Exercise improves cardiorespiratory fitness but not arterial health after spinal cord injury

Alrashidi, Abdullah; Nightingale, Tom E.; Currie, Katharine D; Hubli, Michele; MacDonald, Maureen J; Hicks, Audrey L ; Oh, Paul; Craven, Beverley Catharine; Krassioukov, Andrei

DOI:
10.1089/neu.2021.0071

Document Version
Peer reviewed version

Citation for published version (Harvard):
Alrashidi, A, Nightingale, TE, Currie, KD, Hubli, M, MacDonald, MJ, Hicks, AL, Oh, P, Craven, BC & Krassioukov, A 2021, 'Exercise improves cardiorespiratory fitness but not arterial health after spinal cord injury: the CHOICES trial', *Journal of Neurotrauma*, vol. 38, no. 21, pp. 3020-3029. https://doi.org/10.1089/neu.2021.0071

TITLE PAGE

Title: Exercise improves cardiorespiratory fitness but not arterial health after spinal cord injury: The CHOICES trial

Running title: Arterial stiffness and exercise: CHOICES trial

Authors: Abdullah A. Alrashidi, PT, MSc [1,2,3 *]; Tom E. Nightingale, PhD [1,4 *]; Katharine D. Currie, PhD [1,5]; Michèle Hubli, PhD [1,6]; Maureen J MacDonald, PhD [7]; Audrey L. Hicks, PhD [7]; Paul Oh, MD [8]; Beverley Catharine Craven, MD, MS [8]; Andrei V. Krassioukov, MD, PhD [1,2,9,10]

Affiliations: [1] International Collaboration on Repair Discoveries (ICORD), Vancouver, British Columbia (BC), Canada; [2] Experimental Medicine, Department of Medicine, University of British Columbia (UBC), Vancouver, BC, Canada; [3] Department of Physical Therapy, King Fahad Medical City, Riyadh, Saudi Arabia; [4] School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Edgbaston, Birmingham, UK; [5] Department of Kinesiology, Michigan University, East Lansing, MI, USA; [6] Spinal Cord Injury Center, Balgrist University Hospital, University of Zurich, Zurich, Switzerland; [7] Department of Kinesiology, McMaster University, Hamilton, Ontario (ON), Canada; [8] Department of Medicine University Health Network, Division of Physical Medicine and Rehabilitation, University of Toronto, Toronto, ON, Canada; [9] Division of Physical Medicine and Rehabilitation, Department of Medicine, UBC, Vancouver, BC, Canada; [10] GF strong Rehabilitation Center, Vancouver Coastal Health, Vancouver, BC, Canada.

[*] The first two authors contributed equally to this manuscript.

Authors information:

Abdullah A. Alrashidi: International Collaboration on Repair Discoveries (ICORD), Faculty of Medicine, University of British Columbia, 818 West 10th Avenue, Vancouver, BC, Canada, V5Z 1M9, Tel: +1 (604)-675-8819, Email address: abdu80@student.ubc.ca

Tom E. Nightingale: School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, Tel: +44 (0)121 414 6977, Email address: T.E.Nightingale@bham.ac.uk

Katharine D. Currie: College of Education, School of Kinesiology, Michigan State University, 308 W. Circle Drive, East, Lansing, MI 48824, Tel: +1 (517)-432-4073, Email address: currie4@msu.edu

Michèle Hubli: Spinal Cord Injury Center, Research, Balgrist University Hospital, University of Zurich, Forchstrasse 340, 8008 Zurich, Switzerland, Tel: +41 44 510 72 03, Email address: Michele.Hubli@balgrist.ch

Maureen J MacDonald: Faculty of Science, Department of Kinesiology, McMaster University, Hamilton, Ontario (ON), Canada, Tel: +1 (905)-525-9140 ext. 24183, Email address: macdonmj@mcmaster.ca

Audrey L. Hicks: Faculty of Science, Department of Kinesiology, McMaster University, Hamilton, ON, Canada, Tel: +1 (905)-525-9140 ext. 24643, Email address: hicksal@mcmaster.ca

Paul Oh: Department of Medicine University Health Network, Division of Physical Medicine and Rehabilitation, University of Toronto, Toronto, ON, Canada, Tel: + 1 (416)-597-3422 ext. 7800, Email address: Paul.Oh@uhn.ca

Beverley Catharine Craven: Department of Medicine University Health Network, Division of Physical Medicine and Rehabilitation, University of Toronto, Toronto, ON, Canada, Tel: + 1 (416)-597-3422 ext. 6122 , Email address: Cathy.Craven@uhn.ca

Andrei V. Krassioukov (**Corresponding author)**: International Collaboration on Repair Discoveries (ICORD), Division of Physical Medicine and Rehabilitation, Faculty of Medicine, University of British Columbia, 818 West 10th Avenue, Vancouver, BC, Canada, V5Z 1M9, Tel: (604)-675-8819, Email address*:* Andrei.Krassioukov@vch.ca

Clinical Trial Registration Number: Clinicaltrials.gov identifier: NCT01718977

Data availability statement: The CHOICES trial protocol and statistical analysis plan have been published. The datasets that were collected and analyzed for the purpose of this trial are available with de-identified participants data from the corresponding author upon reasonable request, subject to a standard data-sharing agreement.

ABSTRACT

Arterial stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV), is elevated after spinal cord injury (SCI). In the uninjured population, exercise training has been shown to reduce arterial stiffness. In a randomized, clinical multicenter trial, we evaluated the impact of two exercise interventions on cardiovascular disease risk factors in individuals with chronic SCI. A total of forty-six adults with motor-complete SCI with neurological levels of injury between the fourth cervical and sixth thoracic spinal cord segments were randomly assigned to either body weight-supported treadmill training (BWSTT) or arm-cycle ergometer training (ACET). Participants trained 3 days per week for 24 weeks. Exercise session duration progressed gradually to reach 30 and 60 minutes for ACET and BWSTT, respectively. The primary outcome was arterial stiffness, measured by cfPWV, and was measured at baseline, 12 weeks of training and at 24 weeks. Secondary outcomes included cardiorespiratory fitness (CRF) and cardiometabolic health measures and were measured before and after completion of training. Fourteen participants per intervention arm completed the exercise intervention. Our results show no effect of either exercise intervention on arterial stiffness ($P = .07$) and cardiometabolic health measures ($P>.36$). However, peak oxygen uptake increased with ACET compared with BWSTT ($P = .04$). The findings of this trial demonstrate that while 24 weeks of upper-body exercise improved CRF in individuals with motor-complete SCI ≥ T6, neither intervention was associated with improvements in arterial stiffness or cardiometabolic health measures.

Keywords: Exercise; spinal cord injuries; pulse wave velocity; arterial stiffness.

INTRODUCTION

Premature cardiovascular disease (CVD) is elevated in individuals with spinal cord injury (SCI) compared with uninjured individuals.[1] Individuals with a higher neurological level of injury (NLI) and more severe SCI are at an even greater risk of developing CVD.[2,3] This elevated risk is ascribed to multiple risk factors such as: physical inactivity [4] and reduced cardiorespiratory fitness (CRF) [5], cardiometabolic syndrome [6], and impaired supraspinal sympathetic control.[7] The latter can lead to abnormal daily blood pressure (BP) fluctuations that have recently been associated with increased arterial stiffness,[8] particularly with NLI at or above the sixth thoracic segments (≥ T6).[9] Arterial stiffness, using carotid-femoral pulse wave velocity (cfPWV),[10,11] is associated with increased CVD events and all cause-mortality in the uninjured population.[10] Previous studies have documented elevated cfPWV in the SCI population compared with uninjured individuals.[12,13]

In uninjured individuals, exercise training improves arterial health.[14] Arm-cycle ergometer training (ACET) is a common exercise modality in the SCI population, although it may not provide a sufficient physiological stimulus to alter vascular function given its limited influence on blood redistribution.[15] In contrast to ACET, body weight-supported treadmill training (BWSTT) with motor-complete SCI has previously been associated with cardiovascular-related benefits including increased femoral artery compliance, improved heart rate and BP variability.[16,17] As such, we aimed to assess the hypothesis that BWSTT would have positive effects on central arterial stiffness in individuals with chronic, motor-complete, cervical and upper-thoracic SCI. Furthermore, we compared the effects of BWSTT and ACET on CRF and cardiometabolic health outcomes.

METHODS

This is a prospective, multicenter, randomized clinical trial [The Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (CHOICES)]. The trial protocol has previously been published.[18] All testing and exercise training sessions were performed at three Canadian research centers after the ethical approval of center-specific Institutional Review Boards: International Collaboration on Repair Discoveries (ICORD) at the University of British Columbia in Vancouver; The Lyndhurst Center, Toronto Rehabilitation Institute – University Health Network in Toronto; and McMaster University in Hamilton.

Participants

Participants met the following inclusion criteria: adults 18–60 years of age, with traumatic, ≥ 1 year post-injury SCI with NLI between the fourth cervical and T6 segments, motor-complete [American Spinal Injury Association Impairment Scale (AIS A or B) according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), 2011 version],[19] and cfPWV ≥ norm median value of age-matched uninjured individuals.[20] Exclusion criteria included any active or history of medical issues (e.g. cardiovascular or cardiopulmonary problems/disease) at enrolment. After obtaining written informed consent, eligible participants were randomly assigned (1:1) into BWSTT or ACET using a central, web-based computer randomization service (Empower: http://www.empowerhealthresearch.ca/).

Power calculation and sample size

The sample size was calculated for the primary outcome (i.e., cfPWV). Assuming exercise differences of ≥ 1.0 m/sec (cut-off) between both groups after the training, a significance level of .05 and the standard deviation being 10% of the baseline cfPWV (SD =1.3), 30 participants in

each group were needed to attain 80% power to detect this cut-off value. This cut-off value of 1 m/sec is in line with the reported effects of exercise interventions in other high-risk populations.[21,22] This decrease in cfPWV by 1 m/sec is clinically meaningful, as this decrement translates into a 15% reduced risk of cardiovascular mortality.[10]

Outcomes

Assessment of cfPWV was collected before the commencement of the training, after 12 weeks of training, and after training completion. CRF and cardiometabolic health measures were assessed at baseline and after training completion. The rational for selection and methods for collection of the outcome measures are detailed in the published protocol.[18] A brief descriptions follows:

Arterial stiffness. cfPWV was measured with participants in the supine position after 10-min rest and in accordance with recommended guidelines.[11] During resting, BP was measured using an automated device (Dinamap Carescape V1000; GE Healthcare, Buckinghamshire, UK). For a minimum of 30-sec, carotid and femoral arterial pressure waveforms were measured on the right side of the body using applanation tonometry (model SPT-301; Millar Instruments, Houston, TX, USA). cfPWV was calculated by dividing 80% of the surface distance between carotid and femoral arteries by the pulse transit time and was reported as the average from two 10-sec sections. If the difference between the two values was > 0.5 m/sec, a third value was included and the median of all three was reported as cfPWV. The trial team has previously demonstrated an acceptable intra- and inter-rater reliability of this method in individuals with SCI.[23]

Cardiorespiratory fitness. A cardiopulmonary exercise test (CPET) on an electrically braked arm-crank ergometer was performed. The protocol began with a two-min warm-up at workload of 0 Watts (W) then continued with an increment of 5 or 10 W per minute for cervical and

thoracic NLI, respectively.[24] The participants were instructed to maintain a cadence of 50 revolutions per minute (rpm) throughout the test. Participants continued until volitional fatigue or inability to maintain the cadence >30 rpm. The highest oxygen uptake ($\dot{V}O_2$) of 20-second averaging during the CPET was defined as peak oxygen uptake ($\dot{V}O_{2peak}$). Peak power output (PO_{peak}) was determined as the workload coincidence with volitional fatigue, unless this occur within 20-second of the beginning of the stage, otherwise the PO_{peak} from the previous stage was recorded. Oxygen uptake at ventilatory threshold ($\dot{V}O_2$-VT) was determined using a combination of the three following methods [25]: the ventilatory equivalent, the excess carbon dioxide, and the V-slope. Two independent assessors visually assessed individual participant data using each method. If the averaged values between assessors were not within 3%, a third assessor independently analyzed the data to resolve any conflicts in $\dot{V}O_2$-VT determination.

Cardiometabolic health measures. Glycated hemoglobin (HbA1c), lipid profile (triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), ratio of total cholesterol: HDL-C), and blood glucose were measured. All measurements were collected after a 12-hour overnight fast and assays were conducted in certified clinical laboratories at each trial's center.

Exercise interventions

Participants trained thrice weekly for 24 weeks, with a gradual progression to reach a target of 30 and 60 minutes per session for ACET and BWSTT, respectively (Figure 1). Given the duration of this trial, as well as the associated medical and non-medical complexities with this population, participants were provided with opportunities to complete missed exercise sessions. The intensity of ACET was prescribed to attain a rate of perceived exertion (RPE) between 11 and 16, a

reflection of moderate-to-vigorous aerobic intensity exercise.[26] Currently, there are no accepted guidelines for the most appropriate exercise intensity/volume of BWSTT; the 60 min duration was chosen based on prior BWSTT interventions.[17,27]

Statistical analyses

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (version 24; IBM, Armonk, USA) and GraphPad Prism (GraphPad Prism, version 6) with statistical significance accepted at a priori of $\alpha < .05$. Linear mixed effect models were used with the aim to determine the effects of 'time' and 'time × group interaction'. Time, exercise group, and the interaction were used as fixed factors for the model. Trial centers and model intercept were used as random effects. The effect of pre-set covariates (i.e., sex and time since injury [TSI]) were tested and included in the model if significant. Independent *t*-test and Mann-Whitney U test were used to determine any significant differences between subgroups (e.g. participants who completed the trial vs those who did not, participants with determined VT vs. participants with undetermined VT). We also calculated standardized effect sizes (Cohen's *d*) to determine the magnitude of differences in responses between the two groups with the following thresholds; < 0.2 (trivial), > 0.2 (small), > 0.5 (moderate), and > 0.8 (large).

RESULTS

Participants' enrolment across all trial centers between April 2013 and September 2017 is summarized in a CONSORT flow diagram (Figure 2). Forty-six participants underwent randomization (*M*±SD age: 42±10 years, TSI: 12±10 years). Of these, 14 participants in each group completed all aspects of the trial (Table 1). At baseline, only one participant had HbA1c

(%) above >7.0%, 5% had elevated fasting glucose (≥5.6 mmol/L), 23% had total cholesterol values of ≥5 mmol//L, 34% had elevated LDL-C (≥3 mmol/L), and 38% had depressed HDL-C (≤1.03 mmol/L for men and ≤1.29 mmol/L for women). There were no significant differences in demographic and injury characteristics between those who did not complete all aspects of the trial and the final sample included in the analyses (*P* ranged between .08 and .90).

Intervention characteristics

Participants completed the interventions within an average of 30±3 and 31±7 weeks for ACET and BWSTT, respectively (*P* = .77). In terms of intensity measured by RPE, ACET was associated with a slight progression from start to end of training of 13±2 to 14±2, while BWSTT had an average of RPE of 10±3 to 12±2, respectively (interaction effect; *P* =. 68). The training adherence (i.e., 75% of the scheduled sessions) with ACET and BWSTT was 82% and 84% at 12 weeks and declined to 69% and 70% at 24 weeks, respectively.

Outcome measures

Changes in cfPWV and BP are presented in Figure 3. There was no time × group interaction effect or main effect of time for cfPWV (*Ps* = .07 and .79, respectively), with a small effect size (*d* = 0.47) in favor of ACET. There was a significant time × group interaction for SBP (*P* = .02). Table 3 depicts changes for CRF outcomes and cardiometabolic health measures. Relative and absolute peak oxygen uptake ($\dot{V}O_{2peak}$) increased over time with ACET by 24% and 27% (with moderate-to-large effect sizes relative to BWSTT, *d* = 0.80 and 0.97, respectively), whereas these outcomes remained unchanged with BWSTT. It was not possible to determine $\dot{V}O_2$-VT for either pre or post CPET for nine participants (all with cervical SCI) out of 28 (ACET, n = 6 and BWSTT, n = 3), their data was excluded from the submaximal analysis. Compared with the

cervical SCI participants in whom it was possible to determine $\dot{V}O_2$-VT, individuals with cervical SCI without $\dot{V}O_2$-VT data completed the exercise test at baseline with lower relative $\dot{V}O_{2peak}$ and peak power output (PO_{peak}), and they had a shorter time to fatigue; all with $P < .01$. Relative and absolute $\dot{V}O_2$-VT improved with ACET group by 26% and 17% with moderate effect sizes relative to BWSTT, $d = 0.71$ and 0.73, respectively. There were no significant changes in cardiometabolic health measures over time in either group (time × group interactions; all $P > .36$), with mixed standardized effect magnitudes ($d = –0.35$-0.17). There was a significant main effect for Cholesterol: HDL-C ratio ($P = .04$).

DISCUSSION

We investigated the effects of two exercise modalities on central arterial stiffness, CRF and cardiometabolic health measures in individuals with chronic, motor-complete, high-level SCI. In contrast to our hypothesis, and despite the improvements in CRF with ACET group, neither exercise intervention elicited improvements in cfPWV or cardiometabolic health measures.

Within the SCI literature, there is a considerable degree of heterogeneity in the methods used to assess arterial health.[28] A systematic review concluded that exercise interventions have positive impacts on arterial health in individuals with SCI. However, the majority of studies included tended to focus on peripheral arterial health (e.g. femoral blood flow velocity, peripheral arterial compliance).[29] Only one prior case-study (participant with an acute motor-complete, T11 SCI) reported arterial stiffness, measured by PWV.[30] The authors reported that six weeks (30 min, three times/week) of wheelchair ergometry at 50% and 80% of maximal tolerated power improved lower limb PWV by 5.7% (–0.5 cm/sec). Besides the lower level of

evidence of this case-report, the discrepancy in techniques used to assess central arterial stiffness (carotid-dorsalis/tibialis vs. carotid-femoral) and NLI, may explain the conflicting results with respect to our null cfPWV findings. Injuries ≥T6 are commonly associated with chronotropic incompetence, reduced circulating catecholamines and splanchnic vasoconstriction.[31] Individuals with this NLI also experience abnormal BP fluctuations in the form of episodes of elevated [autonomic dysreflexia (AD)] or reduced (postural hypotension) BP.[32,33] Consequently, this may in turn limit any potential arterial-related adaptations in our sample. Since this seminal review [29] two longitudinal studies have reported no changes in central arterial stiffness with aerobic arm plus resistance exercise and whole-body vibration exercise in individuals with SCI.[34,35] Conversely, a cross-sectional study showed lower cfPWV in athletes compared to non-athletes with SCI, possibly indicating positive effects of maintaining longer-term exercise on arterial stiffness.[36]

The above-mentioned cardiac-autonomic dysfunctions following SCI and exacerbated arterial remodeling may hinder the potential exercise-induced central arterial health benefits compared with that commonly seen in the uninjured population. A study conducted with non-SCI individuals, but with chronic hypertension, showed that moderate-to-vigorous intensity upper-body exercise three times a week for 12 weeks did not improve arterial stiffness.[37] We observed a trend for stability of cfPWV over the trial period with the ACET group. However, the lack of a non-interventional control group impeded our ability to investigate the potential effects of ACET in decelerating the natural increase of cfPWV with aging.[14] The clinically meaningful increase in cfPWV with BWSTT (Figure 3A) remains unclear and is opposite to our hypothesis. While entirely speculative, verticalization with BWSTT may result in facilitating blood flow to lower body vasculature which in turn may promote blood pooling and increase the frequency of

hypotensive events.[16] Furthermore, AD may have developed secondary to peripheral stimuli (e.g. spasticity, irritation from the harness). This aberrant BP instability (i.e., hypotension and AD) is associated with increased central arterial stiffness following SCI.[8] SBP was elevated when cfPWV was assessed at 12 weeks in the BWSTT group, but the values of SBP of both groups returned to the same level as they were at baseline at 24 weeks. This indicates that an increased SBP was likely not driving the observed change in cfPWV.

The improvements in CRF with ACET in our trial confirms the positive impact of upper-body exercise alone on CRF following SCI.[38] Improved CRF in individuals with SCI is reported to be associated with improved functional ability to perform activities of daily living, which in turn, positively impact health-related quality of life.[39] Only a small proportion of our cohort presented with an increased cardiometabolic disease risk at baseline. Nevertheless, the findings of this trial are in accord with previous studies regarding the effects of exercise intervention on specific cardiometabolic health measures.[34,40] A recent review also concluded that upper-body aerobic exercise alone does not improve fasting glucose, HbA1c or lipid profile in this population.[6] It is noteworthy to mention that some studies have reported improvements with these cardiometabolic measures after BWSTT. However, these studies included motor-incomplete SCI.[41-43] Therefore, in these individuals this exercise intervention is not entirely "passive" in nature (as in this current trial) and may augment energy expenditure by a degree of volitional control over larger muscle groups.

This trial has a number of novel aspects – population, intervention duration, and participant retention. We recruited SCI individuals with significant neurological impairments and therefore the potential to experience more severe cardiovascular dysfunctions.[2,3] The majority of previous studies have investigated the effect of BWSTT after motor-incomplete SCI.[41-43] The

current literature contains limited trials investigating the longitudinal effects of exercise interventions in this group of individuals with high-level motor-complete SCI and elevated arterial stiffness. For example, a study [44] investigated the effect of relatively short exercise training (i.e., 10 weeks) in only six individuals with similar injury characteristics to our cohort. Similar to our longer-term findings, the authors reported that ACET improved CRF but not cardiometabolic measures (i.e., fasting glucose and lipid profile). Despite the CHOICES randomized clinical trial being a longer duration than this pre-post study, we report a noticeably smaller attrition rate (20% vs. 40%).

The complexity of delivering a longer duration exercise intervention in individuals with the greatest disability severity (i.e. high-level, motor-complete SCI) cannot be understated. Despite utilizing a multicenter trial design, our enrollment numbers did not achieve our *a priori* sample size target, possibly due to the tight inclusion criteria specified (i.e. the recruitment of at-risk individuals with elevated arterial stiffness at baseline), the intensive nature of the proposed intervention and medical considerations. Besides unanticipated enrollment issues, the CHOICES trial also encountered challenges with maintaining training adherence, which deteriorated especially during the latter few weeks of the intervention. This may be explained by frequent medical issues, lack of access to public transportation, work commitment, and holidays which are notable barriers impacting sustained exercise adherence. Despite these challenges, emphasized in Figure 1, the CHOICES trial represents one of the largest and longest randomized clinical trials investigating the impact of exercise in individuals with SCI. While it could be argued the trial is underpowered, the mean delta change values with ACET group for our primary outcome was below the threshold for a clinically meaningful improvement and revealed a small effect size (at 6 month) relative to BWSTT where cfPWV worsened over time.

Moreover, only trivial to small changes were demonstrated for cardiometabolic measures between exercise interventions. Therefore, we anticipate our conclusions would not be substantially altered with the addition of further participants.

Limitations: We did not control for lifestyle factors (PA level, diet, sodium intake), which are important to arterial health.[45] However, we asked our participants to maintain their lifestyle behaviors. The lack of a control group could be deemed a limitation as we are unable to quantify the inherent variability in our outcome measures or compare the exercise interventions against natural time course changes over 6 months in this population. CRF was assessed using arm-crank ergometry, the same exercise modality as ACET, and improvements may therefore reflect a degree of familiarization and improved mechanical efficiency rather than CRF adaptations *per se*. This specificity of testing and training is supported by a previous longitudinal study that utilized two exercise testing modalities (arm-crank ergometry and robotic BWSTT) to assess CRF in individuals with motor-incomplete SCI.[46] While it would have been interesting to see if these favorable effects on CRF were transferrable across upper and lower-body exercise modalities, performing CPET using BWSTT in motor-complete participants would not have made physiological sense. We could have tested upper-body CRF using a different upper-body exercise modality, i.e. wheelchair propulsion. However, an expensive wheelchair adapted treadmill is required and there are safety/feasibility issues when testing inactive wheelchair users with impaired upper limb function (~25% of our sample used a power wheelchair).

CONCLUSIONS

In chronic, motor-complete, higher-level SCI, 24 weeks of 30 minutes, three times per week of aerobic upper-body exercise improved measures of CRF. However, there were no changes in arterial stiffness or cardiometabolic health measures after either exercise intervention. These results may indicate that CRF is not linked to a direct determinant of central arterial stiffness or other cardiometabolic health measures following SCI. The benefits of aerobic exercise on central arterial stiffness should be further investigated following SCI with higher intensity exercise, better adherence in a cohort that is earlier post injury (to determine whether there is a specific therapeutic window to prescribe exercise). Furthermore, future studies may also want to include a control group to investigate the impact of exercise on time-induced arterial stiffness in this SCI population.

Acknowledgments. We acknowledge the support of a Canadian Institutes of Health Research (CIHR) project grant (funding reference number; TCA 118348, principal investigator (PA): A.V.K.), the primary funding source for CHOICES project. We also thank the Canadian Foundation of Innovation (CFI)/BC Knowledge Development Fund (BCKDF) for funding all equipment required for this study at the Vancouver center (# 35869; PA: A.V.K.). The authors would also like to thank all participants for their commitment in this study and the assistance of numerous volunteers during exercise training sessions. A.A.A. is supported for his PhD scholarship by King Fahad Medical City, Riyadh, Saudi Arabia. T.E.N. was funded by a 2018/2020 Michael Smith Foundation for Health Research in conjunction with Rick Hansen Foundation and the International Collaboration on Repair Discoveries (ICORD) Research Trainee Award (grant number: 17767). K.D.C. was funded by Postdoctoral Fellowship from the Heart and Stroke Foundation (17R26776) and the Craig H. Neilson Foundation (281863). M.H. was funded by two fellowships from the Swiss National Science Foundation for Prospective Researchers (PBEZP3_145704 and P300P3_151153). B.C.C. acknowledges support from the Toronto Rehab Foundation/ University of Toronto for an endowed chair in SCI rehabilitation. A.V.K. holds Endowed Chair in Spinal Cord Rehabilitation Research, Department of Medicine, UBC. We acknowledge the support of Dr. Leanne Ramer in helping with writing and submitting the trial protocol. We also appreciate the support of Dr. Robert Teasel as a chair of Data and Safety Monitoring Committee for the CHOICES trial. We also gratefully acknowledge the administrative support of study coordinators: Andrea Ramirez, Cameroon Gee, Marko Gavric and Martina Franz (Vancouver), Maggie Szeto and Dr. Masae Miyatani (Toronto) and Jason Au (Hamilton) in helping with participants' screening, assessments and training.

Authors contribution. A.A.A was responsible for collection/analysis/interpretation of the data and drafting the manuscript. T.E.N. was responsible for collection/analysis/interpretation of the data and drafting the manuscript. K.D.C. was responsible for collection of the data and revising the manuscript for intellectual content. M.H. was responsible for collection of the data and revising the manuscript for intellectual content. M.J.M. was responsible for managing data collection at Hamilton center, and revising the manuscript for intellectual content. A.L.H. was responsible for collection of the data and revising the manuscript for intellectual content. P.O. was responsible for collection of the data and revising the manuscript for intellectual content. B.C.C was responsible for managing data collection at Toronto center, and revising the manuscript for intellectual content. A.V.K was responsible for study concept/design, managing data collection at Vancouver center, and revising the manuscript for intellectual content. All authors approved the final version of this manuscript.

Author Disclosure Statement

All authors confirm that they have no competing interests exist.

Study funding

Canadian Institutes of Health Research (CIHR) project grant (#TCA 118348) the Canada Foundation for Innovation (CFI)/BC Knowledge Development Fund (BCKDF) (# 35869).

References

1. Cragg, J.J., Noonan, V.K., Krassioukov, A., and Borisoff, J. (2013). Cardiovascular disease and spinal cord injury: results from a national population health survey. Neurology 81, 723–728.
2. Groah, S.L., Weitzenkamp, D., Sett, P., Soni, B., and Savic, G. (2001). The relationship between neurological level of injury and symptomatic cardiovascular disease risk in the aging spinal injured. Spinal Cord 39, 310–317.
3. Krassioukov, A., and Claydon, V.E. (2006). The clinical problems in cardiovascular control following spinal cord injury: an overview. Prog. Brain Res. 152, 223–229.
4. Nightingale, T.E., Williams, S., Thompson, D., and Bilzon, J.L.J. (2017). Energy balance components in persons with paraplegia: daily variation and appropriate measurement duration. Int. J. Behav. Nutr. Phys. Act. 14, 132.
5. Haisma, J.A., van der Woude, L.H., Stam, H. J., Bergen, M.P., Sluis, T.A., and Bussmann, J.B. (2006). Physical capacity in wheelchair-dependent persons with a spinal cord injury: a critical review of the literature. Spinal Cord 44, 642–652.
6. Farrow, M., Nightingale, T.E., Maher, J., McKay, C.D., Thompson, D., and Bilzon, J.L.J. (2020). Effect of Exercise on Cardiometabolic Risk Factors in Adults With Chronic Spinal Cord Injury: A Systematic Review. Arch. Phys. Med. Rehabil. 101, 2177–2205.
7. Phillips, A.A., and Krassioukov, A.V. (2015). Contemporary Cardiovascular Concerns after Spinal Cord Injury: Mechanisms, Maladaptations, and Management. J. Neurotrauma 32, 1927–1942.

8. Currie, K.D., Hubli, M., MacDonald, M.J., and Krassioukov, A.V. (2019). Associations between arterial stiffness and blood pressure fluctuations after spinal cord injury. Spinal Cord 57, 1057–1063.
9. Furlan, J.C., Fehlings, M.G., Shannon, P., Norenberg, M.D., and Krassioukov, A. V. (2003). Descending vasomotor pathways in humans: correlation between axonal preservation and cardiovascular dysfunction after spinal cord injury. J. Neurotrauma 20, 1351–1363.
10. Vlachopoulos, C., Aznaouridis, K., and Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J. Am. Coll. Cardiol. 55, 1318–1327.
11. Van Bortel, L.M., Laurent, S., Boutouyrie, P., Chowienczyk, P., Cruickshank, J.K., De Backer, T., Filipovsky, J., Huybrechts, S., Mattace-Raso, F.U.S., Protogerou, A.D., Schillaci, G., Segers, P., Vermeersch, S., and Weber, T. (2012). Expert consensus document on the measurement of aortic stiffness in daily practice using carotidfemoral pulse wave velocity. J. Hypertens. 30, 445–448.
12. Miyatani, M., Masani, K., Oh, P.I., Miyachi, M., Popovic, M.R., and Craven, B.C. (2009). Pulse wave velocity for assessment of arterial stiffness among people with spinal cord injury: a pilot study. J. Spinal Cord Med. 32, 72–78.
13. Phillips, A.A., Cote, A.T., Bredin, S. S., Krassioukov, A.V., and Warburton, D. E. (2012). Aortic stiffness increased in spinal cord injury when matched for physical activity. Med. Sci. Sports Exerc. 44, 2065–2070.
14. Seals, D.R., Desouza, C.A., Donato, A. J., and Tanaka, H. (2008). Habitual exercise and arterial aging. J. Appl. Physiol. 105, 1323–1332.

15. Thijssen, D.H., Steendijk, S., and Hopman, M.T. (2009). Blood redistribution during exercise in subjects with spinal cord injury and controls. Med. Sci. Sports Exerc. 41, 1249–1254.
16. Ditor, D.S., Macdonald, M.J., Kamath, M.V., Bugaresti, J., Adams, M., McCartney, N., and Hicks, A.L. (2005). The effects of body-weight supported treadmill training on cardiovascular regulation in individuals with motor-complete SCI. Spinal Cord 43, 664–673.
17. Harkema, S.J., Ferreira, C.K., van den Brand, R.J., and Krassioukov, A.V. (2008). Improvements in orthostatic instability with stand locomotor training in individuals with spinal cord injury. J. Neurotrauma 25, 1467–1475.
18. Krassioukov, A.V., Currie, K.D., Hubli, M., Nightingale, T.E., Alrashidi, A.A., Ramer, L., Eng, J.J., Ginis, K.A.M., MacDonald, M.J., Hicks, A., Ditor, D., Oh, P., Verrier, M.C., and Craven, B.C. (2019). Effects of exercise interventions on cardiovascular health in individuals with chronic, motor complete spinal cord injury: protocol for a randomised controlled trial [Cardiovascular Health/Outcomes: Improvements Created by Exercise and education in SCI (CHOICES) Study]. BMJ Open 9, e023540.
19. Kirshblum, S.C., Burns, S.P., Biering-Sorensen, F., Donovan, W., Graves, D.E., Jha, A., Johansen, M., Jones, L., Krassioukov, A., Mulcahey, M. J., Schmidt-Read, M., and Waring, W. (2011). International standards for neurological classification of spinal cord injury (revised 2011). J. Spinal Cord Med. 34, 535–546.
20. Boutouyrie, P., and Vermeersch, S.J. (2010). Determinants of pulsewave velocity in healthy people and in the presence of cardiovascular risk factors: Establishing normal and reference values. Eur. Heart J. 31, 2338–2350.

21. Figueroa, A., Park, S.Y., Seo, D.Y., Sanchez-Gonzalez, M.A., and Baek, Y.H. (2011). Combined resistance and endurance exercise training improves arterial stiffness, blood pressure, and muscle strength in postmenopausal women. Menopause 18, 980–984.
22. Collier, S.R., Kanaley, J.A., Carhart, R., Frechette, V., Tobin, M.M., Hall, A.K., Luckenbaugh, A.N., and Fernhall, B. (2008). Effect of 4 weeks of aerobic or resistance exercise training on arterial stiffness, blood flow and blood pressure in pre- and stage-1 hypertensives. J. Hum. Hypertens. 22, 678–686.
23. Currie, K.D., Hubli, M., and Krassioukov, A.V. (2014). Applanation tonometry: a reliable technique to assess aortic pulse wave velocity in spinal cord injury. Spinal Cord 52, 272–275.
24. Eerden, S., Dekker, R., and Hettinga, F.J. (2018). Maximal and submaximal aerobic tests for wheelchair-dependent persons with spinal cord injury: a systematic review to summarize and identify useful applications for clinical rehabilitation. Disabil. Rehabil. 40, 497–521.
25. Au, J.S., Sithamparapillai, A., Currie, K.D., Krassioukov, A.V., MacDonald, M.J., and Hicks, A.L. (2018). Assessing Ventilatory Threshold in Individuals With Motor-Complete Spinal Cord Injury. Arch. Phys. Med. Rehabil. 99, 1991–1997.
26. Goosey-Tolfrey, V., Lenton, J., Goddard, J., Oldfield, V., Tolfrey, K., Eston, R. (2010). Regulating intensity using perceived exertion in spinal cord-injured participants. Med. Sci. Sports Exerc. 42, 608–613.
27. Ditor, D.S., Kamath, M.V., MacDonald, M.J., Bugaresti, J., McCartney, N., and Hicks, A.L. (2005). Effects of body weight-supported treadmill training on heart rate variability and blood pressure variability in individuals with spinal cord injury. J. Appl. Physiol. 98, 1519–1525.

28. Lee, A.H., Phillips, A.A., and Krassioukov, A.V. (2017) Increased Central Arterial Stiffness after Spinal Cord Injury: Contributing Factors, Implications, and Possible Interventions. J. Neurotrauma 34, 1129–1140.
29. Phillips, A.A., Cote, A.T., and Warburton, D.E. (2011). A systematic review of exercise as a therapeutic intervention to improve arterial function in persons living with spinal cord injury. Spinal Cord 49, 702–714.
30. Tordi, N., Mourot, L., Chapuis, A., Parratte, B., and Regnard, J. (2009). Effects of a primary rehabilitation programme on arterial vascular adaptations in an individual with paraplegia. Ann. Phys. Rehabil. Med. 52, 66–73.
31. Krassioukov, A., and West, C. (2014). The role of autonomic function on sport performance in athletes with spinal cord injury. PM. R. 6, S58–65.
32. Hubli, M., Gee, C.M., and Krassioukov, A.V. (2015). Refined assessment of blood pressure instability after spinal cord injury. Am. J. Hypertens. 28, 173–181.
33. West, C.R., Mills, P., and Krassioukov, A.V. (2012). Influence of the neurological level of spinal cord injury on cardiovascular outcomes in humans: a meta-analysis. Spinal Cord 50, 484–492.
34. Totosy de Zepetnek, J.O., Pelletier, C.A., Hicks, A.L., and MacDonald, M.J. (2015). Following the Physical Activity Guidelines for Adults With Spinal Cord Injury for 16 Weeks Does Not Improve Vascular Health: A Randomized Controlled Trial. Arch. Phys. Med. Rehabil. 96, 1566–1575.
35. Totosy de Zepetnek, J.O., Miyatani, M., Szeto, M., Giangregorio, L.M., and Craven, B. C. (2017). The effects of whole body vibration on pulse wave velocity in men with chronic spinal cord injury. J. Spinal Cord Med. 40, 795–802.

36. Hubli, M., Currie, K.D., West, C.R., Gee, C.M., and Krassioukov, A.V. (2014). Physical exercise improves arterial stiffness after spinal cord injury. J. Spinal Cord Med. 37, 782–785.
37. Westhoff, T.H., Schmidt, S., Gross, V., Joppke, M., Zidek, W., van der Giet, M., and Dimeo, F. (2008). The cardiovascular effects of upper-limb aerobic exercise in hypertensive patients. J. Hypertens. 26, 1336–1342.
38. Eitivipart, A.C., Oliveira, C.Q., Arora, M., Middleton, J., and Davis, G.M. (2019). Overview of Systematic Reviews of Aerobic Fitness and Muscle Strength Training after Spinal Cord Injury. J. Neurotrauma 36, 2943–2963.
39. Nightingale, T.E., Rouse, P.C., Walhin, J.P., Thompson, D., and Bilzon, J.L.J. (2018). Home-Based Exercise Enhances Health-Related Quality of Life in Persons With Spinal Cord Injury: A Randomized Controlled Trial. Arch. Phys. Med. Rehabil. 99, 1998–2006.
40. Nightingale, T.E., Walhin, J.P., Thompson, D., and Bilzon, J.L.J. (2017). Impact of Exercise on Cardiometabolic Component Risks in Spinal Cord-injured Humans. Med. Sci. Sports Exerc. 49, 2469–2477.
41. Fenuta, A.M., and Hicks, A.L. (2014). Metabolic demand and muscle activation during different forms of bodyweight supported locomotion in men with incomplete SCI. Biomed. Res. Int. 632765.
42. Stewart, B.G., Tarnopolsky, M.A., Hicks, A.L., McCartney, N., Mahoney, D.J., Staron, R.S., and Phillips, S.M. (2004). Treadmill training-induced adaptations in muscle phenotype in persons with incomplete spinal cord injury. Muscle Nerve 30, 61–68.
43. Phillips, S.M., Stewart, B.G., Mahoney, D.J., Hicks, A.L., McCartney, N., Tang, J.E., Wilkinson, S.B., Armstrong, D., and Tarnopolsky, M.A. (2004). Body-weight-support

treadmill training improves blood glucose regulation in persons with incomplete spinal cord injury. J. Appl. Physiol. 97, 716–724.

44. Bresnahan, J.J., Farkas, G. J., Clasey, J.L., Yates, J.W., and Gater, D.R. (2019). Arm crank ergometry improves cardiovascular disease risk factors and community mobility independent of body composition in high motor complete spinal cord injury. J. Spinal Cord Med. 42, 272–280.
45. Tanaka, H., and Safar, M.E. (2005). Influence of lifestyle modification on arterial stiffness and wave reflections. Am. J. Hypertens. 18, 137–144.
46. Gorman, P.H., Scott, W., York, H., Theyagaraj, M., Price-Miller, N., McQuaid, J., Eyvazzadeh, M., Ivey, F. M., and Macko, R.F. (2016). Robotically assisted treadmill exercise training for improving peak fitness in chronic motor incomplete spinal cord injury: A randomized controlled trial. J. Spinal Cord Med. 39, 32–44.