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ORIGINAL ARTICLE

A systematic review of exercise as a therapeutic intervention to improve arterial function in persons living with spinal cord injury

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Study design: All randomized controlled trials, prospective cohort, case–controlled, pre–post studies and case reports that assessed exercise interventions, which influence arterial structure and function after spinal cord injury (SCI), were included.
Objective: To review systematically the evidence for exercise as a therapy to alter arterial function in persons with SCI.
Setting: Literature searches were conducted for appropriate articles using several electronic databases (e.g. MEDLINE, EMBASE).
Methods: Three independent reviewers evaluated each investigation's quality, using the Physiotherapy Evidence Database Scale for randomized controlled trials and Downs and Black Scale for all other studies. Results were tabulated and levels of evidence assigned.
Results: A total of 283 studies were found through the systematic literature search. Upon review of the articles, 27 were included. The articles were separated into those investigating arterial benefits, resulting from either acute bouts of exercise or long-term exercise interventions. The ability of both acute and long-term exercise interventions to improve arterial structure and function in those with SCI was supported by limited to moderate methodological quality. Upper body wheeling is the most commonly examined exercise therapy for improving arterial function. It appears from the evidence that a variety of exercise interventions, including passive exercise, upper body wheeling, functional electrical stimulation and electrically stimulated resistance exercise, can improve arterial function in those living with SCI.
Conclusions: Although the quality and volume of evidence is low, the literature supports exercise as a useful intervention technique for improving arterial function in those with SCI.
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Keywords: systematic review; vascular function; exercise; spinal cord injury

Introduction

Cardiovascular disease is a leading cause of death in those with spinal cord injury (SCI).[1–3] Increased vascular stiffness is thought to cause an amplified pulse pressure, a reduction in pressure buffering,[4] propagate increased ventricular tension and is a primary marker of cardiovascular disease risk.[5,6] Increasing vascular stiffness is related to advancing age,[7,8] poor nutrition,[9,10] smoking,[11,12] excessive alcohol consumption,[2,13,14] other chronic conditions (such as heart disease)[15] and low levels of physical activity.[16] Owing to the lack of mobility and the loss of autonomic regulation, people with SCI are particularly susceptible to alterations in both central and peripheral vascular function.[17–20] Moreover, it has been shown recently that those with SCI have increased vascular stiffness when compared with able-bodied (AB) individuals.[21,22]

Shortly after an SCI, femoral artery diameter and leg blood flow decrease significantly,[23] eventually by up to 50% in comparison to AB individuals.[24] It is thought that the loss of voluntary muscle contraction below the lesion level reduces blood flow to the legs: due to both a lack of oxygen demand and reduced release of metabolically stimulated vasodilatory signals (carbon dioxide, potassium, hydron, adenosine, and so on).[25] Another potential mechanism is a loss of the physical lengthening and shortening of muscle tissue, which inhibits the muscle pump and reduces the arterio-venous pressure gradient across the muscle bed.[26–28] Finally, in response to inactive muscular tissue and chronically reduced

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blood flow demand, the arterial system reacts by reducing the diameter[29] and the capillary density,[30] causing an increase in vascular resistance and leading to decreased venous capacitance and compliance.[31]

The loss of autonomic control below the lesion level appears to influence vascular stiffness as well. Although sympathetic denervation would be expected to increase vascular elasticity owing to a reduction in vascular tone, it appears that this occurs only in a transient nature,[32] and with long-term autonomic denervation, affected vessels increase stiffness as compared with pre-injury levels.[33] Supporting this idea is evidence showing that reduced autonomic presence in denervated limbs increases expression of endothelin-1 and reduces expression of nitric oxide, which would lead to increased arterial stiffness and resistance.[34]

It is well established that physical exercise generally improves cardiovascular health[35,36] and has been shown to improve arterial function in a variety of populations, disorders and disease states.[7,36–39] Several papers have been published on the influence exercise has on cardiovascular function in those with SCI (see review of Warburton *et al*.[36]). The purpose of this systematic review is to present a synopsis of the scientific literature investigating the usefulness of various exercise strategies to improve vascular function in denervated limbs of those with SCI. We hypothesize that there will be strong support for the therapeutic vascular benefits of exercise training in persons living with SCI. Furthermore, we expect that exercise modalities, which employ electrical stimulation of denervated muscle, will have stronger support as compared with techniques, which allow passive motion of denervated limbs.

Methods

A keyword literature search for all scientific publications from 1950 to present investigating the influence of exercise on vascular stiffness was conducted using the following online databases: MEDLINE, EMBASE, Cochrane Library, ACP Journal Club, DARE, CCTR, CMR, HTA, NHSEED, PsycINFO, SPORTDiscus and CINAHL. Population key words—spinal cord injuries, spinal cord injury, paraplegia, tetraplegia and quadriplegia—and vascular function keywords—vascular stiffness, vascular compliance, vascular function, vascular elasticity, vascular resistance, arterial stiffness, arterial compliance, arterial resistance, arterial function, arterial elasticity, endothelial function, artery stiffness, artery compliance, artery function, artery elasticity, blood flow, arterial flow, leg blood flow, femoral artery flow and femoral blood flow—as well as exercise phrases—exertion, exercise, movement, locomotion, running, jogging, swimming, walking, dependent ambulation, motor activity, muscle contraction, isometric contraction, isotonic contraction, weight lifting, exercise therapy, physical, physical activity, body weight supported treadmill training (BWSTT) and functional electrical stimulation (FES)—were paired by permutation. A total of 283 papers were found, after which duplicates, review papers, letters to the editor, those not in English and those not evaluating arterial function outcomes were removed from the sample leaving a total of 26 articles (Figure 1). Two additional papers[40,41] were added to the sample as a result of cross-referencing, leaving a total of 28 articles.

An evaluation of the methodological quality of each article was completed by two independent reviewers (AP, AC) and confirmed by a third reviewer with expertise in systematic reviews (DW) using either the 11-item PEDro Scale[42] (randomized controlled trials; RCT) or the Down and Black Tool[43] (non-RCTs). The highest and therefore most methodologically strong score attainable for a given research article is 10 for the PEDro Scale and 27 for the Down and Black Tool. Higher points indicate a superior methodological quality. Further, the level of evidence was evaluated using a five-level scale[43] (simplified form of Sackett),[44] where level 1

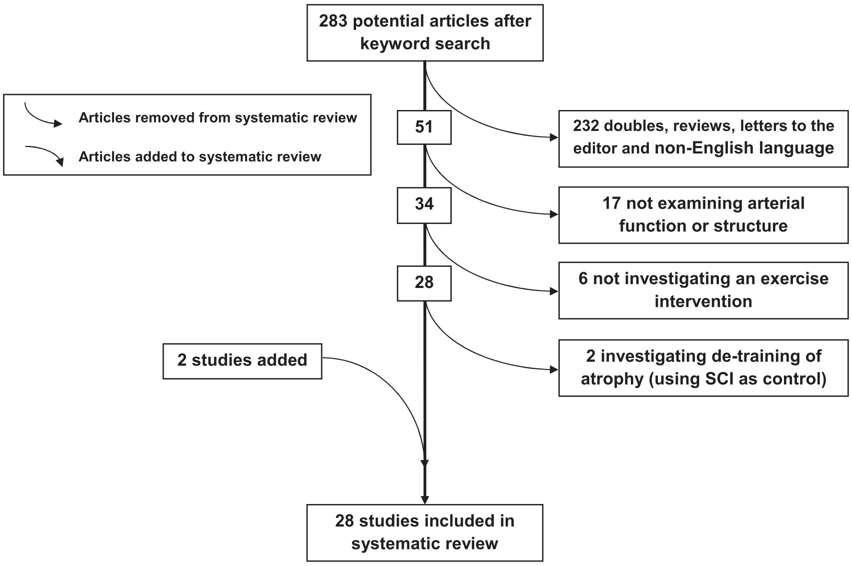

Figure 1 Flow of studies through systematic review.

(the highest level of evidence) = RCT with a PEDro score $\geqslant 6$; level 2 = an RCT with a PEDro score $\leqslant 5$, a non-randomized prospective-controlled study, or a cohort study; level 3 = a case–control study; level 4 = a pre- and post-test or a case series; and level 5 (the lowest level of evidence) = an observational report or case report with only a single subject.[45] There was no minimum sample size owing to the low number of publications in SCI research. Librarians from the University of British Columbia and all authors approved this systematic process and methodology. Ranking scores were performed in duplicate, after which any discrepancies were solved by discussion.

Results

The articles selected for investigation were categorized into two groups: Acute Exercise and Non-Acute Exercise. Within the Acute Exercise group, the Down and Black Tool scores ranged from 10 to 19 out of 27 (limited to moderate methodological strength).[46–48] The lone RCT[49] categorized within the Non-Acute Exercise group received a PEDro Scale score of six out of 10 (good methodological quality),[50] whereas the remaining studies ranged from 10 to 20 out of 27 on the Down and Black Scale (considered limited to moderate methodological quality).[46]

Acute exercise techniques
Fourteen papers investigated the vascular effects of a single acute exercise bout. Eight articles were prospective control trials[31,41,51–56] and six were pre–post design.[40,57–61] Papers investigating acute exercise included: passive leg exercise ($n = 3$),[53,57,60] FES ($n = 3$),[54,55,59] single muscle electrical stimulation ($n = 1$),[56] upper body continuous aerobic exercise (arm cycling or wheeling) ($n = 5$),[31,40,41,52,58] acute combined arm passive leg exercise ($n = 1$)[61] and stretch-induced contractions ($n = 1$).[51] Tables 1 and 2 are a summary of published investigations researching the effect of acute exercise on arterial function in SCI individuals.

Acute passive leg exercise. Passive leg exercise, or the application of external forces on denervated limbs with the purpose of causing motion, is the simplest technique for lower body exercise in the SCI population.[36] Three papers investigated the vascular effect of passive exercise on arterial function in SCI participants. One examined the influence of passive range of motion physiotherapy on leg blood flow in paraplegics (PARA) and tetraplegics (TETRA).[60] This article showed that leg blood flow increases very little, if at all, in response to passive leg movement administered by a physiotherapist.[60] The other two studies from this group investigated passive cycling (denervated legs are strapped to pedals and pedals are mechanically rotated) and showed disagreement in their results. Ter Woerds *et al.*[53] measured arterial function before, during and after 10 min of passive leg movements, and 20 min of passive leg cycling for PARA and AB individuals. These authors showed no change in femoral blood flow or leg vascular resistance (calculated as mean arterial pressure divided by leg blood flow) for either

Table 1 Results of the OVID (MEDLINE, EMBASE, ACP, Cochrane Library, DARE, CCTR, CMP, HTA, NHSEED) literature search

No.	*Searches (29 July 2010)*	*Results*
Population of interest		
1	Spinal cord injuries.mp.	52 021
2	Tetraplegia.mp.	16 354
3	Spinal cord injury.mp.	46 520
4	Paraplegia.mp.	32 551
5	Quadriplegia.mp.	16 684
Outcome variable		
6	Femoral blood flow.mp.	733
7	Femoral artery flow.mp.	744
8	Leg blood flow.mp.	2645
9	Blood flow.mp.	407 721
10	Arterial flow.mp.	4488
11	Vascular stiffness.mp.	549
12	Vascular compliance.mp.	1079
13	Vascular function.mp.	6835
14	Vascular elasticity.mp.	128
15	Arterial stiffness.mp.	6037
16	Arterial compliance.mp.	3132
17	Arterial resistance.mp.	1639
18	Arterial function.mp.	886
19	Arterial elasticity.mp.	588
20	Endothelial function.mp.	20 067
21	Artery stiffness.mp.	772
22	Artery compliance.mp.	4224
23	Artery function.mp.	386
24	Artery elasticity.mp.	320
25	Vascular resistance.mp.	99 579
Intervention strategy		
26	Exertion.mp.	68 664
27	Exercise.mp.	438 789
28	Movement.mp.	427 687
29	Locomotion.mp.	66 937
30	Running.mp.	73 171
31	Jogging.mp.	3073
32	Swimming.mp.	39 218
33	Walking.mp.	84 149
34	Dependent ambulation.mp.	2033
35	Motor activity.mp.	102 057
36	Muscle contraction.mp.	153 083
37	Isometric contraction.mp.	25 546
38	Isotonic contraction.mp.	1465
39	Weight lifting.mp.	7573
40	Exercise therapy.mp.	42 460
41	Physical activity.mp. or motor activity	181 669
42	Body weight supported treadmill training.mp.	205
43	Functional electrical stimulation.mp.	2596
Combined population of interest search terms		
44	1 or 2 or 3 or 4 or 5	95 880
Combined outcome variable search terms		
45	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	502 194
Combined intervention strategy search terms		
46	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	1 335 723
Combined population of interest, outcome variable and intervention strategy search terms		
47	44 and 45 and 46	266

Please note this does not include the results of the EBSCO (PsychINFO, SPORTDiscuss and CINAHL) literature search.

Table 2 Effect of acute exercise interventions on arterial dynamics in SCI

Author, year, country, study design, sample size	*Methods*	*Outcome*
Ballaz *et al.*[57] France D & B Score = 16/27 Pre–post level 4 *N* = 15	Population: T3–L1 SCI Intervention: 10-min passive leg exercise bout (target of 40 r.p.m.) Outcome measures: Maximum and minimum femoral artery blood flow velocity, mean blood flow velocity, velocity index (peripheral resistance) before and after 10-min passive cycling (within 7 s of cycling cessation)	1. Increased maximum and mean femoral blood flow velocity 2. Decreased velocity index 3. No change in heart rate
Ter Woerds *et al.*[53] The Netherlands D & B Score = 13/27 Prospective control trial level 2 *N* = 16 (8 SCI, 8 AB)	Population: T2–L1 SCI Intervention: 10-min passive leg movements and 20-min passive cycling (35 r.p.m.) bouts performed by physiotherapist (hip, knee, ankle) Outcome measures: Beat-by-beat blood pressure Common femoral artery velocity and diameter (echo Doppler)	1. No changes in any vascular measures (leg vascular resistance, total vascular resistance, leg blood flow) after 10-min passive leg movements or passive cycling
Dela *et al.*[54] Denmark D & B Score = 14/27 Prospective control trial level 2 *N* = 16 (10 SCI, 6 AB)	Population: C6–T5 SCI Intervention: 15 min of low-intensity FES followed by 15 min of higher work rate FES (both at 50 r.p.m.) Outcome measures: Leg blood flow (femoral artery and vein catheterization). Beat-by-beat blood pressure. Common femoral artery velocity and diameter	1. Leg blood flow increased at low intensity over rest in both TETRA and PARA, but did not increase further at higher work rate as it did in AB controls 2. Leg vascular resistance and total peripheral resistance decreased as compared to rest at low intensity in both PARA and TETRA. Only TETRA showed further decrease in TPR at higher work rate
Bidart and Maury [51,52] France D & B Score = 11/27 Prospective control trial level 2 *N* = 16 (9 SCI, 7 AB)	Population: Above T9 SCI Intervention: Manual stretch-induced contractions of the gastrocnemius Outcome measures: Resting and contracting gastrocnemius blood flow (disappearance rate of 133-Xenon)	1. Similar muscle blood flow in response to contractions between SCI and AB
Bidart and Maury[51,52] France D & B Score = 10/27 Prospective control trial level 2 *N* = 23 (14 SCI, 9 AB)	Population: PARA Intervention: 4 min of upper limb muscular exercise performed in the supine position (50 W) Outcome measures: Relative foot blood flow (strain gauge plethysmography)	1. Blood flow increases to legs during upper body exercise in SCI, but decreases to legs in AB individuals during the suggestion of exercise and stays low during
Burkett *et al.*[58] USA D & B Score = 12/27 Pre-post level 4 *N* = 20 (16 PARA, 4 TETRA)	Population: C4–L3 Intervention: Maximal arm cycle stress test (minute-by-minute increase in intensity) Outcome measures: Leg blood flow (toe plethysmography)	1. Increased blood flow during exercise (vasodilatation) 2. Reduced blood flow after exercise (vasoconstriction)
Phillips *et al.*[59] USA D & B Score = 12/27 Pre–post level 4 *N* = 8	Population: C6–T12 Intervention: Five minutes hybrid exercise at 60% VO_2 peak and 80% VO_2 peak. Both trials were completed with FES at 0 A (arms only), 40 A and 80 A (50 r.p.m. arm cranking generated intensity not met by FES in legs) Outcome measures: Leg blood flow (toe plethysmography)	1. Increased leg blood flow during exercise (vasodilatation) 2. Leg blood flow increased with increasing intensity of exercise (%VO_2) and FES intensity 3. Leg blood flow was increased with hybrid exercise in comparison to arms only for both intensities
Nash *et al.*[55] USA D & B Score = 10/27 Prospective control trial level 2 *N* = 10 (5 SCI, 5 AB)	Population: TETRA, age and gender-matched AB Intervention: Thirty-min FES at matched work rate Outcome measures: Ankle/brachial indices	1. No difference in ankle/brachial index between TETRA and AB at rest 2. Ankle/brachial index elevated in AB, but not in TETRA
Hopman *et al.*[31] The Netherlands D & B Score = 14/27 Prospective control trial level 2 *N* = 10 (10 SCI, 10 AB)	Population: T4–T12, gender-matched controls Intervention: Twenty-five minutes arm crank exercise at 50% of the individual's maximum load Outcome measures: Both common femoral artery blood flow (estimated from diameter and blood velocity), and pulsatility index (peripheral resistance) were measured at rest and every 5 min during arm exercise (echo Doppler)	1. Maximum blood velocity, diameter and blood flow of the common femoral artery were reduced in SCI as compared with AB. Minimum velocity and peak pulsatility index significantly reduced in SCI group 2. No change in femoral blood flow, diameter or mean velocity occurred in SCI with arm exercise 3. Blood flow increased with exercise in AB group

Table 2 Continued

Author, year, country, study design, sample size	*Methods*	*Outcome*
Svensson *et al.*[60] Sweden D & B Score = 16/27 Pre–post level 4 *N* = 6	Population: C5–T8 SCI Intervention: Passive movement performed by physiotherapist. 10 min, 30 repetitions per minute of maximal passive flexion–extension in all joints of leg Outcome measures: Arterial blood flow (venous occlusion plethysmography) was measured on treated and un-treated legs after 5 and 30 repetitions on one leg. Measures were made on both treated and un-treated legs during 39 separate sessions over 3–4 weeks	1. Blood flow to both treated (69%) and un-treated leg (59%) was increased on most occasions 2. No difference occurred in blood flow between groups after 5 or 30 repetitions
Olive *et al.*[56] USA D & B Score = 15/27 Prospective control trial level 2 *N* = 17 (9 SCI, 8 AB)	Population: Nine males (C5–T1) Intervention: Surface electrical stimulation of right quadriceps femoris muscle. Three bouts (low, moderate and high intensity at work to rest ratios of 1:6, 1:4 and 1:2, respectively). Each bout was 3-min duration Outcome measures: Blood flow was measured in femoral artery (Doppler ultrasound) after exercise bouts	1. Peak femoral blood flow increased with increasing intensity 2. Peak blood flow not different between groups at any exercise intensity
Seifert *et al.*[61] Germany D & B Score = 14/27 Pre–post level 4 *N* = 8	Population: Eight males (T6–L1) Intervention: Hybrid - 30 repetitions of active arm against resistance and 30 passive repetitions of the anterior tibial muscle by a physiotherapist Outcomes measures: Blood flow was measured in tibilias anterior muscle using radioactive isotope disappearance technique	1. Blood flow of tibialis anterior increased after hybrid exercise
Hopman *et al.*[41] Netherlands D & B Score = 13/27 Prospective control trial level 2 *N* = 30 (15 SCI, 15 AB)	Population: 10 males (T4–T12) Intervention: Twenty-five minutes arm crank exercise at 50% of the individual's maximum load Outcomes measures: Blood flow was measured in common femoral artery (Doppler ultrasound) at rest and every 5 min during exercise	1. In SCI group, femoral artery blood flow, mean velocity and diameter did not change with exercise 2. In AB group, femoral artery blood flow and mean velocity increased during exercise with no change in arterial diameter 3. At rest, maximal blood flow velocity, arterial diameter and blood flow of the femoral artery was significantly reduced in SCI
Kinzer and Convertino[40] USA D & B Score = 19/27 Prospective control trial level 2 *N* = 10 (5 SCI, 5 AB)	Population: (T6–T11), age, gender (all male), weight and peak arm–crank oxygen uptake matched controls Intervention: Ten minutes of arm cycling at 35 W Outcome measures: Leg blood flow (heart rate multiplied by leg pulse volume), leg fluid accumulation (impedance plethysmography)	1. Leg fluid accumulation significantly increased in SCI, but decreased in AB 2. There was a nonsignificant increase in leg blood flow after exercise in both SCI and AB

Abbreviations: AB, able bodied; D & B Score, Downs and Black quality score; FES, functional electrical stimulation; PARA, paraplegic; SCI, spinal cord injury; TETRA, tetraplegic; TPR, true positive rate.

group during or after (0, 1, 2, 5 or 10 min post-exercise) either of the passive exercise modalities. In contrast, Ballaz *et al.*[57] reported that leg blood flow (measured using Doppler ultrasound) increased in PARA after 10 min of passive cycling. These authors acknowledged the discrepancy and inferred a number of methodological differences between studies to account for marked disparities (such as higher cadence, continuous exercise without 10-s rest periods for flow measurements, larger sample size and optimal force arm length to involve the maximum musculature for a given pedal rotation).[57]

Conclusions: There is level 4 evidence (indicating available evidence but without comparable groups) that a single bout of passive leg exercise increases leg blood flow,[57] whereas there is level 2[53] (debatable but reliable results) and level 4 evidence[60] suggesting no change in leg blood flow or leg vascular resistance in response to passive leg exercise. As only three papers have published results on leg blood flow changes in response to passive leg exercise, further research, incorporating various exercise intensities and force arm lengths with adequate sample sizes, is warranted.

Acute FES exercise. FES involves muscle stimulators placed over motor points in denervated musculature activated in a synchronized manner as to functionally manipulate an exercise device (e.g. a cycle ergometer). FES is one of the most widely studied rehabilitation techniques for the SCI population. The application of FES has shown promise for a variety of SCI-related issues including obesity[62] and muscle atrophy.[63] A total of three papers have investigated acute arterial function changes in response to FES.[54,55,59] Nash *et al.*[55] showed similar ankle/brachial index (the ratio of blood pressure in the lower legs to the blood pressure in the arms) at rest between age- and gender-matched AB and TETRA men. After an acute 30-min bout of FES, however, ankle/brachial index in AB men increased with no change in TETRA. These findings were explained by increased lower body blood pooling after exercise or decreased vascular response post-exercise in TETRA.[55]

The remaining two papers measuring arterial function in response to acute bouts of FES showed increased leg blood flow after exercise. In the investigation by Phillips *et al.*,[59] pre–post exercise changes in toe photoelectric plethysmography were used to estimate changes in leg blood flow in SCI participants (C6–T12). The participants performed two different FES intensities (40 mA, 80 mA) in conjunction with arm crank exercise (hybrid), and adjusted resistance to create an intensity of 60 or 80% of VO_2 peak (four trials total). These authors reported significantly elevated leg blood flow after hybrid exercise and increasing blood flow with increasing hybrid exercise intensity, suggesting that leg blood flow in SCI is intensity dependent.[59] Dela *et al.*[54] also showed increased leg blood flow with FES and no difference in leg blood flow or leg oxygen uptake between TETRA, PARA or AB after 15 min of low-intensity FES. However, for those with SCI, these variables leveled off and did not increase at the higher FES intensity as was noted in the AB group.

Conclusions: There is level 2 evidence[54,55] (reliable results but debatable) suggesting that FES exercise can improve arterial function in those with SCI. Studies examining acute bouts of FES illustrate its usefulness in identifying vascular changes in those unable to willfully contract musculature. The findings of the three studies investigating SCI arterial function in response to FES show that lower body exercise of this modality can cause an increase in leg blood flow in both TETRA and PARA. It appears that further investigations involving a variety of intensities and durations of FES are needed to clarify disagreement in the dose–response relationship between exercise and arterial dynamics in SCI. In addition, to maximize potential arterial benefits, different modalities (specifically concurrent arm cranking (hybrid) vs resting upper body) need to be compared.

Acute single muscle electrical stimulation. One article investigated the influence of single muscle electrical stimulation on arterial dynamics in those with SCI.[56] This study illustrated that electrical stimulation of the quadriceps femoris leads to increased femoral artery blood flow. In addition, these authors showed that femoral blood flow increases with increasing exercise intensity in SCI participants, suggesting a dose–response relationship.

Conclusions: Currently, there is level 4 (available evidence but without comparable groups) evidence suggesting that single muscle leg electrical stimulation improves femoral artery blood flow in those with SCI. Only one study has investigated this type of intervention ($n = 17$, 9 SCI, 8 AB); therefore, there is a great need to examine further the effect of single muscle electrical stimulation on arterial dynamics in those with SCI.

Acute arm exercise. Upper body exercise for individuals with SCI is a relatively inexpensive and simple technique to increase physical activity. The arterial changes in SCI persons induced by acute bouts of upper body exercise have been studied in five[31,40,41,52,58] articles. Three papers from this group investigated blood flow changes in response to arm cranking.[40,41,52] The common finding from this group of investigations is that the ability of the denervated vasculature to locally regulate blood volume and redistribute it to working muscles (i.e. the upper body during arm cycling) is impaired. Bidart and Maury[52] showed no change in leg blood volume (plethysmography) during 1 min of arm cranking in SCI, whereas leg blood volume decreased substantially during the same exercise in AB. Kinzer and Convertino[40] showed that leg blood volume increases after 10 min of arm cycling in SCI, but decreased in AB. Hopman *et al.*[41] illustrated convincingly the impaired local regulation in denervated lower limbs by showing that both the rate of leg blood volume changes and the absolute level of leg blood volume were significantly reduced in SCI as compared with an AB control group during 25 min of arm cycling.

In addition to investigating leg blood volume changes, leg blood flow was also measured during upper body cycling exercise in four of the five papers.[31,40,52,58] Kinzer and Convertino[40] as well as Bidart and Maury[52] and Burkett *et al*.[58] showed increases in leg blood flow during upper body arm cycling at moderate[40,52] and maximal[58] intensity levels (durations of 4–15 min). The results of Kinzer and Convertino[40] as well as Burkett *et al.*,[58] however, failed to show significant changes, and work by Bidart and Maury[52] did not include a statistical analysis or original data. Hopman *et al.*[31] took this line of research a step further and illustrated that there is no statistically significant increase in femoral artery blood flow during 25 min of upper body cycling. The data from this paper, however, does show a trend of increasing mean femoral artery blood flow velocity, with no change in arterial diameter (flow = velocity × diameter).[31]

Conclusions: There is level 2 evidence[40,41,52] (reliable results but debatable) showing that local blood volume regulation in denervated limbs is impaired during upper body cycling in SCI. In addition, there is level 2 evidence[40,52,58] (reliable results but debatable) suggesting that leg blood flow increases during upper body cycling; however, these conclusions were not verified statistically. There is however level 2 evidence showing that leg blood flow does not increase to a statically significant level during upper body cycling exercise.[31] More research is needed to clarify the minimum duration and intensity of arm exercise required to improve leg blood flow. Also, more research is required with regard to changes in leg blood flow during upper body cycling with larger sample sizes and relevant statistical analyses.[31]

Acute combined arm passive leg exercise. Only one study has examined arterial function after a single bout of active arm exercise combined with passive leg movement.[61] This pre–post investigation showed that blood flow measured by double isotope disappearance rate increased in the tibialis anterior after simultaneous 30 repetition bouts of arm movement against resistance and passive leg movement performed by a physiotherapist.

Conclusions: There is currently one paper with level 4[61] evidence (available evidence but without comparable groups) that reported increased leg blood flow in response to combined arm exercise and passive leg movements. With such limited data, it is difficult to interpret the value of this exercise technique. Further research is required in this area.

Stretch-induced contractions. One study has investigated the changes in arterial structure and function in response to stretch-induced contractions of denervated limbs in those with SCI.[51] The investigation by Bidart and Maury, which describes manually stretching the gastrocnemius to induce a spasmodic reflex contraction, found similar local blood flow responses in the gastrocnemius after stretch-induced contractions in AB and PARA. The authors also noted that because there was no quantitative comparison of the strength of spasmodic manual stretch reflex to voluntary contraction of the AB group, quantitatively comparing the blood flow response is speculative.

Conclusions: There is currently one paper with level 2 (debatable but reliable results) evidence investigating blood flow changes in response to stretch-induced contractions.[51] With such limited data, it is difficult to interpret the value of this exercise technique. More research needs to be completed investigating[64–68] the acute vascular changes in response to stretch-induced contractions.

Exercise training interventions

Fifteen papers met the systematic search criteria that examined changes in arterial function and structure resulting from exercise training (i.e. non-acute exercise) interventions. Two articles were case–control studies,[69,70] 11 were of the pre–post design,[24,71–75] one was a case report and one was an RCT. The Non-Acute Exercise category ($n=15$) included passive leg exercise ($n=1$),[49] FES ($n=5$),[65,70–73] upper body exercise ($n=2$),[69,76] an electrically stimulated resistance training regimen ($n=3$),[24,67,68] hybrid exercise ($n=3$)[66,74,75] and BWSTT ($n=1$).[64] Table 3 is a summary of published investigations examining the effect of non-acute exercise on arterial function in those with SCI.

Passive leg exercise. Only one study investigated the effect of a passive, non-acute exercise program on arterial function in PARA.[49] This study showed that an un-supervised 6-week home-based passive cycling intervention improves femoral artery hemodynamic response (ultra-sound derived femoral blood flow velocity) in those with SCI ($n=9$) after 10-min passive cycling exercise ($P=0.01$), but does not change resting femoral artery blood flow ($P=0.08$). The control group ($n=8$), which continued their habitual daily routine, showed no change in either measure.

Conclusions: There is currently level 1 evidence[49] (highly reliable) supporting a passive leg exercise program as a technique to improve vascular function in PARA. Although only one study has investigated this intervention technique, the high level of evidence suggests that routine passive exercise improves lower body vascular function in PARA. There is a need to investigate long-term passive cycling exercise programs with larger sample sizes that include TETRA.

FES. Several investigations have examined the effect of non-acute FES training for improving arterial dynamics in SCI. All five papers investigating FES cycling showed significant improvements in vascular function in both PARA and TETRA. Overall, FES has led to increased femoral artery blood flow,[70,71,73] improved small artery compliance,[65] femoral artery compliance,[72] normalized femoral flow-mediated dilatation,[72] reduced leg vascular resistance[73] and improved hyperemic response.[70] According to work by De Groot *et al*.,[23] a minimum of 2 weeks FES training is required for arterial dynamic improvements (femoral artery flow-mediated dilatation); however, trends start to appear after the first week. After 4 weeks of FES training, femoral arterial compliance and femoral artery blood flow showed statistically significant improvements.

Conclusions: Based on the available evidence, including a level 3 (ref. 70) (somewhat reliable) investigation, there is promising support for the use of long-term FES training in improving vascular health in SCI.

Arm exercise. Two papers have evaluated the effect of non-acute upper body (arm) exercise on arterial function in SCI participants. Jae *et al*.[69] compared intima–media thickness, compliance and β stiffness index (a measure of arterial elasticity) of the common carotid artery between 28 PARA competitive athletes and 24 age-matched recreationally active AB controls finding no differences between groups. In addition, Tordi *et al*.[76] published a case study examining the aortic pulse wave velocity values of a single SCI participant 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: These studies appear to suggest that long-term upper body exercise can improve arterial structure and function in those with SCI. The study design (level 3[69] and level 5[76] evidence (somewhat reliable–to reliable)) of these investigations illustrates the need for prospective research examining the influence of non-acute upper body exercise on arterial dynamics in SCI participants with larger sample sizes and proper controls.

Electrically stimulated knee extension. Electrically stimulated knee extension, which involves electrical stimulation of the denervated musculature to increase strength, has been investigated by three studies as a potential technique for

Table 3 Effect of non-acute exercise interventions on arterial dynamics in SCI

Author, year, country, study design, sample size	*Methods*	*Outcome*
Gerrits *et al.*[71] The Netherlands D& B Score = 14/27 Pre–post level 4 *N* = 9	Population: C4–T8 SCI Intervention: 30-min FES training 3 times per week for 6 weeks. Resistance altered to allow a cadence of 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 20 min of femoral artery occlusion	1. After training, femoral artery showed increased diameter, peak systolic inflow volume, mean inflow volume and reduced velocity index 2. No change in any vascular measures of the common carotid artery after training 3. After training, hyperemic response improved (increased peak systolic inflow volume and velocity index)
De Groot *et al.*[72] The Netherlands D & B Score = 10/27 Pre–post level 4 *N* = 14 (6 SCI, 8 AB)	Population: T4–L2 SCI Intervention: 30 min of single leg daily FES training for 4 weeks (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. Before training arterial compliance was decreased in the common carotid artery and femoral artery, whereas FMD was elevated in SCI patients when compared with AB 2. Arterial compliance and endothelial function of the brachial artery was not different between groups 3. FES training led to an increase in trained leg femoral artery compliance after 4 weeks 4. FMD was reduced in trained leg femoral artery after 2 weeks training
Jae *et al.*[69] South Korea D & B Score = 17/27 Case–control level 3 *N* = 52 (28 SCI, 24 AB)	Population: Below T6 SCI Group characteristics: SCI trained was physically active competitive wheelchair athletes. AB were recreationally active 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 difference in any arterial values between groups
Hopman *et al.*[73] The Netherlands D & B Score = 14/27 Pre–post level 4 *N* = 9	Population: T4–T12 SCI Intervention: 30-min FES training 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. At baseline (*N* = 11), arterial blood flow reduced and leg vascular resistance increased in SCI vs AB control 2. Within SCI (*N* = 11), arterial blood flow elevated in and vascular resistance reduced in arms vs legs 3. After training (*N* = 9), 30% increase in leg blood flow (no change in blood pressure). Reduced leg vascular resistance
Thijssen *et al.*[74] The Netherlands D & B Score = 20/27 Pre–post level 4 *N* = 9	Population: C5–T12 SCI Intervention: 25-min hybrid training 2 times per week for 6 weeks (tested after 2 and 6 weeks of training). Six weeks of detraining (tested after 1 and 6 weeks no training) Outcome measures: Blood flow and vascular resistance of thigh and forearm (occlusion plethysmography), common femoral artery diameter, blood flow (echo Doppler). Brachial and femoral FMD (echo Doppler)	1. After 2 weeks hybrid training, increased thigh baseline and peak blood flow, increase femoral artery diameter, decrease in common femoral artery FMD 2. After 1 week of detraining, baseline and peak blood flow, vascular resistance and common femoral artery diameter returned to baseline levels. FMD did not return to baseline levels after 6 weeks detraining
Thijssen *et al.*[75] The Netherlands D & B Score = 16/27 Pre–post level 4 *N* = 10	Population: T1–T12 SCI Intervention: 30-min hybrid training 2–3 times per week for 4 weeks (8–12 sessions). Outcome measures: Blood flow and vascular resistance (occlusion plethysmography), FMD, diameter (echo Doppler)	1. Increased baseline and peak thigh blood flow. Decreased thigh baseline vascular resistance and diameter of the common femoral artery 2. No change in FMD of superficial femoral artery 3. No change in calf or forearm vascular parameters
Ballaz *et al.*[49] France Score = 6/10 RCT level 1 *N* = 17	Population: T3–T12 SCI Intervention: Passive cycling training 6 times per week for 6 weeks (up to 30 min at 50 r.p.m.) Outcome measures: Maximum and minimum femoral artery blood flow velocity (duplex Doppler) before and after 10 min of passive cycling	1. After 6 weeks passive cycling, no difference in vascular characteristics between trained and untrained group at rest ($P = 0.08$) 2. After 10-min passive cycling, there was increased mean femoral artery blood flow velocity and a reduction in velocity index (peripheral resistance)
Ditor *et al.*[64] Canada D & B Score = 14/27 Pre–post level 4 *N* = 6	Population: C4–T12 SCI Intervention: Progressive increase from 15 to 60 min BWSTT training 3 times per week for 16 weeks Outcome measures: Beat-by-beat blood pressure, mean femoral and carotid artery blood flow velocity and cross-sectional area. From this calculated femoral and carotid blood flow, compliance and resistance	1. Increase in femoral artery compliance 2. No change in any other femoral or carotid arterial characteristics

Table 3 Continued

Author, year, country, study design, sample size	*Methods*	*Outcome*
Zbogar *et al.*[65] Canada D & B Score = 18/27 Pre–post level 4 *N* = 4	Population: C4–T7 SCI Intervention: 30-min FES training (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
Tordi *et al.*[76] D & B Score = 13/27 Case report level 5 *N* = 1	Population: T11 SCI Intervention: 30-min wheelchair ergometry (alternating between moderate and high-intensity short bouts), 3 times per week for 6 weeks Outcome measures: Carotid–wrist and carotid–ankle pulse wave velocity	1. Decrease in both upper body and lower body pulse wave velocity after training
Nash *et al.*[66] USA D & B Score = 10/27 Pre–post level 4 *N* = 12	Population: T4–T11 SCI Intervention: Parastep training (FES with aid of walker), 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 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. After 5-min thigh occlusion femoral pulse volume, flow velocity integral and arterial inflow volume increased after training
Nash *et al.*[70] D & B Score = 15/27 Case control level 3 *N* = 30 (20 SCI, 10 AB)	Population: C5–C7 SCI Group characteristics: SCI-trained group used FES training for 0.4–7 years. SCI-untrained group had not used FES. Control consisted of 10 age-matched AB Outcome measures: Femoral artery end diastolic diameter and flow–velocity profiles at rest and after 5-min thigh occlusion	1. At rest trained SCI subjects had increased femoral peak systolic volume, cross-sectional area and inflow volume as compared with untrained SCI subjects 2. After 5-min thigh occlusion femoral peak systolic volume, cross-sectional area and inflow volume was elevated in trained SCI vs untrained 3. Both resting and post-occlusive femoral artery cross-sectional area was reduced in SCI trained vs AB. No other vascular parameters differed between SCI trained and AB
Sabatier *et al.*[68] USA D & B Score = 15/27 Pre–post level 4 *N* = 5	Population: C5–T10 SCI Intervention: Neuromuscular electrically stimulated resistance training. Four sets of 10 dynamic knee extensions. Two times per week, 18 weeks Outcome measures: femoral artery end diastolic diameter and flow–velocity profiles at rest and after 5-min thigh occlusion	1. No changes in any vascular measures after training
Taylor *et al.*[24] England D & B Score = 10/27 Pre–post level 4 *N* = 7	Population: 5 males, 2 females, mid to low thoracic Treatment: FES preparation program (knee extension), progressive intensity and duration, 12-week duration Outcome measures: Thigh blood flow (electrical impedance plethysmography)	1. Thigh blood flow increased 115% after training 2. SCI thigh blood flow after training was similar to that found in AB
Stoner *et al.*[67] USA D & B Score = 16/27 Pre–post level 4 *N* = 5	Population: 5 males; C5–T10; treatment: NMES-induced resistance training; the quadriceps femoris muscle group of both legs were trained 2 times per week with 4 × 10 repetitions of unilateral, dynamic knee extensions for 18 weeks Outcome measures: FMD and resting diameter and arterial range (maximum–minimum diameter) of the posterior tibial artery	1. FMD and arterial range improved 2. Resting diameter did not change

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; PARA, paraplegic; RCT, randomized controlled trials; SCI, spinal cord injury; TETRA, tetraplegic.

improving arterial structure and function in those with SCI.[24,67,68] Two studies' training regimen consisted of exercise 2 days per week, for 8 weeks. In the first study, improved quadriceps strength was found, but no improvements in femoral arterial structure or function (artery diameter, hyperemic response, exercise blood flow response).[68] In the follow-up study from the same group, improved femoral artery flow-mediated dilatation was elevated after the training regimen.[67] Another study performed by Taylor *et al.*,[24] which used a progressive 3-month long knee extension exercise with the aim of allowing standing, illustrated increased muscle thickness and thigh blood flow.

Conclusions: It appears from level 4 evidence[24,67,68] (available evidence but without comparable groups) that electrically stimulated knee extension increases quadriceps strength and improves some measures of lower body arterial function in those with SCI. More research is needed with SCI controls to verify the potential benefits of this therapy.

Hybrid exercise. A total of three studies investigated the effects of a long-term hybrid training intervention on arterial dynamics in those with SCI. Of those studies, two used FES cycling of the legs with voluntary arm cranking,[74,75] whereas the third study used a modified approach, which employed FES at the legs to assist with walking, while simultaneously supporting ones' self using a walker to provide semi-autonomous ambulation.[66] These studies reported improvements in femoral vascular function and structure for both TETRA[74] and PARA participants,[66,75] including increased baseline femoral artery blood flow,[74,75] cross-sectional area,[66] peak blood flow,[75] diameter,[74] flow-mediated dilatation[74] and post-occlusion hyperemic response.[66,75] The dependency of these improvements on the exercise intervention is highlighted by Thijssen *et al.*,[74] who showed that improvements occur after only 2 weeks of hybrid training and all vascular changes (with the exception of flow-mediated dilatation) disappear after just 1 week of de-training.

Conclusions: Hybrid exercise is a useful tool for improving vascular function in those with SCI. As of yet, no investigation has compared FES with hybrid exercise to identify whether hybrid exercise yields more vascular function gains than traditional FES training, particularly considering the increased cost of hybrid exercise equipment. The low level of evidence[66,74,75] (level 4—limited reliability) for literature investigating the effect of long-term FES exercise interventions on arterial function and structure highlights the need for valid control groups.

Body weight-assisted treadmill training. Only one study examined the arterial function changes resulting from a non-acute program of BWSTT. Ditor *et al.*[64] showed 4 months of training 3 days per week using BWSTT improved femoral arterial compliance, but did not increase femoral artery blood flow or carotid vascular compliance in those with TETRA or PARA.

Conclusions: It appears from this level 4 evidence[64] (available evidence but without comparable groups), which showed that femoral artery compliance was increased, that BWSTT has the potential to improve vascular function in SCI participants. More studies are needed, however, with relevant (i.e. those with SCI) control subjects using varying intensities, protocols and levels of injury to clarify the maximum and minimum potential benefit, as well as timeline of functional gains for a given population.

Discussion

The purpose of this review was to compile and evaluate relevant literature examining the effect of various modes of exercise on arterial dynamics in those with SCI. We also separated articles into those investigating the effects of acute bouts of exercise and others investigating vascular changes from a multiple-session (non-acute) training intervention. As access to patients with low incidence disabilities such as SCI is very limited[77] and the level of participation in physical activity within this population is lower than that of the AB population,[78,79] there is hesitation from researchers to design studies where half the willing and available participants would receive no intervention. Therefore, most research designs investigating SCI and exercise or physical activity involve poorly matched controls if present at all (level 2–5 evidence[46]). Testing the experimental group before and after a control phase, once the exercise intervention has been completed, may be a viable alternative, which would improve the level of evidence for studies limited in sample size.

Taking into consideration the lack of valid controls (i.e. those with SCI), the evidence still supports exercise as a viable method of improving vascular function in those with SCI. Following that, based on the available evidence, FES and hybrid exercise are the most promising types of exercise for improving arterial dynamics as they have been shown to increase femoral artery blood flow, reduce arterial stiffness and improve hyperemic response.[65,71–75] Finally, according to the available literature, to increase vascular health in those with SCI, hybrid or FES training with increasing levels of intensity should be performed a minimum of two times per week and continued indefinitely. Improvements in arterial structure and function begin to appear as early as 1 week into training and after 8 weeks show a range of arterial health benefits.

It should be noted that there is significant disagreement with regard to the ability of passive leg exercise to improve denervated arterial function, specifically femoral artery blood flow.[49,53,57] In a published *Letter to the editor*,[80] Hopman's group, which had shown no increase in femoral artery blood flow in response to passive leg exercise, questioned the results and methodology of work published by Ballaz *et al.*[57] showing opposite results. Although no definitive conclusion resulted from this discussion, the influence of the muscle pump at increasing femoral artery flow in response to passive exercise was implicated as the potential mechanism. Research from our laboratory supports this concept and has shown the cardiac output to increase during passive exercise in patients with SCI.[81] Further, others have shown the muscle pump to play a relatively small but significant role in leg blood flow during passive movement in AB individuals.[82] Also, Ballaz *et al.*[49] provided follow-up literature illustrating that long-term passive exercise interventions lead to significantly improved vascular function. This literature[49,81–83] strongly suggests that passive leg exercise increases femoral artery blood flow in people with SCI. Further research, with concurrent femoral artery flow measurements and isolated passive knee extension/flexion, is required to resolve this disagreement.

Finally, consideration must be given to the muscle groups stimulated while using FES. Three of the five papers used electrical stimulation sites at the hamstring, gluteal and quadriceps muscles,[65,71,73] whereas De Groot *et al.*[72] used tibialis anterior, gastrocnemius and quadriceps. Thijssen *et al.*[75] have shown that when using FES, only the stimulated muscle tissue receives any improved arterial function or structure. Therefore, muscle groups used for electrical stimulation may be an important consideration when designing a rehabilitation program.

Conclusions

Cardiovascular disease, the primary cause of the death in those with SCI, is often overlooked in the SCI population owing to the multitude of other health issues and the focus on regenerating motor function. According to the available literature, exercise (upper body, electrically stimulated and passive modalities) improves arterial function in those with SCI. It cannot be overstated that more research should be performed investigating exercise as a means to improve arterial function in those with SCI as there is a clear shortage of published articles examining this relationship. Many exercise modalities have been explored by a single published article, and often studies lack matched or relevant control groups. Future investigations exploring exercise as a therapeutic rehabilitation technique for individuals with SCI should include the cost of, and accessibility to, equipment.

Conflict of interest

The authors declare no conflict of interest.

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References

1 DeVivo MJ, Black KJ, Stover SL. Causes of death during the first 12 years after spinal cord injury. *Arch Phys Med Rehabil* 1993; **74**: 248–254.
2 Nakanishi N, Kawashimo H, Nakamura K, Suzuki K, Yoshida H, Uzura S *et al.* Association of alcohol consumption with increase in aortic stiffness: a 9-year longitudinal study in middle-aged Japanese men. *Ind Health* 2001; **39**: 24–28.
3 Garshick E, Kelley A, Cohen SA, Garrison A, Tun CG, Gagnon D *et al.* A prospective assessment of mortality in chronic spinal cord injury. *Spinal Cord* 2005; **43**: 408–416.
4 Wilmer W, Nichols MFOR. *Mcdonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*. Lea & Febiger: Philadelphia, PA, 2007.
5 Glasser SP, Arnett DK, McVeigh GE, Finkelstein SM, Bank AJ, Morgan DJ *et al.* Vascular compliance and cardiovascular disease: a risk factor or a marker? *Am J Hypertens* 1997; **10** (Part 1): 1175–1189.
6 Safar H, Mourad JJ, Safar M, Blacher J. Aortic pulse wave velocity, an independent marker of cardiovascular risk. *Arch Mal Coeur Vaiss* 2002; **95**: 1215–1218.
7 Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE *et al.* Effects of age and aerobic capacity on arterial stiffness in healthy adults. *Circulation* 1993; **88** (Part 1): 1456–1462.
8 Ohmori K, Emura S, Takashima T. Risk factors of atherosclerosis and aortic pulse wave velocity. *Angiology* 2000; **51**: 53–60.
9 Kesse-Guyot E, Vergnaud AC, Fezeu L, Zureik M, Blacher J, Peneau S *et al.* Associations between dietary patterns and arterial stiffness, carotid artery intima–media thickness and atherosclerosis. *Eur J Cardiovasc Prev Rehabil* 2010; **17**: 718–724.
10 Tang W, Cheng LT, Lu XH, Wang T. Effect of nutrition on arterial stiffness in peritoneal dialysis patients. *Am J Nephrol* 2009; **30**: 120–125.
11 Jatoi NA, Jerrard-Dunne P, Feely J, Mahmud A. Impact of smoking and smoking cessation on arterial stiffness and aortic wave reflection in hypertension. *Hypertension* 2007; **49**: 981–985.
12 Yufu K, Takahashi N, Hara M, Saikawa T, Yoshimatsu H. Measurement of the brachial–ankle pulse wave velocity and flow-mediated dilatation in young, healthy smokers. *Hypertens Res* 2007; **30**: 607–612.
13 Mahmud A, Feely J. Divergent effect of acute and chronic alcohol on arterial stiffness. *Am J Hypertens* 2002; **15**: 240–243.
14 Mattace-Raso FU, van der Cammen TJ, van den Elzen AP, Schalekamp MA, Asmar R, Reneman RS *et al.* Moderate alcohol consumption is associated with reduced arterial stiffness in older adults: the Rotterdam study. *J Gerontol A Biol Sci Med Sci* 2005; **60**: 1479–1483.
15 Tsuchikura S, Shoji T, Kimoto E, Shinohara K, Hatsuda S, Koyama H *et al.* Central versus peripheral arterial stiffness in association with coronary, cerebral and peripheral arterial disease. *Atherosclerosis* 2010; **211**: 480–485.
16 Gando Y, Yamamoto K, Murakami H, Ohmori Y, Kawakami R, Sanada K *et al.* Longer time spent in light physical activity is associated with reduced arterial stiffness in older adults. *Hypertension* 2010; **56**: 540–546.
17 Theisen D, Vanlandewijck Y, Sturbois X, Francaux M. Blood distribution adaptations in paraplegics during posture changes: peripheral and central reflex responses. *Eur J Appl Physiol* 2000; **81**: 463–469.
18 Gao SA, Ambring A, Lambert G, Karlsson AK. Autonomic control of the heart and renal vascular bed during autonomic dysreflexia in high spinal cord injury. *Clin Auton Res* 2002; **12**: 457–464.
19 Jacobs PL, Nash MS. Exercise recommendations for individuals with spinal cord injury. *Sports Med* 2004; **34**: 727–751.
20 Brown R, Macefield VG. Assessing the capacity of the sympathetic nervous system to respond to a cardiovascular challenge in human spinal cord injury. *Spinal Cord* 2008; **46**: 666–672.
21 Kooijman M, Rongen GA, Smits P, Hopman MT. Preserved alpha-adrenergic tone in the leg vascular bed of spinal cord-injured individuals. *Circulation* 2003; **108**: 2361–2367.
22 Wecht JM, Radulovic M, Lessey J, Spungen AM, Bauman WA. Common carotid and common femoral arterial dynamics during head-up tilt in persons with spinal cord injury. *J Rehabil Res Dev* 2004; **41**: 89–94.
23 de Groot PC, Bleeker MW, van Kuppevelt DH, van der Woude LH, Hopman MT. Rapid and extensive arterial adaptations after spinal cord injury. *Arch Phys Med Rehabil* 2006; **87**: 688–696.
24 Taylor PN, Ewins DJ, Fox B, Grundy D, Swain ID. Limb blood flow, cardiac output and quadriceps muscle bulk following spinal cord injury and the effect of training for the Odstock functional electrical stimulation standing system. *Paraplegia* 1993; **31**: 303–310.
25 Rowell LB. *Human Cardiovascular Control*. Oxford University Press: London, 1993.
26 Pollack AA, Taylor BE, Myers TT, Wood EH. The effect of exercise and body position on the venous pressure at the ankle in patients having venous valvular defects. *J Clin Invest* 1949; **28**: 559–563.
27 Folkow B, Gaskell P, Waaler BA. Blood flow through limb muscles during heavy rhythmic exercise. *Acta Physiol Scand* 1970; **80**: 61–72.

28 Radegran G, Saltin B. Muscle blood flow at onset of dynamic exercise in humans. *Am J Physiol* 1998; **274** (Part 2): H314–H322.
29 LaBarbera M. Principles of design of fluid transport systems in zoology. *Science* 1990; **249**: 992–1000.
30 Martin TP, Stein RB, Hoeppner PH, Reid DC. Influence of electrical stimulation on the morphological and metabolic properties of paralyzed muscle. *J Appl Physiol* 1992; **72**: 1401–1406.
31 Hopman MT, van Asten WN, Oeseburg B. Changes in blood flow in the common femoral artery related to inactivity and muscle atrophy in individuals with long-standing paraplegia. *Adv Exp Med Biol* 1996; **388**: 379–383.
32 Mangoni AA, Mircoli L, Giannattasio C, Mancia G, Ferrari AU. Effect of sympathectomy on mechanical properties of common carotid and femoral arteries. *Hypertension* 1997; **30**: 1085–1088.
33 Lacolley P, Glaser E, Challande P, Boutouyrie P, Mignot JP, Duriez M *et al*. Structural changes and *in situ* aortic pressure–diameter relationship in long-term chemical-sympathectomized rats. *Am J Physiol* 1995; **269** (Part 2): H407–H416.
34 Aliev G, Ralevic V, Burnstock G. Depression of endothelial nitric oxide synthase but increased expression of endothelin-1 immunoreactivity in rat thoracic aortic endothelium associated with long-term, but not short-term, sympathectomy. *Circ Res* 1996; **79**: 317–323.
35 Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *CMAJs* 2006; **174**: 801–809.
36 Warburton DER, Krassioukov A, Sproule S. Cardiovascular health and exercise rehabilitation in spinal cord injury. *Top Spinal Cord Injury Rehabil* 2007; **13**: 98–122.
37 Gando Y, Kawano H, Yamamoto K, Sanada K, Tanimoto M, Oh T *et al*. Age and cardiorespiratory fitness are associated with arterial stiffening and left ventricular remodelling. *J Hum Hypertens* 2010; **24**: 197–206.
38 Vivodtzev I, Minet C, Wuyam B, Borel JC, Vottero G, Monneret D *et al*. Significant improvement in arterial stiffness after endurance training in patients with COPD. *Chest* 2010; **137**: 585–592.
39 Trzos E, Kurpesa M, Rechcinski T, Wierzbowska-Drabik K, Krzeminska-Pakula M. The influence of physical rehabilitation on arterial compliance in patients after myocardial infarction. *Cardiol J* 2007; **14**: 366–371.
40 Kinzer SM, Convertino VA. Role of leg vasculature in the cardiovascular response to arm work in wheelchair-dependent populations. *Clin Physiol* 1989; **9**: 525–533.
41 Hopman MT, Verheijen PH, Binkhorst RA. Volume changes in the legs of paraplegic subjects during arm exercise. *J Appl Physiol* 1993; **75**: 2079–2083.
42 Moseley AM, Herbert RD, Sherrington C, Maher CG. Evidence for physiotherapy practice: a survey of the Physiotherapy Evidence Database (PEDro). *Aust J Physiother* 2002; **48**: 43–49.
43 Eng JJ, Teasell RJ, Miller WC, Wolfe DL, Townson AF, Aubut J *et al*. Spinal cord injury rehabilitation program: method of the SCIRE systematic review. *Top Spinal Cord Injury* 2007, 1–10.
44 Sackett DL, Rosenberg WMC, Gray JAM, Haynes BR, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; **312**: 71–72.
45 Krassioukov A, Warburton DE, Teasell R, Eng JJ. A systematic review of the management of autonomic dysreflexia after spinal cord injury. *Arch Phys Med Rehabil* 2009; **90**: 682–695.
46 Hing W, Bigelow R, Bremner T. Mulligan's mobilization with movement: a systematic review. *J Man Manip Ther* 2008; **17**: E39–E66.
47 Hartling L, Brison RJ, Crumley ET, Klassen TP, Pickett W. A systematic review of interventions to prevent childhood farm injuries. *Pediatrics* 2004; **114**: e483–e496.
48 Hignett S. Systematic review of patient handling activities starting in lying, sitting and standing positions. *J Adv Nurs* 2003; **41**: 545–552.
49 Ballaz L, Fusco N, Cretual A, Langella B, Brissot R. Peripheral vascular changes after home-based passive leg cycle exercise training in people with paraplegia: a pilot Study. *Arch Phys Med Rehabil* 2008; **89**: 2162–2166.
50 Foley NC, Teasell RW, Bhogal SK, Speechley MR. Stroke rehabilitation evidence-based review: methodology. *Top Stroke Rehabil* 2003; **10**: 1–7.
51 Bidart Y, Maury M. The circulatory behaviour in complete chronic paraplegia. II—circulatory adjustments to local metabolic needs. b—Muscular circulation. *Paraplegia* 1973a; **11**: 1–24.
52 Bidart Y, Maury M. The circulatory behaviour in complete chronic paraplegia. IV—The loss of vasomotor adjustments to general needs. b—Study of arteriolar motricity. *Paraplegia* 1973b; **11**: 1–24.
53 Ter Woerds WT, De Groot PCE, Van Kuppevelt DHJM, Hopman MTE. Passive leg movements and passive cycling do not alter arterial leg blood flow in subjects with spinal cord injury. *Phys Ther* 2006; **86**: 636–645.
54 Dela F, Mohr T, Jensen CMR, Haahr HL, Secher NH, Biering-Sorensen F *et al*. Cardiovascular control during exercise: insights from spinal cord-injured humans. *Circulation* 2003; **107**: 2127–2133.
55 Nash MS, Montefusco CM, Rhodes BA. Peripheral vascular response to exercise-induced and postocclusive reactive hyperemia in quadriplegics. *Surg Forum* 1990; **41**: 498–499.
56 Olive JL, Slade JM, Dudley GA, McCully KK. Blood flow and muscle fatigue in SCI individuals during electrical stimulation. *J Appl Physiol* 2003; **94**: 701–708.
57 Ballaz L, Fusco N, Cretual A, Langella B, Brissot R. Acute peripheral blood flow response induced by passive leg cycle exercise in people with spinal cord Injury. *Arch Phys Med Rehabil* 2007; **88**: 471–476.
58 Burkett LN, Chisum J, Pierce J, Pomeroy K, Fisher J, Martin M. Blood flow and lactic acid levels in exercising paralyzed wheelchair bound individuals. *Adapt Phys Activ Q* 1988; **5**: 60–73.
59 Phillips W, Burkett LN, Munro R, Davis M, Pomeroy K. Relative changes in blood flow with functional electrical stimulation during exercise of the paralyzed lower limbs. *Paraplegia* 1995; **33**: 90–93.
60 Svensson M, Siösteen H, Wetterqvist H, Sullivan L. Influence of physiotherapy on leg blood flow in patients with complete spinal cord injury lesions. *Physiother Theory Pract* 1995; **11**: 97–107.
61 Seifert J, Lob G, Stoephasius E, Probst J, Brendel W. Blood flow in muscles of paraplegic patients under various conditions measured by a double isotope technique. *Paraplegia* 1972; **10**: 185–191.
62 Griffin L, Decker MJ, Hwang JY, Wang B, Kitchen K, Ding Z *et al*. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *J Electromyogr Kinesiol* 2009; **19**: 614–622.
63 Devillard X, Rimaud D, Roche F, Calmels P. Effects of training programs for spinal cord injury. *Ann Readapt Med Phys* 2007; **50**: 490–498, 480–489.
64 Ditor DS, MacDonald MJ, Kamath MV, Bugaresti J, Adams M, McCartney N *et al*. The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI. *Spinal Cord* 2005; **43**: 664–673.
65 Zbogar D, Eng JJ, Krassioukov AV, Scott JM, Esch BTA, Warburton DER. The effects of functional electrical stimulation leg cycle ergometry training on arterial compliance in individuals with spinal cord injury. *Spinal Cord* 2008; **46**: 722–726.
66 Nash MS, Jacobs PL, Montalvo BM, Klose KJ, Guest RS, Needham-Shropshire BM. Evaluation of a training program for persons with SCI paraplegia using the Parasteprho1 ambulation system: Part 5. Lower extremity blood flow and hyperemic responses to occlusion are augmented by ambulation training. *Arch Phys Med Rehabil* 1997; **78**: 808–814.
67 Stoner L, Sabatier MJ, Mahoney ET, Dudley GA, McCully KK. Electrical stimulation-evoked resistance exercise therapy improves arterial health after chronic spinal cord injury. *Spinal Cord* 2007; **45**: 49–56.
68 Sabatier MJ, Stoner L, Mahoney ET, Black C, Elder C, Dudley GA *et al*. Electrically stimulated resistance training in SCI individuals increases muscle fatigue resistance but not femoral artery size or blood flow. *Spinal Cord* 2006; **44**: 227–233.
69 Jae SY, Heffernan KS, Lee M, Fernhall B. Arterial structure and function in physically active persons with spinal cord injury. *J Rehabil Med* 2008; **40**: 535–538.
70 Nash MS, Montalvo BM, Applegate B. Lower extremity blood flow and responses to occlusion ischemia differ in exercise-trained and

sedentary tetraplegic persons. *Arch Phys Med Rehabil* 1996; **77**: 1260–1265.
71 Gerrits HL, de Haan A, Sargeant AJ, van Langen H, Hopman MT. Peripheral vascular changes after electrically stimulated cycle training in people with spinal cord injury. *Arch Phys Med Rehabil* 2001; **82**: 832–839.
72 De Groot P, Crozier J, Rakobowchuk M, Hopman M, Macdonald M. Electrical stimulation alters FMD and arterial compliance in extremely inactive legs. *Med Sci Sports Exerc* 2005; **37**: 1356–1364.
73 Hopman MT, Groothuis JT, Flendrie M, Gerrits KH, Houtman S. Increased vascular resistance in paralyzed legs after spinal cord injury is reversible by training. *J Appl Physiol* 2002; **93**: 1966–1972.
74 Thijssen DH, Ellenkamp R, Smits P, Hopman MT. Rapid vascular adaptations to training and detraining in persons with spinal cord injury. *Arch Phys Med Rehabil* 2006; **87**: 474–481.
75 Thijssen DHJ, Heesterbeek P, Van Kuppevelt DJM, Duysens J, Hopman MTE. Local vascular adaptations after hybrid training in spinal cord-injured subjects. *Med Sci Sports Exerc* 2005; **37**: 1112–1118.
76 Tordi N, Mourot L, Chapuis A, Parratte B, Regnard J. Effects of a primary rehabilitation programme on arterial vascular adaptations in an individual with paraplegia. *Ann Phys Rehabil Med* 2009; **52**: 66–73.
77 Krahn G, McCarthy M, Westwood D, Powers L. Evaluation of an innovative methodology to recruit research participants with spinal cord injury through durable medical equipment suppliers. *Arch Phys Med Rehabil* 2008; **89**: 1341–1349.
78 Dearwater SR, LaPorte RE, Cauley JA, Brenes G. Assessment of physical activity in inactive populations. *Med Sci Sports Exerc* 1985; **17**: 651–655.
79 Buchholz AC, McGillivray CF, Pencharz PB. Physical activity levels are low in free-living adults with chronic paraplegia. *Obes Res* 2003; **11**: 563–570.
80 Groothuis JT, Hopman MT. Does passive cycling induce changes in peripheral blood flow in persons with spinal cord injury? *Arch Phys Med Rehabil* 2007; **88**: 1740.
81 Wong S, Krassioukov AV, Bredin SSD, Warburton DER. Temporal changes in cardiac output during arm cycle versus hybrid exercise in persons with spinal cord injury and able-bodied individuals. *Med Sci Sports Exerc* 2009; **41**: s131.
82 Gonzalez-Alonso J, Mortensen SP, Jeppesen TD, Ali L, Barker H, Damsgaard R *et al*. Haemodynamic responses to exercise, ATP infusion and thigh compression in humans: insight into the role of muscle mechanisms on cardiovascular function. *J Physiol* 2008; **586**: 2405–2417.
83 Ballaz L. Does passive cycling induce changes in peripheral blood flow in persons with spinal cord injury? The author responds. *Arch Phys Med Rehabil* 2007; **88**: 1741.