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Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study

--Manuscript Draft--

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Abstract:	Objective: To investigate the effect of a short-term, robotic-assisted (exoskeleton) gait training (RGT) program on central and peripheral hemodynamic measures in patients with spinal cord injury (SCI). Design: Parallel group, non-randomized trial with before (baseline) and after (follow-up) assessments. Setting: Single-center, community-based neuro-physiotherapy practice. Participants: Twelve individuals with SCI (ASI A to C). Interventions: Participants completed either a 5-day RGT program plus physiotherapy (n=6), or a usual care physiotherapy only program (control group; n=6). The RGT program consisted of daily 60-minute physiotherapy and 90-minutes of RGT. Outcome measures were measured before and after the rehabilitation program. Main Outcome Measure(s): The primary outcome measure was arterial wave reflection (Augmentation index [AIx]), with central and peripheral blood pressures also reported. Data is presented as mean (SD) and effect sizes (partial eta squared; η2p). Results: There was a significant reduction in AIx (30±18 to 21±15 %; η2p=0.75) and mean arterial pressure (89±11 to 82±10 mmHg; η2p=0.47) following completion of the RGT program (both P<0.05). There were no changes in these measures for the control group. Although not significantly different, medium to large effects were observed in

	favor of RGT for all other central and peripheral measures ($\eta 2p=0.06$ to 0.21), except for heart rate and pulse pressure ($\eta 2p<0.04$). Conclusions: RGT using an exoskeleton is a promising therapy for improving cardiovascular health in patients with SCI. Specifically, this study indicates decreased arterial wave reflection, and supports the need for larger randomized controlled trials. Trial Registration: Clinical trials Registry (https://clinicaltrials.gov/; NCT03611803).

Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study

DATE OF SUBMISSION: 14th June 2019

Dear Sir or Madam,

I am re-submitting a manuscript for the Journal of Spinal Cord Medicine (Ref.: Ms. No. JSCM-D-19-00062). The study is entitled "Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study".

We have amended the manuscript in accordance with the recommendations from the Editorial team and reviewers. We look forward to receiving further feedback from the Journal.

Yours sincerely,

Dr James Faulkner

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Ref.: Ms. No. JSCM-D-19-00062
EFFECT OF ROBOTIC-ASSISTED GAIT TRAINING ON THE VASCULAR HEALTH OF INDIVIDUALS WITH SPINAL CORD INJURY
The Journal of Spinal Cord Medicine

Dear Dr. Faulkner,

Your manuscript has undergone our peer review process. It will be recommended for publication in the Journal, pending major revision as suggested by the reviewers. Please review their comments below.

Thank you for your positive response to the manuscript. We have amended the manuscript in line with the Editor and reviewer comments.

Note that we require a minimum of three files for the revision: a response to reviewer file, one blinded manuscript file showing tracked changes and one blinded manuscript file with all changes accepted. Please ensure that the references are cited in Vancouver style in the text,

This has been checked and will be submitted as requested.

Language and language-editing:
If the referees' comments have raised concerns over the use of English in your paper, it is important that you check and revise your paper carefully, preferably with the assistance of a native English speaker, to ensure the work is reported and discussed clearly.
N/A

Comments from the Editors and Reviewers:

Editorial Office Comments:
* Please have the following authors respond to the author verification email (Note: Do not include this item in Response to Reviewers due to blinding of document) - XXX, XXX, and XXX. Ask authors to check spam/junk mail folder. Please note that verification links do not work as well with cell phones. It is best to use a computer when verifying authorship.

I have been informed by these co-authors that they have now completed the verification process.

* Please put a copy of your Conflict of Interest statement with your Funding Statement in your manuscript file above the References section.

Amended as requested

* Please include the title of your manuscript in the manuscript files.

Amended as requested.

* In title of the manuscript, only capitalize the initial word, proper nouns, and the first word after a colon. Please make sure that the title on your title page, manuscript file, and in Editorial Manager all match.

This has been amended.

* In the manuscript file, all text should be double-spaced, including Abstract and References.

This has been amended.

* Reference citations should be in superscript, without parentheses or brackets. Reference citations should

follow punctuation, such as commas or periods, and preceding semi-colons or colons, with no spaces between the citation number and the punctuation mark.

This has been amended in line with the journal requirements.

* The abstract for your paper exceeds the 250-word limit. Please keep the word count in mind if you are required to make any edits on the abstract. If you make any changes to the abstract be sure to update your Abstract in Editorial Manager when resubmitting your manuscript.

The abstract has been amended in line with the 250 word limit and the recommendations from the reviewers.

* Please use "sex" not "gender" to refer to male/female.

This has been amended as requested.

* Please italicize *et al.* wherever it appears in the paper, including references and tables.

Amended as requested.

* No commas following e.g. or i.e.

These have been removed as requested.

* Please use do not abbreviate units of time (e.g. hours not hr or h) - unless referring to a rate. (e.g. 5 min is not okay, but 30 rev/min is okay).

This has been amended as requested

* Images used in figures must have a minimum resolution of 300 dpi.

This has been amended as requested.

* When you submit your revision, please be sure that your Response to Reviewers is blinded - no author names or affiliations in any of the copied comments or responses. No signatures with author names. No letterhead.
This has been checked and amended where needed.

Associate Editor
The topic is novel and addressing the acute of effects of exoskeleton on vascular health in persons with SCI. However, there are major points that need to be addressed prior to final decision.

1. The authors ignored all the published literature about previous exoskeleton work and did not bother acknowledging similar work that has been done in this area.

Thank you for your comment. We have re-structured the introduction so pertinent exoskeleton research is now presented in the second paragraph. The new content in the introduction includes the following:

'Robotic-assisted gait training (RGT) is used in the rehabilitation of patients with SCI, and may be a viable option to improve functional and health outcomes, and independence, in this population group. Task-specific stepping practice enhances the afferent feedback associated with normal locomotion and can induce plasticity in the involved motor centers.[5,6] Robotic powered exoskeletons are wearable robotic units that power a system of motors, pneumatics, levers, or hydraulics to restore locomotion through RGT programs.[7,8] A systematic review and meta-analysis of 14 exoskeleton studies, typically including RGT programs that consisted of training sessions three times per week, 60–120 minutes per session, for 1–24 weeks, demonstrated that 76% of patients were able to ambulate with no physical assistance on completion of an exoskeleton program.[8] The physiological demand of such exoskeleton-assisted walking programs are comparable to self-reported exertion of an able-bodied person walking at 3 miles per hour, and can elicit improvements in spasticity, without any serious adverse events.[8,9] Robotic exoskeletons may decrease seated time, increase standing and walking time,[10,11] thus, potentially ameliorating several of the chronic health-related consequences that negatively impact this population.[12,13]

2. The term ASIA is no longer valid and old term, you need to use AIS or ISNCSCI.

We have amended the terminology to AIS.

3. Please provide a figure on how this test was conducted in persons with SCI. Please explain the sensitivity of this test considering autonomic dysfunction.

As the measurement of the study outcomes (central and peripheral blood pressure) is very simple, that of a blood pressure assessment in a resting supine position, we do not feel a figure is actually necessary. We have however included the following information to improve the clarity of the test. It now reads:

'*At baseline and follow-up assessments, and following 20 minutes undisturbed, supine rest, oscillometric pressure waveforms were recorded by a single operator on the left upper arm using a brachial blood pressure cuff (SphygmoCor XCEL device, AtCor Medical, Sydney, Australia), in accordance with standard manufacturer's guidelines.24'*

If the editorial team are adamant that a figure is necessary, we will duly oblige in any future amendments. However, a visual presentation of the positioning can be found in reference 25 in the reference list.

With regards to the 'sensitivity' of measuring central BP and AIx measures from the SphygmoCor XCEL, our team has shown these measures to be reliable in healthy (Young et al., 2015; Mitchelmore et al., 2018a) and clinical non-SCI (stroke) populations (Mitchelmore et al., 2018b) with intra-class correlations > 0.90 typically recorded in fasted and non-fasted states. However, no known reliability studies have been reported for people with SCI. This could be an area of future research consideration. The manuscript already makes reference to the reliability and validity of the device.

<u>References:</u>

Young YY, Abdolhosseini P, Brown F, Faulkner J, Lambrick D, Williams MA, Stoner L. (2015). Reliability of Oscillometric Central Blood Pressure and Arterial Wave Reflection Readings: Effects of Posture and the Fasted State. Journal of Hypertension. 33, 1588-1593. doi: 10.1097/HJH.0000000000000604.

Mitchelmore, A., Stoner, L., Lambrick, D., Jobson, S., Faulkner, J. (2018a). Reliability of oscillometric central blood pressure and central systolic loading in individuals over 50 years: effects of posture and fasting, Atherosclerosis, 238, 79-85.

Mitchelmore, A., Stoner, L., Lambrick, D., Sykes, L, Eglinton, C, Jobson, S & Faulkner, J. (2018b) 'Oscillometric central blood pressure and central systolic loading in stroke patients: Short-term reproducibility and effects of posture and fasting state', *PLoS ONE,* 13(11): e0206329.

4. The description of the program is rather confusing. Why did you set your program 60 minutes of training in the morning and 90 minutes of RGT in the evening.
This is very impractical who would do 150 minutes per day; 5 days a week; which insurance company or coverage will support this? If we want to translate this research findings into real life situation, is this would be your recommendation. Please review the current ISCOS guidelines.

Participants who took part in the study were provided a 'high-dosage', intense rehabilitation therapy package. This included 60 minutes of conventional physical therapy in the morning, which slightly exceeds the minimum recommendations by the National Institute of Clinical Excellence (NICE) guidelines. The RGT programme was 90 minutes for logistical reasons. This period of time accounts for up-to 60 minutes of Exoskeleton wear time, and 30-minutes to set-up the exoskeleton and to provide ample time to allow participants to transfer in and out of the exsoskeleton. This proposed duration is recommended by Ekso Bionics trainers when training physical therapists to use the Exoskeleton as a training aid, and is standard practice in the rehabilitation center (Hobbs Rehabilitation) whereby this research study was conducted.

Hobbs rehabilitation offer week long intense therapy packages whereby patients have daily access to conventional therapy and RGT. These individuals are either self-funded or supported through UK insurance companies. Patients who live further away often use weekly therapy packages for the logistical reasons of attending the center. For example, in the present study, patients travelled on average 95 ± 30 km to attend the program for those who took part in the RGT group (see Table 1). Daily or weekly travel to the center may not be feasible for this group due to the vast distance. As such, the delivery of 150 minutes of therapy each day, on five consecutive days, is practical for some individuals with SCI who seek support from physical therapists. We have amended the manuscript to improve the clarity of the program.

With regards to whether we would recommend this type of programme, it is too early to tell. Practically, short-duration, intense programmes such as this may be feasible for some individuals living with SCI, but not all. It would be of interest for further research to explore the optimal timings, dosages and durations of such exoskeleton rehabilitation packages (i.e. how often such a programme should be administered [once a month, quarterly etc.), particularly in light of the ISCOS guidelines that recommend that persons with SCI engage in at least 20 min of moderate to vigorous intensity aerobic exercise three times per week to improve cardiorespiratory fitness (Martin Ginis *et al.* 2018). We have now made reference to the ISCOS guidelines in the discussion.

Martin Ginis KA, van der Scheer JW, Latimer-Cheung AE, Barrow A, Bourne C, Carruthers P, Bernardi M, Ditor DS, Gaudet S, de Groot S, Hayes KC, Hicks AL, Leicht CA, Lexell J, Macaluso S, Manns PJ, McBride CB, Noonan VK, Pomerleau P, Rimmer JH, Shaw RB, Smith B, Smith KM, Steeves JD, Tussler D, West CR, Wolfe DL, Goosey-Tolfrey VL. Evidence-based scientific exercise guidelines for adults with spinal cord injury: an update and a new guideline. Spinal Cord 2018; 56: 308-321 [PMID: 29070812 DOI: 10.1038/s41393-017-0017-3]

5. You need to clearly explain on what mode you have trained your patients and how did you progress your training using exoskeleton.
You mentioned using pro-step plus adaptive mode. Have you adjusted at the level of assistance; in other words

have all your participants maintained 100% adaptive mode or did you manage to drop the level of assistance with training. Considering that you have mixed population of AIS A, B and C?

The mode of the patient was included in the original manuscript. However, further clarity regarding 'progressing' patients during the training can be alluded to. In our study, a reduction in the 'level' of motor assistance (to support the exoskeleton during the swing phase of the gait cycle) between the first and fifth day of the programme was recorded. Due to small sample size for AIS B and C (both n = 1), the following interpretation is based on all participants who took part in the RGT program.

We found that on day 1 and day 5 of the program the maximum assistance of the exoskeleton ranged between 98-100%. However, the minimum assistance reduced from 81 ± 1% (day 1) to 67 ± 5% (day 5). Reference to this change is now included in the manuscript in both the methods and results section. However, the interpretation of these values must be treated with caution as the amount of assistance provided by the motor to the exoskeleton can change based on technique/progress etc. as the motor to the exoskeleton detects the required/necessary input and alters the required assistance. There could be significant variability in this as the motor assistance may vary depending upon the walking speed, under- or over- muscular activity, good or poor alignment, cadence, use of mobility aids (walking frame, crutches) etc. As a patient progresses over the course of the short-duration, intense RGT program, the increased time spent upright/walking may increase fatigue, and as such, could lead to increases in motor assistance. The motor assistance is not a key outcome measure for this study due to this variability but data related to it has been included in the manuscript.

Reviewer #1: SUMMARY
Overall, this is nicely written paper which is easy to follow, and which could lead to some important technological and clinical advancements for SCI.

Thank you for your positive overview to the manuscript.

One general comment:
* Perhaps the title should include "feasibility" or "pilot"

Reference to a 'pilot' study has now been included in the title.

ABSTRACT
The abstract is a nicely written. A few revisions are worth considering:
* It would be best to state a primary outcome. It could be stated that central and peripheral hemodynamics are measured, but the story would be stronger with a core focused.

The primary outcome measure has now been included in the abstract as requested.

* How many subjects were randomized to each group?

Six participants were in each group. The sample size for the two groups has now been included in the abstract.

INTRODUCTION
Overall, the introduction is clear and flows well. A couple of minor comments:

* Para 2: the first line ends a bit negatively. It seems to suggest this is not a feasible strategy, but I believe the authors are arguing opposite? Perhaps here simply state that it's a viable options, as discussion about cost etc follows.

This has been amended as suggested. It now reads.

'Robotic-assisted gait training (RGT) is used in the rehabilitation of patients with SCI and may be a viable option to improve functional and health outcomes, and independence, in this population group.'

* Para 2: the second sentence does not transition from the first
* Last para: is this actually a "pilot" study?

Reference to the study being a pilot study has now been included. Due to other amendments made to the introduction in light of editorial and reviewer comments, we believe that the transition of the second sentence is much improved in the revised version.

METHODS
The methods are well described and easy to read. Just one small comment:
* What process was used to randomise subjects? Including, was any attempt made to match?

Due to the pilot nature of the study, a quasi-experimental design was implemented whereby the first 6 participants were allocated to the RGT group. As stated in the discussion, a fully-randomised controlled trial is needed to provide further insight into the effect of RGT on the central vascular health of SCI patients. The following has been inserted into the methods section:

'Due to the pilot nature of the study, a quasi-experimental design was implemented whereby Pthe first six participants were assigned to either athe RGT program, and the remaining six to the or to a control (Con) group.'

* Were there sample size calculations? Otherwise hence my comment about "pilot study"

There were no sample size calculations due to the pilot nature to the study. Emphasis on 'pilot' has now been included in the title and purpose.

RESULTS
The results are logically stated. To help the reader:
* Para 1: following the interaction effect, state the magnitude by which each variable decreased (improved) for the SGT group. Include a confidence would be useful, e.g., Aix decreased 9% (95%CI: XX, XX)

We have amended this section of the manuscript as advised by the reviewer. It now reads:

'Significant Condition x Time interactions were observed for AIx (η2p = 0.74), AIx75 (η2p = 0.67), AP (η2p = 0.44), and MAP (η2p = 0.47) (all P < 0.05; Table 2), with cDBP approaching statistical significance (η2p = 0.35). Each of these outcomes remained constant for Con, but decreased (improved) between baseline and follow-up assessments for RGT (Mean [95%CI]; AIx -9% [-12.2 to -5.8]; AIx75 -7% [-9.8 to -4.2]; AP -6% [-13.1 to -0.7]; MAP -7 mmHg [-10.8 to -2.7]).'

DISCUSSION
Some minor comments:
* Para 1: the statement abut "too expensive" is a little negative. I would consider re-phrasing.

Thank you for your comment. On reflection, we have removed reference to 'too expensive' in this part of the manuscript.

* Para 2: not need to report both AIx forms, I would suggest just the former.

We have removed reference to Aix75 as suggested.

* I would suggest a separate section on implications. This material is somewhat included, but it is buried. i.e.,

how can these findings be used by clinicians, what needs to be done next, what is the feasibility of including this device within clinical practice etc.

We have re-structured the discussion to include a clinical implications and future research considerations section.

Reviewer #2: The authors present findings from a unique study examining the effects of robotic-assisted gait training on markers of central vascular health in people with spinal cord injury. Their results demonstrated that compared to a control condition, the RGT appeared to have a more favorable central hemodynamic response, characterized by a reduction in central MAP, Augmentation pressure and AIx. From a clinical view-point, this is important given the prognostic value of these central vascular health markers, in addition support the need to further optimize standard rehabilitation and physical treatment in those following SCI. The paper is concise, and well-written. The data appear to have been carefully collected.
Thank you for your positive comments to the manuscript.

I have the following recommendations:

Title: Given the types of measurements performed, the authors could add the word 'central' to vascular health ("EFFECT OF ROBOTIC-ASSISTED GAIT TRAINING ON THE CENTRAL VASCULAR HEALTH RESPONSE OF INDIVIDUALS WITH SPINAL CORD INJURY").

The title has been amended as requested.

Did the authors examine the wave-decomposition analysis data to determine the forward and backward pressure components and reflection magnitude? These data could provide support of the physiological mechanisms discussed.

This was not possible when the data was collected using our SphygmoCor XCEL as we did not have the required software update. We now have the potential to examine the wave decomposition of the SphygmoCor XCEL, and this is an area which could be further explored in future SCI, RGT and central hemodynamic studies.

Reviewer #3: Manuscript #: JSCM-D-19-00062
Title: Effect of Robot-assisted gait training on the vascular health of

General comments:
Thank you for the opportunity to read this manuscript. In general, the manuscript is well-written and an important addition to the literature.

Thank you for your positive overview.

Introduction, page 3, line 54 - specify that cost is prohibitive to patients and provide a general estimate of costs.

As there are various different manufacturers of exoskeleton's and RGT's we do not feel it pertinent to provide an estimate of costs as they can vary between brands.

Page 4 - line 32, re: peripheral blood pressure is a measure as specified in the hypothesis. However the preceding paragraph does not support its use, in fact suggesting central BP and AIx. I understand using this measure as well. Perhaps you can add rational in the preceding paragraph about why it is helpful to include as a measure in addition to the stronger cBP.

This is a very good point. We have included an additional sentence to support the rationale as to why peripheral BP was also recorded in the introduction:

'Despite the importance of measuring central BP and AIx, peripheral BP is widely used in clinical and non-clinical settings as a measure of vascular health.'

Methods.
Exclusion criteria needs more detail, starting at line 2 define severely restricted, uncontrolled high levels of spasticity, what are significant problems managing BP, etc. In other words, how were these assessed, what are the cutoffs.

Further clarity surrounding inclusion and exclusion criteria has now been embedded into the methods (participants) section. This includes:

'Participants using the RGT exoskeleton (Ekso bionics, USA) met the manufacturer's guidelines with regards to inclusion criteria for weight (< 100 kg), height (between 1.57 m and 1.93 m), and range of motion (bilateral hip flexion 110º, ≤ 12 º knee contracture, neutral dorsiflexion).'

'Participants were excluded if they had uncontrolled high levels of muscle spasticity (Modified Ashworth Scale ≥ 4), high blood pressure (> 160/90 mmHg), and/or if there were clinically diagnosed concerns with their bone density (e.g. osteoporosis, etc.).'

Page 5 line 46, include 'All' participants… and perhaps state that All participants were instructed to refrain from … (unless there is a clear way that this was tracked/followed-up on later)

This has been amended as requested. It now reads:

'All participants were instructed to refrain from…'

Line 54 - on each occasion is a bit confusing. Are you referring to On days 1 and 5? Add clarity.

Thank you for your observation. We have removed 'on each occasion' and have changed this section to read:

'At baseline and follow-up assessments…'

Page 6, line 21-23 - add justification as to why these measures were selected. Why a difference of 5mmHg? Why >4% for AIx? Are these clinically meaningful differences? Standards, etc. Justify.

The measures reported are considered clinically meaningful changes. They have also been presented as a recommended guidance when measuring PWA. This reference was presented in the original submission (reference 16).

Control group -- why did the control group get 60 minutes of each session vs. 60/90 as seen in the intervention

group?

When designing the study it was anticipated that the 90 minute RGT session could lead to approximately 60 minutes of activity (standing upright, walking, sit to stand transitions) due to the time spent setting up/adjusting the exoskeleton. Accordingly, we felt the time engaged in activity would be matched between the two groups. Both groups would receive 60 minutes of conventional (normal) therapy in the morning and a further 60 minutes of therapy in the afternoon (RGT activity or a further bout of conventional therapy).

More information is needed on the home-based exercise session for the reader to fully understand the equivalence of the control group. How was it delivered? How was it tracked?

We have included the following additional information with respect to the daily home-based exercise sessions:

'This included 30 minutes of static standing using a frame, and 30 minutes of stretches (i.e. hip flexor exercises), sitting balance and core-stability exercises for maintenance (e.g. targeting transverse abdominis), with relevant rest periods incorporated within this time frame.'

Line 51, page 7 - AIx75 is introduced as a measure for the first time here. Describe the measures/rationale for use.

An explanation of AIx75 was presented in the PWA section to the methodology. As such, no further information will be included.

Use of 2-way ANOVAs is fine, effect sizes are reported, and paired t-tests for exoskeleton baseline/follow-up is appropriate.

Thank you

No mention of Table 1 in the text. No previous mention of what demographics were collected (and how) - survey? Patient chart? Combination ?

Table 1 was mentioned at the end of the first sentence in the participants section to the methods section. However, we have amended this section in light of the additional information requested regarding the participant demographics. This section now reads:

'Participant demographics, including age, height, weight, SCI etiology and type, time since SCI, and distance travelled to participate in the research, were collected from a health history questionnaire (Table 1).'

Add ((n=) to Tables next to title.

This has been included as requested.

Were there any specific tests used for small samples?

No

Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study

Abstract

Objective: To investigate the effect of a short-term, robotic-assisted (exoskeleton) gait training (RGT) program on central and peripheral hemodynamic measures in patients with spinal cord injury (SCI).

Design: Parallel group, non-randomized trial with before (baseline) and after (follow-up) assessments.

Setting: Single-center, community-based neuro-physiotherapy practice.

Participants: Twelve individuals with SCI (ASIA classifications A to C).

Interventions: Participants completed either a 5-day , consecutive, RGT program plus physiotherapy (n=6), or a usual care physiotherapy only program (control group; n=6). The RGT program consisted of daily 60-minute physiotherapy sessions and, followed by 90-minutes of gait training in the exoskeletonRGT. Outcome measures were measured before (baseline) and after (follow-up) the rehabilitation program.

Main Outcome Measure(s): Pulse Wave Analysis was used to assess measures of cardiovascular health. The primary outcome measure was arterial wave reflection (Augmentation index [AIx]), with , including supine ccentral and peripheral blood pressures also reported. , and arterial wave reflection (Augmentation index [AIx]). Data is presented as mean (SD) and effect sizes (partial eta squared; η^2_p).

Results: There was a significant reduction in AIx (30±18 to 21±15 %; η^2_p = 0.75) and mean arterial pressure (89±11 to 82±10 mmHg; η^2_p = 0.47) following completion of the RGT program (both P < 0.05). There were no changes in these measures for the control group. Although not significantly different, medium to large effects were observed in favor of RGT for all other central and peripheral measures (η^2_p = 0.06 to 0.21), except for heart rate and pulse pressure (η^2_p < 0.04).

Conclusions: Robotic-assisted gait trainingRGT using an exoskeleton is a promising therapy for improving cardiovascular health in patients with SCI. Specifically, this preliminary short-term study indicates decreased arterial wave reflection, and supports the need for larger randomized controlled trials.

Trial Registration: Clinical trials Registry (https://clinicaltrials.gov/; ~~Trial Registration Number:~~ NCT03611803).

Key Words: SCI, blood pressure, cardiovascular health, rehabilitation, robotics

Introduction

Individuals with spinal cord injury (SCI) have an accelerated trajectory of aging in the cardiovascular system compared with same-age individuals in the general population,[1] ~~(1),~~ and accordingly, have a higher rate of cardiovascular mortality.[2] ~~(2).~~ For example, SCI is significantly associated with an increased risk of heart disease (odds ratio = 2.72) and stroke (odds ratio = 3.72).[3] ~~(3).~~ This is at least partially attributed to their impaired blood pressure regulation as a consequence of the autonomic nervous system dysfunction, physical inactivity and increased sedentary time. As such, there is a pressing need to identify practical strategies for increasing physical activity and decreasing sedentary time in people with SCI.[4] ~~(4).~~

Robotic-assisted gait training (RGT) is used in the rehabilitation of patients with SCI, ~~although individual access is often limited and infrequent~~and may be a viable option to improve functional and health outcomes, and independence, in this population group. ~~.~~ Task-specific stepping practice enhances the afferent feedback associated with normal locomotion and can induce plasticity in the involved motor centers.[5,6] ~~(5, 6).~~ Robotic powered exoskeletons are wearable robotic units that power a system of motors, pneumatics, levers, or hydraulics to restore locomotion through RGT programs.[7,8] A systematic review and meta-analysis of 14 exoskeleton studies, typically including RGT programs that consisted of training sessions three times per week, 60–120 minutes per session, for 1–24 weeks, demonstrated that 76% of patients were able to ambulate with no physical assistance on completion of an exoskeleton program.[8] The physiological demand of such exoskeleton-assisted walking programs are comparable to self-reported exertion of an able-bodied person walking at 3 miles per hour, and can elicit improvements in spasticity, without any serious adverse

events.[8,9] Robotic exoskeletons may decrease seated time, increase standing and walking time,[10,11] thus, potentially ameliorating several of the chronic health-related consequences that negatively impact this population.[12,13]

As RGT enables practitioners to increase the intensity and total duration of physical activity whilst maintaining a physiological gait pattern,[14] ~~(7),~~ there may be significant benefit for people with SCI to manage their risk of cardiovascular disease (CVD). This may be evident if an individual with SCI has regular and continued access to such technology. However, there is a paucity of research which has considered the vascular benefit of implementing ~~robotic-assisted training~~RGT for people with SCI as most research focuses on outcome measures such as gait velocity, gait distance, leg strength, balance and spasticity.[14] ~~(7).~~ Further, while this technology may be practical in terms of application in medical centers and community settings,[7] ~~,~~ the cost is currently prohibitive. Thus, prior to advocating resource intensive longitudinal randomized control trials, there i~~'~~s a need for short-term trials using established measures of cardiovascular health.[15] ~~(8).~~

The measurement of central hemodynamic parameters, including central systolic blood pressure (cSBP) and arterial wave reflection (augmentation index, AIx) have the potential to provide clinicians with important diagnostic and prognostic information beyond traditional blood pressure (BP) readings.[16] ~~(9).~~ Central BP has been reported to be a stronger determinant of cardiovascular events than peripheral BP,[17] ~~(10)~~ while AIx, a measure used to infer the degree of systemic arterial wave reflection, has been demonstrated to predict future cardiovascular events and all-cause mortality independent of peripheral or central BPs.[17,18] ~~(10, 11).~~ These parameters can

be obtained using 'Pulse Wave Analysis' (PWA), a valid and reliable noninvasive procedure.[16,19-22] ~~.~~ A recent study demonstrated that individuals with SCI who have high cord lesions have more severe cardiovascular autonomic disruption, leading to orthostatic BP dysregulation and physical inactivity, which appear to contribute independently to increased arterial stiffness in these individuals.[23] Despite the importance of measuring central BP and AIx, peripheral BP is widely used in clinical and non-clinical settings as a measure of vascular health.

The purpose of this pilot study was to assess the effect of a RGT (exoskeleton) program on central and peripheral hemodynamic markers in people with SCI. It was hypothesized that improvements in vascular health would be evident through a reduction in central and peripheral ~~blood pressure~~BP, and AIx, in people with SCI who used the exoskeleton.

Methods

Participants

A convenience sample of 12 individuals with SCI, who were actively seeking neuro-physiotherapy from a single center (Hobbs Rehabilitation, Winchester, UK), participated in the study ~~(Table 1)~~. Participant demographics, including age, height, weight, SCI etiology and type, time since SCI, and distance travelled to participate in the research study, were collected from a health history questionnaire (Table 1). Due to the pilot nature of the study, a quasi-experimental design was implemented whereby ~~P~~the first six participants were assigned to ~~either a~~the RGT program, and the remaining six to the ~~ or to a~~ control (Con) group. Participants using the RGT exoskeleton (Ekso bionics, USA) met the manufacturer's guidelines with regards to inclusion criteria for weight (< 100 kg), ~~and~~ height (between 1.57 m and 1.93 m), and

range of motion (bilateral hip flexion 110º, ≤ 12 º knee contracture, neutral dorsiflexion). ~~.~~ All participants were standing at least three times a week with therapist support and classified, according to the American Spinal Injury Association Impairment Scale (ASI~~A~~) scale, as either ASI~~A~~ A (Complete SCI), ASI~~A~~ B (Sensory incomplete SCI), ASI~~A~~ C (Motor incomplete SCI) or ASI~~A~~ D (Motor incomplete SCI). Participants were excluded if they~~ had~~ had~~ ~~had a severely restricted range of motion in their lower limbs,~~ uncontrolled high levels of muscle spasticity (Modified Ashworth Scale ≥ 4), ~~significant problems managing their blood pressure~~high blood pressure (> 160/90 mmHg), and/or if there were clinically diagnosed concerns with their bone density (e.g.~~,~~ osteoporosis, etc.). Institutional ethical approval was granted and the study was registered with the Clinical trials Registry (https://clinicaltrials.gov/; Trial Registration Number: NCT03611803). Written informed consent was obtained prior to participation.

Procedures

The measurement procedures were discussed with all eligible participants prior to the start of the study. All participants completed an identical baseline (day 1) and follow-up (day 5) vascular health assessment using PWA at a neuro-physiotherapy practice, between the hours of 11:00 and 12:00 and following a minimum 3-hour fast~~, at a neuro-physiotherapy practice~~. Between the baseline and follow-up assessments, participants in the RGT group attended the~~a~~ neuro-physiotherapy practice on five consecutive days for robotic-assisted gait training using the exoskeleton.

Pulse Wave Analysis

All ~~P~~participants were instructed to refrain~~ed~~ from: i) supplement intake during the morning of the baseline and follow-up assessments, ii) strenuous rehabilitation exercises within 24 hours preceding baseline, and iii) alcohol consumption 24 hours prior to both PWA assessment sessions. ~~On each occasion~~At baseline and follow-up assessments, and following 20 minutes undisturbed, supine rest, oscillometric pressure waveforms were recorded by a single operator on the left upper arm using a brachial blood pressure cuff (SphygmoCor XCEL device, ~~(~~AtCor Medical, Sydney, Australia), ~~following~~ in accordance with standard manufacturer's guidelines.[24] ~~(16).~~ Each measurement cycle lasted approximately 60 s, consisting of a brachial BP recording and then a 10 s subsystolic recording. The merging point (the inflection point) of the forward and reflected waves was identical on the derived aortic pressure waveform. Augmentation pressure is defined as the maximum systolic pressure minus the pressure of the inflection point. The AIx is defined as the augmentation pressure expressed as a percentage of central pulse pressure. AIx is influenced by heart rate, and thus an index corrected for heart rate at 75 beats per minute (AIx75) was also calculated. Two measurements were taken, with a minimum 3 minute interval. If blood pressure differed by more than 5 mmHg or AIx by > 4%, a third recording was taken and the closest two recordings were averaged in line with recommendations.[24,25] ~~(16).~~

RGT exoskeleton training program

On completion of the baseline assessment all participants involved in the RGT exoskeleton program completed a 60 minute ~~normal~~ conventional therapy session (morning) and a 90 minute ~~robotic-assisted gait training~~RGT session (afternoon)

using a wearable ~~RGT~~ exoskeleton, on five consecutive days. The design of the program (conventional therapy in the morning, RGT in the afternoon) was standardized for all RGT participants. As demonstrated in Table 1, patients often travel long distances to receive therapy from neuro-physiotherapy practices. Accordingly, for logistical but also therapeutic reasons, Hobbs Rehabilitation provide patients with the opportunity to engage in intense, short-duration therapy programs. The 90 minute RGT sessions incorporated the time required to set-up the exoskeleton, and all exercise and rest periods. The 60 minute conventional therapy sessions were completed by one physiotherapist and included a variety of treatment techniques depending on the needs of the patient. This typically included lower limb muscle lengthening, core stability and functional sitting balance exercises.

The 90 minute RGT sessions were completed by two physiotherapists and used various settings on the exoskeleton. Patients would commence their program on day 1 with the 'First Step' setting where the therapist dictated the steps taken. ~~Thereafter,~~Following optimal weight transfer, which was determined by a therapist who had > 4 years experience using the exoskeleton, the 'ProStep+ bilateral adapt' setting was administered.~~.~~ This setting allows the participant to control their steps by transferring their body weight. The therapist would ensure progressive overload by altering the following settings to allow the exoskeleton to improve each participant's gait pattern; including degree of leg extension, stride length, step height and step speed. A wheeled frame was initially used at the start of the day 1 session, but all patients progressed to use crutches by the end of first days session, and were used for all remaining RGT training sessions. Participants were allowed rest periods at their request. The participants 'Up Time', 'Walk Time' and number of 'Steps' per session

were recorded, as well as the minimum level of motor assistance provided by the exoskeleton.

Control group

Between baseline and follow-up assessments, participants in the Con group received a daily 60 minute conventional physiotherapy session, similar to that undertaken by the RGT group, and a daily 60 minute home-based rehabilitation exercise session. This included 30 minutes of static standing using a frame, and 30 minutes of stretches (i.e. hip flexor exercises), sitting balance and core-stability exercises (e.g. targeting transverse abdominis), with relevant rest periods incorporated within this time frame. ~~(i.e., sit-to-stand, weight-bearing and core-stability exercises).~~

Statistics

A series of two-way ANOVAs; Condition (RGT, Con) x Time (Baseline, Follow-up) were used to assess changes in PWA (including cSBP, central diastolic blood pressure [cDBP], pulse pressure [PP], peripheral systolic blood pressure [SBP], peripheral diastolic blood pressure [DBP], mean arterial pressure [MAP], heart rate [HR], AIx and AIx75). Data is presented as Mean (SD) with 95% confidence intervals (CI) where necessary. Effect sizes are reported to describe the importance of the relevant findings in practical terms. Partial eta squared (η^2_p) was used as a measure of effect size, with .0099, .0588 and .1379 representing a small, medium and large effect, respectively. ~~(17).~~ Paired sample t-tests were used to assess the participants' time spent upright and walking in the exoskeleton, ~~as well as~~ the number of steps recorded and the minimum amount of motor assistance provided by the exoskeleton ~~at the~~

~~baseline and follow-up assessment~~on completion of the first (day 1) and last day (day 5) to the RGT program. Cohen's d was used as a measure of effect size for these analyses, with 0.2, 0.5 and 0.8 representing a small, medium and large effect, respectively.[26] ~~(17).~~ Statistical significance was set at P = .05. All analysis was undertaken using SPSS Version 24.0.

Results

The mean (SD) peripheral and central hemodynamic values can be observed in Table 2. Significant Condition x Time interactions were observed for AIx (η^2_p = 0.74), AIx75 (η^2_p = 0.67), AP (η^2_p = 0.44), and MAP (η^2_p = 0.47) (all P < 0.05~~; Table 2~~), with ~~.~~ cDBP ~~was~~ approaching statistical significance (η^2_p = 0.35). Each of these ~~measures~~ outcomes remained constant for Con, but decreased (improved) between baseline and follow-up assessments for RGT (Mean [95%CI]; AIx -9% [-12.2 to -5.8]; AIx75 -7% [-9.8 to -4.2]; AP -6% [-13.1 to -0.7]; MAP -7 mmHg [-10.8 to -2.7])~~,~~ ~~between baseline and follow-up assessments~~. There were no interactions for all other peripheral and central hemodynamic variables (all P > 0.05) but, with the exception of HR and PP, medium to large effect sizes were observed (η^2_p = 0.06 to 0.21).

Mean time spent upright by the RGT group in the exoskeleton significantly increased from ~~baseline to follow-up~~day 1 to day 5 (mean [~~(~~SD~~)~~]: 35 [~~(~~14~~])~~ vs. 48 [~~(~~13~~])~~ min per session; P < 0.05; d = 0.95; Figure 1), as did the amount of time spent walking (10 [~~(~~3~~])~~ vs. 24 [~~(~~8~~])~~ min per session; P < 0.05; d = 2.47) and the number of steps taken in the exoskeleton (193 [~~(~~47~~])~~ vs. 523 [~~(~~125~~])~~ steps per session at ~~baseline~~ day 1 and ~~follow-up~~day 5, respectively; P < 0.01; d = 3.51). The minimum level of motor assistance provided by the exoskeleton decreased from 81 (1) % to 67 (5) % between day 1 and 5 of the program (P < 0.01; d = 4.02).

Discussion

This study demonstrated that five days of consecutive RGT, which elicited an increase in time spent upright, walking and stepping whilst wearing the exoskeleton, can decrease (improve) arterial wave reflection (AIx) and MAP in individuals with SCI. These findings are ~~noteworthy~~ particularly interesting when considering that ~~participants only engaged in five~~ RGT training program was of a short duration.~~sessions. Although this form of rehabilitation may prove too expensive for continued use,~~ The present study supports the need for further work to determine how this approach may be beneficial in a patients' long-term rehabilitation strategy.

The mean reduction in AIx ~~and AIx75~~ of 9% ~~and 7%, respectively,~~ is of significant value when considering that AIx has been demonstrated to predict future cardiovascular events and all-cause mortality, independent of peripheral or central BP.[17,18] ~~(10, 11).~~ Vlachopoulos and colleagues[17] ~~(10)~~ demonstrated that a 10% absolute increase in central AIx is associated with a 32% increase in the risk of cardiovascular events and 38% increase in all-cause mortality. Despite our findings, the AIx reported at the baseline and follow-up assessments are widely dispersed. Accordingly, although the mean reduction in AIx is encouraging from less than one week of daily ambulatory robotic training, further research consideration is needed. Furthermore, the present study also demonstrated favourable changes to cDBP and MAP, with mean decreases of 5 mmHg and 7 mmHg, respectively, observed for the RGT group. Although SBP is considered the strongest peripheral BP predictor of CVD risk,[27,28] ~~(18, 19),~~ in subjects aged 40 years and younger – a population which may be at a heightened risk of SCI – DBP has also been shown to be an important predictor of CVD risk.[29]~~(20)~~

While a full mechanistic explanation is beyond the scope of this article, it may be speculated that the changes in peripheral vascular health may lead to a decreased central burden. In SCI, central hemodynamic control is impaired due to autonomic nervous system dysfunction. This is typically confounded by peripheral vascular dysfunction which will increase arterial wave reflection.[30] ~~(21).~~ Previous research has shown that short-term exercise can improve peripheral vascular health, most likely due to an enhanced blood flow-induced shear stress.[31] ~~(22).~~ This is a likely reason as to why our short-term RGT program could majorly benefit the vascular health of people with SCI.

Clinical implications and future considerations

Robotic-assisted gait-training programs allow practitioners to increase the intensity and total duration of physical activity whilst maintaining a physiological gait pattern.[14] ~~(7).~~ The present study demonstrated a mean increase in time spent upright (13 minutes; 46% increase), walking (14 minutes, 140% increase) and stepping (330 steps; 170% increase) between baseline and follow-up. These changes, although practitioner driven at the start of the training program, are highly encouraging, particularly when considering that the mean time spent walking in the exoskeleton (24 minutes) nearly meets physical activity guidelines for ambulatory counterparts.[32] ~~(23).~~ Long-term reductions in sedentary time and an increase in physical activity, which would help to increase blood flow shear stress,[31] ~~(22),~~ could help prevent secondary complications associated with CVD for those with SCI.[4] ~~(4).~~ When considering the prognostic value of central vascular health markers and the observed increases in physical activity, the present study demonstrates the importance of administering a short-duration, intense exoskeleton training program for people living with SCI.

However, as we seek to establish the optimal rehabilitation recommendations for individuals with SCI, further research is needed with regards to how and when to implement short-term RGT programs into the longer-term rehabilitation strategy ~~in people with SCI~~. It would be valuable to know the optimal training program (length, intensity and duration of ~~robotic-assisted gait~~RGT ~~training~~), and over what duration changes in arterial wave reflection remain present following such a training program. Furthermore, when considering that ISCOS guidelines recommend that persons with SCI engage in at least 20 minutes of moderate to vigorous intensity aerobic exercise three times per week to improve cardiorespiratory fitness,[33] further investigation into the cardiometabolic effect of RGT exoskeleton programs is warranted. It appears that such research studies would be applicable and feasible for individuals with SCI as the present study has shown that this population group are willing to travel long distances for the opportunity to engage in such rehabilitation programs (>~~-~~100 km; Table 1). RGT programs have also been shown to impact positively on the users lives and may enhance their perceived well-being.[34]~~(24)~~ Nevertheless, the benefit of the RGT exoskeleton program in comparison to more widely available and less costly ambulatory assistance physiotherapy training programs needs to be assessed.

~~-~~*Study limitations*

Several limitations should be addressed in order to better contextualize the findings. Our preliminary findings are based on only six participants who engaged with the short-duration RGT exoskeleton program and who had different ASI~~A~~ classifications. A larger sample size, and the inclusion of a more specific ASI~~A~~ classification, such as the recruitment of individuals with only ASI~~sia~~ 'A' or 'B' on the impairment scale,

could make future findings more robust. Although we were able to quantify the time spent upright in the RGT group during the exoskeleton sessions, we were unable to obtain a similarly objective assessment during the home-based rehabilitation sessions for the control group. While it should also be recognized that SCI patients are difficult to recruit and require significant resources (therapist time, equipment, etc.), these preliminary data support the need for further funding and research. The inclusion of additional research centers would be necessary if seeking to recruit a larger study population, as our study population was recruited from a single center. When considering that our study assesses the acute effect of the proposed study intervention, the longitudinal effects on central hemodynamic parameters and arterial wave reflection, and the actual delivery of the training program (i.e., frequency of training sessions and/or duration of training program), warrants further consideration.

Conclusion

The aim of this investigation was to determine the effect of a short-term robotic-assisted (exoskeleton) gait training program on central and peripheral hemodynamic variables in people with SCI. Findings suggest that the training program, which elicited increases in time spent upright and walking whilst in an exoskeleton, can improve established measures of cardiovascular health in individuals with SCI. These findings support the need for future research, to examine whether such findings are evident in a RCT with a larger sample size, whereby outcome measures are assessed in both the short- and longer-term. Such studies may help demonstrate whether robotic-assisted training interventions are a practical option for improving cardiovascular health outcomes, morbidity and mortality in individuals with SCI.

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Conflicts of Interest: None to declare.

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.

Suppliers

SphygmoCor XCEL device (AtCor Medical, Sydney, Australia)

Exoskeleton (Ekso bionics, USA)

Figure Legend

Figure 1. Mean (SD) time spent upright and walking in the Exoskeleton at Day 1 and Day 5 to the program

Table 1: Participant demographics

		RGT	Con
Participants (n)		6	6
~~**Gender**~~**Sex**	**Male**	3	3
	Female	3	3

Age (y)[a]		30 (13)	38 (17)
Height (m) [a]		1.75 (0.09)	1.76 (0.11)
Weight (kg) [a]		63.8 (17.4)	62.8 (18.4)
Etiology	**Traumatic**	6	6
	Non-traumatic	0	0
Type	**ASIA A**	4	2
	ASIA B	1	2
	ASIA C	1	2
	ASIA D	0	0
Time since SCI (y) [a]		2.7 (1.3)	3.6 (2.5)
Distance (km) [a*]		95 (30)	71 (56)

Abbreviations: ASIA, American Spinal Cord Association Impairment Scale; Con, Control group; RGT, Robotic-assisted gait training; SCI, Spinal sord injury

[a] Mean (standard deviation)

[*]This refers to the distance between the participants' home and the neuro-physiotherapy center which conducted the study.

Table 2: Mean and SD of PWA indices for individuals with SCI in RGT (n = 6) and Con (n = 6)

		RGT (n = 6)		Con (n = 6)			
		Baseline	**Follow-up**	**Baseline**	**Follow-up**	**P**	**η^2_p**
MAP (mmHg)	X	89	82	86	87	*0.029	0.47
	SD	11	10	17	20		
SBP (mmHg)	X	125	118	130	131	0.157	0.21
	SD	19	10	10	11		
DBP (mmHg)	X	71	66	76	76	0.162	0.21
	SD	8	8	9	13		
PP (mmHg)	X	55	53	54	55	0.577	0.04
	SD	12	3	8	9		
cSBP (mmHg)	X	117	110	118	120	0.135	0.21
	SD	17	11	9	9		
cDBP (mmHg)	X	72	67	77	78	0.055	0.35
	SD	8	8	9	11		

cPP (mmHg)	X	51	48	41	42	0.461	0.06
	SD	21	19	7	6		
HR ($b \cdot min^{-1}$)	X	55	56	67	70	0.714	0.02
	SD	13	10	16	19		
AP (%)	X	18	12	12	13	*0.050	0.44
	SD	16	8	7	6		
AIx (%)	X	30	21	31	33	*0.001	0.75
	SD	18	15	12	14		
AIx75 (%)	X	21	14	22	25	*0.002	0.67
	SD	18	14	12	13		

*Significant difference ($P < .05$)

Abbreviations: AIx, Augmentation index; AP, Augmentation pressure; cDBP, Central diastolic blood pressure; cSBP, Central systolic blood pressure; Con, Control group; DBP, Diastolic blood pressure; HR, Heart rate; MAP, mean arterial pressure; PP, Pulse pressure; RGT, Robotic-assisted gait training; SCI, Spinal cord injury; SBP, Systolic blood pressure

8

Effects of robotic-assisted gait training on the central vascular health of individuals with spinal cord injury: A pilot study

Abstract

Objective: To investigate the effect of a short-term, robotic-assisted (exoskeleton) gait training (RGT) program on central and peripheral hemodynamic measures in patients with spinal cord injury (SCI).

Design: Parallel group, non-randomized trial with before (baseline) and after (follow-up) assessments.

Setting: Single-center, community-based neuro-physiotherapy practice.

Participants: Twelve individuals with SCI (ASI A to C).

Interventions: Participants completed either a 5-day RGT program plus physiotherapy (n=6), or a usual care physiotherapy only program (control group; n=6). The RGT program consisted of daily 60-minute physiotherapy and 90-minutes of RGT. Outcome measures were measured before and after the rehabilitation program.

Main Outcome Measure(s): The primary outcome measure was arterial wave reflection (Augmentation index [AIx]), with central and peripheral blood pressures also reported. Data is presented as mean (SD) and effect sizes (partial eta squared; η^2_p).

Results: There was a significant reduction in AIx (30±18 to 21±15 %; η^2_p=0.75) and mean arterial pressure (89±11 to 82±10 mmHg; η^2_p=0.47) following completion of the RGT program (both P<0.05). There were no changes in these measures for the control group. Although not significantly different, medium to large effects were observed in favor of RGT for all other central and peripheral measures (η^2_p=0.06 to 0.21), except for heart rate and pulse pressure (η^2_p<0.04).

Conclusions: RGT using an exoskeleton is a promising therapy for improving cardiovascular health in patients with SCI. Specifically, this study indicates decreased arterial wave reflection, and supports the need for larger randomized controlled trials.

Trial Registration: Clinical trials Registry (https://clinicaltrials.gov/; NCT03611803).

Key Words: SCI, blood pressure, cardiovascular health, rehabilitation, robotics

Introduction

Individuals with spinal cord injury (SCI) have an accelerated trajectory of aging in the cardiovascular system compared with same-age individuals in the general population,[1] and accordingly, have a higher rate of cardiovascular mortality.[2] For example, SCI is significantly associated with an increased risk of heart disease (odds ratio = 2.72) and stroke (odds ratio = 3.72).[3] This is at least partially attributed to their impaired blood pressure regulation as a consequence of the autonomic nervous system dysfunction, physical inactivity and increased sedentary time. As such, there is a pressing need to identify practical strategies for increasing physical activity and decreasing sedentary time in people with SCI.[4]

Robotic-assisted gait training (RGT) is used in the rehabilitation of patients with SCI, and may be a viable option to improve functional and health outcomes, and independence, in this population group. Task-specific stepping practice enhances the afferent feedback associated with normal locomotion and can induce plasticity in the involved motor centers.[5,6] Robotic powered exoskeletons are wearable robotic units that power a system of motors, pneumatics, levers, or hydraulics to restore locomotion through RGT programs.[7,8] A systematic review and meta-analysis of 14 exoskeleton studies, typically including RGT programs that consisted of training sessions three times per week, 60–120 minutes per session, for 1–24 weeks, demonstrated that 76% of patients were able to ambulate with no physical assistance on completion of an exoskeleton program.[8] The physiological demand of such exoskeleton-assisted walking programs are comparable to self-reported exertion of an able-bodied person walking at 3 miles per hour, and can elicit improvements in spasticity, without any serious adverse events.[8,9] Robotic exoskeletons may decrease seated time, increase

standing and walking time,[10,11] thus, potentially ameliorating several of the chronic health-related consequences that negatively impact this population.[12,13]

As RGT enables practitioners to increase the intensity and total duration of physical activity whilst maintaining a physiological gait pattern,[14] there may be significant benefit for people with SCI to manage their risk of cardiovascular disease (CVD). This may be evident if an individual with SCI has regular and continued access to such technology. However, there is a paucity of research which has considered the vascular benefit of implementing RGT for people with SCI as most research focuses on outcome measures such as gait velocity, gait distance, leg strength, balance and spasticity.[14] Further, while this technology may be practical in terms of application in medical centers and community settings,[7] the cost is currently prohibitive. Thus, prior to advocating resource intensive longitudinal randomized control trials, there is a need for short-term trials using established measures of cardiovascular health.[15]

The measurement of central hemodynamic parameters, including central systolic blood pressure (cSBP) and arterial wave reflection (augmentation index, AIx) have the potential to provide clinicians with important diagnostic and prognostic information beyond traditional blood pressure (BP) readings.[16] Central BP has been reported to be a stronger determinant of cardiovascular events than peripheral BP,[17] while AIx, a measure used to infer the degree of systemic arterial wave reflection, has been demonstrated to predict future cardiovascular events and all-cause mortality independent of peripheral or central BPs.[17,18] These parameters can be obtained using 'Pulse Wave Analysis' (PWA), a valid and reliable noninvasive procedure.[16,19-22] A recent study demonstrated that individuals with SCI who have high cord lesions have

more severe cardiovascular autonomic disruption, leading to orthostatic BP dysregulation and physical inactivity, which appear to contribute independently to increased arterial stiffness in these individuals.[23] Despite the importance of measuring central BP and AIx, peripheral BP is widely used in clinical and non-clinical settings as a measure of vascular health.

The purpose of this pilot study was to assess the effect of a RGT (exoskeleton) program on central and peripheral hemodynamic markers in people with SCI. It was hypothesized that improvements in vascular health would be evident through a reduction in central and peripheral BP, and AIx, in people with SCI who used the exoskeleton.

Methods

Participants

A convenience sample of 12 individuals with SCI, who were actively seeking neuro-physiotherapy from a single center (Hobbs Rehabilitation, Winchester, UK), participated in the study. Participant demographics, including age, height, weight, SCI etiology and type, time since SCI, and distance travelled to participate in the research study, were collected from a health history questionnaire (Table 1). Due to the pilot nature of the study, a quasi-experimental design was implemented whereby the first six participants were assigned to the RGT program, and the remaining six to the control (Con) group. Participants using the RGT exoskeleton (Ekso bionics, USA) met the manufacturer's guidelines with regards to inclusion criteria for weight (< 100 kg), height (between 1.57 m and 1.93 m), and range of motion (bilateral hip flexion 110º, ≤ 12 º knee contracture, neutral dorsiflexion). All participants were standing at least three times a week with therapist support and classified, according to the

American Spinal Injury Association Impairment Scale (ASI) scale, as either ASI A (Complete SCI), ASI B (Sensory incomplete SCI), ASI C (Motor incomplete SCI) or ASI D (Motor incomplete SCI). Participants were excluded if they had uncontrolled high levels of muscle spasticity (Modified Ashworth Scale ≥ 4), high blood pressure (> 160/90 mmHg), and/or if there were clinically diagnosed concerns with their bone density (e.g. osteoporosis, etc.). Institutional ethical approval was granted and the study was registered with the Clinical trials Registry (https://clinicaltrials.gov/; Trial Registration Number: NCT03611803). Written informed consent was obtained prior to participation.

Procedures

The measurement procedures were discussed with all eligible participants prior to the start of the study. All participants completed an identical baseline (day 1) and follow-up (day 5) vascular health assessment using PWA at a neuro-physiotherapy practice, between the hours of 11:00 and 12:00 and following a minimum 3-hour fast. Between the baseline and follow-up assessments, participants in the RGT group attended the neuro-physiotherapy practice on five consecutive days for robotic-assisted gait training using the exoskeleton.

Pulse Wave Analysis

All participants were instructed to refrain from: i) supplement intake during the morning of the baseline and follow-up assessments, ii) strenuous rehabilitation exercises within 24 hours preceding baseline, and iii) alcohol consumption 24 hours prior to both PWA assessment sessions. At baseline and follow-up assessments, and following 20 minutes undisturbed, supine rest, oscillometric pressure waveforms were

recorded by a single operator on the left upper arm using a brachial blood pressure cuff (SphygmoCor XCEL device, AtCor Medical, Sydney, Australia), in accordance with standard manufacturer's guidelines.[24] Each measurement cycle lasted approximately 60 s, consisting of a brachial BP recording and then a 10 s subsystolic recording. The merging point (the inflection point) of the forward and reflected waves was identical on the derived aortic pressure waveform. Augmentation pressure is defined as the maximum systolic pressure minus the pressure of the inflection point. The AIx is defined as the augmentation pressure expressed as a percentage of central pulse pressure. AIx is influenced by heart rate, and thus an index corrected for heart rate at 75 beats per minute (AIx75) was also calculated. Two measurements were taken, with a minimum 3 minute interval. If blood pressure differed by more than 5 mmHg or AIx by > 4%, a third recording was taken and the closest two recordings were averaged in line with recommendations.[24,25]

RGT exoskeleton training program

On completion of the baseline assessment all participants involved in the RGT exoskeleton program completed a 60 minute conventional therapy session (morning) and a 90 minute RGT session (afternoon) using a wearable exoskeleton, on five consecutive days. The design of the program (conventional therapy in the morning, RGT in the afternoon) was standardized for all RGT participants. As demonstrated in Table 1, patients often travel long distances to receive therapy from neuro-physiotherapy practices. Accordingly, for logistical but also therapeutic reasons, Hobbs Rehabilitation provide patients with the opportunity to engage in intense, short-duration therapy programs. The 90 minute RGT sessions incorporated the time required to set-up the exoskeleton, and all exercise and rest periods. The 60 minute

conventional therapy sessions were completed by one physiotherapist and included a variety of treatment techniques depending on the needs of the patient. This typically included lower limb muscle lengthening, core stability and functional sitting balance exercises.

The 90 minute RGT sessions were completed by two physiotherapists and used various settings on the exoskeleton. Patients would commence their program on day 1 with the 'First Step' setting where the therapist dictated the steps taken. Following optimal weight transfer, which was determined by a therapist who had > 4 years experience using the exoskeleton, the 'ProStep+ bilateral adapt' setting was administered. This setting allows the participant to control their steps by transferring their body weight. The therapist would ensure progressive overload by altering the following settings to allow the exoskeleton to improve each participant's gait pattern; including degree of leg extension, stride length, step height and step speed. A wheeled frame was initially used at the start of the day 1 session, but all patients progressed to use crutches by the end of first days session, and were used for all remaining RGT training sessions. Participants were allowed rest periods at their request. The participants 'Up Time', 'Walk Time' and number of 'Steps' per session were recorded, as well as the minimum level of motor assistance provided by the exoskeleton

Control group

Between baseline and follow-up assessments, participants in the Con group received a daily 60 minute conventional physiotherapy session, similar to that undertaken by the RGT group, and a daily 60 minute home-based rehabilitation exercise session. This included 30 minutes of static standing using a frame, and 30 minutes of stretches (i.e.

hip flexor exercises), sitting balance and core-stability exercises (e.g. targeting transverse abdominis), with relevant rest periods incorporated within this time frame.

Statistics

A series of two-way ANOVAs; Condition (RGT, Con) x Time (Baseline, Follow-up) were used to assess changes in PWA (including cSBP, central diastolic blood pressure [cDBP], pulse pressure [PP], peripheral systolic blood pressure [SBP], peripheral diastolic blood pressure [DBP], mean arterial pressure [MAP], heart rate [HR], AIx and AIx75). Data is presented as Mean (SD) with 95% confidence intervals (CI) where necessary. Effect sizes are reported to describe the importance of the relevant findings in practical terms. Partial eta squared (η^2_p) was used as a measure of effect size, with .0099, .0588 and .1379 representing a small, medium and large effect, respectively. Paired sample t-tests were used to assess the participants' time spent upright and walking in the exoskeleton, the number of steps recorded and the minimum amount of motor assistance provided by the exoskeleton on completion of the first (day 1) and last day (day 5) to the RGT program. Cohen's d was used as a measure of effect size for these analyses, with 0.2, 0.5 and 0.8 representing a small, medium and large effect, respectively.[26] Statistical significance was set at $P = .05$. All analysis was undertaken using SPSS Version 24.0.

Results

The mean (SD) peripheral and central hemodynamic values can be observed in Table 2. Significant Condition x Time interactions were observed for AIx ($\eta^2_p = 0.74$), AIx75 ($\eta^2_p = 0.67$), AP ($\eta^2_p = 0.44$), and MAP ($\eta^2_p = 0.47$) (all $P < 0.05$), with cDBP approaching statistical significance ($\eta^2_p = 0.35$). Each of these outcomes remained

constant for Con, but decreased (improved) between baseline and follow-up assessments for RGT (Mean [95%CI]; AIx -9% [-12.2 to -5.8]; AIx75 -7% [-9.8 to -4.2]; AP -6% [-13.1 to -0.7]; MAP -7 mmHg [-10.8 to -2.7]). There were no interactions for all other peripheral and central hemodynamic variables (all $P > 0.05$) but, with the exception of HR and PP, medium to large effect sizes were observed ($\eta^2_p = 0.06$ to 0.21).

Mean time spent upright by the RGT group in the exoskeleton significantly increased from day 1 to day 5 (mean [SD]: 35 [14] vs. 48 [13] min per session; $P < 0.05$; $d = 0.95$; Figure 1), as did the amount of time spent walking (10 [3] vs. 24 [8] min per session; $P < 0.05$; $d = 2.47$) and the number of steps taken in the exoskeleton (193 [47] vs. 523 [125] steps per session at day 1 and day 5, respectively; $P < 0.01$; $d = 3.51$). The minimum level of motor assistance provided by the exoskeleton decreased from 81 (1) % to 67 (5) % between day 1 and 5 of the program ($P < 0.01$; $d = 4.02$).

Discussion

This study demonstrated that five days of consecutive RGT, which elicited an increase in time spent upright, walking and stepping whilst wearing the exoskeleton, can decrease (improve) arterial wave reflection (AIx) and MAP in individuals with SCI. These findings are particularly interesting when considering that RGT training program was of a short duration. The present study supports the need for further work to determine how this approach may be beneficial in a patients' long-term rehabilitation strategy.

The mean reduction in AIx of 9% is of significant value when considering that AIx has been demonstrated to predict future cardiovascular events and all-cause

mortality, independent of peripheral or central BP.[17,18] Vlachopoulos and colleagues[17] demonstrated that a 10% absolute increase in central AIx is associated with a 32% increase in the risk of cardiovascular events and 38% increase in all-cause mortality. Despite our findings, the AIx reported at the baseline and follow-up assessments are widely dispersed. Accordingly, although the mean reduction in AIx is encouraging from less than one week of daily ambulatory robotic training, further research consideration is needed. Furthermore, the present study also demonstrated favourable changes to cDBP and MAP, with mean decreases of 5 mmHg and 7 mmHg, respectively, observed for the RGT group. Although SBP is considered the strongest peripheral BP predictor of CVD risk,[27,28] in subjects aged 40 years and younger – a population which may be at a heightened risk of SCI – DBP has also been shown to be an important predictor of CVD risk.[29]

While a full mechanistic explanation is beyond the scope of this article, it may be speculated that the changes in peripheral vascular health may lead to a decreased central burden. In SCI, central hemodynamic control is impaired due to autonomic nervous system dysfunction. This is typically confounded by peripheral vascular dysfunction which will increase arterial wave reflection.[30] Previous research has shown that short-term exercise can improve peripheral vascular health, most likely due to an enhanced blood flow-induced shear stress.[31] This is a likely reason as to why our short-term RGT program could majorly benefit the vascular health of people with SCI.

Clinical implications and future considerations

Robotic-assisted gait-training programs allow practitioners to increase the intensity and total duration of physical activity whilst maintaining a physiological gait

pattern.[14] The present study demonstrated a mean increase in time spent upright (13 minutes; 46% increase), walking (14 minutes, 140% increase) and stepping (330 steps; 170% increase) between baseline and follow-up. These changes, although practitioner driven at the start of the training program, are highly encouraging, particularly when considering that the mean time spent walking in the exoskeleton (24 minutes) nearly meets physical activity guidelines for ambulatory counterparts.[32] Long-term reductions in sedentary time and an increase in physical activity, which would help to increase blood flow shear stress,[31] could help prevent secondary complications associated with CVD for those with SCI.[4] When considering the prognostic value of central vascular health markers and the observed increases in physical activity, the present study demonstrates the importance of administering a short-duration, intense exoskeleton training program for people living with SCI. However, as we seek to establish the optimal rehabilitation recommendations for individuals with SCI, further research is needed with regards to how and when to implement short-term RGT programs into the longer-term rehabilitation strategy. It would be valuable to know the optimal training program (length, intensity and duration of RGT), and over what duration changes in arterial wave reflection remain present following such a training program. Furthermore, when considering that ISCOS guidelines recommend that persons with SCI engage in at least 20 minutes of moderate to vigorous intensity aerobic exercise three times per week to improve cardiorespiratory fitness,[33] further investigation into the cardiometabolic effect of RGT exoskeleton programs is warranted. It appears that such research studies would be applicable and feasible for individuals with SCI as the present study has shown that this population group are willing to travel long distances for the opportunity to engage in such rehabilitation programs (>100 km; Table 1). RGT programs have also been

shown to impact positively on the users lives and may enhance their perceived well-being.[34] Nevertheless, the benefit of the RGT exoskeleton program in comparison to more widely available and less costly ambulatory assistance physiotherapy training programs needs to be assessed.

Study limitations

Several limitations should be addressed in order to better contextualize the findings. Our preliminary findings are based on only six participants who engaged with the short-duration RGT exoskeleton program and who had different ASI classifications. A larger sample size, and the inclusion of a more specific ASI classification, such as the recruitment of individuals with only ASI 'A' or 'B' on the impairment scale, could make future findings more robust. Although we were able to quantify the time spent upright in the RGT group during the exoskeleton sessions, we were unable to obtain a similarly objective assessment during the home-based rehabilitation sessions for the control group. While it should also be recognized that SCI patients are difficult to recruit and require significant resources (therapist time, equipment, etc.), these preliminary data support the need for further funding and research. The inclusion of additional research centers would be necessary if seeking to recruit a larger study population, as our study population was recruited from a single center. When considering that our study assesses the acute effect of the proposed study intervention, the longitudinal effects on central hemodynamic parameters and arterial wave reflection, and the actual delivery of the training program (i.e. frequency of training sessions and/or duration of training program), warrants further consideration.

Conclusion

The aim of this investigation was to determine the effect of a short-term robotic-assisted (exoskeleton) gait training program on central and peripheral hemodynamic variables in people with SCI. Findings suggest that the training program, which elicited increases in time spent upright and walking whilst in an exoskeleton, can improve established measures of cardiovascular health in individuals with SCI. These findings support the need for future research, to examine whether such findings are evident in a RCT with a larger sample size, whereby outcome measures are assessed in both the short- and longer-term. Such studies may help demonstrate whether robotic-assisted training interventions are a practical option for improving cardiovascular health outcomes, morbidity and mortality in individuals with SCI.

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Conflicts of Interest: None to declare.

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Suppliers

SphygmoCor XCEL device (AtCor Medical, Sydney, Australia)

Exoskeleton (Ekso bionics, USA)

Figure Legend

Figure 1. Mean (SD) time spent upright and walking in the Exoskeleton at Day 1 and Day 5 to the program

Table 1: Participant demographics

		RGT	Con
Participants (n)		6	6
Sex	**Male**	3	3
	Female	3	3
Age (y)[a]		30 (13)	38 (17)
Height (m) [a]		1.75 (0.09)	1.76 (0.11)
Weight (kg) [a]		63.8 (17.4)	62.8 (18.4)
Etiology	**Traumatic**	6	6
	Non-traumatic	0	0
Type	**ASI A**	4	2
	ASI B	1	2
	ASI C	1	2
	ASI D	0	0
Time since SCI (y) [a]		2.7 (1.3)	3.6 (2.5)
Distance (km) [a*]		95 (30)	71 (56)

Abbreviations: ASI, American Spinal Cord Association Impairment Scale; Con, Control group; RGT, Robotic-assisted gait training; SCI, Spinal sord injury

[a] Mean (standard deviation)

[*]This refers to the distance between the participants' home and the neuro-physiotherapy center which conducted the study.

Table 2: Mean and SD of PWA indices for individuals with SCI in RGT (n = 6) and Con (n = 6)

		RGT (n = 6)		Con (n = 6)			
		Baseline	**Follow-up**	**Baseline**	**Follow-up**	**P**	**η^2_p**
MAP (mmHg)	X	89	82	86	87	*0.029	0.47
	SD	11	10	17	20		
SBP (mmHg)	X	125	118	130	131	0.157	0.21
	SD	19	10	10	11		
DBP (mmHg)	X	71	66	76	76	0.162	0.21
	SD	8	8	9	13		
PP (mmHg)	X	55	53	54	55	0.577	0.04
	SD	12	3	8	9		
cSBP (mmHg)	X	117	110	118	120	0.135	0.21
	SD	17	11	9	9		
cDBP (mmHg)	X	72	67	77	78	0.055	0.35
	SD	8	8	9	11		

cPP (mmHg)	X	51	48	41	42	0.461	0.06
	SD	21	19	7	6		
HR ($b \cdot min^{-1}$)	X	55	56	67	70	0.714	0.02
	SD	13	10	16	19		
AP (%)	X	18	12	12	13	*0.050	0.44
	SD	16	8	7	6		
AIx (%)	X	30	21	31	33	*0.001	0.75
	SD	18	15	12	14		
AIx75 (%)	X	21	14	22	25	*0.002	0.67
	SD	18	14	12	13		

*Significant difference ($P < .05$)

Abbreviations: AIx, Augmentation index; AP, Augmentation pressure; cDBP, Central diastolic blood pressure; cSBP, Central systolic blood pressure; Con, Control group; DBP, Diastolic blood pressure; HR, Heart rate; MAP, mean arterial pressure; PP, Pulse pressure; RGT, Robotic-assisted gait training; SCI, Spinal cord injury; SBP, Systolic blood pressure

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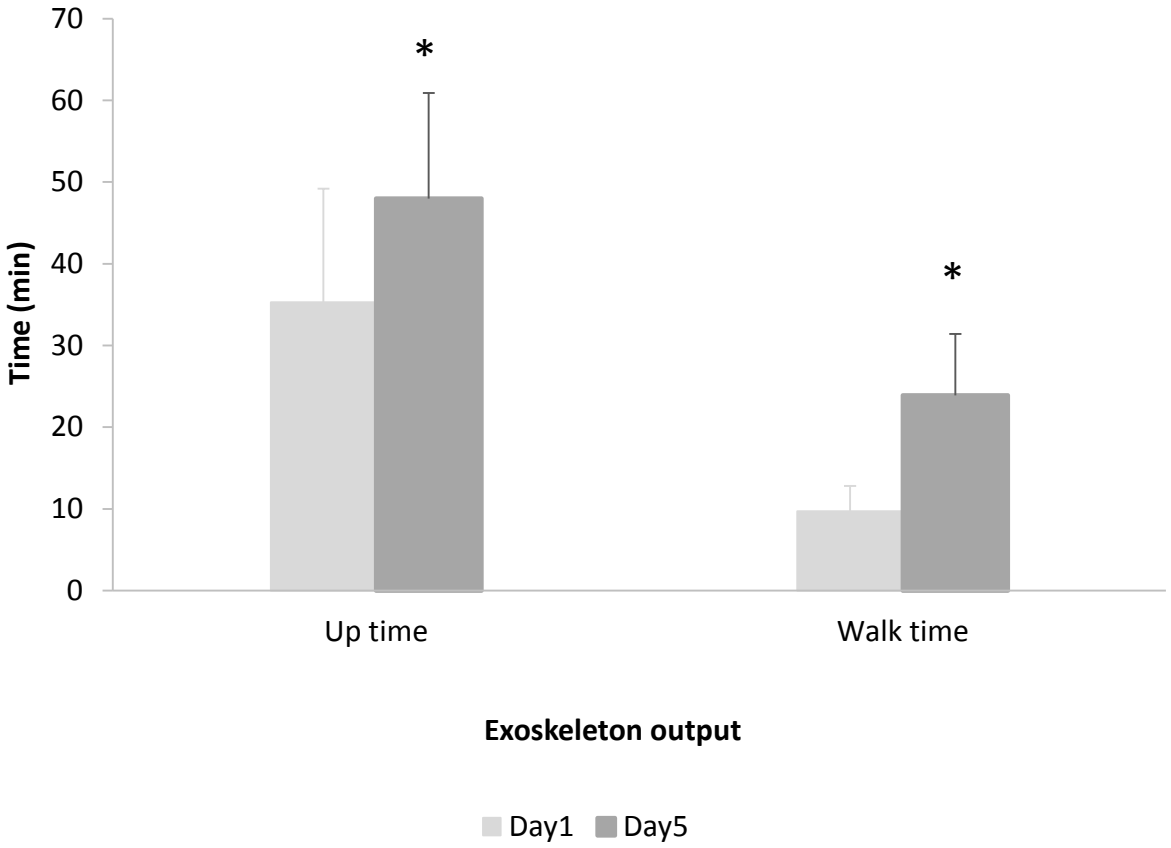

*Significant increase between Day 1 and Day 5 ($P < 0.05$)