exercises (upper body, FES, hybrid electrically stimulated, BWST, endurance and resistance training) improves arterial function and structure in those with SCI. There is a need for research on chronic exercise interventions examining arterial dynamics, especially RCT's. The articles often lack matched or relevant control groups, and therefore we suggest that more articles take crossover designs into consideration when initiating the preparatory research. A lot of the modalities were only examined by a single published article which limit an incisive thesis. Although, we encourage studies to be creative and innovative in conducting intervention strategies to improve arterial function and structure through chronic exercise and improve the health of people with SCI.

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